

Smoking and mental illness. An update for psychiatrists

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Abstract

Objective: We aimed to review research on smoking and mental illness and provide evidence-based guidelines for psychiatrists to help smoking patients quit.

Method: We undertook a narrative review of the literature with a special focus on the Australian context.

Results: Although one in three people with mental illness smoke tobacco, smoking is often neglected in psychiatric practice. Smoking is a significant contributor to the health gap between people with mental illness and the general population. Smokers with mental illness are motivated to quit and are able to do so, albeit with lower quit rates. Quitting can lead to substantial improvements in mental wellbeing and physical health and does not exacerbate pre-existing mental illness. Psychiatrists should advise all smokers to quit and provide counselling, medication and support, based on the 5As framework. Approved pharmacotherapy – nicotine replacement therapy, varenicline and bupropion – is recommended for nicotine-dependent smokers. Smoking induces the metabolism of certain psychotropic drugs such as clozapine and olanzapine and dose reductions may be necessary after cessation.

Conclusions: Psychiatrists have a duty of care to identify the smoking status of their patients and to provide evidence-based support to quit.

Keywords: smoking, nicotine dependence, psychiatry, mental health, mental illness

People with mental illness have higher smoking rates, higher levels of nicotine dependence, lower cessation rates and a disproportionate health and financial burden from smoking compared with the general population.¹ Smokers with mental illness are far more likely to die as a consequence of smoking than from their psychiatric condition.¹

Smoking cessation remains a neglected area in psychiatry, in part due to myths and misconceptions about smoking in the mentally ill.² For example, many mental health workers believe smoking cessation will exacerbate mental illness; however, this is not supported by evidence.^{3,4} In fact, smoking cessation is usually associated with significantly improved mental health.⁵

Smokers with mental illness are as motivated to quit as the general population, and can quit successfully, albeit with lower success rates.² Addressing and managing nicotine dependence should be an integral part of routine psychiatric care.²

Smoking and mental illness

In the most recent national mental health survey in 2007, 32% of Australians with a current mental illness smoked compared with 16% of those without mental illness.⁶ In general, the more severe the psychiatric condition, the higher the smoking prevalence (Figure 1).^{6,7} Smokers with mental health disorders also smoke more heavily.

Smoking rates in people with mental illness remain high while they are declining in the general community. For example, the smoking rate in Australians with psychotic disorders did not fall between 1997 and 2010 while

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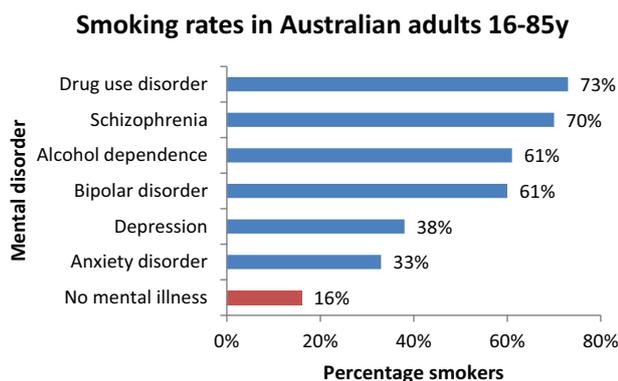


Figure 1. Smoking rates by mental illness.

Source: Australian Bureau of Statistics⁶, Cooper et al.⁷

smoking in the mainstream Australian population declined from 26% to 19%.⁷

Australian men with mental illness live 15.9 years less and women live 12 years less than those without mental illness, and this difference continues to widen.⁸ Most of the excess morbidity and mortality is due to smoking-related illnesses such as cardiovascular disease, respiratory disease and cancer.⁸ Smoking-related diseases are also the leading causes of death for people with alcohol and other substance use disorders.⁹

Smoking as a substance use disorder

Nicotine dependence is a significant substance use disorder that requires treatment. Like other drugs of abuse, nicotine acts via the mesolimbic reward pathway in the midbrain; it activates $\alpha 4\beta 2$ nicotinic acetylcholine (nACh) receptors, releasing dopamine in the nucleus accumbens.¹⁰

Smoking is also maintained by relief of withdrawal symptoms (negative reinforcement) and by conditioned behaviour. Over time, specific situations, activities and affective states can become associated with the rewarding effects of nicotine. Exposure to smoking cues, such as the smell of smoke, can trigger a strong urge to smoke.¹⁰

There are several potential explanations for the higher prevalence of smoking in people with a mental illness. There is a degree of shared genetic predisposition to smoking and mental illness.¹¹ Common environmental factors such as psychosocial stressors can also increase the risk of both smoking and mental illness.¹¹ Nicotine can give transient relief of anxiety and depression, and cigarette smoking may be an attempt to self-medicate. In patients with schizophrenia, smoking improves cognitive function, sensory gating deficits, working memory and negative symptoms, albeit transiently.¹¹ There is also evidence of a bidirectional relationship, by which smoking may increase the risk of mental illness, especially anxiety and depression.

The effect of quitting on mental health

Much of the apparent 'benefit' from smoking is due to the temporary alleviation of nicotine withdrawal symptoms, which erroneously creates the impression that smoking is relaxing (the 'stress paradox'). However, smoking actually increases stress levels overall. Indeed, a recent meta-analysis of 26 studies found that stopping smoking is associated with significant improvements in depression, anxiety, stress, psychological quality of life, and positive affect compared with continuing to smoke.⁵ Smoking is also a predictor of suicide even after controlling for mental illness, and the risk falls after cessation.¹²

Although it is commonly believed that smoking cessation exacerbates pre-existing mental illness, meta-analyses in schizophrenia, depression and severe, stable mental illness have not found any deterioration.^{3,4} Furthermore, a meta-analysis of smokers in treatment for substance use found that including a smoking cessation intervention resulted in a 25% increase in long-term abstinence from alcohol and illicit drugs.¹³

Addressing smoking cessation

Given the disproportionate impact of smoking on the mental and physical health of smokers with mental illness and the interaction between smoking and psychotropic medication, identifying and treating nicotine dependence should be a routine part of psychiatric care.² Psychiatrists are in a position to motivate patients to cease smoking; assist with smoking cessation by counselling techniques, including motivational interviewing; and prescribe and monitor smoking cessation pharmacotherapy.

The optimal treatment for smoking is a combination of counselling, pharmacotherapy and ongoing support.¹⁴ The 5As provide a useful framework for treatment and are described in detail in Figure 2.¹⁴ The elements of the 5As are:

- Ask all patients if they smoke
- Advise all smokers to quit in a clear, non-confrontational, personalised way
- Assess readiness to quit and nicotine dependence
- Assist with quitting
- Arrange follow-up

When time is short, a referral pathway developed by the United Kingdom National Centre for Smoking Cessation and Training (www.ncsct.co.uk) is an alternative. The steps for this are ask, advise and refer for treatment. Referral destinations could include Quitline, a tobacco treatment specialist or a general practitioner with requisite expertise (Figure 2).

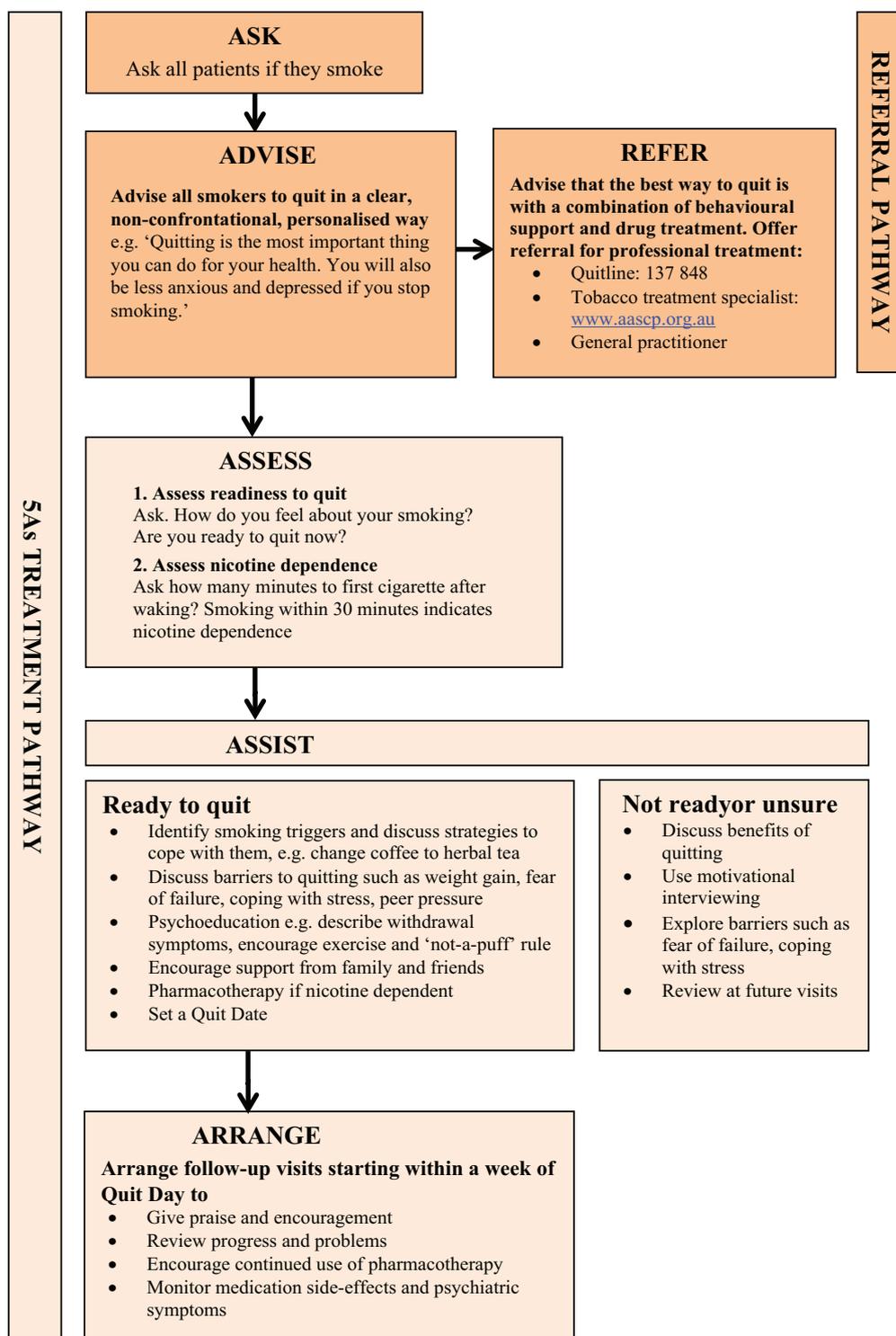


Figure 2. Combined 5As and referral pathway for smoking cessation.

Adapted from Zwar et al.¹⁴ and UKNSCC www.ncsct.co.uk

Motivational interviewing can help motivate ambivalent smokers. A Cochrane meta-analysis of motivational interviewing versus brief advice or usual care yielded a modest but significant 27% increase in quitting.¹⁵

A Cochrane review found that individual counselling increases long-term quit rates by 39% compared with minimal behavioural intervention.^{16,17} Psychiatrists could assist by helping identify smoking triggers and

high-risk smoking situations and developing a plan for coping with them. Discussing barriers to quitting, such as weight gain and stress, can also be very beneficial. Counselling for smokers with mental illness may need to be more intensive or prolonged. Strategies are outlined in Figure 2.

Mindfulness is increasingly being used to treat mental illness and it may also be beneficial for concurrent nicotine dependence. Several studies have found that it can reduce cravings, withdrawal symptoms, cigarette consumption and might improve rates of abstinence.¹⁷

Pharmacotherapy

Approved products for smoking cessation in Australia are nicotine replacement therapy (NRT), varenicline and bupropion (Table 1). Australian guidelines recommend offering pharmacotherapy to all nicotine-dependent smokers who wish to quit. The most efficacious pharmacotherapies are combination NRT (nicotine patch plus a short-acting preparation) and varenicline, both of which are associated with approximately three times the quit rate of placebo.¹⁸ Pharmacotherapy works by relieving cravings and nicotine withdrawal symptoms.^{19–21} The nicotine patch, varenicline and bupropion are all subsidised by the Pharmaceutical Benefits Scheme (PBS).

Patients with mental illness should be offered the same pharmacotherapy as the general population, although with closer monitoring.¹⁴ Because of higher levels of nicotine dependence in smokers with mental illness, larger doses of NRT, combination pharmacotherapy and a longer duration of therapy may be required. In the clinical setting, the single most reliable indicator of nicotine dependence is having the first cigarette within 30 minutes of waking.¹⁴

Nicotine replacement therapy. NRT monotherapy (using a single nicotine product) increases quit rates by 60% compared with placebo.¹⁹ The transdermal patch is applied daily to the skin and provides continuous protection against background cravings. The oral forms (nicotine mouth spray, oral strips, lozenges, gum and inhalator) give faster, flexible relief for breakthrough cravings.

Combining the nicotine patch with an oral form of NRT is significantly more effective than the patch alone¹⁹ and is recommended for most nicotine-dependent smokers using NRT. Treatment is usually started with a daily nicotine patch, and oral NRT products are added on an as-needed or regular basis, for example hourly.²² Smokers should be encouraged to use enough oral nicotine to relieve cravings and withdrawal symptoms and to continue for at least 8–12 weeks.¹⁹ However, oral NRT products are not PBS subsidised and cost can be a deterrent.

Starting the patch 2 weeks before quit day increases quit rates by a further 34% compared with starting on quit day.¹⁹ Adding a second patch may provide a modest increase in efficacy for more dependent smokers.^{19,22}

NRT is also recommended as a harm reduction strategy for smokers who are willing to reduce smoking but are not currently ready to quit. This strategy doubles the odds of quitting completely.²³

Adherence to NRT is often poor, due partly to misguided concerns about safety and addictiveness.²⁴ Patients should be advised that nicotine causes relatively few significant health effects, except in pregnancy. NRT delivers nicotine more slowly than smoking and in lower doses. As a result, NRT is always safer than smoking and the risk of addiction is low. It is also vital to instruct patients on the correct use of the oral forms of NRT as they are often used incorrectly, resulting in lower effectiveness and more side effects (Table 1).²⁴

Varenicline. Varenicline is a partial agonist at the nACh receptor. It also acts as an antagonist at the same receptor, blocking the rewarding effects of nicotine if a cigarette is smoked. Varenicline is the most effective monotherapy for smoking cessation and almost triples the quit rate compared with placebo.²¹ It is commenced at least 1 week prior to the quit date and continued for a full course of 12 weeks. A second 12-week course can provide a further modest increase in efficacy.²¹

Nausea occurs in about 30% of users but can be minimised by gradual up-titration and taking it with food. As varenicline does not undergo liver metabolism it has no known drug interactions, and can be used in combination with psychotropic medications.

After initial marketing there were widespread reports of mood changes, depression, behaviour disturbance and suicidal ideation in varenicline users. However, subsequent data re-analysis, further studies and meta-analyses have not demonstrated a causal link with varenicline.²⁵ Studies of varenicline in smokers with depression and schizophrenia have found the drug to be safe and effective.^{26,27} However, careful explanation of potential side effects should be provided and monitoring instigated.

Bupropion. Bupropion is an antidepressant which increases dopamine and noradrenaline levels and acts as an antagonist at the nACh receptor. Although bupropion may alleviate depressive symptoms, there is no evidence that it is more effective in smokers with current or past depression than in those without.²⁰ It has efficacy comparable with NRT monotherapy.²⁰ Bupropion is commenced at least 1 week prior to smoking cessation and taken for a 9-week course.

There is a 1 in 1000 risk of a seizure with bupropion and it is contraindicated in patients with a history of seizures, eating disorders, head trauma and alcohol dependence.²⁸ Bupropion should be used with caution with other antidepressants and other antipsychotics. Co-administration can lower the seizure threshold and increase seizure risk. Bupropion is contraindicated with monoamine oxidase inhibitors.²⁸

Bupropion also inhibits the CYP2D6 enzyme which metabolises serotonin reuptake inhibitors, tricyclic

Table 1. Approved drugs for treating nicotine dependence.^{19–21,24}

Drug	Recommended dose	Course of treatment	Common adverse effects	Directions for use
Nicotine replacement therapies (NRT)				
Nicotine patch 24 h: 21 mg, 14 mg, 7 mg 16 h: 25 mg, 15 mg, 10 mg	Start with a full strength patch if ≥ 10 cigs/day	12 weeks	Insomnia, disturbed dreams (24h patch). Skin irritation	Apply in morning to upper arm, chest or back and rotate application site daily
Nicotine mouth spray 1 mg per spray	1–2 sprays every 30–60 mins Maximum 4 sprays/hour or 64 sprays/day	12 weeks	Mouth/throat irritation, nausea, dyspepsia, headache, hiccups	Fast acting craving relief. Spray under tongue or onto inside of cheek
Nicotine oral strips 2.5 mg	Initially 1 strip every 1–2 h, up to 15/day	12 weeks	Nausea, throat irritation, hiccups, headache	Fast acting craving relief for less dependent smokers (TTFC ^a ≥ 30 min). Place on tongue and apply to palate. Dissolves in 2–3 min
Nicotine lozenges 2 mg, 4 mg	2 mg and 4 mg: 9–15/day Use 4 mg if TTFC* < 30 mins	12 weeks	Nausea, hiccups, heartburn, flatulence	Allow to dissolve in mouth over 20–30 min, moving around from time to time
Nicotine mini lozenges 1.5mg, 4mg	1.5 mg: 9–20/day 4 mg: 9–15/day Use 4 mg if TTFC* < 30 mins	12 weeks	Nausea, hiccups, heartburn, flatulence	Allow to dissolve in mouth over 10–15 min, moving around from time to time
Nicotine gum 2 mg, 4 mg	2 mg: 8–20/day 4 mg: 4–10/day Use 4 mg if TTFC* < 30 mins	12 weeks	Hiccups, nausea, jaw discomfort, mouth/throat irritation	Instruct patients on 'park and chew' technique. ^b Avoid in people with dentures
Nicotine inhalator 15mg per cartridge	3–6 cartridges/day	12 weeks	Cough, mouth/throat irritation, nausea	Frequent, shallow puffs. Satisfies hand-to mouth habit
Non-nicotine tablets				
Varenicline 0.5 mg, 1 mg	0.5 mg/day for 3 days, then 0.5 mg bd for 4 days then 1 mg bd	12 weeks. Optional second course	Nausea, insomnia, disturbed dreams, headache, drowsiness	Most effective monotherapy. Take with a meal to reduce nausea. No known drug interactions. Contraindicated in pregnancy and lactation
Bupropion 150 mg	150 mg/day for 3 days, then 150 mg bd	9 weeks	Seizure risk 1:1000. Insomnia, headache, dry mouth	Elevated seizure risk. Numerous potential drug interactions. Contraindicated in pregnancy, lactation

^aTTFC: time to first cigarette.

^bChew gum slowly until peppery taste appears and then place gum in the buccal pouch until taste fades. Chew again when until taste appears. Repeat cycle for 30 mins then discard. Avoid swallowing nicotine.

antidepressants, mirtazapine and antipsychotics. The plasma levels of these drugs may rise, with a potential increased risk of adverse effects. A dose reduction should be considered, especially for drugs with a narrow therapeutic index such as tricyclic antidepressants.²⁸

Smoking and psychotropic drugs

Tobacco smoke reduces the blood levels of a number of psychotropic drugs by inducing the cytochrome P450

enzyme CYP 1A2 (Table 2).²⁹ Enzyme activity increases up to 70% in heavy smokers compared with non-smokers³⁰ from as few as seven cigarettes per day.³¹ Importantly, the plasma levels of certain psychotropic drugs can rise significantly within days after quitting or reducing cigarette consumption, and a new steady state is reached after approximately 1 week.³⁰ This effect is largely due to the polycyclic aromatic hydrocarbons in smoke, not nicotine. NRT does not affect medication levels.

Table 2. Clinically relevant psychotropic drug interactions with smoking

<i>Class</i>	<i>Drug</i>	<i>Effect of smoking cessation</i>	<i>Clinical importance</i>	<i>Ref</i>
Antipsychotics	Clozapine	Serum levels rise. Reduce dose by 50%	+++	32
	Olanzapine	Serum levels rise. Reduce dose by 30%	+++	32
	Haloperidol	Serum levels may rise. Clinical significance unclear	+	29, 33
	Chlorpromazine Fluphenazine			
Antidepressants	Fluvoxamine (SSRI)	Plasma levels may increase. May need dose reduction	++	29
	Duloxetine	Serum levels may rise. Clinical significance uncertain	+	34
	Mirtazapine	Serum levels may rise	+	35
	Imipramine	Serum levels may rise. Monitor for side effects	+	33
Other drugs	Caffeine	Caffeine levels rise. Reduce caffeine by half within a week	+++	29
	Alcohol	Increased alcohol levels, cognitive impairment, intoxication, sedation. Advise reduced alcohol intake	+++	29
	Benzodiazepines	Possible increased sedation due to loss of CNS stimulation by nicotine. May need lower dose	+	29
	Beta-blockers	Serum levels rise and effects enhanced. May need lower dose	+	29

Drugs with a narrow therapeutic range, such as clozapine and olanzapine, may require early dose reduction after quitting.³² Patients need monitoring for increased sedation or other side effects as well as more regular testing of clozapine levels. However, progress with quitting needs to be closely monitored, as many quit attempts will not be successful and medication doses may need to be increased promptly if smoking is resumed.

Reductions in caffeine intake may also be necessary. After quitting, rising caffeine levels can cause caffeine toxicity which can mimic nicotine withdrawal or an exacerbation of mental illness.²⁹ Because it activates the sympathetic nervous system, nicotine can counter the pharmacological actions of certain drugs, such as propranolol and benzodiazepines.²⁹

Conclusion

Smoking is a major contributor to the health gap between patients with mental illness and the general population. Quitting can lead to substantial improvements in mental wellbeing and physical health and does not exacerbate pre-existing mental illness.

Psychiatrists have a duty of care to identify the smoking status of their patients and to offer them evidence-based

support to quit. Adjustments of psychotropic medications may be necessary after quitting.

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References

- Williams JM, Steinberg ML, Griffiths KG, et al. Smokers with behavioral health comorbidity should be designated a tobacco use disparity group. *Am J Public Health* 2013; 103: 1549–1555.
- Prochaska JJ. Failure to treat tobacco use in mental health and addiction treatment settings: A form of harm reduction? *Drug Alcohol Depend* 2010; 110: 177–182.
- Ragg M, Gordon R, Ahmed T, et al. The impact of smoking cessation on schizophrenia and major depression. *Australas Psychiatry* 2013; 21: 238–245.

4. Banham L and Gilbody S. Smoking cessation in severe mental illness: What works? *Addiction* 2010; 105: 1176–1189.
5. Taylor G, McNeill A, Girling A, et al. Change in mental health after smoking cessation: Systematic review and meta-analysis. *BMJ* 2014; 348: g1151.
6. Australian Bureau of Statistics. *National survey of mental health and wellbeing: summary of results, 2007*. Cat. No. 4326.0. Canberra: ABS, 2008.
7. Cooper J, Mancuso SG, Borland R, et al. Tobacco smoking among people living with a psychotic illness: The second Australian Survey of Psychosis. *Aust N Z J Psychiatry* 2012; 46: 851–863.
8. Lawrence D, Hancock KJ and Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: Retrospective analysis of population based registers. *BMJ* 2013; 346: f2539.
9. Hurt RD, Offord KP, Croghan IT, et al. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA* 1996; 275: 1097–1103.
10. Benowitz NL. Nicotine addiction. *N Engl J Med* 2010; 362: 2295–2303.
11. Aubin HJ, Rollema H, Svensson TH, et al. Smoking, quitting, and psychiatric disease: A review. *Neurosci Biobehav Rev* 2012; 36: 271–284.
12. Yaworski D, Robinson J, Sareen J, et al. The relation between nicotine dependence and suicide attempts in the general population. *Can J Psychiatry* 2011; 56: 161–170.
13. Prochaska JJ, Delucchi K and Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *J Consult Clin Psychol* 2004; 72: 1144–1156.
14. Zwar N, Richmond R, Borland R, et al. *Supporting smoking cessation: A guide for health professionals*. Melbourne: The Royal Australian College of General Practitioners, 2014.
15. Lai DT, Cahill K, Qin Y, et al. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev* 2010; 1: CD006936.
16. Lancaster T and Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev* 2005; 2: CD001292.
17. Brewer JA, Mallik S, Babuscio TA, et al. Mindfulness training for smoking cessation: Results from a randomized controlled trial. *Drug Alcohol Depend* 2011; 119: 72–80.
18. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: An overview and network meta-analysis. *Cochrane Database Syst Rev* 2013; 5: CD009329.
19. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012; 11: CD000146.
20. Hughes JR, Stead LF, Hartmann-Boyce J, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014; 1: CD000031.
21. Cahill K, Stead LF and Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012; 4: CD006103.
22. Bittoun R. A combination nicotine replacement (NRT) algorithm for hard-to-treat smokers. *J Smoking Cess* 2006; 1: 3–6.
23. Stead LF and Lancaster T. Interventions to reduce harm from continued tobacco use. *Cochrane Database Syst Rev* 2007; 3: CD005231.
24. Mendelsohn C. Optimising nicotine replacement therapy in clinical practice. *Aust Fam Physician* 2013; 42: 305–309.
25. Gibbons RD and Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry* 2013; 170: 1460–1467.
26. Anthenelli RM, Morris C, Ramey TS, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Ann Intern Med* 2013; 159: 390–400.
27. Williams JM, Anthenelli RM, Morris CD, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2012; 73: 654–660.
28. *Zyban SR Prescribing Information*. GlaxoSmithKline Australia. Last amended 19 July 2014.
29. Zevin S and Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet* 1999; 36: 425–438.
30. Faber MS and Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther* 2004; 76: 178–184.
31. Haslemo T, Eikeseth PH, Tanum L, et al. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. *Eur J Clin Pharmacol* 2006; 62: 1049–1053.
32. Tsuda Y, Saruwatari J and Yasui-Furukori N. Meta-analysis: The effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open* 2014; 4: e004216.
33. Desai HD, Seabolt J and Jann MW. Smoking in patients receiving psychotropic medications: A pharmacokinetic perspective. *CNS Drugs* 2001; 15: 469–494.
34. Knadler MP, Lobo E, Chappell J, et al. Duloxetine: Clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2011; 50: 281–294.
35. Lind AB, Reis M, Bengtsson F, et al. Steady-state concentrations of mirtazapine, N-desmethyilmirtazapine, 8-hydroxymirtazapine and their enantiomers in relation to cytochrome P450 2D6 genotype, age and smoking behaviour. *Clin Pharmacokinet* 2009; 48: 63–70.