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EPA Guidance on tobacco dependence and strategies for smoking cessation in people with mental illness

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ABSTRACT

Tobacco dependence is the most common substance use disorder in adults with mental illness. The prevalence rates for tobacco dependence are two to four times higher in these patients than in the general population. Smoking has a strong, negative influence on the life expectancy and quality of life of mental health patients, and remains the leading preventable cause of death in this group. Despite these statistics, in some countries smokers with mental illness are disadvantaged in receiving intervention and support for their tobacco dependence, which is often overlooked or even tolerated. This statement from the European Psychiatric Association (EPA) systematically reviews the current evidence on tobacco dependence and withdrawal in patients with mental illness and their treatment. It provides seven recommendations for the core components of diagnostics and treatment in this patient group. These recommendations concern: (1) the recording process, (2) the timing of the intervention, (3) counselling specificities, (4) proposed treatments, (5) frequency of contact after stopping, (6) follow-up visits and (7) relapse prevention. They aim to help clinicians improve the care, health and well-being of patients suffering from mental illness.

1. Introduction

Tobacco dependence is the most common substance use disorder in adults with mental illness [23,232] and has prevalence rates two to four times higher than in the general population [178,222]. People with severe mental illness (SMI) are often heavy smokers. For example, people with schizophrenia tend to smoke more cigarettes a day and inhale the cigarette smoke more deeply than smokers in the general population [137,248]. People with mental illness (meet DSM-III-R or DSM-IV criteria) make up 44% to 46% of the North American tobacco market, i.e. in the USA, almost every second cigarette is smoked by someone with a mental disorder [107,178]. On the basis of these rates, mental illnesses represent 47% of the attributable risk of tobacco dependence.

Smoking has a strong, negative influence on the life expectancy and quality of life of mental health patients [47,57,181]. Tobacco use is the leading preventable cause of death in patients with psychiatric illness or addictive disorder [57,181,228]. It is also an important factor when managing these patients' significantly increased risk for cardiovascular disease and diabetes [60]. Studies have found that tobacco-associated cardiac and pulmonary illnesses and cancer are more common among people with a mental illness [40,60,181] and life expectancy in general is reduced by 25 years in patients with mental illness, mainly because of chronic diseases related to tobacco use [47]. By comparison, in smokers without psychiatric comorbidity life expectancy is reduced by 10 years [71]. Smoking also predicts suicidal behaviour independent of the presence of a mental illness [34,215].

Tobacco-associated diseases are responsible for 6% to 14% of personal health costs worldwide [188,194,208,271,282]. In

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addition to the costs for the health systems, the individual costs for the mental health patient also have to be considered: a study found that in the USA patients suffering from schizophrenia spent a median of US$142.50 (range $57.15–$319.13) per month on cigarettes, corresponding to 27.4% of the median monthly income of this population, the majority of whom were receiving public assistance [268].

The motivation to quit is as high among psychiatric patients as in the general population [2,78,233,235], and the distribution of the stages of motivation to quit smoking in psychiatric samples, as measured by the stages of change model [229], parallels that for the general population [112]. This is also the case in patients with dependence disorders in general [46,207,293].

Currently, too little attention is paid to the topic of smoking and tobacco dependence in everyday psychiatric care. In a retrospective study on the prevalence of smoking cessation programmes in psychiatric settings, Prochaska et al. found that none of the 250 psychiatric patients studied were diagnosed with tobacco dependence and smoking status was not included in the treatment plan [232]. At discharge, only one patient was advised to stop smoking, referred for smoking cessation counselling or given tobacco withdrawal treatment. Another study, by the same research group, found 52% of the psychiatric patients studied reported never having been encouraged by hospital staff to quit smoking [235]. Psychiatric patients who smoke appear to have poorer access to health care: Himmelhoch et al. showed that schizophrenia patients who smoked and had type 2 diabetes were less likely to receive services and treatments known to improve cardiovascular outcomes [129].

A recent systematic review and quality assessment of guidelines/recommendations published between 2000 and 2010 for cardiovascular risk in patients with schizophrenia shows that smoking cessation is recommended in only half of the evaluated guidelines [61].

Meta-analyses on smoking cessation have shown the large benefit of smoking cessation measures conducted by physicians and nursing staff, in particular that of just giving simple advice [177,245–247]. However, none of the studies included in these meta-analyses were conducted in a psychiatric setting. One large, multi-centre study looked at implementing the 5 A's (Ask, Advise, Assess, Assist, Arrange) for people with SMI attending appointments at community mental health centers. Although no significant difference was found at 6 months, by 12 months increased abstinence and smoking reduction were reported [70].

Despite the high rates of smoking among psychiatric patients, hardly any studies have been conducted in Europe in this group of patients. Although this topic appears to have been better investigated in the USA [70], still relatively few studies have been performed compared to the numbers in other areas of smoking research [112].

Although a small study of 17 alcohol or drug using schizophrenia patients suggested an inverse correlation in prodromal symptom distress and nicotine use [116], increasing evidence shows that smokers with psychiatric comorbidity can be helped to quit smoking without jeopardizing their mental health recovery [23,227]. In view of the gain in life years and quality of life as well as of the favourable cost-benefit ratio, the treatment of tobacco dependence is one of the most important interventions for psychiatric in- and outpatients. Tobacco withdrawal programmes should not be withheld from patients with mental illness. Rather, special emphasis should be placed on this patient group because they have pre-existing disadvantages in obtaining health care. Psychiatrists and primary care physicians need to play an active role in ensuring that patients with mental illness are not put at a disadvantage [179,216,219]. Addiction is an integral part of psychiatry training and the general principles learnt also apply to smoking. Ideally clinicians should have received specialist training as "tobaccologists". In reality few have and so consequently, this paper aims to help those who have not received specialist training to feel confident in treating patients using evidence-based medicine. The active, guideline-based diagnostics and treatment of tobacco dependence should always be part of the care for patients with mental illness.

This position statement was developed by the EPA, based on a review of the evidence that patients with SMI are at serious increased risk of smoking. The aim of this statement is to give recommendations for evidence-based diagnostics and treatment of tobacco dependence that will allow psychiatrists and primary care clinicians to improve the health and well-being of mentally ill patients.

These evidence-based guidance recommendations were derived from current scientific evidence (by means of a systematic literature search – detailed below) in addition to expert experience and consensus. This position statement was developed by the EPA in accordance with the available international guidelines on tobacco withdrawal [17,18,24,88,89].

This statement aims to summarise the current knowledge about tobacco dependence and withdrawal in patients with mental illness and to give recommendations for the core components of diagnostics and treatment in this patient group. Please note that this statement uses the term 'tobacco dependence' rather than 'nicotine dependence' because we can not rule out the complex interaction of biological and psychological factors in smoking dependence.

2. Who is at risk and why?

Sociodemographic variables such as sex and employment status appear to be similar in smoking and non-smoking psychiatric patients. However, considerable differences can be found in age, marital status, psychiatric diagnosis and substance abuse history [232]. Younger patients are more likely to smoke than older patients; smoking rates are higher among single psychiatric patients than among married or divorced patients; and patients with a psychotic illness, bipolar disorder, depression or substance use disorder are significantly more likely to smoke than patients with other diagnoses [234,248]. Over 70% of patients who take illegal drugs [46,64] or suffer from alcoholism [32,69] have been found to be smokers. In fact, the prevalence of tobacco dependence is higher in patients of almost all psychiatric diagnostic groups [178]. The scope of this paper sets out to cover the treatment of patients with schizophrenia, affective disorder or substance use disorder. These major disease entities will be considered in more detail below.

2.1. Schizophrenia

In North America, 44% to 88% of schizophrenia patients in clinical [31,44,144,160,222,292] and population-based [178] samples were found to smoke, compared with 29% of the general population [272].

Schizophrenia patients who smoke have higher blood levels of cotinine than smokers without psychiatric comorbidity, indicating a higher level of consumption or deeper inhalation [213]. The number of cigarettes consumed daily in this patient group correlates positively with the dose of neuroleptic drugs [104,154] and also with the occurrence of prodromal symptoms of schizophrenia [48,116]. People with schizophrenia who had lower functioning were also found to smoke more cigarettes per day [171]. More than 60% of schizophrenia patients start smoking before the first clinical manifestation of the disease and before any treatment with antipsychotics [22,48,62,191].

A 13-year follow-up study in 370 patients with schizophrenia found that fatal, tobacco-associated diseases occurred significantly more often than in the general population [35]. Life expectancy was found to be 20% lower in schizophrenia patients and, besides other lifestyle habits, smoking was identified as one of the most important risk factors for this high mortality [31,127]. Bobes et al. showed that if schizophrenia patients at high/very high risk (above 10%) of experiencing a cardiovascular event in the subsequent 10 years would stop smoking they would benefit from a near 90% reduction in risk [31].

In humans, nicotine enhances motor ability, attention and memory. This almost certainly has implications for the initiation of smoking and maintenance of tobacco dependence [125] even more so for those with mental illness [58]. Detailed consideration to the neurobiological mechanisms of nicotine addiction is beyond the scope of this paper but Stolerman and Shoaib present a solid review [269]. Of central importance in the pathophysiology of schizophrenia is the influence of nicotine on dopaminergic and glutamatergic receptor systems [55]. The interaction between nicotine and the nigrostriatal and mesocorticolimbic dopamine systems, which are known to be involved in this disorder, has been well studied. Chronic nicotine intake may have a positive influence on the assumed dissociation in schizophrenia between cortical hypoactivity and subcortical hyperactivity [59]. In addition to its known dopaminergic effect, nicotine also stimulates glutamate release in the hippocampus [176]. The modulation of these two important neurotransmitters, both of which are involved in the pathogenesis of schizophrenia, could play a role in the increased use of nicotine by schizophrenia patients, for example in the form of 'self-medication'.

Nicotine has been described to have positive effects on the negative symptoms of schizophrenia [53,62]: it increases drive and improves cognitive function [193]. Schizophrenia patients with a high level of negative symptoms are at particular risk of being heavier smokers [62]. Ziedonis et al. found more positive symptoms but fewer negative symptoms in smokers than in non-smokers; heavy smokers had the highest positive and lowest negative symptom scores [291]. Nicotine improves the deficits of schizophrenia patients in cognition (sensory gating) [3,172,173], working memory [152,252] and attentional deficits [65], so that strong self-medication effects can be assumed for these deficits as well. Indeed, the nicotinic acetylcholine receptor agonist varenicline, which was specifically developed for smoking cessation, has been shown to improve cognitive impairments in people with schizophrenia [257] and possesses a unique treatment profile on core schizophrenia-related biomarkers [131].

The relationship between smoking and treatment with antipsychotic medication definitely plays an important role in this patient group: chronic nicotine intake can improve neuroleptic-induced extrapyramidal symptoms [104,191] and reduce the occurrence and severity of parkinsonism [63]. Furthermore, it appears that the prevalence of smoking is somewhat lower among patients treated with modern antipsychotics [22]. Tobacco smoke increases the clearance of many antipsychotic drugs (see Section 8 Smoking and psychopharmacologic medication below), which results in lower plasma levels and can reduce the severity of side effects (e.g. extrapyramidal motor symptoms, sedation) and hence increase the tendency for patients to smoke more [153,192,195].

Besides biological and physiological factors, behavioural aspects are relevant for the high level of tobacco dependence among schizophrenia patients, e.g. strategies for coping with boredom [261] and the lack of a smoke-free hospital environment [253]. Last but not least, in the USA, internal documents of the tobacco industry were released showing that the industry made a multitude of direct and indirect efforts to slow down the reduction of smoking prevalence among people with schizophrenia [15,236].

2.2. Affective disorders

The prevalence of tobacco dependence in clinical samples of patients with major depression [33,144,151,292] and population-based samples of patients with clinically significant depressive symptoms [11] is 40% to 60% higher than in the general population, but not quite as high as among schizophrenia patients or patients with a dependence disorder. In the case of patients with bipolar disorder, García-Portilla et al. found that tobacco use was associated with an increased risk of coronary heart disease and that this risk was reduced dramatically to 10% in those who quit smoking [93]. In a study performed in over 3200 people, Glassman et al. showed that 74% of all patients who had experienced a depressive episode at some time in their lives had a history of smoking [103]. The relationship between tobacco consumption and depressive disorders appears to be reciprocal [156]: smoking appears to increase the risk for a depressive episode [43,157] and the depression appears to sustain the tobacco dependence, as shown by the finding that patients have a much harder time quitting, require more attempts before they quit and show more side effects from quitting [113,140,209]. The main biological hypothesis for these effects is probably the direct antidepressive effect of nicotine or other components in tobacco smoke via inhibition of the monoaminooxidases MAO-A and MAO-B [26,27,94]. Direct cholinergic effects of nicotine also influence cognition, attention and arousal, motivated behaviour and satiety (for a review see [175]). In addition, chronic nicotine intake appears to have serotonergic effects via an influence on $5HT_{1A}$ autoreceptors [165,175]. Animal models (forced swimming test, models of learned helplessness) have indicated that both acute and chronic nicotine administration also have a direct antidepressive effect [13,255,274]. In addition to biological and pathophysiological effects, a large number of behavioural antidepressive effects of smoking play an important role in the difficulties of depressed patients in attaining and maintaining abstinence [74].

The prevalence of smoking is also higher (51% to 70%) in patients with bipolar disorder than in the general population [41,45,52,67,106,242]. Corvin et al. [52] showed a possible association between smoking and psychotic symptoms in bipolar disorder, although results of other studies are inconsistent [41]. Some more recent studies indicate a relationship between smoking and suicidality in this patient group [20,105,217].

Studies indicate that patients report no worsening of depressive symptoms following smoking cessation [114,237], or even improved symptoms [30,159] but that failed attempts do [28]. Long-term cessation rates are lower for smokers with current depressive symptoms (14%) [115] than for those with a history of depression (22%) [114].

2.3. Substance use and dependence disorders

More than 75% of all patients with dependence disorders have comorbid tobacco dependence [32,69]. The health consequences of tobacco and other drug use are synergistic and estimated to be 50% greater than the sum of each individually [29]. Thus, smoking and not alcohol is the leading cause of death in patients who have undergone alcohol withdrawal treatment and is responsible for more than 50% of all deaths in this patient group [149,151].

Recognising the importance of this small field of research, the Cochrane Collaboration has recently published a study protocol aiming to address tobacco cessation interventions specifically in alcohol and drug abuse populations [118]. Alcohol-dependent patients report greater problems in quitting smoking than non-alcohol-dependent smokers [69,211] and a higher degree of dependence than smokers without a comorbid dependence disorder [128]. Addressing heavy-drinking in smokers results in

better smoking cessation rates [158]. In a 24-year study of long-term drug abusers, the death rate among cigarette smokers was found to be four times that of non-smokers [134].

Provision of smoking cessation treatment in conjunction with substance use treatment is currently not standard practice due, in part, to unfounded concern that combining smoking cessation treatment with substance use treatment could lead to poorer outcomes. Treatment of tobacco dependence does not jeopardize alcohol abstinence [162,210] in fact, it is associated with enhanced sobriety from alcohol and other drugs [19,198,227,243,276].

Both ethanol and nicotine appear to interact with the dopaminergic reward system [251], whereby the rewarding effect of alcohol is intensified by nicotine and vice versa [49,110,249]. On the molecular level there are indications that both nicotine and alcohol have similar effects on the cholinergic, glutamatergic and opioid systems [183]. The prevalence of smoking is also much higher in patients with opiate or cannabis dependence or cocaine consumption than in the general population [36,64,259].

3. Patient setting

3.1. Smoke-free psychiatric wards

A few years ago, smoking was banned in hospital buildings and in some hospital grounds in most American states and in many European countries. This ban aims to reduce the dangers of passive smoking among patients, employees and visitors and to encourage people to quit smoking. However, generally psychiatry departments were excluded from this ban because mentally ill patients were thought to need to smoke in order to manage their psychiatric symptoms. Furthermore, a smoking ban is generally presumed to be extremely difficult to enforce in these patients. Practical experience from smoke-free psychiatric wards has shown, however, that this assumption is unjustified [233]. The changeover to a smoke-free ward proves to be less difficult than expected, with studies finding no increases in aggression, disruption, discharges against medical advice, use of medications or restraints or admission refusal, even in acute or closed psychiatric settings [78,235]. Prochaska reported a high interest and uptake (79%) of tobacco cessation treatment in inpatient psychiatry patients [238].

In a study of 322 smokers suffering from depression, no detriment to mental health was found among individuals who quit smoking as compared to those who continued to smoke after inpatient smoking cessation [229]. Furthermore, on psychiatric wards that have voluntarily banned smoking, changes have been seen in the patients' attitude to smoking: their desire to quit smoking and their confidence in being successful were positively influenced by the smoke-free environment [112,233].

3.2. Inpatient vs. outpatient treatment

Smoking cessation treatment should be offered in both the inpatient and outpatient setting. The evidence-based treatment advice laid out in this document can be implemented in either setting.

Although most studies into smoking cessation in patients with mental illness were carried out in an outpatient setting, Prochaska presents a convincing "10-reason" report supporting inpatient cessation treatment [227]. Most recently, Prochaska et al. conducted the first randomized controlled trial evaluating the efficacy of inpatient treatment and reported a decreased re-hospitalization risk [239].

There is a huge difference in how European countries approach tobacco control and treatment. Since nicotine dependence is an ICD-10 defined diagnosis, therapeutic intervention should be paid for by the healthcare system. However, in many European countries the health insurance companies reimburse smoking cessation treatment (although rarely for any pharmacological intervention) since they recognise how cost-effective it is. In the UK the NHS provides smoking cessation programmes at an estimated cost of 209 GBPs per patient [263]. Although the cost for psychiatric patients is not available, it is likely to be lower as these patients have frequent appointments for the management of their illness that could simultaneously address the smoking cessation treatment.

4. Methods

4.1. Guidance development process

The EPA developed the European Guidance Project (EGP) in order to provide a series of guidance papers on a range of topics within mental healthcare, centered on evidence-based medicine [91].

For this guidance document, the EGP's Steering Group appointed Pr. H.J. Möller as the lead author, who as such was responsible for recruiting further experts to develop the document conceptually and methodologically. It was then written and, before publication, jointly edited by all co-authors. The final version of this position statement was reviewed and endorsed by the EGP coordinator [Pr. W. Gaebel].

4.2. Systematic literature search

We performed a systematic literature search based on the methods previously published by the EPA [92], as outlined in Fig. 1 below.

A total of 4241 potentially relevant citations were identified in PubMed using the Medical Subject Headings (MeSH) "Mental Disorders" AND "Tobacco Use Cessation" as the strategy. Articles were excluded if they did not fulfill the following criteria: (1) listed as a Meta-Analysis, Randomized Controlled Trial OR systematic review under publication type, (2) published in English OR German language and (3) published between January 2008 and March 2013.

Additionally, we screened The Cochrane Tobacco Addiction Group's specialized register (currently stands at 82 reviews). This register contains reports of trials on tobacco addiction interventions identified from The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycInfo. One author (T. Rüther) screened the remaining 405 abstracts and all of the Cochrane Tobacco Addiction Group's specialized register's abstracts for relevance. Of these, 427 citations were excluded as irrelevant for this statement (for example study protocols, adolescent or pregnant populations, duplicate studies). Further articles were identified by cross searching reference lists of highly relevant papers.

5. Guidelines for screening and monitoring smoking cessation

The available guidelines on smoking cessation in general, prepared by national and international groups [7,8,12,88,89], present good evidence-based and practice-oriented information for smoking cessation and also consider the treatment of patients with psychiatric comorbidity. However, the need for research in this patient group is made clear by the fact that the guidelines include hardly any concrete instructions or programmes for such patients. The most detailed consideration of the treatment of smoking in psychiatric patients can be found in the guidelines on

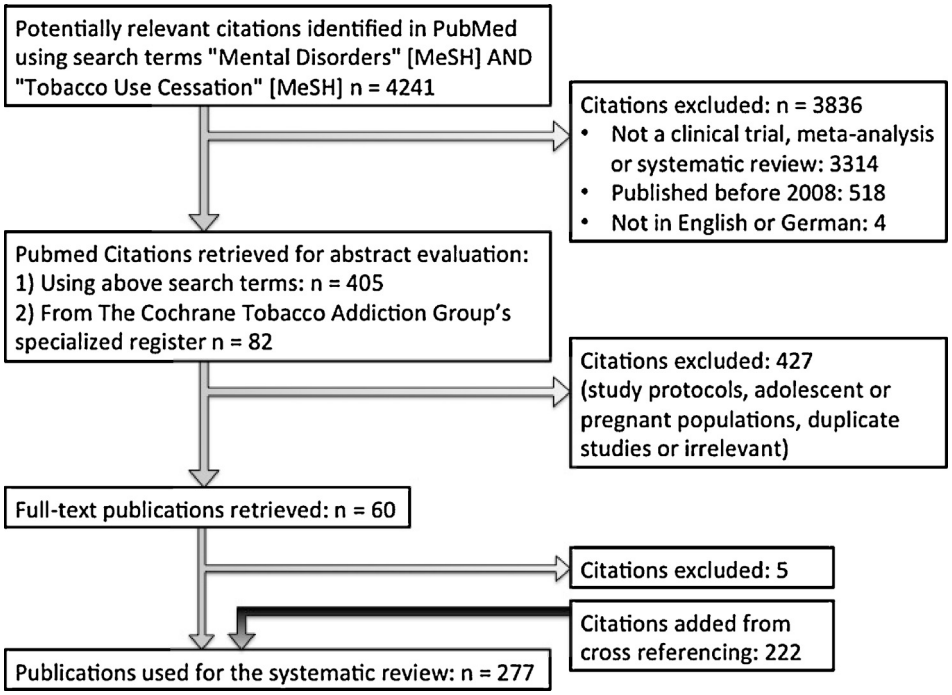

Fig. 1. A flow scheme of the literature search performed for this statement paper.

smoking cessation from the American Psychiatric Association (APA) [7,8], although the APA notes that most of its recommendations are derived from experience in smokers without psychiatric comorbidity because few useful studies have been performed in patients with mental illness.

6. Assessment of tobacco dependency

6.1. Tobacco/nicotine dependence as classified in ICD-10 und DSM-IV

The two main diagnostic classification systems, the International Classification of Diseases, tenth revision (ICD-10) [288] and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [9,10] classify addiction to smoking as a mental disorder. DSM-IV uses the term 'nicotine dependence' and thus emphasises nicotine as the substance causing the dependence. ICD-10, on the other hand, justifies using 'tobacco dependence' by saying that dependence on nicotine is not possible without consuming tobacco and that it has not yet been clearly demonstrated that nicotine is the only substance in tobacco smoke that causes dependence [250].

The classification systems specify very similar definitions and criteria for dependence on smoking. At least 3 of 6 (ICD-10) or 7 (DSM-IV) criteria have to have occurred within the previous 12 months to allow a diagnosis of dependence. The diagnostic criteria of the two systems are shown in Table 1.

Table 1
Diagnostic criteria for tobacco/nicotine dependence according to ICD-10 and DSM-IV.

ICD-10 – Tobacco dependence syndrome (F17.2)	DSM-IV -Nicotine dependence (305.10)
Definition: A cluster of physiological, behavioural, and cognitive phenomena in which the use of tobacco takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take tobacco	**Definition**: A maladaptive pattern of substance use, leading to clinically significant impairment or distress
A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:	**Three (or more) of the following criteria must have occurred at any time in the same 12-month period:**
1. A strong desire or sense of compulsion to take tobacco	**1.** Nicotine is often taken in larger amounts or over a longer period than was intended
2. Difficulties in controlling tobacco-taking behaviour in terms of its onset, termination, or levels of use	**2.** There is a persistent desire or unsuccessful efforts to cut down or control substance use
3. A physiological withdrawal state when tobacco use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for tobacco; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms	**3.** Withdrawal: (a) the characteristic withdrawal syndrome for nicotine or (b) nicotine is taken to relieve or avoid withdrawal symptoms
4. Evidence of tolerance, such that increased doses of tobacco are required in order to achieve effects originally produced by lower doses	**4.** Tolerance: (a) a need for a markedly increased amount of nicotine to achieve intoxication or the desired effect or (b) markedly diminished effect with continued use of the same amount
5. Progressive neglect of alternative pleasures or interests because of tobacco use, increased amount of time necessary to obtain or take the substance or to recover from its effects	**5.** Important social, occupational, or recreational activities are given up or reduced because of nicotine use
6. Persisting with tobacco use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm	**6.** Nicotine use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by nicotine
	7. A great deal of time is spent in activities necessary to obtain nicotine, use nicotine or recover from its effects

Criteria relating to the amount of time spent obtaining, using or recovering from use of the substance and the reduction of time spent on important activities because of using the substance are not only important in the dependence of substances, such as heroin, they also have a role in tobacco dependence. However, the criteria for withdrawal symptoms, continued use despite harmful consequences and reduced control of amount used are key for diagnosing the disorder.

6.2. Tobacco dependence according to the Fagerström Test for Nicotine Dependence

Both ICD-10 and DSM-IV have separate categories for dependent and non-dependent smokers. Such an all-or-nothing approach is unsatisfactory and of little use in everyday clinical care because it does not allow treatment plans to be tailored to an individual's needs [126]. For this reason, the 'Fagerström Test for Nicotine Dependence' (FTND) has become the internationally accepted and proven approach to describing tobacco dependence [123]. This test measures the dependence as a dimensional parameter and represents the severity of the dependence on a continuum. The FTND assesses the severity of a smoker's physical dependence on the basis of six questions, with different answer formats, that are intended to record the construct tobacco dependence one dimensionally (Table 2).

The FTND is analysed by calculating a sum score, which ranges from 0 to 10 points and corresponds to dependence severity, as follows: very low or no dependence (0 to 2 points); low dependence (3 or 4 points); medium dependence (5 points); and high dependence ($\geq$ 6 points) [85]. The average score in smokers in the general population is between 2.8 and 5.6 points [83]. Smokers who sign up for tobacco withdrawal programmes have significantly higher average FTND scores than average consumers: various studies have found that smokers who want to quit smoking have scores between 5.2 and 6.6 points [86].

The reliability and predictive validity of the FTND has been proven in several studies [84,225,270]. The questions about the time of smoking the first cigarette in the morning and the number of cigarettes smoked per day are considered to be the most stable predictors of the severity of dependence and have proven themselves in clinical practice as indicators of high dependence [225]. These two questions alone can account for up to 6 of the total of 10 points.

As a measurement of the severity of physical dependence, the FTND correlates well with the carbon monoxide content of exhaled air, the nicotine and cotinine plasma levels and physiological parameters during the first days of abstinence such as heart rate and body and skin temperature [88]. The sum score of the FTND is one way of assessing the probability of becoming abstinent as a result of a smoking cessation programme. The FTND score allow a prognosis to be made about the likelihood of a smoker who wants to quit actually becoming abstinent as a result of drug-supported and behavioural-therapy oriented withdrawal treatment. The type and dose of pharmacological therapy in particular is determined by the severity of the tobacco dependence [88]. In summary, in the international literature the FTND is deemed to be the gold standard for assessing tobacco dependence.

6.3. Nicotine and cotinine levels and carbon monoxide (CO) measurement

Nicotine and cotinine levels can be measured in blood, saliva and urine. Nicotine levels reflect smoking over the last few hours, whereas cotinine, a metabolite of nicotine, is sensitive to smoking in the past 7 days and thus offers a better measure of total daily nicotine exposure [25]. Carbon monoxide levels can be measured in exhaled air with a half-life of 4.5 hours. In practical terms, a cut-off level of 12 ppm can be used to distinguish between recent smokers and those that have refrained for the past 8 hours [254]. The advantages of assessing carbon monoxide are that it can be measured easily and quickly and can be used to verify that a patient has quit smoking also when the patient has chosen a nicotine preparation as the concomitant drug therapy. It has also been suggested that the measurement of carbon monoxide can reinforce abstinence by making the success of abstinence visible [180].

7. Withdrawal symptoms

Withdrawal symptoms are reported by about half of all smokers who try to quit smoking [143]. It is difficult to predict who will experience withdrawal symptoms and who will not. If withdrawal

Table 2
Items and scale values of the Fagerström Test for Nicotine Dependence (FTND) [123].

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6–30 minutes	2
	31–60 minutes	1
	After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Table 3
American Psychiatric Association (DSM-IV-TR) and World Health Organization (ICD-10) criteria for nicotine or tobacco withdrawal syndrome [141].

DSM-IV-TR nicotine withdrawal[a]	ICD-10 DCR tobacco withdrawal[b]
Anxiety	Anxiety
Difficulty concentrating	Difficulty in concentrating
Dysphoric or depressed mood	Dysphoric mood
Increased appetite or weight gain	Increased appetite
Insomnia	Insomnia
Irritability, frustration or anger	Irritability or restlessness
Restlessness	–
Decreased heart rate	–
–	Craving for tobacco (or other nicotine-containing products)
–	Increased cough
–	Malaise or weakness
–	Mouth ulceration

[a] Also requires "daily use of nicotine for at least several weeks;" that symptoms "cause clinically significant distress or impairment in social occupational, or other important areas of functioning;" and that "symptoms are not due to a general medical disorder and not better accounted for by another medical disorder" [10].
[b] Also requires "clear evidence of recent cessation or reduction of tobacco use after repeated, and usually prolonged and/or high dose, use of tobacco" and "tobacco symptoms and signs are not accounted for by a medical disorder unrelated to substance use, and not better accounted for by another mental or behavioural disorder" [288].

Table 4
Important psychotropic medications with smoking-induced metabolism (modified from [66,214]).

Antidepressants	Antipsychotics	Anxiolytics	Other
Agomelatine	Aripiprazole	Alprazolam	Carbamazepine
Amitriptylline[v]	Chlorpromazine	Clonazepam	Chlordiazepoxide[v]
Clomipramine	Clozapine	Diazepam	Propranolol
Duloxetine	Fluphenazine	Lorazepam	
Fluvoxamine	Haloperidol	Oxazepam	
Imipramine	Olanzapine	Triazolam	
Mirtazapine	Perazine		
Nortriptylline[v]	Quetiapine		
Reboxetine	Risperidone		
Sertraline	Tiotixene		
Trazodone	Zotepine		

[v]: variable.

symptoms occur they manifest themselves as physical symptoms, such as palpitations or low blood pressure, and also in particular as psychovegetative and psychological reactions such as anxiety, concentration difficulties, sleep disorders, feelings of hunger, irritability, restlessness, weight gain, negative affect and strong craving for cigarettes [136,141,143,145]. Table 3 shows a comparison of the common withdrawal symptoms described in the ICD-10 and DSM-IV. Withdrawal symptoms appear as early as a few hours after stopping smoking and peak after 24 to 48 hours. Normally they markedly decrease or disappear within one week to 10 days [256]. Craving and feelings of hunger or increased appetite have also been reported over a period of 6 months and longer, as have depressed mood and clinically relevant depressions [101,102,220]. Studies have found that the degree of withdrawal symptoms is independent of the number of cigarettes smoked daily before the withdrawal and that after partial withdrawal the symptoms are often more severe than after complete cessation, which may speak against a solely pharmacological process through the substance nicotine. Withdrawal symptoms frequently occur as a result of triggering stimuli and can thus also be explained as the result of a conditioning process [1,139,170].

Distinguishing between withdrawal symptoms, such as anxiety, depression, increased REM sleep, insomnia, irritability, restlessness and weight gain, and symptoms arising from the psychiatric condition can be difficult. Withdrawal symptoms can disguise, mimic or aggravate the symptoms of a psychiatric disorder [137,139] and therefore can result in patients falsely attributing relief to effects on mental disorders. For example, nicotine replacement reduced agitation in smokers hospitalised for schizophrenia by one third [5]. In general, patients with SMI show more frequent and severe withdrawal symptoms after quitting smoking [56,139].

8. Smoking and psychopharmacological medication

Smoking has a strong influence on the rate of metabolism of many psychopharmaceuticals, in particular those metabolized by the liver microsomal system of the cytochrome isoform P450 1A2 (Table 4). The induction of this enzyme means that serum levels of many psychopharmaceuticals are lower in smokers than in non-smokers [117]. Stopping smoking may increase the blood levels of these drugs, which in turn can worsen side effects or cause toxicity. This effect appears to be due not to nicotine but rather to the effects of benzopyrenes (tobacco carcinogens) and related compounds on the P450 system [66]. Such effects have been described as being particularly strong with the drug clozapine: smoking patients need to be administered on average 50% higher daily doses than non-smoking patients [281]. Smoking 7–12 cigarettes daily is sufficient for the maximum induction of clozapine and olanzapine metabolism [117]. There are many reports of intoxications during clozapine or olanzapine treatment after smoking cessation [184] so it is advisable to monitor blood levels of clozapine and reduce the dose when patients quit smoking [51,206]. Therapeutic drug monitoring and recording of both smoking status and history of previous or planned attempts at quitting smoking should generally be an essential part of treatment with the above-mentioned psychopharmaceuticals.

9. Treatment of tobacco dependence

The primary objective of every tobacco withdrawal treatment is long-term cessation of smoking. Initial goals include moving smokers from not contemplating smoking cessation to contemplating cessation to initiating a quit attempt to stop smoking for a short period [230]. Data on reduced smoking, i.e. a reduction in the number of cigarettes smoked daily, are inconsistent [265]. Although it seems health benefits are unlikely (perhaps due to compensatory smoking), it may have a valuable role as a step toward smoking cessation particularly in some psychiatric diagnostic groups, e.g. in schizophrenia patients or patients with a substance use disorder [68,118,155,212].

The first version of the US Department of Health and Human Services guideline on treating tobacco withdrawal [88] recommended that psychiatric patients who smoke should receive the same treatment for tobacco dependence as smokers in the general population. At the time of completion of this guideline, hardly any studies had been performed on tobacco withdrawal in a psychiatric setting so recommendations were derived and generalised from those for the general population [258]. The guideline was updated in 2008 [89] and highlighted the value of treating smokers with mental illness. However, even the updated version does not clarify whether or not interventions need to be tailored to particular disorders. The few studies performed in a psychiatric setting did find that treatments developed for the general population produced higher abstinence rates than placebo or other control treatments, although the overall abstinence rates in both psychiatric and substance use disorder treatment populations were lower than in studies performed in participants from the general population. The available meta-analyses on smoking cessation in depressive patients [75,99], schizophrenic patients [279] and patients with a substance use disorder [234] unanimously demand further research in this area. We eagerly await the imminent publication by The Cochrane Collaboration on interventions for tobacco use cessation in people in treatment for or recovery from substance use disorder [16] and depression [280].

Momentum is gaining slowly in this field and the data indicate treatments that work in the general population work as effectively for those with severe mental illness [190,204]. The APA practice guideline specifies that smokers with a psychiatric disorder require more intensive psychotherapeutic support than smokers in the general population and possibly also supportive medication [7,8]. Prolonging the treatment period has been proposed in this population [199]. Nevertheless, treating tobacco dependence in patients with stable psychiatric conditions does not worsen mental state [21].

The combination of psychotherapeutic techniques and concomitant supportive medication is deemed to be the silver bullet in the treatment of tobacco dependence [7,8,89] (Table 5). The objective of combination therapy is to treat possible withdrawal symptoms after smoking cessation and simultaneously expand skills for smoke-free behaviour.

Table 5
Effectiveness of and estimated abstinence rates for the combination of counselling and medication alone: results of a meta-analysis (n = 18 studies) [89].

Treatment	Number of arms	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
Medication alone	8	1.0	21.7
Medication and counselling	39	1.4 (1.2–1.6)	27.6 (25.0–30.3)

9.1. Psychopharmacological treatment

Current clinical practice guidelines from the US department of health on the treatment of tobacco dependence list the following drugs, in combination with concomitant counselling, as first-line treatment: short- or long-acting nicotine replacement therapy (NRT), sustained release bupropion (bupropion SR) and varenicline. These recommendations were made on the basis of extensive meta-analyses in which the effectiveness of the drugs 6 months after smoking cessation was investigated in adults without psychiatric comorbidity [89]. The estimated odds ratios 6 months after smoking cessation were 2.2 to 3.8 (95% confidence interval).

Despite the very good and robust database on the safety and efficacy of drug treatment of tobacco dependence, only a few studies have examined their use in mentally ill patients. These studies are listed in Table 6 for reference. To date, research supports the hypothesis that smoking cessation interventions used in the general smoking population would be also beneficial in smokers with mental illness.

9.1.1. NRT (Nicotine replacement therapy)

NRT can be used as first-line therapy for all smokers [89]. Currently, seven preparations are available—patch, chewing gum, lozenge, sublingual tablets, inhaler/inhalator, nasal spray and mouth spray—although the last two dosage forms are only available in a few European countries. A pill that could reliably produce high enough nicotine levels in the central nervous system would risk causing adverse gastrointestinal effects. To avoid this problem, nicotine replacement products are formulated for absorption through the oral or nasal mucosa (chewing gum, lozenges, sublingual tablets, inhaler/inhalator, nasal and mouth spray) or skin (transdermal patches) [266].

All routes of administration reduce withdrawal symptoms effectively and improve the cessation rate among both male and female smokers [37]. A combination of a long-acting route of administration (patch) with a short-acting one (gum, lozenges, sublingual tablets, inhaler, nasal spray, mouth spray) has proven to be particularly effective. Longer use (for at least 8 weeks) is recommended [266]. Most nicotine preparations available in Europe have been sold for decades as over-the-counter products (i.e., without a prescription) and have an extremely good safety profile. Although the nicotine nasal spray and the inhaler release nicotine somewhat more quickly than the other routes of administration, nicotine absorption is significantly slower with all routes of administration than with cigarettes and the peak nicotine concentration is lower. This phenomenon is probably the reason why hardly any cases of dependence on nicotine preparations have been reported [133,135,147]. The efficacy of NRT in the treatment of smoking in patients with depression is comparable to the general smoking population [100]. In a placebo-controlled, randomised study, smokers with current depression had a 3-month cessation rate of 29.5% in those treated with nicotine chewing gum plus counselling compared with 12.5% in those who received placebo chewing gum plus counselling [166]. In a follow-up study by the same group, the cessation rates at 12 months were 15% in the NRT treatment group and 5.7% in the placebo gum group [167].

The efficacy of NRT has also been shown in schizophrenia [54,96,132] and substance use disorder patients [50,146,150,161,243].

Further trials with longer follow-up periods are needed to determine whether extended treatment leads to higher long-term cessation rates [38] since one recent study suggests that people who quit smoking relapse at equivalent rates, regardless of NRT use [6]. This controversial study goes against the general consensus and received plenty of criticism due to its methods [77] (http://tobaccocontrol.bmj.com/content/early/2012/01/10/tobaccocontrol-2011-050129.abstract/reply).

9.1.2. Bupropion SR

The sustained release formulation of the antidepressant bupropion (bupropion SR) can also be considered a first-line drug treatment in patients who smoke. Its efficacy and tolerability appear to be similar to those of NRT. Treatment with bupropion SR should commence 7 days before quit day and the dose should be gradually increased. Primary side effects are headache, jitteriness, insomnia and gastrointestinal symptoms. Special care needs to be taken when treating patients who suffer from epileptic seizures of any kind because epileptic seizures have been observed during treatment with bupropion.

A few small studies into bupropion use in schizophrenia have been published (Table 6). The best indication of its efficacy and safety comes from a recently updated Cochrane meta-analysis, which found increased abstinence rates both at the end of treatment (7 trials, n = 340; risk ratio 3.03; 95% confidence interval 1.69–5.42) and after 6 months (5 trials, n = 214, risk ratio 2.78; 95% confidence interval 1.02–7.58). Treatment did not jeopardise mental state. Bupropion may also reduce the number of cigarettes these patients smoke [279].

Bupropion is efficacious for smoking cessation in patients with a history of depression or alcoholism [119]. The feasibility of bupropion has been also indicated in a very small pilot study of bipolar smokers [283] and in a double-blind, placebo-controlled trial of opioid-dependent smokers [201]. In combination with NRT

Table 6
Overview of studies investigating drug treatment of tobacco dependence in mentally ill patients.

Mental illness	Treatment	Evidence available
General		[21,190,199,241,264]
Schizophrenia	Cochrane review	[279]
	NRT	[54,96,132]
	Bupropion	[80,97,278,286]
	NRT + Bupropion	[81,98]
	Varenicline	[14,42,73,79,87,218,257, 262,285,287]
Affective disorders	Cochrane review	[280]
	NRT	[115,166,167]
	Bupropion	[119,283]
	NRT + Bupropion	[82]
	Varenicline	[189,289]
Substance use disorders	Cochrane review	[16]
	NRT	[50,146,150,161,243]
	Bupropion	[119,121,164]
	NRT + Bupropion	[163]
	Varenicline	[122,198,223]

and counselling, bupropion slightly improves cessation rates in patients with a history of depression (36% vs. 31% for placebo + NRT + counselling) [82] or alcoholism (11% vs. 6% for placebo + NRT + counselling) [163], although not significantly so.

To date, two double-blind, placebo-controlled trials have been published on the outcome of patients with schizophrenia on combination therapy. Evins et al. found that patients taking bupropion + NRT had a significant increase in smoking reduction at 3 and 6 months (60% vs. 31%; $P = 0.036$), and a greater continuous abstinence rate at week 8, (52% vs. 19%; $P = 0.014$) over patients taking placebo + NRT. However, relapse rates were very high during and after NRT taper and abstinence rates did not differ significantly at 3 months (36% vs. 19%), 6 months (20% vs. 8%) or 12 months (12% vs. 8%) [81]. The other trial of combination therapy found a significant improvement in smoking abstinence for bupropion + NRT (27.6%) compared with placebo + NRT (3.4%) at 6-month post quit date [98].

9.1.3. Varenicline

Varenicline is a nicotinic acetylcholine partial agonist at the $\alpha_4ß_2$ receptor and full agonist at the α_7 receptor. It was specifically developed for smoking cessation, aimed at reducing both withdrawal symptoms and the rewarding properties of nicotine. In registration studies and the first meta-analyses, varenicline showed few side effects and good long-term abstinence rates. The Cochrane Collaboration conducted a systematic review of nicotinic receptor partial agonists for smoking cessation [38]. Their meta-analysis of long-term abstinence data shows that varenicline increases the chances of successful long-term cessation over 2-fold and is superior to bupropion (the pooled risk ratios [95% CI] were 2.27 [14 trials, 6166 people] versus placebo, 1.52 [3 trials, 1622 people] versus bupropion SR and 1.13 [2 trials, 778 people] versus NRT) [38].

Since varenicline was introduced to the market, there have been some reports of exacerbations of symptoms of existing psychiatric disorders during treatment [90,169,226,240] and some reports of psychiatric side effects in patients without a diagnosis of mental illness [202,203]. On July 1st, 2009, following alerts and public health advisories issued by the US FDA, the product labelling and the prescribing and Medication Guide for varenicline were revised. Based on the continued review of post-marketing adverse reports, they now include a boxed warning highlighting the risk of serious neuropsychiatric symptoms. These symptoms include changes in behaviour, hostility, agitation, depressed mood, suicidal thoughts and behaviour, and attempted suicide. Some of these cases may have been confounded by symptoms typically seen in people who have stopped smoking and are experiencing nicotine withdrawal [38].

A meta-analysis of the available placebo-controlled, randomised, double-blind studies found no increase in psychiatric side effects, apart from sleep disorders in patients without an existing mental illness [275]. Indeed the recent Cochrane review concludes that there is "little evidence from controlled studies of any link between varenicline and psychiatric adverse events" [38].

The clinical trials during drug development excluded patients with active psychiatric illnesses and to date, only a few controlled, randomised studies have been published on varenicline use in patients with mental illness. In a retrospective comparison of varenicline and NRT for smoking cessation performed at a routine clinic for tobacco dependence in the UK, varenicline was found to be effective in patients with mental illness. Varenicline showed better efficacy than NRT 4 weeks after quit day. Furthermore, the side effect profile of varenicline was comparable in patients with and without mental illness. In the group treated with varenicline, no exacerbation of psychiatric symptoms over the 4 weeks of treatment was reported in the patients with existing mental illness [264]. In a review, Purvis et al. conclude that for patients with mental illness, varenicline should be considered safe but that attention should be given to treatment initiation, patient education and the development of any mood or behavior changes [241]. In a recent study of varenicline, having a history of psychiatric diagnosis was not associated with worse outcome or side effects [190].

There is now quite a lot of support for the efficacy of varenicline in people with schizophrenia, from open-label studies [73,218,262] as well as case series [79] and case reports [14,87]. The strongest support comes from two recent randomized, double-blind studies [285,287]. They both indicate it is both a safe treatment for this patient group and also highly effective. Williams et al. report that at the end of treatment (12 weeks), 16/84 varenicline-treated patients (19.0%) met smoking cessation criteria vs. only 2/43 (4.7%) for placebo and this difference was still significant at 24 weeks: 10/84 (11.9%) vs. 1/43 (2.3%). Adverse event rates were similar between groups, as were schizophrenia symptoms, mood and anxiety ratings [287]. A systematic review by Cerimele et al. also found that varenicline treatment is not associated with any exacerbation of psychiatric symptoms in stable, closely monitored patients with schizophrenia [42].

Less evidence is available on the efficacy of varenicline in patients with affective or substance use disorders. In a feasibility study, varenicline treatment in three bipolar patients was well tolerated and associated with reductions in smoking [289]. McClure et al. found in the COMPASS trial that smokers with a history of depression were more likely to report common side effects associated with varenicline and/or nicotine withdrawal. However, cessation rates were similar to those published in the clinical efficacy trials for varenicline regardless of history of depression and similar mood and overall side effects were reported [189].

A double-blind, placebo-controlled smoking cessation study in heavy-drinkers found that varenicline produced a sustained decrease in alcohol consumption in addition to a significant decrease in the number of cigarettes smoked [198]. An open-label, pilot study suggests that varenicline may be an effective treatment for tobacco dependence in recovering alcohol-dependent smokers [122]. Another pilot study of cocaine using smokers maintained on methadone reported that treatment with varenicline was associated with a reduction in smoking, even though subjects received only a brief education for smoking cessation [223]. Although no adverse events related to medication were reported during these studies, large, randomised, placebo-controlled, double-blind clinical studies are needed to assess the use of varenicline in these patients.

It should be noted that in one recent study, varenicline use was associated with an increased risk of serious adverse cardiovascular events compared with placebo (odds ratio 1.72, 95% confidence interval) [260]. However, the study received plenty of criticism due to its limitations [76,231]. Furthermore, most agree that any possible risk is greatly outweighed by the benefits of smoking cessation [120]. The Cochrane review states that the incidence of cardiovascular adverse events remains inconclusive [38].

In summary, three effective first-line pharmacological agents, which have also been used successfully in some studies in patients with psychiatric comorbidity, are available for smoking cessation.

9.1.4. Adolescent population

Only a few trials have looked at smoking cessation in adolescents and none specifically in those with mental illness. Most tobacco control programmes focus on the prevention of uptake as those who do not smoke before the age of 20 are less likely to ever start. Grimshaw and Stanton's Cochrane review reports that approaches combining behavioural therapies seem

most promising [108]. They reviewed three pharmacological trials (NRT and bupropion) carried out in in adolescent smokers, and conclude they did not demonstrate effectiveness for long-term abstinence. One of these trials recruited 120 adolescent smokers who met criteria for substantial nicotine dependence [200]. Three-quarters of these participants had one or more psychiatric diagnoses, reflecting the high rate of co-occurring disorders that characterises the adolescent population of heavy smokers.

More high quality trials are needed to identify effective intervention, although this remains difficult as, for example, in the UK, NRT is the only smoking cessation medication licensed for adolescents [109]. To date, there are no published trials of varenicline for smoking cessation in adolescents.

Since the Cochrane review, one study found bupropion plus behavioural counselling efficacious, however abstinence rates were lower than those reported in adults and again, relapse tended to occur soon after the medication was discontinued [205].

9.2. Psychotherapeutic treatment - Counselling

9.2.1. Short-term treatments

Merely the simple recommendation by a physician to quit smoking significantly increases the long-term cessation rate in tobacco-dependent people [89,267] (Table 7).

The most recent US Department of Health and Human Services guideline on treating tobacco withdrawal states: "All physicians should strongly advise every patient who smokes to quit because evidence shows that physician advice to quit smoking increases abstinence rates. (Strength of Evidence = A)" [89] (p. 82). However, future studies still have to show whether this finding is transferable to psychiatric patients. Considering the large number of contacts these patients have with a physician, however, this simple procedure doubtless has a large effect on public health. Besides this brief intervention, meta-analyses show a direct relationship between the length of the physician intervention and the probability of cessation. Even minimal counselling of less than 3 minutes increases the cessation rate significantly compared with no-counselling (e.g. self-help manual only) (odds ratio 1.3 [1.01–1.6]). The cessation rate was further increased by low-intensity counselling of 3 to 10 minutes or intensive counselling of more than 10 minutes (odds ratio 1.6 [1.2–2.0] and odds ratio 2.3 [2.0–2.7], respectively). Therefore to improve cessation success, several counselling sessions should be conducted [89].

The APA recommends that psychiatrists routinely assess a patient's smoking status (e.g., current smoker, ex-smoker, never smoked, number of cigarettes per day). A procedure analogous to the so-called '4 A Intervention' is recommended for short-term interventions by physicians: (1) Ask; (2) Advise; (3) Assist; (4) Arrange. The psychiatrist should thus: (1) ask about the patient's smoking habits; (2) clearly advise the patient to quit smoking; (3) offer the patient psychological support during smoking cessation and explain pharmacological aids; and (4) arrange follow-up visits to check that the patient is still abstinent [89,168].

9.2.2. Specific treatments

The current recommendations in international guidelines on smoking cessation are based mainly on studies that excluded patients with psychiatric comorbidity. However, given the available data in this patient group (as discussed in this paper), we recommend all patients with schizophrenia, affective disorder or substance abuse disorder that are in a stable phase of their condition be treated according to the guidelines for the general population. As always, a psychiatrist must be consulted if the clinician is unsure as to the mental condition of the patient. Clinicians should not be afraid to ask patients with mental illness if they want to stop smoking and if so implement the recommendations listed below in Section 10.

A three-phase orientation, as outlined below, is common to all recommendations [1]: the preparation of smoking cessation, the cessation itself and the stabilisation of smoke-free behaviour. For all three phases of smoking cessation, specific intervention techniques are available as part of a multi-modal procedure. The programme components such as motivation analysis, skills training and relapse prevention should be considered and operationalised [1,89]. Just like behaviour-therapy treatments in the stricter sense, the programme must comply with the treatment phases of relationship-shaping, definition of the treatment goal and the actual training phase.

9.2.2.1. Preparation phase. As tobacco dependence is a chronic relapsing disorder and most smokers require 5 to 7 attempts before they finally quit for good [136], a therapeutic alliance is required so that even after unsuccessful cessation attempts the patient remains in contact with the treating psychiatrist and continues treatment. The clarification perspective is also important; the patient should hereby become aware of abstinence as the treatment goal and of his or her own motivational state. The smoker's ambivalence can be expressed and strengthened by listing the advantages of smoking and not smoking. First, arguments in favour of smoking are collected, then arguments in favour of not smoking. Getting the participant to consciously decide on the goal of abstinence and collect arguments supporting this decision should resolve any resulting unpleasant cognitive dissonance [1].

Psychoeducational elements serve to transfer knowledge so that the patient can gradually develop an illness model of his or her tobacco dependence. A further component of the preparation phase is the diagnostics of the tobacco dependence and smoking behaviour. The diagnosis of tobacco dependence is confirmed by the FTND; the sum score allows conclusions to be drawn about the patient's physical tobacco dependence. Self-observation procedures can be used for the diagnostics of smoking behaviour. These procedures include the completion of registration cards for a week and keeping a simple running tally. The aim in every case is that the smoker observes his or her own smoking behaviour, interrupts the mechanism of automatic smoking and smokes consciously again.

9.2.2.2. Smoking cessation. The aim of the second phase is to cease smoking and achieve abstinence. The necessary preparations have to be made for the day when the participant ceases to smoke. In the abrupt cessation method, a so-called 'quit day' is set and smoking behaviour is changed from one day to the next. The participant stops smoking on quit day, regardless of the number of cigarettes previously smoked per day. The patient is carefully prepared for quit day, and the actual quit day is planned in detail. Differentiated skills training should give the participant sufficient competency

Table 7
Effectiveness of and estimated abstinence rates for advice to quit by physician: results of a meta-analysis ($n = 7$ studies) [89].

Advice	Number of arms	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
No advice to quit (reference group)	9	1.0	7.9
Physician advice to quit	10	1.3 (1.1–1.6)	10.2 (8.5–12.0)

and confidence in his or her ability to quit. To achieve this, the cues and situations associated with smoking are identified and analysed and the patient is advised to avoid possible critical situations on this day; the patient is taught suitable alternative strategies for dealing with such cues and situations if they cannot be avoided.

The 'quit day' approach is the standard way to try to stop smoking. However, if this method is unsuccessful, patients may also gradually reduce the number of cigarettes smoked a day over a longer time period [138]. A recent meta-analysis found a comparable abstinence effect between quitting abruptly and reducing the number of cigarettes smoked a day before the quit day [182]. Thus, both methods can be recommended. For special patient groups, e.g. schizophrenia patients, the reduction of cigarette consumption may be useful at first as an intermediate goal [265] – see Section 10.3.

Smokers who are unable or unwilling to set a fixed quit date may accept a flexible approach. Allowing smokers to start treatment without setting a fixed quit date and to choose the day to quit (between day 8 and 35) was shown to be equally effective [148,244]. This approach may make quitting more appealing to some patients.

9.2.2.3. Stabilisation. The aim of the third phase is to maintain stable abstinence and prevent relapses. One component of relapse prevention is how to deal with lapses and relapses [187,220]. According to the relapse model, the most constructive way for someone to deal with a lapse is to identify the conditions and situations that make it more difficult to remain abstinent [186,187]. An important strategy in relapse prevention is firstly to change the dichotomous thinking about lapses so that they do not become complete relapses into earlier consumption patterns. Lapses can represent a good opportunity to explore, understand and learn from the mechanisms that result in a relapse. It is important to avoid so-called relapse shock, which mainly consists of making a drama and catastrophe of a one-off smoking occurrence, i.e. a lapse [187]. Additional important components of psychotherapeutic relapse prevention include stimulus control (e.g. the removal of smoking tools and the avoidance of typical activities that were otherwise associated with smoking), rehearsing coping strategies (practising alternative behaviour and identifying and addressing potential difficulties) as well as the use of operand learning in the form of reward and self-strengthening [1].

Evidence-based cessation programmes include the above-mentioned components. Many different formal smoking cessation programmes exist and include individual counselling, telephone counselling and group programmes, mostly in combination with pharmacotherapy [130,234,277]. However, there is an urgent need for research on further treatment programmes designed specifically for mental health patients or psychiatric diagnosis groups. The establishment of smoke-free hospitals and wards is also part of an integrated concept of nicotine withdrawal [258]. For example, a five-session, behavioral, group-oriented smoking reduction intervention can significantly reduce the number of cigarettes smoked in hospitalized chronic clients with schizophrenia [95]. Programs for smokers with schizophrenia should focus on teaching coping skills for negative affect, boredom, and specific "high risk situations" for smoking alongside education and pharmacological therapy. Addressing low self-efficacy for quitting, rather than readiness for change alone, benefits people with schizophrenia [185].

In a randomised trial, NRT combined with hypnosis significantly improved long-term abstinence compared to NRT with behavioural therapy. Hypnosis combined with NRT was particularly beneficial for participants with a history of depression [39]. A few small studies have supported the efficacy and feasibility of contingency management intervention for reducing smoking in schizophrenia [273] and substance use disorder patients [4,72].

A meta-analysis on the easy-to-learn, psychotherapeutic technique of 'motivational interviewing' [196,197] showed that shorter, even one-time interventions with this technique, e.g. by general practitioners, result in higher cessation rates than standard advice or self-help [124,174]. Further studies are needed to evaluate whether motivational interviewing is similarly effective for nicotine withdrawal in psychiatric patients.

After successful smoking cessation in psychiatric patients, particular attention should be paid in the further course of treatment to additional cardiovascular risk factors (e.g. weight, blood fats, development of diabetes) and respective steps taken if necessary [60,61]. For example, there are indications that this patient group has an increased short-term risk for developing diabetes mellitus, which is probably due to uncontrolled weight gain [290].

Therapeutic drug monitoring should be performed and the dose of psychopharmacological treatment adjusted if necessary (e.g. clozapine) [51].

10. Practical recommendations for interventions in tobacco dependence in mentally ill patients

The general interventions described below are based on the currently available guidelines [7,8,12,89], whereby not all recommendations are fully validated for mentally ill patients.

The EPA recommends the following interventions for all patients with mental illness who smoke.

10.1. Record the smoking status

Smoking status should be evaluated and documented for every psychiatric patient and the degree of dependence should be documented (preferentially with the FTND).

As described above, the FTND is widely used in treatment studies and can supply useful information about the degree of dependence. It also allows patients to be identified who may benefit from high-dose NRT treatment [84,225,270]. If the clinical treatment setting makes it unfeasible to use this test, at least two of its items (namely the time when the first cigarette is smoked in the morning and the number of cigarettes smoked daily) should be recorded because these parameters also correlate with the degree of nicotine dependence [224]. The patient should also be asked about previous cessation attempts and possible drug treatment attempts.

10.2. Set the time of the intervention

Is there an acute contraindication to cessation of tobacco use or are there psychiatric reasons why the cessation should be postponed?

The best time for cessation would be when the patient is in a stable phase, with no recent or planned changes in medications and no urgent problems take precedence [8,142]. Because little is known so far about the treatment of patients with acute mental illness, the following questions, as specified in the APA treatment guidelines, should be considered before deciding on treatment [8] (p. 73–74): "*Are there any psychiatric reasons for concern about whether this is the best time for cessation? Is the patient about to undergo a new therapy? Is the patient presently in crisis? Is there a problem that is so pressing that time is better spent on this problem than on cessation of tobacco use? What is the likelihood that cessation would worsen the non-nicotine-related psychiatric disorder? Are there any signs or symptoms of other undiagnosed psychiatric or substance*

use disorders that might interfere with efforts to quit tobacco use?" It is important that the consequences of tobacco dependence are clearly explained and that the information on the treatment process is given in detail, allowing the patient to actively participate [23].

Cessation of tobacco use is recommended in substance-dependent patients who are admitted to hospital for withdrawal from a different substance, e.g. alcohol [183,234]. In any case, the diagnosis of tobacco dependence should be among the documented treatment goals being strived for, so that withdrawal treatment can be performed at least at a later date.

10.3. Give counselling

At least a minimum amount of counselling should be performed (psychoeducation, formation of a therapeutic alliance, clinician advice, setting a quit day, additional help).

As mentioned above, a procedure analogous to the so-called '4 A Intervention' is recommended for the short-term intervention by physicians. Many patients do not realise that tobacco dependence is a chronic disorder that usually requires several cessation attempts before complete abstinence is achieved [8,89]. Previous cessation attempts should therefore be discussed in this context, the patient should realise that relapses are not a catastrophe and a therapeutic alliance should be formed [230].

It is particularly important to prepare patients for what can be expected in terms of withdrawal as patients with SMI show more frequent and severe withdrawal symptoms after quitting smoking [141,220]. It is also important to explain that smoking actually increases anxiety and tension. The feeling of relaxation is temporary and soon gives way to withdrawal symptoms and increased cravings, which are similar to the feelings of anxiety [221]. Furthermore, discussing alternative ways to cope with stressful situations and anxious feelings that may arise could improve outcome in these patients.

Clinician advice to discontinue smoking is best given in a non-judgmental, empathic and supportive manner [89]. A quit day should be set or gradual reduction of tobacco consumption could be proposed as an alternative approach [138], especially as this method was recently found to have a comparable abstinence effect to quitting abruptly [182]. Thus, both methods can be recommended.

To increase the quit rate, established programmes (individual therapy, group therapy, telephone coaching) should be employed wherever available [89].

10.4. Offer drug treatment with a first-line product

Drug treatment with a first-line product (NRT, varenicline, bupropion) should be given for even a mild degree of tobacco dependence. Attention must hereby be paid to the severity of tobacco dependence and possible psychiatric side effects and interactions as well as contraindications. Patients should be informed about side effects and the correct use of the drug.

10.5. Contact within first days after quit day

Because the risk of relapse is highest within the first days after stopping smoking, renewed contact (either in person or by telephone) is recommended [111,186,187]. Withdrawal symptoms and drug side effects should be discussed and the drug dose adjusted, if necessary. Any change in the psychopathological picture since smoking cessation should be recorded. Therapeutic drug monitoring is recommended because of the altered enzymatic situation.

10.6. Perform follow-up visits

Almost all studies show that follow-up visits after quit day increase the quit rate; these follow-ups can also be conducted by telephone [8,89]. A patient's mental status should also be monitored. Therapeutic drug monitoring should be performed and the dose of psychopharmacological treatment adjusted if necessary (e.g. clozapine) [51]. Because psychiatric patients generally have a higher risk for weight gain and diabetes, weight and additional cardiovascular risk factors should be checked at follow-up visits and respective measures taken if necessary [60].

10.7. Relapse prevention and management

The patient should be made aware that lapses and relapses are not catastrophes, and a new attempt with different procedures (e.g. psychotherapy, medication) should be discussed with the patient.

Because tobacco dependence is a chronic disorder, lapses and relapses are rather the rules than the exceptions on the path to becoming smoke free. It is important to differentiate between a 'lapse' and 'relapse' [186,187]. Lapses are important experiences that can supply valuable information about further relapse risk and should be discussed with the patient.

Physicians should bear in mind that failed quit attempts have been associated with an increase in depression, anxiety or suicide ideation and that persisting with a quit attempt while unable to achieve abstinence may be associated with mood deterioration [28]. Incorporating expectancies into cognitive-behavioral treatments for smoking cessation may be useful for smokers with a history of depression [284].

11. Summary and conclusion

Tobacco dependence is more prevalent in mentally ill patients than in patients without a mental illness, as many psychiatric disorders are risk factors for tobacco dependence and tobacco dependence is a potential risk factor for some psychiatric disorders. Indeed, the level of dependence seems to be more severe in schizophrenia, other types of addiction or depressive disorder. Nevertheless, mentally ill patients also have motivation to quit smoking, and interventions can be performed in this patient group. Since tobacco dependence is a dependence disorder, psychiatrists are the experts in performing interventions in this area. It is their duty to do so in view of the major impact of tobacco dependence on, for example, the metabolism of psychotropic treatments, morbidity (such as lung cancer) and mortality.

Because of the high prevalence of tobacco dependence among mentally ill patients and the enormous individual suffering it causes, and also because of the high socioeconomic impact of this disorder, it should be ensured that the therapeutic interventions and drug treatment are paid for by the healthcare system.

Psychiatrists and primary care physicians should be given training in tobacco dependence, and the treatment of tobacco dependence should be incorporated into the catalogue of disorders to be studied during specialist training in psychiatry.

The introduction of smoking bans in psychiatric hospitals results in much better protection of staff and fellow patients against the dangers of second-hand smoke. Smoking bans have been shown to be an effective step towards quitting smoking also for staff and patients on psychiatric wards and in hospitals [137,214,258]. Further education and training on this topic are required to dispel uncertainties on the part of hospital staff and to increase their confidence and certainty when addressing patients who smoke.

In addition to the education of physicians and medical personnel, structured tobacco withdrawal programmes that are better tailored to the special characteristics of patients with mental illness need to be developed and implemented through future research. In this context, the approach of harm reduction or 'reduce to quit' approaches should be considered.

Psychiatrists have access to the infrastructure and staff that enable them to offer their smoking patients a way out of their deadly tobacco dependence. However, this requires that the high relevance of this issue and its position in everyday clinical practice are recognised and that respective action is taken.

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