SMOKING AND SCHIZOPHRENIA

EDITED BY: David Castle, Amanda Baker and Billie Bonevski
PUBLISHED IN: Frontiers in Psychiatry

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88963-221-3
DOI 10.3389/978-2-88963-221-3

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

SMOKING AND SCHIZOPHRENIA

Topic Editors:
David Castle, The University of Melbourne, Australia
Amanda Baker, University of Newcastle, Australia
Billie Bonevski, University of Newcastle, Australia

Citation: Castle, D., Baker, A., Bonevski, B., eds. (2019). Smoking and Schizophrenia. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-221-3

Table of Contents

frontiers in Psychiatry

EDITORIAL
published: 17 October 2019
doi: 10.3389/fpsyt.2019.00738

Editorial: Smoking and Schizophrenia

David Castle[1,2]*, *Amanda L. Baker*[3], *Billie Bonevski*[3]

[1] Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia, [2] Mental Health Research Unit, St Vincent's Hospital, Melbourne, VIC, Australia, [3] School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia

Keywords: smoking, schizophrenia, cessation, nicotine, physical health

Editorial on the Research Topic

Smoking and Schizophrenia

The association between cigarette smoking and schizophrenia is well established. Rates of smoking among people with schizophrenia are markedly higher than in the general population. In many countries where public health campaigns have reduced the overall prevalence of smoking amongst the general population, there has been little impact on rates of smoking amongst people with schizophrenia. The series of articles in this collection aims to understand the reason for the high smoking rates amongst people with schizophrenia, as well as to explore both barriers and facilitators towards smoking cessation in this vulnerable group.

The reason why people with schizophrenia do smoke at such high rates is complicated and include psychosocial factors, milieu issues such as initiation of smoking on inpatient wards (albeit many have now banned smoking) as well as social affiliation. However, there is more to it than this and the effects of nicotine on the symptoms of schizophrenia as well as cognition need to be factored into this understanding. The paper by Lucatch et al. tackles the topic of neurobiological underpinnings of tobacco smoking in people with schizophrenia, with an overview of how nicotine may serve to ameliorate some of the perturbations in dopaminergic, glutamatergic, and GABAergic pathways. These authors conclude that an understanding of these neurobiological parameters is important in treatment paradigms where the understandings can be integrated into psychosocial interventions. A case control study presented by Stramecki et al. explores the association between cigarette smoking and cognitive function in people with schizophrenia and controls without schizophrenia; roughly half in each group were cigarette smokers. A comprehensive neuropsychological battery was administered, with results suggesting that cigarette smoking is associated with impairment in delayed memory in people with schizophrenia. The authors noted that longitudinal studies are required to establish causal associations.

Scott et al. address a very interesting issue of whether smoking is a cumulative causal factor for schizophrenia and related disorders. They provide an overview of existing studies that have addressed this issue and conclude that despite methodological shortcomings (including failure to adjust for certain confounders such as childhood trauma or prenatal tobacco exposure), there is "substantial though inconclusive evidence supporting a causal relationship between tobacco smoking and an increased risk of schizophrenia spectrum disorder." The potential public health implications of this finding are profound.

The bulk of the rest of the articles in this collection address the issue of smoking cessation and how to help smokers with schizophrenia to quit. Lum et al. performed a comprehensive systematic review of the literature on psychosocial barriers and facilitators to smoking cessation in people with schizophrenia. They included 23 articles: 20 were quantitative and 3 qualitative. In terms of barriers to smoking cessation, cravings and addiction were the most strongly endorsed, followed by the perception that negative symptoms worsened when quitting smoking. The review also showed that people with schizophrenia believed that smoking helps them manage stress and maintain social

OPEN ACCESS

Edited and reviewed by:
Błażej Misiak, Wroclaw Medical University, Poland

***Correspondence:**
David Castle, david.castle@svha.org.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *20 August 2019*
Accepted: *16 September 2019*
Published: *17 October 2019*

Citation:
Castle D, Baker AL and Bonevski B (2019) Editorial: Smoking and Schizophrenia. Front. Psychiatry 10:738. doi: 10.3389/fpsyt.2019.00738

relationships; health concerns were seen as reasons to quit smoking. These important findings are echoed and expanded by Cocks et al. who bring a "lived experience lens" to this particular issue. The authors suggest that a recovery orientated approach could integrate treatments that have an evidence base in terms of smoking cessation.

A somewhat more challenging view is provided by Twyman et al. in a qualitative study of community mental health staff and consumers about the role of tobacco in their lives as well as the impact of these issues on smoking cessation. Themes identified by staff included some degree of fatalism in that they saw people continuing to smoke as their choice rather than an addiction and identified a tension between offering smoking cessation programs and "free choice." Consumers saw smoking as part of their life and social networks and as a way of "maintaining control." Social support to quit was an important theme. These authors conclude that education and training for staff within community mental health services is imperative.

In terms of specific programs addressing smoking cessation, Curtis et al. assessed the uptake and impact of a smoking cessation program in young people with a psychotic illness. Of 61 young people who were eligible for the program, 41 (67%) engaged in the program; a third of these had the full intervention and further third received only a brief intervention. Nearly half of those receiving the full intervention and a quarter of those receiving the brief intervention dropped out; 28% of those completing the full intervention achieved smoking cessation. The authors emphasised the potential for impacting smoking behaviours in youth in the early phases of severe mental illness.

Baker et al. outline a current randomized controlled trial with smokers with a severe mental illness. A brief peer delivered intervention around smoking is being compared to an intervention that includes the same brief intervention with proactive referral to a tailored cognitive behavioural intervention offered by "Quitline," along with nicotine replacement therapy. This ambitious study aims to recruit nearly 400 smokers over 3 years. The trial asks an important question as to whether a "minimal intervention" can address smoking amongst people with schizophrenia. In such trials, it is important also to have an assessment of cost, and a companion paper by Sweeney et al. provides the protocol for the economic evaluation of this Quitlink program.

Seeking to strengthen future research efforts, the editors and other international experts (Baker et al.) propose research priorities. These are i) understanding more about the associations between smoking, smoking cessation, and symptomatology; ii) targeted, adaptive, and responsive behavioural interventions evaluated by smarter methodologies; and iii) improvements in delivery of interventions, especially within health care settings. A collaborative international research agenda, with partnerships between bodies overseeing mental health treatment and smoking cessation, would likely add momentum to research efforts. Using existing structures to support an international collaborative effort between national psychiatry, mental health, and tobacco control research societies is likely to provide a solid platform for research growth in this area. These societies can connect researchers and break down research siloes. Strategic and targeted funding from international and national organisations focussed on supporting innovation in treatment for smokers with schizophrenia is critical. Finally, it is imperative that we grow our research capacity in this field, bringing together academic researchers and clinicians to ensure research innovations are translated into policy and practice change.

AUTHOR CONTRIBUTIONS

DC, AB and BB all collaborated in the construction of the editorial, shared the writing between them, and all approved the final version.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 06 December 2018
doi: 10.3389/fpsyt.2018.00672

Neurobiological Determinants of Tobacco Smoking in Schizophrenia

Aliya M. Lucatch[1,2]*, *Darby J. E. Lowe*[1,2], *Rachel C. Clark*[1], *Karolina Kozak*[1,2] and *Tony P. George*[1,2,3]*

[1] Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada, [2] Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada, [3] Division and Brain and Therapeutics, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Purpose of review: To provide an overview of the underlying neurobiology of tobacco smoking in schizophrenia, and implications for treatment of this comorbidity.

Recent findings: Explanations for heavy tobacco smoking in schizophrenia include pro-cognitive effects of nicotine, and remediation of the underlying pathophysiology of schizophrenia. Nicotine may ameliorate neurochemical deficits through nicotine acetylcholine receptors (nAChRs) located on the dopamine, glutamate, and GABA neurons. Neurophysiological indices including electroencephalography, electromyography, and smooth pursuit eye movement (SPEM) paradigms may be biomarkers for underlying neuronal imbalances that contribute to the specific risk of tobacco smoking initiation, maintenance, and difficulty quitting within schizophrenia. Moreover, several social factors including socioeconomic factors and permissive smoking culture in mental health facilities, may contribute to the smoking behaviors (initiation, maintenance, and inability to quit smoking) within this disorder.

Summary: Tobacco smoking may alleviate specific symptoms associated with schizophrenia. Understanding the neurobiological underpinnings and psychosocial determinants of this comorbidity may better explain these potential beneficial effects, while also providing important insights into effective treatments for smoking cessation.

Keywords: schizophrenia, nicotine, tobacco, neurobiology, nicotinic acetylcholine receptor

OPEN ACCESS

Edited by:
Amanda L. Baker,
University of Newcastle, Australia

Reviewed by:
Robert C. Smith,
New York University, United States
Jose Antonio Apud,
National Institute of Mental Health (NIMH), United States
Vanessa Clark,
University of Newcastle, Australia

***Correspondence:**
Aliya M. Lucatch
aliya.lucatch@mail.utoronto.ca
Tony P. George
tony.george@camh.ca

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *31 July 2018*
Accepted: *21 November 2018*
Published: *06 December 2018*

Citation:
Lucatch AM, Lowe DJE, Clark RC, Kozak K and George TP (2018) Neurobiological Determinants of Tobacco Smoking in Schizophrenia. Front. Psychiatry 9:672. doi: 10.3389/fpsyt.2018.00672

INTRODUCTION

The high rates of tobacco use in the schizophrenia (SZ) population are widely recognized, but the underlying neurobiological factors contributing to this comorbidity are not fully understood. Rates of tobacco smoking are between 45 and 88% in SZ compared to <16% of the general population (1, 2). In this review, we aim to highlight the recent literature on the latter category of neurobiological determinants and discuss some potential treatment targets.

The high prevalence of smoking in SZ is maintained in large part by resistance to quitting (3); quit rates from an American nationally representative sample range from 10 to 27.2% for those with psychotic disorders compared to 42.5% in the general population (4). Additionally, relapse rates pose a common challenge in delivering cessation treatments, but there is some indication that longer courses of pharmacological treatments could reduce the possibility of relapse (2). Unfortunately, these high smoking rates come with a cost, and smokers with SZ are at higher risk for tobacco-related morbidity and mortality; people with SZ have ∼25 years of shortened lifespan,

with 53% of this being related to tobacco-smoking conditions (5–7). One population-based study in the United States (U.S.) found that among individuals with SZ, cardiovascular disease, lung cancer, and respiratory diseases such as chronic obstructive pulmonary disease and pneumonia contributed to the most deaths (8). It is clear from the evidence that reducing smoking rates has the potential to drastically change mortality rates and improve outcomes for these patients.

ETIOLOGY OF TOBACCO SMOKING IN SZ

Many explanations have been proposed for the higher prevalence of smoking in persons with SZ. In this section, we briefly review some of these important factors before highlighting current findings on the neurobiology of this comorbidity. These major factors include increased craving in SZ, modulating negative symptoms, pro-cognitive effects of nicotine, and genetic factors (3). In addition, we compare the self-medication hypothesis with the addiction vulnerability hypothesis for tobacco use in SZ.

It has been proposed that due to the pathophysiology of SZ, these individuals may have an enhanced experience of the reinforcing effects of nicotine (3, 9). This idea has been corroborated with a study that compared smokers with SZ to non-psychiatric control smokers in an abstinence condition; they found that the SZ group reported stronger cravings and withdrawal symptoms and had a shorter time to smoking lapse compared to the control group (10). This effect was moderated by negative affect and withdrawal symptom severity (10). Another study using an animal model produced lesions in the ventral hippocampus, a region associated with SZ, and found increased reinforcing effects and drug-seeking behavior for nicotine (11).

There appears to be a link between the enhanced reinforcing effects of nicotine and the role that negative affect has on increasing the smoking rate in SZ. This may be due to the deficits in reward processing and alterations in reward-related brain circuitry that is characteristic of negative symptoms in SZ (12, 13). In an fMRI study of smokers with SZ compared to control smokers, researchers found that both groups had brain reactivity to smoking cues, but SZ group had reduced brain reactivity to neutral cues, and that this effect was related to negative symptoms (14). This finding indicates that the enhanced addictive properties of nicotine in SZ is not due to a stronger reactivity to nicotine-related cues, but rather may be related to the underlying negative symptomatology (14). A recent study using a cognitive assessment of reward learning in smokers found a negative correlation between general reward responsiveness and intensity of nicotine craving (15). This finding suggests that individuals with negative affect and a dysfunctional reward circuit, such as those with SZ, may be more susceptible to nicotine addiction (15). Together, these findings indicate that increased negative symptomatology may play a role in the enhanced susceptibility to smoking in SZ, yet does not reveal the full picture.

Pro-cognitive Effects of Nicotine in SZ

Another key etiological factor to consider is the potential pro-cognitive effects that nicotine has on SZ; nonetheless there have been mixed findings in this field. For instance, much of the epidemiological research surrounding this comorbidity has found no effect or worsened cognition within chronic smokers with SZ (16–19). However, lack of control for time since last cigarette may result in nicotine withdrawal-related cognitive impairment (20–22) and may explain some of these negative findings as the participants were likely to be experiencing significant smoking deprivation. **Table 1** has been included below to illustrate the variety of study methodologies examining the pro-cognitive effects of smoking and how each study accounted for the duration since last cigarette. However, studies that carefully control for time since last cigarette have found that smoking produces cognitive deficits in SZ, particularly in working memory, visual learning, and attention (3, 23, 24, 31). In laboratory studies where nicotine is acutely administered or acute overnight abstinence and reinstatement paradigms are used (thereby avoiding any confounding effects of nicotine withdrawal), smoking groups have shown marked improvement for attention, working memory, pre-pulse inhibition, visuospatial working memory, processing speed, and verbal learning and memory(23, 24, 26, 28–37).

Studies have also compared cognitive performance between non-smoking and smoking patients with SZ. These studies account for the level of nicotine in the participant's system by allowing frequent smoke breaks so as to avoid inducing a state of withdrawal (25, 26). Non-smokers revealed significantly worse cognitive deficits, particularly in verbal memory (25, 26).

Interestingly, this effect is specific to those with schizophrenia, as no such finding was observed in patients with major depression, bipolar disorder or non-psychiatric controls (25, 26). Furthermore, individuals categorized as ultra-high-risk (UHR) for developing psychosis may also demonstrate this effect (27).

Other studies employed cognitive testing in both satiated and abstinent states and demonstrated that smokers with SZ show improvements in various cognitive domains (28–30, 33, 38). These studies are shown in **Table 1**. A satiated state was produced by administering nicotine throughout the study session with a patch, gum, or nasal spray, providing the benefit of acute nicotine exposure (28–30, 32); however, these were regular smokers. There are few studies examining acute nicotine administration in non-smokers, due to the nature of tobacco use disorder and the all-or-nothing tendency for people to be regular smokers or non-smokers. The few studies that have examined nicotine administration in non-smokers found an overall improvement in attention following nicotine administration and a specific effect at improving cognitive outcomes in the SZ participants (23, 39). Nonetheless, nicotine administration improves cognitive outcomes in SZ individuals, this may account for the increased frequency and severity of tobacco use in SZ and also the perseverance of tobacco use disorder in this population (40).

There are two primary theories proposed to explain the pro-cognitive effects of nicotine in SZ, and the relationship to the increase prevalence of smoking in SZ. First, the self-medication hypothesis proposes that individuals with SZ choose to smoke to alleviate the clinical symptoms and cognitive deficits that are characteristic of the illness as well as the side effects of antipsychotic medications (41). Many of the studies

TABLE 1 | Cognitive Effects in Acute vs. Chronic Smokers with SZ.

Study	Study design	Control for time since last cigarette	Findings
(16)	Cross-sectional	No control for last cigarette	= cognition No significant differences in cognitive outcomes between smokers and non-smokers with first-episode SZ
(17)	Cross-sectional	Last cigarette an hour prior to testing	↓ cognition Treatment-resistant SZ smokers performed worse on problem-solving cognitive domain compared to smokers. Other cognitive domains were not different between the groups.
(18)	Cross-sectional	No control for last cigarette	↓ cognition Current smokers with SZ or bipolar disorder had worse composite cognitive function compared to non-smokers.
(19)	Cross-sectional	No control for last cigarette	= cognition No significant differences in cognitive outcomes between smokers and non-smokers with first-episode SZ
(23)	Prospective human laboratory study	Deprived of cigarettes for 2 h and given either nicotine or placebo-containing gum	↓ cognition Attention was significantly improved in non-smokers compared to smokers with SZ after nicotine administration.
(24)	Cross-sectional	Last cigarette an hour before testing, cognition administered 2 h in, allowed smoke breaks with 30 min interval before re-initiating cognitive testing	↓ cognition Visual learning significantly improved in non-smokers compared to smokers.
(25)	Cross-sectional	Frequent smoke breaks (smokers never abstinent for >30 min)	↑ cognition Sustained attention, processing speed, response inhibition were significantly improved in smokers compared to non-smokers with SZ. No differences in non-psychiatric controls.
(26)	Cross-sectional	Frequent smoke breaks (smokers never abstinent for >30 min)	↑ cognition Verbal memory was significantly increased in smokers compared to non-smokers with SZ.
(27)	Cross-sectional	No control for last cigarette	↑ cognition Processing speed, spatial working memory, and visual learning was significantly improved in smokers compared to non-smokers with SZ.
(28)	RCT of haloperidol x nicotine	Overnight abstinence with randomized dose of nicotine patches	↑ cognition Nicotine lead to a dose-related reversal of haloperidol-induced cognitive impairments in memory and reaction time.
(29)	Placebo controlled crossover for cigarettes and nicotine nasal spray in current smokers	Administration of nicotine nasal spray or placebo nasal spray, and high nicotine cigarette and denicotinized cigarette.	↑ cognition Nicotine in nasal spray lead to significant improvement on a spatial organization task, verbal memory, and reaction time in SZ. Both cigarettes lead to improvement on spatial organization task.
(30)	Placebo controlled crossover with nicotine and placebo patch	Withdrawn from tobacco and given nicotine patch or placebo patch	↑ cognition Improved performance on n-back (working memory and selective attention) task in SZ smokers vs. non-smokers and worsened performance in control smokers vs. non-smokers
(31)	Cross sectional–3 conditions	3 test conditions—baseline, overnight abstinence, and 1 h after reinstatement with no more than 15 min smoking deprivation	↑ cognition Impaired visuospatial working memory (VSWM) during overnight abstinence in SZ, improved VSWM and CPT upon reinstatement in SZ.
(32)	Cross sectional–3 conditions	3 test conditions—baseline, overnight abstinence, and 3 h nicotine patch	↑ cognition Reaction time was significantly increased in the nicotine patch condition and worse in the abstinence condition in SZ.
(33)	Cross sectional–2 conditions	2 test conditions—after overnight abstinence, normal smoking behavior (No control for last cigarette)	↑ cognition VSWM was significantly increased in the smokers with SZ compared to healthy controls
(34)	Cross sectional	No control for last cigarette	↑ cognition Divided attention was significantly increased in the smoking condition and worse in the abstinence condition in SZ.

examining the procognitive effects of nicotine lend support to the theory, but others have refuted this theory. For example, one group found that it was a stronger tendency for those with SZ to experience withdrawal when abstinent that led to cognitive deficits and that blood nicotine concentration did not affect performance when compared to healthy controls (42). In response to these challenges identified with the self-medication hypothesis, researchers have developed an alternate

theory to explain the heightened prevalence of smoking in SZ which is termed the addiction vulnerability hypothesis (43). This theory proposes that it is due to genetic, neurobiological, and environmental factors that are inherent to the SZ diagnosis that make these patients susceptible to smoking (43). Understanding the unique factors contributing this vulnerability can provide us with novel treatments targeting smoking cessation in this specific population, in particular, building our knowledge about the underlying neurotransmitter systems and brain circuitry is essential (44).

Neurobiological Determinants of Tobacco Smoking in Schizophrenia

Nicotine

Nicotine, the addictive component in tobacco cigarettes, binds to nicotinic acetylcholine receptors (nAChRs), which are endogenously expressed in the human brain and influenced by the native agonist, acetylcholine (45). nAChRs are a heterogeneous family of ion channels, that are expressed on various cellular regions of both excitatory and inhibitory neurons, allowing for modulation of neurotransmitters (45, 46). The composition of the nAChRs is a variety of subunits which define the receptors' actions and properties (47). The most common high-affinity nAChRs include receptors consisting of two α4 subunits, two β2 subunits, and an undefined fifth subunit (48). Single nucleotide polymorphisms (SNPs) found on the CHRNA4 gene coding for the α4 subunit has been associated with nicotine dependence (49–51). Another important nAChR type to consider is that of the α7 receptor, which consists entirely of α7 subunits. SNPs located on the receptor coding gene CHRNA7, has been associated with both SZ diagnoses (52, 53) and nicotine dependence (54). Notably, there are two nicotinic acetylcholine receptors (nAChR) subtypes linked to cognition: high-affinity $\alpha 4\beta 2$ and low-affinity $\alpha 7$ nAChRs (45, 55). High-affinity nAChRs are sensitive to nicotinic antagonists such as mecamylamine (56), and mediate nicotine reinforcement and cognition (36, 57), whereas low-affinity nAChRs are less nicotine-sensitive.

Dopamine, norepinephrine, serotonin, glutamate, aminobutyric acid (GABA) and opioid peptides are neurotransmitter systems influenced by nAChRs (58). The neurobiological phenotype of SZ involves dysfunction of similar neurotransmitters, such as the dopaminergic, glutamatergic and GABAergic systems, as well as overarching dysfunction of cortical and subcortical communicative circuitry. Developmental and genetically predisposed abnormalities observed in the prefrontal and hippocampal regions in individuals with SZ may facilitate neural circuitry dysfunction, promoting a vulnerability toward addiction, such as tobacco use disorder (59). The neurobiological abnormalities of SZ will be discussed after which the corresponding effects of nicotine will be supplemented in order to provide insight into this prevalent comorbidity.

Pathophysiology of SZ and Nicotine Effects

The following section describes the role of each neurotransmitter system on both nicotine addiction and schizophrenia. An overall summary and simplification of these effects is illustrated with **Figure 1**.

Dopaminergic Dysfunction

The dopamine (DA) hypothesis for SZ features the imbalances in dopaminergic neurotransmission throughout the brain, such as presynaptic abnormalities of DA neurons that are described in both SZ and high-risk populations (60, 61). DA dysfunction influences both cortical and subcortical circuitry, facilitating symptomatology of SZ differentially. Subcortical regions in the brain have been associated with increased dopaminergic activity, leading to over-stimulation of D2 receptors (62, 63). Hyper-dopaminergic activity in subcortical regions, specifically in the associative striatum, has been associated with positive symptoms of SZ, including psychosis (61, 64–66). Cortical regions, however, have been linked with dampened dopaminergic activity. This has been investigated through various functional imaging studies, demonstrating an under-stimulation of D1 receptors in the frontal regions of individuals with SZ (67). Additionally, *in vivo* findings of decreased dopaminergic activity in the dorsolateral prefrontal cortex has been associated with cognitive impairment severity, such as worsened working memory, as well as negative symptom severity (68–71). Treatment that targets dopamine dysfunction, the most pervasive form of medication for SZ (targeting dopamine D2 receptors), has proven to aid with positive symptoms; however, in individuals who lack substantial dopaminergic dysfunction, this treatment does not robustly align with symptom improvement (61, 72).

Glutamatergic and GABAergic Dysfunction

A more recent hypothesis for SZ pathology involves glutamatergic dysfunction, involving the hypofunction of *N*-methyl-D-aspartate (NMDA) receptors of which glutamate, the major excitatory transmitter in the brain, binds (73, 74). Supported by genetic convergence, brain tissue analysis and brain imaging studies (74–76), the glutamatergic theory offers a unique conceptualization that encompasses the widespread deficits observed in SZ (73). For example, NMDAR antagonists, such as phencyclidine and ketamine, correlate with the emergence of both negative and positive symptoms as well as general neuropsychological and sensory deficits associated with SZ in contrast to amphetamine, a dopamine receptor agonist, which is mostly associated with inducing the positive symptoms of the disorder (73). NMDA receptors influence the majority of input, output and interneuronal cortical projections and, therefore, have a diffuse influence on brain function (77). In SZ, glutamatergic dysfunction due to NMDAR abnormalities has been noted in regions within the limbic system, the hippocampus and the dorsolateral prefrontal cortex (78–81). NMDAR activity is also important in considering the functioning and maintenance of the brain's main inhibitory transmitter - aminobutyric acid (GABA) (82). Deficits in GABA synthesis (deficits in glutamic acid decarboxylase (GAD)-67, which aids GABA synthesis) have been denoted throughout the cortex of individuals with SZ (83). Decreased functioning of GABAergic interneurons has been posed to contribute to cognitive impairment in SZ by means of decreased synchronization in neuronal cortical activity (84). Specifically, the hypofunctionality of NMDARs in SZ has been proposed to lead to dysfunctional GABAergic transmission (85). Dampened activity of NMDARs

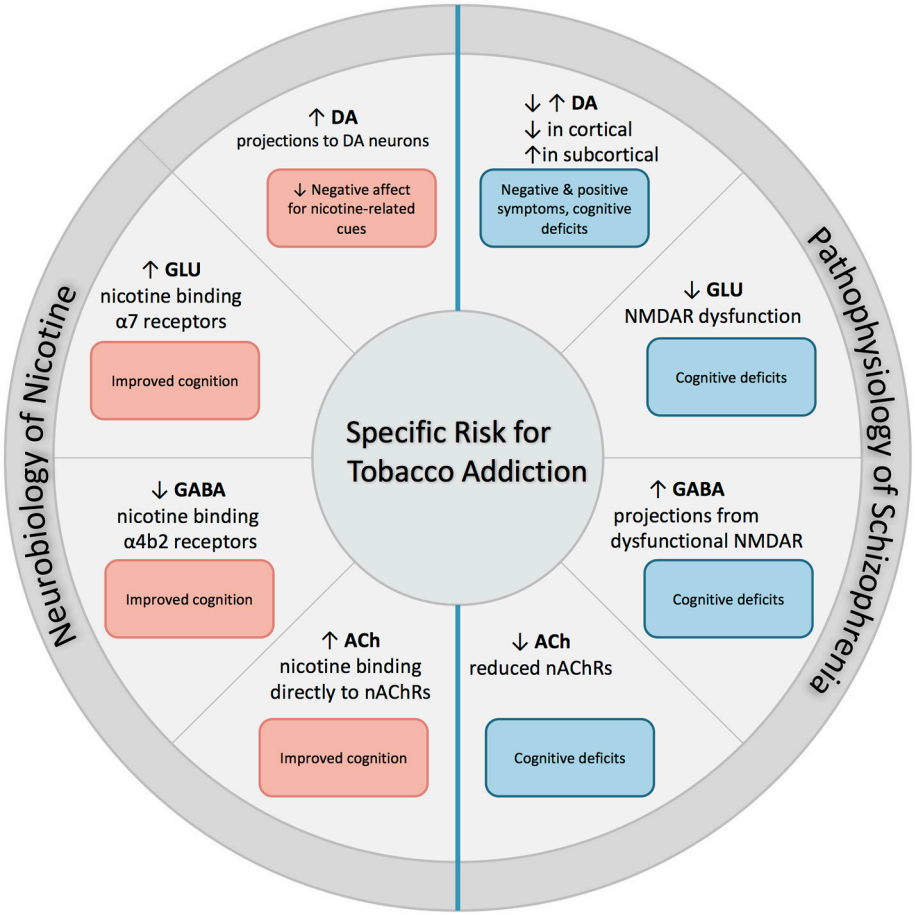

FIGURE 1 | Excessive dopaminergic activity has been proposed within subcortical regions in individuals with SZ, and is associated with positive symptoms of SZ. Conversely, a hypo-dopaminergic state has been postulated in the cortical regions, and is associated with cognitive deficits and increased negative symptoms. NMDAR abnormalities found in SZ contribute to both hypo-glutamatergic activity and hyper-GABAergic activity, and leads to cognitive dysfunction. Individuals with SZ have reduced expression of nAChRs which leads to altered nicotinic cholinergic transmission, which may contribute to cognitive dysfunction. When nicotine is administered through tobacco smoking, these deficits may be partially attenuated. First, nicotine binds directly to nAChRs that are located in mesolimbic dopaminergic pathways, which increases its expression and contributes to reduction in negative affect in response to smoking-related cues. In addition, nicotine binds to α7 and α4β2 receptors on glutamatergic and GABAergic neurons in the prefrontal cortex, attenuating deficits found in SZ and enhancing cognition.

at GABAergic interneurons disrupts and reduces inhibitory control over cortical activity as well as the overall synchrony of gamma oscillations, leading to clinical disruptions in SZ (86).

Additionally, NMDARs, which influence both glutamate and GABA, highly influence dopamine synthesis and transmission (75, 87). Glutamate, stimulated by NMDARs, regulates dopamine neurons that project from the ventral tegmentum area (VTA) toward the nucleus accumbens (NAc) or the prefrontal cortex (PFC), as well as GABA neurons that also play a role in regulating dopamine neurons (88). Dysfunction within the glutamatergic system in SZ has been proposed to facilitate the dopaminergic dysfunction linked to cognitive disruptions of the illness (87, 89). Additionally, presynaptic dopamine released both subcortically and within the frontal regions of the brain are influenced by inhibitory GABA interneurons, therefore disruption in GABA signaling via NMDAR abnormalities has also been linked to abnormalities in dopamine signaling (73, 90, 91).

DA, GLU, GABA, and Nicotine

Nicotine modulates dopaminergic transmission in both subcortical and cortical regions. Primary dopaminergic projections involve transmission from the VTA toward the NAc; major components of reward circuitry in addiction of which nicotine enhances through this pathway (92, 93). Nicotine is able to influence dopamine's activity by directly binding nAChRs on dopaminergic projections sourced in the VTA as well as by regulating glutamate and GABA activity, which excites and inhibits dopaminergic activity, respectively (94). Specifically, nicotine binds to the α7 receptors along glutamatergic neurons, stimulating their activity and enhancing NMDAR function, which together enhances dopaminergic neuronal activity (94). Nicotine also binds α4β2, a high-affinity receptor along GABA neurons, which, with chronic nicotine use, become desensitized, therefore dampening the inhibition on dopaminergic transmission from the VTA to the NAc, while α7, low-affinity nAChRs on glutamatergic

neurons are less prone to desensitization, therefore continue to enhance dopamine transmission (94, 95). Nicotine directly binds nAChRs along dopamine neuronal cells, facilitating burst firing and increased dopamine activity directly (96), which, combined with enhanced glutamatergic tone, leads to an overall increased level of dopamine transmission and release in the NAc that supports the reinforcing effects of nicotine (97).

It has been posed that nicotine leads to increases in dopamine levels within prefrontal regions through direct and indirect (GABA and glutamate influences) enhancement of dopaminergic activity that makes up for the lowered dopamine D1 stimulation and ensuing cognitive deficits observed in SZ (44, 67, 98). Nicotine facilitates increased dopamine in the cortex similarly to observations in subcortical regions in that the drug binds high-affinity nAChRs on dopamine neurons that project from the VTA, but in this case toward the cortex, and binds low-affinity receptors on excitatory glutamatergic neurons projecting toward the prefrontal cortex (99, 100). The reported beneficial effects that nicotine influences in the frontal cortex have been proposed to be largely due to its effects on the α7 nAChR subunit, although there is some evidence surrounding α4b2 receptor subunit activity leading to improved higher cognition (98). Because GABA contains many α7 as well as α4b2 nAChRs, nicotine could counteract the deficits observed in GABAergic transmission in SZ and the coinciding prefrontal dysfunction by stabilizing cortical inhibition through enhancing interneuronal activity and frontal gamma oscillations (3, 83, 101–103).

naChRs and Nicotine

Additionally, SZ involves the dysregulation of both high- and low-affinity nAChRs (98, 104). Studies have shown that individuals with SZ have a reduction in nAChRs expression throughout brain regions that are central to higher cognitive functioning (105). Additionally, it has been found that chronic nicotine use leads to nAChR receptor desensitization and inactivation during stages of withdrawal, which are reactivated upon overnight abstinence (3, 106, 107). Clinically, this pattern of receptor desensitization may explain the phenomenon where smokers prefer the first cigarette in the morning, and why cognitive deficits are present during periods of withdrawal (106). However, in the SZ population, this pattern of desensitization and resensitization may have a different presentation due to the decreased expression of nicotinic receptors, which may account for their increased severity of tobacco addiction (108).

SZ has also been linked genetically to the CHRNA7 gene, a potential site of genetic heritability, which codes for the α7 subunit of nAChRs (109). Individuals with SZ who smoke have exhibited improvements in their cognition, highlighting the potential benefits of stimulating this receptor in this population (26, 29). For example, nAChR agonists and antagonists, such as varenicline and mecamylamine, have been used in various smoking cessation and treatment trials in which the results further support the cognitive improvements observed in smokers with SZ (31, 36, 110). Additionally, levels of CHRNA7 protein and mRNA became comparable to non-psychiatric smokers following smoking in SZ (53). Overall, nAChR dysfunction may influence the aberrant signaling of glutamate, GABA, and dopamine of which nicotine use may partially alleviate (3).

Circuitry Dysfunction

It is posed that each transmitter system, including dopamine, glutamate, GABA and cholinergic neuronal transmission, incorporates a circuit, supported by genetic risk, that facilitates a risk for SZ presentation (61, 111). The dysfunction within SZ and nicotine's influence on these abnormalities do not exist in isolation. The combination of abnormal dopamine neurotransmission and nAChR signaling, along with imbalances in glutamate and GABA transmission, which influences the former dysfunctions, may lead to the widespread deficits and symptoms observed in SZ (3). Nicotine stimulates nAChRs, which are situated along glutamatergic and GABAergic neurons. Nicotine, therefore, may modulate glutamate-GABA interactions and normalize excitation-inhibition influences over dopamine signaling and communication within the brain through improving baseline nAChR-stimulation dysregulated in SZ. The influence nicotine has on the transmission and general circuitry in SZ has been shown to alleviate certain symptomatic characteristics and cognitive deficits, as described above, which may place this population at an enhanced risk to developing tobacco use disorder.

Tobacco Use and Antipsychotic Medication

Cigarette smoking has been found to increase activity of the liver enzyme, cytochrome P450 1A2 (CYP 1A2), which in turn break down drugs in the body, including antipsychotic medications such as olanzapine and clozapine (112). As a result, there is reduced concentration of these antipsychotics in medicated SZ smokers, which predictably leads to a reduction in side effects, motivating further use (113) (supporting the self-medication hypothesis). An important implication of the reduction in antipsychotic medication is the potential for worsened symptoms of psychosis (114), to account for this, researchers of a meta-analysis study have indicated that smokers with SZ should be prescribed antipsychotics at a dose double that of non-smokers (115).

Biomarkers of Vulnerability

P50 Suppression and Mismatch Negativity

P50 suppression is an electroencephalographic measure of cortical inhibition that follows a second tone that is presented 500 ms after an initial tone (116). SZ, as well as the pathological and heritable characteristics of the disorder, is associated with the sensory gating deficit of diminished suppression (117–119). This deficit has been genetically linked to polymorphisms found on the promoter region of the CHRNA7 coding gene for the α7 nAChR subunit, as well as decreased function of the α7 nAChR (120–122). It is thought that GABAergic neurotransmission within the hippocampal region, which is dysfunctional in SZ, mediates the production of P50 suppression, therefore may contribute to this population's sensory deficit (123). Nicotine, through its influence on nAChRs and the downstream effects, has been shown to remediate the deficits in P50 suppression for this population (35, 124, 125). Moreover, nAChR agonists

also show improvements in cognitive functioning, including P50 suppression (126).

MMN is a neurophysiological test that quantitatively and temporally measures central auditory functioning or, more specifically, the neuronal processing in response to an auditory "oddball paradigm," which involves the intervention of a deviant stimulus within sequential auditory tones (127, 128). From clinically high-risk to chronic classifications of SZ, this population exhibits reductions in MMN amplitudes based on frontocentral electroencephalographic recordings that are shown across all dimensions of auditory deviance (127–130). This deficit has been linked to NMDAR dysfunction, which correlates to the glutamatergic hypothesis of SZ pathology (119, 131, 132). Nicotine seems to enhance the duration of MMN amplitude, facilitating improvement in this neurophysiological deficit (119, 133, 134).

Pre-pulse Inhibition (PPI)

PPI is an electromyography measure of eye blink responses (i.e., one's eye muscle movement) to a startling auditory tone. If a "prepulse" tone occurs before the main auditory stimulus, one's blinking response is attenuated; however, individuals with SZ exhibit a deficit in this gating response (135, 136). This deficit has been associated with CHRNA3 polymorphisms, relating to nAChR dysfunction that is characteristic of SZ, and observed as heritable within this population (137–140). Nicotine has been noted to improve this deficit in smokers with and without SZ (137, 141, 142). Furthermore, abstinence related deficits in SZ (vs. non-psychiatric controls) were ameliorated by smoking reinstatement and blocked by nAChR antagonist, mecamylamine (143), suggesting that nAChR stimulation may remediate PPI deficits in SZ.

Smooth Pursuit Eye Movement

Smooth pursuit eye movement (SPEM) tasks involve the measurement of saccades, which are eye movements toward a target stimulus, as well as anti-saccades, which involves the movement away from a stimulus. Individuals with SZ have more intruding saccades to the extent of being described as a heritable characteristic of the diagnosis (144–147). Nicotine has shown to influence this measurement by improving the reliability of saccadic measures in individuals with SZ, but not in non-psychiatric controls, by potentially lowering the hyperactivation in regions facilitating this response and improving cortical inhibitory control (148–152).

PSYCHOSOCIAL DETERMINANTS OF TOBACCO ADDICTION IN SCHIZOPHRENIA

There are a variety of psychosocial factors that increase the vulnerability of individuals with SZ to develop and sustain tobacco addictions. Individuals with SZ tend to be of lower socioeconomic status compared to general population, which is associated with an increased likelihood of smoking initiation and a decreased likelihood of smoking cessation (153, 154). These individuals often have fixed, government-assisted income and may spend close to 30% of this income on cigarettes (155).

Elements of the mental health system itself may make individuals afflicted with SZ more vulnerable to smoking. There is a longstanding and pervasive smoking culture in mental health institutions that tolerates and even encourages tobacco consumption (156). Although, the smoking culture impacts all people with mental illness, SZ patients are particularly likely to be exposed, as they receive treatment largely in institutions and mental health settings (5). In fact, 80% of light smokers and 57% of moderate smokers have actually been found to increase their cigarette consumption following psychiatric admission (157). Despite the fact that programs to treat tobacco addiction in inpatient settings have been shown to be effective, mental health staff are reluctant to treat nicotine dependence in psychiatric patients and counseling for smoking cessation is rarely provided (156, 158, 159). Moreover, they are hesitant to ban cigarette smoking in institutions because of concern over patient resistance, infringing on patients' right to smoke and potential negative effects of smoking cessation on treatment outcomes (160, 161). Despite this common concern, inpatient psychiatric facilities that have implemented smoking bans, have demonstrated positive outcomes and had far fewer problems than anticipated (162, 163).

TREATMENT IMPLICATIONS

The advantage of broadening our understanding about the underlying neurobiology of this comorbidity is that it may lead to more novel, targeted treatments to be developed. In this section, we will briefly discuss some new developments in the area of treating smokers with SZ. Some major advancements in this field have been drugs targeting nAChRs and the potential for neuromodulation.

Currently, the most commonly studied and accepted treatments for this population in the order of effectiveness have been varenicline, bupropion and nicotine replacement therapy (NRT) (164). Varenicline acts as a partial agonist at the $\alpha4\beta2$ nAChR, while buproprion acts at several targets including at the norepinephrine-dopamine receptors and at the nicotinic receptor (165, 166). Pharmacological treatments for smoking are more effective than any behavioral treatments in this population, and maintenance treatment is also an important way to prevent relapse in SZ (164). However, although varenicline has been found effective at reducing overall smoking in SZ, it has not been found to compensate as a cognitive enhancer (167). This is consistent with the findings of a recent meta analysis that determined $\alpha7$-nAChRs as ineffective treatments for improving cognitive and negative symptom outcomes in SZ based on 8 RCTs (168). Additionally, cessation rates in patients with SZ remain significantly lower than those of the general population, and it is evident that a more holistic treatment strategy is required (164).

Neuromodulation is a promising new treatment modality which may have considerable promise for smokers with SZ (169). For example, repetitive transcranial magnetic stimulation (rTMS)

delivers high-frequency magnetic fields to a targeted area of the brain (e.g., dorsolateral prefrontal cortex), stimulating neurons in that region and altering the brain circuitry. One study conducted in our lab found that a short course of rTMS was not effective at reducing craving in an overnight abstinence condition in patients with SZ (170). However, three other studies examined rTMS delivered over a longer course (10, 21, and 28 days, respectively) and found significant improvements on cigarette consumption and craving, but these effects dissipated over time (3, 171, 172). While the mechanism behind the impact of rTMS on nicotine addiction has not be fully elucidated (173), one hypothesis is that rTMS directed to the dorsolateral prefrontal cortex (169) reduces drug craving experienced by the user (174–176) (3. SZ Res.). Another neuromodulation method is transcranial direct current stimulation (tDCS), which provides a weaker electrical current over a longer duration to the brain, modulating neural firing without producing stimulation of neurons (177). A recent RCT of tDCS delivered in 5 sessions over 21 days in smokers with SZ found significant improvements on several cognitive deficits, but no improvements on cigarette use and craving outcomes (178). The findings within the field of neuromodulation are promising, but further studies are needed to corroborate these techniques as an effective treatment for smoking in SZ.

CONCLUSIONS

In summary, it is evident that the comorbidity of SZ and cigarette smoking is widespread, and that the underlying neurobiological factors are complex. Research on these factors is contributing to the development of treatment strategies that may help to reduce smoking and in turn the high mortality rates that arise due to the high smoking prevalence in this population. It is also important to consider a holistic approach because although neurobiology plays a large role in this comorbidity, etiological factors for smoking are multifaceted and all things must be considered. Further research and discussion should continue, and it is important that clinicians work against stigma and toward promoting education about high smoking rates as a specific vulnerability for individuals with SZ.

AUTHOR CONTRIBUTIONS

AL: literature review, drafting manuscript, and final submission. DL and RC: literature review and contributing to content. TG: oversight, editor, and finalizing manuscript. KK: literature review for revision recommendations, contributing to content of revisions and final editing.

FUNDING

This work was supported in part by research support from the Astra H. Flaska Funds/CAMH Foundation and NIDA grant R21-DA-043949 to TG.

REFERENCES

1. Morisano D, Bacher I, Audrain-McGovern J, George TP. Mechanisms underlying the comorbidity of tobacco use in mental health and addictive disorders. *Can J Psychiatry* (2009) 54:356–67. doi: 10.1177/070674370905400603
2. Tidey JW, Miller ME. Smoking cessation and reduction in people with chronic mental illness. *BMJ* (2015) 351:h4065. doi: 10.1136/bmj.h4065
3. Wing VC, Wass CE, Soh DW, George T. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. *Ann N Y Acad Sci.* (2012) 1248:89–106. doi: 10.1111/j.1749-6632.2011.06261.x
4. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA* (2000) 284:2606–10. doi: 10.1001/jama.284.20.2606
5. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res.* (2008) 10:1691–715. doi: 10.1080/14622200802443569
6. George TP, Ziedonis DM. Addressing tobacco dependence in psychiatric practice: promises and pitfalls. *Can J Psychiatry* (2009) 54:353–5. doi: 10.1177/070674370905400602
7. Callaghan RC, Veldhuizen S, Jeysingh T, Orlan C, Graham C, Kakouris G, et al. Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. *J Psychiatr Res.* (2014) 48:102–10. doi: 10.1016/j.jpsychires.2013.09.014
8. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry* (2015) 72:1172–81. doi: 10.1001/jamapsychiatry.2015.1737
9. Brunzell DH, McIntosh JM. Alpha7 nicotinic acetylcholine receptors modulate motivation to self-administer nicotine: implications for smoking and schizophrenia. *Neuropsychopharmacology* (2012) 37:1134–43. doi: 10.1038/npp.2011.299
10. Tidey JW, Colby SM, Xavier EM. Effects of smoking abstinence on cigarette craving, nicotine withdrawal, and nicotine reinforcement in smokers with and without schizophrenia. *Nicotine Tob Res.* (2014) 16:326–34. doi: 10.1093/ntr/ntt152
11. Berg SA, Chambers RA. Accentuated behavioral sensitization to nicotine in the neonatal ventral hippocampal lesion model of schizophrenia. *Neuropharmacology* (2008) 54:1201–7. doi: 10.1016/j.neuropharm.2008.03.011
12. Gold JM, Waltz JA, Prentice KJ, Morris S, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. *Schizophr Bull.* (2008) 34:835–47. doi: 10.1093/schbul/sbn068
13. Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry* (2015) 28:7–12. doi: 10.1097/YCO.0000000000000122
14. Moran LV, Betts JM, Ongur D, Janes AC. Neural responses to smoking cues in schizophrenia. *Schizophr Bull.* (2017) 44:525–34. doi: 10.1093/schbul/sbx085
15. Peechatka AL, Whitton AE, Farmer SL, Pizzagalli D, Janes AC. Cigarette craving is associated with blunted reward processing in nicotine-dependent smokers. *Drug Alcohol Depend.* (2015) 155:202–7. doi: 10.1016/j.drugalcdep.2015.07.015
16. Zhang XY, Chen DC, Xiu MH, Haile CN, Sun H, Lu L, et al. Cigarette smoking and cognitive function in Chinese male schizophrenia: a case-control study. *PLoS ONE* (2012) 7:e36563. doi: 10.1371/journal.pone.0036563
17. Iasevoli F, Balletta R, Gilardi V, Giordano S, de Bartolomeis A. Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. *Neuropsychiatr Dis Treat.* (2013) 9:1113–20. doi: 10.2147/NDT.S47571

18. Depp CA, Bowie CR, Mausbach BT, Wolyniec P, Thornquist MH, Luke JR, et al. Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta Psychiatr Scand.* (2015) 131:333–41. doi: 10.1111/acps.12380
19. Hickling LM, Perez-Iglesias R, Ortiz-García de la Foz V, Balanzá-Martínez V, McGuire P, Crespo-Facorro B, et al. Tobacco smoking and its association with cognition in first episode psychosis patients. *Schizophr Res.* (2018) 192:269–73. doi: 10.1016/j.schres.2017.04.018
20. Hatsukami D, Fletcher L, Morgan S, Keenan R, Amble P. The effects of varying cigarette deprivation duration on cognitive and performance tasks. *J Subst Abuse* (1989) 1:407–16.
21. Snyder FR, Davis FC, Henningfield JE. The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. *Drug Alcohol Depend.* (1989) 23:259–66. doi: 10.1016/0376-8716(89)90090-2
22. Foulds J, Stapleton JA, Bell N, Swettenham J, Jarvis M, Russell MA. Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. *Drug Alcohol Depend.* (1997) 44:105–15. doi: 10.1016/S0376-8716(96)01327-0
23. Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, et al. Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* (2004) 29:1378–85. doi: 10.1038/sj.npp.1300450
24. Reed AC, Harris JG, Olincy A. Schizophrenia, smoking status, and performance on the matrics cognitive consensus battery. *Psychiatry Res.* (2016) 246:1–8. doi: 10.1016/j.psychres.2016.08.062
25. Wing VC, Bacher I, Sacco KA, George TP. Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. *Psychiatry Res.* (2011) 188:320–6. doi: 10.1016/j.psychres.2011.05.037
26. Morisano D, Wing VC, Sacco KA, Arenovich T, George TP. Effects of tobacco smoking on neuropsychological function in schizophrenia in comparison to other psychiatric disorders and non-psychiatric controls. *Am J Addict.* (2013) 22:46–53. doi: 10.1111/j.1521-0391.2013.00313.x
27. Gupta T, Mittal VA. Nicotine usage is associated with elevated processing speed, spatial working memory, and visual learning performance in youth at ultra high-risk for psychosis. *Psychiatry Res.* (2014) 220:687–90. doi: 10.1016/j.psychres.2014.07.085
28. Levin ED, Wilson W, Rose JE, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. *Neuropsychopharmacology* (1996) 15:429–36. doi: 10.1016/S0893-133X(96)00018-8
29. Smith RC, Singh A, Infante M, Khandat A, Kloos A. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. *Neuropsychopharmacology* (2002) 27:479–97. doi: 10.1016/S0893-133X(02)00324-X
30. Jacobsen LK, D'Souza DC, Mencl WE, Pugh K, Skudlarski P, Krystal JH. Nicotine effects on brain function and functional connectivity in schizophrenia. *Biol Psychiatry* (2004) 55:850–8. doi: 10.1016/j.biopsych.2003.12.023
31. Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio J, Krishnan-Sarin S, et al. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Arch Gen Psychiatry* (2005) 62:649–59. doi: 10.1001/archpsyc.62.6.649
32. AhnAllen CG, Nestor PG, Shenton ME, McCarley R, Niznikiewicz MA. Early nicotine withdrawal and transdermal nicotine effects on neurocognitive performance in schizophrenia. *Schizophr Res.* (2008) 100:261–9. doi: 10.1016/j.schres.2007.07.030
33. Beck AK, Baker AL, Todd J. Smoking in schizophrenia: cognitive impact of nicotine and relationship to smoking motivators. *Schizophr Res Cogn.* (2015) 2:26–32. doi: 10.1016/j.scog.2014.12.001
34. Ahlers E, Hahn E, Ta TM, Goudarzi E, Dettling M, Neuhaus AH. Smoking improves divided attention in schizophrenia. *Psychopharmacology* (2014) 231:3871–7. doi: 10.1007/s00213-014-3525-2
35. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *Am J Psychiatry* (1993) 150:1856. doi: 10.1176/ajp.150.12.1856
36. George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, et al. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* (2002) 26:75–85. doi: 10.1016/S0893-133X(01)00296-2
37. Boggs DL, Carlson J, Cortes-Briones J, Krystal JH, D'Souza D. Going up in smoke? A review of nAChRs-based treatment strategies for improving cognition in schizophrenia. *Curr Pharm Des.* (2014) 20:5077–92. doi: 10.2174/1381612819666131216121019
38. AhnAllen CG, Bidwell LC, Tidey JW. Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. *Nicotine Tob Res.* (2015) 17:510–4. doi: 10.1093/ntr/ntu163
39. Barr RS, Culhane MA, Jubelt LE, Mufti R, Dyer MA, Weiss AP, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology* (2008) 33:480–90. doi: 10.1038/sj.npp.1301423
40. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res.* (2005) 76:135–57. doi: 10.1016/j.schres.2005.02.010
41. Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry* (2010) 23:112–9. doi: 10.1097/YCO.0b013e3283366643
42. Hahn B, Harvey AN, Concheiro-Guisan M, Huestis MA, Holcomb HH, Gold JM. A test of the cognitive self-medication hypothesis of tobacco smoking in schizophrenia. *Biol Psychiatry* (2013) 74:436–43. doi: 10.1016/j.biopsych.2013.03.017
43. Chambers RA. A nicotine challenge to the self-medication hypothesis in a neurodevelopmental animal model of schizophrenia. *J Dual Diagn.* (2009) 5:139–48. doi: 10.1080/15504260902869808
44. George TP. Neurobiological links between nicotine addiction and schizophrenia. *J Dual Diagn.* (2007) 3:27–42. doi: 10.1300/J374v03n03_04
45. Picciotto MR, Caldarone BJ, King SL, Zachariou V. Nicotinic receptors in the brain. Links between molecular biology and behavior. *Neuropsychopharmacology* (2000) 22:451–65. doi: 10.1016/S0893-133X(99)00146-3
46. Changeux JP. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. *Nat Rev Neurosci.* (2010) 11:389. doi: 10.1038/nrn2849
47. Gotti C, Zoli M, Clementi F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol Sci.* (2006) 27:482–91. doi: 10.1016/j.tips.2006.07.004
48. Zoli M, Pistillo F, Gotti C. Diversity of native nicotinic receptor subtypes in mammalian brain. *Neuropharmacology* (2015) 96:302–11. doi: 10.1016/j.neuropharm.2014.11.003
49. Hutchison KE, Allen DL, Filbey FM, Jepson C, Lerman C, Benowitz NL, et al. CHRNA4 and tobacco dependence: from gene regulation to treatment outcome. *Arch Gen Psychiatry* (2007) 64:1078–86. doi: 10.1001/archpsyc.64.9.1078
50. Breitling LP, Dahmen N, Mittelstrass K, Rujescu D, Gallinat J, Fehr C, et al. Association of nicotinic acetylcholine receptor subunit alpha 4 polymorphisms with nicotine dependence in 5500 Germans. *Pharmacogenomics J.* (2009) 9:219–24. doi: 10.1038/tpj.2009.6
51. Greenwood PM, Parasuraman R, Espeseth T. A cognitive phenotype for a polymorphism in the nicotinic receptor gene CHRNA4. *Neurosci Biobehav Rev.* (2012) 36:1331–41. doi: 10.1016/j.neubiorev.2012.02.010
52. Stephens SH, Logel J, Barton A, Franks A, Schultz J, Short M, et al. Association of the 5'-upstream regulatory region of the alpha7 nicotinic acetylcholine receptor subunit gene (CHRNA7) with schizophrenia. *Schizophr Res.* (2009) 109:102–12. doi: 10.1016/j.schres.2008.12.017
53. Mexal S, Berger R, Logel J, Ross RG, Freedman R, Leonard S. (2010). Differential regulation of α7 nicotinic receptor gene (CHRNA7) expression in schizophrenic smokers. *J Mol Neurosci.* 40:185–95. doi: 10.1007/s12031-009-9233-4
54. De Luca V, Wong AH, Muller DJ, Wong G, Tyndale RF, Kennedy JL. Evidence of association between smoking and alpha7 nicotinic receptor subunit gene in schizophrenia patients. *Neuropsychopharmacology* (2004) 29:1522–6. doi: 10.1038/sj.npp.1300466
55. Bencherif M, Schmitt JD. Targeting neuronal nicotinic receptors: a path to new therapies. *Curr Drug Targets CNS Neurol Disord.* (2002) 1:349–57. doi: 10.2174/1568007023339094
56. Wooltorton JR, Pidoplichko VI, Broide RS, Dani J. Differential desensitization and distribution of nicotinic acetylcholine receptor

subtypes in midbrain dopamine areas. *J Neurosci.* (2003) 23:3176–85. doi: 10.1523/JNEUROSCI.23-08-03176.2003
57. Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacol Biochem Behav.* (2001) 70:439–46. doi: 10.1016/S0091-3057(01)00652-9
58. Albuquerque EX, Pereira EF, Alkondon M, Rogers SW. Mammalian nicotinic acetylcholine receptors, from structure to function. *Physiol Rev.* (2009) 89:73–120. doi: 10.1152/physrev.00015.2008
59. Kozak K, Barr MS, George TP. Traits and biomarkers for addiction risk in schizophrenia. *Curr Addict Rep.* (2017) 4:14–24. doi: 10.1007/s40429-017-0130-6
60. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies. *Arch Gen Psychiatry* (2012) 69:776–86. doi: 10.1001/archgenpsychiatry.2012.169
61. Kesby J, Eyles D, McGrath J, Scott J. Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience. *Transl Psychiatry* (2018) 8:30. doi: 10.1038/s41398-017-0071-9
62. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl J, Bowers M, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* (1998) 155:761–7.
63. Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, McGuire P, et al. Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study. *Brain* (2013) 136:3242–51. doi: 10.1093/brain/awt264
64. Laruelle M, Abi-Dargham A. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. *J Psychopharmacol.* (1999) 13:358–71. doi: 10.1177/026988119901300405
65. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles L, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA.* (2000) 97:8104–9. doi: 10.1073/pnas.97.14.8104
66. Artiges E, Leroy C, Dubol M, Prat M, Pepin A, Mabondo A, et al. Striatal and extrastriatal dopamine transporter availability in schizophrenia and its clinical correlates: a voxel-based and high-resolution PET study. *Schizophr Bull.* (2017) 43:1134–42. doi: 10.1093/schbul/sbw192
67. Abi-Dargham A, Moore H. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *Neuroscientist* (2003) 9:404–16. doi: 10.1177/1073858403252674
68. Davis KL, Kahn RS. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* (1991) 148:1474. doi: 10.1176/ajp.148.11.1474
69. Okubo Y, Suhara T, Suzuki,K. Kobayashi K, Inoue O, Terasaki O, et al. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* (1997) 385:634. doi: 10.1038/385634a0
70. Goldman-Rakic PS, Castner SA, Svensson TH, Siever L, Siever LJ, Williams GV. Targeting the dopamine D 1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology* (2004) 174:3–16. doi: 10.1007/s00213-004-1793-y
71. Slifstein ME, van de Giessen E, Van Snellenberg J, Thompson JL, Narendran R, Gil R, et al. Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. *JAMA Psychiatry* (2015) 72:316–24. doi: 10.1001/jamapsychiatry.2014.2414
72. Miyamoto S, Duncan G, Marx C, Lieberman J. Treatments for schizophrenia, a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* (2005) 10:79. doi: 10.1038/sj.mp.4001556
73. Kantrowitz JT, Javitt DC. N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Res Bull.* (2010). 83:108–21. doi: 10.1016/j.brainresbull.2010.04.006
74. Poels E, Kegeles L, Kantrowitz J, Slifstein M, Javitt D, Lieberman J, et al. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. *Mol Psychiatry* (2014) 19:20. doi: 10.1038/mp.2013.136
75. Gao WJ, Snyder MA. NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia. *Front Cell Neurosci.* (2013) 7:31. doi: 10.3389/fncel.2013.00031
76. Hu W, MacDonald ML, Elswick DE, Sweet R. The glutamate hypothesis of schizophrenia: evidence from human brain tissue studies. *Ann N Y Acad Sci.* (2015) 1338:38–57. doi: 10.1111/nyas.12547
77. Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* (2012) 37:4. doi: 10.1038/npp.2011.181
78. Gao X-M, Sakai K, Roberts RC, Conley RR, Dean B, Tamminga CA. Ionotropic glutamate receptors and expression of N-methyl-D-aspartate receptor subunits in subregions of human hippocampus: effects of schizophrenia. *Am J Psychiatry* (2000) 157:1141–9. doi: 10.1176/appi.ajp.157.7.1141
79. Ghose S, Gleason KA, Potts BW, Lewis-Amezcua K, Tamminga CA. Differential expression of metabotropic glutamate receptors 2 and 3 in schizophrenia: a mechanism for antipsychotic drug action? *Am J Psychiatry* (2009) 166:812–20. doi: 10.1176/appi.ajp.2009.08091445
80. Stan A, Ghose S, Zhao C, Hulsey K, Mihalakos P, Yanagi M, et al. Magnetic resonance spectroscopy and tissue protein concentrations together suggest lower glutamate signaling in dentate gyrus in schizophrenia. *Mol Psychiatry* (2015) 20:433. doi: 10.1038/mp.2014.54
81. Coyle JT, Konopaske G. Glutamatergic dysfunction in schizophrenia evaluated with magnetic resonance spectroscopy. *JAMA Psychiatry* (2016) 73:649–50. doi: 10.1001/jamapsychiatry.2016.0575
82. De Marco García NV, Karayannis T, Fishell, G. Neuronal activity is required for the development of specific cortical interneuron subtypes. *Nature* (2011) 472:351. doi: 10.1038/nature09865
83. Gonzalez-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. *Curr Psychiatry Rep.* (2010) 12:335–44. doi: 10.1007/s11920-010-0124-8
84. Lewis DA. Inhibitory neurons in human cortical circuits: substrate for cognitive dysfunction in schizophrenia. *Curr Opin Neurobiol.* (2014) 26:22–6. doi: 10.1016/j.conb.2013.11.003
85. Cohen SM, Tsien RW, Goff DC, Halassa M. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. *Schizophr Res.* (2015) 167:98–107. doi: 10.1016/j.schres.2014.12.026
86. Nakazawa K, Zsiros V, Jiang Z, Nakao K, Kolata S, Zhang S, et al. GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology* (2012) 62:1574–83. doi: 10.1016/j.neuropharm.2011.01.022
87. Tost H, Meyer-Lindenberg A. Dopamine-glutamate interactions: a neural convergence mechanism of common schizophrenia risk variants. *Biol Psychiatry* (2011) 69:912–3. doi: 10.1016/j.biopsych.2011.03.013
88. Sesack SR, Carr DB. Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. *Physiol Behav.* (2002) 77:513–7. doi: 10.1016/S0031-9384(02)00931-9
89. Lewis DA, González-Burgos G. Neuroplasticity of neocortical circuits in schizophrenia. *Neuropsychopharmacology* (2008) 33:141. doi: 10.1038/sj.npp.1301563
90. Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL, et al. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* (2000) 48:627–40. doi: 10.1016/S0006-3223(00)00976-8
91. Adell A, Jiménez-Sánchez L, López-Gil X, Romón T. Is the acute NMDA receptor hypofunction a valid model of schizophrenia? *Schizophr Bull.* (2011) 38:9–14. doi: 10.1093/schbul/sbr133
92. Laviolette SR, Van Der Kooy D. The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. *Nat Rev Neurosci.* (2004) 5:55. doi: 10.1038/nrn1298
93. Jasinska AJ, Zorick T, Brody AL, Stein EA. Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. *Neuropharmacology* (2014) 84:111–22. doi: 10.1016/j.neuropharm.2013.02.015
94. Pistillo F, Clementi F, Zoli M, Gotti C. Nicotinic, glutamatergic and dopaminergic synaptic transmission and plasticity in the mesocorticolimbic system: focus on nicotine effects. *Prog Neurobiol.* (2015) 124:1–27. doi: 10.1016/j.pneurobio.2014.10.002
95. Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* (2002) 33:905–19. doi: 10.1016/S0896-6273(02)00625-6
96. Mameli-Engvall M, Evrard A, Pons S, Maskos U, Svensson TH, Changeux JP, et al. Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. *Neuron* (2006) 50:911–21. doi: 10.1016/j.neuron.2006.05.007

97. D'Souza MS, Markou A. The stop and go of nicotine dependence: role of GABA and glutamate. *Cold Spring Harb Perspect Med.* (2013) 3:a012146. doi: 10.1101/cshperspect.a012146
98. Parikh V, Kutlu MG, Gould TJ. nAChR dysfunction as a common substrate for schizophrenia and comorbid nicotine addiction: current trends and perspectives. *Schizophr Res.* (2016) 171:1–15. doi: 10.1016/j.schres.2016.01.020
99. George TP, Verrico CD, Picciotto MR, Roth R. Nicotinic modulation of mesoprefrontal dopamine neurons: pharmacologic and neuroanatomic characterization. *J Pharmacol Exp Ther.* (2000) 295:58–66.
100. Livingstone PD, Srinivasan J, Kew JN, Dawson LA, Gotti C, Moretti M, et al. α7 and non-α7 nicotinic acetylcholine receptors modulate dopamine release *in vitro* and *in vivo* in the rat prefrontal cortex. *Eur J Neurosci.* (2009) 29:539–50. doi: 10.1111/j.1460-9568.2009.06613.x
101. Song C, Murray TA, Kimura R, Wakui M, Ellsworth K, Javedan SP, et al. Role of α7-nicotinic acetylcholine receptors in tetanic stimulation-induced γ oscillations in rat hippocampal slices. *Neuropharmacology* (2005) 48:869–80. doi: 10.1016/j.neuropharm.2005.01.003
102. Wanaverbecq N, Semyanov A, Pavlov I, Walker MC, Kullmann D. Cholinergic axons modulate GABAergic signaling among hippocampal interneurons via postsynaptic α7 nicotinic receptors. *J Neurosci.* (2007) 27:5683–93. doi: 10.1523/JNEUROSCI.1732-07.2007
103. Maloku E, Kadriu B, Zhubi A, Dong E, Pibiri F, Satta R, et al. Selective α 4 β 2 nicotinic acetylcholine receptor agonists target epigenetic mechanisms in cortical GABAergic neurons. *Neuropsychopharmacology* (2011) 36:1366. doi: 10.1038/npp.2011.21
104. Martin LF, Freedman R. Schizophrenia and the α7 nicotinic acetylcholine receptor. *Int Rev Neurobiol.* (2007) 78:225–46. doi: 10.1016/S0074-7742(06)78008-4
105. D'Souza DC, Esterlis I, Carbuto M, Krasenics M, Seibyl J, Bois F, et al. Lower β2*-nicotinic acetylcholine receptor availability in smokers with schizophrenia. *Am J Psychiatry* (2012) 169:326–34. doi: 10.1176/appi.ajp.2011.11020189
106. Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. *Nature* (1997) 390:401. doi: 10.1038/37120
107. Sacco KA, Bannon KL, George TP. Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. *J Psychopharmacol.* (2004) 18:457–74. doi: 10.1177/0269881104047273
108. Leonard S, Adler LE, Benhammou K, Berger R, Breese C, Drebing C, et al. Smoking and mental illness. *Pharmacol Biochem Behav.* (2001) 70:561–70. doi: 10.1016/S0091-3057(01)00677-3
109. Farrell M, Werge T, Sklar P, Owen MJ, Ophoff R, O'Donovan MC, et al. Evaluating historical candidate genes for schizophrenia. *Mol Psychiatry* (2015) 20:555. doi: 10.1038/mp.2015.16
110. Wing VC, Wass CE, Bacher I, Rabin RA, George TP. Varenicline modulates spatial working memory deficits in smokers with schizophrenia. *Schizophr Res.* (2013) 149:190–1. doi: 10.1016/j.schres.2013.06.032
111. Lisman JE, Coyle JT, Green RW, Javitt D, Benes FM, Heckers S, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci.* (2008) 31:234–42. doi: 10.1016/j.tins.2008.02.005
112. Bozikas VP, Papakosta M, Niopas I, Karavatos A, Mirtsou-Fidani V. Smoking impact on CYP1A2 activity in a group of patients with schizophrenia. *Eur Neuropsychopharmacol.* (2004) 14:39–44. doi: 10.1016/S0924-977X(03)00061-0
113. Sagud M, Mihaljevic-Peles A, Muck-Seler D, Pivac N, Vuksan-Cusa B, Brataljenovic T, et al. Smoking and schizophrenia. *Psychiatr Danub* (2009) 21:371–5.
114. Nozawa M, Ohnuma T, Matsubara Y, Sakai Y, Hatano T, Hanzawa R, et al. The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics: Juntendo University Schizophrenia Projects (JUSP). *Ther Drug Monit.* (2008) 30:35–40. doi: 10.1097/FTD.0b013e31816336fd
115. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open* (2014) 4:e004216. doi: 10.1136/bmjopen-2013-004216
116. Nagamoto HT, Adler LE, Waldo MC, Griffith J, Freedman R. Gating of auditory response in schizophrenics and normal controls: effects of recording site and stimulation interval on the P50 wave. *Schizophr Res.* (1991) 4:31–40. doi: 10.1016/0920-9964(91)90007-E
117. Adler LE, Pachtman E, Franks R, Pecevich M, Waldo M, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry* (1982) 17:639–54.
118. Olincy A, Braff DL, Adler LE, Cadenhead K, Calkins ME, Dobie DJ, et al. Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia. *Schizophr Res.* (2010) 119:175–82. doi: 10.1016/j.schres.2010.03.004
119. Hamilton H, Kort N, Ford J, Roach B, Gunduz-Bruce H, Krystal J, et al. 540. Effects of N-methyl-D-aspartate glutamate receptor disruption and nicotinic acetylcholine enhancement on mismatch negativity. *Biol Psychiatry* (2017) 81:S219. doi: 10.1016/j.biopsych.2017.02.1148
120. Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci. USA.* (1997) 94:587–92. doi: 10.1073/pnas.94.2.587
121. Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M, et al. Association of promoter variants in the α7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. *Arch Gen Psychiatry* (2002) 59:1085–96. doi: 10.1001/archpsyc.59.12.1085
122. Houy E, Raux G, Thibaut F, Belmont A, Demily C, Allio G, et al. The promoter– 194 C polymorphism of the nicotinic alpha 7 receptor gene has a protective effect against the P50 sensory gating deficit. *Mol Psychiatry* (2004) 9:320. doi: 10.1038/sj.mp.4001443
123. Freedman R, Adams CE, Leonard S. The α7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. *J Chem Neuroanat.* (2000) 20:299–306. doi: 10.1016/S0891-0618(00)00109-5
124. Chen XS, Li CB, Smith RC, Xiao ZP, Wang JJ. Differential sensory gating functions between smokers and non-smokers among drug-naive first episode schizophrenic patients. *Psychiatry Res.* (2011) 188:327–33. doi: 10.1016/j.psychres.2010.12.009
125. Ishikawa M, Hashimoto K. α7 nicotinic acetylcholine receptor as a potential therapeutic target for schizophrenia. *Curr Pharm Design* (2011) 17:121–9. doi: 10.2174/138161211795049561
126. Freedman R. α7-nicotinic acetylcholine receptor agonists for cognitive enhancement in schizophrenia. *Ann Rev Med.* (2014) 65:245–61. doi: 10.1146/annurev-med-092112-142937
127. Light GA, Näätänen R. Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders. *Proc Natl Acad Sci USA.* (2013) 110:15175–6. doi: 10.1073/pnas.1313287110
128. Erickson MA, Ruffle A, Gold JM. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. *Biol Psychiatry* (2016) 79:980–7. doi: 10.1016/j.biopsych.2015.08.025
129. Murphy JR, Rawdon C, Kelleher I, Twomey D, Markey PS, Cannon M, et al. Reduced duration mismatch negativity in adolescents with psychotic symptoms: further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis. *BMC Psychiatry* (2013) 13:45. doi: 10.1186/1471-244X-13-45
130. Hay RA, Roach BJ, Srihari VH, Woods S, Ford JM, Mathalon DH. Equivalent mismatch negativity deficits across deviant types in early illness schizophrenia-spectrum patients. *Biol Psychol.* (2015) 105:130–7. doi: 10.1016/j.biopsycho.2015.01.004
131. Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol Psychiatry* (2002) 51:400–6. doi: 10.1016/S0006-3223(01)01242-2
132. Lee M, Sehatpour P, Hoptman MJ, Lakatos P, Dias E, Kantrowitz JT, et al. Neural mechanisms of mismatch negativity (MMN) dysfunction in schizophrenia. *Mol Psychiatry* (2017). 22:1585–93. doi: 10.1038/mp.2017.3
133. Dulude L, Labelle A, Knott VJ. Acute nicotine alteration of sensory memory impairment in smokers with schizophrenia. *J Clin Psychopharmacol.* (2010) 30:541–8. doi: 10.1097/JCP.0b013e3181f0c9c6

134. Hamilton HK, D'Souza DC, Ford JM, Roach B, Kort NS, Ahn KH, et al. Interactive effects of an N-methyl-d-aspartate receptor antagonist and a nicotinic acetylcholine receptor agonist on mismatch negativity: Implications for schizophrenia. *Schizophr Res.* (2018) 191:87–94. doi: 10.1016/j.schres.2017.06.040
135. Cadenhead KS, Swerdlow NR, Shafer KM, Diaz M, Braff DL. Modulation of the startle response and startle laterality in relatives of schizophrenic patients and in subjects with schizotypal personality disorder: evidence of inhibitory deficits. *Am J Psychiatry* (2000) 157:1660–8. doi: 10.1176/appi.ajp.157.10.1660
136. Hasenkamp W, Epstein MP, Green A, Wilcox L, Boshoven W, Lewison B, et al. Heritability of acoustic startle magnitude, prepulse inhibition, and startle latency in schizophrenia and control families. *Psychiatry Res.* (2010) 178:236–43. doi: 10.1016/j.psychres.2009.11.012
137. Hong LE, Wonodi I, Lewis J, Thaker GK. Nicotine effect on prepulse inhibition and prepulse facilitation in schizophrenia patients. *Neuropsychopharmacology* (2008) 33:2167. doi: 10.1038/sj.npp.1301601
138. Petrovsky N, Quednow BB, Ettinger U, Schmechtig A, Mössner R, Collier DA, et al. Sensorimotor gating is associated with CHRNA3 polymorphisms in schizophrenia and healthy volunteers. *Neuropsychopharmacology* (2010) 35:1429. doi: 10.1038/npp.2010.12
139. Petrovsky N, Ettinger U, Kessler H, Mössner R, Wolfsgruber S, Dahmen N, et al. The effect of nicotine on sensorimotor gating is modulated by a CHRNA3 polymorphism. *Psychopharmacology* (2013) 229:31–40. doi: 10.1007/s00213-013-3081-1
140. Greenwood TA, Light GA, Swerdlow NR, Calkins M, Green MF, Gur RE, et al. Gating deficit heritability and correlation with increased clinical severity in schizophrenia patients with positive family history. *Am J Psychiatry* (2015) 173:385–91. doi: 10.1176/appi.ajp.2015.15050605
141. Postma P, Gray JA, Sharma T, Geyer M, Mehrotra R, Das M, et al. A behavioural and functional neuroimaging investigation into the effects of nicotine on sensorimotor gating in healthy subjects and persons with schizophrenia. *Psychopharmacology* (2006). 184:589–99. doi: 10.1007/s00213-006-0307-5
142. Woznica AA, Sacco KA, George TP. Prepulse inhibition deficits in schizophrenia are modified by smoking status. *Schizophr Res.* (2009) 112:86–90. doi: 10.1016/j.schres.2009.04.016
143. George TP, Termine A, Sacco KA, Allen TM, Reutenauer E, Vessicchio JC, et al. A preliminary study of the effects of cigarette smoking on prepulse inhibition in schizophrenia: involvement of nicotinic receptor mechanisms. *Schizophr Res.* (2006) 87:307–15. doi: 10.1016/j.schres.2006.05.022
144. Hommer DW, Clem T, Litman R, Pickar D. Maladaptive anticipatory saccades in schizophrenia. *Biol Psychiatry* (1991) 30:779–94. doi: 10.1016/0006-3223(91)90234-D
145. Ross RG, Harris JG, Olincy A, Radant A, Adler L, Freedman R. Familial transmission of two independent saccadic abnormalities in schizophrenia. *Schizophr Res.* (1998) 30:59–70. doi: 10.1016/S0920-9964(97)00133-3
146. Karoumi BB, Saoud MT, d'Amato T, Rosenfeld F, Denise P, Gutknecht C, et al. Poor performance in smooth pursuit and antisaccadic eye-movement tasks in healthy siblings of patients with schizophrenia. *Psychiatry Res.* (2001) 101:209–19. doi: 10.1016/S0165-1781(01)00227-X
147. Krebs MO, Gut-Fayand A, Amado I, Daban C, Bourdel MC, Poirier MF, et al. Impairment of predictive saccades in schizophrenia. *Neuroreport* (2001) 12:465–9. doi: 10.1097/00001756-200103050-00009
148. Avila MT, Sherr JD, Hong E, Myers CS, Thaker GK. Effects of nicotine on leading saccades during smooth pursuit eye movements in smokers and nonsmokers with schizophrenia. *Neuropsychopharmacology* (2003) 28:2184. doi: 10.1038/sj.npp.1300265
149. Larrison-Faucher AL, Matorin AA, Sereno AB. Nicotine reduces antisaccade errors in task impaired schizophrenic subjects. *Prog Neuro Psychopharm Biol Psychiatry* (2004) 28:505–16. doi: 10.1016/j.pnpbp.2004.01.002
150. Tregellas JR, Tanabe JL, Martin LF, Freedman R. FMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. *Am J Psychiatry* (2005) 162:391–3. doi: 10.1176/appi.ajp.162.2.391
151. Tanabe J, Tregellas JR, Martin LF, Freedman R. Effects of nicotine on hippocampal and cingulate activity during smooth pursuit eye movement in schizophrenia. *Biol Psychiatry* (2006) 59:754–61. doi: 10.1016/j.biopsych.2005.09.004
152. Petrovsky N, Ettinger U, Quednow BB, Walter H, Schnell K, Kessler H, et al. Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy. *Psychopharmacology* (2012) 221:27–38. doi: 10.1007/s00213-011-2540-9
153. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci.* (2012) 1248:107–23. doi: 10.1111/j.1749-6632.2011.06202.x
154. Jiang J, See YM, Subramaniam M, Lee J. Investigation of cigarette smoking among male schizophrenia patients. *PLoS ONE* (2013) 8:e71343. doi: 10.1371/journal.pone.0071343
155. Steinberg ML, Williams JM, Ziedonis DM. Financial implications of cigarette smoking among individuals with schizophrenia. *Tobacco Control* (2004) 13:206.
156. Olivier D, Lubman DI, Fraser R. Tobacco smoking within psychiatric inpatient settings: biopsychosocial perspective. *Aust N Z J Psychiatry* (2007) 41:572–80. doi: 10.1080/00048670701392809
157. Keizer I, Eytan A. Variations in smoking during hospitalization in psychiatric in-patient units and smoking prevalence in patients and health-care staff. *Int J Soc Psychiatry* (2005) 51:317–28. doi: 10.1177/0020764005057377
158. Prochaska JJ, Gill P, Hall SM. Treatment of tobacco use in an inpatient psychiatric setting. *Psychiatr Serv.* (2004) 55:1265–70. doi: 10.1176/appi.ps.55.11.1265
159. Prochaska JJ, Fletcher L, Hall SE, Hall SM. Return to smoking following a smoke-free psychiatric hospitalization. *Am J Addict.* (2006) 15:15–22. doi: 10.1080/10550490500419011
160. Willemsen MC, Gorts CA, Van Soelen P, Jonkers R, Hilberink S. Exposure to environmental tobacco smoke (ETS) and determinants of support for complete smoking bans in psychiatric settings. *Tob Control* (2004) 13:180–5. doi: 10.1136/tc.2003.004804
161. Hitsman B, Moss TG, Montoya ID, George T. Treatment of tobacco dependence in mental health and addictive disorders. *Can J Psychiatry* (2009) 54:368–78. doi: 10.1177/070674370905400604
162. Lawn S, Pols R. Smoking bans in psychiatric inpatient settings? A review of the research. *Aust N Z J Psychiatry* (2005) 39:866–85. doi: 10.1080/j.1440-1614.2005.01697.x
163. Riad-Allen L, Dermody SS, Herman Y, Bellissimo K, Selby P, George TP. Becoming tobacco-free: changes in staff and patient attitudes and incident reports in a large academic mental health and addictions hospital. *Am J Addict.* (2017) 26:183–91. doi: 10.1111/ajad.12513
164. Cather C, Pachas GN, Cieslak KM, Evins A. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs* (2017) 31:471–81. doi: 10.1007/s40263-017-0438-8
165. Dwoskin LP. *Emerging Targets and Therapeutics in the Treatment of Psychostimulant Abuse*. Elsevier Science (2014).
166. Tashkin DP. Smoking cessation in chronic obstructive pulmonary disease. *Semin Respir Crit Care Med.* (2015) 36:491–507. doi: 10.1055/s-0035-1555610
167. Smith RC, Amiaz R, Si TM, Maayan L, Jin H, Boules S, et al. Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: a double-blind randomized trial. *PLoS ONE* (2016) 11:e0143490. doi: 10.1371/journal.pone.0143490
168. Jin Y, Wang Q, Wang Y, Liu M, Sun A, Geng Z, et al. Alpha7 nAChR agonists for cognitive deficit and negative symptoms in schizophrenia: a meta-analysis of randomized double-blind controlled trials. *Shanghai Arch Psychiatry* (2017) 29:191–9. doi: 10.11919/j.issn.1002-0829.217044
169. Coles AS, Kozak K, George TP. A review of brain stimulation for treatment of substance use disorders. *Am J Addict.* (2018) 27:71–91. doi: 10.1111/ajad.12674
170. Kozak K, Sharif-Razi M, Morozova M, Gaudette EV, Barr M, Daskalakis ZJ, et al. Effects of short-term, high-frequency repetitive transcranial magnetic stimulation to bilateral dorsolateral prefrontal cortex on smoking behavior and cognition in patients with schizophrenia and non-psychiatric controls. *Schizophr Res.* (2018). 197:441–3. doi: 10.1016/j.schres.2018.02.015
171. Amiaz R, Levy D, Vainiger D, Grunhaus L, Zangen A. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal

cortex reduces cigarette craving and consumption. *Addiction* (2009) 104:653–60. doi: 10.1111/j.1360-0443.2008.02448.x

172. Prikryl R, Ustohal L, Kucerova HP, Kasparek T, Jarkovsky J, Hublova V, et al. Repetitive transcranial magnetic stimulation reduces cigarette consumption in schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 49:30–5. doi: 10.1016/j.pnpbp.2013.10.019
173. Barr MS, Farzan F, Wing VC, George TP, Fitzgerald PB, Daskalakis ZJ. Repetitive transcranial magnetic stimulation and drug addiction. *Int Rev Psychiatry* (2011) 23:454–66. doi: 10.3109/09540261.2011.618827
174. de la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. *Lancet Neurol.* (2002) 1:85–91. doi: 10.1016/S1474-4422(02)00038-8
175. Perkins K, Sayette M, Conklin C, Caggiula A. Placebo effects of tobacco smoking and other nicotine intake. *Nicotine Tob Res.* (2003) 5:695–709. doi: 10.1080/1462220031000158636
176. Ernst E. Placebo: new insights into an old enigma. *Drug Discov Today* (2007) 12:413–18. doi: 10.1016/j.drudis.2007.03.007
177. Wu AD, Fregni F, Simon DK, Deblieck C, Pascual-Leone A. Noninvasive brain stimulation for Parkinson's disease and dystonia. *Neurotherapeutics* (2008) 5:345–61. doi: 10.1016/j.nurt.2008.02.002
178. Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. *Schizophr Res.* (2015) 168:260–6. doi: 10.1016/j.schres.2015.06.011

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 December 2018
doi: 10.3389/fpsyt.2018.00642

Assessment of the Association Between Cigarette Smoking and Cognitive Performance in Patients With Schizophrenia-Spectrum Disorders: A Case-Control Study

Filip Stramecki[1], Kamila D. Kotowicz[1], Patryk Piotrowski[1], Dorota Frydecka[1], Joanna Rymaszewska[1], Jan Aleksander Beszłej[1], Jerzy Samochowiec[2], Marcin Jabłoński[2], Michał Wroński[2], Ahmed A. Moustafa[3,4] and Błazej Misiak[5]*

[1] Department of Psychiatry, Wroclaw Medical University, Wroclaw, Poland, [2] Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland, [3] School of Social Sciences and Psychology, Marcs Institute of Brain and Behaviour, Western Sydney University, Penrith, NSW, Australia, [4] Department of Social Sciences, College of Arts and Sciences, Qatar University, Doha, Qatar, [5] Department of Genetics, Wroclaw Medical University, Wroclaw, Poland

OPEN ACCESS

Edited by:
Billie Bonevski,
University of Newcastle, Australia

Reviewed by:
Teresa Sanchez-Gutierrez,
Universidad Internacional De La Rioja, Spain
Marina Šagud,
University of Zagreb, Croatia

***Correspondence:**
Filip Stramecki
fstramecki@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *28 August 2018*
Accepted: *15 November 2018*
Published: *03 December 2018*

Citation:
Stramecki F, Kotowicz KD, Piotrowski P, Frydecka D, Rymaszewska J, Beszłej JA, Samochowiec J, Jabłoński M, Wroński M, Moustafa AA and Misiak B (2018) Assessment of the Association Between Cigarette Smoking and Cognitive Performance in Patients With Schizophrenia-Spectrum Disorders: A Case-Control Study. Front. Psychiatry 9:642. doi: 10.3389/fpsyt.2018.00642

The prevalence of cigarette smoking is significantly higher in patients with schizophrenia compared to the general population. Schizophrenia is also characterized by cognitive impairments that can be detected in the premorbid phase of illness. However, studies addressing the association between cigarette smoking and cognition in patients with psychosis have provided mixed findings. Therefore, the aim of this study was to assess the relationship between tobacco smoking and cognitive performance in patients with schizophrenia. In this case-control study, we recruited 67 inpatients with schizophrenia (34 cigarette smokers) and 62 healthy controls (30 cigarette smokers) at two clinical sites (Wroclaw and Szczecin, Poland). Cognitive performance was examined using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Smoking dependence was determined using the Fagerström Test for Nicotine Dependence (FTND) and the pack-year index. Results show that, after adjustment for potential confounders, smokers with schizophrenia presented significantly lower scores on delayed memory tests compared to non-smokers with schizophrenia ($F = 11.07$, $p = 0.002$). In healthy controls, after adjustment for age, sex, and education level, smokers had significantly lower scores in immediate memory (47.1 ± 6.4 vs. 52.0 ± 4.0, $F = 11.64$, $p = 0.001$), visuospatial/constructional functions (34.8 ± 3.8 vs. 37.7 ± 1.8, $F = 12.86$, $p = 0.001$) and global cognition (177.0 ± 15.7 vs. 191.2 ± 14.0, $F = 12.63$, $p = 0.001$) compared to non-smokers. There were no significant correlations between FTND scores or pack-year index and cognitive performance neither in patient nor control group. Our results show that cigarette smoking is related to worse delayed memory performance in schizophrenia patients as well as deficits of immediate memory, visuospatial/constructional functions, and global cognition in controls. Longitudinal studies are required to establish causal interference between smoking and cognition in patients with schizophrenia.

Keywords: schizophrenia, tobacco, smoking, nicotine, cognition

INTRODUCTION

Schizophrenia is a severe mental illness resulting from complex interactions between genetic and environmental factors (1). Several studies indicate a high prevalence of tobacco smoking in patients with schizophrenia that has been estimated at around 58–88%, which is significantly higher than in the general population (23%) (2). There are many hypotheses attempting to explain this observation. For instance, it has been proposed that cigarette smoking is a "self-medication" process, by which the patients cope with the negative symptoms of the disease, compensating for neurotransmission abnormalities in the central nervous system (3). Based on this hypothesis, patients might also smoke to alleviate the extrapyramidal side effects associated with antipsychotic treatment since nicotine induces the 1A2 isoform of cytochrome P450 (CYP1A2) that is involved in metabolizing a number of antipsychotic drugs (4, 5). Finally, it has been proposed that the occurrence of schizophrenia and nicotine dependence are related to overlapping genetic backgrounds and environmental factors (6).

Several studies show that smoking among patients with schizophrenia has a significant impact on the psychopathological manifestation of the disease. However, these studies have provided mixed results showing either higher, lower or similar severity of positive and negative symptoms in smokers compared to non-smokers (7–12). Similarly, there is some evidence that smoking might impact cognitive performance in schizophrenia patients. It is widely known that cognitive deficits represent one of the main elements of schizophrenia psychopathology and are present in the majority of patients, largely influencing functional outcomes (13, 14). Cognitive impairments in schizophrenia include, among others, deficits in verbal learning, memory, attention, working, and visuospatial memory as well as processing speed (15). There is a growing body of evidence suggesting that cigarette smoking might also impact cognitive performance in patients with schizophrenia. However, studies addressing this link between cigarette smoking and cognition have provided mixed results. Some studies have shown that cigarette-smoking patients might present with better cognitive performance compared to non-smokers with schizophrenia (16). It has also been reported that smoking cessation in patients with schizophrenia might result in the deterioration of visuospatial memory and attentional deficits with subsequent improvement in cognition after re-starting tobacco smoking (17).

However, it has also been shown that tobacco smoking might be associated with worse cognitive performance in schizophrenia patients, especially in the domain of visuospatial memory (18, 19). Finally, several studies revealed that there is no significant association between tobacco smoking and cognition in schizophrenia (10, 20, 21). Interestingly, studies investigating the impact of tobacco smoking in non-clinical populations have provided more consistent results. It has been shown that young adults, who are addicted to nicotine experienced significantly higher deficits in attention and greater visuospatial working memory impairments compared to non-smokers (22, 23).

Interestingly, experimental studies have revealed that intranasal nicotine administration might improve spatial organization and memory in patients with schizophrenia (17, 24, 25). Moreover, transdermal nicotine administration has been found to improve memory performance (24, 26). However, the effects of short-term nicotine administration do not equal long-term cohort studies in cigarette smokers. The opposite findings of these studies can results from the multifactorial etiology of cognitive disturbances. The impairments may be caused not exclusively by nicotine, but by a large number of cytotoxic compounds present in a cigarette smoke and cause adverse effects in the brain (27). In general, large long-term cohort studies by Depp et al. (19) and Vermeulen et al. (27) have reported poorer cognitive functioning in cigarette smokers with psychotic disorders.

As mentioned above, studies addressing the impact of cigarette smoking on cognition have provided mixed findings. The majority of these studies have been performed in multiple-episode schizophrenia patients and have not included a group of healthy controls. Therefore, the aim of this study was to investigate the association between cigarette smoking and cognitive functioning in patients with schizophrenia and in the group of healthy controls.

MATERIALS AND METHODS

Participants

Participants were 67 patients with schizophrenia-spectrum disorders (34 smokers and 33 non-smokers) and 62 healthy controls (30 smokers and 32 non-smokers). There were following inclusion criteria for the patients: (1) age between 18 and 65 years and (2) a diagnosis of schizophrenia-spectrum disorders according to the DSM-IV criteria. The exclusion criteria for the patients were as follows: (1) co-occurrence of neurological disorders; (2) intellectual disability; (3) drug and alcohol dependence (except for nicotine dependence). In the healthy control group, the exclusion criteria included also psychiatric treatment and the presence of past, present, or family history of neurological and psychiatric disorders (except for nicotine dependence). There was no history of cardiovascular diseases, diabetes, and hypertension in the group of patients and controls.

All patients were recruited at Lower Silesian Center of Mental Health (Wroclaw, Poland), Department of Psychiatry (Wroclaw Medical University, Wroclaw, Poland) and Department of Psychiatry (Pomeranian Medical University, Szczecin, Poland) in the years 2016–2018. A diagnosis of schizophrenia-spectrum disorders was established using the DSM-IV criteria and validated with the Operational Criteria for Psychotic Illness (OPCRIT) checklist (28). There were 17 multiple-episode schizophrenia patients and 50 first-episode psychosis (FEP) patients. The latter group represented the following diagnoses: schizophrenia ($n = 28$), schizophreniform disorder ($n = 14$), brief psychotic disorder ($n = 4$), schizoaffective disorder ($n = 3$) and delusional disorder ($n = 1$). Current psychopathological manifestation was assessed using the Positive and Negative Syndrome Scale (PANSS), which consists of three subscales: positive symptoms, negative symptoms,

and general psychopathology (29). Based on a differential receptor affinity profiles of antipsychotics (30, 31), patients were divided into three groups: (1) those receiving antipsychotics with high anticholinergic activity: clozapine, olanzapine, chlorpromazine, zuclopenthixol, levopromazine, and perazine ($n = 30$); (2) those receiving antipsychotics with low anticholinergic activity: amisulpride, aripiprazole, haloperidol, risperidone, sertindol, sulpride, quetiapine, and ziprasidone ($n = 23$) and (3) those receiving at least two antipsychotics with opposite anticholinergic activity ($n = 14$). Healthy controls were recruited at the Wroclaw Medical University through advertisements. Patients and controls were selected as a convenience sample of individuals with data regarding cigarette smoking and cognitive performance. Both groups were matched for age, sex, and cigarette smoking status.

Tobacco smoking dependence was assessed with the use of the Fagerström Test for Nicotine Dependence (FTND) (32) and the pack-year index (33). Patients were classified as smokers if they reported smoking more than one cigarette per day for at least 12 months. Cognitive performance of all participants in the study was examined using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (34). The RBANS has been validated in several studies of patients with schizophrenia, showing good psychometric properties (35–37). The RBANS captures the following cognitive domains: (1) immediate memory (measured by word List Learning and Story Memory test), (2) visuospatial and constructional working memory (Figure Copy and Line Orientation), (3) language capacity (Picture naming and Semantic Fluency), (4) attention (Digit Span and Coding), and (5) delayed memory (List Recall, List Recognition, Story Memory, and Figure Recall). Assessment of cognition was performed by psychologists, who were blind to the cigarette smoking status of participants. The FTND and questions regarding cigarette smoking status were administered after assessment of cognitive performance.

The study protocol was approved by the Ethics Committee at Wroclaw Medical University (Wroclaw, Poland) and followed the Declaration of Helsinki of ethical principles for human research. All participants gave a written informed consent.

Statistical Analysis

The normality of data distribution was tested using the Kolmogorov–Smirnov test. Due to non-normal distribution of continuous variables, non-parametric tests were used to perform bivariate comparisons between the groups. Similarly, correlations were assessed using the Spearman's rank correlation coefficients. Distribution of categorical variables in patients and controls was compared using the χ^2 test. The analysis of co-variance (ANCOVA) was performed to test the effects of cigarette smoking status on cognitive performance after co-varying for age, sex, education level, and the chlorpromazine equivalent dosage (CPZeq). In the case of patients, the stage of illness (FEP patients or multiple-episode patients) was also added as a co-variate. We included scores of cognitive performance on domains that differed significantly between patients and controls as dependent variables in the ANCOVA. Before running the ANCOVA, scores of cognitive performance were transformed to Z-scores because of non-normal distribution. The results of statistical analysis were considered significant if p-value was <0.05. Statistical analysis was performed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA).

TABLE 1 | General characteristics of patients and controls.

	Patients ($n = 67$)	Controls ($n = 62$)	p
Age, years	30.3 ± 9.7	30.5 ± 6.4	0.349
Sex, M/F (%)	36 (53.7)/31 (46.3)	28 (45.2)/34 (54.8)	0.331
Education, higher/other than higher (%)	18 (26.9)/49 (73.1)	5 (8.1)/57 (91.9)	**0.005**
FTND score	2.4 ± 2.9	2.1 ± 3.1	0.535
Pack-year index	5.6 ± 8.8	4.1 ± 6.9	0.554
Immediate memory	40.5 ± 10.9	49.7 ± 5.8	**<0.001**
Visuospatial/ constructional functions	33.6 ± 5.4	36.3 ± 3.3	**0.005**
Language	27.8 ± 6.1	31.8 ± 5.8	**<0.001**
Attention	49.4 ± 13.7	63.2 ± 10.8	**<0.001**
Delayed memory	42.9 ± 9.8	53.1 ± 4.6	**<0.001**
Global cognition	153.6 ± 28.6	184.3 ± 16.4	**<0.001**

FTND, the Fagerström Test for Nicotine Dependence. Data expressed as mean ± SD or the number of cases. Raw scores of cognitive performance are provided. Significant differences were marked with bold characters ($p < 0.05$).

RESULTS

Scores of all cognitive domains and education level were significantly lower in the group of patients compared to controls (**Table 1**). General characteristics of patients and controls with respect to cigarette smoking status are shown in **Table 2**. All subgroups of participants did not differ significantly in terms of age and sex. The level of education was significantly lower in smokers compared to non-smokers. There were no significant differences in the FTND score and pack-year index between smoking patients and smoking controls.

Smokers with schizophrenia scored significantly lower on delayed memory compared to non-smokers with schizophrenia (**Table 3**). Smoking controls had significantly lower scores of immediate memory, visuospatial/constructional abilities, language, and global cognition compared to non-smoking controls.

The results of ANCOVA testing for differences in cognitive performance between smokers and non-smokers, controlling for the effects of age, sex, education, stage of illness (FEP vs. multiple-episode patients), type of antipsychotics based on anticholinergic activity, and CPZeq are presented in **Table 4**. The ANCOVA test confirmed a significant association between cigarette smoking status and delayed memory performance in the group of patients. This ANCOVA test also revealed a significant association between sex and delayed memory. The association between cigarette smoking and immediate memory, visuospatial/constructional functions, as well as global cognition

TABLE 2 | General characteristics of schizophrenia patients and healthy controls with respect to cigarette smoking status.

	SZ-S ($n = 34$)	SZ-NS ($n = 33$)	HCs-S ($n = 30$)	HCs-NS ($n = 32$)	*p*
Age, years	31.6 ± 9.6	29.0 ± 9.8	30.9 ± 5.9	30.0 ± 6.8	0.251
Sex, M/F (%)	21 (61.8)/13 (38.2)	15 (45.4)/18 (54.6)	13 (43.3)/17 (56.7)	15 (46.9)/17 (53.1)	0.423
Education, higher/other than higher (%)	5 (14.7)/29 (85.3)	13 (39.4)/20 (60.6)	1 (3.3)/29 (96.7)	4 (12.5)/28 (87.5)	**0.001**
CPZeq, mg/day	362.8 ± 210.4	324.7 ± 239.9	–	–	0.284
PANSS-P	13.2 ± 4.9	14.7 ± 5.7	–	–	0.348
PANSS-N	20.2 ± 9.8	19.0 ± 8.0	–	–	0.773
PANSS-G	30.1 ± 9.5	31.8 ± 8.9	–	–	0.301
PANSS-total	61.6 ± 20.7	65.6 ± 19.1	–	–	0.486
FTND score	4.6 ± 2.4	–	4.5 ± 3.1	–	0.770
Pack-year index	11.1 ± 9.6	–	8.3 ± 8.1	–	0.238

CPZeq, chlorpromazine equivalent dosage; FTND, the Fagerström Test for Nicotine Dependence; 12HCs-S, smoking controls; HCs-NS, non-smoking controls; PANSS-G, the Positive and Negative Syndrome Scale (a severity of general psychopathology); PANSS-N, the Positive and Negative Syndrome Scale (a severity of negative symptoms); PANSS-P, the Positive and Negative Syndrome Scale (a severity of positive symptoms); PANSS-total, the Positive and Negative Syndrome Scale (total score); SZ-NS, non-smokers with schizophrenia; SZ-S, smokers with schizophrenia.
Significant differences were marked with bold characters ($p < 0.05$).

TABLE 3 | Cognitive performance with respect to cigarette smoking in patients with schizophrenia and healthy controls.

	SZ-S	SZ-NS	*p*	HCs-S	HCs-NS	*p*
Immediate memory	37.7 ± 8.6	43.3 ± 12.4	0.077	47.1 ± 6.4	52.0 ± 4.0	**0.001**
Visuospatial/constructional functions	33.0 ± 5.1	34.1 ± 5.8	0.232	34.8 ± 3.8	37.7 ± 1.8	**0.001**
Language	26.7 ± 6.0	28.8 ± 6.0	0.245	30.3 ± 5.4	33.2 ± 5.8	**0.049**
Attention	49.0 ± 12.5	49.8 ± 15.0	0.702	60.2 ± 9.9	66.0 ± 11.0	0.053
Delayed memory	40.2 ± 9.0	45.7 ± 9.8	**0.013**	51.7 ± 5.1	54.4 ± 3.7	0.059
Global cognition	148.9 ± 26.5	158.4 ± 30.3	0.146	177.0 ± 15.7	191.2 ± 14.0	**0.002**

HCs-S, smoking controls; HCs-NS, non-smoking controls; SZ-NS, non-smokers with schizophrenia; SZ-S, smokers with schizophrenia. Raw scores are presented as mean ± SD. Significant differences were marked with bold characters ($p < 0.05$).

appeared to be significant in healthy controls after adjustment for age, sex, and education level. The ANCOVA model testing for differences in global cognition between smoking and non-smoking controls also demonstrated a significant association with age.

There were no significant correlations between the FTND score or the pack-year index and cognitive performance neither in the group of smoking patients nor in smoking controls (**Table 5**).

DISCUSSION

This study investigated whether cognitive deficits observed in schizophrenia are associated with smoking behavior. We found worse performance of delayed memory in the group of smoking patients after adjustment for age, sex, educational attainment, illness stage, and medication effects. Further, smoking controls performed worse on immediate memory, visuospatial/constructional functions, and global cognition when compared to non-smoking healthy individuals. A severity of nicotine dependence was not related to the extent of cognitive impairments in our sample. The previous study by Zhang et al. (38), which was also based on the use of RBANS, revealed worse performance of visuospatial/constructional abilities, immediate memory and global cognition in male smokers with schizophrenia compared to non-smokers. Cigarette smoking has also been associated with impairments in attention (15), semantic fluency (39), visual learning (18), and global cognition (19). A large, prospective 6-year follow-up study by 26], revealed that cigarette smoking is related to worse processing speed in patients with non-affective psychosis. Other studies have revealed improved cognitive performance in smokers with schizophrenia (40) or a lack of association between nicotine dependence and cognition (20, 21).

Discrepancies across studies addressing the effects of cigarette smoking on cognition in schizophrenia patients can be attributed to several methodological differences. Firstly, it should be noted that patients were recruited during various stages of illness in the above-mentioned studies. Indeed, some studies were performed in FEP patients (20, 21, 41) while other studies assessed cognition in multiple-episode schizophrenia patients (15, 18, 39). Although the dosage of medications was controlled in the majority of these studies, antipsychotics largely differ in terms of pro-cognitive activity and side effects (42, 43). This is particularly related to the self-medication hypothesis. According to this theory, patients may unintentionally engage in smoking habits to increase the metabolism of antipsychotics

TABLE 4 | ANCOVA results testing for differences in cognitive performance between smokers and non-smokers after co-varying for education level, global psychopathology, and medication effects.

	Smoking (yes/no)	Age	Sex	Education level	CPZeq	Anticholinergic activity of antipsychotics (high vs. low vs. mixed)	Group (FEP vs. MES)
Delayed memory, SZ patients	***F* = 11.07** ***p* = 0.002**	$F = 1.26$ $p = 0.266$	***F* = 4.36** ***p* = 0.041**	$F = 0.60$ $p = 0.442$	$F = 0.24$ $p = 0.627$	$F = 0.53$ $p = 0.470$	$F = 3.28$ $p = 0.075$
Immediate memory, HCs	***F* = 11.64** ***p* = 0.001**	$F = 0.83$ $p = 0.366$	$F = 0.46$ $p = 0.500$	$F = 0.001$ $p = 0.978$	–	–	–
Visuospatial/ constructional functions, HCs	***F* = 12.86** ***p* = 0.001**	$F < 0.001$ $p = 0.999$	$F = 1.99$ $p = 0.163$	$F = 0.79$ $p = 0.377$	–	–	–
Language, HCs	$F = 3.30$ $p = 0.074$	$F = 0.27$ $p = 0.603$	$F = 1.51$ $p = 0.223$	$F = 0.503$ $p = 0.481$	–	–	–
Global cognition, HCs	***F* = 12.63** ***p* = 0.001**	***F* = 7.91** ***p* = 0.007**	$F = 0.17$ $p = 0.683$	$F = 0.36$ $p = 0.552$	–	–	–

CPZeq, chlorpromazine equivalent dosage; FEP, first-episode psychosis; MES, multiple-episode schizophrenia; PANSS, the Positive and Negative Syndrome Scale. Significant effects were marked with bold characters ($p < 0.05$).

TABLE 5 | Correlations between FTND score, pack-year index cognitive performance in smokers.

	SZ-S patients		HCs-S	
	FTND score	Pack-year index	FTND score	Pack-year index
Immediate memory	$r = 0.073$ $p = 0.681$	$r = -0.044$ $p = 0.807$	$r = 0.297$ $p = 0.125$	$r = -0.039$ $p = 0.843$
Visuospatial/constructional functions	$r = 0.026$ $p = 0.882$	$r = 0.008$ $p = 0.967$	$r = -0.187$ $p = 0.341$	$r = -0.099$ $p = 0.617$
Language	$r = 0.180$ $p = 0.309$	$r = -0.011$ $p = 0.949$	$r = 0.247$ $p = 0.205$	$r = -0.095$ $p = 0.630$
Attention	$r = 0.006$ $p = 0.973$	$r = 0.039$ $p = 0.830$	$r = -0.163$ $p = 0.408$	$r = -0.148$ $p = 0.454$
Delayed memory	$r = -0.023$ $p = 0.898$	$r = 0.044$ $p = 0.807$	$r = 0.186$ $p = 0.343$	$r = -0.092$ $p = 0.640$
Global cognition	$r = 0.102$ $p = 0.568$	$r = 0.022$ $p = 0.903$	$r = 0.009$ $p = 0.963$	$r = -0.163$ $p = 0.406$

FTND, the Fagerström Test for Nicotine Dependence; HCs-S, smoking controls; SZ-S, smokers with schizophrenia.

and alleviate extrapyramidal symptoms or improve cognitive deficits and negative symptoms (44). Moreover, there is some evidence that treatment-resistance might be related to cognitive impairments in this group of patients (30). Another point is that various definitions of cigarette smoking have been used and a detailed history of smoking habits has not been recorded in most studies. In addition, a severity of nicotine dependence has not been controlled in a number of previous studies. Finally, schizophrenia is also associated with high prevalence rates of comorbid cardiovascular diseases that might further contribute to cognitive deficits (45, 46). A recent meta-analysis revealed that a diagnosis of metabolic syndrome together with its single components (central obesity, dyslipidaemia, diabetes, and hypertension) is related to cognitive impairment in patients with schizophrenia (47). Therefore, it might be assumed various prevalence rates of metabolic syndrome and related conditions in distinct studies might impact the association between cigarette smoking and cognition in schizophrenia.

The results of this study should be interpreted with caution, taking into account certain limitations. First, it should be noted that power analysis was not performed and our study had a relatively small sample size. Although this may suggest that our results could have occurred by coincidence, our findings are consistent with several previous studies. Second, our cross-sectional study design does not enable us to explain the reciprocal interactions between tobacco smoking and cognitive performance. Cigarette smoking might contribute to cognitive impairment via various mechanisms, including the effects on neurotransmission systems and vascular endothelium (48). However, certain cognitive deficits might make the patients more prone to engage in smoking behaviors. For instance, it has been reported that impairments in sustained attention and control of impulsivity may be a risk factor for cigarette smoking (49). Another limitation of our study is that the majority of our patients were not drug-naïve. However, the measures of antipsychotic treatment did not differ significantly between smoking and non-smoking patients and were included in the

ANCOVA tests. In addition, our sample was not representative and thus it is difficult to generalize our findings over the entire population of patients. At this point, it is important to note that patients with schizophrenia and comorbid addictions other than nicotine dependence were excluded. Moreover, we did not record the use of other drugs that are frequently used by patients with psychotic disorders, such as cannabis. It also has to be noted that we did not take into account the influence of specific drugs on cognitive functions, different doses of these drugs, and the complex effect of drug-nicotine interaction on the symptoms of the disease. Finally, we did not control for a severity of extrapyramidal side effects that might be related to both cognitive deficits and cigarette smoking.

In summary, our study demonstrated that cigarette smoking is associated with impairments of delayed memory in patients with schizophrenia. However, in healthy, controls, cigarette smoking was related to worse performance of immediate memory, visuospatial/constructional abilities, and global cognition. The mechanisms underlying these differential associations in patients and controls remain unknown and require further studies. The association between cigarette smoking and cognitive impairment may not be related to the severity of nicotine dependence. Longitudinal studies are required to establish the direction of causality between cigarette smoking and cognition in schizophrenia.

AUTHOR CONTRIBUTIONS

FS, DF, and BM contributed conception and design of the study. FS, KK, PP, DF, JB, JS, MJ, and MW performed clinical assessment of patients. FS organized the database. BM performed the statistical analysis. FS wrote the first draft of the manuscript. FS, BM, JR, and AM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

Participants were recruited in frame of the following grants: the Iuventus Plus grant awarded by the Ministry of Science and Higher Education (grant number: IP2015 052474), the Preludium grant awarded by the National Centre of Science (grant number: 2011/03/N/NZ5/00248) and the Sonata grant awarded by the National Centre of Science (grant number: 2013/11/D/HS6/04619).

ACKNOWLEDGMENTS

We are deeply grateful to all patients and healthy controls participating in this study.

REFERENCES

1. Misiak B, Stramecki F, Gaweda Ł, Prochwicz K, Sasiadek MM, Moustafa AA, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. *Mol Neurobiol*. (2018) 55:5075–100. doi: 10.1007/s12035-017-0708-y
2. Boggs DL, Carlson J, Cortes-Briones J, Krystal JH, D'Souza DC. Going up in smoke? A review of nAChRs-based treatment strategies for improving cognition in schizophrenia. *Curr Pharm Des*. (2014) 20:5077–92. doi: 10.2174/1381612819666131216121019
3. D'Souza MS, Markou A. Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. *Neuropharmacology* (2012) 62:1564–73. doi: 10.1016/j.neuropharm.2011.01.044
4. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv*. (2004) 55:491–3. doi: 10.1176/appi.ps.55.5.491
5. Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, et al. The effects of transdermal nicotine on cognition in non-smokers with schizophrenia and non-psychiatric controls. *Neuropsychopharmacology* (2008) 33:480–90. doi: 10.1038/sj.npp.1301423
6. Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* (2001) 50:71–83. doi: 10.1016/S0006-3223(01)01134-9
7. Schwartz K, Iancu I, Stryjer R, Chelben J, Kotler M, Weizman A, et al. Reduced platelet vesicular monoamine transporter density in smoking schizophrenia patients. *Eur Neusopsychopharmacol*. (2005) 15:557–61. doi: 10.1016/j.euroneuro.2005.02.005
8. Salokangas RKR, Honkonen T, Stengard E, Koivisto AM, Hietala J. Cigarette smoking in long-term schizophrenia. *Eur Psychiatry* (2006) 21:219–23. doi: 10.1016/j.eurpsy.2005.07.008
9. Zhang XY, Chen DC, Xiu MH, Haile CN, He SC, Luo X, et al. Cigarette smoking, psychopathology and cognitive function in first- episode drug-naive patients with schizophrenia: a case–control study. *Psychol Med*. (2013) 43:1651–60. doi: 10.1017/S0033291712002590
10. Iasevoli F, Balletta R, Gilardi V, Giordano S, de Bartolomeis A. Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. *Neuropsychiatr Dis Treat*. (2013) 9:1113–20. doi: 10.2147/NDT.S47571
11. Misiak B, Kiejna A, Frydecka D. Assessment of cigarette smoking status with respect to symptomatic manifestation in first-episode schizophrenia patients. *Compr Psychiatry* (2015) 58:146–51. doi: 10.1016/j.comppsych.2014.11.024
12. Jiang J, See YM, Subramaniam M, Lee J. Investigation of cigarette smoking among male schizophrenia patients. *PLoS ONE* (2013) 8:e71343. doi: 10.1371/journal.pone.0071343
13. Brekke JS, Hoe M, Long J, Green MF. How neurocognition and social cognition influence functional change during community-based psychosocial rehabilitation for individuals with schizophrenia. *Schizophr Bull*. (2007) 33:1247–56. doi: 10.1093/schbul/sbl072
14. Brekke JS, Hoe M, Long J, Green MF. Neurocognitive change, functional change and service intensity during community-based psychosocial rehabilitation for schizophrenia. *Psychol Med*. (2009) 39:1637–47. doi: 10.1017/S003329170900539X
15. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. (2004) 72:29–39. doi: 10.1016/j.schres.2004.09.007
16. Wing VC, Bacher I, Sacco KA, George TP. Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. *Psychiatry Res*. (2011) 188:320–6. doi: 10.1016/j.psychres.2011.05.037
17. Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, et al. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Arch Gen Psychiatry* (2005) 62:649–59. doi: 10.1001/archpsyc.62.6.649
18. Reed AC, Harris JG, Olincy A. Schizophrenia, smoking status, and performance on the matrics cognitive consensus battery. *Psychiatry Res*. (2016) 246:1–8. doi: 10.1016/j.psychres.2016.08.062
19. Depp CA, Bowie CR, Mausbach BT, Wolyniec P, Thornquist MH, Luke JR, et al. Current smoking is associated with worse cognitive and adaptive

functioning in serious mental illness. *Acta Psychiatr Scand*. (2015) 131:333–41. doi: 10.1111/acps.12380
20. Sánchez-Gutiérrez T, García-Portilla MP, Parellada M, Bobes J, Calvo A, Moreno-Izco L, et al. Smoking does not impact social and non-social cognition in patients with first episode psychosis. *Schizophr Res*. (2018) 199:64–74. doi: 10.1016/j.schres.2018.03.025
21. Hickling LM, Perez-Iglesias R, Ortiz-García de la Foz V, Balanzá-Martínez V, McGuire P, Crespo-Facorro B, et al. Tobacco smoking and its association with cognition in first episode psychosis patients. *Schizophr Res*. (2018) 192:269–73. doi: 10.1016/j.schres.2017.04.018
22. Chamberlain SR, Odlaug BL, Schreiber LR, Grant JE. Association between tobacco smoking and cognitive functioning in young adults. *Am J Addict*. (2012) 21 (Suppl. 1):S14–9. doi: 10.1111/j.1521-0391.2012.00290.x
23. Bashir S, Alghamdi F, Alhussien A, Alohali M, Alatawi A, Almusned T, et al. Effect of smoking on cognitive functioning in young Saudi adults. *Med Sci Monit Basic Res*. (2017) 23:31–5. doi: 10.12659/MSMBR.902385
24. Barr AM, Procyshyn RM, Hui P, Johnson JL, Honer WG. Self-reported motivation to smoke in schizophrenia is related to antipsychotic drug treatment. *Schizophr Res*. (2008) 100:252–60. doi: 10.1016/j.schres.2007.11.027
25. Smith RC, Warner-Cohen J, Matute M, Butler E, Kelly E, Vaidhyanathaswamy S, et al. Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology* (2006) 31:637–43. doi: 10.1038/sj.npp.1300881
26. Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, et al. Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* (2004) 29:1378–85. doi: 10.1038/sj.npp.1300450
27. Vermeulen JM, Schirmbeck F, Blankers M, van Tricht M, Bruggeman R, van den Brink W, et al. Association between smoking behavior and cognitive functioning in patients with psychosis, siblings, and healthy control subjects: results from a Prospective 6-year follow-up study. *Am J Psychiatry* (2018) 2:appiajp201818010069. doi: 10.1176/appi.ajp.2018.18010069
28. McGuffin P. A polydiagnostic application of operational criteria in studies of psychotic illness. *Arch Gen Psychiatry* (1991) 48:764. doi: 10.1001/archpsyc.1991.01810320088015
29. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. (1987) 13:261–76. doi: 10.1093/SCHBUL/13.2.261
30. Frydecka D, Beszłej JA, Gościmski P, Kiejna A, Misiak B. Profiling cognitive impairment in treatment-resistant schizophrenia patients. *Psychiatry Res*. (2016) 235:133–8. doi: 10.1016/j.psychres.2015.11.028
31. Sadock B, Sadock V, Sussman N. *Kaplan and Sadock's Pocket Handbook of Psychiatric Drug Treatment*. Baltimore, MD: Lippincott Williams & Wilkins (2006).
32. Pomerleau CS, Majchrzak MJ, Pomerleau OF. Nicotine dependence and the Fagerström Tolerance Questionnaire: a brief review. *J Subst Abuse* (1989) 1:471–7.
33. Prignot J. Quantification and chemical markers of tobacco-exposure. *Eur J Respir Dis*. (1987) 70:1–7.
34. Randolph C, Tierney MC, Mohr E, Chase TN. The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. (1998) 20:310–9. doi: 10.1076/jcen.20.3.310.823
35. Gold JM, Queern C, Iannone VN, Buchanan RW. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia I: sensitivity, reliability, and validity. *Am J Psychiatry* (1999) 156:1944–50.
36. Hobart MP, Goldberg R, Bartko JJ, Gold JM. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia, II: convergent/discriminant validity and diagnostic group comparisons. *Am J Psychiatry* (1999) 156:1951–7.
37. Chianetta JM, Lefebvre M, LeBlanc R, Grignon S. Comparative psychometric properties of the BACS and RBANS in patients with schizophrenia and schizoaffective disorder. *Schizophr Res*. (2008) 105:86–94. doi: 10.1016/j.schres.2008.05.024
38. Zhang XY, Chen DC, Xiu MH, Haile CN, Sun H, Lu L, et al. Cigarette smoking and cognitive function in Chinese male schizophrenia: a case-control study. *PLoS ONE* (2012) 7:e36563. doi: 10.1371/journal.pone.0036563
39. Núñez C, Stephan-Otto C, Cuevas-Esteban J, Maria Haro J, Huerta-Ramos E, Ochoa S, et al. Effects of caffeine intake and smoking on neurocognition in schizophrenia. *Psychiatry Res*. (2015) 230:924–31. doi: 10.1016/j.psychres.2015.11.022
40. Morisano D, Wing VC, Sacco KA, Arenovich T, George TP. Effects of tobacco smoking on neuropsychological function in schizophrenia in comparison to other psychiatric disorders and non-psychiatric controls. *Am J Addict*. (2013) 22:46–53. doi: 10.1111/j.1521-0391.2013.00313.x
41. Zabala A, Eguiluz JI, Segarra R, Enjuto S, Ezcurra J, González Pinto A, et al. Cognitive performance and cigarette smoking in first-episode psychosis. *Eur Arch Psychiatry Clin Neurosci*. (2009) 259:65–71. doi: 10.1007/s00406-008-0835-6
42. Moustafa AA, Garami JK, Mahlberg J, Golembieski J, Keri S, Misiak B, et al. Neural and cognitive function in schizophrenia: conflicting findings and future directions. *Rev Neurosci*. (2016) 27:435–48. doi: 10.1515/revneuro-2015-0060
43. Moustafa AA, Gluck MA. Computational cognitive models of prefrontal-striatal- hippocampal interactions in Parkinson's disease and schizophrenia. *Neural Netw*. (2011) 24:575–91. doi: 10.1016/j.neunet.2011.02.006
44. Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry* (2010) 23:112–9. doi: 10.1097/YCO.0b013e3283366643
45. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. *Dialogues Clin Neurosci*. (2018) 20:31–40.
46. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol*. (2018) 1. doi: 10.1038/s41569-018-0075-z
47. Bora E, Akdede BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. *Psychol Med*. (2017) 47:1030–40. doi: 10.1017/S0033291716003366
48. Mackowick KM, Barr MS, Wing VC, Rabin RA, Ouellet-Plamondon C, George TP. Neurocognitive endophenotypes in schizophrenia: modulation by nicotinic receptor systems. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 3:79–85. doi: 10.1016/j.pnpbp.2013.07.010
49. Yakir A, Rigbi A, Kanyas K, Pollak Y, Kahana G, Karni O, et al. Why do young women smoke? III Attention and impulsivity as neurocognitive predisposing factors. *Eur Neuropsychopharmacol*. (2007) 17:339–51. doi: 10.1016/j.euroneuro.2006.09.004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 20 November 2018
doi: 10.3389/fpsyt.2018.00607

Evidence of a Causal Relationship Between Smoking Tobacco and Schizophrenia Spectrum Disorders

James G. Scott[1,2,3]*, *Lori Matuschka*[1,2], *Solja Niemelä*[4,5], *Jouko Miettunen*[6,7], *Brett Emmerson*[1,3] and *Antti Mustonen*[6,7]

[1] Faculty of Medicine, The University of Queensland, Herston, QLD, Australia, [2] Queensland Centre for Mental Health Research, Wacol, QLD, Australia, [3] Metro North Mental Health, Royal Brisbane and Women's Hospital, Herston, QLD, Australia, [4] Faculty of Medicine, University of Turku, Turku, Finland, [5] Department of Psychiatry, South-Western Hospital District, Turku, Finland, [6] Center for Life Course Health Research, University of Oulu, Oulu, Finland, [7] Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

OPEN ACCESS

Edited by:
David Jonathan Castle, The University of Melbourne, Australia

Reviewed by:
Peter Bosanac, St Vincent's Hospital (Melbourne), Australia
Boris B. Quednow, University of Zurich, Switzerland

***Correspondence:**
James G. Scott
james.scott@health.qld.gov.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *07 September 2018*
Accepted: *30 October 2018*
Published: *20 November 2018*

Citation:
Scott JG, Matuschka L, Niemelä S, Miettunen J, Emmerson B and Mustonen A (2018) Evidence of a Causal Relationship Between Smoking Tobacco and Schizophrenia Spectrum Disorders. Front. Psychiatry 9:607. doi: 10.3389/fpsyt.2018.00607

There has been emerging evidence of an association between tobacco smoking and schizophrenia spectrum disorders (SSD). Two meta-analyses have reported that people who smoke tobacco have an ∼2-fold increased risk of incident schizophrenia or psychosis, even after adjusting for confounding factors. This study aimed to critically appraise the research which has examined the association between tobacco smoking and SSD against the Bradford Hill criteria for causality, to determine the strength of the evidence for a causal relationship. Eight longitudinal studies (seven cohort studies and one case control study) were identified which examined tobacco smoking as an exposure and psychosis as an outcome. All seven cohort studies were assessed as being of high quality using the Newcastle-Ottawa Scale. Six of the eight studies found a statistically significant positive association between tobacco smoking and onset of SSD. These studies reported a consistent association with a moderate to large effect size and a dose response relationship. The studies adjusted for multiple potential confounders including age, sex, socioeconomic status, shared genetic risk, prodromal symptoms, and comorbid cannabis and other substance use. The studies did not adjust for exposure to childhood trauma or prenatal tobacco. There was substantial though inconclusive evidence supporting a causal relationship between tobacco smoking and increased risk of SSD. If a causal relationship does exist, nicotine is most likely responsible for this association. This raises serious public health concerns about the increasing use of e-cigarettes and other products, particularly by adolescents whose nicotine use may increase their risk of SSD. Research is urgently needed to examine the association between e-cigarette use and incident psychosis, particularly in adolescents and young adults.

Keywords: schizophrenia, psychosis, nicotine, smoking, causal, association, e-cigarette

INTRODUCTION

Schizophrenia spectrum disorders (SSD) are heterogeneous syndromes with well-established risk factors including exposure to childhood adversity, cannabis use during adolescence, a history of obstetric complications, stressful events during adulthood, and low maternal serum folate level (1). In recent years, there has been a growing interest in tobacco smoking as a risk factor for SSD (2, 3).

Tobacco smoking is known to cause a wide range of physical health problems. It is the leading cause of preventable death, through increasing the risk of lung and other malignancies, chronic obstructive pulmonary disease (COPD), coronary heart disease, cerebrovascular disease, asthma and diabetes (4). Two systematic reviews and meta-analyses have examined the association between tobacco smoking and psychotic disorders (2, 3). In pooling longitudinal studies ($n = 5$), Gurillo and colleagues reported a 2-fold increase in the risk of incident psychotic disorders in people who were daily tobacco smokers compared to those who were not (RR = 2.18; 95% CI 1.23–3.85). Similarly, Hunter et al. (3) who pooled data from studies identified using inclusion criteria with the outcome restricted to schizophrenia ($N = 5$) also reported smoking tobacco was associated with a 2-fold risk of schizophrenia (RR = 1.99; 95% CI 1.10–3.61). Both studies concluded that further research was needed to examine the potential causal role of tobacco smoking in the onset of SSD.

The association between tobacco smoking and SSD is of growing significance. There is evidence that nicotine alters signaling in the dopaminergic, cholinergic, and glutamatergic neurotransmitter systems, particularly in adolescence (5). Whilst the smoking of tobacco by young people has declined in many high income countries, there has been an increase in exposure to nicotine by this demographic through the availability of e-cigarettes (6). It is therefore important to critically examine the evidence for a causal relationship between tobacco smoking and SSD.

In this review we aimed to evaluate the relationship between tobacco smoking and SSD which we defined as any non-affective psychotic disorder against causal criteria based on the Bradford Hill Framework (7, 8). The Bradford Hill Framework provides nine criteria for establishing a causal relationship between an exposure and outcome. This review examined longitudinal studies identified from the two recent systematic reviews of tobacco smoking and incident SSD and other identified studies. The evidence for a causal relationship between tobacco smoking and SSD, alternative explanations for the association and the health implications are discussed.

METHODS

Literature Search

We used the results of the two recently conducted systematic reviews (2, 3) to identify studies which examined tobacco smoking as an exposure and SSD as an outcome. As the review by Hunter et al. (3) restricted the outcome to a diagnosis of schizophrenia, we used the broader search strategy of Gurillo et al. (2) to identify studies from January 2014 to May 2018 that included the broader outcome of psychosis. These psychosis outcomes included schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, non-affective psychotic disorder, atypical psychosis, psychotic depression, and bipolar mania with psychotic features.

The inclusion criteria of the current review were: (a) longitudinal case control or cohort studies; (b) study populations of participants with psychosis or schizophrenia as the outcome (defined as those who meet the diagnostic criteria by structured interview or diagnosed by treating clinician); (c) presence of tobacco smoking prior to psychosis or schizophrenia diagnosis. Studies which were cross sectional in design or only provided sub-diagnostic outcomes of psychosis (e.g., psychotic symptoms, hallucinations, delusions) were excluded.

Data Extraction

Titles and abstracts of the articles were reviewed to identify studies that met the eligibility criteria. The following characteristics were extracted from each study when available: (a) study methodology (including author, publication year, location, study design, follow-up period, sample numbers, loss to follow-up, age at baseline, tobacco smoking measures, and assessment of psychosis or schizophrenia), and (b) study findings (effect size metrics, 95% CI, and confounders adjusted for).

The quality or the studies assessing for risk of bias was evaluated using Newcastle–Ottawa Scale (NOS) (9) as shown in **Supplementary Table 1**. The NOS is a method recommended by the Cochrane Non-randomized Studies Methods Working Group to evaluate the quality of the study. Points are assigned based on the selection process of cohorts (0–4 points), the comparability of the cohorts (0–2 points) and the identification of the exposures and the outcomes of research participants (0–3 points). A score of 7 or greater out of 9 was defined as high quality. Studies were assessed independently by two reviewers (LM and JS).

Assessment of Causality

Studies that met inclusion and exclusion criteria were assessed using causal criteria based on the Bradford Hill Framework shown in **Supplementary Table 2**. Of the nine criteria, five were chosen as most relevant for the purposes of this study (strength of association, consistency, temporality, dose-response, and biological plausibility). Given that smoking is known to cause a wide range of health problems, the criteria of specificity was not applicable. No studies have performed experimental manipulation exposing adolescents to tobacco because of the known harmful effects therefore this criteria was not included. Coherence was not included because of the lack of homogenous pathology evident in psychosis. In relation to analogy, the association between cannabis use and psychosis, reported to be causal (1) has some analogy to that of tobacco and psychosis. However, it is widely recognized that adolescents who smoke tobacco are more likely to smoke cannabis (10–12). Thus, cannabis rather than being analogous to tobacco in its relationship with psychosis may in fact be an important confounder. Similarly there are other important environmental

TABLE 1 | Assessment of study quality using the Newcastle Ottowa Scale*.

Criteria	Kendler et al. (13)	Mustonen et al. (21)	McGrath et al. (19)	Sørensen et al. (15)	Weiser et al. (14)	Wium-Andersen et al. (18)	Zammit et al. (16)
Representativeness of exposed cohort	+	+	+	+	+	+	+
Selection of non-exposed cohort	+	+	+	+	+	+	+
Ascertainment of exposure	+	–	–	+	–	–	–
Demonstration that outcome of interest was not present at start of study	+	+	+	+	+	+	+
Comparability of cohorts on basis of design and analysis	++	++	++	+	+	+	++
Ascertainment of outcome	+	+	+	+	+	+	+
Follow-up adequate for outcome to occur	+	+	+	+	+	+	+
Adequacy of follow-up of cohorts	–	–	–	–	+	+	–
Total Score	8/9	7/9	7/9	7/9	7/9	7/9	7/9

*A score of 7/9 or greater represents a high-quality study.

factors which might confound the relationship between tobacco smoking and incident psychotic disorder. To address this concern, for the purpose of assessing evidence of causality, we included an extra criteria "accounted for confounding." These six criteria were deemed appropriate by the research team in order to grade the associations reported between adolescent tobacco smoking and future risk of SSD as a basis for causality discussion (7).

RESULTS

Gurillo and colleagues (2) identified four studies which met the specified inclusion criteria (13–16). One of the longitudinal studies (17) which they included in their pooled analysis did not determine the presence of tobacco smoking before the schizophrenia diagnosis and was therefore excluded. Hunter et al. (3) included another study (18) and the updated search identified a further three studies which met inclusion criteria (13, 19–21). In total, eight studies (seven cohort and one case-control studies) were included for assessment of a causal relationship between tobacco smoking in adolescence and incident SSD. Using the NOS, all seven cohort studies scored 7/9 or greater demonstrating they were of high quality (**Table 1**).

Study Characteristics

Table 2 summarizes the study characteristics. They utilized birth cohort studies of offspring (19, 21) or mothers (15), cohorts of young male conscripts from defense forces (14, 16), two cohorts combined, the first consisting of mothers recruited from a birth cohort, the second were male conscripts Kendler et al. (13) and two general population cohorts to assess cardiovascular risk factors (18). The longitudinal case control study was of participants at clinical high risk of psychosis (20). All studies were from high income countries. The follow-up period of all cohort studies was adequate to ascertain incident cases of SSD, ranging from a minimum of 4 years (14) to a maximum of 48 years (15). Two of the studies were genetically informed with one examining psychosis risk in family members discordant for smoking (13), the other examining schizophrenia in people with different alleles of the rs1051730 genotype in the nicotinic acetylcholine receptor gene stratified by smoking status (18).

Assessment of Studies Against Bradford Hill Criteria

Using causal criteria, based on the Bradford Hill Framework Hill (8), of the eight studies examined, six reported a positive association between tobacco smoking and risk of schizophrenia spectrum disorder. The strength of the associations were robust ranging from an almost 50% increased risk (15) to a 6-fold increased risk of schizophrenia in heavy smokers (18). In these six studies, all reported a temporal association with appropriate adjustment for confounding variables, particularly comorbid substance use. All but one (19) demonstrated a dose response relationship between tobacco use and SSD. By contrast, one study (16) reported that smoking tobacco reduced the risk of schizophrenia and the case control study (20) found no association.

DISCUSSION

Two meta-analyses have demonstrated that smoking tobacco is associated with a 2-fold increase in risk of incident schizophrenia (3) or broader psychosis (2). Based on these systematic reviews and our own literature search, we identified eight studies that examined the longitudinal association between tobacco smoking and incident SSD of which six demonstrated a positive association (13–15, 18, 19, 21), one a negative association (16) and the final study showed no association (20). Using the Bradford Hill framework, a causal association between tobacco smoking and onset of SSD is discussed on the basis of strength of association, temporality, dose-response, adjustment

TABLE 2 | Longitudinal studies examining the association between tobacco smoking and later schizophrenia and related disorders.

Reference (Country and Methodology)	Sample size (psychosis prevalence)	Diagnoses and how they were ascertained	Definition of smoking (prevalence of smoking)	Length of follow-up	Results (95% CI)	Covariates	Interpretation
Buchy et al. (20) (USA; Prospective Case-Control study)	362 Clinical High Risk participants (90 transitioned to psychosis over 2 years)	Any psychotic disorder or a rating of ≥6 on any positive symptom of Scale of Prodromal Symptoms	At least occasionally	2 years	Baseline tobacco use (frequency or severity) was not different between those participants who later transitioned to psychosis ($n = 90$) from those without transition ($n = 272$). Cannabis and alcohol use were not associated with psychosis transition.	Demographic variables, cannabis use, alcohol use, cocaine, opiates, other substances	Tobacco, alcohol and cannabis use (frequency or severity) were not associated with increased risk of transition to psychosis. The prevalence of tobacco and cannabis dependence were very low in this cohort with likely inadequate power to examine these longitudinal associations.
Kendler et al. (13) (Two Swedish Cohorts using birth and conscript registries)	1,413,849 women and 233,879 men	Schizophrenia and non-affective psychosis (ICD)	At least 1 cigarette/day (NA)	Females 18.5 years, males 7.9 years	Increased risk of subsequent schizophrenia in females who were light smokers (1–9 cigarettes/ day: HR = 2.21; 95% CI 1.90–2.56) and for heavy smokers (≥10 cigarettes/day) (HR = 3.45; 95% CI 2.95–4.03). Increased risk of subsequent schizophrenia for male light smokers (HR = 2.15; 95% CI 1.25–3.44) and for heavy smokers: HR = 3.80; 95% CI 1.19–6.60). Increased risk persisted after adjusting for covariates and was present in monozygotic twins who were discordant for smoking status.	Neighborhood and parental socioeconomic status, prior drug abuse, psychosis prodrome, family-level and community-level socioeconomic status and genetic liability to psychosis	Cigarette smoking increased the risk of schizophrenia in a dose response fashion. The association cannot be attributed to incident smoking in the prodromal phase. Accounting for genetic disposition using monozygotic twins discordant for smoking resulted in an attenuation of the association however it was still significant suggesting the relationship between smoking cigarettes and future schizophrenia risk is only partially explained by shared risk genes.
McGrath et al. (19) (Australia: Mater University of Queensland Birth Cohort (MUSP)	2,441 of whom 65 (2.6%) received a diagnosis of psychosis	Non-affective psychotic disorder based on the Composite International Diagnostic Interview	Age at first tobacco use self-reported at 21 years. Participants grouped into age of tobacco use ≤15 years (24.1%), 16–21 years (25.8%) and no use.	6 years	Early onset tobacco use was associated with non-affective psychosis after adjusting for age and sex (OR 3.1; 95% CI 1.8-5.6). After excluding those with a history of cannabis use, the association attenuated (OR 1.9; 95% CI 0.09–4.3).	Age, sex and cannabis use	Early onset tobacco use was associated with later psychosis. The loss of significance of this relationship after excluding those with a history of cannabis use may be attributed to a loss of power as the direction of the relationship (positive association) remained.
Mustonen et al. (21) (Northern Finland Birth Cohort; 1986)	6,081 of whom 110 (1.8%) developed psychosis	Any psychotic disorder (ICD) based on clinical diagnoses from hospital summaries, primary health care and specialists	At least 1 cigarette/day (12.3%)	14 years	Smoking 1–9 cigarettes/ day was not associated with psychosis. Smoking ≥ 10 cigarettes/day was associated with increased risk of psychosis (Unadjusted HR = 3.15, 95% CI 1.94–5.13; Fully adjusted HR = 2.00, 95% CI 1.13–3.54). A dose–response was reported with a positive trend test (fully adjusted OR = 1.05; 95% CI: 1.01–1.08).	Prodromal symptoms, Cannabis use, alcohol use, other substance use, parental substance abuse, parental psychosis	Smoking cigarettes was associated with an increased risk of psychosis after adjusting for a wide range of covariates. There was a dose response relationship between smoking cigarettes and future risk of psychosis.

(Continued)

TABLE 2 | Continued

Reference (Country and Methodology)	Sample size (psychosis prevalence)	Diagnoses and how they were ascertained	Definition of smoking (prevalence of smoking)	Length of follow-up	Results (95% CI)	Covariates	Interpretation
Sørensen et al. (15) (Denmark; Mothers from the Copenhagen Perinatal Cohort)	7926 of whom 309 (3.9%) developed schizophrenia spectrum disorder	Diagnosis of Schizophrenia spectrum disorder (schizoaffective disorder, schizophrenia, schizophrenia-like psychosis) in the Danish National Registry	At least 1 cigarette/day (52.1%)	46–48 years	There was an association between smoking and increased risk of subsequent schizophrenia spectrum disorder: (OR and 95% CI 1.42; 1.12–1.80). There was a linear effect of smoking (1.18; 1.07–1.30).	Age, social status, psychopharmacological treatment at baseline	Cigarette smoking in women attending antenatal care increased the risk of subsequent schizophrenia spectrum disorder in a dose response fashion.
Weiser et al. (14) (Young Male Cohort (16–17 years) from the Israel Defence Force)	14,248 of whom 44 (0.3%) were hospitalized for schizophrenia	Hospitalized with an ICD 10 diagnosis of Schizophrenia	At least 1 cigarette/day (28.4%)	4-16 years (mean = 10.2 years, SD = 3.6)	Those who smoked at least one cigarette/ day were at increased risk of schizophrenia (adjusted relative risk = 1.94, 95% CI 1.05–3.58). There was a significant linear association between number of cigarettes smoked and risk of schizophrenia where smoking increased risk of subsequent schizophrenia.	Non-psychotic psychiatric disorder, below-normal social or intellectual functioning in adolescence and socioeconomic status	Cigarette smoking in young adult males increased the risk of schizophrenia. A dose response relationship was reported.
Wium-Andersen et al. (18) (Two General Danish Population Cohorts: Copenhagen General Population Study and Copenhagen City Heart Study	63,296 (0.1% hospitalized for schizophrenia and 6% had purchased antipsychotic medication)	ICD diagnoses of Schizophrenia and purchasing of antipsychotic medication obtained from the national Danish Patient Registry.	Ever smoked (63%), Cigarettes/ day and pack-years calculated from a self-report questionnaire.	3–21 years	Compared with never-smokers, participants smoking >20 cigarettes/day had an increased risk of schizophrenia (adjusted OR and 95% CI 6.18; 2.77–13.8).	Alcohol use, weekly physical activity, level of education after lower secondary school, basic vocational training, level of income, civil status, plasma levels of C-Reactive Protein and comorbid physical illness	Smoking tobacco was associated with higher risk of schizophrenia and antipsychotic medication use. The rs1051730 genotype in the nicotinic acetylcholine receptor gene was associated with psychosis outcomes in the ever smokers but not the never smokers suggesting a causal relationship between cigarettes and psychosis outcomes.
Zammit et al. (16) (Cohort of males conscripted into the Swedish army between 1969 and 1970)	50,053 of whom 363 (0.7%) were diagnosed with schizophrenia	ICD Diagnoses of schizophrenia and other psychoses extracted from the Swedish National Register of Inpatient Care	At least 1 cigarette/day (59%)	27 years	There was no association between any daily smoking and subsequent schizophrenia (adjusted Hazard Ratio (aHR) 0.8, 95% CI 0.7–1.1). Those who smoked ≥ 20 cigarettes/ day were less likely to develop schizophrenia (aHR 0.5; 95% CI 0.3–0.9) and there was a significant linear trend where smoking decreased the risk of subsequent schizophrenia (aHR 0.8; 95% CI 0.7–0.9).	Cannabis and drug use, poor social integration, disturbed behavior, IQ, place of upbringing, family economy, and family psychiatric history	After adjusting for potential confounders, there was a decrease in the risk of schizophrenia in people who smoked cigarettes. There was a dose response reduction with those who smoked the most cigarettes having the lowest risk of schizophrenia.

TABLE 3 | Assessment of studies against Bradford Hill criteria.

References	Strength of Association	Temporality	Dose-response	Confounding
Buchy et al. (20)	No Association	Not examined	Not examined	Limited adjustment
Kendler et al. (13)	Smoking cigarettes was associated with a twofold (light smokers) to threefold (heavy smokers) increase in risk of schizophrenia	Yes, longitudinal cohort study.	Yes	Adequately adjusted
McGrath et al. (19)	Smoking cigarettes before age of 15 was associated with a threefold risk of psychosis	Yes, longitudinal cohort study.	Not examined	Adequately adjusted
Mustonen et al. (21)	Smoking ≥10 cigarettes/day was associated with an almost threefold increased risk of psychosis	Yes, longitudinal cohort study.	Yes	Adequately adjusted
Sørensen et al. (15)	Smokers had a 42% increase in risk of incident schizophrenia spectrum disorder	Yes, longitudinal cohort study.	Yes	Adequately adjusted
Weiser et al. (14)	Smoking cigarettes had a twofold risk in incident schizophrenia	Yes, longitudinal cohort study.	Yes	Adequately adjusted
Wium-Andersen et al. (18)	Smoking ≥20 cigarettes/day had a six fold risk of developing schizophrenia	Yes, longitudinal cohort study.	Yes	Adequately adjusted
Zammit et al. (16)	Smoking ≥20 cigarettes/day had a 50% reduction in risk of developing schizophrenia	Yes, longitudinal cohort study.	There was a significant linear trend where smoking decreased the risk of subsequent schizophrenia.	Adequately adjusted

Green, supportive of causal association; Yellow, not examined or not applicable; Red, no association or negative association.

for confounding factors, biological plausibility, and consistency of the association.

Strength

Of the six studies that found a positive association (13–15, 18, 19, 21), five reported moderate to large effect sizes (22) (**Tables 2**, **3**) consistent with a causal relationship (8). Sørensen et al. (15) reported a smaller effect size with a 42% increase in the odds of schizophrenia spectrum disorder in people who smoked cigarettes.

Consistency

Consistency of the association is assessed through multiple studies of independent cohorts confirming the same result. In the eight longitudinal studies, six reported a positive association between tobacco smoking and incident SSD. Of the two which did not report a positive association, one was a case-control study of participants at clinical high risk for psychosis which found that neither tobacco nor cannabis smoking were associated with transition to psychosis. The prevalence of tobacco and cannabis dependence in this cohort was low and the study may have been underpowered to examine the effects of these substances on transition to psychosis. Zammit et al. (16) reported that smoking tobacco was associated with a lower risk of future schizophrenia, and was therefore inconsistent with the main body of research. The overwhelming majority of studies showed a positive relationship fulfilling criteria for consistency.

Temporality

The six studies that reported a positive association demonstrated a clear temporal relationship with the exposure of tobacco smoking preceding the onset of SSD. Schizophrenia spectrum disorders frequently have an insidious onset with a long prodrome. In order to address this concern, (21), adjusted for prodromal psychotic symptoms at baseline and Kendler et al. (13) accounted for the possible prodrome by conducting a subanalysis restricting the onset of SSD to at least 5 years following initial exposure to tobacco. The relationship between tobacco smoking and onset of schizophrenia was largely attenuated after accounting for the prodrome rendering reverse causality an unlikely explanation for the association between tobacco use and SSD thus suggesting tobacco smoking precedes the illness.

Dose-Response

A dose response between tobacco smoking and incident SSD was reported in five of the six studies reporting a positive association. In three studies (14, 15, 21) a significant linear trend was demonstrated where the risk of SSD increased with the an increase in tobacco smoking. In two studies (13, 18), those who smoked more daily tobacco had an increase in the odds of developing SSD.

Potential Confounders

The relationship between tobacco use and SSD remained significant even after adjusting for factors that might confound

the relationship including family socio-economic status, cannabis use (1), parental substance abuse and parental psychosis (23–27). A shared genetic liability was also accounted for in two genetically informed studies (13, 18). Adjustment for confounders attenuated the strength of the association but significance was maintained in all but one study (19), probably due to a lack of power for the analysis. None of the studies adjusted for childhood trauma (28).

Biological Plausibility

Tobacco and tobacco smoke contain almost 5,000 different chemicals. Nicotine is the most important pharmacologically active and psychotogenic compound in tobacco smoke because of its interaction with nicotinic acetylcholine receptors (29). Previous reports on tobacco smoking suggests that nicotine could alter signaling of dopaminergic, cholinergic, and glutamatergic neurotransmitter systems (5, 30) and thus could potentially influence brain development as suggested by studies of adolescent nicotine exposure and neurodevelopmental trajectories (5). Also, excess nicotine intake during early adolescence is associated with abnormal white matter maturation in adults (31), and chronic cigarette smoking has been linked to structural brain changes such as gray matter decreases in the prefrontal cortex, which correspond with areas where functional alterations occur from nicotine exposure (32).

Furthermore, recent evidence suggest that adolescent nicotine use could have persistent effects on nicotine receptor responsiveness, which results in the strengthening of negative emotional changes and alterations in cognitive functioning (5).

Alternative Explanations

There are other explanations for the positive association between tobacco smoking and SSD. Individuals who develop schizophrenia are more likely to have externalizing symptoms in childhood and adolescence (33, 34) and children with externalizing symptoms are more likely to smoke tobacco during adolescence (35). There may be unmeasured confounding. None of the studies adjusted for childhood trauma, a well-established risk factor for SSD (1, 28) and for tobacco use (36). Similarly there was no adjustment for prenatal tobacco smoking exposure which is associated with both an increased risk of smoking in adolescence (37) and an increased risk of schizophrenia even after adjusting for life time smoking (3, 38). Furthermore, recent studies have suggested bidirectional associations by revealing single nucleotide polymorphisms associated with nicotine dependence (CHRNA5) that are also associated with schizophrenia (39, 40).

LIMITATIONS

Each study included in this review is observational in methodology, and the majority of cohort studies included had significant attrition. Participants who are most likely to be lost to follow up are more likely to be socioeconomically disadvantaged and be at increased risk of both tobacco smoking and mental illness. Therefore, it is unlikely that attrition would significantly affect reported associations. Measurement of tobacco smoking has been measured via self-report or by interview, generally at one point in time and often retrospectively recalled. Only one study measured the long-term smoking exposure prior the psychotic illness using pack-years (18) which provides a more precise measurement of tobacco smoke exposure. Further, no studies have used biological markers for tobacco smoking such as expired air carbon monoxide (41) or serum cotinine measurement (42). These limitations are inherent to large cohort and registry studies and are difficult to overcome. Finally, as two recent systematic reviews had been published on this topic, we relied on these to identify the studies included in this review rather than replicating the searches in these studies.

Implications

Given tobacco is known to have widespread adverse health outcomes and governments around the world are adopting policies to reduce tobacco smoking, why is it important to clarify if smoking tobacco has a causal role in the onset of SSD? The first reason is that better understanding the aetiopathogenesis of SSD will inform our knowledge of this syndrome which may lead to better treatments. The second, a much more urgent consideration is the growing availability of electronic (e) cigarettes. These have been developed as a safer alternative to cigarettes by enabling nicotine use without the exposure to carcinogenic chemicals associated with smoking tobacco.

However, there is growing use of e-cigarettes and other nicotine products by adolescents (6) and it is acknowledged that the health effects of e-cigarettes on youth are not fully understood (43). In addition to tobacco and cannabis, there is now evidence that adolescents who use inhalants are at increased risk of psychotic disorders (44) suggesting that adolescence is the developmental period where adverse neuropsychiatric outcomes from psychoactive substances are most likely to occur. There is substantial though not conclusive evidence that the association between tobacco smoking and SSD is causal and may well be a result of the effects of nicotine on multiple neurotransmitter systems. Therefore, policy makers must be cautious when developing regulations for the availability of e-cigarettes, nicotine replacement therapy products and smokeless tobacco. Similarly, health practitioners who recommend e-cigarettes or smokeless tobacco products as a safe alternative to smoking need to consider the findings of the studies identified in this review, especially when providing advice to adolescents.

It is essential that future well designed observational studies are undertaken examining the risk of SSDs in those who use e-cigarettes, particularly in adolescence. A major challenge is the low prevalence of SSD. Recruiting samples large enough to examine the association between e-cigarettes and SSD will take many years. Previous longitudinal research has shown positive associations between cannabis, tobacco and alcohol use and psychotic experiences (PE) which are proxy markers for psychosis risk. PE have the advantage of being higher in prevalence compared to SSD thereby reducing the required sample size to identify associations. Schizophrenia endophenotypes may also have a role to inform the association between nicotine exposure through e-cigarettes and risk of SSD. Previous research has shown that smoking tobacco modulates

the association between polymorphisms of transcription factor 4 and reduced sensory gating, an endophenotype of schizophrenia suggesting that the smoking of tobacco might play a role in early information processing deficits in schizophrenia (45). Use of research paradigms such as PE and endophenotypes PE would expedite research into the association between e-cigarette use and SSD risk. Further research is urgently needed to determine if nicotine is causally associated with incident SSD. In the interim, it is important that policy makers consider the available evidence between tobacco smoking and risk of schizophrenia when evaluating the potential health consequences that might arise from community access to e-cigarettes.

AUTHOR CONTRIBUTIONS

JS and AM planned the review. LM conducted the initial literature search and JS and LM assessed papers for suitability for inclusion. JS and LM reviewed all the papers and assessed them for quality. JS, LM, and AM wrote the first draft of the manuscript and all authors contributed to further drafts. All authors reviewed and approved the final draft.

FUNDING

JS is supported by a National Health and Medical Research Council Practitioner Fellowship Grant APP1105807 and employed by The Queensland Centre for Mental Health Research which receives core funding from the Queensland Health. AM is supported by Juho Vainio Foundation, Scholarship Fund of the University of Oulu, Oulun Lääketieteellinen tutkimussäätiö and The Hospital District of South Ostrobothnia, Finland. JM is supported by Academy of Finland (#268336).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00607/full#supplementary-material

REFERENCES

1. Belbasis L, Köhler CA, Stefanis N, Stubbs B, Os Jv, Vieta E, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses. *Acta Psychiatr Scand.* (2018) 137:88–97. doi: 10.1111/acps.12847
2. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* (2015) 2:718–25. doi: 10.1016/S2215-0366(15)00152-2
3. Hunter A, Murray R, Asher L, Leonardi-Bee J. The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of schizophrenia: a systematic review and meta-analysis. *Nicotine Tob Res.* (2018). doi: 10.1093/ntr/nty160. [Epub ahead of print].
4. Collaborators GT. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* (2017) 389:1885–906. doi: 10.1016/s0140-6736(17)30819-x
5. Smith RF, McDonald CG, Bergstrom HC, Ehlinger DG, Brielmaier JM. Adolescent nicotine induces persisting changes in development of neural connectivity. *Neurosci Biobehav Rev* (2015) 55:432–43. doi: 10.1016/j.neubiorev.2015.05.019
6. Perikleous EP, Steiropoulos P, Paraskakis E, Constantinidis TC, Nena E. E-cigarette use among adolescents: an overview of the literature and future perspectives. *Front Public Health* (2018) 6:86. doi: 10.3389/fpubh.2018.00086
7. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the bradford hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol.* (2015) 12:14. doi: 10.1186/s12982-015-0037-4
8. Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* (1965) 58:295–300.
9. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa: The Ottawa Hospital (2018).
10. Hindocha C, Shaban NDC, Freeman TP, Das RK, Gale G, Schafer G, et al. Associations between cigarette smoking and cannabis dependence: a longitudinal study of young cannabis users in the United Kingdom. *Drug Alcohol Depend.* (2015) 148:165–71. doi: 10.1016/j.drugalcdep.2015.01.004
11. Badiani A, Boden JM, De Pirro S, Fergusson DM, Horwood LJ, Harold GT. Tobacco smoking and cannabis use in a longitudinal birth cohort: evidence of reciprocal causal relationships. *Drug Alcohol Depend.* (2015) 150:69–76. doi: 10.1016/j.drugalcdep.2015.02.015
12. Weinberger AH, Platt J, Copeland J, Goodwin RD. Is cannabis use associated with increased risk of cigarette smoking initiation, persistence, and relapse? longitudinal data from a representative sample of US adults. *J Clin Psychiatry* (2018) 79:17m11522. doi: 10.4088/JCP.17m11522
13. Kendler KS, Lönn SL, Sundquist J, Sundquist K. Smoking and schizophrenia in population cohorts of swedish women and men: a prospective co-relative control study. *Am J Psychiatry* (2015) 172:1092–100. doi: 10.1176/appi.ajp.2015.15010126
14. Weiser M, Reichenberg A, Grotto I, Yasvitzky R, Rabinowitz J, Lubin G, et al. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. *Am J Psychiatry* (2004) 161:1219–23. doi: 10.1176/appi.ajp.161.7.1219
15. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA. A prospective study of smoking in young women and risk of later psychiatric hospitalization. *Nordic J Psychiatry* (2011) 65:3–8. doi: 10.3109/08039481003786386
16. Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingsson T, Lewis G. Investigating the association between cigarette smoking and schizophrenia in a cohort study. *Am J Psychiatry* (2003) 160:2216–21. doi: 10.1176/appi.ajp.160.12.2216
17. Riala K, Hakko H, Isohanni M, Pouta A, Räsänen P. Is initiation of smoking associated with the prodromal phase of schizophrenia? *J Psychiatry Neurosci.* (2005) 30:26–32.
18. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Tobacco smoking is causally associated with antipsychotic medication use and schizophrenia, but not with antidepressant medication use or depression. *Int J Epidemiol.* (2015) 44:566–77. doi: 10.1093/ije/dyv090
19. McGrath JJ, Alati R, Clavarino A, Williams GM, Bor W, Najman JM, et al. Age at first tobacco use and risk of subsequent psychosis-related outcomes: a birth cohort study. *Aust N Z J Psychiatry* (2016) 50:577–83. doi: 10.1177/0004867415587341
20. Buchy L, Cadenhead KS, Cannon TD, Cornblatt BA, McGlashan TH, Perkins DO, et al. Substance use in individuals at clinical high risk of psychosis. *Psychol Med.* (2015) 45:2275–84. doi: 10.1017/S0033291715000227
21. Mustonen A, Ahokas T, Nordström T, Murray GK, Mäki P, Jääskeläinen E, et al. Smokin' hot: adolescent smoking and the risk of psychosis. *Acta Psychiatr Scand.* (2018) 138:5–14. doi: 10.1111/acps.12863
22. Rosenthal JA. Qualitative descriptors of strength of association and effect size. *J Soc Serv Res.* (1996) 21:37–59. doi: 10.1300/J079v21n04_02
23. McAdams TA, Neiderhiser JM, Rijsdijk FV, Narusyte J, Lichtenstein P, Eley TC. Accounting for genetic and environmental confounds in associations between

parent and child characteristics: a systematic review of children-of-twins studies. *Psychol Bull.* (2014) 140:1138–73. doi: 10.1037/a0036416
24. Niemi-Pynttäri JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. *J Clin Psychiatry* (2013) 74:e94–9. doi: 10.4088/JCP.12m07822
25. Patrick ME, Wightman P, Schoeni RF, Schulenberg JE. Socioeconomic status and substance use among young adults: a comparison across constructs and drugs. *J Stud Alcohol Drugs* (2012) 73:772–82. doi: 10.15288/jsad.2012.73.772
26. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot - a review of the association between cannabis and psychosis. *Front Psychiatry* (2014) 5:54. doi: 10.3389/fpsyt.2014.00054
27. Starzer MSK, Nordentoft M, Hjorthøj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. *Am J Psychiatry* (2018) 175:343–50. doi: 10.1176/appi.ajp.2017.17020223
28. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull.* (2012) 38:661–71. doi: 10.1093/schbul/sbs050
29. Thielen A, Klus H, Müller L. Tobacco smoke: unraveling a controversial subject. *Exp Toxicol Pathol.* (2008) 60:141–56. doi: 10.1016/j.etp.2008.01.014
30. Davis J, Eyre H, Jacka FN, Dodd S, Dean O, McEwen S, et al. A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. *Neurosci Biobehav Rev.* (2016) 65:185–94. doi: 10.1016/j.neubiorev.2016.03.017
31. Gogliettino AR, Potenza MN, Yip SW. White matter development and tobacco smoking in young adults: a systematic review with recommendations for future research. *Drug Alcohol Depend.* (2016) 162:26–33. doi: 10.1016/j.drugalcdep.2016.02.015
32. Sutherland MT, Riedel MC, Flannery JS, Yanes JA, Fox PT, Stein EA, et al. Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotinic drug-induced functional modulations. *Behav Brain Funct.* (2016) 12:16. doi: 10.1186/s12993-016-0100-5
33. Scott J, Martin G, Welham J, Bor W, Najman J, O'Callaghan M, et al. Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: a 21-year birth cohort study. *Am J Psychiatry* (2009) 166:567–74. doi: 10.1176/appi.ajp.2008.08081182
34. Matheson SL, Shepherd AM, Laurens KR, Carr VJ. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. *Schizophr Rese.* (2011) 133:133–42. doi: 10.1016/j.schres.2011.09.020
35. Miettunen J, Murray GK, Jones PB, Maki P, Ebeling H, Taanila A, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychol Med.* (2014) 44:1727–38. doi: 10.1017/S0033291713002328
36. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Med.* (2012) 9:e1001349. doi: 10.1371/journal.pmed.1001349
37. Niemela S, Raisanen A, Koskela J, Taanila A, Miettunen J, Ramsay H, et al. The effect of prenatal smoking exposure on daily smoking among teenage offspring. *Addiction* (2017) 112:134–43. doi: 10.1111/add.13533
38. Niemela S, Sourander A, Surcel HM, Hinkka-Yli-Salomaki S, McKeague IW, Cheslack-Postava K, et al. Prenatal nicotine exposure and risk of schizophrenia among offspring in a national birth cohort. *Am J Psychiatry* (2016) 173:799–806. doi: 10.1176/appi.ajp.2016.15060800
39. Chen J, Bacanu SA, Yu H, Zhao Z, Jia P, Kendler KS, et al. Genetic relationship between schizophrenia and nicotine dependence. *Sci Rep.* (2016). 6:25671. doi: 10.1038/srep25671.
40. Hartz SM, Horton AC, Hancock DB, Baker TB, Caporaso NE, Chen LS, et al. Genetic correlation between smoking behaviors and schizophrenia. *Schizophr Res.* (2018) 194:86–90. doi: 10.1016/j.schres.2017.02.022
41. Jarvis MJ, Russell MA, Saloojee Y. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *Br Med J.* (1980) 281:484–5.
42. Vartiainen E, Seppala T, Lillsunde P, Puska P. Validation of self reported smoking by serum cotinine measurement in a community-based study. *J Epidemiol Commun Health* (2002) 56:167–70. doi: 10.1136/jech.56.3.167
43. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. *Public Health Consequences of E-Cigarettes.* In: Eaton DL, Kwan LY, Stratton K, editors. Washington, DC: National Academies Press (US) (2018).
44. Mustonen A, Niemela S, McGrath JJ, Murray GK, Nordstrom T, Maki P, et al. Adolescent inhalant use and psychosis risk-a prospective longitudinal study. *Schizophr Res.* (2018). doi: 10.1016/j.schres.2018.05.013. [Epub ahead of print].
45. Quednow BB, Brinkmeyer J, Mobascher A, Nothnagel M, Musso F, Grunder G, et al. Schizophrenia risk polymorphisms in the TCF4 gene interact with smoking in the modulation of auditory sensory gating. *Proc Natl Acad Sci USA.* (2012) 109:6271–6. doi: 10.1073/pnas.1118051109

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 06 November 2018
doi: 10.3389/fpsyt.2018.00565

A Systematic Review of Psychosocial Barriers and Facilitators to Smoking Cessation in People Living With Schizophrenia

Alistair Lum, Eliza Skelton, Olivia Wynne and Billie Bonevski*

School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia

Background: People living with schizophrenia are less likely to quit smoking compared with the general population and people living with other psychiatric disorders. Understanding the schizophrenia-specific psychosocial barriers and facilitators to smoking cessation is important for designing effective smoking cessation interventions. We aimed to systematically review research examining psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia.

Methods: We followed the PRISMA statement to conduct a systematic literature review examining psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. We searched EMBASE, Medline, PsycINFO, and CINAHL databases from inception to 14 June 2018 to identify relevant articles. We included peer-reviewed original research articles that examined psychosocial barriers and facilitators to smoking cessation, as well as factors associated with maintenance of smoking habits in people living with schizophrenia spectrum disorders. Qualitative, quantitative, or mixed-methods study designs were included. Three authors screened titles, abstracts, and full-texts using the eligibility criteria. We conducted a narrative synthesis of the data to account for the heterogeneity of study designs. We analyzed qualitative and quantitative studies separately.

Results: We identified 685 studies from our systematic search and screened the full-text of 134 articles. The final set of 23 articles included 20 quantitative studies and 3 qualitative studies. The most commonly cited barrier to smoking cessation in people living with schizophrenia was cravings and addiction, followed by a perceived increased risk of negative affect associated with quitting smoking. People living with schizophrenia reported smoking to manage stress and to maintain social relationships. People living with schizophrenia were found to be less likely to receive cessation support from health professionals than smokers without schizophrenia. Health concerns were the most commonly mentioned facilitator to quit smoking.

Conclusions: People living with schizophrenia experience a wide range of barriers to smoking cessation. The influence of these barriers on smoking cessation likelihood

OPEN ACCESS

Edited by:
Błazej Misiak,
Wroclaw Medical University, Poland

Reviewed by:
Marina Šagud,
University of Zagreb, Croatia
Letitia Travaglini,
United States Department of Veterans Affairs, United States

****Correspondence:***
Alistair Lum
alistair.lum@newcastle.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *07 August 2018*
Accepted: *18 October 2018*
Published: *06 November 2018*

Citation:
Lum A, Skelton E, Wynne O and Bonevski B (2018) A Systematic Review of Psychosocial Barriers and Facilitators to Smoking Cessation in People Living With Schizophrenia. Front. Psychiatry 9:565. doi: 10.3389/fpsyt.2018.00565

may be greater among people living with schizophrenia than people without psychiatric disorders. Health professionals play an important role in smoking cessation for people living with schizophrenia and should consider barriers and facilitators identified in this review to support quitting in this vulnerable population.

Keywords: systematic review, barriers, facilitators, smoking cessation, schizophrenia, psychosocial

INTRODUCTION

Approximately 65% of people living with schizophrenia smoke cigarettes (1, 2). People living with schizophrenia are significantly less likely to quit smoking compared with the general population and those living with other psychiatric disorders, such as bipolar disorder and depression (1). Given the elevated prevalence of tobacco smoking and low cessation rates, people living with schizophrenia are at higher risk of developing smoking-related malignancies, cardiovascular disease, and respiratory disease and are more likely to experience premature mortality than the general population (3). Improving smoking cessation rates in people living with schizophrenia will be integral to improving the health of this vulnerable population. Clinical Practice Guidelines for the treatment of tobacco smoking suggest clinicians provide a dual approach consisting of both pharmacological (e.g., bupropion, varenicline, and nicotine replacement therapy [NRT]) and psychosocial (e.g., cognitive behavioral therapy [CBT], motivational interviewing [MI], information and education interventions, and social support) strategies for people living with schizophrenia (4–6).

Research examining the pharmacological treatments for tobacco smoking among people living with schizophrenia exceeds the quantity of corresponding psychosocial research, potentially limiting the depth and breadth of smoking cessation advice that clinicians can provide. Pharmacological interventions appear to be effective with few safety concerns. A meta-analysis of five trials comparing bupropion or bupropion and NRT with placebos or placebos with NRT found that participants in the bupropion group were almost three times more likely to abstain from smoking at 6 month follow-up compared with those in the placebo group (7). Two trials that compared varenicline with placebo found almost five times greater smoking cessation rates in the varenicline group at end of treatment (7). Pharmacological smoking cessation interventions appear to be appropriate for people living with schizophrenia, however the percentage of successful quitters is reportedly small, between 12 and 19% (7).

In line with clinical guidelines, many randomized clinical trials of pharmacological interventions were delivered alongside psychosocial strategies for treatment of tobacco smoking (7). Yet, few trials assessed the benefits associated with psychosocial strategies in these combined interventions. The limited number of combined trials have shown limited long-term effect. One such trial compared a smoking cessation program founded on CBT and MI principles plus NRT with usual care plus NRT, and found higher smoking reduction rates in the intervention group at 3 months, but no differences in smoking abstinence or reduction rates beyond 6 months (8). Contingency reinforcement using money with or without NRT or bupropion have been associated with higher smoking abstinence compared with a minimal intervention group (9) and smoking reduction rates compared with a pharmacotherapy only group (10), however long-term effects were not reported.

Very few randomized controlled trials of psychosocial interventions for smoking cessation or reduction in people living with schizophrenia have been conducted (11–14). Psychosocial programs for smoking cessation in people living with schizophrenia have used a variety of approaches, including psychoeducation, MI, CBT, social skills training, relapse prevention, monetary contingent reinforcement strategies, or a combination of these approaches (15). One study compared a high-intensity program incorporating MI, social skills training, NRT education, and relapse prevention with a moderate-intensity program focused on medication compliance and NRT education (13). Smoking cessation rates did not differ between groups, with 21% abstinent at 12-weeks after the target quit date, 17% at 6 month follow-up, and 14% at 12 month follow-up. A comparison of the American Lung Association (ALA) smoking cessation program with a schizophrenia-targeted program comprised of MI, psychoeducation, and relapse prevention strategies found significantly higher abstinence rates in the ALA group at 6-month follow-up (11). The 6 month smoking cessation rates of the psychosocial interventions described above range between 11 and 18% (11, 13), which are comparable to rates achieved in pharmacotherapy trials, which range between 12 and 19% (16–18).

Research examining the neurobiological factors associated with smoking maintenance among people living with schizophrenia is substantial and continues to grow (19). This research is helping inform advances in pharmacological treatment options (19). In contrast, the theory underlying psychosocial interventions for people living with schizophrenia has not been well-defined in the literature, which may limit the effectiveness of psychosocial interventions for smoking cessation for people living with schizophrenia. Ziedonis and George (20) reviewed the literature on smoking cessation and schizophrenia prior to the development and evaluation of a psychosocial intervention promoting smoking cessation in people living with schizophrenia. However, their review of neurobiological and clinical issues failed to address psychosocial factors associated with smoking cessation consistent with their psychosocial intervention. Steinberg and Williams (21) examined the necessary modifications to treatment components of smoking cessation programs to better match the needs of people living with schizophrenia. They found that people living with schizophrenia may require more intervention sessions or sessions over a longer duration, content delivery adaptations to account for neurocognitive deficits common in people living

with schizophrenia and social skills training (21). While these findings are important, this examination of intervention factors does not account for barriers of smoking cessation in people living with schizophrenia identified in the non-intervention literature.

Current reviews on barriers to smoking cessation in people living with schizophrenia have included people with other mental illnesses, such as bipolar disorder or severe depression. Common individual barriers to smoking cessation identified in these reviews include the desire to manage stress and avoid withdrawal symptoms, and the belief that smoking provides a sense of identity. Many people living with mental illness are not given cessation support from health care providers (22, 23). Smoking tobacco is often socially accepted among people living with mental illness (23, 24). Current evidence on facilitators of smoking cessation among people with schizophrenia, including perceived health, and financial benefits and social support for quitting, are also commonly experienced by people with other mental illnesses and the general population (23, 25).

Schizophrenia-specific barriers and facilitators to smoking cessation are less well-understood than those affecting people with all mental illness. One commonly mentioned reason for smoking among people with schizophrenia is the desire to manage negative symptoms (23, 24, 26). Managing negative symptoms, such as negative affect, anhedonia, and loss of motivation, can improve social and vocational functioning among people living with schizophrenia (27). While this self-medication hypothesis is recognized as a schizophrenia specific barrier to smoking cessation, continued efforts to determine other barriers and facilitators are required to ensure comprehensive support is available (28).

A stronger understanding of schizophrenia-specific barriers and facilitators to smoking cessation, such as reduction of negative symptoms, is required to help clinicians to provide optimal treatment options and intervention developers to better tailor their programs to the unique needs of people living with schizophrenia (28–31). Currently, psychosocial interventions have been developed without consideration of the full range of psychosocial barriers and facilitators. Thus, we cannot be confident that current interventions adequately address the unique psychosocial factors contributing to smoking cessation in people living with schizophrenia. Therefore, we aimed to systematically review research examining the psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. We asked two research questions:

1. What psychosocial barriers and facilitators affect smoking cessation in people living with schizophrenia?
2. Do people living with schizophrenia experience more psychosocial barriers that affect smoking cessation than people without mental illness?

METHODS

Design

We systematically reviewed original research examining psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. The PRISMA statement guided the conduct of the review (32). We used the Covidence software in screening articles (33). We registered the review with Prospero (CRD42018103332).

Search Strategy

We searched EMBASE, Medline, PsycINFO, and CINAHL databases using keywords from inception to 14 June 2018 to identify relevant articles. Our search terms were [smoking OR tobacco OR cigarette OR nicotine OR e-cig] AND [schizophrenia OR psychosis OR schizoaffective OR schizophreniform OR delusional disorder OR psychotic OR psychoses] AND [factor$ OR determinant$ OR variable$ OR covariable$ OR predictor$ OR barrier$ OR facilitator$] AND [smoking cessation OR quitting smoking OR abstinence OR withdrawal OR quit$]. $ indicated truncation.

Eligibility

We included peer-reviewed original research articles that examined psychosocial barriers and facilitators to smoking cessation, as well as factors associated with maintenance of smoking habits, in people living with schizophrenia spectrum disorders. Articles that included mixed diagnosis samples composed of 50% or more of participants with schizophrenia were included. We included participants living with schizophrenia as well as healthcare providers working with people living with schizophrenia in 50% or more of their cases. We included articles that reported outcomes relating to people who identify as smokers without a requirement that the study define the smoking status of participants. This inclusive approach was designed to increase the number of studies included in our review. We included qualitative, quantitative, and mixed-methods study designs. Cross-sectional and longitudinal quantitative study designs with or without a comparison group were eligible for this review. We chose to include studies with baseline data from intervention trials to increase the amount and quality of relevant data, yet the results must be interpreted with caution due to the potential bias associated with recruitment into an intervention trial. Articles published in gray literature or in languages other than English were excluded.

Study Selection

Two authors (AL and ES) simultaneously screened titles and abstracts using the eligibility criteria. All articles not excluded were screened using the full text by one author (AL), with two-thirds of articles screened by a second author (ES or OW). These three authors discussed any conflicts in screening.

Data Extraction

One author (AL) extracted data from all included articles using a standardized pre-piloted data extraction form. Data extracted included age, sex, study design, country of study, sample size, control group characteristics, diagnostic characteristics (e.g., recruitment site, percentage of sample which was diagnosed with schizophrenia, and criteria to assess diagnosis), smoking characteristics (i.e., number of cigarettes smoked daily, age

smoking commenced, tool to assess smoking status, and nicotine dependence), barrier and facilitators characteristics (i.e., maintenance factors relating to smoking or barriers or facilitators to smoking cessation, assessment tool to measure factors, and relationship to outcome measure) and outcome measure (i.e., type of smoking outcome and assessment tool of outcome).

Quality Appraisal

One author (AL) critically appraised the risk of bias in all articles using the QualSyst tool (34). The QualSyst tool was developed as a tool designed to measure the risk of bias in a range of studies, including randomized trials and quantitative, qualitative, and mixed methods studies. Two checklists with manuals to guide scoring are available; one for quantitative studies with 14 items and one for qualitative studies with 10 items. We report the percentage of checklist items met for all studies to improve interpretability, with higher percentages indicating lower risk of bias.

Data Analysis

We conducted a narrative synthesis of the data to account for the heterogeneity of study designs. We synthesized data on barriers and facilitators to quitting and motivators to smoke. We analyzed qualitative and quantitative studies separately. Due to the lack of theory underlying psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia, we took an inductive approach to data synthesis.

RESULTS

Search Results

We identified 685 studies from our systematic search, of which 14 were duplicates. We removed 537 of the 671 articles based on titles and abstracts that indicated the article was not relevant to our aims. We screened the full-text of the remaining 134 articles, and removed a further 111. The main reasons for excluding articles at the full-text screening stage were that the article did not examine psychosocial barriers or facilitators to smoking cessation, did not examine smoking cessation, did not present original data, or did not include a sample comprised of at least 50% of participants with schizophrenia (see **Figure 1**). The final set of articles included 23 articles, of which 20 had quantitative designs and 3 had qualitative designs.

Study Characteristics

Of the 3,557 participants in included studies, 3,257 had a diagnosis of schizophrenia (91.6%). All articles were published between 1996 and 2017. Eleven (48%) articles were published in the United States, five (22%) in Australia, three (13%) in Canada and one each in Turkey, Greece, Israel, the United Kingdom, and Scotland (4%). Of the 20 quantitative studies, 12 (60%) had cross-sectional designs, 6 (30%) examined baseline data from intervention trials, 1 (5%) was a non-randomized within-group trials, and 1 (5%) was a non-randomized controlled trial.

The quantitative articles met between 50 and 88% (median = 80%) of the QualSyst risk of bias criteria, while

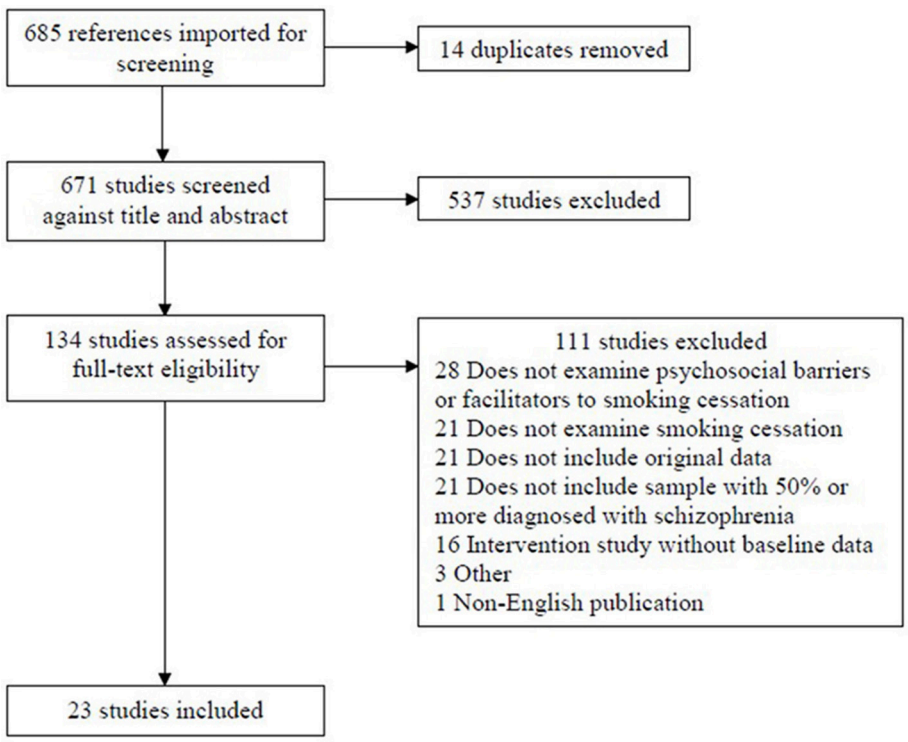

FIGURE 1 | Flow diagram of screening process and outcomes.

the qualitative articles met between 45 and 85% of the criteria (median = 85%). Seventy percent of quantitative (14/20) and 67% of qualitative (2/3) studies met 75% or more of the QualSyst criteria. These outcomes indicate that the combined data has a low risk of bias and the findings can be considered as reliable indicators of barriers and facilitators to smoking cessation in people living with schizophrenia. The majority of quantitative studies met the QualSyst criteria of reporting study objectives, sufficiently disclosing participant characteristics, recruiting an appropriate sample size, describing methods of data analysis, reporting an estimate of variance, reporting results in sufficient details, and drawing conclusions supported by the results. Outcome variables and method of participant selection were inconsistently reported with sufficient detail and study design was often not explicitly reported. The context of the study, sampling strategy, data analysis techniques, and coding biases were only partially described in at least two of the three qualitative studies. Study and participant characteristics, QualSyst scores, and a summary of key study outcomes are presented in **Table 1** for quantitative studies (see sections Cravings and Addiction, To Reduce Negative Affect, Social Facilitation, Stress Management, Concern for Health Risks, Physician Advice to Quit Smoking, Systemic Barriers, Social Pressure to Quit, and Additional Barriers and Facilitators to Smoking Cessation) and **Table 2** for qualitative studies (see section Qualitative Findings).

Cravings and Addiction

The most commonly cited barrier to smoking cessation in people living with schizophrenia was cravings and addiction (nine studies). Two quantitative studies examining concerns associated with quitting found that cravings and addiction were the highest reported risks associated with smoking cessation (35, 36). Cravings were also frequently reported as a concern related to smoking cessation in two studies (37, 38), however one study indicated that cravings were not perceived as a reason for people living with schizophrenia to smoke cigarettes (39). Perceived or actual cravings associated with smoking abstinence were significantly higher among people living with schizophrenia compared with people without mental illness in three studies (36, 40, 41), yet were similar across groups in two studies (42, 43). One of the two studies in which cravings were reportedly higher in people living with schizophrenia than people without mental illness found that cravings increased over 72 h of abstinence in people living with and without schizophrenia, with no difference in the rate of increase across groups (41). Three studies examining whether sex and age was associated with cravings found no association (40, 42, 43). Two of the three studies which found higher perceived risk of cravings in people living with schizophrenia were based on small group sizes of 18 and 28.

To Reduce Negative Affect

A perceived increased risk of negative affect associated with quitting smoking was examined in seven studies. Perceived risk of increased negative affect was higher in people living with schizophrenia compared with people without mental illness in two studies (41, 43) and equal in three studies (36, 42, 44). One study reported that 31% of people living with schizophrenia smoked to reduce symptoms of anxiety and depression (45), while another reported that reducing negative affect would be the strongest motivator to smoke during abstinence (38). Filia et al. (43) found that females reported significantly higher perceived risk of negative affect associated with quitting compared with males.

Social Facilitation

Seven studies examined the relationship between smoking cessation and social facilitation in people living with schizophrenia. One study found that people living with schizophrenia were more likely to smoke to improve social functioning than people without mental illness (42). Another study found that people with schizoaffective disorder reported that positive social effects were related to lower intention to quit; a relationship that was not identified in people living with schizophrenia or without mental illness (44). One study reported that people living with schizophrenia felt equally as likely as people without schizophrenia to be socially ostracized if they were to quit smoking (43). Non-comparison studies also indicated that smoking was an important factor contributing to social comfort. One study found social factors were considered to be the second strongest factor contributing to smoking temptations in people living with schizophrenia (38). Krishnadas et al. (45) reported that 14% of respondents reported smoking to socialize better, while Kourakos and Koukia (46) found that 83% of psychiatric inpatients with schizophrenia believed that visitors should be allowed to smoke with patients. Neither age (42) nor did sex (43) appear to be associated with perceived social facilitation as a motivator to smoke.

Stress Management

Five studies reported on the impact of smoking on stress reduction in relation to smoking cessation. One study reported that people living with schizophrenia were significantly more likely to smoke to reduce stress compared with people from the general population (40). A second study found no differences in ratings of stress as a concern related to quitting smoking between people living with schizophrenia and people without mental illness (36). However, the small group size of people living with schizophrenia may have reduced the likelihood of identifying true group differences (i.e., Type 2 error). Two other studies identified stress reduction as the main reason for smoking (35, 37), while another found that 60% of people living with schizophrenia smoke to relax (45). Two studies found that sex and age were not associated with stress management as a motivator to smoke (40, 42).

Concern for Health Risks

We identified eight studies examining perceptions of health risks as facilitators to smoking cessation in people living with schizophrenia. In four of these studies, people living with schizophrenia reported perceptions that the health benefits associated with quitting smoking were equal to perceptions of people without mental illness (36, 40, 43, 44). One included study reported that concern for health was the highest rated

TABLE 1 | Quantitative study characteristics and key findings.

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Baker; 2007; Australia	To describe demographic and clinical characteristics, smoking behaviors, stage of change, and reasons for smoking and quitting in community-residing smokers with a psychotic disorder; and to compare smoking behaviors in this sample with data reported for other samples.	298; 3 groups; G1 = 298 (56.7% schizophrenia/ schizoaffective disorder, 9.1% bipolar disorder with mania, 6.4% severe depression with psychosis, 27.9 other psychosis), G2 = 387 (General population from Pederson et al. study), G3 = 1,215 (volunteer sample of smokers in smoking cessation study from Curry et al. study)	G1 = 37.24 (11.09), G2/G3 unknown	G1 = 156 (52.3%), G2/G3 unknown	Reasons for Smoking Questionnaire; Reasons for Quitting scale; Readiness and Motivation to Quit Smoking Questionnaire	Reasons for smoking: Stress reduction: G1 > G2; Stimulation: G1 > G2; Addiction G1 > G2; Reasons for quitting: Desire for self-control G1 > G3; Desire for immediate reinforcement: G1 > G3; Social influence G1 > G3; Health concerns G1 = G3.	83
Briskman; 2012; Israel	To compare preventative intervention and treatment rates for comorbidities in hospitalized patients with psychiatric illness with patients without psychiatric illness.	192; 2 groups; G1 = 93 (88% schizophrenia/ schizoaffective disorder, 8% bipolar disorder, 4% other), G2 = 99 (100% hospitalized patients without psychiatric illness)	G1 = 53.3 (15.1), G2 = 55.2 (14.3)	G1 = 47 (51%), G2 = 55 (56%)	Reported receipt of instruction to quit smoking	Received physician instruction to quit: G1 < G2.	58
Brown; 2015; USA	To examine effectiveness of psychiatrists implementing the 5 A's on smoking rates among clinic patients diagnosed with serious mental illness.	49; 1 group; G1 = 49 (100% mental health clinicians)	NA	NA	Clinicians' attitudes and beliefs regarding smoking cessation treatments and the 5 A's	Main perceived barriers to carrying out 5A's: Lack of interest among patients about smoking and/or smoking cessation; Too many demands on staff already to begin a new practice; Too time demanding to carry out 5 A's; Staff skepticisms of 5 A's.	79
Brunette; 2017; USA	To examine age differences on smoking habits and examine age, gender, attitudes and beliefs, social norms, and perceived behavioral control in smokers with schizophrenia in relation to intention to quit and use of cessation treatment.	184; 1 group; G1 = 184 (100% schizophrenia)	42.96 (12.7)	132 (71.4%)	Attitudes toward smoking scale; Self-developed theory of planned behavior questionnaire; Stigma of smoking questionnaire; Stages of Change questionnaire	Perceived adverse effects of smoking were greater than benefits and pleasures of smoking. Positive attitude to NRT or smoking cessation medication associated with higher intention to quit.	79
Coletti; 2015; USA	To assess smoking-related knowledge and the effects of health messages on smoking knowledge and behavior.	148; 2 groups; G1 = 69 (100% schizophrenia), G2 = 79 (100% healthy controls)	G1 = 22.67 (5.2), G2 = 27.97 (5.6)	G1 = 55 (79.7%), G2 = 30 (38.0%)	Self-developed smoking knowledge questionnaire; Valence and Arousal items of Self-Assessment Manikin	Health concerns: G1 < G2 Smoking warning's effectiveness: G1 = G2.	83

(Continued)

TABLE 1 | Continued

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Duffy; 2012; USA	To estimate the prevalence of tobacco use and receipt of cessation services among Veterans Affair patients with mental illness, and determine the clinical, treatment, and demographic factors associated with receipt of cessation services.	224,193; 2 groups; G1 = 1,430 (100% smokers with schizophrenia), G2 = 27,652 (100% smokers without mental disorder)	Total sample = 3.4% <45 years, 37.4% 45 to 64, 59.2% ≥65	NA	Reported receipt of advice to quit smoking by physician, provision of medication, and discussion of quitting methods	Received physician advice to quit: G1 < G2 Recommendations for smoking cessation medications: G1 = G2; Physician discussed quitting methods: G1 = G2.	71
Filia; 2011; Australia	To examine CHD-related behavioral risk factors in smokers with schizophrenia, their reasons for engaging in risky behaviors, and level of motivation and confidence to change.	43; 1 group; G1 = 43 (100% schizophrenia)	36.3 (8.42)	25 (58.1%)	Reasons for Smoking Questionnaire; Reasons for Quitting scale; Readiness and Motivation to Quit Smoking Questionnaire	Reason for smoking: Addiction: 52.5%; Reasons for quitting, from highest to lowest: Health concerns; Desire for self-control; Perceived immediate reinforcement; Social influence; Received physician advice to quit: 81.4%.	82
Filia; 2014; Australia	To examine gender differences in perceived risks and benefits of quitting smoking in people diagnosed with psychosis presenting for a smoking cessation intervention study and compare risks and benefits with smokers in the general population.	200; 5 groups; G1 = 79 females (43% schizophrenia, 33% bipolar disorder, 24% other psychotic disorder), G2 = 121 males (67% schizophrenia, 17% bipolar disorder, 17% other psychotic disorder), G3 = 273 females (100% smokers in general population seeking cessation treatment), G4 = 300 males (100% smokers in general population seeking cessation treatment), G5 = 188 (non-treatment seeking smokers in general population)	G1 = 42.67 (9.93), G2 = 40.53 (11.76), G3-G5 = NA	G1 = 0 (0%), G2 = 121 (100%), G3 = 0 (0%), G4 = 300 (100%), G5 = NA	Perceived Risks and Benefits Questionnaire	Total risks: G1 < G3, G2 < G4, G1/G2 = G5; Weight gain: G1 < G3, G2 < G4, G1/G2 = G5; Increased negative affect: G1 = G3, G2 < G4, G1/G2 > G5; Poorer attention or concentration: G1 < G3, G2 < G4, G1/G2 = G5; Social ostracism: G1 < G3, G2 < G4, G1/G2 = G5; Loss of enjoyment: G1 < G3, G2 < G4, G1/G2 < G5; Increased cravings: G1 < G3, G2 < G4, G1/G2 = G5; Total benefits: G1 < G3, G2 < G4, G1/G2 = G5; Improved health: G1 < G3, G2 < G4, G1/G2 = G5; Improved wellbeing: G1 < G3, G2 < G4, G1/G2 > G5; Improved self-esteem: G1 < G3, G2 < G4, G1/G2 > G5; Improved finances: G1 < G3, G2 < G4, G1/G2 = G5; Greater physical appeal: G1 < G3, G2 < G4, G1/G2 > G5; Greater social approval G1 < G3, G2 < G4, G1/G2 = G5.	88

(Continued)

TABLE 1 | Continued

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Forchuk; 2002; Canada	To determine whether individuals with schizophrenia were motivated to smoke to relieve psychiatric symptoms and relieve medication side-effects.	100; 1 group; G1 = 100 (100% schizophrenia)	36.2 (10.90)	72 (72%)	Modified Smoking Motives Questionnaire; Written responses to qualitative questions	Strongest motivators to smoke, from highest to lowest: Sedative effect; Control negative symptoms; Addiction; Control side effects of medication.	82
Himelhoch; 2009; USA	To determine whether individuals with schizophrenia and type 2 diabetes who smoke received appropriate care related to managing modifiable risk-factors associated with heart disease.	199; 2 groups; G1 = 61 (100% smokers with schizophrenia and diabetes), G2 = 34 (100% smokers with no serious mental illness and diabetes)	G1 = 48.6 (8.7), G2 = 49.9 (8.4)	G1 = 33 (54.1%), G2 = 18 (52.9%)	Reported receipt of smoking cessation counseling	Received physician advice to quit: G1 = G2	79
Hippisley-Cox; 2007; England	To determine whether coronary heart disease patients with schizophrenia were less likely than patients without mental illness to receive good quality care in accordance with UK agreed national standards.	127,932; 2 groups; G1 = 332 (100% schizophrenia), G2 = 127,231 (100% without mental illness)	Modal age groups = G1 = 65–74 years (30.7%), G2 = 75 years+ (44.9%)	G1 = 175 (52.7%), G2 = 75,283 (59.2%)	Clinician reported receipt of smoking cessation advice in past 15 months in smokers	Received physician advice to quit: G1 = G2	83
Kelly; 2012: USA	To compare knowledge and perception of smoking risks and motivation for quitting in smokers with and without schizophrenia	200; 2 groups; G1 = 100 (100% schizophrenia), G2 = 100 (no mental disorder)	G1 = 43.3 (11.4), G2 = 37.1 (10.6)	G1 = 71 (71%), G2 = 65 (65%)	Smoking Consequences Questionnaire; Reasons for Quitting Scale; Stages of Change Questionnaire	Reasons for quitting: Desire for self-control G1 = G2; Desire for immediate reinforcement: G1 < G2; Social pressure G1 > G2; Health concerns G1 < G2: Perceived smoking consequences: Stimulation: G1 > G2; Health risks: G1 < G2; Social facilitation: G1 > G2; Reduce negative affect: G1 = G2; Taste manipulation: G1 = G2; Appetite/weight control: G1 = G2; Craving/addiction: G1 = G2; Negative physical feelings: G1 = G2; Reduce boredom: G1 = G2; Social impression: G1 = G2.	83

(Continued)

TABLE 1 | Continued

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Kourakos; 2014; Greece	To examine mental health patients' attitudes regarding smoking habits in the inpatient setting.	80; 1 group; G1=80 (65% schizophrenia/ schizoaffective disorders, 8% bipolar disorder, 28% other psychiatric illnesses)	52.55 (12.91)	54 (68%)	Patients' self-reported attitudes toward smoking	Received physician advice to quit: 25%; Staff should be able to smoke on the ward: 62.5% agreed; Visitors should be able to smoke with patients: 62.5% agreed; Seeing other patients smoke makes it difficult to quit: 62.5% agreed; Staff should encourage smokers to quit: 65% agreed.	50
Krishnadas; 2012; Scotland	To examine clinical variables associated with schizophrenia in an epidemiologically defined geographical area.	131; 2 groups; G1 = 70 (100% smokers with schizophrenia), G2 = 61 (100% non-smokers with schizophrenia)	G1 = 49.61 (14.48), G2 = 57.79 (17.21)	G1 = 47 (67.1%), G2 = 25 (41%)	Semi-structured questionnaire about smoking, smoking benefits and intentions of quitting	Reasons for smoking: Stress reduction: 60%; Manage depression or anxiety: 31%; Relieve loneliness: 16%; Socialize better: 14%.	83
Mann-Wrobel; 2011; USA	To understand the relationship between smoking and quit history, negative consequences due to smoking, stage of change, smoking temptation, and self-efficacy in people with schizophrenia participating in a smoking cessation trial.	41; 1 group; G1 = 41 (100% schizophrenia)	49.22 (8.0)	34 (82.9%)	Smoking Consequences Questionnaire; University of Rhode Island Change Assessment-Maryland	Perceived negative consequences of smoking, from highest to lowest: Health risks; Craving/addiction; Negative social impression. Perceived positive expectancies of smoking, from highest to lowest: Boredom reduction; Negative affect reduction; Social facilitation.	73
Spring; 2003; USA	To test two hypotheses: that patients with schizophrenia find smoking more rewarding then patients with depression; and, that patients with schizophrenia and patients with depression find smoking more rewarding than smokers without a psychiatric disorder other than nicotine dependence.	78; 3 groups; G1 = 26 (100% schizophrenia), G2 = 26 (100% depressive disorder), G3 = 26 (100% no psychiatric disorder)	G1 = 40.00 (10.85), G2 = 35.31 (11.13), G3 = 26.20 (11.69)	G1 = 19 (73%), G2 = 13 (50%), G3 = 21 (81%)	Decisional Balance Scale; Self-developed tool of preferences for engaging in smoking vs. other rewarding activities and magnitude of reward felt necessary for quitting	Decisional balance (pros minus cons): G1 = G2, G1/G2 > G3; Pros of smoking: G1 = G2, G1/G2 > G3; Cons of smoking G1 = G2 = G3; Alternative rewards were less favorable than smoking: G1 = G2, G1/G2 > G3; More rewards required to quit: G1 = G2, G1/G2 > G3	79
Tanriover; 2013; Turkey	To examine the frequency of smoking, smoking status, and smoking dependence in inpatients with schizophrenia, bipolar disorder, and major depression disorder.	160; 2 groups; G1 = 80 (53% schizophrenia, 31% bipolar disorder, 16% depressive disorder), G2 = 80 (100% no psychiatric diagnosis)	G1 = 36.83 (12.18), G2 = 37.65 (12.26)	G1 = 44 (55%), G2 = 39 (49%)	Self-developed tool to measure reason for tobacco use	Habit: G1 = 15%, G2 = 7.5% Addiction: G1 = 0%, G2 = 2.5%; Don't know: G1 = 1.3%, G2 = 1.3%; Society: G1 = 0%, G2 = 5%; Need: G1 = 1.3%, G2 = 0%; Desire to experiment: G1 = 1.3%, G2 = 17.5%; Boredom: G1 = 31.3%, G2 = 17.5%; Loneliness: G1 = 8.8%, G2 = 0%; Pleasure: G1=11.3%, G2=3.8%	63

(Continued)

TABLE 1 | Continued

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Tidey; 2009; USA	To compare expected positive and negative smoking outcomes in smokers with schizophrenia, schizoaffective disorder, and equally-nicotine dependent smokers without psychiatric disorder, and to examine relationships between expected outcomes and intentions to quit smoking.	152; 3 groups; G1 = 46 (100% schizophrenia), G2 = 35 (100% schizoaffective disorder), G3 = 71 (no psychiatric disorder)	G1 = 45.1 (7.7), G2 = 43.9 (8.5), G3 = 44.5 (12.2)	G1 = 35 (76%), G2 = 19 (54%), G3 = 39 (55%)	Smoking Effects Questionnaire	Positive social effects: G1 = G2, G1 = G3, G2 > G3, G2 participants who did not intend to quit in 6 months > G2 participants who intended to quit in 6 months; Negative psychosocial effects: G1 = G2, G1 = G3, G2 > G3; Negative physical effects: G1 < G2, G1 = G3, G2 > G3	83
Tidey.; 2014; USA	To compare craving and withdrawal symptoms in smokers with schizophrenia and without schizophrenia across a 72-h period of abstinence, compare reinforcing effects of nicotine before and after abstinence, compare latency to smoking lapse, and examine predictors of lapse	55; 2 groups; G1 = 28 (100% schizophrenia, G2 = 27 (100% no psychiatric disorder)	G1 = 44.0 (10.6), G2 = 43.9 (10.8)	G1 = 16 (57%), G2 = 17 (63%)	Questionnaire on Smoking Urges—Brief form; Minnesota Nicotine Withdrawal Scale; Hedonic Rating Scale	Anticipated relief of negative affect: G1 > G2; Change in desire to smoke and withdrawal symptoms over 72 h abstinence: G1 = G2	83
Tulloch; 2016; Canada	To better understand the quit experience of smokers with and without psychiatric illness.	732; 2 groups; G1 = 302 (100% no psychiatric disorder), G2 = 18 (100% psychotic disorders)	G1 = 48.54 (11.01), G2 = 48.61 (10.83)	G1 = 188 (62.3%), G2 = 15 (83.3%)	List of reasons for relapsing smoking and motives and concerns about quitting	Cravings a concern for quitting: G1 < G2 (aOR = 4.16, 95%CI = 1.44, 12.06); Boredom a concern for quitting: G1 < G2 (aOR = 8.03, 95% CI = 2.25, 28.69)	67

ANOVA, analysis of variance; aOR, adjusted odds ratio; CI, confidence intervals; G, group; N, number; NA, Not available; NRT, nicotine replacement therapy; SD, standard deviation; USA, United States of America.

TABLE 2 | Qualitative study characteristics and key findings.

First author; year of publication; country	Study aims	Total sample size; N of relevant groups; sample size and group composition	Age in years (SD)	N male (%)	Assessment of barrier	Key findings	QualSyst score (%)
Esterberg; 2005; USA	To examine the role of decisional balance in smoking and smoking cessation and the impact of external factors on smoking cessation attempts in people with schizophrenia, and differences between first-episode psychosis and chronic schizophrenia in relation to the transtheoretical model of change.	12; 1 group; G1 = 12 (100% schizophrenia)	Median = 25.5, Range = 19–43	10 (83%)	Semi-structured interview of pros and cons of smoking, beliefs about smoking cessation, external influences on smoking and quitting, and negative attitudes toward NRT	People living with schizophrenia smoke to relax and relieve negative symptoms Half the sample felt quitting was easy, with the other half citing quitting as challenging. Majority of participants believed there were more pros to smoking than cons. Lack of smoking cessation programs in hospitals, friend and family support to smoke, and negative views of NRT were additional barriers.	85
Goldberg; 1996; Canada	To obtain an overview of the smoking habits of people with schizophrenia, their stage of change, and their perceptions of influencing factors for smoking	105; 1 group; G1 = 105 (100% schizophrenia)	35, range 20–58	71 (68%)	Semi-structured interview on smoking habits, stage of change, and perceptions of factors that influence smoking behaviors	Most common barriers to quitting were addiction (53%), pleasure (20%), coping with symptoms/ clearing thought/ calming and relaxing effects (20%) and habit (19%). Most common motivators to quit were health concerns (33%), social support to address smoking (22%), cost (19%) and meaningful activities (16%).	45
Lawn; 2002; Australia	To describe smoking behavior experiences of people receiving mental health services, the relationship between smoking behavior and course of mental illness and management and quit attempts.	24; 1 group; G1 = 6 (100% schizophrenia)	G1–4 = 43	12 (50%)	Semi-structured interview exploring reasons underlying smoking behaviors	Main themes were the belief that smoking prevents relapse; provides control and freedom in otherwise powerless situation; health concerns not considered significant; alleviates positive symptoms; improves cognitive capacity and motivation; provides an identity; that peer and family encourages or accepts smoking; and that they would prefer to cut down than quit.	85

G, group; N, number; NRT, nicotine replacement therapy; SD, standard deviation; USA, United States of America.

reason to quit smoking (35) and another study reported that people living with schizophrenia perceived smoking-related health implications were the most negative consequences of smoking (38). However, two studies found that people living with schizophrenia reported lower health-related concerns than people without mental illness (42, 47). A greater proportion of people with recent onset psychosis compared with smokers without mental illness believed smoking had fewer adverse health effects, including for stroke, brain damage, lung disease, heart disease, cancer, and miscarriage (47). No differences in concern for health between males and females or relating to age were identified (40, 42, 43).

One study compared picture and video health warnings on perceived effectiveness and emotional valence and arousal in people living with schizophrenia and people without mental illness (47). People living with schizophrenia perceived the health warnings as more effective than controls. Perceived effectiveness of health warnings was positively associated with the emotional valence and arousal reported by participants.

Physician Advice to Quit Smoking

Seven studies reported on advice to quit by a health professional. One study reported that people living with schizophrenia were less likely to have received instruction for smoking cessation than people without mental illness (48), two found equal levels of advice provided to people living with and without schizophrenia (49, 50), while a fourth study found mixed results depending on the type of advice provided (51). The median percentage of people living with schizophrenia reporting receipt of advice to quit by a health professional was 80%, with a range between 25 and 94% (35, 46, 49–51), while the median for people without schizophrenia was 83%, ranging from 79 to 98% (49–51). Four studies comparing rates of physician advice were conducted in samples with smoking-related comorbidities, such as cardiovascular heart disease or diabetes, or in unique populations, such as members of Veterans' Affairs.

Brown et al. (52) examined the perceptions of mental health clinicians in providing the "5 A's" (ask, advise, assess, assist, arrange) of smoking cessation advice to their patients, which included a majority percentage of people living with schizophrenia. Clinicians rated their perceived lack of interest among patients of all diagnoses to discuss smoking and/or smoking cessation, too many demands on staff already to begin a new practice, too time demanding to carry out 5 A's, and staff skepticisms about the value of the 5 A's as the strongest barriers preventing implementation of the 5 A's.

Systemic Barriers

Patients with schizophrenia in a psychiatric inpatient unit with few rules regarding smoking on the ward were generally supportive of the hospital's smoking policy (46). Seventy-five per cent agreed that the liberal ward rules about smoking were correct, while 63% believed that visitors and/or staff should be allowed to smoke on the ward. However, 90% of participants reported that it was too difficult to quit, with 63% believing that seeing other patients smoke would make it difficult to quit and 65% reporting that staff should set a good example.

Social Pressure to Quit

Two studies identified social pressures to quit smoking as reportedly higher among people living with schizophrenia compared with people without mental illness (40, 42), however another two studies found equal levels of social pressure across groups (36, 43). No study identified a link between age or sex and social pressure to quit among people living with schizophrenia (40, 42). One study also reported that people living with schizophrenia who perceived their friends would be more likely to approve of NRTs or smoking cessation medication had higher intentions to quit smoking using these two pharmacotherapies (53).

Additional Barriers and Facilitators to Smoking Cessation

Reduction of boredom was another common reason people living with schizophrenia smoke. Five studies examined boredom as a reason to smoke, with one study finding people living with schizophrenia were eight times more likely than people without mental illness to report boredom as the reason for smoking (36). Three studies reported that boredom was the highest rated reason that people living with schizophrenia smoked cigarettes (38, 39, 42). Yet one of these studies found no difference between people living with schizophrenia and people without mental illness in ratings of boredom as a reason to smoke cigarettes (42).

Five studies examined stimulation as a reason to smoke, with two studies identifying people living with schizophrenia as significantly more likely to smoke for stimulation or arousal when compared with people without mental illness (40, 42). Two studies found no difference between people living with and without schizophrenia (43, 44). Stimulation as a reason to smoke was not associated with age or sex (40, 42).

People living with schizophrenia were equally as likely as people without mental illness to smoke for the purpose of managing weight in four studies (36, 42–44). Mann-Wrobel et al. (38) reported prevention of weight gain as the least important positive consequence of smoking among people living with schizophrenia. One study found that females were more likely than men to report higher perceived risk of weight gain associated with quitting (43).

One study compared perceptions of the pros and cons of smoking in three groups comprised separately of people living with schizophrenia, depression, or without mental illness (54). People living with schizophrenia and depression reported similar levels of pros and cons of smoking, with the combined schizophrenia and depression group reporting significantly more pros of smoking than the control group and an equal number of cons. The combined schizophrenia and depression group also reported that smoking was more rewarding than a higher number of alternative pleasurable activities than the control group. People living with schizophrenia reported requiring more rewards, such as coffee or money, to quit smoking than people without a mental illness. Age was not associated with perceived pros and cons of smoking.

Qualitative Findings

The qualitative studies supported the quantitative findings. Esterberg and Perneger (55) reported that people living with schizophrenia smoke to relax, gain relief from negative symptoms, and relieve boredom. Similar to Spring et al. (54), Esterberg and Perneger (55) reported that the majority of participants believed there were more pros to smoking than cons. Lawn et al. (56) found that people living with schizophrenia expressed little concern for their physical health, preferring to smoke as a way to manage positive symptoms and improve problem solving skills. In contrast, Esterberg and Perneger (55) reported that people living with schizophrenia were aware of the negative health implications, including cancer, and reduced engagement in physical activity, and the financial burden of smoking. Health concerns and a desire to increase self-esteem prompted eleven of the twelve participants to attempt quitting, yet feelings of tension and nervousness led them to begin smoking again. Two studies reported that people living with schizophrenia felt that their family, friends, and health professionals provided little reinforcement for them to quit (55, 56).

Following cravings as the most commonly reported barrier to smoking cessation (53%), Goldberg et al. (57) reported that pleasure and enjoyment associated with smoking, as well as coping with symptoms of anxiety were both reported as barriers to quitting by 20% of people living with schizophrenia. Habit (19%), boredom (17%), and a social environment associated with pressure to smoke and that provided little support to quit (13%) were other important barriers to smoking cessation. Other barriers reported in the qualitative studies were that people living with schizophrenia smoke for a sense of identity as it has shaped their development and contributes to their current sense of self and to feel freedom from their powerlessness in deciding their future (56). People living with schizophrenia also reported that the lack of smoking cessation programs in hospitals was also a barrier to quitting (55). People living with schizophrenia generally viewed NRT as negative and associated NRT with a sense of increasing rather than decreasing cravings, being unhealthy, unwanted side-effects and viewed NRT as unnecessary to quit (55). Participants believed that reducing, rather than quitting, would be a more realistic goal (56).

DISCUSSION

We systematically reviewed barriers to smoking cessation in 23 studies including 3,257 people living with schizophrenia. People living with schizophrenia reported that the main reasons for smoking are to manage cravings and addiction, as well as negative symptoms such as their desire to reduce negative affect, facilitate social relationships, manage stress, and relieve boredom. Medical professionals may be less likely to provide smoking cessation advice to people living with schizophrenia when compared with people without mental illness. The social networks of people living with schizophrenia may show little support for smoking cessation, which may reduce the likelihood people living with schizophrenia will attempt to quit smoking. While people living with schizophrenia appeared to be as aware of the smoking-related health risks as people without mental illness, they may be less likely to act on this awareness. Overall, it appears that people living with schizophrenia experience a greater number of barriers to smoking cessation than people without mental illness.

Cravings and addiction to smoking were reported as one of the main reasons for smoking in people living with schizophrenia in five studies (35–38, 57). The highly addictive properties of nicotine may have a greater influence on people living with schizophrenia compared with those without mental illness (36, 40, 41). Past research suggests that people living with schizophrenia have a higher nicotine dependence than people in the general population (1). These findings indicate the need to address the physical addiction to smoking with NRT, such as patches or gum, or smoking cessation medications, such as varenicline or bupropion.

While pharmacotherapy may increase smoking cessation rates, one qualitative study included in this review highlighted the strong negative attitudes that people living with schizophrenia have toward NRT, such as the belief that NRT increased cravings rather than decreased them, that NRT made them feel sick and that NRT was unhealthy (55). Negative attitudes toward NRT are also common among smokers without schizophrenia (58, 59). These findings are concerning, as we identified one study examining people living with schizophrenia which found that positive attitudes toward NRT held the strongest relationship with greater intention to use NRT (53). Attitudes toward pharmacotherapy may be an important psychosocial component of combined pharmacological and psychosocial interventions. Further intervention research examining the role of psychosocial support in promoting adherence to pharmacological treatments, including NRT, in people living with schizophrenia is required.

People living with schizophrenia also reported smoking to reduce negative affect, relieve boredom, manage stress, and facilitate social relationships. These reasons for smoking all target negative symptoms of schizophrenia, supporting previous research that has identified a link between greater negative symptom severity and increased smoking rates or nicotine dependence (2, 60, 61). However, in contrast to the views of people living with schizophrenia, smoking cessation is associated with lower levels of stress, anxiety, and depression than continued smoking (62). Psychoeducation on the effects of smoking on negative symptoms and other psychological treatment to manage negative symptoms may help reduce smoking rates in people living with schizophrenia. The National Institute for Health Care and Excellence (NICE) guidelines recommend CBT as a psychological treatment for schizophrenia (63). A 2014 meta-analysis found that psychological treatments, such as CBT, and pharmacological treatments, such as antidepressants and second-generation antipsychotics, significantly reduced negative symptoms in people living with schizophrenia (64).

Only one study has examined CBT to promote smoking cessation in people living with schizophrenia, which found significantly higher abstinence and reduction rates at 3, 6, and 12 months in participants who attended all 8 treatment sessions when compared with participants receiving treatment as usual (8). Continued research examining CBT on smoking cessation

in people living with schizophrenia is required. Behavioral activation, an important component of CBT, is an effective standalone treatment for depression and may have a unique influence on negative symptoms of schizophrenia (65, 66), however no research examining the effect of behavioral activation on smoking cessation has been conducted in people living with schizophrenia. Future research examining the mediating role of negative symptoms in treatment effect on smoking cessation will enhance the evidence linking smoking with negative symptoms.

Most people living with schizophrenia appear to have some awareness of the health risks associated with smoking (36, 40, 43, 44) and health risks are often cited as a facilitator to quit smoking (35, 38). Health concerns are also considered the most important reason to quit smoking among the general population (25, 67). Health professionals should continue to raise awareness of the health risks of smoking among people living with schizophrenia. A review found that half of the reviewed interventions to improve health literacy among primary care patients led to reduced smoking rates, with significant outcomes most commonly associated with information that was provided via individual counseling or through written resources (68).

Considering our findings that people living with schizophrenia rate health risks as an important reasons to quit smoking, the authors strongly encourage health professionals to follow the 5 A's (ask, assess, advice, assist, arrange) when working with people living with schizophrenia. Unfortunately, we found mixed evidence from the seven studies examining receipt of advice to quit from a physician. Two studies found that people living with schizophrenia were less likely to be advised to quit smoking compared with people without mental illness (48, 51), while a third non-comparison study found that only 25% of people living with schizophrenia were advised to quit (46). Barriers impeding clinicians' likelihood of administering smoking cessation advice to people with mental illness included a perceived lack of interest to quit in patients and insufficient staff and time to provide such support (52). Training that aims to improve physicians' attitudes and perceived competence to deliver the 5 A's may increase their likelihood of delivering smoking cessation advice, especially when training is combined with other interventions components, such as patient counseling, patient access to tailored information resources, and free NRT (69).

Strengths and Limitations

Our review amalgamated a diverse range of studies that included individuals from a variety of geographical locations and community or clinical settings, thereby enhancing the generalizability of the findings. However, we failed to identify eligible articles from Asia, South America, or Africa. Thus, our findings may be limited to people living with schizophrenia residing in Western societies.

We limited our review to include samples in which people living with schizophrenia were the majority. Six studies included a mixed sample of people living with schizophrenia or other mental illnesses, yet 91.6% of participants in groups including people living with schizophrenia were diagnosed with schizophrenia. Thus, we can be confident that our findings are specific to the target population and that they overcome limitations of previous reviews that combine results for people living with severe mental illness, such as bipolar disorder and severe depression.

We chose to include articles that contained baseline data from intervention studies. In doing so, we increased the evidence base and quality of available evidence. Yet, we may have biased the sample by including studies that excluded people living with schizophrenia who were ineligible to participate in the intervention. Common exclusion criteria of intervention studies included in our review were cognitive impairments, diagnosis of a medical condition precluding use of NRT, or brain injury. Our findings may not extend to people living with schizophrenia with these comorbidities.

The 23 articles included in our study held a number of limitations that may also affect the reliability of our findings. Nine studies (39%) included samples with fewer than 50 participants and eight studies (35%) had sample sizes between 51 and 100. Small sample sizes reduce the reliability and generalizability of the findings. Six of the 20 (30%) quantitative studies did not include a control sample limiting our understanding of whether the findings were different for people without schizophrenia or other mental illnesses. We found that there was inconsistent use of validated assessment tools. Three studies used the Reasons For Quitting scale (70), two used the Reasons for Smoking Questionnaire (71) and two used the Smoking Consequences Questionnaire (72). Most other studies used assessment tools purposively developed for their study. The reliability of evidence will be improved with more studies using the same assessment tool. Future research may also wish to validate these assessment tools in people living with schizophrenia and should continue to explore reasons for smoking and quitting that are not addressed in these assessment tools.

Recommendations for Future Research and Practice

Our review highlighted the presence of a number of important psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. A 2013 Cochrane review found only five randomized controlled trials examining psychosocial intervention effects on smoking cessation in people living with schizophrenia (7). Our findings can be used to inform the development of psychosocial interventions that are combined with pharmacological treatments. Future research that examines the effects of separate treatment components (e.g., cognitive vs. behavioral components of CBT) and the role of possible mediators, such as reduced negative symptoms or baseline nicotine dependence, will continue to inform the literature of the mechanisms facilitating smoking cessation among people living with schizophrenia.

Our findings strongly support current smoking cessation guidelines for physicians to advise people living with schizophrenia that cravings, withdrawal symptoms, nicotine dependence, and health risks will continue if they continue to smoke (73). Physicians may also assist people living with schizophrenia quit smoking by providing information on

smoking-related health risks, delivering brief counseling or MI, or referring patients to specialized smoking cessation services. Future research may be required to examine strategies to overcome barriers reducing physicians' likelihood of providing advice and assistance, such as through brief professional training programs. In addition to increasing physicians' likelihood of providing advice and assistance, future research should assess the impact of information resources educating people living with schizophrenia of the smoking-related health risks on their motivation to quit smoking and smoking cessation rates.

While the evidence is far from conclusive, electronic nicotine devices (i.e., e-cigarettes) may help reduce smoking rates by managing both the physical and psychological addictive properties of cigarettes (74). The regulation of e-cigarettes and nicotine liquids for use in e-cigarettes varies worldwide. In some countries, nicotine liquids cannot be purchased without a prescription. Ongoing research in this area is needed to help determine whether e-cigarettes increase smoking cessation rates, whether people living with schizophrenia are open to using e-cigarettes, and how physicians may influence the uptake of e-cigarettes for smoking cessation purposes.

CONCLUSION

Our systematic review found a range of important barriers and facilitators to smoking cessation in people living with schizophrenia. Addiction and cravings appear to be a primary reason why people living schizophrenia smoke cigarettes, yet there is also strong evidence that they smoke to manage features of negative symptoms, such as stress, negative affect, boredom, and social isolation. Health professionals also play an important role in smoking cessation for people living with schizophrenia and should support quitting in people living with schizophrenia as much as they do for people without mental illness. The barriers and facilitators identified in this review should be used to inform the development of targeted psychosocial components of smoking cessation interventions for people living with schizophrenia.

AUTHOR CONTRIBUTIONS

AL, ES, OW, and BB contributed to the study conception and design. AL, ES, and OW collected, analyzed, and interpreted data. AL wrote the first draft of the manuscript. AL, ES, OW, and BB contributed to critical revision of the manuscript, read and approved the submitted version.

FUNDING

BB was funded by a National Health and Medical Research Council (NHMRC) Career Development Fellowship (1063206) and a Faculty of Health and Medicine, University of Newcastle, Faculty of Health and Medicine Gladys M Brawn Career Development Fellowship.

REFERENCES

1. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res.* (2005) 76:135–57. doi: 10.1016/j.schres.2005.02.010
2. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian Survey of Psychosis. *Aust N Z J Psychiatry* (2012) 46:851–63. doi: 10.1177/0004867412449876
3. Hausswolff-Juhlin V, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. *Acta Psychiatr Scand.* (2009) 119:15–21. doi: 10.1111/j.1600-0447.2008.01309.x
4. Fiore MC, Jaen CR, Baker T, Bailey W, Benowitz N, Curry SE, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Department of Health and Human Services (2008).
5. Zwar N, Richmond R, Borland R, Peters M, Litt J, Bell J, et al. *Supporting Smoking Cessation: A Guide for Health Professionals.* Melbourne, VIC: The Royal Australian College of General Practitioners (2011).
6. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry* (2015) 23:37–43. doi: 10.1177/1039856214562076
7. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev.* (2013) 2:Cd007253. doi: 10.1002/14651858.CD007253.pub3
8. Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *Am J Psychiatry* (2006) 163:1934–42. doi: 10.1176/ajp.2006.163.11.1934
9. Gallagher SM, Penn PE, Schindler E, Layne W. A comparison of smoking cessation treatments for persons with schizophrenia and other serious mental illnesses. *J. Psychoactive Drugs* (2007) 39:487–97. doi: 10.1080/02791072.2007.10399888
10. Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Reid N. Effects of contingency management and bupropion on cigarette smoking in smokers with schizophrenia. *Psychopharmacology* (2011) 217:279–87. doi: 10.1007/s00213-011-2282-8
11. George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* (2000) 157:1835–42. doi: 10.1176/appi.ajp.157.11.1835
12. Steinberg ML, Ziedonis DM, Krejci JA, Brandon TH. Motivational interviewing with personalized feedback: a brief intervention for motivating smokers with schizophrenia to seek treatment for tobacco dependence. *J Consult Clin Psychol.* (2004) 72:723. doi: 10.1037/0022-006X.72.4.723
13. Williams J, Steinberg ML, Zimmermann MH, Gandhi KK, Stipelman B, Budsock PD, et al. Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. *J Subst Abuse Treat.* (2010) 38:384–93. doi: 10.1016/j.jsat.2010.03.006
14. Gelkopf M, Noam S, Rudinski D, Lerner A, Behrbalk P, Bleich A, et al. Nonmedication smoking reduction program for inpatients with chronic schizophrenia: a randomized control design study. *J Nerv Ment Dis.* (2012) 200:142–6. doi: 10.1097/NMD.0b013e3182438e92
15. Addington J, El-Guebaly N, Addington D, Hodgins D. Readiness to stop smoking in schizophrenia. *Can J Psychiatry* (1997) 42:49–52. doi: 10.1177/070674379704200107
16. George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* (2002) 52:53–61. doi: 10.1016/S0006-3223(02)01339-2
17. George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biol Psychiatry* (2008) 63:1092–6. doi: 10.1016/j.biopsych.2007.11.002

18. Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* (2012) 73:654–60. doi: 10.4088/JCP.11m07522
19. Wing VC, Wass CE, Soh DW, George TP. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. *Ann N Y Acad Sci.* (2012) 1248:89–106. doi: 10.1111/j.1749-6632.2011.06261.x
20. Ziedonis DM, George TP. Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophr Bull.* (1997) 23:247. doi: 10.1093/schbul/23.2.247
21. Steinberg ML, Williams J. Psychosocial treatments for individuals with schizophrenia and tobacco dependence. *J Dual Diagn.* (2007) 3:99–112. doi: 10.1300/J374v03n03_08
22. Goldberg JO. Successful change in tobacco use in schizophrenia. *J Am Psychiatr Nurses Assoc.* (2010) 16:30–5. doi: 10.1177/1078390309357084
23. Trainor K, Leavey G. Barriers and facilitators to smoking cessation among people with severe mental illness: a critical appraisal of qualitative studies. *Nicotine Tob Res.* (2017) 19:14–23. doi: 10.1093/ntr/ntw183
24. Twyman L, Bonevski B, Paul C, Bryant J. Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. *BMJ Open* (2014) 4:e006414. doi: 10.1136/bmjopen-2014-006414
25. McCaul KD, Hockemeyer JR, Johnson RJ, Zetocha K, Quinlan K, Glasgow RE. Motivation to quit using cigarettes: a review. *Addict Behav.* (2006) 31:42–56. doi: 10.1016/j.addbeh.2005.04.004
26. Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry* (2010) 23:112–9. doi: 10.1097/YCO.0b013e3283366643
27. Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* (2005) 162:495–506. doi: 10.1176/appi.ajp.162.3.495
28. Ziedonis DM, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: national institute of mental health report. *Nicotine Tob Res.* (2008) 10:1691–715. doi: 10.1080/14622200802443569
29. de Leon J, Gurpegui M, Diaz F. Epidemiology of comorbid tobacco use and schizophrenia: thinking about risks and protective factors. *J Dual Diagn.* (2007) 3:9–25. doi: 10.1300/J374v03n03_03
30. Morisano D, Bacher I, Audrain-McGovern J, George TP. Mechanisms underlying the comorbidity of tobacco use in mental health and addictive disorders. *Can J Psychiatry* (2009) 54:356–67. doi: 10.1177/070674370905400603
31. Rae J, Pettey D, Aubry T, Stol J. Factors affecting smoking cessation efforts of people with severe mental illness: a qualitative study. *J Dual Diagn.* (2015) 11:42–9. doi: 10.1080/15504263.2014.992096
32. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
33. Covidence systematic review software. *Veritas Health Innovation.* (Melbourne, VIC)
34. Kmet LM, Cook LS, Lee RC. *Standard Quality Assessment Criteria for Evaluating Primary Research Papers From a Variety of Fields* (2004).
35. Filia SL, Baker AL, Richmond R, Castle DJ, Kay-Lambkin FJ, Sakrouge R, et al. Health behaviour risk factors for coronary heart disease (CHD) in smokers with a psychotic disorder: baseline results. *Mental Health Subst Use Dual Diagn.* (2011) 4:158–71. doi: 10.1080/17523281.2011.555088
36. Tulloch HE, Pipe AL, Clyde MJ, Reid RD, Els C. The quit experience and concerns of smokers with psychiatric illness. *Am J Prev Med.* (2016) 50:709–18. doi: 10.1016/j.amepre.2015.11.006
37. Forchuk C, Norman R, Malla A, Martin ML, McLean T, Cheng S, et al. Schizophrenia and the motivation for smoking. *Perspect Psychiatr Care* (2002) 38:41–9. doi: 10.1111/j.1744-6163.2002.tb00656.x
38. Mann-Wrobel MC, Bennet ME, Weiner EE, Buchanan RW, Ball MP. Smoking history and motivation to quit in smokers with schizophrenia in a smoking cessation program. *Schizophr Res.* (2011) 126:277–83. doi: 10.1016/j.schres.2010.10.030
39. Tanriover O, Karamustafalioglu N, Tezvaran Z, Kaplan A, Tomruk N. Frequency of cigarette smoking among psychiatric inpatients evaluated by the Fagerstrom test for nicotine dependence. *Asian Pac J Cancer Prev.* (2013) 14:579–82. doi: 10.7314/APJCP.2013.14.1.579
40. Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, et al. Characteristics of smokers with a psychotic disorder and implications for smoking interventions. *Psychiatry Res.* (2007) 150:141–52. doi: 10.1016/j.psychres.2006.05.021
41. Tidey JW, Colby SM, Xavier EMH. Effects of smoking abstinence on cigarette craving, nicotine withdrawal, and nicotine reinforcement in smokers with and without schizophrenia. *Nicotine Tob Res.* (2014) 16:326–34. doi: 10.1093/ntr/ntt152
42. Kelly DL, Raley HG, Lo S, Wright K, Liu F, McMahon RP, et al. Perception of smoking risks and motivation to quit among nontreatment-seeking smokers with and without schizophrenia. *Schizophr Bull.* (2012) 38:543–51. doi: 10.1093/schbul/sbq124
43. Filia SL, Baker AL, Gurvich CT, Richmond R, Kulkarni J. The perceived risks and benefits of quitting in smokers diagnosed with severe mental illness participating in a smoking cessation intervention: gender differences and comparison to smokers without mental illness. *Drug Alcohol Rev.* (2014) 33:78–85. doi: 10.1111/dar.12091
44. Tidey JW, Rohsenow DJ. Smoking expectancies and intention to quit in smokers with schizophrenia, schizoaffective disorder and non-psychiatric controls. *Schizophr Res.* (2009) 115:310–6. doi: 10.1016/j.schres.2009.09.032
45. Krishnadas R, Jauhar S, Telfer S, Shivashankar S, McCreadie RG. Nicotine dependence and illness severity in schizophrenia. *Br J Psychiatry* (2012) 201:306–12. doi: 10.1192/bjp.bp.111.107953
46. Kourakos M, Koukia E. A study of patients' smoking habits in a psychiatric hospital. *Int J Car Sci.* (2014) 7:592–601.
47. Coletti DJ, Brunette M, John M, Kane JM, Malhotra AK, Robinson DG. Responses to tobacco smoking-related health messages in young people with recent-onset schizophrenia. *Schizophr Bull.* (2015) 41:1256–65. doi: 10.1093/schbul/sbv122
48. Briskman I, Bar G, Boaz M, Shargorodsky M. Impact of co-morbid mental illness on the diagnosis and management of patients hospitalized for medical conditions in a general hospital. *Int J Psychiatry Med.* (2012) 43:339–48. doi: 10.2190/PM.43.4.d
49. Hippisley-Cox JP, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart* (2007) 93:1256–62. doi: 10.1136/hrt.2006.110171
50. Himelhoch S, Leith J, Goldberg R, Kreyenbuhl J, Medoff D, Dixon L. Care and management of cardiovascular risk factors among individuals with schizophrenia and type 2 diabetes who smoke. *Gen Hosp Psychiatry* (2009) 31:30–2. doi: 10.1016/j.genhosppsych.2008.07.007
51. Duffy SA, Kilbourne AM, Austin KL, Dalack GW, Woltmann EM, Waxmonsky J, et al. Risk of smoking and receipt of cessation services among veterans with mental disorders. *Psychiatr Serv.* (2012) 63:325–32. doi: 10.1176/appi.ps.201100097
52. Brown CH, Medoff D, Dickerson FB, Fang LJ, Lucksted A, Goldberg RW, et al. Factors influencing implementation of smoking cessation treatment within community mental health centers. *J Dual Diagn.* (2015) 11:145–50. doi: 10.1080/15504263.2015.1025025
53. Brunette MF, Feiron JC, Aschbrenner K, Colctti D, Devitt T, Greene MA, et al. Characteristics and predictors of intention to use cessation treatment among smokers with schizophrenia: young adults compared to older adults. *J Subst Abus Alcohol.* (2017) 5:1055.
54. Spring B, Pingitore R, McChargue DE. Reward value of cigarette smoking for comparably heavy smoking schizophrenic, depressed, and nonpatient smokers. *Am J Psychiatry* (2003) 160:316–22. doi: 10.1176/appi.ajp.160.2.316
55. Esterberg ML, Compton MT. Smoking behavior in persons with a schizophrenia-spectrum disorder: a qualitative investigation of the transtheoretical model. *Soc Sci Med.* (2005) 61:293–303. doi: 10.1016/j.socscimed.2004.11.057
56. Lawn SJ, Pols RG, Barber JG. Smoking and quitting: a qualitative study with community-living psychiatric clients. *Soc Sci Med.* (2002) 54:93–104. doi: 10.1016/S0277-9536(01)00008-9

57. Goldberg JO, Moll S, Washington A. Exploring the challenge of tobacco use and schizophrenia. *Psychiatr Rehab Skills* (1996) 1:51–63. doi: 10.1080/10973435.1996.10387541
58. Etter JF, Perneger TV. Attitudes toward nicotine replacement therapy in smokers and ex-smokers in the general public. *Clin Pharmacol Ther.* (2001) 69:175–83. doi: 10.1067/mcp.2001.113722
59. Uppal N, Shahab L, Britton J, Ratschen E. The forgotten smoker: a qualitative study of attitudes towards smoking, quitting, and tobacco control policies among continuing smokers. *BMC Public Health* (2013) 13:432. doi: 10.1186/1471-2458-13-432
60. Patkar AA, Gopalakrishnan R, Lundy A, Leone FT, Certa KM, Weinstein SP. Relationship between tobacco smoking and positive and negative symptoms in schizophrenia. *J Nerv Ment Dis.* (2002) 190:604–10. doi: 10.1097/00005053-200209000-00005
61. Saliba M, Assaad S, Haddad C, Hallit S, Hachem D, Haddad G. Schizophrenia and smoking: impact on negative symptoms. *Revista Internacional Investig Adicciones* (2017) 3:28–35. doi: 10.28931/riiad.2017.1.04
62. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* (2014) 348:g1151. doi: 10.1136/bmj.g1151
63. NICE (2014). *Psychosis and Schizophrenia in Adults: Prevention and Management*. NICE.
64. Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull.* (2014) 41:892–9. doi: 10.1093/schbul/sbu170
65. Mairs H, Lovell K, Campbell M, Keeley P. Development and pilot investigation of behavioral activation for negative symptoms. *Behav Modif.* (2011) 35:486–506. doi: 10.1177/0145445511411706
66. Choi K-H, Jaekal E, Lee G-Y. Motivational and behavioral activation as an adjunct to psychiatric rehabilitation for mild to moderate negative symptoms in individuals with schizophrenia: a proof-of-concept pilot study. *Front Psychol.* (2016) 7:1759. doi: 10.3389/fpsyg.2016.01759
67. Curry SJ, Grothaus L, McBride C. Reasons for quitting: intrinsic and extrinsic motivation for smoking cessation in a population-based sample of smokers. *Addict Behav.* (1997) 22:727–39. doi: 10.1016/S0306-4603(97)00059-2
68. Taggart J, Williams A, Dennis S, Newall A, Shortus T, Zwar N, et al. A systematic review of interventions in primary care to improve health literacy for chronic disease behavioral risk factors. *BMC Fam Pract.* (2012) 13:49. doi: 10.1186/1471-2296-13-49
69. Papadakis S, McDonald P, Mullen K-A, Reid R, Skulsky K, Pipe A. Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis. *Prev Med.* (2010) 51:199–213. doi: 10.1016/j.ypmed.2010.06.007
70. Curry S, Wagner EH, Grothaus LC. Intrinsic and extrinsic motivation for smoking cessation. *J Consult Clin Psychol.* (1990) 58:310. doi: 10.1037/0022-006X.58.3.310
71. Pederson LL, Bull SB, Ashley MJ, MacDonald JK. Quitting smoking: why, how, and what might help. *Tob Control* (1996) 5:209–14. doi: 10.1136/tc.5.3.209
72. Copeland AL, Brandon TH, Quinn EP. The smoking consequences questionnaire-adult: measurement of smoking outcome expectancies of experienced smokers. *Psychol Assess.* (1995) 7:484. doi: 10.1037/1040-3590.7.4.484
73. RACGP (2011). *Supporting Smoking Cessation: A Guide for Health Professionals*. Melbourne, VIC: The Royal Australian College of General Practitioners.
74. Schivo M, Avdalovic MV, Murin S. Electronic nicotine delivery systems for smoking cessation: where are we? *Curr Respir Care Rep.* (2014) 3:192–9. doi: 10.1007/s13665-014-0088-y

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

PERSPECTIVE
published: 15 August 2019
doi: 10.3389/fpsyt.2019.00565

Psychosocial Factors Affecting Smoking Cessation Among People Living With Schizophrenia: A Lived Experience Lens

Nadine Cocks[1], Lisa Brophy[1,2,3], Catherine Segan[2,4], Anthony Stratford[1], Simon Jones[2] and David Castle[5,6]*

[1] Research and Advocacy, Mind Australia Limited, Heidelberg, VIC, Australia, [2] Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [3] School of Allied Health, Human Services and Sport, College of Science, Health and Engineering, La Trobe University, Bundoora, VIC, Australia, [4] Quit Victoria, Cancer Council Victoria, Melbourne, VIC, Australia, [5] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia, [6] Department of Psychiatry, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

Introduction: People living with schizophrenia smoke at much higher rates than the general population, and find it more difficult to quit. To date, lived experience has received little attention from researchers. Personal recovery perspectives may generate further insights into established psychosocial barriers and enablers of smoking cessation.

Methods and Results: A lived experience account is provided by one of our authors that places the current evidence in context, and highlights the role of marginalization and stigma in reinforcing smoking. Key concepts from the personal recovery paradigm, such as connectedness, hope, and empowerment are discussed. The relevance of these factors and the value of shared lived experience in challenging stigma, marginalization, and low expectations demonstrates the contribution that peer support can offer to support smoking cessation.

Conclusions: Recovery-oriented approaches when integrated with existing evidence-based treatments designed to meet the needs of people living with schizophrenia have potential to improve outcomes by helping to take a more holistic approach to break down barriers and facilitate increased uptake of treatment and support. Further research to evaluate the effectiveness of integrated approaches is warranted.

Keywords: smoking, schizophrenia, recovery, lived experience, stigma, marginalization, peers

OPEN ACCESS

Edited by:
Stefan Borgwardt,
University of Basel, Switzerland

Reviewed by:
Daniel Schöttle,
University Medical Center Hamburg-Eppendorf, Germany
Alexis E. Cullen,
King's College London, United Kingdom

***Correspondence:**
Lisa M. Brophy
L.Brophy@latrobe.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *03 October 2018*
Accepted: *18 July 2019*
Published: *15 August 2019*

Citation:
Cocks N, Brophy L, Segan C, Stratford A, Jones S and Castle D (2019) Psychosocial Factors Affecting Smoking Cessation Among People Living With Schizophrenia: A Lived Experience Lens. Front. Psychiatry 10:565. doi: 10.3389/fpsyt.2019.00565

INTRODUCTION

People living with schizophrenia are at least five times more likely than people in the general population to smoke tobacco and are less likely to quit successfully (1). Moreover, a person living with schizophrenia consumes more cigarettes per day with a greater preference for unfiltered, high nicotine and high tar cigarettes than does a smoker in the general population (2, 3). Overrepresentation of social risk factors for smoking such as social norms that support smoking, social and economic disadvantage, unemployment, and alcohol and substance misuse contribute to these high smoking rates. As smoking kills around one in two long-term users, it makes a significant contribution to the premature mortality observed in people living with schizophrenia (4). Recent

studies have found that there is up to 20 years reduction in life expectancy associated with a diagnosis of schizophrenia, largely due to smoking-related diseases (5).

A 2010 Australian national survey of people living with psychotic illness reported a smoking rate of 67%, unchanged from the previous survey conducted 15 years prior and contrasting with a 7% decline in smoking in the general population over the same period. Despite these high smoking rates, studies involving people living with schizophrenia recruited from a range of mental health service settings indicate that they are as motivated to quit smoking as other people in the general community (6). This motivation to quit is not necessarily dependent on level of symptoms. It has been found that people with more symptoms related to their mental illness have been more highly motivated to stop smoking than those with less (7).

Understanding the reasons why people living with schizophrenia continue to smoke at such high rates despite increasing efforts at the general population level to support smoking cessation is vital to informing the development of more nuanced and effective policy and interventions. The reasons why people living with schizophrenia continue to smoke may be not dissimilar to the general population. People living with schizophrenia are more likely to experience established barriers to cessation, such as higher levels of addiction, greater likelihood of living with smokers, more prosmoking social norms, greater financial stress, and increased depression and anxiety. In addition, they are often less likely to be formally supported in their efforts to stop smoking and are also less likely to be able to afford nicotine replacement products. Ongoing stigma, discrimination, inequality, and social exclusion are also considered to play a part in both why people smoke and add to the challenges of quitting (8, 9).

It is not the purpose of this paper to further stigmatize people living with schizophrenia by rarefying their experiences around smoking. Alternatively, our aim is to try to understand the challenges this group faces in quitting and how best to offer them support to address their smoking. Regular tobacco use has a devastating impact not only on physical health but also on psychosocial recovery as it entrenches people in a cycle of financial, social, and emotional disadvantage (10). Thus, there is a current imperative to reduce the very high rates of smoking among people living with schizophrenia and other severe mental health conditions even though there are significant challenges associated with both supporting individuals to quit and making the services they access more responsive to this issue.

While considerable progress has been made in introducing smoke-free environments into mental health settings, embedding smoking cessation care, such as brief advice that links smokers to effective behavioral and pharmacological treatments, remains limited. The role of societal factors, particularly stigma and discrimination, highlights the need to address the attitudes of some health professionals and other service providers who have been commonly found to not support the efforts of disadvantaged and marginalized people to quit smoking (9).

The introduction of a lived experience 'lens' on this situation presents an opportunity to include a recovery perspective on the question of both why people living with schizophrenia smoke and how smoking cessation programs could adopt a more recovery-oriented approach. Experiential knowledge, such as first-person experience, has the potential to extend—and critique—professional knowledge that has been derived mainly from the traditional hierarchy of evidence. It gives voice to those who are experts through their lived experience and enables a shift in power, bringing greater respect to the value of subjectivity (11). Hence its relevance to a recovery orientation that emphasizes concepts such as empowerment and the value of peer support (12, 13).

BACKGROUND

The Cancer Council of Victoria (Australia) presents a comprehensive review of smoking and health issues in Australia (14). This report synthesizes data and information in relation to Australia's tobacco control program including smoking consumption and trends, the health effects of tobacco use, addiction, smoking cessation programs, smoking and social disadvantage, and smoking and public education campaigns. The following reflects a number of findings presented in this report.

Excess Mortality and Schizophrenia

The problem of people living with schizophrenia dying much earlier than expected is well established (4). Although premature death has commonly been explained as being the result of unnatural causes such as suicide and violence, it is now understood that premature death from natural causes, such as heart disease and cancer, is "at least as important a source of the excess mortality in mental disorder as death from unnatural causes" (p. 51) (15).

The life expectancy of people living with schizophrenia is approximately 20% shorter than that of the general population (16) and there is evidence that this gap widening over time (4, 17). The mortality risks for people with schizophrenia has been compared to the impact of heavy smoking (17). Moderate to heavy smoking can result in an 8 to 10 year loss in life expectancy; however, some recent studies have found that there is up to 20 years reduction in life expectancy associated with a diagnosis of schizophrenia, largely due to smoking-related diseases (5). Smoking is just one of the indicators of poor health among people living with schizophrenia and what is required is a more holistic approach to improving physical health (18). People living with schizophrenia are also at higher risk of other serious health challenges including poor dental health, obesity, diabetes, hypertension, and cardiovascular (CV) disease and about half of total deaths in people living with schizophrenia can be attributed to these smoking related health conditions (14, 19–21) (22). Comorbidity with other psychiatric disorders, including the mood and anxiety disorders, is common in schizophrenia (23) and these disorders are also associated with smoking (24). Also, people living with schizophrenia may also experience problems with alcohol and illicit drugs at higher rates than the general community (25) and this may also be linked to increased smoking and decreased mortality. Therefore, supporting people to quit

smoking is an important strategy to deal with this significant and potentially increasing mortality gap, especially where cessation treatments also encourage the adoption of a healthy lifestyle that may concurrently address other physical health risk factors that people living with schizophrenia commonly experience. Lum et al. (8) found that for people living with schizophrenia, health concerns are the highest reason to quit, and in some cases, the perceived smoking related health implications are the most negative consequence of smoking.

Survey of High Impact Psychosis: SHIP (2010)

Based on the 2010 Australian National Survey of High Impact Psychoses (SHIP), Cooper et al. (26) present the patterns of smoking for Australians living with a psychotic illness and relationship of smoking to other health, psychosocial, and demographic characteristics (26). They concluded that the prevalence of smoking for people living with mental illness is not changing, in contrast to the mainstream Australian population, and more research is needed to further understand what other barriers may exist for this cohort upon which targeted interventions may be based. In a discussion with a group of people living with psychosis about findings from the Australian Study of Low Prevalence (Psychotic) Disorders conducted in 1997, participants expressed considerable feelings of hopelessness and lack of social connection that they linked to smoking in comments such as '*What is there to stop for?*" and "*When you wake up in the morning, what else is there*?" (p. 11) (27). Hence it may be that in the time between surveys efforts to support smoking cessation among people living with high impact psychosis have not adequately addressed issues of marginalization, lack of social inclusion, and minimal meaningful occupation.

BARRIERS TO SMOKING CESSATION—PSYCHOSOCIAL PERSPECTIVES

Through their systematic review Lum et al. (8) examined the barriers and facilitators to smoking cessation in people living with schizophrenia. They note that there is much more research into pharmacological smoking cessation interventions for people with schizophrenia and little research examining psychosocial interventions. The review focused on psychosocial factors in order to inform the development of psychosocial interventions (rather than review psychosocial interventions per se). However, in identifying psychosocial smoking cessation interventions, such as psychoeducation, motivational interviewing, and cognitive behavioral therapy, they observe that very few randomized controlled trials have been conducted with people living with schizophrenia or examination of their underlying theories. This is in contrast to the neurobiological links that have been identified to inform pharmacological treatment.

Lum et al. (8) found that cravings and addiction was the most commonly cited barrier to smoking cessation in people living with schizophrenia, and in some cases perceived or actual cravings associated with smoking cessation was "significantly higher among people living with mental illness" (p. 5). Negative affect was also identified as a major barrier to cessation. Smokers report using smoking as a tool to alleviate symptoms of anxiety and depression and to manage stress and boredom and are often concerned how they might cope without smoking, including that they may become unwell again [Lawn et al. (28) in Ref. (8)]. This fear of increased negative affect, together with the fact that negative affect is also a nicotine withdrawal symptom, are barriers to initiating quit attempts. In addition, once people make a quit attempt, increased negative affect is a strong predictor of smoking relapse.

People living with schizophrenia are at high risk of social exclusion and boredom in their everyday lives and smoking has been found to provide some opportunity for social affiliation and inclusion (8, 14). In relation to social barriers, Trainor and Leavey (29) refer to smoking enabling consumers to fit in and feel included, relieving loneliness and alleviating stigma. Lum et al. (8) identified social reasons why people living with schizophrenia smoke and are unlikely to quit. Consumers use smoking to improve social functioning and fear they will be socially ostracized if they give up (8).

There is also a historical and environmental context that potentially explains high rates of smoking among people with schizophrenia (14). High rates of institutionalization in the past were associated with an institutional ethos in which smoking was often central to daily activities. Despite deinstitutionalization many argue that the culture and traditions of institutions often remain in the approach to care that predominantly now occurs in the community. Hall and Prochaska (6) refer to the smoking culture in mental health settings which is based on the priority of mental health treatment, ambivalence of the health effects of smoking, and belief that psychiatric patients are unable to quit. In one study, reviewed by Lum et al. (8), 83% of psychiatric inpatients with schizophrenia believed that visitors should be allowed to smoke with patients (30). In this culture, cigarettes have been provided by clinicians as a reward and to ensure compliance. In agreement, Lawn (31) identifies cigarettes as 'currency' for psychiatric patients in mental health institutions. In this environment, where smoking is supported and promoted by staff and patients alike, escaping from this culture and quitting is extremely difficult (14).

Hahn et al. (32) investigated the rates of smoking for people living with mental illness in a disadvantaged area of Adelaide in South Australia and identified social barriers that increase smoking rates in the community (32). They found 'strikingly' high rates of smoking for both men and women within their environment of social disadvantage marked by high unemployment, low rates of education, high rates of public housing and poorer health outcomes. In their view, smoking cessation programs for this cohort cannot be provided in isolation from other supports in the community. In parallel, other measures to promote employment,

physical activity, health, and well-being and social engagement in the community are more likely to help people quit.

Access to Smoking Cessation Support

Lum et al. (8) found that while 80% of people living with schizophrenia receive advice from health professionals to quit, the "5 A's" (ask, advise, assess, assist, arrange) smoking cessation strategy has not been effectively implemented—with practitioners citing lack of interest from patients, too many demands (including time) on staff, and skepticism of the program as barriers. Lack of smoking cessation programs in hospitals is seen as a barrier to quitting and nicotine replacement therapy (NRT) is seen as negative, unhealthy with unwanted side effects, and unnecessary. Generally, staff support liberal smoking rules in psychiatric inpatient units (8). A high proportion of participants in studies reviewed find it too difficult to quit especially when seeing other patients smoke and when staff do not set a good example. There appears to be persistent 'myths' associated with smoking and schizophrenia that may entrench a lack of support for people to quit. In an Australian study, Wye et al. (33) investigated the implementation of smoking bans in psychiatric inpatient services. While the researchers note that general hospitals have successfully transitioned to smoke-free environments, they also found that there were ongoing challenges in implementing change in clinical mental health settings, even though there is widespread support for smoking bans among staff. Staff presented concerns in relation to perceived patient aggression and the lack of capacity and organizational support for change. The researchers identified that more cultural and systematic change, strong leadership, and staff training and support is necessary to help those with mental illness quit and alleviate their health inequalities associated with smoking.

In summary, people living with schizophrenia face significant challenges and barriers to quitting smoking (29). While consumers acknowledge the negative health consequences associated with smoking, they find little support from mental health practitioners, and cessation programs, especially psychosocial interventions to help them quit (8, 34).

THE LIVED EXPERIENCE OF ONE OF OUR AUTHORS

A Personal Reflection on Reasons for Smoking and What Helps

Through exploring some of the reasons why people with mental health issues smoke, and the difficulties they experience with smoking cessation, from a lived experience perspective, my smoking experiences highlight reasons to do with loss of connection, isolation, stigma, boredom, loss of identity, and a desire to belong as my story explains:

I began smoking regularly during my first psychotic episode. Before that, I was a smoker just on occasions such as parties and usually associated with drinking. Something, however, happened when I became ill. I was frightened, overwhelmed and scared. I seemed not to be able to control the thoughts in my head and the smoking became my comfort. The rush of nicotine somehow made me feel better and though I was breathing in deadly toxins and poisons, smoking actually forced me to breathe deep breaths. It also enabled me to structure my day around smoking breaks and forced me to spend some time outdoors as I had a rule to never smoke indoors.

Smoking also had the benefit of making me feel like I belonged. I would love to smoke with other smokers (usually with mental health issues) and this gave me a sense of camaraderie. We felt like we were part of a group and the smoking places became ours. This also played a part in combatting stigma and made each of us feel included.

I would regularly smoke with coffee and the cigarettes combined with the coffee helped combat some of the sedating effects of the medication. Together they gave me a 'lift" and it soon became a ritual I practised often.

I believe I was self-medicating, that is, using the cigarettes to somehow limit the effect of the illness. However, I was not only smoking to achieve this outcome, smoking also had other benefits. It relieved me of boredom and a sense of things being out of control, and I became hooked as much on the nicotine, as the ritual of rolling my own cigarettes—a ritual I became very skilled at.

I tried several times to quit with the help sometimes of Quitline telephone support services but always returned to smoking.

It wasn't until the graphic ad campaign of the 2000's that I became shocked and frightened about what the cigarettes were doing to my body that really helped me to finally quit. I did it with the help of nicotine-replacement and the Quitline telephone support service and have been smoke free for years.

Since I quit, I have been able to focus much more on my health. Being able to breathe properly made exercise easier and more enjoyable and has added benefits of giving me an endorphin rush which has replaced the cigarette rush. I was also able to practice mindfulness, yoga and other activities where concentrating on the breath is so important. I have developed an intense appreciation of nature and the natural environment. I am able to appreciate the outdoors without a cigarette and really connect and appreciate my environment without the crutch of a cigarette. My mental health improved greatly and I was generally a lot calmer and more relaxed. The money saved from quitting has contributed to me being able to travel overseas and experience many diverse cultures.

It was very important for me to develop alternative strategies to replace smoking and also to work on my protective behaviours to help manage some of the withdrawal effects and changes in mood. What I found helpful was a holistic approach to improving my physical health but I found this only happened when I quit smoking.

Connecting Lived Experience With the Literature

As this reflection describes, smoking helps address some of the psychosocial dimensions of people's experience with serious mental illness such as lack of connection, social isolation, stigma

and loss of identity. Schizophrenia is a very stigmatizing condition and therefore these dimensions are even more pronounced.

The reasons why people living with schizophrenia smoke from a lived experience perspective include stigma and marginalization and a sense that hope or a positive sense for the future is lacking. However, even though people living with schizophrenia face significant stigma and discrimination, their voices on stigma are largely underrepresented in the literature (35). Hence the importance of future research that privileges the voices of people with lived experience to enable greater recognition of these factors.

The current literature, and this personal story, support the perspective that smoking in groups can make people feel they are not alone and cigarettes play a role in helping people bond and develop a sense of camaraderie. Conversely, with current restrictions regarding public places where people can smoke, some smokers experience isolation by their smoking behavior and share a sense of 'camaraderie in exile' with other fellow smokers in designated smoking areas (36). Smokers report stigmatizing attitudes from the community when smoking in public. Alternatively for some smokers there might be an experience of having 'permission' to smoke when they see others smoking in public (36). As cigarette smoking is banned in many places and smoking is more prevalent in groups of people experiencing mental ill health, people living with schizophrenia are being further stigmatized and marginalized for being smokers. Indeed, Lum et al. (8) concluded that social pressure to quit smoking is reportedly higher among people living with schizophrenia. This in turn impacts on their self-esteem and sense of self-worth but also paradoxically, or as an unintended consequence, creates a group identity or a subgroup of belonging.

Smoking with groups of smokers may negate the stigma that people living with schizophrenia face through having a sense of group identity. Illness identity is another factor that may impact on the hope and self-esteem of people who smoke and are living with a mental illness (37). This illness identity can be pervasive and contribute to feelings of hopelessness, and not having a positive sense of the future.

Resilence may also play a part in why people living with schizophrenia smoke and others do not. Lawn et al. (38) outline a resilience construct which may explain why some people are able to draw on protective behaviors that act as a buffer against taking up smoking.

Regardless of negative factors in people's lives some people are able to draw on resources to help them deal with challenging experiences and situations. This is described by Lawn et al. (38) as the resilience construct. From a critical view of the literature, Lawn et al. (38) propose that resilience be defined as "the interaction between the internal properties of the individual, and the set of external conditions, that allow individual adaptation, or resistance to different forms of adversity at different points in the life course" (p. 47) (38).

It could be that when a person is experiencing mental ill health their protective behaviors and resistance is low or lower than usual. Perhaps by helping people develop and learn alternative coping skills and strategies that sit within a recovery framework (discussed below), both people who are at risk of smoking and smokers wanting to quit could benefit.

Most people are not offered best practice treatment and there is a need to offer support and treatment to all smokers, not just those interested in stopping smoking (39). Taking into account the discussion above, best practice treatment would recognize that smoking cessation rates are maximized when brief intervention from a health or support worker links people living with schizophrenia to both a multisession specialist behavioral intervention [from, for example, Quitline telephone support (40) or a group course] plus pharmacotherapy (nicotine products or cessation medications).

THE RECOVERY FRAMEWORK

A recovery framework is defined by the *National Framework for Recovery-Oriented Mental Health Services* (41) as providing holistic and 'person first' services that supports personal recovery, an organizational commitment, workforce development, and action on social inclusion and the social determinants of health.

Fundamental to any recovery framework are the elements of hope, social connection and empowerment (42). In championing these elements of recovery; marginalization, stigma, and social disconnection can be addressed. Corrigan et al. (43) outline the ways stigma operates through fear and exclusion, authoritarianism, and benevolence, and they suggest that stigma can be tackled by protesting for people with mental illness, educating the community and increasing the amount of contact people have with other people who live with mental health issues. Through people with mental health issues being supported to empower themselves, regain a sense of social connection, and hope for the future they can regain autonomy and control of their lives.

If people living with mental health issues, and more specifically schizophrenia, are supported to develop alternate coping skills, resilience, and strategies for smoking cessation within a recovery framework that acknowledges the impact of stigma and discrimination and encourages hope, social connection, and empowerment, they may have a better chance in quitting smoking.

Malpass and Higgs (44) have hypothesized that by using smoking to cope with their mental ill health, alternative coping skills and strategies may not be explored, maintaining their mental ill health and smoking behaviors. However, the act of quitting smoking itself is very empowering and can increase confidence and self-esteem for the person who has quit. Quitting can also lead to an increased interest and focus on physical health from a holistic perspective and should be seen as an important aspect of the recovery journey supported with recovery oriented smoking cessation strategies.

Smoking is just one of many risk factors for poor health that are more common among people with schizophrenia. Integrating recovery-oriented approaches with existing evidence-based treatments for individual risk factors can provide a more holistic

approach (18). As the consumer movement has moved toward rearticulating recovery in terms of well-being, consumers are now expecting services and treatments to be both holistic and person centred. It may be useful to view smoking cessation as one of the many aspects of recovery and well-being that consumers engage with.

In the lived experience example presented above, the author developed alternate coping strategies such as yoga, mindfulness, and getting outdoors to support both the quit attempt and also to put in place some long lasting permanent strategies for health and well-being. Such strategies can be combined with supports such as Quitline telephone support (40) and pharmacotherapy to increase the chances of quitting successfully thus experiencing recovery-oriented cessation support

Significant reductions or cessation of tobacco smoking provides positive opportunities for people to achieve their individual social and economic goals and improve both their physical and mental health. Mental health settings urgently require a recovery-oriented approach to smoking that is flexible, evidence based and sustainable.

RECOMMENDATIONS

As indicated in the personal story above, evidence-based treatments work. In this situation best practice treatment that includes a combination of a multisession behavioral intervention (e.g., Quitline telephone support) plus NRT made an important contribution to quitting. A major challenge remains to make routine the delivery of brief smoking cessation advice by mental health service staff, including peer workers, that proactively links people who smoke to these effective forms of help.

Incorporating a recovery orientation approach to smoking cessation treatment highlights the value of peer support. This requires the intentional use of lived experience in the support of others, and recognition that concepts like connectedness, hope, identity, meaning, and empowerment have an important role in supporting the efforts of people living with severe mental illness to quit (42).

Peer support models are being adopted in mental health contexts in many different ways including management, representation, advocacy, direct service, training, and research. Evidence suggests that peers can engage persons who have been difficult to reach and have not benefitted from traditional services and that peer workers can decrease the costly use of acute services like emergency room visits and hospitalizations while increasing the use of outpatient care. Furthermore, peer work can reduce demoralization and the use of alcohol, while increasing hope, empowerment, and self-care (13). Informal supporters and peer supporters have also been found to support smoking cessation in people living with schizophrenia and other serious mental illness (45–47). A further example of this peer led approach is the Quitlink randomized controlled trial of peer worker facilitated Quitline support plus combination NRT, for smokers receiving mental health services [Ref. (48) in this issue].

Multisession behavioral interventions that tailor to the needs of people living with schizophrenia include monitoring of nicotine withdrawal symptoms, many of which overlap with mental health symptoms, so this dually acts as mood monitoring that helps to distinguish nicotine withdrawal from a relapse of mental illness. Monitoring of medication side effects is also required as smoking cessation increases blood levels of some medications and of alcohol and caffeine (49). Helping individuals to identify triggers to smoking and building skills to use alternate coping strategies is a mainstay of smoking cessation treatment. For people living with schizophrenia a focus needs to be given to building skills to manage negative affect, given its role as a barrier to both making and sustaining quit attempts. Lum et al. (8) discuss the potential of CBT behavioral activation approaches to address negative affect. Many mood management strategies can dually act as smoking cessation strategies. Building smoking refusal skills is also critical as is instituting alternative ways to feel rewarded to help reduce feelings of deprivation following smoking cessation (49–51).

Relapse is a common experience that needs to be normalized, recognizing that cessation may require multiple attempts to quit. The role of higher doses of NRT may also need to be considered as well as extended use of NRT or other cessation pharmacotherapies to prevent relapse. Feedback to the person's treatment team about their progress is recommended to facilitate coordinated care.

Supporting people living with schizophrenia to quit also requires system change including increased training for staff, and policies and procedures that embed smoking cessation brief interventions that link people to multisession behavioral support, and availability of NRT to address nicotine dependence. Smoke-free inpatient experiences, in particular those that provide NRT at sufficient levels to actively manage nicotine withdrawal provide important smoke-free experiences that need to be further built on, for example by routinely offering on discharge further cessation pharmacotherapy and enrolment in multisession behavioral treatment by telephone (52).

CONCLUSION

People living with schizophrenia want to quit smoking as much as people with other mental health issues, and the general community, but cessation rates remain low and this is contributing to significant physical health problems and premature death. Quitting smoking can lead to greater consideration of physical health, and as one of our authors describes, "being able to breathe properly enabled me to take up walking, yoga and mindfulness which in turn became powerful strategies to replace smoking". The perspective of people with lived experience of mental ill health, smoking cessation and personal recovery further assists in thinking through how to address all the complex psychosocial factors we have discussed. This is a social justice issue that presents opportunities for people with lived experience to enhance the recovery orientation in current and future efforts

to support smoking cessation. Integrating recovery-oriented approaches with existing evidence-based treatments designed to meet the needs of people living with schizophrenia have potential to improve outcomes by helping to take a more holistic approach to break down barriers and facilitate increased uptake of treatment and support. Further research to evaluate the effectiveness of integrated approaches is warranted.

The peer support model is based on shared responsibility, respect, and mutual understanding of what is helpful and together with the NRT and Quitline counselling, it is a potentially powerful strategy to support smoking cessation (53, 54). It is hoped that this approach will engage people with schizophrenia in successful quitting, thus enhancing their physical and mental health and psychosocial well-being and making an important and urgently needed contribution to reducing the mortality gap for those living with schizophrenia.

AUTHOR CONTRIBUTIONS

NC and LB led the writing of this paper and wrote core components. DC was senior author contributing oversight and core concepts. AS worked with NC on specialist content. SJ provided research assistance and summarized key literature. CS contributed specialist input and also wrote key section of the manuscript. LB prepared the paper for submission.

FUNDING

This project is funded by the National Health and Medical Research Council (APP1139125). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* (2005) 76(2-3):135–57. doi: 10.1016/j.schres.2005.02.010
2. Manzella F, Maloney SE, Taylor GT. Smoking in schizophrenic patients: a critique of the self-medication hypothesis. *World J Psychiatry* (2015) 5(1):35. doi: 10.5498/wjp.v5.i1.35
3. de Beaurepaire R, Rat P, Beauverie P, Houery M, Niel P, Castéra S, et al. Is smoking linked to positive symptoms in acutely ill psychiatric patients? *Nord J Psychiatry* (2012) 66(4):225–31. doi: 10.3109/08039488.2011.610468
4. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* (2007) 64(10):1123–31. doi: 10.1001/archpsyc.64.10.1123
5. Callaghan RC, Veldhuizen S, Jeysingh T, Orlan C, Graham C, Kakouris G, et al. Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. *J Psychiatr Res* (2014) 48(1):102–10. doi: 10.1016/j.jpsychires.2013.09.014
6. Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. *Annu Rev Clin Psychol* (2009) 5:409–31. doi: 10.1146/annurev.clinpsy.032408.153614
7. Anzai N, Young-Wolff KC, Prochaska JJ. Symptom severity and readiness to quit among hospitalized smokers with mental illness. *Psychiatr Serv* (2015) 66(4):443–4. doi: 10.1176/appi.ps.201400181
8. Lum A, Skelton E, Wynne O, Bonevski B. A systematic review of psychosocial barriers to smoking cessation in people living with schizophrenia. *Front Psychiatry* (2018) 9:565. doi: 10.3389/fpsyt.2018.00565
9. Twyman L, Bonevski B, Paul C, Bryant J. Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. *BMJ Open* (2014) 4(12):1–15. doi: 10.1136/bmjopen-2014-006414
10. Lawn S. Tobacco control policies, social inequality and mental health populations: time for a comprehensive treatment response. *Aust N Z J Psychiatry* (2008) 42(5):353–6. doi: 10.1080/00048670801961180
11. Faulkner A. Randomised controlled trials: the straitjacket of mental health research. McPin Talking Point Papers (2015). Available at: http://mcpin.org/resources/talking-point-papers/ (Accessed September 4, 2018).
12. Davidson L. The recovery movement: implications for mental health care and enabling people to participate fully in life. *Health Aff* (2016) 35(6):1091–7. doi: 10.1377/hlthaff.2016.0153
13. Davidson L, Bellamy C, Chinman M, Farkas M, Ostrow L, Cook JA, et al. Revisiting the rationale and evidence for peer support. *Psychiatr Times* (2018) 35(6):1–3.
14. Scollo MM, Winstanley MH. *Tobacco in Australia: facts and issues*. Melbourne: Cancer Council Victoria (2018). www.TobaccoInAustralia.org.au.
15. Harris C, Barraclough B. Excess mortality of mental disorder. *Brit J Psychiat* (1998) 173(1):11–53.
16. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. *Can J Psychiatry* (1991) 36(4):239–45. doi: 10.1177/070674379103600401
17. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry* (2014) 13(2):153–60. doi: 10.1002/wps.20128
18. Moore S, Shiers D, Daly B, Mitchell AJ, Gaughran F. Promoting physical health for people with schizophrenia by reducing disparities in medical and dental care. *Acta Psychiatr Scand* (2015) 132(2):109–21. doi: 10.1111/acps.12431
19. Meyer J, Barrington-Martin R, Parker A. U.S. Patent Application No. 10/125,835(2003). doi: 10.1080/713840360
20. Galletly CA, Foley DL, Waterreus A, Watts GF, Castle DJ, McGrath JJ, et al. Cardiometabolic risk factors in people with psychotic disorders: the second Australian national survey of psychosis. *Aust N Z J Psychiatry* (2012) 46(8):753–61. doi: 10.1177/0004867412453089
21. Filia SL, Baker AL, Richmond R, Castle DJ, Kay-Lambkin FJ, Sakrouge R, et al. Health behaviour risk factors for coronary heart disease (CHD) in smokers with a psychotic disorder: baseline results. *Ment Health Subst Use* (2011) 4(2):158–71. doi: 10.1080/17523281.2011.555088
22. Ösby U, Correia N, Brandt L, Ekbom A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* (2000) 45(1–2):21–8.
23. Bosanac P, Castle DJ. Schizophrenia and depression. *Med J Aust* (2013) 199(6):36–9. doi: 10.5694/mjao12.10516
24. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull* (2008) 35(2):383–402. doi: 10.1093/schbul/sbn135
25. Moore E, Mancuso SG, Slade T, Galletly C, Castle DJ. The impact of alcohol and illicit drugs on people with psychosis: the second Australian National Survey of Psychosis. *Aust N Z J Psychiatry* (2012) 46(9):864–78. doi: 10.1177/0004867412443900
26. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian Survey of Psychosis. *Aust N Z J Psychiatry* (2012) 46(9):851–63. doi: 10.1177/0004867412449876
27. Morgan VA, Janca A, Jablensky A. National study of psychotic disorders in Australia: feedback from individuals with psychosis. *East Asian Arch Psychiatry* (2002) 12:8–12.
28. Lawn SJ, Pols RG, Barber JG. Smoking and quitting: a qualitative study with community-living psychiatric clients. *Soc Sci Med* (2002) 54(1):93–104. doi: 10.1016/S0277-9536(01)00008-9
29. Trainor K, Leavey G. Barriers and facilitators to smoking cessation among people with severe mental illness: a critical appraisal of qualitative studies. *Nicotine Tob Res* (2016) 19(1):14–23. doi: 10.1093/ntr/ntw183

30. Kourakos M, Koukia E. A study of patients' smoking habits in a psychiatric hospital. *Int J Curr Sci* (2014) 7:592–601. (cited in Lum et al 2018).
31. Lawn SJ. Systemic barriers to quitting smoking among institutionalised public mental health service populations: a comparison of two Australian sites. *Int J Soc Psychiatr* (2004) 50(3):204–15. doi: 10.1177/0020764004043129
32. Hahn L, Rigby A, Galletly C. Determinants of high rates of smoking among people with psychosis living in a socially disadvantaged region in South Australia. *Aust N Z J Psychiatry* (2014) 48(1):70–9. doi: 10.1177/0004867413491158
33. Wye P, Bowman J, Wiggers J, Baker A, Carr V, Terry M, et al. Providing nicotine dependence treatment to psychiatric inpatients: the views of Australian nurse managers. *J Psychiatr Ment Health Nurs* (2010) 17(4):319–27. doi: 10.1111/j.1365-2850.2009.01524.x
34. Mitchell AJ, Vancampfort D, De Hert M and Stubbs B. Do people with mental illness receive adequate smoking cessation advice? A systematic review and meta-analysis. *Gen Hosp Psychiatry* (2015) 37(1):14–23. doi: 10.1016/j.genhosppsych.2014.11.006
35. Schulze B, Angermeyer MC. Subjective experiences of stigma. A focus group study of schizophrenic patients, their relatives and mental health professionals. *Soc Sci Med* (2003) 56(2):299–312. doi: 10.1016/S0277-9536(02)00028-X
36. Paul CL, Ross S, Bryant J, Hill W, Bonevski B, Keevy N. The social context of smoking: a qualitative study comparing smokers of high versus low socioeconomic position. *BMC Public Health* (2010) 10(1):211. doi: 10.1186/1471-2458-10-211
37. Yanos PT, Roe D, Lysaker PH. The impact of illness identity on recovery from severe mental illness. *Am J Psychiatr Rehabil* (2010) 13(2):73–93. doi: 10.1080/15487761003756860
38. Lawn S, Hersh D, Ward PR, Tsourtos G, Muller R, Winefield A, et al. 'I just saw it as something that would pull you down, rather than lift you up': resilience in never-smokers with mental illness. *Health Educ Res* (2010) 26(1):26–38. doi: 10.1093/her/cyq065
39. Bartlem KM, Bowman JA, Bailey JM, Freund M, Wye PM, Lecathelinais C, et al. Chronic disease health risk behaviours amongst people with a mental illness. *Aust N Z J Psychiatry* (2015) 49(8):731–41. doi: 10.1177/0004867415569798
40. Segan CJ, Borland R, Wilhelm KA, Bhar SS, Hannan AT, Dunt DR, et al. Helping smokers with depression to quit smoking: collaborative care with Quitline. *Med J Aust* (2011) 195:S7–11. doi: 10.5694/j.1326-5377.2011.tb03258.x
41. Australian Health Ministers' Advisory Council. *A national framework for recovery-oriented mental health services: Guide for practitioners and providers*. Canberra: Commonwealth of Australia (2013) Available from: https://www1.health.gov.au/internet/main/publishing.nsf/content/67D17065514CF8E8CA257C1D00017A90/$File/recovgde.pdf
42. Leamy M, Bird V, Le Boutillier C, Williams J, Slade M. Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. *Br J Psychiatry* (2011) 199(6):445–52. doi: 10.1192/bjp.bp.110.083733
43. Corrigan PW, Watson AC, Gracia G, Slopen N, Rasinski K, Hall LL. Newspaper stories as measures of structural stigma. *Psychiatr Serv* (2005) 56(5):551–6. doi: 10.1176/appi.ps.56.5.551
44. Malpass D, Higgs S. How is cigarette smoking maintained in depression? Experiences of cigarette smoking in people diagnosed with depression. *Addict Res Theory* (2009) 17(1):64–79. doi: 10.1080/16066350802079356
45. Dickerson F, Bennett M, Dixon L, Burke E, Vaughan C, Delahanty J, et al. Smoking cessation in persons with serious mental illnesses: the experience of successful quitters. *Psychiatr Rehabil J* (2011) 34(4):311. doi: 10.2975/34.4.2011.311.316
46. Goldberg JO. Successful change in tobacco use in schizophrenia. *J Am Psychiatr Nurses Assoc* (2010) 16(1):30–5. doi: 10.1177/1078390309357084
47. Dickerson FB, Savage CL, Schweinfurth LA, Medoff DR, Goldberg RW, Bennett M, et al. The use of peer mentors to enhance a smoking cessation intervention for persons with serious mental illnesses. *Psychiatr Rehabil J* (2016) 39(1):5. doi: 10.1037/prj0000161
48. Baker A, Borland R, Bonevski B, Castle DJ, Williams J, Segan C, et al. T92. QUITLINK: accessible smoking cessation support for people living with severe and enduring mental illness. *Schizophr Bull* (2018) 44(suppl_1):S151–1. doi: 10.1093/schbul/sby016.368
49. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry* (2015) 23(1):37–43. doi: 10.1177/1039856214562076
50. Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs* (2017) 31(6):471–81. doi: 10.1007/s40263-017-0438-8
51. Cieslak K, Freudenreich O. 4 Ways to help your patients with schizophrenia quit smoking. *Curr Psychiatry* (2018) 17(2):28–30.
52. Stockings EA, Bowman JA, Baker AL, Terry M, Clancy R, Wye PM, et al. Impact of a post discharge smoking cessation intervention for smokers admitted to an inpatient psychiatric facility: a randomized controlled trial. *Nicotine Tob Res* (2014) 16(11):1417–28. doi: 10.1093/ntr/ntu097
53. Mead S, Hilton D, Curtis L. Peer support: a theoretical perspective. *Psychiatr Rehabil J* (2001) 25(2):134.
54. Williams JM, Dwyer M, Verna M, Zimmermann MH, Gandhi KK, Galazyn M, et al. Evaluation of the CHOICES program of peer-to-peer tobacco education and advocacy. *Community Ment Health J* (2011) 47(3):243–51. doi: 10.1007/s10597-010-9310-8

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 17 July 2019
doi: 10.3389/fpsyt.2019.00503

'They're Going to Smoke Anyway': A Qualitative Study of Community Mental Health Staff and Consumer Perspectives on the Role of Social and Living Environments in Tobacco Use and Cessation

Laura Twyman[1,2], Carla Cowles[3], Scott C. Walsberger[1], Amanda L. Baker[2], Billie Bonevski[2] and the Tackling Tobacco Mental Health Advisory Group*

[1] Tabacco Control Unit, Cancer Council NSW, Woolloomooloo, NSW, Australia, [2] School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia, [3] Human Capital Alliance, Potts Point, NSW, Australia

OPEN ACCESS

Edited by:
Kelly Anne Allott,
University of Melbourne,
Australia

Reviewed by:
Michael W. Best,
Queen's University, Canada
Jackie Curtis,
University of New South Wales,
Australia

***Correspondence:**
Laura Twyman
Laura.Twyman@nswcc.org.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: 18 September 2018
Accepted: 25 June 2019
Published: 17 July 2019

Citation:
Twyman L, Cowles C, Walsberger SC, Baker AL, Bonevski B and the Tackling Tobacco Mental Health Advisory Group (2019) 'They're Going to Smoke Anyway': A Qualitative Study of Community Mental Health Staff and Consumer Perspectives on the Role of Social and Living Environments in Tobacco Use and Cessation. Front. Psychiatry 10:503. doi: 10.3389/fpsyt.2019.00503

Background: Addressing the high prevalence of tobacco use experienced by people with severe mental illness (SMI) requires consideration of the influence of wider cultural, socioeconomic and environmental factors. This qualitative study aimed to examine the impact of social and living environments on tobacco use and cessation by people with SMI accessing community managed mental health services. The perspectives of both staff and consumers with SMI were explored.

Methods: Semi-structured focus groups were undertaken with a purposive sample of community mental health staff and consumers from three sites in three major cities in NSW, Australia. Two sites provided outreach support, and one site provided residential support. Data were collected (2017–2018) until saturation was reached. Focus groups were audio-recorded and transcribed, and thematic analysis was conducted.

Results: Thirty-one staff and 17 consumers participated separately in six focus groups. Themes identified by staff included a degree of fatalism, conceptualising tobacco use as choice rather than addiction and tensions between cessation support and broader models of care. Staff viewed smoke-free home and mental health service policies as effective at promoting quitting but contradictory to recovery-oriented models of care. Consumers identified smoking as an integral part of life and social networks, as a way of maintaining control and lack of social support to quit as key themes. While many consumers reported smoking inside the home, others described enforcing smoke-free rules.

Conclusion: Social and living environments played an integral role in tobacco use and cessation for both staff and consumers. The role of community managed mental health organisations in addressing tobacco use within social and living environments was not strongly supported by staff and sometimes seen as antithetical to recovery-oriented models

of care. Potential ways to address this include education and training for prospective and current community mental health organisation staff highlighting the synergy between the recovery-oriented model and provision of preventive health support.

Keywords: community mental health, tobacco, mental illness, housing, living environment, social networks, qualitative

INTRODUCTION

The prevalence of tobacco use in Australia reached a historic low of ~13% in 2016 (AIHW 2017); however, prevalence is disproportionately higher amongst people experiencing mental illness. Prevalence varies with symptom severity and mental health disorder. For example, in Australia, tobacco use is consistently higher for people experiencing psychological distress (22%) (1); people who have ever been diagnosed or treated for a mental health condition (29%) (1) and people living with anxiety disorders (33%) (2), affective disorders (43%) (2) and psychotic disorders (67%) (3).

There is evidence that reductions in smoking prevalence seen in the general population have not occurred in groups with severe mental illness (SMI) and that rates have remained relatively stable among people with psychotic disorders (1). There are numerous definitions of severe (or serious) mental illness. Definitions tend to include reference to specific disorders, the severity of symptoms and the extent to which they impact on a person's functioning. In the current study, we use SMI to refer to diagnosed mental disorders including schizophrenia and other psychoses, bipolar disorder, severe anxiety and depression that result in functional impairment which substantially limits one or more major life activities (4).

Tobacco use is a leading risk factor for cancer, cardiovascular disease and respiratory disease. The disproportionate use of tobacco by people with SMI contributes to the gap in mortality experienced in this group (5). The financial and social harms of tobacco use are also exacerbated within this group (6). Tobacco use often increases the financial stress and social stigma felt by people with SMI. Studies have estimated that people with SMI spend approximately 27% of their income on tobacco (7, 8). There are numerous reasons for the disproportionate use of tobacco by people with SMI. These include genetic, individual, interpersonal, community, social and environmental factors. Shared genetic predispositions to both mental illness and tobacco, smoking to manage stress, mental health symptoms and medication side effects, the historic influence of institutionalisation and use of tobacco to control and reward behaviour, normalisation of tobacco and use of tobacco to combat boredom and social isolation have been documented (6, 9, 10). Additionally, documentation acquired reveals that the tobacco industry actively targets and markets to people with SMI and the organisations that provide mental health support (11, 12).

While smokers with SMI have higher levels of nicotine dependence (13, 14) and may require additional support to quit compared to people without SMI, smoking cessation is possible among people with SMI. Service providers' lack of knowledge and skills and negative attitudes towards addressing smoking (15–17) and systemic barriers within mental healthcare settings (18, 19) prevent people with SMI from receiving optimal smoking cessation support. Beliefs that people with SMI are not interested in quitting smoking and that quitting may jeopardise a person's mental health are commonly reported misperceptions held by health and other professionals (16, 17). However, evidence demonstrates that people with SMI are just as likely to express motivation and desire to quit smoking as the general population (20, 21). Furthermore, quitting smoking is not associated with increased depression, anxiety or stress (22).

There is a critical need to improve on the way tobacco is addressed with people with SMI (10, 23). Successfully addressing tobacco use in people with SMI requires examination of the wider social and environmental context (24). Socio-ecological models can help increase understanding of the factors within living and social environments of people with SMI that impact on tobacco use. Community managed mental health organisations (hereafter referred to as community mental health organisations) provide a large portion of care to people with SMI in Australia. In 2015–2016, 9.4 million service contacts were provided to approximately 410,000 people (25). In the same year, the most common principal diagnosis of people receiving care in these settings was schizophrenia, followed by depressive episode and bipolar affective disorder. In Australia, mental health settings in general are increasingly providing care through recovery-oriented models (26). Recovery-oriented models prioritise the lived experience of the consumer, challenge traditional notions of expertise and power differentials between staff and consumers and support consumers to define recovery through their own goals, wishes and aspirations (27). Definitions of recovery are not limited to ameliorating symptoms and instead are developed by individuals with influence from social processes. Community mental health organisations are well positioned to address tobacco with people who access their services, providing psychosocial support in a trusted setting. Using qualitative methodology, the current research study sought to gain an in-depth understanding of the ways in which living and social environments shape tobacco use and cessation within these settings from the perspective of both staff and consumers.

METHODS

Study Design

The aim of qualitative research is to gain in-depth understanding of real-world problems. In contrast to quantitative research, generalizability is not a guiding principle of qualitative research

(28–31). Semi-structured focus groups were conducted separately with staff and consumers of community mental health organisations from July 2017 to February 2018. Focus groups were chosen because they enable group discussion with members stimulating each other in sharing experiences and views and the potential for individual reflection in the context of hearing others' views (31). This study was carried out in accordance with the recommendations of the National Statement on Ethical Conduct in Human Research. The Cancer Council NSW Human Research Ethics Committee (#306) approved the study protocol, and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

Setting

This qualitative study was conducted in community mental health organisations in NSW, Australia. Community mental health organisations provide support through government-funded programs that are underpinned by an integrated care and support model (32). These programs involve partnerships between non-government organisations specialising in mental health who provide psychosocial support and NSW government health teams who provide clinical support. Services provided by the community mental health services include employment and education, leisure and recreation, family and carer support, helpline and counselling services, accommodation support and outreach and promotion, information and advocacy. The provision of smoking cessation services in this sector varies across and within organisations. Most support is provided *via* outreach; however, a small proportion of services also provide residential support. Community mental health organisations primarily support people with SMI (32), such as schizophrenia, bipolar disorder or schizoaffective disorder.

Sampling

Sites were eligible to participate in these focus groups if they provided community-based psychosocial support to people with SMI (including outreach and residential support). Purposeful sampling was used to attempt to include sites from both metropolitan and regional areas. Senior management of community mental health organisations provided permission for their organisation to participate in the qualitative research. Once organisational consent was provided, the research team worked with management to identify individual sites to participate. Site-specific managers and team leaders were briefed on the study aims and methods and asked to support recruitment of consumers for focus groups. Consumers were eligible to participate in the focus groups if they were currently engaged with the service, were either current smokers or ex-smokers or lived with a current smoker, aged 16 years or older and able to provide informed consent. Ability to provide informed consent was defined as ability to understand the study's purpose, risk and benefits as detailed in the information sheet (33). Staff at sites assessed consumer eligibility. Staff were eligible to participate in the study if they were currently providing support to consumers at the site. Staff could participate regardless of their own smoking status.

Procedure

Six focus groups were conducted across three sites. All focus groups were conducted by CC, a research consultant with a background in science communication and extensive experience in qualitative health research, tobacco control and the community mental health sector. A second consultant with a background in qualitative health research and health workforce planning attended two focus groups. All focus groups were conducted at participating sites in private meeting rooms. Focus groups were conducted separately for staff and consumers. Staff and consumer participants were informed that they could elect to complete one-on-one interviews if they preferred; however, none took up this offer. Participants were provided with an information sheet and consent form and were given the opportunity to ask questions about the research study before the group began. Short surveys were conducted with both consumers and staff prior to commencement of the focus group. Surveys for staff assessed age, gender, Aboriginal and/or Torres Strait Islander status, smoking status and role in the organisation. Surveys for consumers were identical except where 'role' was replaced with 'current mental health diagnoses'. Consumers were provided with a $50 grocery card gift voucher for participating. Staff did not receive reimbursement for participating. Data were collected until saturation was reached (i.e., no new themes were occurring in either staff or consumer groups).

Discussion Guide

Semi-structured discussion guides were tailored to staff and consumer focus groups. The questions were developed by the project team based on the research aims. Discussion guides for staff and consumers covered the following topics: smoking history and current smoking behaviour; smoke-free environments (community mental health organisations and consumer living environments); role of community mental health organisations in providing cessation support and the enablers and barriers to cessation.

Analysis

Data were collected, transcribed and analysed once all focus groups had been completed. Transcripts were analysed using thematic analysis. Summary notes of observations and impressions were developed by CC after each focus group. Data were continuously reviewed and compared to identify similarities and differences between sites, participant groups and responses to specific questions. Questions were modified for subsequent focus groups.

Transcription was undertaken by CC once all focus groups were completed, allowing for immersion in the data. Each transcript was reviewed by CC to note initial impressions and understanding of the data. Impressions and initial emerging themes were discussed by the researchers. This process was used to develop an initial set of codes. The transcripts were then re-read and coded by CC for relevant or meaningful phrases and sections of the transcripts, such as themes or comments that were repeated by several participants. Codes were modified and revised as required to best represent the data and then arranged

according to emerging themes. Final themes were reviewed and discussed with the second research consultant and the study authors to confirm accuracy of interpretation of the data.

Trustworthiness (Validity)

A vital part of qualitative methodology is the reporting of strategies to ensure the rigour of the qualitative work (34). The current study employed many of these strategies. During this study, the researchers considered how their professional background, experience and prior assumptions (as public health and behavioural science researchers) would impact on data collection and the ability to facilitate open and honest responses from participants. This included being sensitive to the different values and priorities that mental health staff may have around addressing tobacco compared to tobacco control public health researchers. During analysis and synthesis, an attempt was made to ensure that data were not presented as being representative of all consumers and/or staff. Rather, information was analysed and reported by comparing similarities and differences between, within and across groups. Where relevant, a majority view was reported. However, it was equally important to acknowledge individual experience and perspectives. A reflexive approach was adopted for all stages of the research process. Researchers would summarise, reflect and feed back information to confirm or clarify data collected within focus groups. Data were deliberately collected from a variety of sources, namely staff and consumers with varying demographic characteristics, geographic locations and services provided at sites (primarily residential versus outreach). This increased transferability of the research findings. The dependability of the research findings was enhanced by involving two researchers in the data collection and coding. A preliminary report of the research findings was presented to a panel of research academics, consumer experts and community mental health sector workers to ascertain further feedback and refine themes.

RESULTS

Recruitment and Demographic Survey Results

Three sites from two organisations provided consent to participate (see **Table 1**). Two sites provided outreach support for consumers. One site provided 24-h residential support to consumers.

Table 2 provides the results of the short demographic surveys completed by staff and consumers at the beginning of each focus group. Many consumer participants had a current diagnosis of schizophrenia (47%) or depression (47%). The majority of staff were mental health support workers. Aboriginal or Torres Strait Islander people were over-represented as consumer participants; however, no staff participants identified as Aboriginal or Torres Strait Islander peoples.

TABLE 1 | Focus group site, location and participant numbers.

	Location	Consumers (*n* = 17)	Staff (*n* = 31)
Organisation 1			
Site 1A (Outreach support)	Regional	5	7
Site 1B (Residential support)	Regional	5	12
Organisation 2			
Site 2A (Outreach support)	Metropolitan	7	12

Smoking as an Integral Part of Living and Social Environments

Most consumers reported long histories of smoking, starting when they were in their early teenage years. Consumers identified factors in the living and social environments they grew up in as influential in their initiation of smoking. Living with a parent or carer who smoked, being surrounded by other peers

TABLE 2 | Results of demographic surveys for consumers and staff.

Demographic information	Staff (*n* = 31)	Consumers (*n* = 16)[a]
Age range		
16–25	3 (9%)	2 (13%)
26–45	16 (52%)	6 (38%)
46–65	12 (38%)	8 (50%)
Gender[b]		
Female	23 (74%)	7 (41%)
Male	8 (25%)	8 (47%)
Aboriginal and/or Torres Strait Islander status		
Yes	0 (0%)	3 (19%)
No	29 (93%)	13 (81%)
Smoking status[c]		
Current smoker	7 (23%)	14 (86%)
Ex-smoker	8 (26%)	2 (13%)
Non-smoker	14 (45%)	0
Role of health professional		
Mental health support worker	17 (55%)	–
Other[d]	6 (19%)	–
Peer worker	4 (13%)	–
Manager	3 (10%)	–
Team leader	1 (3%)	–
Current mental health diagnosis[e]		
Depression	–	8 (50%)
Schizophrenia	–	8(50%)
Anxiety	–	4 (25%)
Bipolar disorder	–	3 (19%)
Schizoaffective disorder	–	3 (19%)
Personality disorder	–	1 (6%)
Other[f]	–	2 (13%)

[a]*While 17 consumers participated in the focus groups, 16 completed the demographic survey.*
[b]*Gender missing for one consumer participant*
[c]*Smoking status missing for one consumer participant.*
[d]*'Other' includes students on work placement, Health Promotion Officers and participants who preferred not to answer.*
[e]*Mental illness diagnosis missing for one consumer participant, consumers could tick more than one mental health disorder when responding.*
[f]*'Other' includes post-traumatic stress disorder and one consumer participant who preferred not to answer.*

who smoked or working in industries where smoking was the norm was common.

"I was brought up in a foster home where everyone smoked, and it was chronic."
–Consumer participant (male, occasional smoker, aged 46–55)

"I worked in hospitality industry for 9 years, and it was like a smoke-filled environment anyway. Smoking back then, you walked into the club, and you walked into the smoke."
–Consumer participant (male, daily smoker, aged 46–55)

"I used to like it as a kid. My old man used to smoke cigars, smoke at least one a day, big fat cigars, and I used to love the smell of it. And then when I was probably in year 6, I started pinching my mother's cigarettes; she used to smoke Winfield menthol cigarettes."
–Consumer participant (male, daily smoker, aged 46–55)

The culture of smoking, which included sharing cigarettes and use of smoking to socialise and maintain social networks, was discussed as a significant barrier for quitting smoking and addressing tobacco in general. Opportunities for socialising were limited to being with peers who also smoked. Consumers also talked about the high prevalence of smoking in their communities.

"I think the majority of people smoke. Everywhere you go, there are people in front of you smoking."
–Consumer participant (female, daily smoker, aged 46–55)

"All my friends smoke, and my mum smokes heaps. Most of my family smoke."
–Consumer participant (female, daily smoker, aged 18–25)

Staff talked about the historical effects of institutionalisation continuing to have an impact in the present day, particularly for older consumers who may have spent extended periods of time in institutions. Staff criticised systemic issues that led to non-smokers beginning to smoke to access perceived benefits of smoking, for example, short-term leave from inpatient settings.

"Many of these people [consumers] have come out of the local mental health unit or an institution and have had long periods of time, years, in those places. And there is a real culture around smoking in these places; there's a bartering culture, so some of this stuff is entrenched."
–Staff participant (female, ex-smoker, aged 56–65)

"[Consumers will] attend mental health–specific groups, and all of them go and stand in the back garden and smoke together. I met someone who was admitted to rehab, and doctors give 15-minute leave, so what else are they supposed to do? Consumers actually picked up smoking just so they could get that 15 minutes' leave; then they come out, and they make friends in rehab, and they all smoke, and it becomes a habit and a social thing."
–Staff participant (male, ex-smoker, aged 46–55)

Smoke-Free Living Environments

The majority of consumers were living in a unit, bedsit or apartment in an apartment complex. One consumer talked about living in a house. Most lived alone, some were living with co-tenants, and some consumers had children that visited and stayed with them periodically. A number of consumers talked about neighbours in nearby apartments who smoked. Smoking in the home was a common and normal occurrence for almost all consumers.

"You're not allowed to smoke inside, but I do … In the kitchen, I smoke bumpers. I don't smoke a full cigarette inside, just a little short one."
–Consumer participant (female, daily smoker, aged 46–55)

"…when I'm there on my own, I smoke anywhere I want in the house."
–Consumer participant (male, daily smoker, aged 46–55)

Reasons for smoking inside the home included practical considerations such as hot or cold weather, lack of balconies, neighbours asking for cigarettes, unsafe neighbourhoods, living alone and social isolation. Consumers and staff highlighted smoking in the home as an act of consumers maintaining control and sense of choice in lives where there was a limited sense of choice and control.

"…there's not many places you can smoke anymore; you're sort of limited. There's lots of places that people would like to smoke in, but they're not allowed to."
–Consumer participant (female, daily smoker, aged 46–55)

"The isolation, living alone, it's their space; they're not impacting on anyone else but themselves in that space."
–Staff participant (female, daily smoker, aged 36–45)

"People don't have a lot of control in their life, so in their own home, they choose to smoke inside because that's their choice."
–Staff participant (female, daily smoker, aged 26–35)

A small number of consumers talked about enforcing their own 'no smoking' rules inside the home because they did not like the smell of smoke in the home, they had previously quit smoking or they had children and were worried about the impact on their health.

"If you're on your own, I think it's acceptable. But if you've got kids and you're smoking in front of them, and then they're inhaling the toxins."
–Consumer participant (female, daily smoker, aged 26–35)

Staff confirmed that smoking inside the home was a regular and normal occurrence for consumers and expressed fatalistic views regarding the utility of attempting to address smoking in consumers' living environments.

"They're going to smoke when we're not there. They're not supposed to smoke in their property, but they do. You can't stop it, but you could discourage it."
–Staff participant (male, ex-smoker, aged 46–55)

"They're going to smoke anyway; better to be open about it, and if we put that boundary, there then we'll never have that opportunity to have those conversations."

–Staff participant (male, ex-smoker, aged 36–55)

The physical design of apartment complexes was also discussed by staff who felt that the configuration of complexes could either enable or inhibit consumers to implement smoke-free homes. Shared common areas in complexes tended to be designated smoking areas (either formally or informally), particularly for people who lived on their own. Complexes with less shared common space were seen as promoting smoke-free homes by discouraging socialising. The design of units and proximity of neighbours who smoked was also raised as a contributing factor to increased second-hand smoke exposure.

"The two [consumers] that keep on smoking, they share a wall, and so they talk over the wall, and they can smell the smoke."

–Staff participant (male, ex-smoker, aged 46–55)

"…the configuration of the units was slightly different … it was slightly less social in those properties. There was no common area; other properties do have a common area. I think that could help."

–Staff participant (female, daily smoker, aged 36–55)

However, there was unanimous agreement across all participants that passive smoking was a risk to health.

"Passive smoking can make you ill. When I was a non-smoker and my friend used to smoke, and when I breathed it in, I had to go on antibiotics."

–Consumer participant (female, daily smoker, aged 46–55)

"If consumers want to have a smoke, I let them know I don't want to be part of it; I'll be over here away from them."

–Staff participant (male, non-smoker, aged 46–55)

Smoke-Free Environments and Consumer Engagement

All staff expressed positive views on the potential role of community mental health organisations to help smokers quit. Staff who were smokers were primarily concerned about their responsibility to be positive role models for consumers. Staff who smoked described strategies they used to ensure that consumers did not see them smoking and even to avoid smelling of cigarette smoke. Many staff who were smokers preferred that consumers were not even aware that they were smokers because they felt hypocritical and disingenuous.

"I would never smoke in front of someone I support; I don't like them to know I smoke. I always try to mask the smell. If I have one at work, I go far away so no one can see."

–Staff participant (female, daily smoker, aged 26–35)

Promoting or implementing smoke-free organisations was a conflicting issue for most staff. All staff expressed recognition and concern about the financial, health and social impacts of smoking. Staff understood why consumers smoked and the impact of consumers' wider social and living environments on the difficulty of quitting smoking. Yet most staff talked about feeling ambivalent about implementing smoke-free areas, services and homes managed by their organisations. The greatest concern for staff was related to consumers not accessing support if services were smoke-free. Arguments for making services smoke-free were weighed up against the potential for consumers to cease accessing support and risk becoming more socially isolated. Some staff viewed current designated smoking areas as problematic but felt reluctant to remove those areas because they were perceived as often the only opportunities for consumers to socialise and leave the home. Reconfiguring the design of designated smoking areas was raised as a possible compromise by some staff. Current smoking areas were perceived as areas that promoted socialising. Staff suggested making designated smoking areas less inviting so that consumers would be less inclined to remain in the area.

"…if we were to say that you can't smoke here anymore, I think a significant amount of people would not come [to the community mental health service]."

–Staff participant (female, daily smoker, aged 36–45)

Tensions Between Cessation Support and Models of Care

Underpinning the ambivalence of staff for smoke-free environments and homes was the conflict with recovery-oriented support, that it was the antithesis of autonomy and undermined self-efficacy.

"I think a blanket rule to say you can't smoke wouldn't work for this setting. It wouldn't fit in with our recovery focus. Our role would need to be recovery focus that gives consumers choice."

–Staff participant (female, occasional smoker, aged 26–35)

Staff expressed reluctance to provide smoking cessation support to consumers who had not requested it due to the focus in recovery-oriented models of care on choice. Staff emphasised that their role was to provide reactive support to consumers who requested help regarding their smoking, rather than provide proactive support. Staff felt that it was the role of community mental health organisations to support smokers to quit, but this needed to be done in line with recovery and goal-oriented support that focussed on consumer goals and choices.

"…make it very clear that it's their choice. That's part of our role; it's not our place to tell people what they should and shouldn't do. It's about supporting their decisions even if we don't think it might be the best thing. Independence and autonomy."

–Staff participant (female, daily smoker, aged 26–35)

Lack of Support and Attitudes of Other People

Other people's unsupportive attitudes towards quitting smoking and an overall lack of social support were raised as barriers to

quitting smoking by consumers. Some consumers talked about a lack of support in relation to being isolated or disconnected from family or other networks. Other consumers with more social support had largely negative views about the prospect of telling someone in their network that they were thinking about quitting smoking. Similarly, staff felt that involving friends and family in a quit attempt may not be a helpful strategy or could even be an impediment to quitting smoking for some consumers.

> "…they've just laughed at me; it was kind of like "ye sure", and then you just think, well … what's the point? You aren't supporting me in any way, so forget it."
>
> –Consumer participant (female, daily smoker, aged 46–55)

> "…sometimes family just can't cope with supporting that person, and that causes tension and trauma and pain. So then in those situations, if you don't feel like you're supported by your family, why would you ask for help?"
>
> –Staff participant (female, daily smoker, aged 26–35)

Social Isolation and Exclusion

Across the staff and consumer focus groups, boredom, isolation and loneliness were raised as critical barriers to quitting smoking. Consumers used smoking as a form of company or socialising and as a recreational activity to pass the time in lieu of any other distractions or activities.

> "I'm quite isolated where I live, so I tend to, if I'm feeling stressed from the isolation, I'll smoke for the company of the smoke…"
>
> –Consumer participant (male, occasional smoker, aged 46–55)

> "Loneliness is one kind of factor. They're just really lonely. I asked one of my consumers, "how can you afford this amount of money in the week to spend on smoking?" And he said, "this is my friend; I talk to him while I'm smoking". He is cut out from the world; he has no family contact, limited friends, so he's saying this from his heart. 'When I light this, it brightens me up.'"
>
> –Staff participant (male, non-smoker, aged 36–45)

> "Social inclusion and lack of social participation that the majority of our consumers have. We're all sitting at work today, and we're not having a cigarette because we have to be in this room and office, so we can't. But when you're in your home and if there isn't a barrier, apart from whether you can afford to have a cigarette, you can just chain-smoke all day long."
>
> –Staff participant (female, non-smoker, aged 18–25)

DISCUSSION

This study aimed to explore the factors within consumer's social networks and living environments that facilitated or inhibited smoking cessation from the perspective of staff and consumers with SMI. Both staff and consumers discussed the pivotal role that living and social environments play in tobacco use and cessation by people with SMI. Consumers identified smoking as an integral part of life and identified a lack of social support, isolation and loneliness as key barriers to quitting. While many consumers reported smoking inside the home, others described enforcing smoke-free rules. Staff spoke about tobacco use with a degree of fatalism, conceptualised tobacco use as a choice rather than an addiction and highlighted tensions between cessation support and broader models of care. Staff viewed smoke-free home and mental health service policies as effective at promoting quitting but contradictory to recovery-oriented models of care.

Social isolation (including alienation, stigma and loneliness) is commonly reported by people with SMI (35) and is a barrier to quitting smoking (36, 37). Evidence suggests that smoking behaviour is influenced by social networks and that groups of people quit together *via* social contagion (38). Quitting smoking in and of itself may expand a person's social environment (39). Effective interventions for enhancing social networks exist (40) and can involve guided peer support groups focussing on enhancing social relationships (41) and cognitive and social skills training (42). There is also potential for incentives-based programs paired with peer support to improve social functioning (43). Such programs could address the barrier of social isolation by promoting the positive effects of strengths-based social support in tandem with offering smoking cessation support. The use of peer support to deliver tobacco cessation programs also has potential to overcome social isolation (44). Further research is required to establish the effectiveness of addressing social isolation and use of peer-delivered interventions as part of tobacco cessation programs. Use of tobacco to self-medicate and cope with stress has been identified as a barrier to quitting by people with SMI. In a sample of smokers with schizophrenia, 60% reported smoking to relieve stress and 31% to alleviate symptoms of anxiety and depression (45). Additionally, the tobacco industry has also funded internal and external research to support the self-medication hypothesis (9, 12). However, this did not arise as a key theme in this study. This is most likely due to the focus of the discussion guides, which looked at the factors specifically within a person's living and social environments.

People with SMI are less likely to live in smoke-free homes than people without SMI (46), and many consumers in the current study were breaching their tenancy agreements by smoking inside the home. One Australian study found that only 31.5% of people with SMI lived in a smoke-free home (46). On a population level, smoke-free homes are associated with increased smoking cessation and decreased cigarette consumption in adult smokers (47). Existing programs are effective at decreasing exposure to second-hand smoke within homes (48). Reflecting the existing literature (49, 50), the factors that facilitated smoke-free homes in the current study included presence of children and those with health issues that are exacerbated by tobacco smoke, concern over effects of second-hand smoke, suitable designated smoking areas, safe neighbourhoods and not liking the smell of smoke in the home. Further research is required to examine effective interventions for promoting smoke-free homes for people with SMI. Tenants and public and private stakeholders should be involved in developing, implementing and evaluating smoke-free home policy (51).

Fatalism that tobacco use is inevitable and that quit attempts will fail has been documented in previous studies exploring staff attitudes to addressing tobacco (52). Evidence suggests that fatalistic beliefs may serve several functions including to save face, to manage uncertainty, to relieve stress or to make sense of current experiences (53). In the current context, staff fatalism may be a response to the perceived complexity of addressing tobacco and a sense of powerlessness to affect change. Between 2.5% and 55.1% of mental health professionals believe that smoking cessation interventions are ineffective (15). Even trained smoking cessation counsellors in the UK Stop Smoking Services identify a need for further training to support people with mental illness, with 77.4% of counsellors wanting more training on the effects of quitting smoking on mental health (54). It is especially important to address staff fatalism given the association between consumers' *perceptions* of staff support and quitting. Higher levels of perceived staff support have been associated with a greater number of quit attempts (55). Opportunities to increase staff optimism about the possibility of consumers quitting smoking including training for staff and targeted marketing campaigns to the community mental health sector may help to address fatalistic attitudes.

Staff consistently upheld the view that tobacco use was a consumer's choice and that reactive rather than proactive support should be offered. This is supported by a meta-analysis of mental health professionals' attitudes that found that 51.4% (pooled proportion) of staff felt that people with SMI were not interested in quitting smoking (15). This is despite evidence indicating that people with mental illness are just as motivated to quit smoking as those in the general population. A meta-analysis found aggregated data from nine studies that indicated that more than 50% of smokers with mental illness are planning to quit within the next 30 days to six months (20). Conceptualising smoking as a choice is problematic as it ignores the physiological addiction caused by nicotine (56), the young average age of smoking initiation (57) and the social determinants of tobacco use and health (58). Additionally, the tobacco industry uses the argument of choice to shift the responsibility of the harms of tobacco to smokers and to minimise the powerful role the industry has in shaping individuals' environments in ways that are detrimental to individuals' health (59).

Tensions between recovery-oriented models of care and addiction treatment have been documented (60). The tension described by staff between addressing tobacco and recovery-oriented models of care deserves further discussion. Staff were concerned that smoke-free environments were antithetical to the principles of recovery-oriented models of care that emphasise autonomy, independence and consumer-driven goals. Viewing tobacco use as a choice and low confidence in the efficacy of staff-delivered support were interlinked with this perspective. However, this perspective does not acknowledge the contribution of quitting smoking to recovery in mental health including reducing stress and increasing quality of life (22). Furthermore, staff rarely referenced consumers' goals or preferences in receiving support for smoke-free environments or cessation or factors within social and living environments that may prevent consumers from making informed decisions about cessation. The extent of this tension between recovery-oriented models of care and provision of other preventive health support or advice is unknown. It is possible that staff also experience a tension when required to address other behaviours, for example, illicit drug use, nutrition, physical activity, alcohol and sexual health. This has implications for the broader aim of addressing the physical health needs of people experiencing mental illness. In acknowledging the broader influence of living and social environments, creating smoke-free environments and addressing nicotine dependence enable people with SMI to exercise autonomy in considering alternatives to smoking. Further research is required to ascertain how addressing tobacco may be conceptualised as part of recovery models of care from the perspective of consumers, staff and carers.

Pooled proportions from the published literature indicate that mental health professionals report lack of knowledge, training and skills (35.8%) and low confidence (31%) as barriers to supporting people with mental illness to quit (15). The published literature and the results of the current study highlight the importance of continuing to provide education and training to community mental health staff that people with mental illness are interested in quitting and are capable of quitting smoking and that quitting smoking positively impacts on mental health and quality of life and supports recovery (9). Training could also address the physiological effects of nicotine, tobacco industry interference and the broader social determinants of health and how these influences might curtail the ability of a person to make informed choices. There is the potential to review learning curricula in key tertiary courses at both universities and technical colleges to ensure that people entering these professions understand these concepts early on in their professional careers. Training to address these myths and impart smoking cessation support skills needs to form part of broader, organisation-wide interventions. Organisational or systems change interventions require a multifaceted approach, involving multidisciplinary and 'multi-level' collaboration from senior management, staff, consumers and carers to develop, implement and evaluate policies, procedures and processes that support the routine and consistent addressing of tobacco. Organisational interventions are effective at changing practice within healthcare settings (61) and have potential to be effective in mental health services settings (62).

Community mental health organisations are well placed to address issues such as social inclusion and smoke-free homes as part of their provision of psychosocial care (6, 63). A sample of community service sector managers surveyed found that 86% felt positively about providing support and encouragement to quit to their clients (64). However, community mental health organisations will require additional resourcing and support to do so. These findings indicate that engagement with a broader range of key stakeholders will be required to address tobacco within the living and social environments of people with SMI, e.g., housing, employment, planning and development and all levels of government. It is not the intention of this research to reflect negatively on the work of staff or their perceptions of smoking and mental health consumers. Staff

clearly articulated knowledge on the negative impacts of smoking and even the broader social and economic factors that drive smoking rates in populations such as people with SMI. The aim of this work was to highlight areas where staff require further support to continue the important work they do in providing care for consumers. It is equally important to recognise the scope and boundaries of the work done by community mental health staff. Issues such as appropriate smoking cessation pharmacotherapy, medication interactions and monitoring of withdrawal symptoms require input and collaboration with those who provide clinical care. Carers also play a role in advocating for the provision of smoking cessation support by staff (65) and supporting cessation for people with SMI (55).

Strengths and Limitations

The inclusion of services that provide psychosocial support to people with SMI including primarily psychotic disorders is a strength of this study. Additionally, the sampling frame allowed the inclusion of services that provided outreach or residential support, ensuring participation by consumers with varying levels of support needs. The findings of this study may reflect the social and living environment impacts of other priority populations without SMI, e.g., people seeking treatment for drug and alcohol problems and people from more disadvantaged socioeconomic backgrounds. However, the results of this study should be interpreted considering a number of study limitations. The results of this study may not be transferable to other mental health services (e.g., inpatient or private) and may not reflect experiences within rural communities. It is possible that there may have been key differences between consumers who decided to participate and those that did not, and these findings may not generalise beyond those who took part in the study. However, generalisability is not an aim of qualitative enquiry. Rather, the aim is to gather rich and detailed data from a specific sample.

Key future recommendations arising from this paper include:

- Examining the effectiveness of tobacco cessation interventions that include components to improve social inclusion, social support and organisational change within community mental health organisations
- Utilising population- and targeted-based interventions, adapted for mental health populations, to enhance awareness and implementation of smoke-free environments, including smoke-free homes
- Exploring the impact that resourcing has on community mental health organisations' ability to provide routine and comprehensive smoking cessation support
- Exploring staff, consumer and carer perspectives on definitions of recovery and how addressing tobacco can align with these models
- Continuing to build on the work already done with carers and family as support networks to help people with SMI quit smoking
- Ensuring that education and training programs for prospective and current staff in the community mental health sector address the key misconceptions identified in this paper
- Promoting multisectoral partnerships in addressing tobacco including fields other than health, e.g., housing, employment, planning and development and all levels of government

Conclusions

Consumers identified smoking as an integral part of life and identified a lack of social support, isolation and loneliness as key barriers to quitting within their social networks. While many consumers reported smoking inside the home, others described enforcing smoke-free rules. Staff spoke about tobacco use with a degree of fatalism, conceptualised tobacco use as a choice rather than an addiction and highlighted tensions between cessation support and broader models of care. Staff viewed smoke-free home and mental health service policies as effective at promoting quitting but contradictory to recovery-oriented models of care. There is great potential for the community mental health sector to address tobacco use by consumers through addressing some of the factors within consumers' living and social environments. However, more education and training to increase staff awareness of the issue coupled with effective programs that target factors within the social and living environment of people with SMI are required. Community mental health organisations are well placed to address many of the factors within consumers' living and social environments; however, they must be properly resourced to do so. Multisectoral involvement in addressing tobacco is required at the level of living and social environments.

TACKLING TOBACCO MENTAL HEALTH ADVISORY GROUP

Karina Ko, Centre for Population Health, NSW Ministry of Health, North Sydney, NSW, Australia; Christopher Oldmeadow, Clinical Research Design, IT, and Statistical Support (CReDITSS), Hunter Medical Research Institute, Wallsend, NSW, Australia; Sharon Lawn, Flinders Human Behaviour and Health Research Unit, Department of Psychiatry, Flinders University, Adelaide, SA, Australia; Marianne Weber, Cancer Research Division, Cancer Council NSW, Woolloomooloo, NSW, Australia; Jennifer Bowman, School of Psychology, Faculty of Science and Information Technology, The University of Newcastle, University Drive, Callaghan, NSW, Australia and Hunter Medical Research Institute, Clinical Research Centre, New Lambton Heights, NSW, Australia; Marita Hefler, Tobacco Control Research Program, Wellbeing & Preventable Chronic Diseases Division, Menzies School of Health Research, Casuarina, NT, Australia; Philippa Boss, Sydney Medical School, University of Sydney, Camperdown, NSW, Australia.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the National Statement on Ethical Conduct in Human Research. The Cancer Council NSW Human Research Ethics Committee (#306) approved the study protocol and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

LT, SCW, ALB and BB conceived and designed the analysis. CC collected the data and performed the analysis. LT and CC wrote the initial draft of the paper. All authors including the Advisory Group were involved in reviewing draft manuscripts and contributing to interpretation of results. All authors read and approved the submitted version.

FUNDING

This study was funded by the NSW Ministry of Health.

ACKNOWLEDGMENTS

The authors acknowledge Lee Ridoutt, who contributed valuable feedback on data collection and analysis, and the staff and consumers who participated and made this body of work possible.

REFERENCES

1. AIHW. *National Drug Strategy Household Survey 2016: detailed findings*. Canberra: Australian Institute of Health and Welfare (2017).
2. Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health* (2009) 9:285. doi: 10.1186/1471-2458-9-285
3. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian Survey of Psychosis. *Aust N Z J Psychiatry* (2012) 46(9):851–63. doi: 10.1177/0004867412449876
4. RANZCP. *The economic cost of serious mental illness and comorbidities in Australia and New Zealand*. Victoria, Australia: Royal Australian and New Zealand College of Psychiatrists (2016).
5. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* (2013) 346. doi: 10.1136/bmj.f2539
6. Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. *Annu Rev Public Health* (2010) 31:297–314, 1p following. doi: 10.1146/annurev.publhealth.012809.103701
7. Steinberg ML, Williams JM, Ziedonis DM. Financial implications of cigarette smoking among individuals with schizophrenia. Tobacco control (2004) 13(2):206-. doi: 10.1136/tobaccocontrol-2014-051849
8. Lawn S. Australians with mental illness who smoke. *Br J Psychiatry* (2001) 178(1):85-. doi: 10.1192/bjp.178.1.85
9. Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annu Rev Public Health* (2017) 38:165–85. doi: 10.1146/annurev-publhealth-031816-044618
10. Williams JM, Steinberg ML, Griffiths KG, Cooperman N. Smokers with behavioral health comorbidity should be designated a tobacco use disparity group. *Am J Public Health* (2013) 103(9):1549–55. doi: 10.2105/AJPH.2013.301232
11. Apollonio DE, Malone RE. Marketing to the marginalised: tobacco industry targeting of the homeless and mentally ill. *Tob Control* (2005) 14(6):409–15. doi: 10.1136/tc.2005.011890
12. Prochaska JJ, Hall SM, Bero LA. Tobacco use among individuals with schizophrenia: what role has the tobacco industry played? *Schizophr Bull* (2008) 34(3):555–67. doi: 10.1093/schbul/sbm117
13. Forman-Hoffman VL, Hedden SL, Glasheen C, Davies C, Colpe LJ. The role of mental illness on cigarette dependence and successful quitting in a nationally representative, household-based sample of U.S. adults. *Ann Epidemiol* (2016) 26(7):447–54. doi: 10.1016/j.annepidem.2016.05.004
14. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA* (2000) 284(20):2606–10. doi: 10.1001/jama.284.20.2606
15. Sheals K, Tombor I, McNeill A, Shahab L. A mixed-method systematic review and meta-analysis of mental health professionals' attitudes toward smoking and smoking cessation among people with mental illnesses. *Addiction* (2016) 111(9):1536–53. doi: 10.1111/add.13387
16. Koch JR, Breland A. Behavioral healthcare staff attitudes and practices regarding consumer tobacco cessation services. *J Behav Health Serv Res* (2017) 44(3):399–413. doi: 10.1007/s11414-015-9477-4
17. Rogers ES, Gillespie C, Smelson D, Sherman SE. A qualitative evaluation of mental health clinic staff perceptions of barriers and facilitators to treating tobacco use. *Nicotine Tob Res* (2018) 20(10):1223–30. doi: 10.1093/ntr/ntx204
18. Lawn SJ. Systemic barriers to quitting smoking among institutionalised public mental health service populations: a comparison of two Australian sites. *Int J Soc Psychiatry* (2004) 50(3):204–15. doi: 10.1177/0020764004043129
19. Rojewski AM, Bailey SR, Bernstein SL, Cooperman NA, Gritz ER, Karam-Hage MA, et al. Considering systemic barriers to treating tobacco use in clinical settings in the United States. *Nicotine Tob Res* (2018). doi: 10.1093/ntr/nty123
20. Siru R, Hulse GK, Tait RJ. Assessing motivation to quit smoking in people with mental illness: a review. *Addiction* (2009) 104(5):719–33. doi: 10.1111/j.1360-0443.2009.02545.x
21. Ashton M, Rigby A, Galletly C. What do 1000 smokers with mental illness say about their tobacco use? *Aust N Z J Psychiatry* (2013) 47(7):631–6. doi: 10.1177/0004867413482008
22. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *Br Med J (Clin Res Ed)* (2014) 348:g1151. doi: 10.1136/bmj.g1151
23. Bonevski B, Borland R, Paul CL, Richmond RL, Farrell M, Baker A, et al. No smoker left behind: it's time to tackle tobacco in Australian priority populations. *Med J Aust* (2017) 207(4):141–2. doi: 10.5694/mja16.01425
24. Sallis JF, Owen N, Fisher EB. Ecological models of health behavior. In: *Health behavior and health education: theory, research, and practice*. San Francisco CA US: Jossey-Bass 4th ed. (2008). p. 465–85.
25. AIHW. *Mental health services in Australia*. Canberra, Australia: Australian Institute of Health and Welfare (2018).
26. Department of Health. *The fifth national mental health and suicide prevention plan*. Canberra, Australia: Commonwealth of Australia represented by the Department of Health (2017).
27. Anthony WA. Recovery from mental illness: the guiding vision of the mental health service system in the 1990s. *Psychiatr Rehabil J* (1993) 16(4):11–23. doi: 10.1037/h0095655
28. Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 2: context, research questions and designs. *Eur J Gen Pract* (2017) 23(1):274–9. doi: 10.1080/13814788.2017.1375090
29. Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 4: trustworthiness and publishing. *Eur J Gen Pract* (2018) 24(1):120–4. doi: 10.1080/13814788.2017.1375092
30. Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 1: introduction. *Eur J Gen Pract* (2017) 23(1):271–3. doi: 10.1080/13814788.2017.1375093

31. Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 3: sampling, data collection and analysis. *Eur J Gen Pract* (2018) 24(1):9–18. doi: 10.1080/13814788.2017.1375091
32. AIHW. *Mental health services in Australia*. Canberra: Australian Institute of Health and Welfare (2017).
33. Hickman NJ, Prochaska JJ, Dunn LB. Screening for Understanding of research in the inpatient psychiatry setting. *J Empir Res Hum Res Ethics* (2011) 6(3):65–72. doi: 10.1525/jer.2011.6.3.65
34. Shenton, AK. "Strategies for ensuring trustworthiness in qualitative research projects." *Education for Information* (2004) 22(2):63–75. doi: 10.3233/EFI-2004-22201
35. Linz SJ, Sturm BA. The phenomenon of social isolation in the severely mentally ill. *Perspect Psychiatr Care* (2013) 49(4):243–54. doi: 10.1111/ppc.12010
36. Lum A, Skelton E, Wynne O, Bonevski B. A systematic review of psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. *Front Psychiatry* (2018) 9:565-. doi: 10.3389/fpsyt.2018.00565
37. Twyman L, Bonevski B, Paul C, Bryant J. Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. *BMJ Open* (2014) 4(12):e006414. doi: 10.1136/bmjopen-2014-006414
38. Christakis NA, Fowler JH. The collective dynamics of smoking in a large social network. *N Engl J Med* (2008) 358(21):2249–58. doi: 10.1056/NEJMsa0706154
39. Bray BC, Smith RA, Piper ME, Roberts LJ, Baker TB. Transitions in smokers' social networks after quit attempts: a latent transition analysis. *Nicotine Tob Res* (2016) 18(12):2243–51. doi: 10.1093/ntr/ntw173
40. Anderson K, Laxhman N, Priebe S. Can mental health interventions change social networks? A systematic review. *BMC Psychiatry* (2015) 15:297. doi: 10.1186/s12888-015-0684-6
41. Castelein S, Bruggeman R, van Busschbach JT, van der Gaag M, Stant AD, Knegtering H, et al. The effectiveness of peer support groups in psychosis: a randomized controlled trial. *Acta Psychiatr Scand* (2008) 118(1):64–72. doi: 10.1111/j.1600-0447.2008.01216.x
42. Villalta-Gil V, Roca M, Gonzalez N, Domènec E, Cuca, Escanilla A, et al. Dog-assisted therapy in the treatment of chronic schizophrenia inpatients. *Anthrozoös* (2009) 22(2):149–59. doi: 10.2752/175303709X434176
43. Sheridan AJ, Drennan J, Coughlan B, O'Keeffe D, Frazer K, Kemple M, et al. Improving social functioning and reducing social isolation and loneliness among people with enduring mental illness: report of a randomised controlled trial of supported socialisation. *Int J Soc Psychiatry* (2015) 61(3):241–50. doi: 10.1177/0020764014540150
44. McKay CE, Dickerson F. Peer supports for tobacco cessation for adults with serious mental illness: a review of the literature. *J Dual Diagn* (2012) 8(2):104–12. doi: 10.1080/15504263.2012.670847
45. Krishnadas R, Jauhar S, Telfer S, Shivashankar S, McCreadie RG. Nicotine dependence and illness severity in schizophrenia. *Br J Psychiatry* (2012) 201(4):306–12. doi: 10.1192/bjp.bp.111.107953
46. Bowden JA, Miller CL, Hiller JE. Smoking and mental illness: a population study in South Australia. *Aust N Z J Psychiatry* (2011) 45(4):325–31. doi: 10.3109/00048674.2010.536904
47. Mills AL, Messer K, Gilpin EA, Pierce JP. The effect of smoke-free homes on adult smoking behavior: a review. *Nicotine Tob Res* (2009) 11(10):1131–41. doi: 10.1093/ntr/ntp122
48. Rosen LJ, Myers V, Winickoff JP, Kott J. Effectiveness of interventions to reduce tobacco smoke pollution in homes: a systematic review and meta-analysis. *Int J Environ Res Public Health* (2015) 12(12):16043–59. doi: 10.3390/ijerph121215038
49. Passey ME, Longman JM, Robinson J, Wiggers J, Jones LL. Smoke-free homes: what are the barriers, motivators and enablers? A qualitative systematic review and thematic synthesis. *BMJ Open* (2016) 6(3):e010260. doi: 10.1136/bmjopen-2015-010260
50. Stevenson L, Campbell S, Bohanna I, Gould GS, Robertson J, Clough AR. establishing smoke-free homes in the indigenous populations of Australia, New Zealand, Canada and the United States: a systematic literature review. *Int J Environ Res Public Health* (2017) 14(11):E1382. doi: 10.3390/ijerph14111382
51. Snyder K, Vick JH, King BA. Smoke-free multiunit housing: a review of the scientific literature. *Tob Control* (2016) 25(1):9–20.
52. Gollust SE, Schroeder SA, Warner KE. Helping smokers quit: understanding the barriers to utilization of smoking cessation services. *Milbank Q* (2008) 86(4):601–27. doi: 10.1111/j.1468-0009.2008.00536.x
53. Keeley B, Wright L, Condit CM. Functions of health fatalism: fatalistic talk as face saving, uncertainty management, stress relief and sense making. *Sociol Health Illn* (2009) 31(5):734–47. doi: 10.1111/j.1467-9566.2009.01164.x
54. Simonavicius E, Robson D, McEwen A, Brose LS. Cessation support for smokers with mental health problems: a survey of resources and training needs. *J Subst Abuse Treat* (2017) 80:37–44. doi: 10.1016/j.jsat.2017.06.008
55. Metse AP, Wiggers J, Wye P, Moore L, Clancy R, Wolfenden L, et al. Smoking and environmental characteristics of smokers with a mental illness, and associations with quitting behaviour and motivation; a cross sectional study. *BMC Public Health* (2016) 16(1):332. doi: 10.1186/s12889-016-2969-1
56. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol* (2009) 49:57–71. doi: 10.1146/annurev.pharmtox.48.113006.094742
57. US Department of Health and Human Services. *Preventing tobacco use among young people. A report of the Surgeon General*. US Department of Health and Human Services Editor. Atlanta, GA: Public Health Service, Centers for Disease Control and Prevention, Office on Smoking and Health (1994).
58. Marmot M. Social determinants of health inequalities. *Lancet* (2005) 365(9464):1099–104. doi: 10.1016/S0140-6736(05)71146-6
59. Balbach ED, Smith EA, Malone RE. How the health belief model helps the tobacco industry: individuals, choice, and "information". *Tob Control* (2006) 15 Suppl 4:iv37–43. doi: 10.1136/tc.2005.012997
60. Brekke E, Lien L, Nysveen K, Biong S. Dilemmas in recovery-oriented practice to support people with co-occurring mental health and substance use disorders: a qualitative study of staff experiences in Norway. *Int J Ment Health Syst* (2018) 12:30. doi: 10.1186/s13033-018-0211-5
61. Thomas D, Abramson MJ, Bonevski B, George J. System change interventions for smoking cessation. *Cochrane Database Syst Rev* (2017) (2).
62. Bartlem KM, Bowman J, Freund M, Wye PM, Barker D, McElwaine KM, et al. Effectiveness of an intervention in increasing the provision of preventive care by community mental health services: a non-randomized, multiple baseline implementation trial. *Implement Sci* (2016) 11:46. doi: 10.1186/s13012-016-0408-4
63. Hull P, Salmon AM, O'Brien J, Chapman K, Williams K. Can social and community service organisations embrace tobacco control for their disadvantaged clients? *Health Promot J Austr* (2012) 23(3):188–93. doi: 10.1071/HE12188
64. Bryant J, Bonevski B, Paul C, O'Brien J, Oakes W. Delivering smoking cessation support to disadvantaged groups: a qualitative study of the potential of community welfare organizations. *Health Educ Res* (2010) 25(6):979–90. doi: 10.1093/her/cyq051
65. Bailey JM, Wye PM, Stockings EA, Bartlem KM, Metse AP, Wiggers JH, et al. Smoking cessation care for people with a mental illness: family carer expectations of health and community services. *J Smok Cessat* (2016) 12(4):221–30. doi: 10.1017/jsc.2016.23

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 14 December 2018
doi: 10.3389/fpsyt.2018.00683

y-QUIT: Smoking Prevalence, Engagement, and Effectiveness of an Individualized Smoking Cessation Intervention in Youth With Severe Mental Illness

Jackie Curtis[1,2], *Charry Zhang*[3], *Bernadette McGuigan*[1], *Esther Pavel-Wood*[1], *Rachel Morell*[2], *Philip B. Ward*[2]*, *Andrew Watkins*[1,4] *and Julia Lappin*[1,2]

[1] *Bondi Junction Youth Mental Health Services, South Eastern Sydney Local Health District, Sydney, NSW, Australia,* [2] *Faculty of Medicine, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia,* [3] *Faculty of Medicine, Medical School, University of New South Wales, Sydney, NSW, Australia,* [4] *Faculty of Health, University of Technology, Sydney, NSW, Australia*

OPEN ACCESS

Edited by:
David Jonathan Castle,
The University of Melbourne, Australia

Reviewed by:
Kristen McCarter,
University of Newcastle, Australia
Eliza Skelton,
University of Newcastle, Australia

***Correspondence:**
Philip B. Ward
p.ward@unsw.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *31 August 2018*
Accepted: *26 November 2018*
Published: *14 December 2018*

Citation:
Curtis J, Zhang C, McGuigan B, Pavel-Wood E, Morell R, Ward PB, Watkins A and Lappin J (2018) y-QUIT: Smoking Prevalence, Engagement, and Effectiveness of an Individualized Smoking Cessation Intervention in Youth With Severe Mental Illness. Front. Psychiatry 9:683. doi: 10.3389/fpsyt.2018.00683

Introduction: Young people with psychosis are six times more likely to be tobacco smokers than their gender- and age-matched peers. Smoking is a major contributor to the 15-year reduced life expectancy among people experiencing severe mental illness (SMI). There is a lack of evidence-supported interventions for smoking cessation among young people with SMI.

Material and Methods: The study comprised two phases and aimed to assess (i) the prevalence of smoking among a community sample of young people with psychotic illness or at high risk of developing psychosis; (ii) the proportion who engaged in the intervention; (iii) the proportion who achieved smoking cessation; and (iv) secondary smoking-related outcomes. In phase one, prevalence of smoking was assessed among young people with psychotic illness or at high risk of developing psychosis attending a community-based youth mental health service between 16/5/2017 and 16/11/2017. In phase two, over a 1-year period, individuals identified as smokers were invited to participate in a 12-week tailored smoking cessation intervention program that included pharmacological treatment, motivational interviewing, and behavioral change techniques. Those unwilling to participate in a full intervention were offered a brief intervention. Participants of the full intervention were assessed at baseline and at week 12 endpoint on: daily cigarettes smoked (self-report), exhaled CO, nicotine dependence, readiness to quit, and confidence to quit.

Results: In phase one, smoking prevalence was 48.2% (53 of 110) among clients of the youth mental health service. Smokers were significantly more likely to be male ($X^2 = 6.41$ $p = 0.009$). During phase two, 41 of 61 eligible clients engaged in a smoking cessation intervention (67.2%). Effectiveness: twenty-one clients participated in a full intervention (34.4%), of whom three (14.3%) received a brief intervention initially and during engagement converted to full intervention. Twenty participants (32.8%) received a brief intervention only. Ten participants in the full intervention (47.6%) and five in the

brief intervention (25%) dropped out. Six (28.6% of full intervention) reported smoking cessation verified by CO monitoring. Participants who completed the full intervention ($n = 9$) reduced number of cigarettes smoked, nicotine dependence, and exhaled CO, while readiness to quit and confidence to quit increased. Pharmacotherapy was predominantly combination NRT ($n = 18$; 85.7%), varenicline (4.8%), oral NRT only (4.8%), or none (4.8%). No adverse events were reported.

Conclusion: This pilot real-world study demonstrates that both screening for smoking and offering an effective smoking cessation intervention are achievable in youth experiencing or at risk of psychosis.

Keywords: smoking, tobacco, youth, adolescent, psychosis, first episode psychosis, at-risk for psychosis, intervention

INTRODUCTION

Among people experiencing severe mental illness (SMI), tobacco smoking is a modifiable risk factor for poor physical and mental health and thus a key priority for intervention. Approximately two thirds of people who experience psychotic illness smoke (1, 2). Very high smoking rates (59%) are also observed among individuals experiencing first episode psychosis (FEP), a rate six *times* that observed in age-matched peers (3). Individuals at high risk for the development of psychosis have higher tobacco use than healthy controls (4). Regular tobacco use is initiated on average (mean) 5.3 years prior to psychosis onset (3). A possible causal link between psychosis and tobacco smoking is suggested by a large meta-analysis which found overall relative risk of new onset psychotic disorders to be double that in tobacco smokers compared to non-smokers (5).

These findings suggest that daily tobacco use is associated with both increased risk for and earlier onset of psychotic illness and are thus highly relevant to populations with established FEP and those at high risk of developing psychotic illness. Within these populations, smoking among youth is a key consideration given that adolescence (12–17 years) and young adulthood (18–24 years) are critical periods in which smoking behaviors are established (6). The first cigarette is often smoked in adolescence, with tobacco experimentation generally developing into nicotine dependence before age 25 (6). Both young age and poor mental health are associated with higher levels of nicotine addiction which contribute to and sustain high smoking rates (7).

The benefits for smoking cessation and reduction in people experiencing SMI are clear, including a lowering of risk for cardiovascular and respiratory diseases and cancer—all of which are implicated in the known 10–20 year life expectancy gap (8–10). Further, smoking cessation/reduction demonstrably lowers stress levels, alleviates the financial burden associated with sustained nicotine addiction, and decreases the need for high-dose psychotropic medication, consequently lessening adverse side effects (11). Finally, long-term cessation may lead to direct clinical improvements in mental health, with improvements in anxiety and depression at levels of effect equal to or greater than those of antidepressant medication for anxiety and mood disorders (12).

Nonetheless, despite significant reductions in smoking rates among general adult populations over the past two decades, the very high smoking rates among people experiencing psychotic illness have remained almost unchanged (2, 13). It would be erroneous, however, to conclude that this reflects that people with mental health issues do not wish to stop smoking. Evidence suggests otherwise: most individuals questioned—in both mental health inpatient and community health settings—express a desire to quit (14–17) and welcome help to do so (18). Among people experiencing psychosis, 73% have attempted to quit smoking (2). Indeed, people with mental health disorders have similar or higher levels of motivation to quit when compared to the general population (19). Importantly, individuals with SMI, including young people with FEP, have poorer health literacy than healthy controls but, when shown smoking-related health warnings, they perceive them as effective (20). Nonetheless, individuals with SMI make fewer quit attempts and successful quit rates remain low (21, 22).

Understanding why individuals experiencing SMI are more likely to fail quitting is important as this will inform interventions aimed at overcoming the barriers to quit. It has been suggested that individuals experiencing SMI find quitting more difficult than do other smokers because of a range of factors including socioeconomic disadvantage, lack of familial and/or peer abstinence support and cognitive deficits (23, 24). Standard population cessation advice, which typically involves planning a quit strategy and setting a quit date, may be too cognitive an approach in some individuals with SMI, and indeed may prove counterproductive by increasing anxiety, self-stigma, and ideas of failure (25). Nonetheless, a review of smoking cessation interventions in SMI found behavioral and pharmacological interventions to be of similar effectiveness in smokers with or without SMI (26). It is unclear, however, whether these interventions would be effective in real-world settings, or be generalizable to all SMI populations, as the people with SMI who took part in those trials may have had better psychosocial function than the general SMI population (24).

Alternative interventions may be needed which are tailored to individuals experiencing SMI, or strategies employed to support their progress through cessation attempts. Intensive tailored support, provision of cessation medication, and access to peer

support have each been highlighted as important elements for successful interventions (7, 27). Among youth with mental health issues, it has been suggested that cigarette smoking may act as a tool for socialization and acceptance, which should be taken into account when designing smoking cessation interventions (19). In fact, little is known about what interventions will be effective among youth smokers experiencing SMI. Among youth smokers in the general population, smoking prevalence is successfully impacted by adult-directed population-based strategies such as cigarette price increases and implementation of clean indoor air policies (28).

A recent smoking cessation trial demonstrated the feasibility of offering tailored smoking cessation interventions to adult individuals experiencing SMI. The intervention—comprising behavioral support and pharmacotherapy delivered by a specialist mental health nurse with tobacco cessation training—increased engagement with services and sustained abstinence at rates almost 3 times higher than usual care (29). Interventions such as these are yet to be trialed in youth SMI populations. The present study (y-QUIT) involved an individualized 12-week smoking cessation intervention in youth experiencing psychotic illness or at high risk of developing psychosis. The aims of the study were:

1. to measure the prevalence of self-reported smoking among a community sample of young people with FEP or at high risk of developing psychotic illness
2. to assess the proportion of individuals who engaged in the intervention
3. to assess the proportion of individuals who achieved smoking cessation, and
4. to assess secondary smoking-related outcomes.

MATERIALS AND METHODS

Setting

This study was undertaken as part of the y-QUIT program, a local health district-funded project based in specialist early intervention in psychosis, community youth mental health (YMH) services in the South Eastern Sydney Local Health District, Sydney Australia. These comprised all YMH services across the three community mental health sites of the catchment area. The YMH services offer care to young people who have experienced first episode psychosis (FEP) or are deemed to be at ultra-high risk for development of psychosis. Inclusion criteria are age at presentation between 14 and 25 years inclusive. A 2-year program of care is offered with some individuals remaining with the service for a longer period. Ethics approval was granted by the Prince of Wales Hospital Human Research Ethics Committee [HREC ref no: 17/031 (LNR/17/POWH/50)].

Procedures

Screening and Prevalence [Phase One]

Cross-sectional smoking prevalence and eligibility for the y-QUIT program was determined by administration of the Brief Assessment for Tobacco Use (Appendix 1) The Brief Assessment for Tobacco Use tool includes questions about past and current smoking (including tailor made cigarettes, roll your own, cannabis mixed with tobacco, cigars, chop chop, or waterpipe/hubbly bubbly). All clients who answered affirmatively to smoking anything in the past 30 days were identified as smokers. The screening tool was administered by the individual's caseworker or other treating clinician, the tobacco treatment specialist (BM) or the researcher-medical student (CZ). Screening was conducted either in person or by phone. Cross-sectional smoking prevalence was evaluated among all individuals who were clients of the YMH services between 16/5/2017 and 16/11/2017.

Identification of Eligible Participants to Engage in an Intervention [Phase Two]

All individuals who were clients of the YMH service between 16/5/2017 and 16/11/2017 [Phase One] who were identified as smokers through screening were approached to engage in the intervention. In addition, any young people newly joining the YMH services between 17/11/2017 and 15/5/2018 who were identified as smokers were approached to engage in intervention. All smokers were offered a full intervention. Those unwilling to participate in a full intervention were offered a brief intervention. Clients who denied ever smoking, or smoking in the past 12 months, were deemed ineligible.

Measures [Phase Two]

1. Assessment of daily cigarettes smoked by self-report.
2. Exhaled carbon monoxide (CO) measured using a Bedfont Micro Smokerlyzer (Air-met Scientific).
3. Nicotine dependence, assessed using the Heaviness of Smoking Index (HSI) (30). The HSI was developed as a test to measure nicotine dependence by using two questions from the Fagerstrom Test for Nicotine Dependence: time to first smoking in the morning and number of cigarettes per day. It uses a six-point scale calculated from the number of cigarettes smoked per day (1–10, 11–20, 21–30, 31+) and the time to first cigarette after waking (less than/equal to 5, 6–30, 31–60, and 61+ minutes). Nicotine dependence is then categorized into a three-category variable: low (0–1), medium (2–4), and high (5–6).
4. Readiness to quit by self-report (scale ranging 1–10:1 = low readiness; 10 = high readiness) (31)
5. Confidence to quit by self-report (scale ranging 1–10:1 = low confidence; 10 = high confidence) (31)

Scores on these measures were recorded by the y-QUIT tobacco treatment specialist throughout interventions on the Smoking Monitoring Form (available on request). The proportion of smokers who engaged in full and/or brief interventions was recorded by the tobacco treatment specialist. Smoking cessation by self-report was confirmed by biochemically verified CO breath test.

Interventions [Phase Two]

All interventions were delivered by the y-QUIT tobacco treatment specialist, a mental health nurse with additional tobacco cessation training. The tobacco treatment specialist worked closely with the multi-disciplinary YMH teams and was

embedded within the Keeping the Body in Mind program which provides lifestyle interventions for these young people (32).

Full intervention

The intensive tobacco dependence intervention comprised an individualized 12-week program incorporating motivational interviewing, counseling support and pharmacological agents. Intensive tobacco dependence intervention involves the delivery of sessions over the phone or face to face that last longer than 10 min, with a minimum of 4 sessions. Duration of face to face appointments was typically 1 h for the first, and 30 min for subsequent sessions. Pharmacological interventions including nicotine replacement therapy (NRT) as transdermal patches, oral gum, nicotine inhaler or a combination, and varenicline, were discussed with the participant and where appropriate prescribed. NRT and prescribed smoking cessation treatments were provided as part of the y-QUIT program to participants at no cost (NRT) or cost only of prescription (varenicline). Ongoing support was provided throughout (face-to-face and by phone) and there was regular monitoring of mental state changes and adverse side effects through clinical assessment by the treatment specialist in conjunction with the clinical team. Psychotropic medications were monitored, and doses adjusted by the treating psychiatrist as required. At baseline and at 4-weekly intervals thereafter terminating at week 12, participants completed the following smoking-related measures: daily cigarettes smoked, exhaled CO, nicotine dependence, readiness to quit, and confidence to quit.

Brief intervention

Brief interventions typically comprised 1–2 sessions delivered face to face or by telephone. The goal of a brief intervention was to initiate change in behavior, utilizing the 5A's model (33). A person's smoking risk level was assessed using a validated CO monitor. Motivational interviewing, counseling, and measurement of exhaled CO were used to engage the individual in a discussion about readiness to change smoking behavior. Pharmacotherapy was available as NRT. Participants were encouraged to convert to the full intervention. Harm reduction strategies were offered to those who chose to continue to smoke.

Outcomes [Phase Two]

The primary outcome was smoking cessation by self-report at 12-week endpoint in the full intervention with confirmation of abstinence by exhaled CO measure of $\leq$4 ppm. Secondary outcomes (number of cigarettes smoked per day; exhaled CO; nicotine dependence; readiness to quit; confidence to quit) and pharmacotherapy used were recorded at 12-week endpoint for all those who completed the full intervention.

Statistical Analysis

Statistical analyses were conducted with IBM SPSS Statistics Version 24 (IBM Corp 2016). For continuous variables, means and standard deviations (SD) or medians and interquartile ranges were calculated. For tests of linear trend for categorical variables chi square was calculated. Secondary smoking-related outcomes were analyzed descriptively using mean (SD) or median (range).

TABLE 1 | Comparison of demographic characteristics between smokers and non-smokers among youth engaged with a community early intervention in psychosis service.

	Smokers (n = 53)	Non-smokers (n = 57)	
Male (n)	41	31	$X^2 = 6.41$ $p = 0.009$
Female (n)	12	26	
Age (median, range)	21 (18–27)	22 (16–26)	$t = 0.309$ $p = 0.76$
Age (mean, SD)	21.3 (2.3)	21.5 (2.3)	

RESULTS

Prevalence of Smoking [Phase One]

The prevalence of self-reported smoking among young people with FEP or at high risk of developing psychotic illness was 48.2% (53 of 110). Smokers were significantly more likely to be male ($X^2 = 6.41$ $p =$ 0.009; **Table 1**).

Engagement: Proportion of Individuals Who Engaged in an Intervention [Phase Two]

During Phase Two, of the 61 clients offered y-QUIT, 41 engaged in a smoking cessation intervention (67.2%). Twenty-one clients participated in a full intervention (34.4%), of whom three (14.3%) received a brief intervention initially and during engagement converted to full intervention. The mean number of sessions for full intervention was 5.1 (SD = 3.4; median = 6 (range 15). Twenty participants (32.8%) received a brief intervention only. Sixteen individuals (26.2%) declined participation in any intervention, and a further four clients (6.6%) were unable to participate due to discharge from the service. The vast majority of the individuals who participated in the full (90.5%), and brief intervention (80.0%), were male (**Table 2**). Mean ages were 22.1 (2.0) and 20.6 (2.0) years, respectively. Ten participants in the full intervention (47.6%) dropped out and two (9.6%) were discharged from the YMH service before completion.

Effectiveness: Proportion of Individuals Who Achieved Smoking Cessation [Phase Two]

Six individuals (28.6% of full intervention; 14.6% of all interventions) reported smoking cessation (verified by CO monitoring) at completion of the full intervention (**Table 2**).

Effectiveness: Secondary Smoking-Related Outcomes [Phase Two]

A further 3 participants (14.3% of full intervention) completed the full intervention and reduced the number of cigarettes smoked each day. As a group, participants who completed the full intervention (n = 9) reduced number of cigarettes smoked, nicotine dependence, and exhaled CO (**Table 3**). Both readiness to quit and confidence to quit increased (**Table 3**).

TABLE 2 | Demographic characteristics, quit prevalence, and pharmacotherapy received among smokers who received full or brief intervention.

	Full intervention ($n = 21$)	Brief intervention ($n = 20$)	All participants ($n = 41$)
Age (median, range)	22 (19–25)	20 (18–25)	21 (18–25)
Age (mean, SD)	22.1 (2.0)	20.6 (2.0)	21.3 (2.1)
GENDER			
Male (n)	19	16	35
Female (n)	2	4	6
Quit smoking (n, %)	6 (28.6)	0	6 (14.6)
PHARMACOTHERAPY (*n*, %)			
Oral NRT only	1 (4.8)	2 (10.0)	3 (7.3)
Combination NRT	18 (85.7)	4 (20.0)	22 (53.7)
Varenicline	1 (4.8)	–	1 (2.4)
None	1 (4.8)	14 (70.0)	15 (36.6)

Pharmacotherapy in the full intervention was predominantly combination NRT ($n = 18$; 85.7%), with one client each prescribed varenicline (4.8%), oral NRT only (4.8%) or no pharmacotherapy (4.8%; **Table 2**). No adverse events were reported.

DISCUSSION

y-QUIT Smoking Cessation Intervention

To our knowledge, the engagement of youth with severe mental illness and the effectiveness of tailored smoking cessation interventions in this population have never previously been reported. This real-world study demonstrated that the delivery of an individualized smoking cessation intervention is both achievable and effective in a community youth mental health service.

Smoking Prevalence Among Youth With SMI

The prevalence of self-reported smoking of 48.2% was somewhat lower than typical rates found in general SMI populations, but is consistent with the estimated prevalence rate of 59% in individuals with FEP (3). Smokers were significantly more likely to be male, even accounting for the greater proportion of males making up this population of FEP and at-risk for psychosis, in this younger-age demographic ($\leq$25 years at presentation).

Engagement With Intervention

Uptake rates of 67.2% in either a full or brief smoking cessation intervention in this sample confirm that youth with SMI have an interest in quitting tobacco smoking. Indeed, just over a quarter of YMH service clients declined participation in either intervention. Despite this high interest however, the full intervention was engaged in by just over half of these individuals. Of note, three individuals initially offered a brief intervention converted to the full intervention once engaged. One further young person offered brief intervention was discharged from the YMH service before completing the brief intervention as he had elected to trial an inpatient rehabilitation for comorbid cannabis use. He subsequently reported that he had quit both tobacco and cannabis. While this quit was not included in the numbers reported here, it is evidence of another positive impact of the y-QUIT program on smoking behavior in young people. This provides support for offering a brief intervention in order to provide a gateway to sustaining interest in and garnering commitment to engagement in a full intervention. A notable proportion of individuals dropped out: almost half of those who initiated a full intervention. Some individuals who initially declined engaging with the full intervention or who dropped out became engaged or re-engaged with the tobacco treatment specialist after the study period had completed. Previous studies investigating smoking cessation interventions in people with SMI have similarly noted high dropout rates and that both smoking cessation and smoking reduction are more likely among those individuals who engage fully with the intervention (34). This is consistent with knowledge that tobacco dependence is a chronic condition and that repeated attempts are typically required to stop smoking successfully (29, 35).

Successful Quitting

Approximately one third of individuals who participated in the full intervention reported smoking cessation at the 12-week endpoint. This is a highly encouraging outcome and suggests that this intervention is effective in youth with SMI, at least in the short-term. Nonetheless, two-thirds of participants were unsuccessful in quitting. This, together with the high drop-out rates, also raises the question whether current evidence and/or service user feedback might enhance the current approach to make the interventions more acceptable. Future interventions may need to incorporate recognition of these factors as obstacles to quitting, and perhaps discuss strategies of harm minimization (smoking reduction, use of NRT) as an initial alternative goal to quitting.

Secondary Smoking-Related Outcomes

All participants who completed the full intervention reduced daily number of cigarettes smoked, nicotine dependence, and exhaled CO. This is important particularly in the youth population, where there is evidence of a dose-response relationship between increased number of cigarettes smoked and risk for psychosis (36–38). In a large 15-year follow-up study of psychosis risk and its relationship to tobacco use in adolescence, smoking 10 or more cigarettes daily was associated with a significantly increased risk for psychosis compared to not smoking, while light smoking (1–9 cigarettes daily) was not (38). This provides an additional argument to support harm minimization of smoking in youth with SMI, and, if tobacco smoking were causal in increasing psychosis risk, is particularly relevant to those at high-risk for psychosis. Young people reported increased readiness and confidence to quit on completion of the full intervention. While both measures showed a range of scores across participants, baseline scores were high in the majority. This concords with previous evidence that smokers with SMI have the desire to quit, but may require

TABLE 3 | Smoking-related measures at baseline in clients who received the full intervention ($n = 21$), and at baseline and 12-week endpoint in those who completed the full intervention ($n = 9$).

	Baseline ($n = 21$)	Baseline (completers; $n = 9$)	Endpoint (completers; $n = 9$)
Number of cigarettes (mean, SD)	15.3 (9.8)	14.2 (11.8)	1.1 (1.9)
Number of cigarettes (median, IQR)	12.5 (0–35)	12.5 (0–35)	0 (0–6)
Heaviness smoking index (median, IQR)	3 (0–6)	3 (0–5)	0 (0–3)
Exhaled carbon monoxide (ppm; mean, SD)	15.8 (7.2)	14.8 (7.7)	5.9 (7.3)
Exhaled carbon monoxide (ppm; median, IQR)	16 (3–28)	15 (3–24)	3 (2–25)
Readiness to quit score (median, IQR)	7 (1–10)	7 (3–10)	10 (3–10)
Confidence to quit score (median, IQR)	7 (1–10)	7 (6–10)	10 (4–10)

additional assistance in order to successfully do so (19). Finally, pharmacotherapy used was predominantly combination NRT but a range of approaches—including use of varenicline or alternatively use of no pharmaceutical agent—was applied, in keeping with the focus on individualized care.

Limitations of y-QUIT

The present study presents preliminary 12-week outcomes only and cannot speak to long-term effectiveness of this intervention. Previous smoking cessation studies including the SCIMITAR trial in SMI adults have assessed smoking cessation at 1 year following randomization to intervention (29). Screening for smoking status was only conducted routinely during Phase One, that is, the first 6 months of the 12-month program. During the latter 6 months, an additional eight young people who were identified as smokers were offered the program. It is, however, possible that among all young people newly entering the YMH services in that 6-month period there may have been additional smokers who were not identified in the absence of screening. Lastly, brief interventions did not routinely assess smoking-related measures or include follow-up evaluation to assess their effectiveness in increasing desire, confidence, and readiness to quit. This is an important area for future development, particularly given the potential that brief interventions act as segue into full interventions.

Implications of y-QUIT for Future Interventions

Internationally, there is growing recognition of the need to integrate smoking cessation into the treatment of people experiencing SMI and the need to adapt programs developed in the general population to address the specific needs of people living with mental illness (24, 39). There remains an overwhelming need for smoking to be addressed more adequately in mental health services. A combination of culture change, increased accessibility to intervention programs (both pharmacological and non-pharmacological), and staff training are necessary to address the life expectancy gap and inequality experienced by youth with SMI. Future studies which include varenicline as part of a routine intervention should also be considered and may increase the quit rates, given recent evidence indicating the efficacy and relative safety of this treatment in SMI populations (40).

y-QUIT incorporated all elements recommended as necessary to reduce the very high rates of smoking amongst this population, namely training in brief interventions, motivational interviewing, and pharmacological support (41). That delivery of all interventions was by a mental health nurse with additional tobacco cessation training demonstrates that this model is immediately translatable to community mental health settings where there is sufficient funding and support from clinicians and managers to do so.

Conclusion

Smokers experiencing SMI are a priority target group for smoking cessation interventions. The need to provide smoking cessation to youth with SMI is all the more urgent, as successful quitting at as early a stage as possible will optimally reduce risk for smoking-related disease and life expectancy shortening. This first-of-its-kind real-world smoking cessation program demonstrates that both screening for smoking and offering an effective smoking cessation intervention is acceptable and effective in youth mental health services. Individuals with SMI should be asked about smoking and should be provided with smoking cessation interventions. The very high rates of tobacco smoking in this population, and the failure of public health measures to have had significant impact demand further urgent work in tailoring interventions effective in this priority group.

AUTHOR CONTRIBUTIONS

JC, EP-W, AW, and PW conceived the initial project. AW and BM designed the intervention. CZ, BM, RM, and AW contributed to data collection. EP-W and CZ conducted the background literature review. JL, CZ and RM conducted data analysis. JL and JC wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

FUNDING

Funding for the y-QUIT project was provided by South Eastern Sydney Local Health District, The Inspiring Ideas Challenge (TIIC) grant with additional support by an Agency for Clinical Innovation (ACI) grant, NSW Health, and the Prince of Wales Hospital Foundation.

ACKNOWLEDGMENTS

We wish to thank the members of the y-QUIT steering and advisory groups for their advice and guidance in the development of the y-QUIT program including: Professor Renee Bittoun, Katarzyna Bochynska, Professor Jonathan Campion, Dr. Ryan Courtney, Professor Gail Daumit, A/Professor Faith Dickerson, Kimberley Fitzpatrick, Tracey Greenberg, Myna Hua, Karina Ko, Professor Sharon Lawn, Dr. Mark Montebello, Dr. Hannah Myles, Kenneth Murray, Dr. David Shiers, Mariela Silveira, and Becky Walsh.

REFERENCES

1. Morgan VA, Waterreus A, Jablensky A, Mackinnon A, McGrath JJ, Carr V, et al. People living with psychotic illness in 2010: the second Australian national survey of psychosis. *Aust N Z J Psychiatry* (2012) 46:735–52. doi: 10.1177/0004867412449877
2. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian Survey of Psychosis. *Aust N Z J Psychiatry* (2012) 46:851–63. doi: 10.1177/0004867412449876
3. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *J Clin Psychiatry* (2012) 73:468–75. doi: 10.4088/JCP.11r07222
4. Buchy L, Cadenhead K, Cannon T, Cornblatt B, McGlashan T, Perkins D, et al. Substance use in individuals at clinical high risk of psychosis. *Psychol Med*. (2015) 45:2275–84. doi: 10.1017/S0033291715000227
5. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* (2015) 2:718–25. doi: 10.1016/S2215-0366(15)00152-2
6. Dessaix A, Maag A, McKenzie J, Currow DC. Factors influencing reductions in smoking among Australian adolescents. *Public Health Res Pract*. (2016) 26:e2611605. doi: 10.17061/phrp2611605
7. Harker K, Cheeseman H. Shifting culture and taking action to reduce smoking and premature death among people with a mental health condition. *J Public Mental Health* (2016) 15:184–7. doi: 10.1108/JPMH-09-2016-0046
8. Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. prevalence, impact of medications and disparities in health care. *World Psychiatry* (2011) 10:52–77. doi: 10.1002/j.2051-5545.2011.tb00014.x
9. Reininghaus U, Dutta R, Dazzan P, Doody GA, Fearon P, Lappin J, et al. Mortality in schizophrenia and other psychoses: a 10-year follow-up of the Æ SOP first-episode cohort. *Schizophrenia Bull*. (2015) 41:664–73. doi: 10.1093/schbul/sbu138
10. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* (2013) 346:f2539. doi: 10.1136/bmj.f2539
11. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. an update for psychiatrists. *Austr Psychiatry* (2014) 2014:1039856214562076. doi: 10.1177/1039856214562076
12. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* (2014) 348:g1151. doi: 10.1136/bmj.g1151
13. Szatkowski L, McNeill A. Diverging trends in smoking behaviors according to mental health status. *Nicotine Tob Res*. (2015) 17:356–60. doi: 10.1093/ntr/ntu173
14. Addington J, el-Guebaly N, Campbell W, Hodgins DC, Addington D. Smoking cessation treatment for patients with schizophrenia. *Am J Psychiatry* (1998) 155:974–6. doi: 10.1176/ajp.155.7.974
15. Lucksted A, McGuire C, Postrado L, Kreyenbuhl J, Dixon LB. Specifying cigarette smoking and quitting among people with serious mental illness. *Am J Addict*. (2004) 13:128–38. doi: 10.1080/10550490490436000
16. Etter M, Mohr S, Garin C, Etter JF. Stages of change in smokers with schizophrenia or schizoaffective disorder and in the general population. *Schizophr Bull*. (2004) 30:459–68. doi: 10.1093/oxfordjournals.schbul.a007092
17. Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. *Annu Rev Clin Psychol*. (2009) 5:409–31. doi: 10.1146/annurev.clinpsy.032408.153614
18. Aschbrenner KA, Brunette MF, McElvery R, Naslund JA, Scherer EA, Pratt SI, et al. Cigarette smoking and interest in quitting among overweight and obese adults with serious mental illness enrolled in a fitness intervention. *J Nerv Ment Dis*. (2015) 203:473–6. doi: 10.1097/NMD.0000000000000309
19. Siru R, Hulse GK, Tait RJ. Assessing motivation to quit smoking in people with mental illness: a review. *Addiction* (2009) 104:719–33. doi: 10.1111/j.1360-0443.2009.02545.x
20. Coletti DJ, Brunette M, John M, Kane JM, Malhotra AK, Robinson DG. Responses to tobacco smoking-related health messages in young people with recent-onset schizophrenia. *Schizophr Bull*. (2015) 41:1256–65. doi: 10.1093/schbul/sbv122
21. Annamalai A, Singh N, O'Malley SS. Smoking use and cessation among people with serious mental illness. *Yale J Biol Med*. (2015) 88:271–7.
22. McClave AK, McKnight-Eily LR, Davis SP, Dube SR. Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. *Am J Public Health* (2010) 100:2464–72. doi: 10.2105/AJPH.2009.188136
23. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. *Tobacco Use and Cessation in Psychiatric Disorders: National Institute of Mental Health report*. Society for Research on Nicotine and Tobacco (2008).
24. Gartner C, Hall W. Tobacco harm reduction in people with serious mental illnesses. *Lancet Psychiatry* (2015) 2:485–7. doi: 10.1016/S2215-0366(15)00238-2
25. Moeller-Saxone K, Segan C. The role of planning in naturalistic quitting success among people with severe mental illness. *Int J Mental Health Addict*. (2016) 14:526–38. doi: 10.1007/s11469-015-9609-3
26. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? Addiction. (2010) 105:1176–89. doi: 10.1111/j.1360-0443.2010.02946.x
27. Davidson L, Bellamy C, Guy K, Miller R. Peer support among persons with severe mental illnesses: a review of evidence and experience. *World Psychiatry* (2012) 11:123–8. doi: 10.1016/j.wpsyc.2012.05.009
28. White VM, Warne CD, Spittal MJ, Durkin S, Purcell K, Wakefield MA. What impact have tobacco control policies, cigarette price and tobacco control programme funding had on Australian adolescents' smoking? Findings over a 15-year period. *Addiction* (2011) 106:1493–502. doi: 10.1111/j.1360-0443.2011.03429.x
29. Gilbody S, Peckham E, Man M-S, Mitchell N, Li J, Becque T, et al. Bespoke smoking cessation for people with severe mental ill health (SCIMITAR): a pilot randomised controlled trial. *Lancet Psychiatry* (2015) 2:395–402. doi: 10.1016/S2215-0366(15)00091-7
30. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. (1991) 86:1119–27. doi: 10.1111/j.1360-0443.1991.tb01879.x
31. Boudreaux ED, Sullivan A, Abar B, Bernstein SL, Ginde AA, Camargo CA. Motivation rulers for smoking cessation: a prospective observational examination of construct and predictive validity. *Addict Sci Clin Pract*. (2012) 7:8. doi: 10.1186/1940-0640-7-8
32. Curtis J, Watkins A, Rosenbaum S, Teasdale S, Kalucy M, Samaras K, et al. Evaluating an individualized lifestyle and life skills intervention to prevent antipsychotic-induced weight gain in first-episode psychosis. *Early Intervent Psychiatry* (2016) 10:267–76. doi: 10.1111/eip.12230
33. Fiore MC, Jaen CR, Baker T, Bailey W, Benowitz N, Curry SE, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Department of Health and Human Services (2008).

34. Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *Am J Psychiatry* (2006) 163:1934–42. doi: 10.1176/ajp.2006.163.11.1934
35. Zwar N, Richmond R, Borland R, Peters M, Litt J, Bell J, et al. *Supporting Smoking Cessation: A Guide for Health Professionals*. Melbourne: The Royal Australian College of General Practitioners (2011).
36. Kendler KS, Lönn SL, Sundquist J, Sundquist K. Smoking and schizophrenia in population cohorts of Swedish women and men: a prospective co-relative control study. *Am J Psychiatry* (2015) 172:1092–100. doi: 10.1176/appi.ajp.2015.15010126
37. Weiser M, Reichenberg A, Grotto I, Yasvitzky R, Rabinowitz J, Lubin G, et al. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. *Am J Psychiatry* (2004) 161:1219–23. doi: 10.1176/appi.ajp.161.7.1219
38. Mustonen A, Ahokas T, Nordström T, Murray GK, Mäki P, Jääskeläinen E, et al. Smokinhot: adolescent smoking and the risk of psychosis. *Acta Psychiatr Scand.* (2018) 138:5–14. doi: 10.1111/acps.12863
39. Schroeder SA. Smoking cessation should be an integral part of serious mental illness treatment. *World Psychiatry* (2016) 15:175–6. doi: 10.1002/wps.20332
40. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* (2016) 387:2507–20. doi: 10.1016/S0140-6736(16)30272-0
41. Rowley D, Lawn S, Coveney J. Two heads are better than one: Australian tobacco control experts' and mental health change champions' consensus on addressing the problem of high smoking rates among people with mental illness. *Austr Health Rev*. (2016) 40:155–62. doi: 10.1071/AH15028

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

CLINICAL STUDY PROTOCOL
published: 19 March 2019
doi: 10.3389/fpsyt.2019.00124

"Quitlink"—A Randomized Controlled Trial of Peer Worker Facilitated Quitline Support for Smokers Receiving Mental Health Services: Study Protocol

Amanda L. Baker[1], Ron Borland[2,3], Billie Bonevski[1], Catherine Segan[2,3], Alyna Turner[1,4,5], Lisa Brophy[3,6,7], Kristen McCarter[1], Peter J. Kelly[8], Jill M. Williams[9], Donita Baird[1], John Attia[1], Rohan Sweeney[10], Sarah L. White[2], Sacha Filia[2] and David Castle[5,11]*

[1] Faculty of Health and Medicine, University of Newcastle, Newcastle, NSW, Australia, [2] Cancer Council Victoria, Melbourne, VIC, Australia, [3] Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [4] IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, VIC, Australia, [5] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia, [6] Mind Australia Limited, Melbourne, VIC, Australia, [7] School of Allied Health, Human Services and Sport, La Trobe University Melbourne, Melbourne, VIC, Australia, [8] Illawarra Health and Medical Research Institute and the School of Psychology, University of Wollongong, Wollongong, NSW, Australia, [9] Division of Addiction Psychiatry, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States, [10] Centre for Health Economics, Monash University, Melbourne, VIC, Australia, [11] Department of Psychiatry, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

OPEN ACCESS

Edited by:
Błażej Misiak, Wroclaw Medical University, Poland

Reviewed by:
Alain Dervaux, University Hospital Center (CHU) of Amiens, France
Kazutaka Ohi, Kanazawa Medical University, Japan

***Correspondence:**
Amanda L. Baker
amanda.baker@newcastle.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *30 August 2018*
Accepted: *19 February 2019*
Published: *19 March 2019*

Citation:
Baker AL, Borland R, Bonevski B, Segan C, Turner A, Brophy L, McCarter K, Kelly PJ, Williams JM, Baird D, Attia J, Sweeney R, White SL, Filia S and Castle D (2019) "Quitlink"—A Randomized Controlled Trial of Peer Worker Facilitated Quitline Support for Smokers Receiving Mental Health Services: Study Protocol. Front. Psychiatry 10:124. doi: 10.3389/fpsyt.2019.00124

Introduction: Although smokers with severe mental illnesses (SSMI) make quit attempts at comparable levels to other smokers, fewer are successful in achieving smoking cessation. Specialized smoking cessation treatments targeting their needs can be effective but have not been widely disseminated. Telephone delivered interventions, including by quitlines, show promise. However, few SSMI contact quitlines and few are referred to them by health professionals. Mental health peer workers can potentially play an important role in supporting smoking cessation. This study will apply a pragmatic model using peer workers to engage SSMI with a customized quitline service, forming the "Quitlink" intervention.

Methods: A multi-center prospective, cluster-randomized, open, blinded endpoint (PROBE) trial. Over 3 years, 382 smokers will be recruited from mental health services in Victoria, Australia. Following completion of baseline assessment, a brief intervention will be delivered by a peer worker. Participants will then be randomly allocated either to no further intervention, or to be referred and contacted by the Victorian Quitline and offered a targeted 8-week cognitive behavioral intervention along with nicotine replacement therapy (NRT). Follow-up measures will be administered at 2-, 5-, and 8-months post-baseline. The primary outcome is 6 months continuous abstinence from end of treatment with biochemical verification. Secondary outcomes include 7-day point prevalence abstinence from smoking, increased quit attempts, and reductions in cigarettes per day, cravings and withdrawal, mental health symptoms, and other substance use, and improvements in quality of life. We will use a generalized linear mixed model (linear regression for continuous outcomes and logistic regression for dichotomous outcomes) to handle clustering and the repeated measures at baseline, 2-, 5-, and

8-months; individuals will be modeled as random effects, cluster as a random effect, and group assignment as a fixed effect.

Discussion: This is the first rigorously designed RCT to evaluate a specialized quitline intervention accompanied by NRT among SSMI. The study will apply a pragmatic model to link SSMI to the Quitline, using peer workers, with the potential for wide dissemination.

Clinical Trial Registration:
Trial Registry: The trial is registered with ANZCTR (www.anzctr.org.au): ACTRN12619000244101 prior to the accrual of the first participant and updated regularly as per registry guidelines.
Trial Sponsor: University of Newcastle, NSW, Australia.

Keywords: smoking, smoking cessation, quitline, peer worker, mental illness, severe mental illness, psychosis, depression

INTRODUCTION

Smokers living with severe mental illness (SSMI) die around two decades earlier than the general population, due largely to smoking-related diseases (1). Survey data from the United States (2, 3), United Kingdom (4), and Australia (5) consistently highlight that smoking is not declining at the same rate among SSMI as among the general population. In Australia, smoking rates in 2010 for people with psychotic illness were 67 vs. 65% in 1997/98 (5). Rates of smoking increase with severity of the mental illness. The Australian National Drug Strategy Household Survey (6) showed that in 2016, among those diagnosed with a mental illness in the previous 12 months, daily smoking rates were highest among people with a psychotic disorder (schizophrenia 49.3%, bipolar 37.3%, other psychotic disorder 32.2%), followed by anxiety disorders (28.5%), depression (27.3%), and eating disorders (24%). In comparison, 12% of people from the general population in Australia smoke daily (7). Economic costs associated with smoking in people with mental illness are significant and include costs of treatment of tobacco-related diseases, work-related absenteeism, and premature mortality. In the UK, in the 2009/2010 financial year, the estimated economic cost of smoking in people with mental disorders was at £2.3 billion (8).

There is a vicious cycle between smoking and poorer mental and physical health. In addition to increased mortality, SSMI have more psychiatric symptoms, increased hospitalizations, and the requirement for higher doses of some psychiatric medications (9). This is because components of tobacco smoke accelerate their metabolism (10). Smoking cessation benefits mental health as well as physical health. A recent meta-analysis of primarily non-controlled trials found that quitting smoking is associated with significantly improved quality of life and reduced depression, mixed anxiety/depression, and improved positive affect. Effect sizes for these differences were as large in people with SMI (0.40, −0.39, −0.21, 0.68, respectively) as in the general population (0.15, −0.30, −0.32, 0.16). The effect sizes were equal to or larger than those of people receiving anti-depressant treatment for mild to severe depression (range: −0.17 to −0.11) and generalized anxiety disorder (range: −0.23 to −0.50) (11). In addition, the recent Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) randomized controlled trial (RCT) found no significant difference in the occurrence of adverse events between the smoking cessation medications, varenicline, bupropion, nicotine replacement therapy (NRT), or placebo (12) among people with or without psychiatric disorders. Further, sustained reductions in smoking have important financial benefits and may increase the chance of future cessation (13).

SSMI are about as likely to want to quit as those in the general population (14), and some are able to quit (9). However, they often require additional assistance, and overall have lower rates of success with cessation. This can potentially be reduced or eliminated by the delivery of additional assistance targeted to their specific needs. SSMI are not uniformly being provided with the additional smoking cessation assistance they need. The problem is often overlooked by health care providers, being seen as either too hard or a low priority (15, 16), while SSMI report a lack of encouragement to quit (16). Mental health staff have reported that they lack knowledge about tobacco dependence and smoking's relationship with mental illness (17). In addition, existing evidence-based interventions for this population are rare, mainly face-to-face and intensive, so without substantial additional resources, they cannot feasibly be taken up by mental health services.

Telephone smoking cessation support tailored for SSMI may improve access and enhance cessation (18). Quitline smoking cessation counseling is effective in the general population (19). A 2013 Cochrane review found that proactive telephone counseling (where the counselor initiates one or more calls to provide support) is more effective, with better outcomes than a single-session reactive support call or brief interventions (19). Quitlines offer enormous potential for SSMI. As an existing service that can be accessed from the community, quitlines can offer an intervention for SSMI that does not require a significant increase in resources.

We are aware of three RCTs that have evaluated the effectiveness of quitline interventions among SSMI. In an underpowered pilot randomized trial ($N = 123$) among a community mental health sample, Morris et al. (20) reported that five quitline sessions plus NRT were equivalent to a much more intensive intervention consisting of five quitline sessions plus NRT and also 10 group face-to-face sessions. A breath carbon monoxide (CO) verified point prevalence abstinence rate of 10% overall was achieved at 6 months. In a second RCT, Van der Meer and colleagues compared a standard quitline service to standard quitline service plus a mood management component for callers with past major depression ($N = 485$) (21). Participants in both conditions were advised to use pharmacological aids for cessation if they smoked more than 10 cigarettes per day. Cessation rates were higher for the treatment group who received the additional mood module (31 vs. 22% at 6 months and 24 vs. 14% at 12 months), but biochemical verification was available only for a small sub-sample. In the third RCT, Rogers et al. (22) compared standard quitline counseling with specialized quitline counseling developed for smokers attending Veterans Health Administration mental health facilities ($N = 577$), referred via electronic medical record consult. Participants in the specialized counseling condition were significantly more likely to report 30-day abstinence compared to the standard quitline (26 vs. 18%) at 6 months. Together, these three RCTs suggest that telephone interventions accompanied by smoking cessation medication among SSMI are likely to be effective and that tailoring the intervention specifically for mental health symptomatology is likely to enhance results. We are aware of no adequately powered RCT evaluating a tailored quitline intervention (addressing mood and other symptomatology) accompanied by NRT, for people drawn from mental health services, with biochemical verification of self-reported abstinence. The present study aims to address this gap.

In Australia, the Victorian Quitline has been building counselor skills in order to support SSMI better. Segan et al. found that a specialized quitline intervention for smoking cessation among people with depression was workable, valued by smokers, and increased the probability of quit attempts (23). They then integrated key elements of our mainly telephone delivered smoking cessation intervention, demonstrated to be as effective as a more intensive face-to-face delivered intervention, among people with psychotic disorders (24, 25). The revised tailored Victorian Quitline intervention includes structured monitoring of mental health symptoms, nicotine withdrawal symptoms, and medication side-effects (26). These procedures help to distinguish temporary withdrawal symptoms from psychiatric symptoms and facilitate targeted treatment. Feedback indicated that the structured monitoring, combined with Quitline's established focus on the relationship between smoking and mood control, had a high level of acceptance by both Quitline counselors and clients and led to better integration of quitting with management of ongoing mental health conditions (26). The resulting tailored smoking cessation intervention, when coupled with peer referral, is called Quitlink, and if shown to be effective, is likely to be widely adopted.

Despite promising work in providing a more appropriate, supportive, and engaging service, quitlines remain underutilized in part because health professionals lack awareness of their free callback service and its expertise in helping SSMI (27). Mental health peer workers can potentially play an important role in supporting smoking cessation. Peer workers have been a mental health consumer or carer and this lived experience along with their training allows them to be highly credible sources of support for SSMI (28). Peer support, which is one element of peer work, is based on the belief that people who have faced, endured, and overcome adversity can offer useful support, encouragement, hope, and mentorship to others facing similar situations (29). As part of the recovery-oriented practice framework (encompassing principles of self-determination and personalized care (30), people with their own lived experience of mental ill-health and recovery (i.e., peer workers) are viewed as highly valuable members of the mental health workforce (31). The peer workforce is the most rapidly growing workforce in the Australian mental health sector, with existing research examining peer workers finding they are effective (32). Peer workers are strong role models, and are particularly successful in developing hope, promoting self-esteem, and empowering consumers (32). These unique skills are likely to be extremely valuable in helping to promote engagement of SSMI with quitline services (29).

Communication between quitline and the mental health service will be a key component of this link. The mental health service provider (utilizing peer workers) will identify smokers who may benefit from intervention and peer workers will make the referral to the Victorian Quitline for proactive telephone counseling (accompanied by free NRT). With the permission of the participant, quitline counselors will keep peer workers and other mental health professionals updated as to quitline participation. This project will examine program and cost-effectiveness of "Quitlink" for people with SMI compared with standard smoking care.

An important component of the present research is a nested qualitative study exploring experiences of peer workers, mental health staff, and participants (from both intervention and control arms), including those participants who do and do not stop smoking and/or engage with the quitline service. We will also explore in detail the barriers to cessation people face and the impact of smoking culture, support people (carers/family/partners) and other factors on intervention uptake, ongoing participation, and outcome. Future dissemination, ongoing development of resources, and improvement of our intervention will be informed by an enhanced understanding of the mechanisms by which the intervention is effective as well as refining who is likely to be successful, and why.

AIMS

The primary aim of this research is to test the effectiveness of the Quitlink intervention for smoking cessation among SSMI. It is hypothesized that the intervention will be associated with higher

rates of continued abstinence from smoking following the end of the treatment period, relative to the control condition. Secondary aims are to examine: (i) the cost-effectiveness of Quitlink compared to the control condition; (ii) barriers and enablers to making and sustaining quit attempts using qualitative methods so as to better understand why cessation rates among SSMI remain low; and (iii) the effect of Quitlink on 7-day point prevalence abstinence at 8-months, and effects on reported cigarette consumption, rates of quit attempts, nicotine withdrawal, expenditure on cigarettes, smoking cessation motivation and self-efficacy, mental health, quality of life and alcohol, and cannabis use. We will also assess process measures such as extent of use of advice and use of quit smoking medications (regardless of condition). The cost-effectiveness protocol is described elsewhere by Sweeney et al. (in submission) and the nested qualitative study and outcome measures are described below.

METHODS

Design

A multi-center prospective, cluster-randomized, open, blinded endpoint (PROBE) design will be employed to compare standard smoking care alone against Quitlink. See **Figure 1** for an overview.

Rationale for Study Design

Due to the nature of the intervention under investigation (i.e., linking smokers to existing smoking cessation care options readily available in the community, quitline, and NRT) there is a high risk of contamination among residential services where participants are living under the same roof and hence may compare treatment received. Therefore, we will use a partial clustering design where cluster randomization will be used in situations where risk of contamination is particularly high (e.g., in residential services). Individual randomization will be used in settings where participants are approached individually (e.g., clinics). Conceptually, this can be considered as a cluster RCT where some clusters only contribute a single person (see statistical methods section). This is sometimes called a split-plot design (33).

Setting

Participants will be recruited across participating community mental health services in Victoria, Australia, including St Vincent's Mental Health, and non-government organizations such as Mind Australia Limited. Residential and non-residential community services will be included in the study. These services are widely distributed across the state and we will recruit from an as yet unknown subset of sites. The majority of people accessing these services will have been diagnosed with severe mental illnesses such as schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, and depressive disorders.

Eligibility Criteria

Participant inclusion criteria are: aged at least 18 years; residing in Victoria; smoking at least 10 cigarettes per day; and accessing treatment or support from participating mental health agencies. Exclusion criteria are: current engagement in Victorian Quitline's callback service; no ready access to a telephone; inability to complete informed consent and/or the screening survey; acute suicidality; myocardial infarction or unstable arrhythmia or angina within the previous 2 weeks (NRT contraindications); and pregnancy (as smokers who are pregnant already receive a different extended Quitline callback service).

Around three-quarters of individuals accessing mental health services own mobile phones (34). Landlines will be used where people do not own mobile phones, as in our previous studies (25, 35).

Quitline counselors: Experienced quitline counselors who have been provided with specialist training on counseling people with mental health issues, and who have demonstrated competence in this work have been allocated to the study (one dedicated counselor per caller for all calls, or to co-ordinate with a substitute where they may be unavailable for some calls).

Standard Smoking Care

An active control condition, involving brief advice on the importance of quitting and provision of printed information on where to access assistance, is being utilized in this study as it reflects what is expected of mental health services as part of routine care (even though it is not routinely delivered).

The brief intervention provided to all participants includes advice to quit, encouragement to use NRT, and a Quit Victoria pack of written materials to motivate a quit attempt (e.g., costs of smoking and benefits of quitting) and resources to support self-management (e.g., Quitline phone number, "4Ds" strategy: 'Delay, Deep-breathe, Drink water, Do something else' to manage cravings; using NRT products).

With consent, a letter will be sent by the research team to nominated health professionals general practitioner (GP)/psychiatrist with information about their client's trial participation and a link to Australia's smoking cessation guidelines for health professionals, which includes a list of medications affected by smoking. No further intervention will be provided as part of the project for those in the control condition.

Quitlink Intervention

The Quitlink intervention consists of all of the above plus:

- Referral to Quitline: immediately following the brief intervention, the peer worker will make a proactive referral to Quitline.
- Manual guided Quitline counseling: Quitline will then call the participant to offer the Quitlink service. This service includes up to seven scheduled calls with additional calls allowed to deal with relapse crises within an 8-week period. It includes structured monitoring of mental health symptoms, nicotine withdrawal symptoms, and medication side-effects; and a focus on psychoeducation including the relationship between smoking and mood; goal setting; identification of triggers to smoke; and facilitating problem solving and skills building, including the use of mood management strategies that also act to aid cessation (e.g., exercise, scheduling pleasant

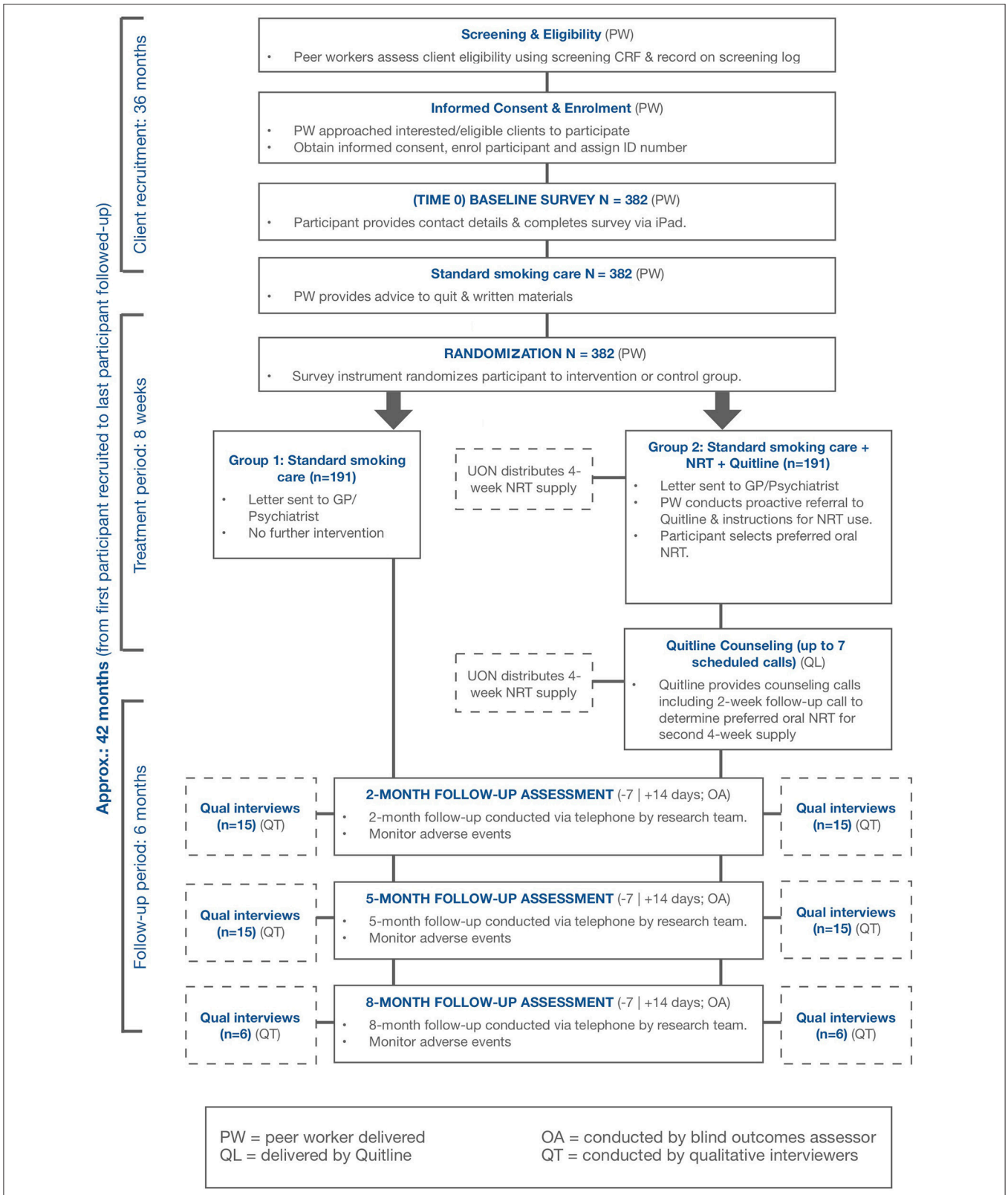

FIGURE 1 | Quitlink study design.

activities). A dedicated Quitline counselor will manage the quitting process for each participant.

- As in the control condition, with consent, a letter will be sent to the person's GP and/or psychiatrist. Additionally for the intervention condition, peer reviewed articles that provide practical advice to assist doctors in helping people with mental illness to quit smoking will be included (36, 37). Additionally, participants will receive a Quit Victoria brochure for carers and a Quitting Mood and Experiences Diary.
- Quitline engagement with mental health services: Quitline will provide written feedback to treatment providers at the end of the telephone counseling program. Providers will be encouraged to monitor and support cessation efforts whenever appropriate. In addition, Quitline will contact the mental health treatment provider, if concerns arise about mental health issues.
- NRT: Participants will initially be provided with a 4 week supply of patches (one 21 mg patch/day) plus their choice of an oral-form NRT (gum, lozenge, inhalator, spray). The research team will post NRT to participants with an information pack that includes printed instructions on how to use NRT correctly, for how long, potential side effects (and when to notify a health care provider), and safe storage and handling. Quitline counselors will monitor and encourage correct use of NRT and address barriers to use. Intervention participants that decide to use the supplied NRT will receive a final 4-week supply of NRT as per the initial supply. Quitline counselors will ask participant preferences for oral dose forms during the Week 2 call (for those participants that do not engage with Quitline, the peer worker will attempt to contact participants to determine participant preferences for NRT) in order for NRT to be delivered to the participant by Week 4. Participants who desire to shift to use of a prescription-based stop smoking medication (e.g., varenicline) will be supported to do so, but the study will not fund the purchase (which is low for those with health care cards as it is heavily government subsidized).

The Quitlink intervention is similar to the Quitline's routine care for clients disclosing mental health issues. Components unique to this trial include the peer worker referring to Quitline, a dedicated Quitline counselor for each participant and provision of NRT.

Discontinuation of the Quitlink Intervention

This may occur if there are alterations in the participant's condition which justifies the discontinuation of treatment in the investigator's opinion. All intervention components are voluntary and non-essential to participation. The participant may refuse to engage, miss scheduled telephone sessions, or discontinue with the Quitlink intervention without affecting study participation.

NRT use is also optional (recommended, but not expected), and use or non-use will not affect whether they can participate in Quitline counseling or follow-up interviews.

Intervention Training and Supervision

Quitline counseling delivery will be provided by existing Quitline Victoria counselors, holding at least a Certificate III level qualification in counseling and trained in the World Health Organization Smoking Cessation approach (38) by a Quit psychologist. In addition, all are experienced in conducting smoking interventions among SSMI and in 2014 received a 1-day face to face training workshop led by experienced investigators focusing on the provision of structured monitoring of mood, nicotine withdrawal, and psychiatric medication side-effects. It is standard practice for the Quitline counselors to receive monthly group supervision led by a qualified counselor and monthly individual supervision which entails a psychologist reviewing notes and listening to two calls ($<$10 and $>$20 min) to facilitate reflective practice and quality assurance. Counselors will also receive a minimum of 1 day of additional training focused on refreshing these skills and processes contained in the Quitlink treatment manual. The Quitlink treatment manual developed for this study will be used to ensure that all participants receive a minimum standard of behavioral counseling, are supported to use NRT therapy provided and that communication with mental health services occurs as necessary.

Peer workers will identify as being or having been a mental health consumer and preferably will also be ex-smokers or non-smokers who have experience working with SSMI and are aware of the challenges involved in smoking cessation for this group. Peer workers will receive training and ongoing supervision from investigators experienced in working with peer workers (including investigators with lived experience). Training and supervision will cover recruitment issues, delivery of standard care (brief intervention), baseline assessment, the automated randomization procedure, how to refer to Quitline, fidelity, distress management procedures, and suicide risk assessment and referral.

Intervention Fidelity

For purposes of the present study, a random selection of 20% of Quitlink intervention participants will be made, and routinely recorded calls will be rated for fidelity to the treatment manual by an independent rater using a checklist derived from the treatment manual which includes core behavior change techniques (BCTs) relevant to smoking cessation. BCTs are defined as the smallest identifiable components of an intervention that in themselves have the potential to change behavior (39).

Concurrent Treatment

In both the Standard Smoking Care and Quitlink Intervention conditions, participants will be able to partake of any interventions initiated by themselves or their health providers during the course of the study and these will be monitored at the follow-up assessments.

Outcome Measures

Outcome measures will be assessed at 2-, 5-, and 8-months post baseline, by telephone. These will be conducted by independent assessors who will remain blind to intervention allocation. Outcome measures will all be assessed before any process measures where answers could suggest experimental condition. All assessment instruments are widely used in mental health and/or tobacco treatment research and practice (see **Table 1**) and cover the domains hypothesized to be impacted upon by the intervention.

TABLE 1 | Assessment schedule.

Assessments	Baseline	2 month	5 month	8 month
Demographic characteristics	X			
MENTAL ILLNESS DIAGNOSIS				
Self-report - Have you ever received a mental health diagnosis? - Have you ever been diagnosed with a psychotic disorder?	X			
MINI (diagnostic interview)		X	*	*
McLean screening instrument for borderline personality disorder		X	*	*
MEDICATIONS				
Current medications	X/E			
Medication side effects	X			
SMOKING MEASURES:				
Current smoking and quit attempts	X	X	X	X
7 day point prevalence abstinence (self-reported)		X	X	X
6 month prolonged abstinence (primary outcome)				X
CO Monitoring (those reporting abstinence)				A
Heaviness of Smoking Index	X	S	S	S
Tobacco types	X			
Cost	X	S	S	S
History (age first smoked)	X			
Social influences	X			
Cravings	X	X	X	X
Smoking use motives	X			
Situations not allowed to smoke		X	X	X
Goal	X			
Motivation to quit	X	S	S	S
Confidence to quit	X			
Self-efficacy		X	X	X
Products/services to help quit (including NRT, Quitline)	X	X	X	X
Nicotine replacement products (helpfulness, likely use)	X			
Counseling preference (in person or telephone)	X			
Minnesota Nicotine Withdrawal Scale (only two items in follow ups)	X	X	X	X
MENTAL HEALTH:				
Kessler-10	X	X	X	X
SUBSTANCE USE:				
Alcohol (AUDIT-C)	X	X	X	X
Cannabis use with tobacco question	X	X	X	X
Cannabis (First question of CUDIT-R)	X	X	X	X
QUALITY OF LIFE:				
AQoL-8D	X	X	X	X
MEDICATIONS—NRT/CESSATION:				
Process measure (i.e., provided to intervention participants)		E		
Perceived support— GP, Psychiatrist, other health professional		X		
QUITLINE USE:				
Number, length, content and timing of calls		E		
SERVICE USE				
Hospitalizations and other intensive health service use		X		X
Time off from work and usual duties		X	X	X
Financial stress questions	X	X	X	X
Therapeutic Alliance:		X		
WAIT-3		X[$]		
Peer worker brief intervention question		X		
Qualitative interviews		I	I	I
PBS/MBS cost data				E

AUDIT-C, Alcohol Use Disorders Identification Test – Brief (40); AQoL-8D, Assessment of Quality of Life-8D (41); CUDIT-R, Cannabis Use Disorders Identification Test – Revised (42); CO, Carbon monoxide; GP, General Practitioner; Kessler-10, Kessler Psychological Distress Scale (43); MINI, Mini International Neuropsychiatric Interview (44); NRT, Nicotine Replacement Therapy; WAIT-3, Working Alliance Inventory for Tobacco-–3 (45); MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

Key

*******If not captured at previous assessment.*

E *Extracted data.*

S *Current smokers.*

$*If used Quitline.*

A *Those reporting abstinence.*

I *Selected subsample.*

Primary Outcome

The primary outcome is defined as continued abstinence from smoking since the end of the treatment period, i.e., 6 months sustained abstinence, with no relapse (defined as 7+ days of continuous smoking, and no reported smoking in the last week), with biochemical verification at 8-month follow-up. Sustained abstinence will be assessed via the following question: "When did you last smoke a cigarette, even a puff?" If a participant reports prolonged abstinence at the 8 month follow up, and no smoking in the last week, they will be asked to attend a face to face visit to complete CO testing for objective validation using a Micro+ Smokelyzer, with a reading of 8 ppm or higher defined as indicative of recent smoking.

Secondary Outcomes

Smoking

Secondary outcomes assessed at 2-, 5-, and 8-months post baseline will include:

7-day point prevalence abstinence, based on "Have you smoked at least part of a cigarette in the last 7 days?"
Reported cigarettes smoked per day (for daily smokers) or cigarettes per week (for non-daily smokers).
Expenditure on cigarettes.
Number of quit attempts of 24 h or more, 1 week or more, and 1 month or more in the previous 3 months or since last assessed.
Time to relapse: in those who do relapse will be determined by asking when they first smoked after a quit attempt.
Number of subsequent quit attempts among those who relapsed.
Hospitalizations and other intensive health service use.
Financial stress questions adapted from Siahpush and Carlin (46).
Productivity impacts (time off work or other duties).

Heaviness of Smoking Index (HSI): Nicotine dependence is assessed using this two item Index (47, 48). It uses a six-point scale calculated from the number of cigarettes smoked per day (1–10, 11–20, 21–30, 31+) and the time to first cigarette after waking (≤5, 6–30, 31–60, and 61+ min). Nicotine dependence is then categorized into a three-category variable: low (0–1), medium (2–4), and high (5–6). The HSI has been found to have good reliability and reasonable predictive validity (49).

Cravings: assessed by one item taken from the International Tobacco Control (ITC) Four Country Survey (50, 51), "Currently, how often do you get strong cravings to smoke tobacco?" with the response options of: (1) Hourly or more often; (2) Several times per day; (3) At least once a day; and (4) Less than daily. Difficulty in coping with situations in which smoking is not allowed is also assessed, on a 4-point Likert Scale from "very," "moderately," "mildly" to "not at all difficult."

Withdrawal symptoms: as assessed by the Minnesota Nicotine Withdrawal Scale [MNWS; (52)], an eight item ordinal scale rating withdrawal symptoms from 0 (not present) to 3 (severe). At baseline the MNWS is administered, with two symptoms (concentration and appetite) assessed at follow-up. The MNWS has been shown to have good reliability and predictive validity (53).

Mental health

Kessler Psychological Distress Scale [Kessler-10; (43)] a 10-item scale of non-specific psychological distress. Low scores (10–15) indicate little or no psychological distress and higher scores indicate increasing levels of distress (moderate, 16–21; high, 22–29; and very high, 30–50). It has shown consistent psychometric properties across major sociodemographic subsamples (54).

Substance use

The Alcohol Use Disorders Identification Test—Brief [AUDIT-C; (40)] a three item screening tool used to identify hazardous alcohol use or active alcohol use disorders. It is scored on a scale of 0–12 with a cut off of 3 (women) or 4 (men). For men, it has been shown to have a sensitivity of 0.90 and specificity of 0.45; for women the sensitivity is 0.80, and specificity is 0.87.

The Cannabis Use Disorders Identification Test—Revised [CUDIT-R; (42)] is a briefer (8-item) and more refined version of the CUDIT (55), a simple modification of the AUDIT. Items cover the domains of consumption, cannabis problems, dependence, and psychological features. The CUDIT-R was found to comprise a single factor, with high test-retest reliability ($r = 0.871$), high internal consistency ($\alpha = 0.914$), and discriminant validity (area under the curve = 0.960). Only question 1, "How often do you use cannabis? (over the last 2 months)" is included in the present study (never, monthly or less, 2 to 4 times a month, 2 to 3 times a week, 4 or more times a week). In addition, participants who use cannabis are asked "Do you ever mix tobacco with your cannabis?" with response options of "Yes, always or nearly always," "Yes, sometimes" or "No, never or very rarely."

Quality of life

The Assessment of Quality of Life 8 Dimension [AQoL-8D; (41)] instrument is comprised of 35 items from which eight dimensions (independent living, pain, senses, mental health, happiness, coping, relationships, and self-worth) and two "super-dimensions" (physical and psychosocial) are derived. It has demonstrated strong content validity and has been found to perform relatively well in populations with SMI (56). The 35 items may be reduced to a single utility score. Use of the instrument enables calculation of quality adjusted life years (QALYs) experienced across the two study arms, which will be reported in the cost-effectiveness analysis.

Covariate or process measures

Demographic variables (e.g., gender and age).
History of tobacco smoking and quitting.
Types of tobacco used.
Social influences on smoking, e.g., lives with other smokers.

Smoking Use Motives: As part of this trial self-reported reasons for smoking are assessed using a modified version of the Drinking Motives Questionnaire (57), with additional items developed by Spencer et al. (58) to explore the use of substances to alleviate psychotic symptoms (positive and negative).

At baseline, participants will be asked whether they have a preference for in person or telephone counseling. They will also be asked to rate the likely helpfulness of NRT to long term

quitting (not at all, some, moderately, extremely) and likelihood of use in the longer term (not at all, some, moderately, extremely).

Motivation to quit: assessed by a single question adapted from Crittenden et al. (59), "How much do you want to quit smoking?" (not at all, a little, some, very much). At follow-up assessments, "Are you trying to quit smoking altogether or are you planning to keep smoking at this level?"

Confidence to quit (at baseline) is measured by the following question: "How confident are you that you can stop smoking for good in the next 2 months if you wanted to?" (not at all, somewhat, moderately, very, extremely).

Self-efficacy in quitting is measured by the following question adapted from Perkins et al. (60): "How confident are you that you will not smoke at all tomorrow?" (not at all, somewhat, moderately, very, extremely). For those who quit at follow-up, "How confident are you that you will be able to stay quit long-term and become a permanent ex-smoker?" (not at all, somewhat, moderately, very, extremely).

Medications: Changes in use of prescribed psychotropic medication.

Medication side effects: At baseline, participants will be asked to rate 10 symptoms during the past week (e.g., dry mouth, increased thirst) on an ordinal scale from 0 (not present) to 3 (severe). This measure is informed by the most common adverse side effects of psychiatric medications as identified in the Side Effect Survey, which has demonstrated validity and reliability (61).

Treatment received (use of NRT and Quitline—number and length of calls).

Objective data on service use (number and length of calls) will be extracted from the Quitline database for all participants (as some control participants may have self-referred).

Therapeutic alliance with Quitline counselor: the three-item Working Alliance Inventory for Tobacco (45), measuring goal, task, and bond on a five item Likert Scale (seldom, sometimes, fairly often, very often, always) will be administered at the 2-month follow-up. The three-item measure has been found to have acceptable-good internal consistency and construct validity.

Self-reported service use and satisfaction: participants' use and assessment of level of support they have received for quitting from their mental health service, doctors, and other health professionals.

Linked data on service and prescription medication use from the Australian Government subsidized Medicare and Pharmaceutical Benefits Schemes.

Safety data

Adverse events will be collected at all follow-up time points, with prompting via questions asking how the participant has been feeling in general and if they have any health concerns.

Sample Size Determination

Based on our previous study (23) which achieved a 15% prolonged abstinence rate in depressed smokers, and knowing rates are considerably less among those with more severe mental illnesses (62) we anticipate that for the primary outcome of prolonged abstinence at 8 months, prolonged abstinence will occur in 1% of the control arm vs. 8% in the intervention arm. To detect this effect with 80% power at $p = 0.05$, we require 134 per arm. We expect ∼30% attrition, inflating the sample size to 191/arm or 382 overall. Thus, we will recruit 382 smokers over 36 months and follow up at 2-, 5-, and 8-months post-baseline, completing the study over a 4.5-year period.

Participant Recruitment and Retention

Peer workers will visit sites and provide information to both staff and potential participants about the study to encourage recruitment. Service staff will be asked to refer potential participants (at any stage of their treatment) to the study via the peer worker. Additional recruitment strategies will be by advertising (e.g., flyers, newsletters, online via service websites) and peer workers attending community meetings and other events to inform potential participants directly about the study to encourage self-referral.

For those who meet eligibility criteria and decide to participate in the study, the peer worker will gain written informed consent from the participant. Provision is made on the consent form for opting in or out of possible participation in a qualitative study of experiences of trying to stop smoking and for participation in further studies.

Telephone follow-up and compensation for completed assessments will aid in increasing retention rates. Monthly check-in texts (to remind participants to inform the researchers if their contact details change) will be conducted to help maintain contact with participants, and 3 monthly follow-up will assist with accurate participant recall of smoking and quitting history. Participants will receive a $40 gift card for baseline and for each completed follow-up assessment and a $40 gift card for the 8-month face-to-face assessment for biochemical verification of self-reported smoking cessation (if required).

Upon completion of the baseline assessment, the peer worker will provide standard smoking care (described above) to all participants. The peer worker will then access the randomization allocation for the participant via the eCRF program, and communicate appropriately with the participant.

Randomization

Following completion of the baseline assessment, a brief intervention will be delivered by a peer worker—prior to randomization—to ensure all participants receive the recommended minimum standard care, in a manner that is unbiased by the outcome of randomization. Following this, the computer program used to complete the baseline will randomize to condition using 1:1 randomization. Participants will be randomly allocated to either no further intervention, or to be contacted by Quitline who will offer a targeted callback counseling intervention with NRT provided, over an 8-week period. As stated above, cluster randomization will be used in situations where risk of contamination is higher, such as residential services, stratified by short- or long-term residence, with 1:1 allocation. Individual randomization will be used in services where contamination of risk is lower, via permutated block sizes of 4 and 6 to avoid incomplete blocks, stratified for site. Participants will be allocated a unique computer-generated

study number. Randomization will be independently managed by the trial epidemiologist (JA) and uploaded to a web-based data capture tool (Research Electronic Data Capture; REDCap) that will also have case report forms (eCRF) created for the project using REDCap.

Following randomization, those in the intervention group will be told of the additional supports they will be getting (see above). Controls will be simply told the session is over and reminded of when the first follow-up survey might be expected.

Blinding

Outcome assessors will be blinded to study design and allocation and will have training and regular supervision on practices to maintain blinding in a PROBE design study. These have been previously used successfully by our team (63). Importantly, outcomes assessors will ask participants about smoking outcomes prior to any questions about use of cessation supports, questions that often produce answers which can indicate likely experimental condition.

The mental health practitioners, follow-up assessors, qualitative interviewers, and Quitline counselors are located in separate organizations, which will maximize maintenance of the outcomes assessors' blindness to study design and treatment allocation. Outcomes assessors will access only contact details, and not treatment files. The eCRF permissions will not allow outcomes assessors to access information about the participant's treatment allocation.

Participants will be aware of what support they are receiving, but not of the comparison condition due to the "limited disclosure" approach. Participants will be informed about what is involved (i.e., the follow-up assessments) and that they may be offered support with smoking cessation. They will not be informed of the specifics of the support (i.e., intervention will receive proactive referral to Quitline and be supplied with NRT). Control participants will be informed of the options available and encouraged to follow up on any they are interested in, in the usual manner (GP/other health professional/self-referral to Quitline). The outcomes assessment team will remain blinded to treatment allocation until completion of the study. Data analysts will be blinded by labeling the intervention conditions "A" and "B."

Unblinding

Following baseline assessment and delivery of the brief intervention, peer workers, the trial coordinator, quitline counselors, qualitative staff, and associated investigators will be unblinded to treatment allocation**.**

Stepwise Procedures

This protocol is presented in accordance with the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement (see **Supplementary Material**). The schedule of enrolment, interventions, and assessments is summarized in **Table 2**.

Data Management

All data will be entered electronically via eCRF using (REDCap) tools (64) hosted at Hunter New England Local Health District on a secure server. Redcap is a secure, web-based application designed to support data capture for research studies providing an intuitive interface for data entry, audit trails for tracking data manipulation and export, automated export procedures for downloads to statistical packages and procedures for importing data from external sources. The lead investigator (and/or delegate) and study coordinators will conduct ongoing data checking and cleaning.

Participants' personal details will be accessed, used, and stored according to relevant legislations. Access to external health data (e.g., Quitline, MBS/PBS, health records) will only occur with the consent of the participant in accordance with protocols of relevant external agencies (e.g., Commonwealth Department of Human Services for MBS/PBS data). The trial conduct and safety data will be monitored by a Data Safety Monitoring Board (DSMB).

Statistical Methods

Primary and Secondary Outcomes

Independent and blinded statisticians from the CReDITSS Unit at the Hunter Medical Research Institute, Australia, supervised by AI Attia, will conduct analyses of the primary and secondary outcomes.

Analyses will be carried out using a cluster randomized trial framework where the individuals ($n = 150$) are treated as clusters that contribute only one person, the short-term residential programs are clusters that contribute an average of 15 people each (10 programs $\times$ 15 people/program $=$ 150 total) and the long-term programs are clusters that contribute 10 people each (6 programs $\times$ 10 people/program $=$ 60). We will use a generalized linear mixed model (linear regression for continuous outcomes and logistic regression for dichotomous outcomes) to handle the clustering and the repeated measures at baseline, 2-, 5-, and 8-months; individuals will be modeled as random effects, cluster as a random effect, and group assignment as a fixed effect. Mixed models allow for missing data for the primary intention to treat analysis, but a sensitivity analysis using a worst case scenario (baseline value for continuous outcomes or relapse for dichotomous outcomes in case of missing value) will also be carried out.

Intervention participants who do not complete the intervention, and participants who miss an assessment follow-up time point, will be kept in the study and contacted for later assessments (unless they choose to withdraw from the follow-up assessments).

Exploratory Analyses

We plan to examine whether the amount of intervention (Quitline counseling, NRT) received by participants is related to outcomes. We will also explore different imputation strategies for missing data related to outcomes.

TABLE 2 | Stepwise procedures.

Contact/visit			Intervention period								Follow-up period							
Week	**−1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**…**	**21**	**22**	**…**	**34**	**35**
Visit number		1									2			3			4	
ENROLLMENT																		
Screening (inclusion/exclusion)	X	X																
Informed consent	X	X																
BASELINE ASSESSMENT		X																
Standard smoking care		X																
Randomization		X																
INTERVENTION*																		
Referral to Quitline		X																
Contacted by Quitline and smoking cessation initiated			X															
Quitline determines preferred oral NRT for second 4-week supply				X														
NRT dispensing		X		X														
Smoking cessation program			X	X	X	X	X	X	X	X								
FOLLOW-UP ASSESSMENTS											X			X			X	
Blinded follow up assessment conducted (all participants)											X			X			X	
Potential qualitative interviewees identified**											X			X			X	
Qualitative interviews conducted**												X			X			X
CO monitoring (on reported abstainers)																	X	
ADVERSE EVENTS																		
Unprompted (serious/severe)			X	X	X	X	X	X	X	X								
Prompted (all)											X			X			X	

**Intervention group only. **Participants will be purposely selected at each of the assessment timepoints (2, 5, and 8 months) to be invited for interview.*

Economic Evaluation

A cost-effectiveness analysis of Quitlink will be conducted alongside the trial described here, using data 8 months post randomization. A modeled analysis will estimate future costs and benefits of smoking cessation beyond the trial period, over the life course. Full protocol details of this are presented in this Special Issue in Sweeney et al. (in submission). In brief, incremental cost-effectiveness ratios (ICER) will be calculated for the cost ($AUD) per successful quit and quality adjusted life year (QALY) gained (i.e., cost-utility) as a result of Quitlink when compared with usual care. Healthcare system and limited societal perspectives will be taken.

Qualitative Evaluation

A nested qualitative study will be conducted. All interviews (participants and workers) will be audio recorded, transcribed, and a general inductive approach will be taken to the analysis (65).

Participant Interviews

Semi-structured individual in-depth interviews will be conducted with 72 participants. The (unblinded) qualitative researchers will access assessment data (REDCap) to view participants' cigarette consumption and service use data. They will use these data to purposively invite participants at each of the assessment timepoints (2-, 5-, and 8-months) for interview. Potential participants will be sent a flyer via text, mail, or email (depending on contact information available) asking them to participate in an interview. Upon affirmation, they will be provided the full Information Statement on the interview component.

Participant Selection

At 2 months, 30 participants will be interviewed (15 in each study arm, with cessation outcomes balanced across groups to negate any potential therapeutic effect of the additional qualitative interviews). The majority of the interviews (∼10 per arm) will be with participants who have either not reduced smoking levels or have made only some reduction in smoking (<50%). Having a mix of those who have engaged with the intervention (attended 4+ Quitline sessions; or engaged in other treatments) and those who have not engaged or under-engaged (1–3 sessions) will enable identification of both barriers to engagement and barriers to change.

At 5 months, another 30 participants will be interviewed (15 per treatment arm, balanced for smoking outcomes). The

majority (∼10 per arm) will be "relapsers" (defined as those who have reduced consumption by 50–100% at 2 months but have resumed or increased use by 5 months), to allow a focus on medium term barriers to cessation maintenance, again with a mix of those who are engaged and those who are non- or under-engaged.

At 8 months, 12 participants will be interviewed (no balancing required as this is after primary endpoint collection), including ∼6 who have relapsed (in order to focus on longer term barriers to cessation maintenance). At each time point, interviews will also be conducted with people who have successfully quit and maintained cessation to determine whether those who are successful face the same barriers as others but overcome them, and/or use the intervention in different ways. Participants in the qualitative study will be remunerated $40 for participation in individual interviews expected to take ∼45 min.

Mental Health and Quitline Victoria Counselor Interviews

Interviews will evaluate the acceptability of the intervention among mental health practitioners (including peer workers) and Quitline counselors. Semi-structured individual in-depth interviews will be conducted with 15 mental health practitioners to enable data collection to reach saturation and for key themes to be identified (66). For Quitline counselors, three group interviews (4–5 counselors per group) will be conducted. Interviews with mental health practitioners and Quitline counselors will explore their experience of the program and its strengths and weaknesses from their perspective. Mental health practitioners will also be asked to focus on the implementation and sustainability of the Quitlink intervention.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established. The DSMB will monitor safety and adverse events reported and will convene as required throughout the duration of the trial. The DSMB will be composed of individuals with appropriate expertise (e.g., clinical trials, statistical expertise, mental health expertise) who are independent from the study and free of conflict of interest, and where this is not practical, measures will be taken to minimize the perceived conflict of interest. The DSMB will have the capacity to contribute to decisions regarding continuation or discontinuation of the trial based on scientific and ethical factors. The DSMB will operate under the rules of an approved charter that will be written and reviewed by the DSMB. Each data element that the DSMB needs to assess will be clearly defined in the DSMB charter. The DSMB will provide its input to the Chief Investigator, and this will be reported to HRECs and other regulatory bodies as per local guidelines.

Safety Monitoring

Adverse events (AEs) will be collected and reported as per Good Clinical Practice guidelines, from the point of enrolment until end of their participation. Follow-up assessors will prompt for all AEs as part of the interview schedule, while Quitline counselors will record any serious or severe events (SAEs) reported during counseling, as per current Quitline protocols, and will report these to research staff. If a participant withdraws from the study with an ongoing AE during the treatment phase, AEs will be followed up until it is resolved; or 7 days following withdrawal, at which time participants will be advised to contact their treating physician if AEs persist. The DSMB will review safety data on a regular basis, with SAEs and other significant safety issues reported immediately to the DSMB and further (e.g., governing ethics committee/s) as necessary as per local guidelines.

ANTICIPATED RESULTS

This RCT will test the effectiveness of the Quitlink intervention for smoking cessation among SSMI. We anticipate that the intervention will be associated with significantly higher rates of continued abstinence from smoking at 8-month follow-up, relative to the control condition. We also anticipate the intervention will be more cost-effective compared to the control condition of usual care and reduced financial stress for participants. Using qualitative methods, we will also identify barriers and enablers to making and sustaining quit attempts. A range of secondary outcomes will be measured on follow-up occasions and we expect that the Quitlink intervention will be associated with significantly better outcomes on these variables (higher rates of 7-day point prevalence abstinence, quit attempts, smoking cessation motivation and self-efficacy, mental health, and quality of life and lower reported cigarette consumption, nicotine withdrawal symptoms, expenditure on cigarettes, and alcohol, and cannabis use).

ETHICS AND DISSEMINATION

Prior to participation in the trial, the person will be fully informed about the research and given ample time and opportunity to enquire about details and decide whether or not to participate. If they agree to participate they will be asked to sign the study specific consent form. To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at the time of randomization. Results arising from the RCT will be published in peer-reviewed journals and disseminated at international conferences. Results will be reported in such a way that participants will not be identifiable.

Research Ethics Approval

Ethics approval has been obtained through St Vincent's Hospital, Melbourne (HREC Reference Number: HREC/18/SVHM/154), the University of Newcastle HREC (HREC Reference Number: H-2018-0192) and the Cancer Council Victoria, HREC (HREC Reference Number: 1807).

Protocol Amendments

Each study site will only be able to start data collection once the relevant Ethics Committee approval is obtained. In the case of proposed protocol changes, an amendment will be submitted to the Ethics Committees for approval, and the trial coordinating center will ensure all study staff are provided with new documentation. Any significant protocol changes will be updated on the ANZCTR and reported in the final outcomes paper.

Consent or Assent

The study is based on the principles of Good Clinical Practice according to the Declaration of Helsinki. Potential participants will be given oral and written explanation of the study including the potential risks, their right to withdraw at any time and the details of data protection and confidentiality and sufficient time to ask questions. A signed consent form will be obtained. Participants will be given the opportunity to agree or decline to being contacted for ancillary studies, without effecting participation in the main trial. A copy of the PICF will be given to the person.

Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants will be treated in strict confidence. Participants' identifying details will be stored separately from other data. Participants will be informed of the potential reasons for breaching confidentiality in the PICF (risk of harm to self or others). Data, which identify any trial participant, will not be revealed to anyone not directly involved in the trial or the clinical care of that participant.

Access to Data

All data will be considered the property of the trial chairperson, who, in consultation with the trial management committee, will be responsible for presentations and publications arising from this trial.

Dissemination Policy

Trial findings will be summarized and posted to participants who have indicated they would like a copy of the results.

DISCUSSION

The Quitlink study is the first rigorously designed RCT to evaluate a specialized quitline intervention accompanied by NRT, for people with SMI, with biochemical verification of self-reported abstinence. Accessible smoking interventions like quitlines are clearly required to improve the mental and physical health of smokers in receipt of mental health treatment and links with mental health services are crucial to ensure maximum utilization. A major strength of this study is that it is demonstrably an intervention that can and will be used if the trial demonstrates it helps: it uses two strategies that are currently funded, i.e., quitline and peer workers, but not currently co-ordinated. Quitlines exist but are underutilized by those with SMI; likewise, peer workers are employed but do not uniformly see smoking cessation as part of their role. The study investigates a model for how these two existing strategies can be co-ordinated to maximize the health impact for SSMI, who often wish to quit but are not properly supported to do so. Having peer workers trained in assessment, brief smoking cessation advice, and proactive referral to quitline is more likely to attract SSMI to consider smoking cessation. It is a simple and potentially cost effective method of increasing access to smoking cessation services in the mental health sector.

Limitations

There are three main limitations associated with this trial. Firstly, due to cluster randomization of residential sites, the peer workers will become aware of each site's allocation. Peer workers will be carefully trained and supervised not to communicate this information. They will also be supervised so as to encourage equal recruitment across control and intervention sites. Secondly, outcome to 8-months has been chosen as the focus of this study so as to examine medium term smoking, which parallels that for well populations (67). However, it would be informative to follow the sample over a longer timeframe to measure longer-term health and other benefits.

Conclusions

If Quitlink is shown to be effective, it has the potential to greatly improve individuals' longevity, quality of life, mental health, and reduce health care costs. This is an innovative and practical service delivery model that has the potential to ensure that smokers with SMI have access to best-practice smoking cessation treatment. Secondly, regardless of effectiveness outcomes, the project's qualitative study will provide greater insights into the barriers faced by smokers with SMI and will assist in the development of even more effective interventions.

The intervention can be quickly and directly translated to quitlines and mental health services, to improve rates of smoking cessation among SSMI. Study findings will be of significant interest to consumer and carer groups, the broader community sector, as well as researchers and clinicians. The rigorous study design, inclusion of cost-effectiveness evaluation and qualitative study are key strengths.

AUTHOR CONTRIBUTIONS

The first draft of the paper was written by AB with significant input from KM and AT before receiving input from remaining authors. The study was conceived and designed by all authors.

FUNDING

This project is funded by the National Health and Medical Research Council (APP1139125). The funder had no role

in study design, data collection and analysis, decision to publish, or preparation of the manuscript. AB and BB hold NHMRC Fellowships (APP1135901 and 1063206) and Faculty of Health and Medicine, University of Newcastle, Faculty of Health and Medicine Gladys M Brawn Fellowships. RB holds the position of Nigel Gray Distinguished Fellow in Cancer Prevention at the Cancer Council, Victoria, Australia. Kristen McCarter holds a University of Newcastle Postdoctoral Scholarship. DB is funded by a University of Newcastle PhD scholarship.

ACKNOWLEDGMENTS

We thank Zoe Jenkins for assisting in the ethics submission to St Vincent's Hospital and commenting on this paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00124/full#supplementary-material

REFERENCES

1. Callaghan RC, Veldhuizen S, Jeysingh T, Orlan C, Graham C, Kakouris G, et al. Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. *J Psychiatr Res.* (2014) 48:102–10. doi: 10.1016/j.jpsychires.2013.09.014
2. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA.* (2000) 284:2606–10. doi: 10.1001/jama.284.20.2606
3. Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA.* (2014) 311:172–82. doi: 10.1001/jama.2013.284985
4. Szatkowski L, McNeill A. Diverging trends in smoking behaviors according to mental health status. *Nicot Tobacco Res.* (2015) 17:356–60. doi: 10.1093/ntr/ntu173
5. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian Survey of Psychosis. *Aust N Z J Psychiatry.* (2012) 46:851–63. doi: 10.1177/0004867412449876
6. Australian Institute for Health and Welfare (2017). *National Drug Strategy Household Survey 2016*. Canberra.
7. Australian Institute of Health and Welfare. Australia's Health 2018. Australia's health series no. 16. AUS 221. Canberra, ACT: AIHW (2018).
8. Wu Q, Szatkowski L, Britton J, Parrott S. Economic cost of smoking in people with mental disorders in the UK. *Tob Control.* (2015) 24:462–8. doi: 10.1136/tobaccocontrol-2013-051464
9. Prochaska JJ. Smoking and mental illness–breaking the link. *N Engl J Med.*. (2011) 365:196–8. doi: 10.1056/NEJMp1105248
10. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction.* (2010) 105:1176–89. doi: 10.1111/j.1360-0443.2010.02946.x
11. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ.* (2014) 348:g1151. doi: 10.1136/bmj.g1151
12. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* (2016) 387:2507–20. doi: 10.1016/S0140-6736(16)30272-0
13. Hitsman B, Moss TG, Montoya ID, George TP. Treatment of tobacco dependence in mental health and addictive disorders. *Can J Psychiatry.* (2009) 54:368–78. doi: 10.1177/070674370905400604
14. Siru R, Hulse GK, Tait RJ. Assessing motivation to quit smoking in people with mental illness: a review. *Addiction.* (2009) 104:719–33. doi: 10.1111/j.1360-0443.2009.02545.x
15. McNally L, Oyefeso A, Annan J, Perryman K, Bloor R, Freeman S, et al. A survey of staff attitudes to smoking-related policy and intervention in psychiatric and general health care settings. *J Public Health.* (2006) 28:192–6. doi: 10.1093/pubmed/fdl029
16. Kerr S, Woods C, Knussen C, Watson H, Hunter R. Breaking the habit: a qualitative exploration of barriers and facilitators to smoking cessation in people with enduring mental health problems. *BMC Public Health.* (2013) 13:221. doi: 10.1186/1471-2458-13-221
17. Ratschen E, Britton J, Doody GA, Leonardi-Bee J, McNeill A. Tobacco dependence, treatment and smoke-free policies: a survey of mental health professionals' knowledge and attitudes. *Gen Hospital Psychiatry.* (2009) 31:576–82. doi: 10.1016/j.genhosppsych.2009.08.003
18. Baker AL, Turner A, Beck A, Berry K, Haddock G, Kelly PJ, et al. Telephone-delivered psychosocial interventions targeting key health priorities in adults with a psychotic disorder: systematic review. *Psychol Med.* (2018) 48:2637–57. doi: 10.1017/S0033291718001125
19. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev.* (2013) 8:CD002850. doi: 10.1002/14651858.CD002850.pub3
20. Morris CD, Waxmonsky JA, May MG, Tinkelman DG, Dickinson M, Giese AA. Smoking reduction for persons with mental illnesses: 6-month results from community-based interventions. *Commun Ment Health J.* (2011) 47:694–702. doi: 10.1007/s10597-011-9411-z
21. Van Der Meer RM, Willemsen MC, Smit F, Cuijpers P, Schippers GM. Effectiveness of a mood management component as an adjunct to a telephone counselling smoking cessation intervention for smokers with a past major depression: a pragmatic randomized controlled trial. *Addiction.* (2010) 105:1991–9. doi: 10.1111/j.1360-0443.2010.03057.x
22. Rogers ES, Fu SS, Krebs P, Noorbaloochi S, Nugent SM, Gravely A, et al. Proactive tobacco treatment for smokers using veterans administration mental health clinics. *Am J Prevent Med.* (2018) 54:620–9. doi: 10.1016/j.amepre.2018.02.011
23. Segan CJ, Borland R, Wilhelm KA, Bhar SS, Hannan AT, Dunt DR, et al. Helping smokers with depression to quit smoking: collaborative care with Quitline. *Med J Aust.* (2011) 195:S7–11. doi: 10.5694/j.1326-5377.2011.tb03258.x
24. Baker AL, Richmond R, Kay-Lambkin FJ, Filia SL, Castle D, Williams JM, et al. Randomized controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders. *Nicotine Tob Res.* (2015) 17:946–54. doi: 10.1093/ntr/ntv039
25. Baker AL, Richmond R, Kay-Lambkin FJ, Filia SL, Castle D, Williams JM, et al. Randomised controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders: outcomes to 36 months. *Aust N Z J Psychiatry.* (2018) 52:239–52. doi: 10.1177/0004867417714336
26. Segan CJ, Baker AL, Turner A, Williams JM. Nicotine withdrawal, relapse of mental illness, or medication side-effect? Implementing a monitoring tool for people with mental illness into quitline counseling. *J Dual Diagnosis.* (2017) 13:1–7. doi: 10.1080/15504263.2016.1276657
27. Cummins S, Bailey L, Campbell S, Koon-Kirby C, Zhu SH. Tobacco cessation quitlines in North America: a descriptive study. *Tobacco Control.* (2007) 16:i9–i15. doi: 10.1136/tc.2007.020370
28. Health Workforce Australia (2014). *Mental Health Peer Workforce Literature Scan*.
29. Davidson L, Bellamy C, Guy K, Miller R. Peer support among persons with severe mental illnesses: a review of evidence and experience. *World Psychiatry.* (2012) 11:123–8. doi: 10.1016/j.wpsyc.2012.05.009
30. Department of Health (2011). *Framework for Recovery-Oriented Practice*. Canberra, ACT.
31. National Mental Health Commission (2013). *A Contributing Life, the 2013 National Report Card on Mental Health and Suicide Prevention*. Sydney, NSW.
32. Lloyd-Evans B, Mayo-Wilson E, Harrison B, Istead H, Brown E, Pilling S, et al. A systematic review and meta-analysis of randomised controlled trials of peer

support for people with severe mental illness. *BMC Psychiatry.* (2014) 14:39. doi: 10.1186/1471-244X-14-39
33. Goulao B, MacLennan G, Ramsay C. The split-plot design was useful for evaluating complex, multilevel interventions, but there is need for improvement in its design and report. *J Clin Epidemiol.* (2018) 96:120–5. doi: 10.1016/j.jclinepi.2017.10.019
34. Ben-Zeev D, Davis KE, Kaiser S, Krzsos I, Drake R. Mobile technologies among people with serious mental illness: opportunities for future services. *Admin Policy Ment Health.* (2013) 40:340–3. doi: 10.1007/s10488-012-0424-x
35. Baker A, Turner A, Kelly PJ, Spring B, Callister R, Collins C, et al. 'Better Health Choices' by telephone: a feasibility trial of improving diet and physical activity in people diagnosed with psychotic disorders. *Psychiatry Res.* (2014) 220:63–70. doi: 10.1016/j.psychres.2014.06.035
36. Mendelsohn CP, Montebello ME. Smokers with mental illness: breaking down the myths. *Med Today.* (2013) 14:53–6. Available online at: http://medicinetoday.com.au/2013/august/feature-article/smokers-mental-illness-breaking-down-myths
37. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry.* (2015) 23:37–43. doi: 10.1177/1039856214562076
38. World Health Organisation (2014). *Training for Tobacco Quitline Counsellors: Telephone Counselling.* Available online at: http://www.who.int/tobacco/publications/smoking_cessation/9789241507264/en/
39. Michie S, Johnston M, Carey R. Behavior change techniques. In: Gellman M, Turner JR. editors. *Encyclopedia of Behavioral Medicine.* New York, NY: Springer (2016). p. 1–8.
40. Bush K, Kivlahan DR, Mcdonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory care quality improvement project (ACQUIP) alcohol use disorders identification test. *Arch Intern Med.* (1998) 158:1789–95. doi: 10.1001/archinte.158.16.1789
41. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the assessment of quality of life (AQoL)-8D multi-attribute utility instrument. *Patient.* (2014) 7:85–96. doi: 10.1007/s40271-013-0036-x
42. Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, et al. An improved brief measure of cannabis misuse: the cannabis use disorders identification test-revised (CUDIT-R). *Drug Alcohol Depend.* (2010) 110:137–43. doi: 10.1016/j.drugalcdep.2010.02.017
43. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. *Arch Gen Psychiatry.* (2003) 60:184–9. doi: 10.1001/archpsyc.60.2.184
44. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* (1998) 59 (Suppl. 20) 22–33.
45. Warlick C, Richter KP, Catley D, Gajewski BJ, Martin LE, Mussulman LM. Two brief valid measures of therapeutic alliance in counseling for tobacco dependence. *J Subst Abuse Treat.* (2018) 86:60–4. doi: 10.1016/j.jsat.2017.12.010
46. Siahpush M, Carlin JB. Financial stress, smoking cessation and relapse: results from a prospective study of an Australian national sample. *Addiction.* (2006) 101:121–7. doi: 10.1111/j.1360-0443.2005.01292.x
47. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addiction.* (1989) 84:791–9. doi: 10.1111/j.1360-0443.1989.tb03059.x
48. Kozlowski LT, Porter CQ, Orleans CT, Pope MA, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. *Drug Alcohol Depend.* (1994) 34:211–6. doi: 10.1016/0376-8716(94)90158-9
49. Borland R, Yong HH, O'Connor RJ, Hyland A, Thompson, ME. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control Four Country Study. *Nicotine Tob Res.* (2010) 12 (Suppl.) S45–50. doi: 10.1093/ntr/ntq038
50. Herd N, Borland R. The natural history of quitting smoking: findings from the international tobacco control (ITC) four country survey. *Addiction.* (2009) 104:2075–87. doi: 10.1111/j.1360-0443.2009.02731.x
51. Herd N, Borland R, Hyland A. Predictors of smoking relapse by duration of abstinence: findings from the international tobacco control (ITC) four country survey. *Addiction.* (2009) 104:2088–99. doi: 10.1111/j.1360-0443.2009.02732.x
52. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* (1986) 43:289–94. doi: 10.1001/archpsyc.1986.01800030107013
53. Toll BA, O'Malley SS, McKee SA, Salovey P, Krishnan-Sarin S. Confirmatory factor analysis of the Minnesota Nicotine Withdrawal Scale. *Psychol Addict Behav.* (2007) 21:216–25. doi: 10.1037/0893-164X.21.2.216
54. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med.* (2002) 32:959–76. doi: 10.1017/S0033291702006074
55. Adamson SJ, Sellman JD. A prototype screening instrument for cannabis use disorder: the cannabis use disorders identification test (CUDIT) in an alcohol-dependent clinical sample. *Drug Alcohol Rev.* (2003) 22:309–15. doi: 10.1080/0959523031000154454
56. Mihalopoulos C, Chen G, Iezzi A, Khan MA, Richardson J. Assessing outcomes for cost-utility analysis in depression: Comparison of five multi-attribute utility instruments with two depression-specific outcome measures. *Br J Psychiatry.* (2014) 205:390–7. doi: 10.1192/bjp.bp.113.136036
57. Cooper ML, Russell M, Skinner JB, Windle M. Development and validation of a three-dimensional measure of drinking motives. *Psychol Assess.* (1992) 4:123–32. doi: 10.1037/1040-3590.4.2.123
58. Spencer C, Castle D, Michie PT. Motivations that maintain substance use among individuals with psychotic disorders. *Schizophr Bull.* (2002) 28:233–47. doi: 10.1093/oxfordjournals.schbul.a006934
59. Crittenden KS, Manfredi C, Lacey L, Warnecke R, Parsons J. Measuring readiness and motivation to quit smoking among women in public health clinics. *Addict Behav.* (1994) 19:497–507. doi: 10.1016/0306-4603(94)90005-1
60. Perkins KA, Parzynski C, Mercincavage M, Conklin CA, Fonte CA. Is self-efficacy for smoking abstinence a cause of, or a reflection on, smoking behavior change? *Exp Clin Psychopharmacol.* (2012) 20:56–62. doi: 10.1037/a0025482
61. Lapshin O, Skinner CJ, Finkelstein J. How do psychiatric patients perceive the side effects of their medications? *German J Psychiatry.* (2006) 9:74–93.
62. Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *Am J Psychiatry.* (2006) 163:1934–42. doi: 10.1176/ajp.2006.163.11.1934
63. Baker AL, Kavanagh DJ, Kay-Lambkin FJ, Hunt SA, Lewin TJ, Carr VJ, et al. Randomized controlled trial of cognitive-behavioural therapy for coexisting depression and alcohol problems: short-term outcome. *Addiction.* (2010) 105:87–99. doi: 10.1111/j.1360-0443.2009.02757.x
64. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* (2009) 42:377–81. doi: 10.1016/j.jbi.2008.08.010
65. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. *Am J Evalu.* (2006) 27:237–46. doi: 10.1177/1098214005283748
66. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods.* (2006) 18:59–82. doi: 10.1177/1525822X05279903
67. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tobacco Res.* (2003) 5:13–25. doi: 10.1080/1462220031000070552

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

CLINICAL STUDY PROTOCOL
published: 03 September 2019
doi: 10.3389/fpsyt.2019.00618

Protocol for an Economic Evaluation of the Quitlink Randomized Controlled Trial for Accessible Smoking Cessation Support for People With Severe Mental Illness

Rohan Sweeney[1], Marj Moodie[2], Amanda L. Baker[3], Ron Borland[4,5], David Castle[6,7], Catherine Segan[4,8], Alyna Turner[9,10], John Attia[3], Peter J. Kelly[11], Lisa Brophy[8,12], Billie Bonevski[3], Jill M. Williams[13], Donita Baird[3], Sarah L. White[4] and Kristen McCarter[3]*

[1] Centre for Health Economics, Monash Business School, Monash University, Melbourne, VIC, Australia, [2] Deakin Health Economics, Centre for Population Health Research, Deakin University, Geelong, VIC, Australia, [3] Faculty of Health and Medicine, University of Newcastle, Newcastle, NSW, Australia, [4] The Cancer Council Victoria, Melbourne, VIC, Australia, [5] School of Psychological Sciences, University of Melbourne, Melbourne, VIC, Australian [6] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia, [7] Department of Psychiatry, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia, [8] Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia, [9] IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia, [10] Barwon Health, Geelong, VIC, Australia, [11] Illawarra Institute for Mental Health, School of Psychology, University of Wollongong, Wollongong, NSW, Australia, [12] Mind Australia, Melbourne, VIC, Australia, [13] Division of Addiction Psychiatry, Rutgers Robert Wood Johnson Medical School and Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, United States

OPEN ACCESS

Edited by:
Błażej Misiak, Wroclaw Medical University, Poland

Reviewed by:
Kim Dalziel, The University of Melbourne, Australia
Ernest Marek Tyburski, University of Szczecin, Poland

***Correspondence:**
Rohan Sweeney
rohan.sweeney@monash.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *31 August 2018*
Accepted: *01 August 2019*
Published: *03 September 2019*

Citation:
Sweeney R, Moodie M, Baker AL, Borland R, Castle D, Segan C, Turner A, Attia J, Kelly PJ, Brophy L, Bonevski B, Williams JM, Baird D, White SL and McCarter K (2019) Protocol for an Economic Evaluation of the Quitlink Randomized Controlled Trial for Accessible Smoking Cessation Support for People With Severe Mental Illness. Front. Psychiatry 10:618. doi: 10.3389/fpsyt.2019.00618

Introduction: Smoking is a major cause of disease burden and reduced quality of life for people with severe mental illness (SMI). It places significant resource pressure on health systems and financial stress on smokers with SMI (SSMI). Telephone-based smoking cessation interventions have been shown to be cost effective in general populations. However, evidence suggests that SSMI are less likely to be referred to quitlines, and little is known about the effectiveness and cost effectiveness of such interventions that specifically target SSMI. The Quitlink randomized controlled trial for accessible smoking cessation support for SSMI aims to bridge this gap. This paper describes the protocol for evaluating the cost effectiveness of Quitlink.

Methods: Quitlink will be implemented in the Australian setting, utilizing the existing mental health peer workforce to link SSMI to a tailored quitline service. The effectiveness of Quitlink will be evaluated in a clustered randomized controlled trial. A cost-effectiveness evaluation will be conducted alongside the Quitlink clustered randomized controlled trial (RCT) with incremental cost-effectiveness ratios (ICERs) calculated for the cost (AUD) per successful quit and quality adjusted life year (QALY) gained at 8 months compared with usual care from both health care system and limited societal perspectives. Financial implications for study participants will also be investigated. A modeled cost-effectiveness analysis will also be conducted to estimate future costs and benefits associated with any treatment effect observed during the trial. Results will be extrapolated to estimate the cost effectiveness of rolling out Quitlink nationally. Sensitivity analyses will be undertaken to assess the impact on results from plausible variations in all modeled variables.

Discussion: SSMI require additional support to quit. Quitlink utilizes existing peer worker and quitline workforces and tailors quitline support specifically to provide that increased cessation support. Given Quitlink engages these existing skilled workforces, it is hypothesized that, if found to be effective, it will also be found to be both cost effective and scalable. This protocol describes the economic evaluation of Quitlink that will assess these hypotheses.

Ethics and dissemination: Full ethics clearances have been received for the methods described below from the University of Newcastle (Australia) Human Research Ethics Committee (H-2018-0192) and St Vincent's Hospital, Melbourne (HREC/18/SVHM/154). The trial has been registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000244101). Participant consent is sought both to participate in the study and to have the study data linked to routine health administrative data on publicly subsidized health service and pharmaceutical use, specifically the Medicare Benefits and Pharmaceutical Benefits Schemes (MBS/PBS). Trial findings (including economic evaluation) will be published in peer reviewed journals and presented at international conferences. Collected data and analyses will be made available in accordance with journal policies and study ethics approvals. Results will be presented to relevant government authorities with an interest in cost effectiveness of these types of interventions.

Keywords: smoking, smoking cessation, mental illness, quitline, peer worker, economic evaluation, cost-effectiveness

INTRODUCTION

While smoking rates have declined in many countries, the rate of decline among people living with severe and enduring mental illness (SMI) has been significantly slower (1, 2). For example, in the USA, over the period 2004–2011, smoking among individuals with no mental illness declined from 19.5% to 15.6% ($p < 0.001$), compared with 28.8% to 27.0% ($p = 0.006$) among individuals living with mental illness (2). Smoking rates in people living with SMI have been found to be around double the general population and up to four times higher for those living with bipolar disorder or schizophrenia (1, 3, 4). Smoking increases the risk of a number of tobacco-related illnesses, including lung, throat and bowel cancers, stroke, chronic obstructive pulmonary disease (COPD), and myocardial infarction (5). Consequently, smoking is the leading cause of preventable death among people living with SMI—significantly shortening their life expectancy compared to the general population and accounting for almost half of all smoking-related deaths (4, 6–9).

Smoking-related conditions also cause significant morbidity and reduce the quality of life of affected people, with or without the presence of SMI (5, 10). Exacerbating this for people living with SMI, smoking has been associated with increased psychiatric symptoms and hospitalizations, as well as a requirement for higher psychiatric medication dosages because smoking accelerates the metabolism of some antidepressant and antipsychotic medications (11, 12).

Data on the economic burden associated with smoking in people with SMI are limited, but evidence suggests that it is significant. In Australia in 2007, it was estimated, that when compared to smokers without mental illness, the additional cost of health care, lost productivity, carer costs, cigarette expenditure, and other costs associated with observed heavier levels of smoking among ~1.25 million smokers with mental illness (not just SMI), was around AUD3.5 billion annually (or about AUD4.5 billion in 2018[1]) (13). This is in addition to expected costs if smokers with mental illness smoked at similar levels to smokers with no mental illness—the main cost drivers being productivity losses (63%), health costs (12%), and cigarette expenditure (12%) (13). In the 2009/2010 UK financial year, it was estimated that the costs associated with smoking-related health care treatment, work-related absenteeism, and premature mortality among people with SMI was £2.3 billion (or about £3 billion in 2018[2]) (14).

Numerous smoking cessation strategies have been shown to be both effective and cost effective in the general population (15, 16). However, smokers with severe mental illness (SSMI) report lower cessation rates, in part attributable to higher levels of nicotine dependence, and they are likely to benefit from more intensive or extended interventions tailored to their needs (17). SSMI also report a lack of encouragement to quit by health professionals, who often mistakenly believe that people with mental illness are not interested in quitting and that it will interfere with their mental health recovery (12, 18).

Given the significant disease burden caused by smoking among people with SMI, improving access to smoking cessation interventions—and ensuring they are effective for SSMI—is

[1] Reserve Bank of Australia—https://www.rba.gov.au/calculator/annualDecimal.html.
[2] Bank of England—https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator

a vital health priority for this target group. Telephone-based smoking cessation counseling services (such as quitlines) are helpful for many smokers, but SSMI are infrequently referred to such services by mental health practitioners as it is uncommon for smoking cessation to be included in mental health planning (19). This has led to the development of Quitlink—a randomized controlled trial (RCT) of peer worker facilitated quitline support for smokers with mental health problems, implemented in an Australian setting (20). It aims to coordinate and enhance the services of Quitline Victoria and engage mental health peer workers to bridge the persistent gap between mental health services and Quitline. The primary aim of the intervention is to help SSMI quit smoking. Secondary aims include assessment of the extent to which Quitlink improves health-related quality of life (HRQoL) and reduces the burden on the health care system in both the short and longer terms.

Examining the cost effectiveness of proven or potentially effective interventions is increasingly important for public sector funding decisions and priority setting (21, 22). Telephone-based counseling interventions with or without complementary nicotine replacement therapy (NRT) can be a relatively cost-effective way to achieve smoking abstinence in general populations in both upper and lower income country settings (16). Furthermore, modeling suggests such interventions may even be cost saving from a health care system perspective due to cost offsets resulting from prevented health costs in the future (23–26).

While it has been well established that telephone-based counseling interventions (with or without NRT) can be a very cost-effective strategy for improving health and extending lives (15, 16), there is little evidence regarding the cost effectiveness of any smoking cessation strategies specifically targeting SSMI (27). Barnett et al. (28) compared a cessation program (including psychological counseling, NRT, and bupropion) given in an outpatient care setting in the USA for smokers with depression measured against a brief care comparator. After 18 months, the intervention group had a 5.5% increased chance of ceasing smoking ($p < 0.05$) at a cost of USD11,496 per successful quit and USD9,580 per life year gained, concluding that it was a relatively cost-effective intervention in the short run. In a more recent RCT, Barnett et al. (29) found a stage-based intervention (including computer-based assessment, regular feedback, face to face sessions, and up to 10 weeks of NRT) initiated with people during a psychiatric hospitalization, was highly cost effective. The intervention achieved around a 12 percentage point increase in smoking abstinence after 18 months compared with usual care [18.8% abstinence in the intervention arm versus 6.8% abstinence in usual care ($p < 0.05$)] at an estimated USD428 per additional quality adjusted life year (QALY) gained when modeled over the life course of participants. Rejas-Gutiérrez et al. (30) constructed a model to estimate the budgetary impact for the Spanish health care system from funding varenicline, bupropion, and NRT combined with medical follow-up and counseling for people with a major depressive disorder. They estimated that the cost of funding such interventions (€25.3 million) was offset by health costs avoided (€26.5 million) after 5 years, suggesting that cost offsets for the health care system might increase over a longer time period (30).

The Quitlink intervention will utilize existing and skilled Quitline and mental health peer workers. The peer workforce is developing in Australia and internationally, working alongside clinical staff to provide support based on shared lived experience of mental illness and recovery (31). In Australia, quitlines are government-funded services providing smoking cessation counseling across each state and territory. In addition, in the Australian setting, some of the medications to aid smoking cessation are currently subsidized. The presence of these funded health resources suggests that the additional resources required to implement Quitlink would be relatively modest. It is hypothesized then that, if effective, it is likely to be a highly cost-effective intervention, which can feasibly be scaled up beyond the trial setting. Such *a priori* expectations make the case for a rigorous economic evaluation to be conducted alongside the Quitlink RCT. This paper presents a protocol for the economic evaluation of the Quitlink intervention to address the following research question:

From the Australian health care system and limited societal perspectives, what is the cost effectiveness of the Quitlink intervention to increase smoking cessation and QALYs among people living with SMI when compared with usual care?

THE QUITLINK TRIAL

Study Design

Quitlink is a cluster RCT, the design of which is described in detail in Baker et al. (20). In brief, a multicenter prospective, randomized, open, blinded endpoint design will be utilized to compare Quitlink against usual smoking care in helping SSMI to quit smoking. The trial aims to recruit 382 participants with SMI from participating residential and nonresidential, hospital, and community-based mental health services in Victoria, Australia. The trial will entail cluster randomization: where individuals are part of a short- or long-term residential rehabilitation program, that residential program will be considered a cluster. Where individuals are not part of a residential rehabilitation program, they will be randomized individually, i.e., a cluster of 1. Participants randomized to the intervention group will receive the full Quitlink intervention as described below. All participants will undergo follow-up at 2, 5, and 8 months postbaseline. The main outcomes are described below in the section *Identification, Measurement, and Valuation of Outcomes* and described in detail in Baker et al. (20). A qualitative study will investigate the experience of participants with a focus on further enhancing engagement with the intervention. Full ethics approval for the methods described here and in Baker et al. (20) was obtained from the University of Newcastle (H-2018-0192) and St Vincent's Hospital, Melbourne (HREC/18/SVHM/154).

Screening, Randomization, and the Usual Care Control Group

Potential participants will be engaged and screened for eligibility by a trained mental health peer worker at specialist mental health services [see Baker et al. (20) for further details].

For eligible persons, upon provision of informed consent, a baseline assessment will be undertaken. Following this, participants will receive a brief smoking cessation intervention consisting of brief advice and provision of Quit Victoria written materials that include the Quitline telephone number.

After the provision of this brief smoking cessation intervention, participants will be randomly allocated to the control group or the Quitlink intervention group. The control group will continue with usual care in relation to smoking cessation support, as provided by their health care team, that is, no further intervention will be provided by the research team.

The Intervention

Following randomization, those allocated to the intervention will be referred to an enhanced quitline call-back service for SSMI and have the option of receiving up to 8 weeks of NRT (patches, complemented by an oral form of NRT, to be used as per pack guidelines). Quitline will proactively contact the participant to offer up to 8 weeks of telephone smoking cessation counseling with a dedicated counselor, which will include monitoring of mental health symptoms, nicotine withdrawal symptoms, and medication side effects, as well as mood management strategies that aid cessation.

METHODS AND ANALYSIS

Economic Evaluation Overview

A cost-effectiveness evaluation will be conducted with incremental cost-effectiveness ratios (ICER) calculated for the cost (AUD) per person who quits and QALYs gained compared with usual care from both health care system and limited societal perspectives. Cost effectiveness will be estimated at 8 months postrandomization (trial-based evaluation with costs and outcomes as per the trial). Given that most of the anticipated benefits associated with smoking cessation will occur well beyond the trial period (15, 16, 24), downstream costs and benefits will be estimated *via* a modeled economic evaluation. Health care system costs and health and QALY benefits will be estimated over the life course of study participants and extrapolated to estimate the cost effectiveness of rolling out Quitlink nationally.

The health care system perspective will be of most relevance to agencies that are likely to fund scaleup beyond the trial setting. Data on important personal out-of-pocket impacts of Quitlink will also be collected and incorporated with the health care system data to construct the limited societal perspective analysis. In the Australian setting, cigarettes are highly taxed (to reduce smoking) and are among the most expensive in the world, while the population of people with SMI is generally financially disadvantaged and often marginalized economically (32, 33). This makes it important to also assess any consequent financial impacts on study participants as a result of receiving the Quitlink intervention.

Future costs and benefits will be discounted using an annual discount rate of 3% in the base-case. Furthermore, annual discount rates of 0 and 5% will be applied in sensitivity analysis to facilitate comparison with results from other economic evaluations of preventive health interventions, including smoking cessation interventions in people with SMI (25, 29, 34). To further aid decision-makers, cost-effectiveness findings will be presented alongside descriptive assessments of the acceptability to stakeholders, feasibility of scaleup, sustainability, and equity implications of Quitlink implementation to be assessed by the research team in consultation with participating organizations (34, 35).

Trial-Based Economic Evaluation

Identification, Measurement, and Valuation of Outcomes

The clinical and HRQoL outcomes detailed below will be collected as part of participant assessments conducted at baseline, 2 months (= end of treatment), 5 months (= 3 months posttreatment), and 8 months (= 6 months posttreatment).

Health and Health-Related Behavioral Outcomes

The primary health outcome will be successful quits at 8 months postrandomization. A successful quit is defined as 6 months sustained abstinence, with no relapse of 7 or more days of continuous smoking, and no reported smoking in the past week with biochemical verification). Self-reported cigarette consumption will also be measured and for the purposes of the economic evaluation, used to assess changes in out of pocket expenditure associated with Quitlink.

Health-Related Quality of Life

Despite common beliefs that smoking cessation might worsen the mental health symptoms of smokers, some studies indicate that smoking cessation leads to no worsening and possibly improvement in mental health and psychological-related quality of life (36). It is also plausible that mood and mental well-being symptoms may change over time, e.g., deteriorate in the short term while quitting (e.g., first few weeks), and improve after that (e.g., months after successfully quitting) (36). To explore this, HRQoL data will be collected using the Assessment of Quality of Life-8 Dimension (AQoL-8D) instrument at baseline and follow-up observations at 2, 5, and 8 months. The AQoL-8D is a preference-based HRQoL instrument which enables calculation of QALYs experienced across the two study arms. Data from all time points will be plotted for both arms, and the difference in areas under the respective curves will be calculated. While the majority of benefit of this preventive intervention are expected in the future and *a priori* expectations of measurable change in HRQoL during the trial period are modest, among preference-based HRQoL instruments, the AQoL-8D is considered relatively sensitive to changes in psychosocial dimensions of HRQoL (while also capturing important changes in other dimensions of HRQoL) (37). This means that it will be more likely to identify smaller changes in mental-health-related quality of life than other preference-based instruments.

Financial Stress

Respondents will be asked a short module of questions relating to their financial stress at baseline and follow-up observations (38).

For example, have they foregone meals; asked for financial help; or been unable to pay electricity, gas, or telephone bills because of a lack of money (see **online Appendix** to view questions)? This will provide further evidence for decision-makers and mental health and smoking program organizations regarding potential financial impacts of Quitlink on this financially disadvantaged population (32).

Identification and Measurement of Costs

Table 1 summarizes the costs included and the data collection strategy from both a health sector and societal perspective. Costs included from the health care system perspective will include direct intervention costs (e.g., opportunity cost of Quitline and peer worker staff, telephone calls, NRT) for both Quitlink and usual care, as well as drug and health service utilization costs. Pathway analysis will be undertaken to ensure all relevant costs are identified. These data will be collected from project administrative records, respondent surveys (baseline, 2, 5, and 8 months) and with participant consent, linked data on their service and prescription medication use from the Australian Government subsidized Medicare (MBS) and Pharmaceutical Benefits (PBS) schemes, which are predominantly out-of-hospital resource use.

Data on important out-of-pocket impacts of Quitlink will also be collected and incorporated with the health care system data to estimate costs from a limited societal perspective. These costs will include out-of-pocket co-payments associated with drug and health service utilization, expenditure on cigarettes, and cessation aids purchased in addition to those provided as part of the intervention, as well as time costs and productivity losses associated with absenteeism from paid and unpaid work and productive activities (see **online Appendix** to view questions).

Where data relies on respondent recall, for example, number of allied health visits or cigarettes smoked, the recall period will be deliberately kept relatively short (1 month and 1 week, respectively). Recall bias may remain an issue though, so the potential impact of this will be tested in sensitivity analyses (39). In general, a simple extrapolation rule will be followed where reported rates are applied for the full period since previous follow-up, where appropriately justified.

One-off costs for products which could be used in other settings, such as costs of developing the training and intervention materials, will be excluded. The costs and health implications from passive smoking will also be excluded.

Valuing Costs

All resource use will be costed using nationally published reference costs or market prices where appropriate. Personnel time (paid, unpaid, volunteer time) will be costed using opportunity cost principles, where volunteer/leisure time

TABLE 1 | Costs included in trial-based cost-effectiveness analyses.

Cost category	Costs	Perspective	Collection strategy
Direct intervention costs	Costs associated with training of peer workers and Quitline staff, including personnel time (facilitators and participants), venue/catering, printing/stationery.	HS & S	Project administrative records.
	Personnel time for intervention delivery: Quitline and peer worker support time spent per study participant in both Quitlink and usual care arms. Costs of telephone calls. Program management time. On-costs will be included.	HS & S	Project administrative records and administrative data provided by participating organizations.
Health service utilization	Hospitalizations (including length of stay) and other intensive health services, including ED and community care units (CCUs) and prevention and recovery care services (PARCS).	HS & S	Respondent surveys.
	Community-based (noninpatient) government subsidized health (including mental health) services.	HS & S	Linkage to Australian Department of Human Services data on Medicare and PBS use. Literature review.
	Allied health services (nonsubsidized) including (non-Quitline) counseling, acupuncture, hypnotherapy, group therapies.	S	Respondent surveys.
Nicotine replacement therapies and other quitting aids	e.g., patches, gum, lozenges, inhalator, sprays, e-cigarettes.	HS & S	Respondent surveys.
Medicines	Including varenicline, bupropion, psychotropic medicines.	HS & S	Australian Department of Human Services data on Medicare and PBS use, literature review.
Cigarettes	Cost of cigarette purchases.	S	Respondent surveys.
Productivity losses and gains	Absenteeism from paid and unpaid work (e.g., volunteering, study, caring). Potential increases in employment.	S	Respondent surveys. Project records on session numbers and duration.

HS, Health care system; S, societal; ED, emergency department; PBS, Pharmaceutical Benefits Scheme.

will be valued at 25% of appropriate average wage rates (34). Resource use of nonhealth sector goods and services will be valued at market prices and be informed by best available evidence from Australian-based studies. Where relevant, health resources will be costed as per the Manual of Resource Items for use in submissions to the Commonwealth of Australia's Pharmaceutical Benefits Advisory Committee (40). Health care cost information will also be drawn from the Australian Institute of Health and Welfare (AIHW) health care cost data. All costs will be inflated to current Australian dollars for the year of study completion (2022) using the all-items Consumer Price Index from the Australian Bureau of Statistics.

Modeling Long-Term Cost Effectiveness

A decision analytic Markov model will be developed using *TreeAge* software to estimate the future benefits and cost savings arising from any increase in successful quits observed in the Quitlink arm. We will adapt and update the smoking cessation model developed with an Australian context by Hurley et al. (41). The model projects the future smoking status of the population where smoking status impacts on the risk of experiencing (progressing into the following health states)—myocardial infarction (MI), stroke, COPD, or lung cancer. These four health states are known to have the largest disease, mortality, and health cost burden among smokers (41). For simplicity, the model does not include the potential for comorbid health states where a person may have more than one of these four states concurrently. Death following transition into one of these diagnosed health states can be caused by that condition or any other cause. "Healthy" smokers and ex-smokers can also die from other causes without experiencing these health states. This approach is intentionally conservative (i.e., it likely underestimates the benefits of quitting) and has been taken in a number of smoking models (24).

We plan to extend the Hurley and Matthews (41) model. **Figure 1** depicts the potential health states that the modeled Quitlink cohort will face over repeat model annual cycles. Given smokers with SMI (compared to ex-smokers with SMI) face increased risk of hospitalization for a psychiatric episode, a psychiatric episodic health state will be added to the model to capture the costs related to hospitalizations and the impact on QALYs (12). QALY weights for the psychiatric episodic health state will be obtained where possible, from the literature or by expert opinion, guided by the AQoL-8D questionnaire. In the model, we will also consider that smoking cessation may reduce suicide risk—attempts and, more rarely, deaths (42, 43). Uncertainty remains around this mechanism of action. However, the known links between smoking and reduced effectiveness of antipsychotic medication, and between smoking cessation and mood improvement, suggest that any increased smoking cessation achieved by Quitlink may plausibly reduce suicide attempts and deaths—especially if the program was scaled up. A review of the literature of the causal link between smoking and suicidality will be undertaken at the end of the trial period to determine the strength of evidence and suitability of including a suicidal health state in the Markov model and suicide as an additional smoking-related cause of death.

The trial cohort at the end of the trial follow-up will enter the Markov model as either a healthy smoker or healthy ex-smoker (i.e., successful quitter), where "healthy" means they have not had a stroke, MI, or developed COPD or lung cancer. Their commencement QALY weight in the model will be their final observed QALY weight from the trial (i.e., 8-month follow-up). Individuals will be modeled through annual cycles. In the first cycle, people have a probability of either remaining a healthy smoker or ex-smoker, relapsing from healthy ex-smoker to healthy smoker, experiencing a fatal or nonfatal MI, stroke, COPD, lung cancer, or entering a severe psychiatric episodic health state (e.g., psychiatric hospitalization and/or suicide attempt), or they may die from another cause.

Each health transition and health state incurs associated treatment/management costs. Associated health costs and risk of disease-related mortality can differ over time since initial episode/diagnosis (41). The Markov cycles will continue until the entire cohort has either died or reached aged 85 years (41). The same model structure will be used to estimate the broader benefits and cost savings of scaling up Quitlink to a larger population cohort of people with SMI.

Existing evidence for transition probabilities for the different disease states and utility weights attached to life lived with those health states used in Hurley et al. (41) and Godfrey et al. (24) will be considered for use in this model, subject to an updated literature search. Smoking relapse rates will be estimated using the large longitudinal Household Income Labour Dynamics in Australia (HILDA) survey data. Specifically, relapse rates of data for people who self-report poor mental-health-related quality of life in the early HILDA waves on the included Short Form-12 item (SF-12) instrument will be analyzed.

The longer term health care system costs incurred by the two intervention arms will comprise actual health care resource usage obtained from the government subsidized MBS and PBS database (which will provide data of up to 4 years for the early study enrolments) and health care cost information from the Australian Institute of Health and Welfare (AIHW)—to estimate costs of acute and ongoing management associated with the stated main model health states. Where there is potential for double counting across the two data sources, conservative inclusion decisions will be made.

Where transition rate, utility weight, and health cost data are available specifically for people living with SMI (and if possible, in Australia), it will be used to populate the model. Given that most of such data are currently unavailable, data from general population studies will be employed, coupled with a discussion on how the likely cost effectiveness of Quitlink may be impacted. All model parameters will be subject to an updated literature search at the end-point of the clinical trial to identify if potentially more suitable model data have become available.

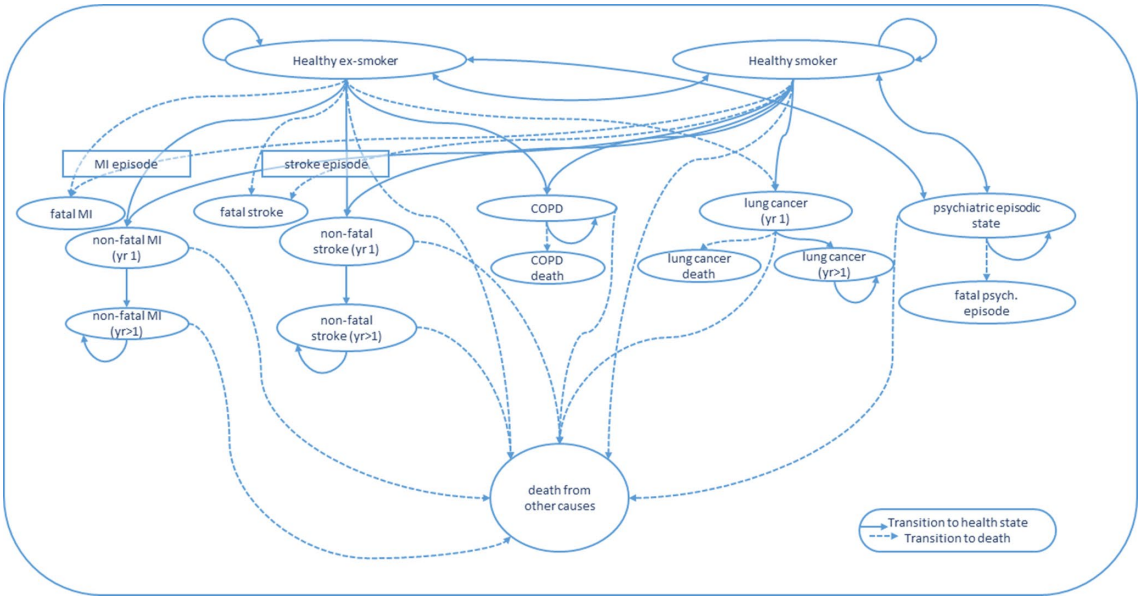

FIGURE 1 | State transitions for Markov Model. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; yr 1, first year in a given health state; yr > 1, subsequent years lived in a given health state.

Uncertainty and Scenario Analyses

All analyses in both the trial-based cost-efficacy and modeled cost-effectiveness evaluations will be subjected to both one-way and probabilistic sensitivity analysis where the impacts of plausible variation in data parameters will be tested, using confidence intervals around for example, utility weights, and health costs associated with different health states. This will provide an understanding of which values or assumptions are associated with the greatest amount of uncertainty. As previously mentioned, by necessity, some model parameters will be populated with data from the general population, rather than specifically people with SMI. Given this, scenario analyses will be conducted to investigate the impact of SMI-related data adjustments, which expert opinion suggests is, *prima facie* appropriate, where there is only poor quality or no data available for a given parameter to test uncertainty. These will include, for example, different transition risks and lower utility scores attached to health states for people with SMI compared with general population data used, as well as uncertainty around treatment costs for the main modeled health states for people with SMI. These analyses will also enable estimates of the probability that Quitlink is cost effective to aid funding decision-makers in light of such model uncertainty.

Results of a number of sensitivity tests will be reported on a cost-effectiveness plane and as acceptability curves. The Australian Government has no explicit threshold for what it considers cost effective; however, there exists implicit evidence that the Pharmaceutical Benefits Advisory Committee view interventions that achieve an incremental cost effectiveness ratio (ICER) of no more than AUD45,000 per additional QALY gained, as cost effective (44). This threshold will be applied for the cost-effective acceptability analysis. Published results will include a discussion of model validity, comparing results with those of other smoking cessation models including those reported in the literature review by (24).

DISCUSSION

This protocol sets out a plan to assess the cost effectiveness of Quitlink versus usual care *via* both trial-based and modeled economic evaluations. The publication of this protocol has two purposes. First, we aim to inform the research and broader public health communities of the conduct of this economic evaluation alongside the Quitlink trial. Second, we set out the plan for analyses *a priori,* thereby reducing potential biases made from *ad hoc* analytic decisions. Any deviations from this protocol will be described and justified in final analyses. In the event that no significant difference is found for the primary outcome, the described economic evaluation may be undertaken where there is a) significant change in key secondary outcomes (QALYs or number of cigarettes smoked) or b) compelling evidence suggesting the sample lacked power or insufficient follow-up to detect a likely significant difference. While we are setting out to identify and collect the best available data to establish the cost effectiveness of Quitlink, there are a number of potential limitations. The exclusion of so-called second-hand (or passive) smoking effects may result in an underestimation of the true benefits to the health care system and broader society as a result of any observed Quitlink treatment effect. For the trial-based evaluation, there is a risk of recall bias in the respondent surveys, relating to—among other data—health service use, medications used, NRTs, and cigarettes purchased. To minimize this potential bias, actual health and medication use data will be obtained from Australian Government MBS and PBS schemes. Further, in the

respondent surveys, the recall period that participants will be asked to consider will be deliberately kept short. A further potential risk to data reliability relates to HRQoL. While the AQoL-8D has been shown to be more sensitive to changes in people's mental health than other instruments (37), there is a risk that the sample size and duration may be insufficient to identify the expected small changes in mental-health-related quality of life within the trial period.

The *a priori* expectation for benefits to largely occur well beyond the trial period (as has been largely demonstrated for smoking cessation interventions) justifies the decision to model future benefits and costs. However, the model-based analyses also carry a number of potential limitations. For the sake of transparency, a Markov model structure has been proposed that includes only a limited number of the full range of smoking-related health states experienced by current and past smokers (24, 25) concentrating on the health and health system impacts of MI, stroke, COPD, lung cancer, and psychotic-related hospitalizations. While these conditions are responsible for an estimated 80% of the diseases and economic burden associated with smoking morbidity and mortality in the Australian setting, there are other smoking-related health issues which will not be included (41). Should Quitlink be found to be effective, the exclusion of other diseases from the model underestimates the true cost effectiveness of Quitlink. Furthermore, it is anticipated that much of the data for the smoking cessation modeling will come from the general population estimates; such data may not reflect the utilities or health costs or transition risks of people with SMI. An updated literature review for all parameters will be conducted at the end of the trial period to ensure up to date and relevant data is used for all model parameters.

Smoking places significant additional financial burden on people with SMI, a particularly financially vulnerable subpopulation. Any financial implications for people with SMI, seen through changes in cigarette consumption, out of pocket costs of health resource utilization and productivity will be presented, providing valuable information on the equity impacts of Quitlink. This research project will conduct analyses and present results of most relevance to smoking cessation program designers and health-funding decision makers. Quitlink has been designed for and will be trialed in a setting where Quitline and mental health peer workers are established parts of the health sector. The cost-effectiveness findings may not be generalizable to settings where such foundations for Quitlink are not in place.

CONCLUSION

The primary aim of this economic evaluation will be to establish the cost effectiveness of Quitlink. This protocol for the economic evaluation sets out *a priori,* the intended analyses to be undertaken. Any deviations from this plan that occur in the final publication of results will be clearly described and justified.

Smoking is a major cause of increased mortality and morbidity, as well as poorer mental-health-related quality of life and financial stress for people with SMI. The cost effectiveness of telephone-based smoking cessation interventions like Quitline (with and without NRT) has been well established in general populations; however, there is little evidence of cost effectiveness for such interventions that specifically target SSMI. Furthermore, evidence suggests that SSMI are less likely to be referred to quitlines. The Quitlink intervention, therefore, aims to bridge this gap. Quitlink utilizes existing mental health peer workforce to link SSMI with a tailored quitline service for SSMI. The research team hypothesizes that the use of these existing workforces and tailored quitline support for SSMI will result in Quitlink being found to be both effective and cost effective and also scalable.

ETHICS STATEMENT

Full ethics clearances have been received for the methods described below from the University of Newcastle (Australia) Human Research Ethics Committee (H-2018-0192) and St Vincent's Hospital, Melbourne (HREC/18/SVHM/154).

The study is based on the principles of Good Clinical Practice (GCP) according to the Declaration of Helsinki. Potential participants will be given oral and written explanation of the study including the potential risks, their right to withdraw at any time, and the details of data protection and confidentiality and sufficient time to ask questions. A signed consent form will be obtained. Participants will be given the opportunity to agree or decline to being contacted for ancillary studies, without effecting participation in the main trial. A copy of the PICF will be given to the person.

AUTHOR CONTRIBUTIONS

RS led the conceptual design and writing of this work. MM made substantial contributions to the conceptual design of the work as well as to the writing of this paper. Coauthors all made substantial contributions to the conceptual design of the methods described in this Economic Evaluation Protocol, and all made important contributions in revising the manuscript critically for important intellectual content. All authors have approved of the final version of the submitted manuscript.

FUNDING

This study is supported by an NHMRC Project Grant titled "Quitlink: Accessible smoking cessation support for people living with severe and enduring mental illness" (APP1139125).

ACKNOWLEDGMENT

We would like to thank the paper's peer reviewers and also Dennis Petrie for valuable advice on the protocol and manuscript

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00618/full#supplementary-material

REFERENCES

1. Cooper J, Mancuso SG, Borland R, Slade T, Galletly C, Castle D. Tobacco smoking among people living with a psychotic illness: the second Australian survey of psychosis. *Aust N Z J Psychiatry* (2012) 46(9):851–63. doi: 10.1177/0004867412449876
2. Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA* (2014) 311(2):172–82. doi: 10.1001/jama.2013.284985
3. McManus S, Howard M, Campion J. *Cigarette smoking and mental health in England: data from the adult psychiatric morbidity survey 2007*. Melbourne: National Centre for Social Research (NatCan) (2010).
4. Callaghan RC, Veldhuizen S, Jeysingh T, Orlan C, Graham C, Kakouris G, et al. Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. *J Psychiatr Res* (2014) 48(1):102–10. doi: 10.1016/j.jpsychires.2013.09.014
5. Reitsma MB, Fullman N, Ng M, Salama JS, Abajobir A, Abate KH, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* (2017) 389(10082):1885–906. doi: 10.1016/S0140-6736(17)30819-X
6. Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. *Annu Rev Public Health* (2010) 31(1):297–314. doi: 10.1146/annurev.publhealth.012809.103701
7. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. *Br J Psychiatry* (2011) 199(6):453–8. doi: 10.1192/bjp.bp.110.085100
8. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* (2013) 346: 1–14. doi: 10.1136/bmj.f2539
9. Tam J, Warner KE, Meza R. Smoking and the reduced life expectancy of individuals with serious mental illness. *Am J Prev Med* (2016) 51(6):958–66. doi: 10.1016/j.amepre.2016.06.007
10. Vogl M, Wenig CM, Leidl R, Pokhrel S. Smoking and health-related quality of life in English general population: implications for economic evaluations. *BMC Public Health* (2012) 12(1):203. doi: 10.1186/1471-2458-12-203
11. Lindsay B, Simon G. Smoking cessation in severe mental illness: what works? *Addiction* (2010) 105(7):1176–89. doi: 10.1111/j.1360-0443.2010.02946.x
12. Prochaska JJ. Smoking and mental illness—breaking the link. *N Engl J Med* (2011) 365(3):196–8. doi: 10.1056/NEJMp1105248
13. Access Economics (2007). Smoking and mental illness: costs. Report for SANE Australia. Canberra, Australia. https://www.sane.org/information-stories/facts-and-guides/smoking-and-mental-illness?highlight=WyJzbW9raW5nIiwiJ3Ntb2tpbmciLCJzbW9raW5nJyJd
14. Wu Q, Szatkowski L, Britton J, Parrott S, Economic cost of smoking in people with mental disorders in the UK. *Tob Control* (2015) 24(5):462–8. doi: 10.1136/tobaccocontrol-2013-051464
15. Parrott S, Godfrey C. Economics of smoking cessation. *BMJ* (2004) 328(7445):947–9. doi: 10.1136/bmj.328.7445.947
16. West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, et al. Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. *Addiction* (2015) 110(9):1388–403. doi: 10.1111/add.12998
17. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry* (2015) 23(1):37–43. doi: 10.1177/1039856214562076
18. Kerr S, Woods C, Knussen C, Watson H, Hunter R. Breaking the habit: a qualitative exploration of barriers and facilitators to smoking cessation in people with enduring mental health problems. *BMC Public Health* (2013) 13(1):221. doi: 10.1186/1471-2458-13-221
19. Sharma R, Meurk C, Bell S, Ford P, Gartner C. Australian mental health care practitioners' practices and attitudes for encouraging smoking cessation and tobacco harm reduction in smokers with severe mental illness. *Int J Ment Health Nurs* (2018) 27(1):247–57. doi: 10.1111/inm.12314
20. Baker AL, Borland R, Bonevski B, Segan C, Turner A, Brophy L, et al. 'Quitlink'—a randomised controlled trial of peer worker facilitated Quitline support for smokers receiving mental health services: study protocol. *Front Psychiatry* (2018) 10:124. doi: 10.3389/fpsyt.2019.00124
21. Oortwijn W, Mathijssen J, Banta D. The role of health technology assessment on pharmaceutical reimbursement in selected middle-income countries. *Health Policy* (2010) 95(2):174–84. doi: 10.1016/j.healthpol.2009.12.008
22. Stafinski T, Menon D, Philippon DJ, McCabe C. Health technology funding decision-making processes around the world. *Pharmacoeconomics* (2011) 29(6):475–95. doi: 10.2165/11586420-000000000-00000
23. Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tob Control* (2007) 16 Suppl 1:i53–9. doi: 10.1136/tc.2006.019794
24. Godfrey CA, Ali S, Parrott S. Pickett K. *Economic model of adult smoking related costs and consequences for England*. York, United Kingdom Public Health Research Consortium (2011).
25. Lal A, Mihalopoulos C, Wallace A, Vos T. The cost-effectiveness of call-back counselling for smoking cessation. *Tob Control* (2014) 23(5):437–42. doi: 10.1136/tobaccocontrol-2012-050907
26. Berndt N, Bolman C, Lechner L, Max W, Mudde A, de Vries H, et al. Economic evaluation of a telephone- and face-to-face-delivered counseling intervention for smoking cessation in patients with coronary heart disease. *Eur J Health Econ* (2016) 17(3):269–85. doi: 10.1007/s10198-015-0677-x
27. Park A-L, McDaid D, Weiser P, Von Gottberg C, Becker T, Kilian R. Examining the cost effectiveness of interventions to promote the physical health of people with mental health problems: a systematic review. *BMC Public Health* (2013) 13(1):787. doi: 10.1186/1471-2458-13-787
28. Barnett PG, Wong W, Hall S. The cost-effectiveness of a smoking cessation program for out-patients in treatment for depression. *Addiction* (2008) 103(5):834–40. doi: 10.1111/j.1360-0443.2008.02167.x
29. Barnett PG, Wong W, Jeffers A, Hall SM, Prochaska JJ. Cost-effectiveness of smoking cessation treatment initiated during psychiatric hospitalization: analysis from a randomized, controlled trial. *J Clin Psychiatry* (2015) 76(10):e1285–91. doi: 10.4088/JCP.14m09016
30. Rejas-Gutiérrez J, Bruguera E, Cedillo S. Modelling a budgetary impact analysis for funding drug-based smoking cessation therapies for patients with major depressive disorder in Spain. *Eur Psychiatry* (2017) 45:41–9. doi: 10.1016/j.eurpsy.2017.05.027
31. Stratford AC, Halpin M, Phillips K, Skerritt F, Beales A, Cheng V, et al. The growth of peer support: an international charter. *J Ment Health* (2017) 1–6. doi: 10.1080/09638237.2017.1340593
32. Enticott JC, Meadows GN, Shawyer F, Inder B, Patten S. Mental disorders and distress: associations with demographics, remoteness and socioeconomic deprivation of area of residence across Australia. Australian & New Zealand Journal of Psychiatry (2016) 50(12): 1169-79. doi: 10.1177/0004867415615948
33. Hirono KT, Smith KE. Australia's $40 per pack cigarette tax plans: the need to consider equity. *Tob Control* (2018) 27(2):229–33. doi: 10.1136/tobaccocontrol-2016-053608
34. Vos, T, Carter R, Barendregt J, Mihalopoulos C, Veerman L, Magnus A, et al. *Assessing Cost-Effectiveness in Prevention (ACE-Prevention): Final Report*. Melbourne: University of Queensland, Brisbane and Deakin University (2010).
35. Carter R, Vos T, Moodie M, Haby M, Magnus A, Mihalopoulos C. Priority setting in health: origins, description and application of the Australian assessing cost–effectiveness initiative. *Expert Rev Pharmacoeconomics Outcomes Res* (2008) 8(6):593–617. doi: 10.1586/14737167.8.6.593
36. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* (2014) 348: 1–22. doi: 10.1136/bmj.g1151
37. Mihalopoulos C, Chen G, Iezzi A, Khan MA, Richardson J. Assessing outcomes for cost-utility analysis in depression: comparison of five multi-attribute utility instruments with two depression-specific outcome measures. *Br J Psychiatry* (2014) 205(5):390–7. doi: 10.1192/bjp.bp.113.136036
38. Siahpush M, Carlin JB. Financial stress, smoking cessation and relapse: results from a prospective study of an Australian national sample. *Addiction* (2006) 101(1):121–7. doi: 10.1111/j.1360-0443.2005.01292.x
39. Dalziel K, Li J, Scott A, Clarke P. Accuracy of patient recall for self-reported doctor visits: is shorter recall better? *Health Econ* (2018) 27(11):1684–98. doi: 10.1002/hec.3794

40. Commonwealth of Australia (2016). Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 5.0). Canberra.
41. Hurley SF, Matthews JP. The quit benefits model: a Markov model for assessing the health benefits and health care cost savings of quitting smoking. *Cost Eff Resour Alloc* (2007) 5(1):2. doi: 10.1186/1478-7547-5-2
42. Poorolajal J, Darvishi N. Smoking and suicide: a meta-analysis. *Plos One* (2016) 11(7):e0156348. doi: 10.1371/journal.pone.0156348
43. Sankaranarayanan A, Castle D. Burden associated with smoking as a suicidal risk factor in an Australian sample of patients with psychosis. *Australas Psychiatry* (2016) 24(5):437–40. doi: 10.1177/1039856216646232
44. Ngo P. The influence of cost-effectiveness evaluations on reimbursement in Australia: a retrospective study of decisions made by the Pharmaceutical Benefits Advisory Committee. *Pharm Med* (2014) 28(4):187–93. doi: 10.1007/s40290-014-0063-5

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer KD declared a shared affiliation, with no collaboration, with one of the authors, DC, the handling editor.

frontiers in Psychiatry

PERSPECTIVE
published: 18 December 2018
doi: 10.3389/fpsyt.2018.00711

Reducing Smoking Among People With Schizophrenia: Perspectives on Priorities for Advancing Research

Amanda L. Baker[1], Debbie Robson[2], Sharon Lawn[3], Marc L. Steinberg[4], Sandra Bucci[5,6], Ann McNeill[2], David J. Castle[7,8] and Billie Bonevski[1]*

[1] School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia, [2] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [3] Flinders Human Behaviour and Health Research Unit, Department of Psychiatry, Margaret Tobin Centre, College of Medicine & Public Health, Flinders University, Adelaide, SA, Australia, [4] Division of Addiction Psychiatry, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States, [5] Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [6] Greater Manchester Mental Health NHS Foundation Trust, Manchester, United Kingdom, [7] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia, [8] Department of Psychiatry, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

Although tobacco smoking is very common among people with schizophrenia and has devastating effects on health, strategies to ameliorate the risk are lacking. Some studies have reported promising results yet quit rates are much lower than in the general population. There is a need to advance research into smoking cessation efforts among people with schizophrenia. We posed the following question to five leading international experts in the field: "What are the top three research ideas we need to prioritize in order to advance the field of reducing smoking amongst people with schizophrenia?" They identified three broad priorities: (i) deeper understanding about the relationship between smoking, smoking cessation and symptomatology; (ii) targeted, adaptive and responsive behavioral interventions evaluated with smarter methodologies; and (iii) improvements in delivery of interventions. Efforts should be made to establish a collaborative international research agenda.

Keywords: smoking, smoking cessation, schizophrenia, research, health priorities, severe mental illness, mentally ill persons, vulnerable population

OPEN ACCESS

Edited by:
Thomas W. Weickert, University of New South Wales, Australia

Reviewed by:
Suresh Sundram, Monash University, Australia
Julia M. Lappin, University of New South Wales, Australia

****Correspondence:***
Amanda L. Baker
amanda.baker@newcastle.edu.au

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *31 August 2018*
Accepted: *04 December 2018*
Published: *18 December 2018*

Citation:
Baker AL, Robson D, Lawn S, Steinberg ML, Bucci S, McNeill A, Castle DJ and Bonevski B (2018) Reducing Smoking Among People With Schizophrenia: Perspectives on Priorities for Advancing Research. Front. Psychiatry 9:711. doi: 10.3389/fpsyt.2018.00711

INTRODUCTION

We live in an era when tobacco, which is one of the most harmful substances for human health, is legal and widely available in combustible form. Whilst tobacco control strategies have greatly reduced smoking rates among the general population in high income countries, smoking rates among people with schizophrenia remain very high [e.g., (1, 2)]. Schizophrenia is often complicated by physical comorbidities and substance use (1). That well over half of people worldwide with a diagnosis of schizophrenia smoke, should be (1) of great concern (given our knowledge of the effects of smoking on quality of life, morbidity and mortality) and (2) a dynamic area of research (given the often intractable nature of schizophrenia and what its relationship with smoking might tell us). Sadly, neither of these are true and up until recently, little attention was paid to this issue. We (AB, BB and DC) asked leading researchers from Australia, the UK and the USA the following question, "What are the top three research ideas we need to prioritize in order to advance the field of reducing smoking amongst people with schizophrenia?" Their views represent opinion rather

than systematic review, and are provided below, followed by our commentary.

THE PERSPECTIVE OF A SOCIAL WORK CLINICIAN AND MENTAL HEALTH CARER (AUSTRALIA)

Professor Sharon Lawn's top three research ideas are drawn from her experiences in the past 20 years of undertaking ethnographic research, being a community-based clinician observing (at close quarters and over extended periods) the lives of people with schizophrenia, and from living with a smoker with schizophrenia.

Understanding More About the Overlap Between Symptoms of Schizophrenia and Withdrawal

We need to understand more about how the experience of schizophrenia and the experience of nicotine dependence and withdrawal interact with each other, at the basic level of "the science" right through to the person's day-to-day attempts to manage the two. Many of the interventions proposed focus on mental illness symptoms and nicotine dependence/withdrawal as separate processes rather than investigating how the person navigates the two at the levels of symptoms, pharmacotherapy and subjective experience. I flagged this need a long time ago (3), calling for the integration of care to recognize and treat psychosis and nicotine withdrawal together. The problem is that research, and then clinical practice, has resorted to offering standard quit strategies and nicotine replacement therapy (NRT) use. Outcomes of these interventions have lagged for smokers with schizophrenia and sustaining quit status has been elusive. People with schizophrenia tend to relapse quickly to smoking because schizophrenia is a condition that is lived with every day, is changeable and complex to manage and—in the absence of support that addresses symptoms and dependence together—reaching for a cigarette becomes the default option for coping.

Prevention and Early Intervention

Once the person becomes a smoker, a complex interplay of need, coping, psychological, and physiological interactions between their mental health and their smoking is established and becomes insidiously reinforced. Also, from the carer's perspective, there is overwhelming frustration and sadness as the smoker ages prematurely, trying to battle multimorbidity, and dying before their time. Therefore, research must focus on prevention and early intervention for people at risk and those with emerging psychosis, so that they never become smokers in the first place, or that they quit early.

Targeted Pharmacotherapies and Practical Quit Strategies

Finally, we need more efficacious smoking cessation interventions that take account of the knowledge gained from my first identified priority (above). This includes pharmacological treatments that are safe and effective, as well as interventions that provide real support to the person "in the moment," not just sending them away with NRT and brief counseling. Interventions that involve quit strategies that are predominantly "abstract" (e.g., weighing up the pros and cons, planning and identifying a range of strategies) have limits for many people with schizophrenia and are likely to be completely useless in the moments of escalating stress and distress when the person is unable to "call to mind" the reasoning that underlies such abstract quit strategies. It may in fact escalate the person's anxiety, demanding clarity of thinking when thinking through options is at its most difficult. Additionally, repeated failure reinforces feelings of hopelessness. This is why apps that help address "the moments" in the "here and now" without the need to work out how to operationalise abstract concepts, are also worth further research.

THE PERSPECTIVE OF A CLINICAL PSYCHOLOGIST / CO-DIRECTOR OF A COMPLEX TRAUMA AND RESILIENCE RESEARCH UNIT, GREATER MANCHESTER MENTAL HEALTH NHS FOUNDATION TRUST (UK)

Dr. Sandra Bucci's top three ideas are drawn from her clinical and research experience focusing on psychological treatments of people diagnosed with schizophrenia, those in the early stage of psychosis and young people at ultra-high risk of psychosis.

Research Needs to Acknowledge Clinical Complexity and Treatment Should Aim for Realistic Goals Chosen by Patients

Asking people with a severe mental health problem to give up or reduce smoking is complex. Researchers more often than not argue that the ultimate goal for someone with a diagnosis of schizophrenia should be cessation (4). However, motivational problems, self-medication, being part of a social group, the physiological effects associated with nicotine intake, and health and social inequalities apparent in people with severe mental health problems are just a few of the factors that influence the complex interaction between smoking and mental health. It may therefore be preferable to encourage patients to set realistic goals, working toward cessation.

Providing Digital Technologies to Impact on Daily Living and Newer Methodologies

Many programs target smoking behaviors in people with severe mental health problems, with varied outcomes. We can provide smokers all the information they need regarding the negative health effects of smoking. We can also attempt to replace smoking behaviors with other, more adaptive strategies during times of stress. However, these approaches in and of themselves are limited as they do not impact people in-the-moment, at the time the smoker experiences a craving and is in most need of support. There is a mismatch between the rather static nature of providing support for smoking cessation to people who often find it difficult to resist cravings and urges to smoke, and stressors

that are momentary and contextual (5). This is where the digital revolution, primarily through the availability of smartphones and smartphone apps, may help. We must leverage the opportunities digital technology afford, by developing intervention packages that can be delivered in the moment, in the context in which stressors occur. Digital technologies provide an unprecedented opportunity to reach people in a timely manner in the context of their daily life. There is a narrowing gap in smartphone ownership in individuals with a diagnosis of schizophrenia (6), highlighting the potential for healthcare programs targeting smoking behavior to be taken from the clinic to people's personal environment, unconstrained by location and time.

Methodologies such as Just In Time Adaptive Interventions (JITAI) that use digital technology as the modality for intervention delivery, may be the optimal platform to provide timely, contextual, in-the-moment support to people who find it difficult to recall or use treatment strategies during stressful moments where pressures on cognitive load and resources are most intense (5). JITAI can provide the right type and amount of support, at the right time by adapting to the individual's changing internal and contextual state (7). This approach is particularly well-suited to delivering smoking cessation/reduction programs among people with schizophrenia, affording us the opportunity to prompt and nudge people at the time they are most vulnerable.

Developing evidence-based interventions that are rapidly available and accessible at the population level are a priority. Historically, researchers have relied on using randomized controlled trials (RCTs) to explore the effectiveness of smoking cessation/intervention programs. However, RCTs are time consuming and do not in fact tell us which aspects of the intervention are effective. In standard RCTs, the intervention is typically fixed at trial onset and does not evolve over the course of the trial. As we move toward using digital technologies to nudge and prompt people regarding smoking behaviors in-the-moment, we run the risk that the technology is outdated or even obsolete at the end of the trial period. Adaptive approaches to clinical trials should explore the implementation of more rapid trial designs to ensure effective interventions are available in a timely and accessible way (8).

Staff Attitudes

Thirdly, to ensure effective dissemination of effective programs, we need more research into how best to change staff attitudes to smoking cessation in mental health settings. Staff can be reticent to encourage people with severe mental health problems to quit smoking. The success of smoking cessation programs is influenced not by patient uptake, but also clinician views and attitudes about smoking behaviors.

THE PERSPECTIVE OF RESEARCHERS IN TOBACCO ADDICTION (UK)

In their perspective, Dr. Debbie Robson combines experience in mental health nursing and research in tobacco addiction with that of Professor Ann McNeill, who has led numerous research and policy initiatives to reduce smoking among those with mental illness.

We Don't Know Enough About the Relationship Between Smoking and Schizophrenia

Why is the relationship so strong? Evidence has been found for shared familial and genetic risk factors, limited evidence for schizophrenia causing people to smoke, and limited evidence for smoking causing schizophrenia (9, 10). Research is hampered by poor routine surveillance of smoking prevalence, in contrast to internationally agreed robust measures used to track smoking in general populations. There is a paucity of large longitudinal studies exploring causal mechanisms, assessing frequency/heaviness of smoking, nicotine intake, quitting behaviors, and detailed objective measurement of the mental illness and their interactions.

We Have Failed to Identify Appropriate Ways Out of Tobacco Addiction for People With Schizophrenia

Tobacco control and smoking cessation interventions are usually derived/adapted from evidence generated in general population samples (11). Very few are co-designed by smokers with schizophrenia. Although the outcomes from using existing evidence-based treatments for smoking cessation could be improved by finding ways to promote better adherence, people with schizophrenia deserve investment to develop bespoke interventions tailored to their illness-related psychological, cognitive, and social needs (12). For example, we should ascertain what outcomes smokers with schizophrenia value most and what treatments are acceptable. We then need to co-design interventions with people with schizophrenia and key stakeholders.

A Lack of Engagement of the Health Workforce

People with lived experience of schizophrenia have more frequent contact with health services (13) and a visit to a hospital inpatient/outpatient setting should be an opportune time to promote key messages about smoking and offers of support to quit. This is undermined by poor knowledge and therapeutic nihilism (14) among health professionals and resistance to implementing comprehensive smokefree policies (15). Improving the capability of the health workforce so that every clinician is committed to and has the competence to initiate conversations and support those with lived experience of schizophrenia to quit smoking, is vital. We need to develop and evaluate novel ways to integrate smoking and tobacco dependence treatment, education and training into routine healthcare.

THE PERSPECTIVE OF A CLINICAL PSYCHOLOGY RESEARCHER WITH A SPECIAL INTEREST IN ENHANCING MOTIVATION TO CHANGE (USA)

Dr. Marc Steinberg (16–23) has a long-standing interest in researching smoking cessation treatments among people from

socially disadvantaged backgrounds, including people with schizophrenia.

Evaluating How to Best Address Reduced Distress Tolerance/Task Persistence in This Population

Given low abstinence rates, we should consider additional behavioral supports to combine with empirically supported pharmacological approaches. Smokers with schizophrenia have reduced task persistence/distress tolerance as compared to smokers without psychiatric comorbidity (16–18), and this may be a fertile target for counseling. Approaches such as traditional cognitive behavior therapy (CBT) focusing on thoughts related to persistence or distress tolerance, and Acceptance and Commitment Therapy (ACT) focusing on increasing psychological flexibility should be examined in this population. As Baker (19) recently suggested, the field should consider factorial designs to determine optimal counseling components for people with schizophrenia, and to empirically test whether various intervention combinations are more or less effective.

Examining Motivational Interviewing Interventions

While smokers with schizophrenia report being as interested in quitting as their peers without psychiatric comorbidity (20), the field needs to do better in increasing the number of quit attempts, and, importantly, increasing the number of appropriately *aided* quit attempts. An empirically validated approach likely to be useful in this endeavor is Motivational Interviewing (MI) (21). Adaptations of MI can support quit attempts as well as tobacco dependence treatment seeking in smokers with schizophrenia (21, 22). The literature on MI for smokers with schizophrenia is sparse, however, with many important questions remaining unanswered. Future studies should examine MI not only for motivating quit attempts, but also enhancing such attempts.

Training Providers to Address Tobacco Use

Finally, the field should strive to increase the number of quit attempts by encouraging the healthcare system to address tobacco use in their patients. In addition to providing and evaluating continuing education opportunities, we must increase the number of graduate programs and medical schools that include tobacco dependence treatment in their curricula because preliminary evidence suggests that training behavioral healthcare providers improves the chances of their addressing tobacco in their patients (23).

DISCUSSION

Three broad areas were highlighted as priorities for research by our invited experts. The contributions by Lawn and also by Robson and McNeill call for more understanding about the relationship between smoking, smoking cessation and symptomatology, ranging from large longitudinal datasets to monitoring interactions between smoking and symptoms. Intriguingly, two smoking cessation studies among people with schizophrenia recently conducted by the current authors (24–26), in the US and Australia, have found that face-to-face or telephone-delivered interventions with core components consisting of monitoring psychiatric symptoms and understanding medication interactions with tobacco smoking appear promising. In this issue, we[1] describe the "Quitlink" randomized controlled trial, in which such components will be delivered via quitline.

The second major area for further research was in the area of behavioral interventions. Better preventive measures, early interventions and motivational strategies tailored for people with schizophrenia were seen as important by Lawn and Steinberg. Bucci and Steinberg highlighted the complexity of presentations that take into account specific aspects of schizophrenia that are likely targets of intervention (e.g., distress tolerance and also flexible goals toward smoking cessation). Lawn and Bucci argue strongly for more research into interventions which can be used by smokers with schizophrenia in everyday settings, to strengthen the likelihood of them being able to address smoking in challenging situations. Bucci promotes digital interventions but Lawn also notes the need for smarter medications which could address both mental health and smoking. Bucci and Steinberg both point to the need for new and emerging behavioral interventions to require better and faster methodologies, supporting identification of effective key components and faster dissemination and adaptation to individual needs. Importantly, co-design was noted by Robson and McNeill as likely to yield vital information about valued outcomes and interventions.

Thirdly, all experts lamented the paucity of smoking cessation care provided by health systems and staff. Shifting health care systems and culture, building the capacity and confidence of clinical staff to address smoking and implementing smoke free policies are challenging changes within organizations. Emerging research however suggests that systems and organizational change interventions may provide a sustainable approach to integrating smoking cessation support in settings that care for people with schizophrenia (27–29).

There are a few notable limitations of this paper. Topics identified related mainly to high-income countries. Also, the utility of existing yet contentious smoking cessation treatments such as electronic cigarettes and varenicline was not explored.

The perspectives presented here provide a clear agenda for further research. National and international research collaborations (e.g., Mental health and smoking partnership[2]) should target these priorities with a view to impacting upon the very high rates of smoking among people with schizophrenia.

AUTHOR CONTRIBUTIONS

AB conceived of the idea for this paper. AB, DC, and BB suggested contributors. All authors wrote sections of the manuscript and contributed to manuscript revisions.

[1] Baker AL, Borland R, Bonevski B, Segan C, Turner A, Brophy L, et al. "Quitlink" - A randomised controlled trial of peer worker facilitated Quitline support for smokers receiving mental health services: study protocol. (Under review in Frontiers in Psychiatry).

[2] http://smokefreeaction.org.uk/smokefree-nhs/smoking-and-mental-health/

REFERENCES

1. Morgan VA, Waterreus A, Jablensky A, Mackinnon A, McGrath JJ, Carr V, et al. People living with psychotic illness in 2010: the second Australian national survey of psychosis. *Aust NZ J Psychiatry* (2012) 46:735–52. doi: 10.1177/0004867412449877
2. Szatkowski L, McNeill A. Diverging trends in smoking behaviors according to mental health status. *Nicotine Tobac Res*. (2015) 17:356–60. doi: 10.1093/ntr/ntu173
3. Lawn S, Pols R. Nicotine withdrawal: pathway to aggression and assault in the locked psychiatric ward? *Aust Psychiatry*. (2003) 11:199–203. doi: 10.1046/j.1039-8562.2003.00548.x
4. Sagud M, Vuksan-Cusa B, Jaksic N, Mihaljevic-Peles A, Rojnic Kuzman M, Pivac N. Smoking in schizophrenia: an updated review. *Psychiatria Danubina* (2018) 30 (Suppl 4):216–23.
5. Naughton F. Delivering "just-in-time" smoking cessation support via mobile phones: current knowledge and future directions. *Nicotine Tobac Res*. (2017) 19:379–83. doi: 10.1093/ntr/ntw143
6. Firth J, Cotter J, Torous J, Bucci S, Firth JA, Yung AR. Mobile phone ownership and endorsement of "mHealth" among people with psychosis: a meta-analysis of cross-sectional studies. *Schizophr Bull*. (2016) 42:448–55. doi: 10.1093/schbul/sbv132
7. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. *Ann Behav Med*. (2018) 52:446–62. doi: 10.1007/s12160-016-9830-8
8. Bucci S, Lewis S, Ainsworth J, Haddock G, Machin M, Berry K, et al. Digital interventions in severe mental health problems: lessons from the actissist development and trial. *World Psychiatry* (2018) 17:230–1. doi: 10.1002/wps.20535
9. Gage SH, Jones HJ, Taylor AE, Burgess S, Zammit S, Munafò MR. Investigating causality in associations between smoking initiation and schizophrenia using Mendelian randomization. *Sci Rep*. (2017) 7:40653. doi: 10.1038/srep40653
10. Kendler KS, Lonn SL, Sundquist J, Sundquist K. Smoking and schizophrenia in population cohorts of Swedish women and men: a prospective co-relative control study. *Am J Psychiatry* (2015) 172:1092–100. doi: 10.1176/appi.ajp.2015.15010126
11. Royal College of Physicians, Royal College of Psychiatrists. *Smoking and Mental Health. A Report of the Tobacco Advisory Group of the Royal College of Physicians*. London: RCP, Royal College of Psychiatrists Council Report CR178 (2013).
12. Gilbody S, Peckham E, Man M-S, Mitchell N, Li J, Becque T, et al. Bespoke smoking cessation for people with severe mental ill health (SCIMITAR): a pilot randomised controlled trial. *Lancet Psychiatry* (2015) 2:395–402. doi: 10.1016/S2215-0366(15)00091-7
13. Szatkowski L, McNeill A. The delivery of smoking cessation interventions to primary care patients with mental health problems. *Addiction* (2013) 108:1487–94. doi: 10.1111/add.12163
14. Ratschen E, Britton J, Doody GA, Leonardi-Bee J, McNeill A. Tobacco dependence, treatment and smoke-free policies: a survey of mental health professionals' knowledge and attitudes. *Gen Hospital Psychiatry* (2009) 31:576–82. doi: 10.1016/j.genhosppsych.2009.08.003
15. Robson D, Spaducci G, McNeill A, Stewart D, Craig TJK, Yates M, et al. Effect of implementation of a smoke-free policy on physical violence in a psychiatric inpatient setting: an interrupted time series analysis. *Lancet Psychiatry* (2017) 4:540–6. doi: 10.1016/S2215-0366(17)30209-2
16. Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs* (2017) 31:471–81. doi: 10.1007/s40263-017-0438-8
17. Steinberg ML, Williams JM, Gandhi KK, Foulds J, Brandon TH. Lower task persistence in smokers with schizophrenia ascompared to non-psychiatric control smokers. *Psychol Addict Behav*. (2010) 24:724–9. doi: 10.1037/a0020972
18. Steinberg ML, Williams JM, Gandhi KK, Foulds J, Epstein EE, Brandon TH. Task persistence predicts smoking cessation in smokers with and without schizophrenia. *Psychol Addict Behav*. (2012) 26:850–8. doi: 10.1037/a0028375
19. Baker TB. The 2016 Ferno Award Address: Three Things. *Nicotine Tobac Res*. (2017) 19:891–900. doi: 10.1093/ntr/ntx039
20. Kowalczyk WJ, Wehring HJ, Burton G, Raley H, Feldman S, Heishman SJ, et al. Predictors of the perception of smoking health risks in smokers with or without schizophrenia. *J Dual Diagn*. (2017) 13:29–35. doi: 10.1080/15504263.2016.1260190
21. Steinberg ML, Williams JM, Stahl NF, Budsock PD, Cooperman NA. An adaptation of motivational interviewing increases quit attempts in smokers with serious mental illness. *Nicotine Tobac Res*. (2016) 18:243–50. doi: 10.1093/ntr/ntv043
22. Steinberg ML, Ziedonis DM, Krejci JA, Brandon TH. Motivational interviewing with personalized feedback: a brief intervention for motivating smokers with schizophrenia to seek treatment for tobacco dependence. *J Consult Clin Psychol*. (2004) 72:723–8. doi: 10.1037/0022-006X.72.4.723
23. Williams JM, Miskimen T, Minsky S, Cooperman NA, Miller M, Budsock PD, et al. Increasing tobacco dependence treatment through continuing education training for behavioral health professionals. *Psychiatr Serv*. (2015) 66:21–6. doi: 10.1176/appi.ps.201300523
24. Williams JM, Steinberg ML, Zimmermann MH, Gandhi KK, Stipelman B, Budsock PD, et al. Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. *J Substance Abuse Treat*. (2010) 38:384–93. doi: 10.1016/j.jsat.2010.03.006
25. Baker AL, Richmond R, Kay-Lambkin FJ, Filia SL, Castle D, Williams JM, et al. Randomised controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders: outcomes to 36 months. *Aust NZ J Psychiatry* (2018) 52:239–52. doi: 10.1177/0004867417714336
26. Baker AL, Richmond R, Kay-Lambkin FJ, Filia SL, Castle D, Williams JM, et al. Randomized controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders. *NicotineTobac Res*. (2015) 17:946–54. doi: 10.1093/ntr/ntv039
27. Skelton E, Tzelepis F, Shakeshaft A, Guillaumier A, McCrabb S, Bonevski B. Integrating smoking cessation care in alcohol and other drug treatment settings using an organizational change intervention: a systematic review. *Addiction* (2018) 113:2158–72. doi: 10.1111/add.14369
28. Thomas D, Abramson MJ, Bonevski B, George J. System change interventions for smoking cessation. *Cochr Database Syst Rev*. (2017) 2:CD010742. doi: 10.1002/14651858.CD010742.pub2
29. Bonevski B, Guillaumier A, Shakeshaft A, Farrell M, Tzelepis F, Walsberger S, et al. An organisational change intervention for increasing the delivery of smoking cessation support in addiction treatment centres: study protocol for a randomized controlled trial. *Trials* (2016) 17:290. doi: 10.1186/s13063-016-1401-6

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership