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# Smoking and depression

## A review

### Background

People with a lifetime history of depression are twice as likely to smoke as those who do not suffer from depression. Smoking is a major health issue in this population, but is often overlooked by health professionals.

### Objective

This article examines the relationship between smoking and depression, and reviews the evidence for the use of specific therapies in general practice.

### Discussion

All patients with depression should be asked if they smoke. Smokers with depression have higher nicotine dependence and, after quitting, experience more severe negative moods and are at increased risk of major depression. However, they are motivated to quit and many achieve long term abstinence.

Effective strategies for smoking cessation in this population include cognitive behavioural mood management, nicotine replacement therapy, varenicline and bupropion. Additional support and longer courses of treatment may be needed. Smokers with depression should be monitored for mood changes after quitting. Preventive antidepressants may have a role in high-risk cases, especially for those with recurrent depression.

### Keywords

smoking; depression; smoking cessation; general practice

There is a strong association between smoking and depression. People with current or past depression are about twice as likely to be current smokers and smoke more cigarettes per day than people without depression.<sup>1,2</sup>

However, in this population the focus of health professionals tends to be on depression and smoking behaviour is frequently neglected.<sup>3</sup> It is often falsely assumed that people with depression are not motivated, or able, to quit and that quitting is bound to exacerbate their depression.<sup>3</sup> But quitting is an important health priority for smokers with depression. They are at higher risk of smoking related disease than the general population of smokers.<sup>4,5</sup>

Smokers with depression can achieve long term abstinence in many cases and success rates could be greatly enhanced by evidence based

therapies,<sup>6</sup> although they are more nicotine dependent and may experience more challenges when attempting to quit.<sup>4</sup>

### Why do people with depression smoke?

There are a number of models to explain the high rate of smoking in people with depression. These include:

- shared genetic factors: there is some evidence from twin studies for shared genes that predispose individuals to both smoking and depression<sup>7</sup>
- shared environmental influences: social difficulties or stressful events may trigger both smoking and depression<sup>7</sup>
- self medication: nicotine has central antidepressant properties and depressed patients could be using it as a form of self-medication to relieve symptoms.<sup>8</sup> Nicotine releases dopamine in the mesolimbic reward pathway, elevating mood and improving wellbeing. It also increases the bioavailability of serotonin, acting in a similar manner to some antidepressant drugs. Nicotine has some positive effects, which may be of benefit in depression. It can improve attention and cognitive function, reduce stress and act as a distraction
- bidirectional causality: young adults with a history of depression are three times more likely to commence smoking than those without a history of depression.<sup>9</sup> Conversely, there is also evidence that chronic smoking increases a person's risk of depression as a result of changes in neurophysiology.<sup>10</sup>

### Motivation to quit

Contrary to popular belief, evidence suggests that smokers with depression are highly motivated to quit smoking.<sup>11,12</sup> In one study, female smokers who were depressed were more motivated to quit than those with a lower depression score.<sup>12</sup>

## Depression after quitting

Depressed mood is part of the nicotine withdrawal syndrome and is a common symptom in the first 2 weeks after quitting.<sup>13</sup> Research shows that smokers with depression experience more severe negative moods on quitting and this is a powerful trigger for relapse.<sup>4,14–16</sup>

Smokers with a history of depression have been reported as having twice the risk of developing a major depression in the first 12 months after quitting.<sup>17</sup> In a review of seven studies, the incidence of major depression after quitting was 0–14% among all smokers, and 3–24% among those with a history of depression.<sup>18</sup>

## Quit rates and relapse

A meta-analysis of 26 trials found that smokers with depression had a 34% lower rate of long term abstinence (OR: 0.66).<sup>19</sup> Patients with recurrent depression have significantly lower quit rates than those who had only a single episode.<sup>19</sup>

Smokers with depression have been shown to suffer from more intense cravings and more severe nicotine withdrawal symptoms, which make quitting more difficult.<sup>4,15,20</sup> Quit attempts may also be undermined by the cognitive deficit caused by depression and a lowered self efficacy.<sup>12</sup>

## Drug interactions

Some drugs used for depression are metabolised more quickly in smokers, resulting in lower blood levels.<sup>21</sup> Affected antidepressants include fluvoxamine (blood levels are 25% lower in smokers),<sup>21</sup> duloxetine (15% reduction),<sup>22</sup> mirtazapine<sup>23</sup> and tricyclic antidepressants.<sup>21</sup> Benzodiazepines, clozapine and olanzapine are also affected and may be relevant for some patients with depression.

## Treatments for depression

A review of the literature is shown in *Table 1*.

### Psychological and lifestyle treatments

A meta-analysis of five trials found a benefit for adding cognitive behavioural mood management to conventional smoking cessation treatment (RR: 1.45).<sup>4</sup> This treatment may be more effective for patients with a history of recurrent depression than for those with a single episode.<sup>24,25</sup>

A number of other psychological strategies (eg. problem solving, coping skills, stress management,

mindfulness, distraction) and lifestyle counselling (eg. exercise, diet, sleep, pleasant activity scheduling) have also been tested. These treatments may assist with mood management, motivation and overall health, but evidence for their effectiveness overall in smoking cessation is mixed.<sup>6</sup>

### Preventive antidepressants

The initiation of preventive antidepressants before quitting is sometimes recommended for patients with a past history of depression to stabilise mood and reduce the risk of relapse.<sup>6,26</sup> But there is little research on the benefits of this practice and it is uncertain whether antidepressants actually prevent postcessation depression<sup>18</sup> or improve smoking cessation rates.<sup>4</sup>

Prophylactic treatment may be most beneficial for high risk cases such as those with recurrent depression, a history of severe depression or a significant episode of depression after a previous quit attempt.

### Quitline and co-managed care

A recent Australian trial studied co-management of smokers with depression by the Victorian Quitline and the patient's general practitioner.<sup>27</sup> Exacerbation of depression was reported in 18% of participants, but occurred equally in those who quit compared to those that did not. Overall, 20% achieved sustained cessation at 6 months. The co-management protocol used in this trial is being shared with Quitline services nationally.

## Smoking cessation pharmacotherapy

A review of the literature is shown in *Table 1*.

### Nicotine replacement therapy

Nicotine replacement therapy (NRT) appears to be effective in smokers with depression. A review of three trials found cessation rates of 14–22% at 12 months or longer,<sup>4</sup> which are comparable to NRT quit rates in the general population. Nicotine replacement therapy has also been shown to have some antidepressant qualities.<sup>28</sup>

Long term quit rates with NRT were lower for patients with current depressive symptoms than for those who had a previous history of depression (14% vs 22% respectively).<sup>4</sup>

Nicotine replacement therapy can be used concurrently with antidepressants.

## Antidepressants

### Bupropion

Bupropion almost doubles the quit rate compared to placebo (RR: 1.69) and appears to be equally effective in smokers with or without a history of depression.<sup>29</sup> Although it may alleviate some symptoms of depression during treatment, there is no evidence that bupropion benefits patients with depression more than those without a history of depression.<sup>29</sup>

There are safety concerns about the interaction between bupropion and other antidepressants and this combination should be used with caution.<sup>30</sup> Bupropion has been associated with depression and suicide risk. Whether this association is causal is unclear.<sup>29</sup>

### Nortriptyline

The tricyclic antidepressant nortriptyline approximately doubles quit rates compared to placebo in clinical trials (RR: 2.03) in smokers, both with or without depression.<sup>29</sup>

Nortriptyline is considered a second line treatment<sup>31</sup> due to its side effects and the risk of cardiovascular toxicity and fatal overdose. Use for smoking cessation is currently off-label in Australia.

### Other antidepressants

The literature does not support the efficacy of selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine, sertraline, citalopram; monoamine oxidase inhibitors (MAOIs): moclobemide, selegiline; venlafaxine or St John's wort (*Hypericum perforatum*) for smoking cessation.<sup>29</sup>

### Varenicline

Varenicline is an effective smoking cessation aid, which more than doubles quit rates compared to placebo (RR: 2.31).<sup>32</sup> Although there have been postmarketing reports of depressed mood and suicidal ideation and behaviour, causality has not been established.<sup>32</sup> Furthermore, recent analysis of large clinical trials has not demonstrated that varenicline is associated with more depression or suicidality than other smoking treatments.<sup>33</sup> Further studies are currently being conducted to help clarify this possible association.

Studies have suggested that varenicline may actually reduce symptoms of depression after

**Table 1. Treatment for smokers with depression**

Depression	
Cognitive behavioural mood management	Small positive effect (RR: 1.45). Most beneficial for patients with recurrent depression <sup>4</sup>
Problem solving, coping skills, stress management, mindfulness, lifestyle counselling	Mixed results <sup>6</sup>
Preventive antidepressants	Evidence for preventing postcessation depression and for improving cessation rates unclear. May be most beneficial in high risk cases <sup>4,18</sup>
Current depression	Treat and stabilise depression before quitting <sup>26</sup>
Smoking cessation	
Nicotine replacement therapies	Effective. Lower quit rates in patients with current depressive symptoms. Precessation patch and combination therapy probably more effective <sup>4</sup>
Bupropion	Equally effective in smokers with and without depression. Additional antidepressant action may be beneficial. Association with increased depression and suicide risk but unproven <sup>29</sup>
Varenicline	Most effective single agent. Probably equally effective in smokers with and without depression. Association with increased depression and suicide risk but unproven <sup>32</sup>
Nortriptyline	Equally effective in smokers with and without a history of depression. Additional antidepressant action may be beneficial. Second line treatment <sup>29</sup>
Other antidepressants including SSRIs, MAOIs, SRNIs, St John's wort	No evidence of benefit <sup>29</sup>
Longer and more intensive support	May be beneficial <sup>3,24</sup>
Co-managed care with Quitline	Effective <sup>27</sup>

smoking cessation.<sup>34,35</sup> This is consistent with its action of stimulating the dopaminergic reward pathway. Varenicline can be used in combination with antidepressants.

A recent meta-analysis found that varenicline could cause a small increased risk of serious cardiovascular events (absolute risk 0.24%).<sup>36</sup> This should be weighed up against the substantial cardiovascular benefit that results from smoking cessation.

### Anxiolytics

A Cochrane review found no evidence to support the use of anxiolytics in smoking cessation.<sup>37</sup>

### Guidelines for practice

All patients with depression should be asked if they smoke and managed according to best practice guidelines.<sup>24,31,38</sup>

There may be further benefit from additional

support<sup>24</sup> and a longer than standard course of treatment.<sup>3</sup>

It is important to ask all smokers planning to quit about their history, as depression is a common comorbidity and should be identified before cessation.

It is generally recommended that current depression is stabilised with antidepressants and counselling before attempting smoking cessation, as even a moderate decrease in mood predicts failure.<sup>15,26</sup> However, there is little evidence to demonstrate that this is more effective than concurrent treatment.<sup>4</sup>

All patients with current or past depression should be carefully monitored during the quitting process for mood changes.<sup>16</sup> Daily charting can be useful to plot mood and lifestyle habits.<sup>26</sup>

Cognitive behavioural mood management may be of benefit, especially for smokers with recurrent depression. Additional psychological therapies and

lifestyle advice can also be recommended.

Smokers already taking antidepressants should continue to take them when quitting.<sup>26</sup> Preventive antidepressants should be considered for high risk cases, especially those with recurrent depression, severe depression or previous postcessation depression. Antidepressants should be continued for 6 months or more after treatment is completed.<sup>26</sup>

Blood levels rise when taking some antidepressant drugs after smoking cessation, increasing the risk of drug side effects and toxicity. Close monitoring is recommended and dose reductions may be required.

All first line smoking cessation pharmacotherapies can be used for smokers with depression.

Varenicline is more effective than bupropion for quitting,<sup>32</sup> but the additional antidepressant action of bupropion may be beneficial in some cases.

Nortriptyline is an effective second line option, but should be used with caution. Nicotine replacement therapy may be the preferred choice because of its safety profile.

Treatments should be optimised as smokers with depression are more nicotine dependent and have lower quit rates. For example, the combination of a nicotine patch with a quick acting form of nicotine such as gum or lozenge and precessation use of nicotine patches are likely to increase success rates further.

Collaborative care with Quitline is an option for general practitioners who do not wish to manage the patient's entire quitting process.

### Author

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