Continuing Professional Development

MODULE 8: MARCH 2011

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Tobacco smoking and mental illness: important considerations

Sabina Feeney, Brian Hallahan

Tobacco smoking is a contributory factor in the death of 50% of individuals who are regular or heavy smokers (The Office of Tobacco Control Ireland defines a regular smoker as someone who smokes 11-20 per day and a heavy smoker as someone who smokes 21 or more cigarettes per day).[1] The World Health Organisation (WHO) regards tobacco smoking as the leading preventable cause of death worldwide.[2,3] In Ireland, approximately 750,000 people smoke tobacco regularly (23.5% of the population) with 7,000 Irish people dying annually from smoking-related causes.[1] Although there are no exact figures for prevalence rates of smoking in individuals with mental illness in Ireland, international studies unequivocally state that the prevalence of smoking is significantly higher in those with mental illness,[4] with greater nicotine intake and increased prevalence of nicotine dependence also reported.[4,5] Furthermore people with mental illness experience greater withdrawal symptoms and have lower cessation rates when attempting to stop smoking compared to the general population.[6-10]

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In this review article, we will discuss the prevalence of tobacco smoking in individuals with mental illness; the risks and possible benefits of tobacco smoking in individuals with mental illness; the pharmacokinetics of tobacco smoke and important considerations in relation to smoking cessation for individuals with mental health issues.

Prevalence of tobacco smoking

The prevalence of smoking in individuals with mental illness is one and a half to three times higher than that of the general population.[4,11] The prevalence of smoking varies between mental illnesses and has been reported as follows for those living in the community: 50% in psychotic disorders, 57% in major depressive disorder, 48% in generalised anxiety disorder, 60% in panic disorder and 40% in obsessive compulsive disorder have been reported in the UK.[12]

In mental health provided facilities including hospitals, hostels and group homes, prevalence rates of tobacco smoking are even higher with rates of 74% in psychotic disorders, 70% in mood disorders and 74% in neurotic disorders noted.[13,14] These and other findings suggest that individuals with mental illness have a greater tobacco consumption, account for a disproportionate percentage of the tobacco purchasing market and spend a greater percentage of their overall income on cigarettes than individuals without a mental illness.[15]

For example, individuals with schizophrenia who smoke tobacco, are estimated to spend approximately 33% of their entire income on cigarettes.[16]

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Reasons for smoking

While there is no definitive data in relation to why individuals with mental illness (notably depression, anxiety disorders, and schizophrenia) have a higher prevalence of tobacco smoking, several biological, psychological and social factors have been purported to explain this higher prevalence.[17] Nicotine's interaction with dopamine is probably the most common biological factor suggested as a putative cause for individuals smoking tobacco. Nicotine stimulates the release of dopamine in the nucleus accumbens and prefrontal cortex, resulting in a feeling of wellbeing, reduced anxiety and improved vigilance.[3,11,17] Differences in several dopamine genes have been linked with increased rates of smoking, with perhaps the greatest evidence to date, suggesting that increased numbers of dopamine receptor D2 (DRD2) A1 alleles,[21,22] are associated with higher rates of smoking with this effect greater in individuals with depressive symptoms.[21] Some evidence also exists suggesting a possible association between increased cigarette smoking and individuals homozygous for the short alleles of DRD4, with this effect again greater in individuals with depressive symptoms.[23] These results suggest genetic associations may increase smoking reward and reinforcement owing to negative mood. Putative psychological reasons for smoking in individuals with depression include the smokers expectation of a positive reinforcing effect,[24] and subjective reports of a reduction of negative affect.[25] Social factors may also play a role in the increased rate of smoking in individuals with depression, with some preliminary evidence suggesting that peer influences for adolescent girls to smoke are associated with higher rates of smoking for those with depressive symptoms compared to those without significant depressive symptoms.[26]

In anxiety disorders, proposed factors predisposing to higher rates of smoking and nicotine dependence include a negative affect (eg. stress, anger etc),[18] alterations in the hypothalamic-pituitary axis (see review by Rasmussen et al 2006),[19] and attempts to self-regulate or cope with adverse emotional distress.[20]

Possible reasons for smoking in individuals with schizophrenia may include perceived positive effects such as improved attention and memory,[17,27,28] and the association between tobacco smoking and a reduction in extra-pyramidal symptoms and negative affect.[29,30]

Tobacco smoking-related morbidity

Tobacco smoking is associated with increased rates of morbidity and mortality with 50% of regular smokers dying 15 years earlier than similarly matched non-smokers, while 25% of smokers die 23 years earlier than similarly matched non-smokers.[31] Tobacco smoke is an amalgam containing over 4,000 chemicals with tar, carbon monoxide and to a lesser extent nicotine most implicated in the increased medical mortality associated with smoking.[32] Tar in particular is associated with much of this mortality and morbidity and has been implicated in several neoplastic diseases (particularly lung and oro-facial cancers),[33,34] and in pulmonary diseases including chronic obstructive airways disease and emphysema.[35]

Nicotine and carbon monoxide are major risk factors in cardiovascular diseases and are associated with an increased risk of coronary heart disease, myocardial infarction, cardiac failure, peripheral vascular disease and cerebrovascular disease.[36] Further morbidity is associated with women including an increased prevalence of miscarriage, ectopic pregnancy and premature detachment of the placenta.[37]

Possible beneficial effects of nicotine for patients with psychiatric disorders

In addition to the significant adverse effects of tobacco, an increasing evidence base describes several therapeutic benefits for nicotine in a variety of psychiatric disorders,[38] including mood disorders,[11,39,40] anxiety disorders,[41] schizophrenia,[17,27,28,42] Alzheimer's disease,[3] attention deficit hyperactivity disorder (ADHD),[43,44] Parkinson's disease,[45,46] autism spectrum disorders (ASD),[3] and Tourette's syndrome.[3,46]

In major depressive disorder, nicotine has been shown to increase the release of serotonin, dopamine and noradrenaline via its action on the nicotinic acetylcholine receptors (nAChRs) which may be associated with improved mood.[17, 39, 47] Nicotine has also been found to improve emotional responses in smokers who are prone to depression.[17, 48] While there is some evidence that nicotine can reduce anxiety and relieve stress, these effects are complex and nicotine has also been noted to be anxiogenic.[39]

In addition to nicotine's proposed benefits for ameliorating negative symptoms in schizophrenia,[26, 27, 42] preliminary work has suggested that nicotine may lead to transient improvements in filtering sounds and may help reduce the frequency of auditory hallucinations.[49, 50] Nicotine administration through smoking has also been shown to improve working memory, attention, verbal learning and pre-attentional measures in smokers with schizophrenia.[17, 26, 42]

In ADHD, preliminary work using transdermal nicotine patches and the nicotinic agonist ABT-418 has demonstrated significant improvements in concentration and observer-rated global disease severity (in both adult smokers and non-smokers with ADHD).[44, 51] In Parkinson's disease nicotine receptor numbers are reduced,[52] and nicotine intake has been associated with a reduction in extra-pyramidal symptoms and improved cognitive function. Furthermore in Parkinson's disease, α-synuclein in Lewy bodies is fibrillated and this process is correlated with disease severity, however nicotine blocks this and consequently slows the disease progression.[53] Post-mortem studies in ASD demonstrate a depletion of nAChRs which are involved in attention and sensory processes, and treatment with acetylcholinesterase inhibitors have shown some albeit preliminary promise in decreasing irritability and hyperactivity and improving expressive speech in ASD.[27] Nicotine administration both via intravenous and transdermal routes has also been found to improve attention in Alzheimer's disease.[38, 54] Finally in Tourette's syndrome the combination of transdermal nicotine and neuroleptics has been shown to significantly reduce tic frequency and severity, compared to neuroleptic treatment alone.[55] In summary, nicotine may prove to be of some benefit in the treatment of a wide variety of psychiatric disorders, with greatest efficacy for improving attention. However, much of this evidence is preliminary and further research into these beneficial effects are required.

Tobacco smoking and pharmacokinetics

Tobacco smoke contains polycyclic aromatic hydrocarbons, in the tar component,[56, 57] which induce the cytochrome p450 (CYP450) enzyme system in the liver (increase activity and consequently reduce the plasma levels), in particular the CYP1A2 iso-enzyme. These polycyclic aromatic hydrocarbons can reduce drug plasma levels of certain chemical compounds

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by up to 50%,[58] and therefore an accurate smoking history is essential prior to the prescribing or altering of an individuals' pharmacotherapy. Any significant alteration in the smoking habits of an individual should thus be known by the treating clinician to ensure appropriate dosing of medications thereby reducing the risk of either drug toxicity or sub-therapeutic plasma levels of the psychotropic agent being prescribed. Nicotine replacement therapy (NRT) has no such effect on the CYP1A2 iso-enzyme as nicotine does not contain polycyclic aromatic hydrocarbons.[56, 57]

Some psychotropic agents due to their interaction with the CYP1A2 iso-enzyme are affected to a greater extent by alterations in smoking habits than others.[58] Clozapine levels can be reduced in smokers by up to 50%,[59, 60] with similar effects found for other antipsychotic agents including olanzapine,[61] fluphenazine,[62] and to a lesser extent haloperidol.[63, 64] Therefore careful monitoring of plasma levels are required, with an initial dose reduction of 25% required in the first week post smoking cessation with clozapine administration and further reductions frequently required (depending on clozapine plasma levels).[58,59] If an individual resumes smoking, an increased dose of the psychotropic agent may be necessary depending on plasma levels or clinical assessment.[56,57,59] With regard to antidepressants, the dose of tricyclic antidepressants may need to be reduced by 10-25% within one week of smoking cessation,[58] with adjustments of the dose of mirtazapine and duloxetine also often necessary.[65,66] The dose of fluvoxamine often may require a similar reduction,[67] although other selective serotonin reuptake inhibitors which have a lower affinity for this iso-enzyme rarely require dose adjustment secondary to alterations in smoking habits.[57] Several benzodiazepines particularly diazepam, alprazolam and oxazepam are also reduced by tobacco smoking and thus a dose reduction of 25% in the week following cessation may be required, however other agents including chlordiazepoxide, lorazepam, midazolam and triazolam often do not require any such dose alteration.[56, 57]

Smoking cessation therapies

Smoking reduction and cessation has the potential to improve the physical health and longevity of individuals with mental illness. Fifty per cent of smokers with mental health problems (or psychiatric conditions) in the UK have expressed a desire to stop smoking.[68] Currently, there are a variety of therapeutic interventions available for smoking cessation, including NRT and non-nicotine pharmacologic agents (eg. bupropion and varenicline) that have demonstrated efficacy for smoking cessation in these populations.[17, 69] However, smokers with certain psychiatric disorders have had little investigation to date in relation to the efficacy of these techniques, eg. bipolar disorder.[17, 69]

As in individuals without mental illness, NRT has been shown to double cessation rates in smokers with a variety of mental illnesses including depression,[70] and schizophrenia,[71] with even greater rates of smoking cessation noted when specialised supportive counselling (individual and group) is included.[17, 69, 72] In populations prescribed atypical antipsychotics, there may be a higher prevalence of smoking cessation compared to those prescribed typical agents.[73] Even when NRT has not resulted in total smoking cessation, reduced rates of cigarette consumption in heavy smokers (> 25 cigarettes per day),[74] have been documented and higher longer-term abstinence rates in this group have been found.[74]

The non-NRT medications that have demonstrated greatest smoking cessation efficacy in general populations to date are bupropion and varenicline. Bupropion is a noradrenaline and dopamine reuptake inhibitor and is licensed for smoking cessation in Ireland (and as an antidepressant in the US). Bupropion has demonstrated efficacy for use in smoking cessation with and without NRT, in people with a history of depression and schizophrenia.[75-79] However bupropion may induce hypomania in bipolar disorder,[80] and is associated in its immediate-release (IR) formulation with an increased risk of seizures particularly within the first six weeks of treatment or with doses of greater than 450g per day.[81,82] This risk of seizures however appears to be significantly reduced, but not eradicated with the sustained release (SR),[83-85] and the extended release (ER) formulations.[86,87] Therefore it is important to consider this possible adverse effect in individuals who already have an increased risk of seizures (eg. individuals with epilepsy, acute alcohol or benzodiazepine withdrawal, active eating disorders, and a history of trauma with loss of consciousness). Caution is also recommended for individuals who are on drugs metabolised by CYP2D6 or CYP1A2 enzymes (including many antidepressants and antipsychotics) and reference to an appropriate drug formulary is recommended (eg. British National Formulary).[88]

Varenicline is a nicotinic receptor partial agonist and is a licensed agent in Ireland for enabling smoking cessation. It reduces cravings and decreases the pleasurable effects of cigarettes when consumed.[88,89] Whilst several psychological problems have been reported with its use including depression, suicidal ideation and (hypo)mania,[88-90] a cohort study of over 10,000 users of varenicline found that in the subgroup of patients with a history of affective disorders, episodes of depression were not increased.[91]

There are a number of other agents not licensed for smoking cessation, that have shown efficacy in trials for smoking cessation in the general population. These include a variety of antidepressants including nortriptyline,[92] venlafaxine,[93] and baclofen the Gamma-aminobutryic acid B (GABA-B) agonist.[94] However, the use of any of these agents needs to be clearly balanced with both the individuals mental health requirements and the pharmacological agents they are already prescribed.

As described above, psychotherapeutic interventions such as group therapy and cognitive behaviour therapy (CBT) can augment pharmacological smoking cessation interventions.[94-101] When CBT has focused predominantly on mood management post smoking cessation, increased abstinence rates have been noted.[100,101] Alternative therapies including hypnotherapy and acupuncture have been utilised for smoking cessation but systematic reviews have not demonstrated efficacy for their use in smoking cessation to date.[102,103]

When assessing individuals regarding their likelihood of achieving smoking cessation the National Institute of Clinical Excellence (NICE) guidelines, UK recommend consideration be given to the following five factors: motivation to stop smoking, availability of counselling, previous experience with smoking cessation aids, contraindications to any of the available aids and the personnel preference of the smoker.[88,104-106] The level of nicotine dependence which is also important when ascertaining the likelihood of achieving smoking cessation can be assessed using the Fagerstrom Tolerance Questionnaire.[107]

Populations vary significantly in their smoking prevalence and smoking reduction and cessation rates. Knowledge of these differences among populations, including those with mental

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illness is essential to assessing an individual's ability to achieve smoking cessation. This awareness will help inform the development of improved behavioural and pharmacological interventions to reduce and eliminate cigarette smoking. Combined with the National Institute of Clinical Excellence (NICE) guidelines, UK and Department of Health UK guidelines,[105,106] this knowledge should help the clinicians achieve greater smoking cessation rates for their patients.

Conclusion

Smoking is the single largest preventable cause of morbidity and mortality in individuals with mental illness. In this review, we have outlined the increased prevalence of tobacco smoking in individuals with mental illness and describe various techniques to enable smoking cessation, with a combination of both pharmaco-therapeutic and psychological interventions demonstrating best results. Individuals who are successful at reducing or stopping smoking and are being treated with psychotropic agents would benefit from having regular pharmaco-therapeutic reviews as modification of psychotropics (often a reduction in dosage on smoking cessation or possible increase in dosage if smoking recommences) is often required to maintain stable plasma levels of the agents being prescribed. While there are many adverse effects of nicotine, there is a burgeoning, albeit preliminary evidence base suggesting a wide variety of beneficial effects in psychiatric disorders attributable to nicotine supplementation, many of which are described in this review.

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Multiple Choice Questions: Module 8

1. Tobacco smoking related morbidity is associated with:

Nicotine being the greatest contributor	T	F
Tar-associated oro-facial cancers	T	F
Tar is mostly associated with cardiovascular diseases	T	F
Increased rates of ectopic pregnancy	T	F
Increased rates of miscarriage	T	F

2. There is evidence suggesting that tobacco smoking is associated with benefits in relation to:

Improving negative symptoms in schizophrenia	T	F
Improving delusions in schizophrenia	T	F
Improving working memory in schizophrenia	T	F
Reducing tic frequency in Tourette's syndrome	T	F
Improving anxiety symptoms significantly in panic disorder	T	F

3. In relation to pharmacokinetic effects, tobacco smoke:

Interacts significantly with the CYP2D6 system	T	F
Interacts significantly with the CYP1A2 system	T	F
Increases clozapine levels by up to 50%	T	F
Reduces tricyclic antidepressant levels by up to 25%	T	F
Does not significantly effect most benzodiazepines	T	F

4. Smoking cessation therapies:

Nicotine replacement therapies are ineffective in individuals who have schizophrenia	T	F
Bupropion has dopamine receptor agonist activity	T	F
Bupropion XL is not associated with seizures	T	F
Varencline is a nicotine receptor partial agonist	T	F
Hypnotherapy has proven efficacy for smoking cessation	T	F

5. Smoking prevalence:

Is the same in all psychiatric disorders	T	F
Approximately 33% of income for individuals with schizophrenia is spent on tobacco	T	F
Is increased in inpatient compared to outpatient mental health facilities	T	F
Serotonin is the neurotransmitter associated with tobacco smoking	T	F
Hypothalmic-pituitary axis alterations have been associated with higher rates of tobacco smoking in anxiety disorders	T	F

Answers on www.ijpm.org

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