

# Pharmacotherapy Summary for the Treatment of Nicotine Withdrawal and Nicotine Dependence<sup>1</sup>

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Corroborating evidence for this document is posted on: [www.HealthCPR.ca](http://www.HealthCPR.ca)

## NICOTINE WITHDRAWAL

Withdrawal from nicotine is not synonymous with treatment of nicotine dependence. Nicotine withdrawal is managed by offering sufficient doses of nicotine replacement therapy (NRT) either to remedy or to prevent withdrawal<sup>2</sup> from nicotine:

- NRT patch
- NRT gum
- NRT inhaler
- NRT lozenge
- Combination NRT

### Protocol for Managing Nicotine Withdrawal

Start with one slow-release NRT form (i.e. patch) and combine ad lib short-acting (e.g. gum/inhaler/lozenge) for break-through cravings:

| Number of Cigarettes per Day (cpd) | Start Dose of NRT Patch |
|------------------------------------|-------------------------|
| < 5 cpd                            | None                    |
| 5 - 10 cpd                         | 7mg                     |
| 11 - 17 cpd                        | 14mg                    |
| 18 - 24 cpd                        | 21mg                    |
| 25 - 31 cpd                        | 28mg (21 + 7)           |
| 32 – 40 cpd                        | 35mg (21 + 14)          |
| > 40 cpd                           | 42mg (21 + 21)          |

*Cautions and contra-indications are similar to those listed in Nicotine Dependence Treatment below.*

## NICOTINE DEPENDENCE TREATMENT

For the treatment of nicotine (tobacco) dependence, there are six (6) medication options available in Canada. Medication (unless contraindicated) is always combined with counseling (psychosocial interventions) for the treatment of nicotine dependence.

- Four (4) nicotine replacement therapy (NRT) options:
  - nicotine transdermal patch
  - nicotine gum
  - nicotine inhaler
  - nicotine lozenge
- Bupropion SR
- Varenicline.

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<sup>1</sup> *Disclaimer: The information contained in this summary is for the purpose of guidance only and is not intended to replace clinical judgment.*

<sup>2</sup> *Withdrawal symptoms are listed at: [www.tracii.ca](http://www.tracii.ca)*

| Medication or Modality   | Benefits  | Considerations  | Dosage Considerations  | Comments   |
|--|---|---|--|--|
| <b>NRT Combinations</b>  | <p>The goal of combining nicotine replacement therapies with each other is to achieve sustained levels of nicotine with rapid adjustment for acute needs, to remedy withdrawal symptoms.</p> <p>Combinations may be more efficacious than single NRT (monotherapy).</p> <p>Recipients report greater levels of comfort.</p> <p>Combinations should be considered as first-line.</p> <p><b>Or:</b></p> <p>Second-line: Combinations may be for those who have failed mono-therapy, or based on patient preference.</p> <p>More efficacious for those who are more addicted (i.e. higher FTND scores).</p> <p>Approved by Health Canada (5, 10, or 15mg plus nicotine gum 2mg).</p> | <p>Cost factor.</p> <p>As listed in individual sections of NRT.</p> <p>Combinations may increase risk of nicotine toxicity (non-lethal).</p>  | <p><b>Within Label:</b> Currently the only Health Canada approved NRT for combination is 16hr patch delivering 15, 10 or 5mg combined with nicotine gum 2mg prn.</p> <p><b>Off Label:</b> 21mg per day plus gum or inhaler or lozenge ad lib prn. when acute withdrawal symptoms and urges to smoke occur.</p> <p>Adjust dose of patch (e.g. add increments of 7mg patch to existing regime) if frequent use of other NRT: goal is to minimize need for short-acting NRT dosing.</p>   | <p>Nicotine administered when a person continues to smoke does not constitute clinically relevant excess cardiovascular risk.</p> <p>Nicotine is addictive, and a substantial percentage of users report difficulty reducing or abstaining from pharmaceutical-grade short-acting nicotine (gum).</p> <p>Smokeless tobacco is not recommended as a nicotine replacement preparation for the treatment of dependence.</p> <p>Reduce to quit approaches may be considered.</p>   |
| <p><b>Nicotine Patch</b></p> <p>7mg.</p> <p>14mg.</p> <p>21mg.</p> <p>24-h delivery.</p> <p><b>Or:</b></p> <p>5mg</p> <p>10mg</p> <p>15mg</p> <p>16-h delivery</p> | <p>Goal: As above: To achieve sufficient saturation of nicotine receptors.</p> <p>Safe and effective.</p> <p>Most recipients report relative easy of use.</p> <p>Application only once a day.</p>   | <p>May require additional directions in persons with severe and persistent mental illness.</p> <p>Patch alone allows for limited flexibility in dosing.</p> <p>Many report mild skin rashes.</p> <p>Time to relief of nicotine withdrawal symptoms often 2-4 hours and may be incomplete.</p> | <p>Simple dosing: 21mg if smoking 1 pack per day or more.</p> <p>42mg if smoking more than 40 cigarettes per day</p> <p>Dosing greater than 21mg per day should be done in consultation with a physician.</p> <p>Titrate dose upwards, based on emergence of withdrawal symptoms, continued smoking without toxicity while using NRT, urges, and comfort.</p> <p>After 4-6 weeks of abstinence from smoking, reducing patch dose every 2-4 weeks in 7-14 mg steps allowing for symptoms relief.</p> <p>Flexibility of dosing is vital.</p> | <p>Over the counter (OTC)</p> <p>Patches should not be cut in half.</p> <p>Patches should not be chewed, boiled, or smoked.</p> <p>Disposing of used patches is done by folding sticky side onto itself and safely discarding such.</p> <p>Patches are applied to a dry and clean area of the skin.</p> <p>Patches vary in strengths and the length of time over which nicotine is delivered. Depending on the brand of patch used, may be left on for anywhere from 16 to 24 hours. If insomnia is reported, consideration should be given to removal 2 hours prior to bedtime.</p> <p>Patches may be placed anywhere on the upper body-including arms and back, avoiding nipples, hairy areas, or skin folds.</p> <p>Rotate the patch site each time a new patch is applied.</p> |

| Medication or Modality   | Benefits   | Considerations   | Dosage Considerations  | Comments   |
|--|--|--|--|--|
| <p><b>Nicotine Lozenge</b></p> <p>1mg<br/>2 mg<br/>4 mg</p>                      | <p>Relatively easy to use.<br/>Rapid relief of breakthrough cravings.</p>                        | <p>Nausea is frequent.<br/>Local irritation.<br/>Hiccups.</p>  | <p>Use at least 8-9 lozenges/day initially. Dose-dependent efficacy and frequency of side-effects.</p> <p>Based on <b>cigarettes/day (cpd)</b>:</p> <p>&gt;20 cpd: 4 mg<br/>&lt;20 cpd: 2 mg</p> <p>Based on <b>time to first cigarette</b> of the day:</p> <p>&lt;30 minutes = use 4 mg<br/>&gt;30 minutes = use 2mg</p> <p>Initial dosing is 1-2 lozenges every 1-2 hours (minimum of 9/day).</p> <p>Increase as tolerated and taper as allowing for symptom relief.</p> | <p>Over the counter (OTC)<br/>Monotherapy or combination NRT.<br/>Delivers nicotine through the lining of the mouth while the lozenge dissolves.<br/>Avoid eating or drinking 15 minutes before use or during use.<br/>Lozenge tablets should not be chewed or swallowed, as this would limit absorption and efficacy.</p>   |
| <p><b>Nicotine Gum</b></p> <p>2mg<br/>4mg<br/>Flavors: Orange, Mint, Regular</p> | <p>Convenient/flexible dosing.<br/>Faster delivery of nicotine than the monotherapy patches.</p> | <p>May be inappropriate for people with dental problems and those with temporomandibular joint (TMJ) syndrome.<br/>Frequent use during the day required to obtain adequate nicotine levels.<br/>Many people use this medication incorrectly.<br/>Review package directions carefully to maximize benefit of product.</p> | <p>Dosing as Monotherapy**</p> <p>Based on <b>cigarettes/day (cpd)</b></p> <p>&gt;20 cpd: 4 mg gum<br/>&lt;20 cpd: 2 mg gum</p> <p>Based on <b>time to first cigarette</b> of the day:</p> <p>&lt;30 minutes = 4 mg<br/>&gt;30 minutes = 2 mg</p> <p>Initial dosing is 1-2 pieces every 1-2 hrs (10-12 pieces/day).</p> <p>Increase as tolerated and taper as allowing for symptom relief.</p>   | <p>Over the counter (OTC)<br/>Monotherapy or combination therapy.<br/>The term "gum" is misleading. It is not chewed like regular gum but rather is chewed briefly and then "parked" between cheek and gum.<br/>Nicotine is absorbed through the lining of the mouth.<br/>Should not be chewed as regular gum.<br/>Should not be swallowed.<br/>Should not be combined with regular chewing gum.<br/>Should not eat or drink 15 minutes before use or during use.<br/>Should not be chewed while consuming caffeinated (or selected other/acidic) beverages.<br/>Dispose of properly.<br/>Reduce to quit approaches may be considered.</p> |

| Medication or Modality             | Benefits  | Considerations   | Dosage Considerations   | Comments  |
|------------------------------------|---|--|---|---|
| <b>Nicotine Inhaler</b>            | Flexible dosing.<br>Mimics the hand-to-mouth behavior of smoking.<br>Patient does not need to inhale deeply to achieve an effect.<br>Few side effects.  | Frequent use during the day required to obtain adequate nicotine levels .<br>May cause mouth or throat irritation.<br>Puffing must be done frequently, far more often than with a cigarette.<br>Each cartridge designed for 80 puffs over 20 minutes of use.   | Dosing as monotherapy<br>Minimum of 6 cartridges/day, up to 16/day<br>Taper as tolerated  | A plastic cylinder containing a cartridge that delivers nicotine when puffed.<br><br>The inhaler delivers nicotine to the oral mucosa, not the lung, and enters the body much more slowly than the nicotine in cigarettes.  |
| <b>Bupropion SR</b><br>150mg       | Easy to use,<br>Pill form<br>Few side effects   | May be used in combination with NRT.<br><br>Contraindicated with certain medical conditions, e.g. eating disorders (anorexia/bulimia), seizures/epilepsy, brain injuries, active alcohol addiction, withdrawal from alcohol and benzodiazepines, and medications (lowering seizure threshold), or MAOis. | Dosing: Take doses at least 8 hours apart.<br>Start 150mg/d one week prior to the selected "target quit date" (TQD) 150mg once daily for 3 days, then 150 mg twice daily for 4 days, taken 8 hours apart, then on TQD, person is expected to quit smoking.<br><br>Continue at 150 mg bid for 12 weeks, or longer if necessary.<br>May stop abruptly; no need to taper.<br>150mg may be efficacious so lower doses if the patient is unable to tolerate the full dose. | Associated with a slight risk of seizure (1:1000).<br><br>Although XL formulations of bupropion are available, these are not registered for tobacco addiction treatment.<br><br>Should not be used concomitantly with other bupropion preparations.<br><br>If mood reported to have improved as a result of treatment, consider extending and screen for underlying depression. |
| <b>Varenicline</b><br>0.5mg<br>1mg | Easy to use.<br>Pill form.<br>Generally well-tolerated.<br>No known drug interactions.<br><br>Does not cause psychiatric illness, but quitting smoking may trigger mood and behavioral disturbances.<br><br>Can be used in combination with bupropion and/or NRT. | Nausea is common (1/3 of recipients).<br><br>Taking every dose of medication with food.<br><br>Titrating the dose as directed will help with nausea.<br><br>Contraindicated in severe renal impairment.  | Start medication one week prior to the TQD/Target Quit Date (TQD) 0.5 mg once daily X 3 days, then 0.5 mg twice daily X 4 days, then ON TQD STOP SMOKING AND Take 1.0 mg twice daily X 11 weeks If not smoking at the end of twelve weeks, may continue at 1.0 mg twice daily for an additional 12 weeks May stop abruptly.<br><br>No need to taper.<br><br>Maintenance dose of 1mg per day (in divided doses) also approved by Health Canada.                        | Dose may have to be adjusted if kidney function is impaired.<br><br>Neuropsychiatric consequences of smoking cessation should be observed.<br><br>Persons with trouble tolerating the dose of 1mg bid may be trialed on 0.5mg bid.  |

## General Comments

1. Nicotine replacement therapy is available over-the-counter, but for coverage consideration under selected medical schemes, a prescription may be issued.
2. Bupropion and varenicline are available only by prescription.
3. NRT acts as a pure agonist at the  $\alpha 4\beta 2$  nicotinic receptor, while bupropion modulates this receptor and also inhibits reuptake of dopamine and norepinephrine. Varenicline is a partial agonist at the  $\alpha 4\beta 2$  nicotinic receptor.
4. Some persons may use medication for longer than 3 months and at higher doses than what the monographs direct.
5. When persons reduce or quit smoking, consideration should be given to reducing the consumption of caffeine as well.
6. E-cigarettes are not recommended for the treatment of nicotine dependence.
7. Smokeless tobacco is not recommended for the treatment of tobacco dependence.
8. Nicotine replacement therapies can be combined with each other, e.g. patch plus gum, or patch plus inhaler, or patch plus gum plus inhaler, etc.
9. Bupropion can be combined with NRT.
10. Varenicline can be combined with nicotine (cautionary statement).
11. Varenicline can be combined with bupropion.
12. All six options available in Canada are proven to be safe and effective in a broad range of populations.
13. Mental illness per se is not a contra-indication for the use of varenicline.
14. Varenicline, although associated in some rare cases, is not causally related to the development of psychosis, mania, depression, or suicide.
15. Abstaining from tobacco (i.e. quitting smoking) can lead to the deterioration of mood, in persons with or without a history of mood disorders.
16. Heavy smokers are at greater risk of committing suicide.
17. Empiric evidence suggests that bupropion and varenicline may be of benefit in the population of tobacco users with mental illness and/or addiction, using the dosing guidelines recommended for cigarette smokers.
18. Nortriptyline and clonidine are available as second-line options for the treatment of tobacco dependence (including in Section 19).
19. Treatment recommendations for addiction to smokeless tobacco (snus):
  - a. 24 hour nicotine patch. Consider double-patching.
  - b. Consider combination NRT.
  - c. Symptom-triggered protocols: Increase dose of NRT to remedy withdrawal symptoms, urges, and to achieve comfort.
  - d. Taper gradually after 4-6 weeks of abstinence, taper every 2-4 weeks in 7-14 mg steps as tolerated.
  - e. Nicotine inhaler is not recommended for use in ST users.
  - f. Bupropion and/or varenicline may be of benefit, but replicated RCTs are not currently available.
20. The dosages of concomitant medications (ie those metabolized by CYP P450 1A2) e.g. clozapine, olanzapine, may have to be adjusted if person undergoes reduction or cessation attempts, irrespective of whether pharmacotherapy for tobacco treatment is used. Consumption of caffeine also requires reduction when quitting smoking as caffeine is also a substrate for 1A2.

**Disclaimer:** "This treatment guideline is offered for purposes of guidance only. Individual clinical decisions regarding patient care needs to be made on the merit of each case, and clinical decision-making and duty of care resides with the attending physician/care provider making the recommendations".

### References:

1. The Tobacco Reduction and Cessation Process: TRaC II (Alberta Medical Association/Primary Care): [www.TRaCII.ca](http://www.TRaCII.ca)
2. Fiore M, et.al. U.S. Public Health Service Guideline
3. Product Monographs: Nicotine replacement therapy, bupropion, varenicline.
4. MAYO Clinic Summary of treatment recommendations.
5. Tonstad S, Els C. (2010): Clinical Therapeutics.