Smoking cessation and neuropsychiatric adverse events

Are family physicians caught between a rock and a hard place?

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In May 2010, following reports of neuropsychiatric adverse events, Health Canada compelled the makers of the newest smoking cessation prescription medication, varenicline, to carry a boxed warning label.[1] Warnings regarding increased risk of aggression and suicidal thoughts and behaviour have been in place for bupropion, another smoking cessation prescription medication, since 2004.[2] These warnings are usually reserved for drugs that have been linked with the most serious safety issues or adverse events. In 2008, a clinical review[3] in *Canadian Family Physician* provided an update on the safety and efficacy of pharmacologic therapies in tobacco cessation, but the recent Health Canada warnings related to mood changes, hostility, suicidal behaviour, and serious, sometimes fatal, skin reactions postdate this review and are of importance to family physicians.

The Canadian Medical Association issued its first warning about the hazards of tobacco in 1954 and maintains that helping patients become tobacco-free is among the most important services physicians can offer.[4] Clinical practice guidelines recommend that every patient willing to make a quit attempt should be offered counseling and pharmacotherapy (from among 6 registered options in Canada) unless contraindicated.[5-7] Outcomes for cessation interventions are widely recognized as effective, cost-effective, and clinically meaningful. With reported numbers need to treat (to save 1 life) as low as 9, they compare very favourably with interventions for other chronic diseases.[8]

The reports of neuropsychiatric adverse events and issued regulatory cautions can place family practitioners in a precarious position when managing patients with tobacco dependence. Weighing neuropsychiatric risks with the known benefits of cessation medications (nicotine replacement therapy or bupropion roughly double cessation success rates and varenicline roughly triples success rates)[6] poses considerable challenges. This commentary discusses the relationships between mood and tobacco use, abstinence, and cessation medications. An algorithm guiding the detection and management of neuropsychiatric issues will be discussed. To our knowledge, this is the first formal integration of neuropsychiatric considerations into a treatment algorithm for smoking cessation (**Figure 1**).

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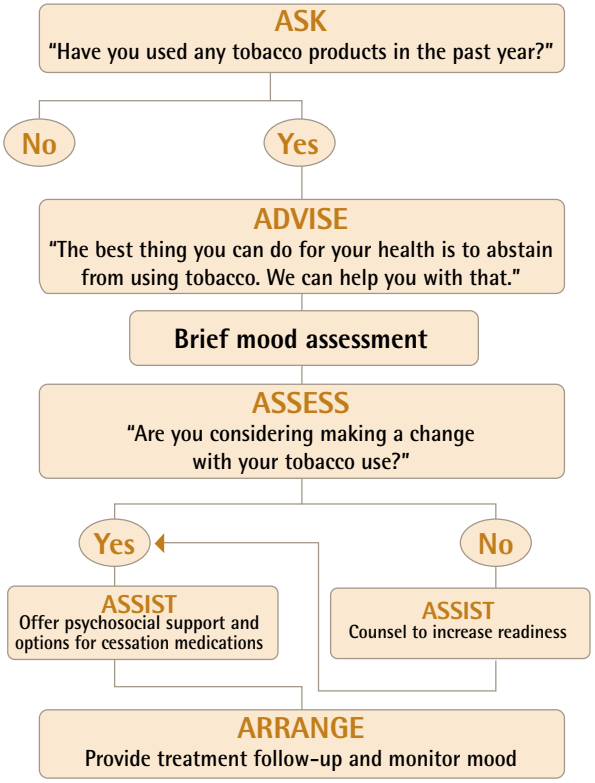
Neuropsychiatric considerations and tobacco use

Existing evidence supports substantial comorbidity between tobacco dependence and mental illness.[9] There exists a direct dose-dependent relationship between tobacco consumption and severity of depressive symptoms, as well as risk of suicide. When compared with those who have never smoked, the rate of depression among smokers doubles,[10] and the relative risk of successful suicide is 2.5 times greater for light smokers and 4.3 times greater for heavy smokers.[11]

Nicotine is the key addictive driver in tobacco and it affects a variety of neurotransmitters that influence mood

Figure 1. Safety-sensitive algorithm: *Treating tobacco use and dependence across the continuum of care.*



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and cognitive function.[12] Nicotine withdrawal-related symptoms include, among others, depressed mood, anxiety, insomnia, irritability, frustration, anger, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain.[13] Nicotine withdrawal might be more pronounced in those with pre-existing mental illness.

Tobacco also contains other psychoactive compounds, namely harman and norharman, which inhibit the activity of the monoamine oxidase (MAO) enzyme.[14] These mimic the antidepressant effect of commercially available MAO-inhibiting antidepressants. With cessation, the abrupt withdrawal of nicotine and these MAO-like agents in a neuro-adapted smoker offers a biologically plausible hypothesis for the development of some neuropsychiatric symptoms.[14] In those with pre-existing history of depression or suicide, these effects might be considerably more pronounced and might contribute to the neuropsychiatric sequelae observed in some cases.

The polycyclic aromatic hydrocarbons in tar from tobacco smoke induce a liver cytochrome (P450 1A2) enzyme, leading to faster metabolism of its substrates, including several psychotropic medications and caffeine.[15] When smokers substantially reduce consumption or completely abstain from tobacco, metabolism of these substrates can decrease considerably. This has been documented to lead to increased therapeutic blood levels of medications like olanzapine, clozapine, haloperidol, chlorpromazine, and diazepam. Conversely, relapsing to smoking following extended abstinence might result in decreased bioavailability of these medications, with the related increased risk of relapse to conditions like schizophrenia or bipolar disorder. Hence, current smoking status, level of consumption, and changes in consumption have meaningful clinical implications for the management of individuals taking any of these medications. In a similar pattern, individuals might experience symptoms of caffeine intoxication following reduction or abstinence from smoking.[16]

Cessation medications and neuropsychiatric adverse events

Although they are rare, the reported adverse events related to the use of varenicline or bupropion in those with or without pre-existing mental illness can include changes in mood, agitation, hostility, depressed mood, suicidal thoughts, and attempted and completed suicide. Some of the reported cases were apparently complicated by nicotine withdrawal symptoms, while others occurred in those who continued to smoke. In May 2008, an Institute for Safe Medical Practices report[17] cited almost 1000 incidents of serious injuries related to varenicline. Immediate concerns were expressed about the use of varenicline among people operating aircraft, trains, and other vehicles or those in other settings where a lapse in alertness or motor control could lead to serious injury. However, concerns have been raised about the validity of the findings and recommendations of this report.[18]

In Canada, the suicide risk warnings for bupropion and varenicline are similar to those for anticonvulsants, antidepressants, and montelukast.[18] Not unlike the Institute for Safe Medical Practices report, Health Canada's postmarketing surveillance does not allow for statements on frequency or putative causality of any adverse event, rendering the nature of neuropsychiatric adverse events difficult to interpret.[18] Most reports to date have inadequately addressed the relative and contributory weight of related cessation variables (ie, nicotine withdrawal, MAO effects, caffeine levels, and putative medication effects). To date, the sum of the evidence has not demonstrated a causal link between the use of nicotine replacement therapy, bupropion, or varenicline and the development of depression, suicide, or other neuropsychiatric phenomena, with the exception of sleep disturbances. As varenicline is a partial agonist at $\alpha 4\beta 2$ nicotinic acetylcholine receptors,[18] there is no known biologically plausible hypothesis whereby a partial agonist would be directly and causally associated with depression, psychosis, or suicide. Neuropsychiatric risks for varenicline are deemed rare; this compound is not associated with an increased risk of development of psychiatric illness and it is considered an appropriate cessation aid for patients with medical or psychiatric comorbidity.[19]

Despite the dearth of evidence suggesting a causal link between medication (nicotine replacement therapy, bupropion, or varenicline) and neuropsychiatric risks, there is a real and exceedingly relevant risk of developing depression when quitting smoking. This might be the case with or without cessation medications, in patients with or without pre-existing psychiatric history. It is generally accepted that the risks associated with pharmacotherapy are outweighed by the risks of exposure to the 172 toxic substances, 33 hazardous air pollutants, 47 chemicals restricted as hazardous waste, and 67 known human or animal carcinogens found in tobacco and tobacco smoke.[20]

Integrating neuropsychiatric considerations into tobacco-dependence treatment

It is challenging for physicians to incorporate sufficient levels of vigilance to neuropsychiatric adverse events into their routine tobacco-dependence management, irrespective of which cessation medication is chosen to assist patients with quit attempts. As 50% of smokers have a history of depression,[10] and the leading cause of disability is depression,[21] mood screening has particular salience in primary care settings. Prudence suggests screening for mood issues in patients who use or who are dependent on tobacco, regardless of their readiness to quit or whether cessation medications are prescribed.

An algorithm that includes mood and safety screening was developed in collaboration with primary care physicians to address abstinence-induced associated neuropsychiatric risks (**Figure 1**). This algorithm, adapted from the US Department of Health and Human Services, identifies key points for brief mood screening within the 5-*A* approach[5] (*ask, advise, assess, assist, arrange*) to tobacco-addiction treatment and reflects the serial cycles of tobacco use, abstinence, and relapse. Physicians proceed with pharmacotherapy decisions, according to best practice guidelines and clinical judgment, knowing that positive screening results at any of these points indicate that further mood assessment is warranted.

The most important predictive question to our patients in this context might be, "What happened to your mood, emotions, thoughts, and behaviour the last time you cut back or quit smoking?" Risk of relapse to symptoms of depression suggests serial monitoring is needed, and the use of a structured rating scale might be of value. Major depressive episodes or neuropsychiatric conditions should be treated based on individual merit. Depression treatment should be maintained for no less than 6 months after cessation, and treatment can be individualized to extend for longer periods.

Clinical intuition suggests that prophylactic antidepressant therapy might be reasonably warranted in those patients cutting back or quitting smoking who have histories of severe depression or previous imminent risk of harm or psychosis. Nortriptyline, an antidepressant associated with increased quit rates, is not registered for use for cessation in Canada. Bupropion is also used to treat depression and has been used to augment other antidepressants, and patient eligibility should be assessed individually based on odds of success, risk-benefit variables, and patient preference. Bupropion is associated with a lower risk of inducing mania, compared with other antidepressants, but might pose similar neuropsychiatric risks to varenicline.

Further, it is important to distinguish between true suicidal thoughts and related behaviour versus other forms of self-harm behaviour with different motivations. All threats should be taken seriously and handled accordingly. For those patients who experience symptoms that are not typical for them, or if suicidal thoughts or suicidal behaviour develop, the prudent advice is to discontinue use of the cessation medication and seek medical attention immediately to minimize harm and adverse events. Friends and family members of those quitting smoking (with or without medications) should be encouraged to maintain the same increased vigilance.

Conclusion

Tobacco addiction is a prevalent, lethal, yet treatable chronic disease that is associated with high levels of comorbid mood disorders. Every individual, with or without mental illness, interested in quitting smoking should be offered a combination of psychosocial interventions and pharmacotherapy, and nicotine replacement therapy, bupropion, or varenicline might be viewed as first-line options. Mood screening and management should be integrated into routine cessation monitoring. This includes serial assessments to rule out imminent suicide risk. A safety-sensitive algorithm offers guidance for navigating risk-benefit decisions.

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Competing interests

Up to 2009, **Dr Els** received unrestricted funding for education and research from Pfizer and Johnson & Johnson. **Ms Kunyk** and **Dr Sidhu** have no competing interests to declare.

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