Comorbidity of Smoking with Psychiatric Disorders

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Contents

Abstract

Indications for comorbidity of smoking with psychiatric disorders have been derived from numerous epidemiological studies. This suggests either an involvement of smoking in the development of psychiatric diseases or the importance of smoking as a habit and the neurobiological effects of nicotine in the context of coping strategies for the psychiatric disorders. Neurobiological and genetic research focuses on the cerebral transmitter function including the serotonergic, dopaminergic, and noradrenergic system and cholinergic transmission. Moreover, effects of smoking on medication might motivate medicated psychiatric patients to practice smoking as a form of self-medication.

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This chapter will also discuss the need for an intense psychotherapy and when necessary pharmacotherapeutic support in smokers with a psychiatric comorbidity.

20.1 Introduction

The significance of nicotine or tobacco consumption in correlation with mental disorders is obvious but still not completely clarified up to now.

Numerous epidemiological studies confirm consistently increased smoking prevalence rates among patients with mental disorders. This is most outspoken in the context of other substance use disorders, e.g., alcohol or drug dependence, but also in patients suffering from schizophrenia and depressive disorders (overview in Batra 2000; Rüther et al. 2014). Inversely, smokers and especially heavy smokers show increased rates of psychopathological disorders and psychological disturbances (Lasser et al. 2000). Within clinical populations, comorbidity prevalences are even higher than within general population samples. Patients with substance use disorders (SUDs) in a therapeutic setting show up to four times higher rates of tobacco smoking than age-matched controls in the general population (Cole et al. 2012). Overall, this high prevalence of smoking in patients with psychiatric disorders is associated with a substantial increase of risks for morbidity and premature death (Bobes et al. 2010; Colton and Manderscheid 2006).

Presumed causes for this high comorbidity may be found in a common biological disposition by a concordant influence of the endogenous self-rewarding system, increased affective irritation, avolition, or a need for dopaminergic stimulation, which is related to pathological neurobiological patterns in subjects with psychiatric disorders. In this line of thinking, a (common) genetic background might also account for both the psychiatric diseases and the intensive smoking behavior as well (Batra 2005; Bauer et al. 2007). The high comorbidity between smoking behavior and numerous mental disorders can be, at least partly, explained by the quasi-therapeutic chemical function of both nicotine as a single substance and many other chemicals released in the process of tobacco smoking. The discussion on possible positive effects on the mental abnormalities or symptoms (e.g., enhance cognition and mood) via a therapeutic nicotine supply (e.g., via a transdermal application, administration of nicotine gums or nicotine tablets), however, is still not concluded.

Within the general population, due to prevention campaigns and most importantly more severe regulations the prevalence of smoking has decreased substantially. This effect has not been found within individuals suffering from psychiatric disorders. Indeed, tobacco consumption decrease turns out to be significantly lower in patients with mental disorders compared to the general population during the last couple of years. It is assumed (Lê Cook et al. 2014) that the corresponding prevention policy does not reach this target group sufficiently. Smoking initiation

invariably occurs within the period of adolescence. Many youngsters experiment, but many of them stop smoking after a short time. This seems to be much harder for adolescents with mental disorders and/or alcohol and drug dependence, who are especially vulnerable for continued tobacco consumption.

Overall, therapeutic approaches ("smoking cessation therapy") aiming at achieving abstinence or reduction of smoking have shown only very moderate to low effect sizes when treating nicotine-dependent patients. . Importantly, results of smoking cessation programs seem to have even less effect in patients with psychiatric comorbidities. One of the reasons might be that the occurrence of withdrawal symptoms, intensifying many psychiatric symptoms, makes a tobacco detoxification especially difficult among people with mental disabilities or mental disorders (Smith et al. 2014).

Thus, taken together, given the high prevalence, the outspoken negative consequences, and the low effect sizes of the current treatments, it seems reasonable to adapt treatment strategies to special needs of individual mental clinical pictures and the persons involved (Batra et al. 2010; Thornton et al. 2012).

20.2 Nicotine Has Short-Term and Long-Term Influences on Mental States

Nicotine stimulates numerous biological systems in the brain and one of its effects is an increase of the dopamine concentration. Subjectively this is associated with a feeling of well-being or pleasure. Additionally via noradrenaline, smoking stimulates and improves the vigilance, and also reduces the sensation of hunger. The stimulation of acetylcholine receptors by nicotine leads to an enhancement of cognitive functions. The cognitive enhancing effect of smoking is also attributed to nicotine's effect on vasopressin. The direct stimulation of the serotonergic system is correlated with a positive impact on anxiety, depressive effects, or the sensation of hunger. Finally, also the beta-endorphin system is supposed to be responsible for a reduction of anxiety or tension and is stimulated by nicotine. Relaxation, overcoming boredom, and increased activity but also social-communicative effects of collective smoking, the legitimation of a break, die influence of moods, stimulation and cognitive functions can offer certain advantages of nicotine consumption for patients with mental disorders and thus encourage smoking. The reduction of stress feelings influencing these different mental qualities is connected with the subjective mental state.

The withdrawal symptoms of nicotine are often very similar to some distressing symptoms associated with mental disorders. A lack in nicotine leads to dysphoria, anxiety, depressive moods, diminished experiencing of pleasure and delight, irritability, sleeping disorders, changes in drive, or attentional problems (Hughes et al. 2006; Jähne et al. 2012). By confusing nicotine withdrawal symptoms with mental symptoms associated with mental disorders, due to the similarity of these symptoms, people with mental illnesses are reluctant, much more than any other smoker, to reduce unpleasant sensations by nicotine consumption.

Therefore depressive and anxious individuals but also people with emotional instability resulting in a lower frustration tolerance and increased stress intolerance are especially at risk of continuing tobacco use. Also for individuals withdrawing from other substances, the overlapping symptomatology with nicotine withdrawal symptoms also stimulates a continuation or often an intensification of smoking behavior. Following we will give a differentiated explanation for the comorbidity connected with smoking for each clinical picture.

Regardless of the positive effects for many people with mental problems via the intake of nicotine, i.e., smoking, it has to be taken into account that the intensity of smoking as performed by patients with mental disorders is correlated with an enormous health risk. The excess mortality among schizophrenic patients is estimated by nearly 20 years. This is due to the interaction of tobacco and many other concomitants, e.g., inactivity, medications, and many others. Therefore each smoker, with or without other mental illnesses, should be advised to quit tobacco consumption and offered appropriate treatment interventions (Taylor et al. 2014). Indeed, reducing or abstaining from smoking does not have only major health benefits, but can also positively impact psychological functioning. Tobacco detoxification is associated with reduced depressiveness, anxiety, stress, and improved positive moods all associated with improvement of life quality compared to constant smoking. This holds true for persons both with and without mental disorders. The effect sizes are even larger than the traditional pharmaceutical treatment of anxiety disorders or depressive disorders. This important finding has recently been documented by Taylor and colleagues (2014) on the basis of 26 studies assessed within the scope of a meta-analysis.

Following a short overview on the most important findings on relation of smoking with different psychiatric disorders, specifically those highly associated with smoking, will be given.

20.3 Affective Disorders

Depressive disorders of all types and smoking behavior are closely linked together. The increases in these comorbidities' prevalence go both ways. Within samples of smoking individuals, the probability to suffer from depressive disorders is increased about factor 2 compared to the nonsmoking population (Boden et al. 2010, Rüther et al. 2014). Inversely, numerous epidemiological studies document a high prevalence of smokers among depressive patients (Batra 2000). Female adolescents with depressive disorders or anxiety disorders smoke double as much as healthy individuals (Romans et al. 1993). Additionally, daily number of cigarettes is increased specifically during acute depressive disorders (Breslau et al. 1993).

The causal pathways explaining this comorbidity are complex. Some prospective studies on this subject did not lead to any clarification on the causation even though there are some indications that adolescents, who start nicotine consumption before 20 years, will have a higher risk of developing anxiety disorders or depressive disorders later on in life (Ajdacic-Gross et al. 2009). However, this could also

be an effect of a selection of children and adolescents with increased anxiety symptoms, a higher disposition for risky behavior, or other psychological disturbances, which initially in an unspecific way find expression through substance consumption, but which might also have occurred without nicotine consumption.

Despite numerous studies on the comorbidity between affective disorders and addictive smokers the causes could not be definitely clarified. Many hypotheses are suggested. Some authors assume that smoking supports the development of anxiety disorders and depression via intrinsic aversively perceived psychological stimuli. Bonevski and colleagues (2014) also emphasize the correlation between the socio-economic status, depression, and smoking behavior. Finally, in a study on 227 traumatized smokers with posttraumatic stress disorders and addictive disorders, Hruska and colleagues (2014) could show that the patient's expectations concerning smoking effects reflect a modulation of the negative affect. This group of patients displays higher expectations on beneficial effects of smoking, which should be taken into account concerning efforts for smoking cessations.

Additionally it is assumed that the reduced capability of many depressive patients to achieve smoking cessation could be responsible for the increased smoker prevalence. The expectation of reaching abstinence among depressive smokers only amounts to about 50 % than that of psychologically healthy smokers (Stage et al. 1996; Batra et al. 2008). A common genetic basis associated with underlying abnormalities in the serotonergic transmission has also been suggested as a likely hypothesis explaining the smoking–depression association (Brody et al. 2005; Tsuang et al. 2012).

Clinical observations indicate that nicotine has positive effects on the mental state of depressive patients. Some earlier investigations already suggested a lower concentration and activity of the monoamine oxidase in the thrombocytes of smokers, which can lead to a reduced depletion of monoaminergic neurotransmitters and thus to increased availability of the neurotransmitter serotonin. The neurochemical effect of nicotine to modulate the serotonergic system and its associated anti-depressive effects led to the conclusion that smoking could serve as a form of self-medication. This hypothesis is supported by an inhibition of the monoamine oxidase in smokers. The central inhibition of the monoamine oxidase (MAO)-B, around 40 % in smokers compared to nonsmokers or ex-smokers, initially reported by Fowler and colleagues (1996) can, however, not be assumed as a pure nicotine-mediated effect but rather be attributed to other tobacco smoke ingredients. This effect cannot be elicited by one-time smoking, so that it must be assumed that an anti-depressive effect mediated by the inhibition of the monoaminase oxidase only occurs following chronic cigarette consumption (Fowler et al. 1999).

The MAO-B concentration in thrombocytes correlates with thiocyanate, an ingredient of tobacco smoke and cotinine (Berlin et al. 2000). In both cases the intensity of tobacco consumption, i.e., inhalation of the different tobacco ingredients is reproduced. The number of daily consumed cigarettes probably does, however, not correlate with the reduction of the peripheral MAO-B activity, which is probably associated with inter-individually different inhalation habits (Berlin et al. 2000).

Studies on genetics of smokers and depression still are highly interesting, even if clear evidence for an important impact of single genes is lacking (Tsuang et al. 2012). The question if smoking is specifically correlated with a genetic predisposition for mental disorders could not be clearly evidenced up to now. Various publications deal with this subject (Chen et al. 2012) but could not show a clear connection for individual subforms of candidate genes with mental disorders in interaction with tobacco consumption.

The therapeutic approach using antidepressants in smoking cessation did, however, not lead to any significant results. Tricyclic antidepressants (doxepine or nortriptyline), monoamine oxidase inhibitors (moclobemide), serotonin reuptake inhibitors (various SSRIs, e.g., fluoxetine), as well as the atypical anxiolytic buspirone were applied without any success, i.e., without any indications for a significant superiority over to the established compounds in smoking cessation studies (e.g., nicotine patches, varinecline). Only bupropion, a selective low noradrenaline and dopamine reuptake inhibitor, was approved for smoking cessation due to convincing study results (Jorenby et al. 1999). In later studies, however, the superiority of the new substance does not emerge as clearly as suggested earlier. It has to be assumed that the positive effect was probably initially also caused by expectancy effects. Only future studies will be able to show if a smoking cessation treatment with bupropion will really be more successful than a treatment with nortriptyline or other antidepressants and if the therapy will especially be more successful than the administration of nicotine-substitute compounds). A recent Cochrane review favors individualized behavioral support for depressed patients (van der Meer et al. 2013).

20.4 Schizophrenia and Psychotic Disorders

More recent studies confirm the very high prevalence of tobacco consumption in patients with schizophrenic psychoses. In an Australian investigation, Cooper and colleagues (2012) found that 66.6 % of schizophrenic patients were smoking, and 81 % had already smoked in the course of their lives. The probability for tobacco consumption is especially high in cases, where the disorder started early and patients had a low education level. Male patients smoke more frequently than female. Especially with negative symptoms smoking seems to be of major importance. Sankaranarayanan and colleagues (2014) found data on increased smoking and suicidality in patients with a psychotic disorder indicating the relevance of smoking as an important risk factor for suicidal behaviors.

On the other hand schizophrenic patients seem to benefit from nicotine in many ways. Besides the hepatic enzyme induction mediated by different tobacco ingredients followed by an accelerated decrease of different neuroleptics some positive effects can be attributed to nicotine effects (Wing et al 2012).

Of importance, cognitive impairments, resulting from the administration of neuroleptics, could be improved by nicotine (Levin et al. 1996). Furthermore, an increase in energy with a prevailing negative symptomatology is described, which

might be correlated with dopaminergic stimulation mainly in the prefrontal cortex (McEvoy et al. 1995). Another hypothesis suggests a nicotine-mediated inhibition of an affective psychotic over-excitement. Finally the dopaminergic effect of nicotine against the neuroleptics-induced Parkinsonism increases the disposition to uptake high doses of nicotine.

Furthermore, schizophrenic patients show a neuropsychological deficit described as "filter impairment," i.e., a lacking the ability to separate relevant from irrelevant information. Patients with schizophrenic disorders do not habituate to this stimulation after a temporarily repeated presentation of a stimulus. Nicotine has the "therapeutic feature" to intensify the adaptation performance to acoustic stimuli in the animal model and in smoking and nonsmoking individuals (Kumari et al. 1997). This result can be explained by the "latent inhibition": "Latent inhibition defines the physiological blinding out of irrelevant stimuli by a delayed adaptation of the neuronal information-processing system. An impaired "latent inhibition" in the animal model can be regulated by low doses of nicotine (1.5 mg/kg). This result can also be replicated in the human model (Thornton et al. 1996).

Interestingly, schizophrenic patients as well as some of their relatives also show an impairment of a "latent inhibition," which can be regulated temporarily by nicotine intake, e.g., nicotine gums (Stevens et al. 1995). The impairment of a "latent inhibition" correlates with a polymorphism in the gene of the alpha7-acetylcholine receptor protein, so that a connection with the cholinergic receptor system might be possible. Although a correlation with schizophrenia can be observed, this result is rather related to the vulnerability for a psychotic experience than with the intensity of the psychopathology. It can also be found in healthy individuals, showing a predisposition for psychotic reactions. The impairment of a "latent inhibition" is not specific for schizophrenia or psychotic experiences but can also be determined in manic patients and healthy individuals under stress.

To what extent this will have an impact on smokers remains controversial. While Allan and colleagues (1995) found a less distinct "latent inhibition" in smokers than in nonsmokers, other authors could not replicate these findings (Thornton et al. 1996). Despite the fact that our own investigation could confirm that schizophrenic patients experience a regulation of their delayed adaptation performance to irrelevant stimuli after supply of nicotine, differences between strong smokers and nonsmoking control probands could not be demonstrated. In a classically experimental investigation we presented klick noises 30 dB and 50 dB to probands via headphones above the hearing threshold level. Within 50 ms the EEG records a positive wave (p50) above the lead location CZ. After repeated presentation the amplitude of the p50 was reduced in nonsmokers as well as in strong smokers but not in schizophrenic patients. Only after nicotine supply via cigarettes schizophrenic patients showed a significantly improved and regulated habituation performance. These findings might be correlated with some more genetic associations of schizophrenic symptoms and the intensity of smoking (deLeon and Diaz 2012).

Therapeutic interventions should be offered after stabilization of the patient; medical supply, first of all nicotine replacement, is recommended (Tsoi et al. 2013).

20.5 Alcohol or Drug Dependence

Many hypotheses explaining the high coincidence of alcohol, drug, and tobacco consumption exist, e.g., favoring environmental conditions, milieu, or leisure behavior, during which both substances are normally consumed and the associated availability of both substances is supposed to be responsible. Additionally, addictive effects in connection with an increased positive reinforcing process by a simultaneous effect on the dopaminergic system or a general, partly genetically determined vulnerability for risky behavior, which among others is correlated with increased consumption of addictive substances, are assumed to be a possible cause.

Furthermore, it is reported that a coincident consumption of tobacco, nicotine, and alcohol might partly compensate alcohol-related impairments of cognitive performances. Especially alcohol-related impairments of the perception and reaction ability are supposed to decrease by coincident nicotine stimulation (Batra and Buchkremer 2001). Gould and colleagues (2001), for instance, investigated the effect of a combined administration of alcohol and nicotine in the animal model and confirmed a positive effect of nicotine on alcohol-associated disorders of the "latent inhibition" in alcohol-dependent smokers. The concurrent intake of nicotine and alcohol reversed the alcohol-associated suppression of the inhibition. Presumably a stimulation of neuronal nicotinergic acetylcholine receptors with the consecutive activation of further transmitter systems might be crucial.

Nevertheless alcoholic patients are interested in tobacco abstinence as well and are rather successful in smoking cessation (Batra et al. 2011).

20.6 Neurodegenerative and Other Disorders

For the association of nicotine and the Parkinson's disease and a dementia of the Alzheimer's type contradictive results exist. Nonsmokers carry double the risk for both diseases according to former investigations. Therefore it was assumed previously that smoking would have a direct protective effect on the development of the Alzheimer's disease. Although findings in the literature earlier suggested that smokers would be protected against the development of a Parkinson's disease, more recent studies claim that the observed relative risk of about 0.4 could only be explained by the excess mortality of smokers (Morens et al. 1995). Acetylcholine receptors are located on dopaminergic cells in the substantia nigra pars compacta. Since about one-third of all striatal nicotine receptors are connected with dopaminergic structures, a stimulation of the presynaptic nicotinergic acetylcholine receptors on the dopaminergic neurons also leads to increased central dopamine release. Therefore it might be presumed that this connection of nicotinergic acetylcholine receptors and dopaminergic tracts is the basis for mild improvements in the results, experienced by Parkinson's patients after experimental nicotine intake.

It is also discussed that patients with a disposition for a Parkinson's disease are less responsive for reinforcing nicotine effects. This would mean that the

predisposition for developing the Parkinson's disease would have protective effects concerning the development of nicotine dependence. The lower incidence of the Parkinson's disease among smokers could, however, also be explained by an inhibition of the monoamino oxidase B observed in smokers and with an associated increase of dopamine (Berlin et al. 1997). Prasad and colleagues (1994) finally reported on a retardation of the natural age-related reduction of nigrostriatal dopamine-D1 and D2 receptors. Yet it is unclear whether this possible neuroprotective influence of nicotine is correlated with the lower probability for the Parkinson's disease.

The discussion on the possible protective effects of nicotine against the Alzheimer's disease still continues. Twin studies suggested a reduced risk for the development of the Alzheimer's dementia in smokers (Plassman et al. 1995). A possible explanation could be seen in the nicotine-mediated neuroadaptation in terms of an amplification of nicotinergic acetylcholine receptors. An induction of the synthesis of the Nerve Growth Factor (NGF) and the NGF receptors and an increase of the cerebral blood flow, which could be effective neuroprotectively, are also being discussed. Regardless of this hypothesis some indications of a slight improvement of cognitive functions in patients with Alzheimer's disease after intake of nicotine exist.

More recent prospective studies, however, lead to doubts about the statement that smokers dispose of a lesser risk for developing a dementia of the Alzheimer's disease type. Instead more recent publications discuss the exact opposite. Some earlier studies lead to the assumption that smokers provide a higher risk for the development of dementia disease, especially of the Alzheimer's type (Almeida et al. 2000). These new results challenge the existing investigations based on other methodological approaches (retrospective case–control studies or randomized group comparisons). A final conclusion, however, cannot be made, yet the existing approach postulating a protective effect of nicotine intake for the development of neurodegenerative diseases should be relativized carefully.

In cases of the Gilles de la Tourette syndrome nicotine also showed some therapeutic effects. After intake of transdermal nicotine the frequency of motoric and linguistic tics lessened. This effect still continues after discontinuation of the therapeutically administered nicotine or nicotine chewing gum for a certain time.

Concerning ADHD high smoking prevalences are found in both adolescents and adult ADHD populations (Matthies et al. 2013). An association with a dopaminergic neurotransmission and smoking could be shown. In this case, the immediate effect on the dopaminergic disorder could probably be the correlation to intensive tobacco consumption.

20.7 Smoking and Psychopharmacological Medications

Many patients with psychiatric and addictive disorders receive some form of pharmacotherapy during their treatment. Their smoking status can have a significant effect on their medication. Ingredients of tobacco smoke induce metabolism of

many psychopharmaceutical drugs. The turnover of antidepressants (e.g., tricyclic antidepressants like amitriptyline, clomipramine, serotonin reuptake inhibitors (SSRIs) like fluvoxamine or sertraline, and serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine) and antipsychotics (e.g., butyrophenones, phenothiazines, and—most important—clozapine, olanzapine, and quetiapine) is influenced and in most cases enhanced by induced activation of the cytochrome P450 isoforms. As a result, blood levels of these medications are decreased as a consequence of smoking. So, smokers receive higher daily dosages to obtain the same therapeutic effect as nonsmokers get with lower dosing (e.g., more than 50 % higher clozapine doses) (Cormac et al. 2010). However, these higher dosings result in increased rates of many adverse effects (e.g., tardive dyskinesia) including the risk of toxic serum levels after quitting smoking. Therefore, a ttherapeutic drug monitoring and adjustment of psychopharmacological treatment dosages is mandatory as soon as smoking is significantly reduced or terminated (Lowe and Ackman 2010).

20.8 Practical Recommendations for Interventions in Tobacco Dependence in Mentally Ill

It is of utmost importance that every patient with psychiatric disorders, as part of the therapeutic standard workout, should be screened on and offered the possibility of treatment for smoking cessation. Treatment of tobacco dependence in mentally ill smokers should follow the general recommendations as described in the available guidelines for non-mentally ill smokers. These are summarized and modified for treatment of psychiatric patients in the "European Psychiatric Association (EPA)

Table 20.1 EPA guidance on tobacco dependence and strategies for smoking cessation in people with mental illness (Rüther et al. 2014): Main suggestions

1. Smoking status should be evaluated and documented for every psychiatric patient and the degree of dependence should be documented (preferentially with the Fagerstrom Test for Nicotine Dependence, FTND)
2. As soon as the patient with any psychiatric disorder, excepting a substance-related disorder, is in a stable phase, i.e., with no recent or planned changes in medications and no urgent problems, consequences of tobacco dependence are to be explained and the patient should be actively motivated to quit smoking. Substance-dependent inpatients should be motivated as an integral part of their withdrawal treatment
3. A minimum amount of counseling on smoking cessation should be performed
4. Taking into account the possible side effects and contraindications in the therapeutic decision-making, suggestions to use nicotine replacement therapy, varenicline, or bupropion should be part of the interventions offered
5. In order to minimize relapse rates a contact within the first days after a quit day should be offered for motivational support and supervision of medical treatment
6. Follow-up visits should be arranged in order to increase long-term abstinence rates

Besides relapse prevention (follow-up visits, medication, behavioral techniques) the patients should always be motivated for another quit attempt in case of a relapse

recommendations" (Rüther et al. 2014). Main suggestions of this European Guidance paper are summarized in Table 20.1.

20.9 Summary

A variety of psychiatric and neuropsychiatric disorders are associated with an increased smoking prevalence. The interaction between psychiatric disorders and smoking behavior remains complex and largely unknown. However, one of the key factors is the neurochemical properties of nicotine and in second order the many chemicals released during tobacco smoking. In addition to its highly addictive properties, nicotine can have protective effects in cases of neurological or psychiatric clinical pictures (neurodegenerative disorders), a quasi-therapeutic effect (schizophrenia and affective disorders), or a reinforcing function as desired by patients (other substance disorders). The underlying neurochemical bases of the desired and positive effects are the direct cholinergic or secondary dopaminergic, serotonergic, and noradrenergic effects of nicotine intake.

The causal coherences are of great interest for the understanding of the etiopathogenesis of neuropsychiatric clinical pictures. Also regarding possible therapeutic implications for neurodegenerative diseases and the development of new approaches in the treatment of addictions the research in this field is of major importance.

The presumed positive effects of nicotine are however largely overshadowed by the enormous negative impact of smoking (associated with the inhalation of more than 4,000 chemicals) on the health, morbidity, and mortality of patients with psychiatric disorders. These negative effects and the high prevalences of smoking should motivate the implementation of smoking cessation programs in every mental health care facility.

Finally it has to be taken into account that the obvious significance of the factor "smoking" for the mental state and the cognitive performance as well as the effect of medications has been underestimated in the past. Many investigations on psychiatric and neurological clinical pictures neglect the effects of smoking unreasonably and thus do not describe disorder-specific effects of certain psychotropic drugs but rather show pseudo-correlations caused by smoking or nicotine intake!

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