

## Update on pharmacologic and nonpharmacologic therapies for smoking cessation

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### ABSTRACT

**OBJECTIVE** To review the evidence on the efficacy and safety of pharmacologic and nonpharmacologic therapies for smoking cessation.

**QUALITY OF EVIDENCE** MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for randomized controlled trials, meta-analyses, and systematic reviews (level I evidence) pertinent to pharmacologic and nonpharmacologic smoking cessation therapies.

**MAIN MESSAGE** Pharmacologic smoking cessation aids are recommended for all smokers trying to quit, unless contraindicated. A new pharmacologic smoking cessation aid, varenicline, is now available in Canada. Level I evidence at 1-year follow-up indicates that it is effective for smoking cessation. Adverse effects include nausea, insomnia, and abnormal dreaming. Nausea is mild or moderate and decreases over time. Varenicline is more effective than placebo or bupropion. Counseling also increases the likelihood of achieving cessation.

**CONCLUSION** Preliminary data indicate that varenicline is more effective than other available pharmacologic smoking cessation aids. Pharmacologic therapy should be combined with nonpharmacologic therapy.

### RÉSUMÉ

**OBJECTIF** Revoir les preuves concernant l'efficacité et l'innocuité des traitements pharmacologiques et non pharmacologiques pour cesser de fumer.

**QUALITÉ DES PREUVES** On a identifié dans MEDLINE, EMBASE et le Cochrane Database of Systematic Reviews les essais randomisés, méta-analyses et revues systématiques (preuves de niveau I) traitant de traitements pharmacologiques et non pharmacologiques visant l'arrêt du tabac.

**PRINCIPAL MESSAGE** À moins de contre-indications, on recommande des mesures pharmacologiques favorisant l'abandon du tabac à tous ceux qui tentent d'arrêter de fumer. On dispose maintenant au Canada d'une nouvelle substance qui agit dans ce sens, la varénicline. Des preuves de niveau I et un suivi d'un an indiquent que cette substance est efficace pour susciter l'abandon du tabac. Les effets indésirables incluent nausées, insomnie et rêves anormaux. Les nausées sont de légères à modérées et s'atténuent avec le temps. La varénicline est plus efficace qu'un placebo ou que le bupropion. Le counseling favorise aussi l'abandon du tabagisme.

**CONCLUSION** Des résultats préliminaires indiquent que la varénicline est plus efficace que les autres agents pharmacologiques disponibles visant l'arrêt du tabac. Le traitement pharmacologique devrait être combiné à une thérapie non pharmacologique.

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Cigarette smoking is the leading preventable cause of death and disease in Canada.<sup>1</sup> It was estimated that in 1998 smoking was responsible for 22% of all deaths in the country.<sup>2</sup> Approximately 19% of the population 15 years of age and older in Canada—nearly 5 million people—are current smokers.<sup>3</sup> Most smokers who attempt to quit do not use cessation aids and are usually unsuccessful; two-thirds relapse within 48 hours.<sup>4</sup> Pharmacologic smoking cessation aids are recommended for all smokers trying to quit, unless contraindicated.<sup>5</sup> Smokers should also be provided with counseling when attempting to quit.<sup>6</sup> Family physicians can play an important role in smoking cessation, given that 70% of smokers consult family physicians annually.<sup>5</sup> In this article, we present the current evidence on pharmacologic and nonpharmacologic smoking cessation therapies.

### Quality of evidence

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews (Cochrane Tobacco Addiction Group) were searched. Search terms and MeSH headings used included *smoking, smoking cessation, tobacco use disorder, varenicline, Champix, Chantix, bupropion, Zyban, nicotine replacement therapy, nicotine, and counseling*. No limitations were placed on the search. Reference lists in selected articles were reviewed to identify additional relevant information. Randomized controlled trials, meta-analyses, and systematic reviews (level I evidence) were assessed.

### Nicotine replacement therapy

Nicotine replacement therapies (NRTs) available in Canada include nicotine gum, patches, and inhalers. These therapies aid in smoking cessation by replacing the nicotine-mediated neuropharmacologic effects achieved by smoking.<sup>7</sup> Authors of a systematic review and meta-analysis, which reviewed randomized trials of NRT compared with placebo or no treatment that had follow-up periods of 6 months or longer, determined that NRT doubles the likelihood of smoking cessation compared with no therapy (odds ratio [OR] 1.77, 95% confidence interval [CI] 1.66-1.88).<sup>8</sup> Evidence also indicates that the nicotine patch combined with another NRT is more effective than any single NRT.<sup>9</sup> Treatment length, dosage, and efficacy of nicotine gum, patches, and inhalers are outlined in **Table 1**.<sup>8,10,11</sup> The potential

side effects of nicotine gum include upset stomach, hiccups, and sore jaw. Nicotine patches are associated with headaches, upset stomach, dizziness and nausea, sleep disturbances, and rash at the site of patch application. Adverse effects experienced by users of nicotine inhalers include throat and nasal irritation, runny nose, sneezing, and coughing.<sup>12</sup>

### Bupropion

Bupropion (Zyban) was launched as a smoking cessation aid in 1997 in the United States and has been approved in more than 50 countries.<sup>13</sup> Bupropion blocks the reuptake of dopamine and norepinephrine, which is thought to be the mechanism behind its effect on smoking cessation.<sup>14</sup> In a systematic review and meta-analysis of 31 bupropion trials in which bupropion was the sole agent used for cessation (compared with placebo or no pharmacotherapy), with 6 months follow-up or longer, the reviewers found the likelihood of cessation almost doubled with bupropion therapy (**Table 1**<sup>8,10,11</sup>).<sup>10</sup> Additional treatment with bupropion after cessation did not provide significant long-term advantage. Bupropion alone or in combination with the nicotine patch has been found to significantly increase long-term cessation rates compared with the patch alone ( $P < .001$ ). The greater abstinence rate with combination therapy compared with bupropion alone, however, was not statistically significant.<sup>15</sup> The most common side effects associated with bupropion are dry mouth and insomnia. Additionally, the risk of seizures is thought to be 1 in 1000, and is associated with risk factors such as seizure disorders and eating disorders.<sup>16</sup>

### Varenicline

A new agent, varenicline (Champix), was introduced in Canada in April 2007.<sup>17,18</sup> Varenicline is the first partial agonist of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor to be developed. The dependency effects of nicotine are thought to be mediated at these receptors.<sup>19</sup> Varenicline might diminish withdrawal symptoms (agonist effect) and reduce craving (antagonist effect); and, with nicotine exposure, the receptor occupancy of varenicline is expected to block the reinforcing effects of nicotine.<sup>20</sup> The most common side effect associated with varenicline is nausea. Other side effects include insomnia and abnormal dreaming.<sup>11,21</sup>

Another systematic review and meta-analysis assessed the efficacy and safety of varenicline<sup>22</sup> by reviewing randomized controlled trials in which varenicline was compared with placebo. Comparisons with bupropion were included when available (see **Table 1**<sup>8,10,11</sup> for the results of one of these trials<sup>11</sup>). The outcome measure was continuous abstinence at 6 months or longer from the start of treatment. Almost 5000 individuals participated in the selected studies, of which 2451 received varenicline. Participants were men and women aged 18 to 75 years

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**Table 1. Efficacy of pharmacologic therapy for smoking cessation**

PHARMACOLOGIC TREATMENT	TREATMENT LENGTH	DOSAGE	EXPERIMENTAL GROUP EVENT RATE (%)	CONTROL GROUP EVENT RATE (%)	ODDS RATIO (95% CONFIDENCE INTERVAL)
Nicotine gum <sup>8*</sup>	1-3 mo	2-mg or 4-mg pieces used for cravings or on a fixed schedule	19.5	11.5	1.66 (1.52-1.81)
Nicotine patch <sup>8*</sup>	Various	Various	14.6	8.6	1.81 (1.63-2.02)
Nicotine inhaler <sup>8*</sup>	6 mo	6-16 cartridges tapered daily in fourth mo	17.1	9.1	2.14 (1.44-3.18)
Bupropion <sup>10*</sup>	7-12 wk	150 mg once daily for 3 d, then 150 mg twice daily	20	10.2	1.94 (1.72-2.19)
Varenicline <sup>11†</sup>	12 wk	0.5 mg once daily for 3 d, then 0.5 mg twice daily for 4 d, then 1 mg twice daily for 11 wk	29.7	13.2	2.83 (1.91-4.19) <sup>‡</sup>
Varenicline <sup>11§</sup>	12 wk	0.5 mg once daily for 3 d, then 0.5 mg twice daily for 4 d, then 1 mg twice daily for 11 wk	23	10.3	2.66 (1.72-4.11) <sup>¶</sup>

\*Therapy was considered effective if patients achieved abstinence at 6 mo or longer follow-up.

†Therapy was considered effective if patients achieved continuous abstinence wk 9 through 24.

\*Number needed to treat = 6.

§Therapy was considered effective if patients achieved continuous abstinence wk 9 through 52.

¶Number needed to treat = 8.

who had smoked more than 10 cigarettes daily with no period of abstinence greater than 3 months in the previous year. The treatment period was 12 weeks, with the exception of 1 study in which patients were treated for 6 weeks, and abstinence was determined by expired carbon monoxide levels. Five studies comparing varenicline with placebo fit the study inclusion criteria, and 4 were selected for meta-analysis. (The trial not included was a safety trial of varenicline compared with placebo [52-week treatment], with cessation measured as a secondary outcome.) Participants who were lost to follow-up or who withdrew were considered continuing smokers in the analysis. Researchers assessed continuous abstinence at 52 weeks for those taking 1 mg of varenicline twice daily compared with those taking placebo. The effects of titration and dosage were examined in 2 of the studies (phase 2 trials). The pooled OR for continuous abstinence at 52 weeks for varenicline compared with placebo was 3.22 (95% CI 2.43-4.27); at 24 weeks the OR was 3.53 (95% CI 2.74-4.54); and at 12 weeks (end of treatment) the OR was 4.07 (95% CI 3.28-5.05). Three trials also compared varenicline to bupropion (150 mg twice daily); the OR was 1.66 (95% CI 1.28-2.16). Nausea, the most common side effect, was largely mild or moderate and not associated with high study discontinuation rates. Findings from the trials indicated a reduction in withdrawal and cravings; however, investigators did not assess these beyond the week following treatment, so it is not

known to what extent withdrawal symptoms and cravings were experienced after completion of treatment.

### Nonpharmacologic treatment

Nonpharmacologic cessation strategies include brief interventions, such as patient education and advice, behavioural therapy, self-help materials, and telephone counseling (Table 2<sup>23-26</sup>).<sup>23</sup> Brief physician advice has been shown to be effective in increasing the likelihood of cessation, and follow-up likely offers further benefit.<sup>24</sup> A review of randomized or quasi-randomized trials of individual behavioural counseling for smoking cessation by trained therapists not involved in routine medical care, with 6 months or longer follow-up, indicated that individual counseling was more effective than no intervention at all. Counseling consisted of 1 or more face-to-face sessions of 10 minutes or longer, often accompanied by telephone contact for support. Evidence was insufficient to determine whether more intensive counseling was more effective.<sup>25</sup> Group counseling is more effective than self-help and other less intensive intervention methods for smoking cessation.

**Table 2. Efficacy of nonpharmacologic therapy for smoking cessation: Therapy was considered effective if patients had achieved abstinence at follow-up of 6 mo or longer.**

NONPHARMACOLOGIC TREATMENT	EXPERIMENTAL GROUP EVENT RATE (%)	CONTROL GROUP EVENT RATE (%)	ODDS RATIO (95% CONFIDENCE INTERVAL)
Individual counseling <sup>23</sup>	12.7	8.9	1.56 (1.32-1.84)
Group counseling <sup>24</sup>	17.2	7.7	2.17 (1.37-3.45)
Self-help <sup>25</sup>	5.6	4.8	1.24 (1.07-1.45)
Telephone counseling <sup>26</sup>	10.5	7.5	1.41 (1.27-1.57)

It is unclear if group counseling is more effective than individual counseling, but it is more effective than no intervention.<sup>26</sup> Self-help materials might improve quit rates among smokers compared with those who receive no intervention, but the effect is small.<sup>27</sup> Proactive telephone counseling, in which the counselor initiates client contact, enhances the benefit of telephone counseling relative to reactive counseling, in which the client initiates contact. Multiple sessions of call-back counseling improve quit rates.<sup>28</sup> Web-based cessation programs have been found to be effective in smoking cessation<sup>29,30</sup>; however, more research is needed.<sup>31</sup> An example of a smoking cessation flow sheet is available from the Clinical Tobacco Intervention Program at [www.ctica.org/new\\_fee\\_code\\_cessation.pdf](http://www.ctica.org/new_fee_code_cessation.pdf).

### Combined therapy

Pharmacotherapy and counseling should be used in conjunction to further improve the chances of successful cessation.<sup>5,6</sup> Brief counseling combined with NRT has been found to be more effective than counseling alone in a randomized study of hospital patients receiving smoking cessation interventions.<sup>32</sup> Intensive cognitive behavioural therapy initiated in-hospital, with 3 months of follow-up telephone counseling combined with 2 months of nicotine patch therapy, has been compared with hospital-initiated minimal counseling combined with nicotine patch therapy and found to be more effective for achieving long-term cessation.<sup>33</sup> In another randomized study of telephone counseling combined with nicotine patch therapy, individuals who received both counseling and NRT had significantly greater abstinence rates compared with those who received NRT alone (28-day abstinence,  $P = .01$  at 6 months; 90-day abstinence,  $P = .004$  at 6 months).<sup>34</sup>

### Discussion

Smoking cessation at 1-year follow-up is the preferred outcome measure. However, with the exception of the varenicline systematic review (in which end-of-treatment, 6-month, and 1-year outcome measures were calculated), the meta-analyses included in this review calculated outcomes based on pooled data from studies with variable follow-up periods of 6 months or longer. Additionally, the number needed to treat (NNT) is the preferred comparison measure. Owing to validity issues related to NNTs calculated from meta-analyses, only the NNT for varenicline was calculated; this calculation was based on an individual trial (Table 1<sup>8,10,11</sup>).<sup>11</sup> The NNT from pooled results can be misleading owing to variation between trial event rates; differences in outcomes, clinical settings, and baseline risks; and imbalances in the number of patients between arms of individual trials.<sup>35,36</sup>

Several limitations of the preliminary research on varenicline are noteworthy. The generalizability of the trials might be limited given the extensive exclusion

### Smoking cessation resources for patients and physicians

Canadian Cancer Society: [www.cancer.ca](http://www.cancer.ca)

Canadian Council for Tobacco Control: [www.cctc.ca](http://www.cctc.ca)

Canadian Lung Association: [www.lung.ca](http://www.lung.ca)

Clinical Tobacco Intervention Program:  
[www.omacti.org](http://www.omacti.org)

Go Smokefree (Health Canada):  
[www.hc-sc.gc.ca/hl-vs/tobac-tabac/index\\_e.html](http://www.hc-sc.gc.ca/hl-vs/tobac-tabac/index_e.html)

Heart and Stroke Foundation of Canada:  
<http://heartandstroke.com>

*On the Road to Quitting.*

*Guide to becoming a non-smoker:* [www.hc-sc.gc.ca/hl-vs/pubs/tobac-tabac/orq-svr/index\\_e.html](http://www.hc-sc.gc.ca/hl-vs/pubs/tobac-tabac/orq-svr/index_e.html)

Physicians for a Smoke-Free Canada:  
[www.smoke-free.ca](http://www.smoke-free.ca)

Public Health Agency of Canada:  
[www.phac-aspc.gc.ca](http://www.phac-aspc.gc.ca)

Quit4Life (Health Canada): [www.quit4life.com](http://www.quit4life.com)

Smokers' Helpline (Canadian Cancer Society):  
[www.smokershelpline.ca](http://www.smokershelpline.ca)

*Smoking Cessation Guidelines.*

*How to Treat your Patient's Tobacco Addiction:*  
[www.smoke-free.ca/pdf\\_1/smoking\\_guide\\_en.pdf](http://www.smoke-free.ca/pdf_1/smoking_guide_en.pdf)

Stupid.ca: [www.stupid.ca](http://www.stupid.ca)

criteria.<sup>37</sup> With increased exclusion criteria, the probability that treatment groups represent the greater population decreases.<sup>38</sup> For example, positive associations exist between smoking and alcohol abuse, mental distress such as depression and anxiety, and decreased physical activity; however, alcohol abuse or dependence and treatment for depression during the previous 12 months were exclusion criteria.<sup>39</sup> Minimal justification for selecting these specific exclusion criteria is provided.

The study protocol represents an ideal intervention, which might lend itself to an increased treatment effect. With the exception of 1 trial, all participants were provided with brief counseling ( $\leq 10$  minutes) during treatment and follow-up. For example, in 2 of the trials each patient received a cessation self-help booklet at the baseline visit and a telephone call 3 days after the selected quit date. During the 12-week treatment phase, participants received brief counseling during weekly clinic visits. In the follow-up periods of the trials (13-52 weeks), patients attended clinics during weeks 13, 24, 36, 44, and 52, and received telephone calls at weeks 16, 20, 28, 32, 40, and 48.<sup>11,21</sup>

The average completion rates across the 4 studies included in the meta-analysis were 62.2% for patients treated with varenicline, 57.9% for those treated with bupropion, and 49.7% for those receiving placebo. Losses to follow-up were substantially different among groups in 3 of the studies. Losses to follow-up and study withdrawal can result in a threat to the power needed to detect a treatment effect and can contribute to attrition bias, whereby characteristics of the baseline participants differ from those who were lost to follow-up or withdrew.<sup>40</sup> If a difference in the number of people leaving each arm exists, it is likely that the groups are not balanced.<sup>41</sup> Intention-to-treat analysis, which is preferable in randomized controlled trials, was used in the studies. All randomized participants were included in the efficacy analysis regardless of whether they received treatment or complied with study protocol.<sup>42</sup> However, given that individuals who dropped out of the study or were lost to follow-up were deemed continuing smokers and that intention-to-treat analysis was used, the efficacy of bupropion and placebo might have been misrepresented relative to varenicline owing to the higher completion rates in the varenicline groups.

Studies to date have been funded by varenicline's manufacturer, Pfizer Inc, and the company was involved in all elements of each study. Independently funded and administrated studies are needed to more confidently determine the efficacy and tolerability of varenicline. Head-to-head studies are also needed to help determine the relative efficacy of treatments. It is unclear whether the cost of varenicline, which is approximately \$150 monthly, will have an effect on its use.

## Conclusion

The evidence illustrates the effectiveness of pharmacologic and nonpharmacologic smoking cessation therapy compared with no treatment. Varenicline appears to be more effective than other available pharmacologic smoking cessation aids. Offering the choice of pharmacologic therapy in addition to supportive counseling and telephone support, which is now available in all provinces, should help family physicians achieve greater success assisting their patients with smoking cessation. Family physicians should share the evidence with patients and encourage them to combine pharmacologic therapy and counseling to improve the likelihood of success. ✨

## Competing interests

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### EDITOR'S KEY POINTS

- Pharmacologic therapies (nicotine replacement therapy, bupropion, and varenicline) and nonpharmacologic therapies (patient education, behavioural therapy, self-help materials, and telephone counseling) improve the likelihood of successful smoking cessation.
- Preliminary data suggest that varenicline is more effective than other pharmacologic therapies, but some important study limitations (extensive exclusion criteria, substantially different losses to follow-up between groups, and industry funding) might affect the reliability and generalizability of the results.
- All smokers who are trying to quit should be offered both pharmacologic and nonpharmacologic smoking cessation therapies.

### POINTS DE REPÈRE DU RÉDACTEUR

- Les traitements pharmacologiques (thérapie nicotinique de substitution, bupropion et varénicline) et non pharmacologiques (éducation du patient, thérapie comportementale, outils d'aide personnelle et conseils par téléphone) sont efficaces pour amener l'arrêt du tabagisme.
- Des données préliminaires suggèrent que la varénicline est plus efficace que les autres traitements pharmacologiques, mais certaines limitations importantes de l'étude (critères d'exclusion sévères, pertes au suivi différant considérablement entre les groupes et financement industriel) pourraient affecter la fiabilité et la possibilité de généralisation des résultats.
- On devrait offrir de tels traitements pharmacologiques ou non pharmacologiques à tous ceux qui tentent d'arrêter de fumer.

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