Evidence report for smoking cessation

Prepared by EBSCO Health Innovations and EBM Development Department:

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Evidence report for smoking cessation

Scoping

Prepared by EBSCO Information Services

February 17, 2020
Revised March 2, 2020 to add FAQ5 Will it affect my weight?
Revised March 10, 2020 to modify FAQ4 (US variant) to What will it cost?

Prepared by EBSCO Health Innovations and EBM Development Department:

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Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NMA – network meta-analysis
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report that may appear in this report

NADAC – National Average Drug Acquisition Cost
NDC – National Drug Code
NRT – nicotine replacement therapy

Methods

Scoping was completed on February 17, 2020. Scoping was revised and agreed with UKSH on March 2, 2020.

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ. For example, we might say: "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis." Otherwise, where we say: "We will include a description of", "We will include descriptive responses", or something similar, we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

Results – Criteria Selection for Critical Appraisal

Population:

Inclusion criteria

Adults who smoke and are willing to make attempt to quit. Trials that also recruit adolescents will be included if majority of included participants are adults.

Exclusion criteria

Adolescents or children as the primary participants.
Trials which limit inclusion criteria to special populations (such as specific comorbidities).

Intervention and Comparator/Options:

No treatment

Quitting without the assistance of counseling or medication

Note: This option is not explicitly scoped for UKSH but is added for use in other derivative works from this Evidence Review which is also used to support DynaMed Shared Decisions content predating the UKSH work.

Counseling (talking with a coach)

Interventions may include individual or group counseling, in-person or telemedicine-based counseling, any counseling technique, and any combination of counseling interventions. However, the primary intervention of interest is "counseling in general", so broadly inclusive systematic reviews will be preferred if available. If not, then individual in-person counseling would be the most relevant example for counseling, and evidence limited to other counseling variations would not be of primary interest.

Trials comparing different counseling approaches with each other will be excluded.

The intervention of interest is counseling as an additional therapeutic intervention, generally manifested as referral or taking action to obtain, use, or receive additional counseling services. We are not interested in "counseling" as used in the definition of providing advice or instruction. We will not include studies that evaluate brief interventions such as advice from a physician or nurse in the context of their usual and customary practice without additional encounters for the specific purpose of therapeutic counseling.

Nicotine replacement - gum

Nicotine replacement therapy is the use of nicotine in any approved delivery form. This option is specific to gum form.

Nicotine replacement - patch

Nicotine replacement therapy is the use of nicotine in any approved delivery form. This option is specific to skin patch or transdermal form.

Nicotine replacement - inhaler

Nicotine replacement therapy is the use of nicotine in any approved delivery form. This option is specific to inhaler form.

Nicotine replacement - nose spray

Nicotine replacement therapy is the use of nicotine in any approved delivery form. This option is specific to nose spray form.

Nicotine replacement - lozenge

Nicotine replacement therapy is the use of nicotine in any approved delivery form. This option is specific to lozenge form.

Bupropion

Bupropion, with the labeled dosing target being 300 mg/day (often/typically given as 150 mg of bupropion twice a day and titrated upward from an initial dose of 150 mg once a day).

Varenicline

Varenicline, with the labeled dosing target being 1 mg twice a day (often/typically titrated upward from initial doses of 0.5 mg once daily followed by 0.5 mg twice daily).

Outcomes:

FAQ 1: What does the treatment involve?

We will include a description of the treatment or procedure, including frequency of dosing, form of delivery for nicotine replacement option (e.g., chewing gum, patch, etc.), and need for continuation of treatment after quitting.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: Will it help me quit smoking?

The outcome of interest is smoking cessation ≥ 24 weeks from the start of the intervention. Whenever possible, we will use a measure of sustained cessation rather than point prevalence. We will use the strictest available criteria to define abstinence. For example, we will use biochemically verified rates preferentially over rates based on self-report of quitting. When available, we will use 6-month/24-week outcome data in preference to other timepoints or summary data with variable timepoints, because this is the most common timepoint used across the evidence base.

We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist.

For all medication interventions, the comparator of key interest is placebo. Trials that include a co-intervention equally applied in both groups will be allowed. As many medication trials include counseling as a co-intervention for all people in the trial, the "placebo" group may be better thought of as "placebo + counseling" and the medication group may be better thought of as "medication + counseling".

For counseling, the preferred comparator is attention control. If attention control is not available, then usual care is the next preferred comparator.

If evidence for the various forms of nicotine replacement therapy do not demonstrate clear heterogeneity of treatment effect, we may consider an overall pooled estimate for efficacy that combines the different forms of nicotine replacement therapy to avoid spurious impressions of differences in efficacy that are more likely attributable to statistical fluctuation around a "true" effect.

FAQ 3: What are the side effects?

The outcomes of interest are named side effects and specific risk estimates if available, as preferred over an overall rate of side effects or overall withdrawal rates due to side effects.

We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist, using the evidence identified for FAQ 2.

Where direct comparative evidence across options is available for estimated rates of side effects, this evidence will be preferentially used. This is specifically intended to reduce the need for creating "common control event rates" for numerous side effects across numerous options.

For counseling as an option, the placebo control rates from other evidence identified will be used with an explanation that this is a common experience of rates without medication and not an adverse effect of counseling.

For different nicotine replacement therapy options, in the absence of data suggesting different rates of systemic side effects, we will use the same estimates for side effects across all options.

For adverse events related to site of application that may only occur with specific nicotine formulations, we will use Micromedex drug monographs. For these side effects, directly observed rates with nicotine formulation will be considered most informative as "placebo rates" are likely attributable to the delivery method rather than what would occur without the medication. If quantitative rates are not available these adverse events may be described qualitatively.

FAQ 4: Is a generic version available?

Variant FAQ 4 for United States use: What will it cost?

We will include (for the drug options) whether a nonbranded generic version is available.
For United States use, we will estimate the acquisition cost of the drug options in the United States based on National Average Drug Acquisition Cost (NADAC) data.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 5: Will it affect my weight?

The outcome of interest is weight change attributable to the intervention.

Smoking cessation (regardless of interventions used to facilitate smoking cessation) is associated with weight gain (Aubin 2012, Tian 2015). However, this is not informative regarding the effects of smoking cessation interventions on modification of this change in weight.

We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist. If direct comparative data are available that compare all the options against each other, this will be preferentially used. In the absence of such data, the comparator of key interest for the agents will be placebo (or no treatment if placebo-controlled evidence is lacking).

We will conduct an evidence review with quantitative analysis to inform the effects of interventions on weight change, but we will plan for qualitative synthesis to provide patient-friendly answers to this question. Literature regarding postcessation weight gain concern is inconsistent with respect to: (1) the effect on modification of smoking cessation rates and (2) specification or validation of a minimially important difference to use as a threshold for quantitative analysis (Germeroth 2018).

For the placebo/no treatment and counseling options, we will provide a qualitative statement that, on average, people gain some weight when they quit smoking.

For medication options, we will follow this statement with a qualitative statement about the effect (or absence of effect) of the medication on this weight gain.

Additional considerations for the report for Universitätsklinikum Schleswig-Holstein (UKSH):

- In the background information for the report, we will note:
    - the website www.anbieter-raucherberatung.de, which has a database for smoking cessation courses of the Deutsches Krebsforschungszentrum (DKFZ) and the Bundeszentrale für gesundheitliche Aufklärung (BZgA)
    - that some people may consider complementary / alternative approahces to smoking cessation (e.g., acupuncture, hypnosis), but that these modaliites have uncertain / limited evidence
    - that e-cigarettes / "vaping" products are not recommended as either an alternative to smoking cigarettes or as a modality to help quit smoking
        - we will explcitly mention the Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP) Positionspapier
        - we will explicilty note research is in its infancy for e-cigarettes / "vaping"
- UKSH may include information about local insurance coverage for the scoped interventions
- These concepts are not scoped for evidence review by EIS.

Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ. 2012 Jul 10;345:e4439. doi:10.1136/bmj.e4439. PubMed

Germeroth LJ, Levine MD. Postcessation weight gain concern as a barrier to smoking cessation: Assessment considerations and future directions. Addict Behav 2018 Jan;76:250-257. PubMed

Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. Obes Rev 2015 Oct;16(10):883-901. PubMed

Evidence report for smoking cessation

Evidence Synthesis

Prepared by EBSCO Information Services

February 24, 2020
Revised March 9, 2020 to add FAQ5 Will it affect my weight?
Revised March 10, 2020 to modify FAQ4 (US variant) to What will it cost?

Prepared by EBSCO Health Innovations and EBM Development Department:

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Eric Manheimer, PhD, EBM Editor

Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, we will summarize the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis; we will prefer using a tabular format for this summary in most cases, but depending on the circumstances, we may adopt a non-tabular form instead. For each outcome, we will then articulate the method selected for evidence synthesis and justification of that method; again, we will prefer a tabular approach in most cases, but we may articulate the justification in a non-tabular form depending on the circumstances. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the evidence synthesis process will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of descriptive sources

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

No treatment

You will stop smoking without help from medicines or counseling.

Counseling (talking with a coach)

You will talk with a skilled guide or coach about ways to help you quit.

Nicotine gum

You will chew gum 9 or more times a day for 6 weeks. Then you will chew gum less often for the next 6 weeks.

Nicotine patch

You will wear a skin patch all day for 8 to 10 weeks. The dose of the patch will be changed at times.

Nicotine inhaler

You will breathe from an inhaler 20 minutes at a time. You will use the inhaler 6 to 16 times a day for 3 weeks. Then you will use the inhaler less often for the next 9 weeks.

Nicotine nose spray

You will use a nose spray 8 to 40 times a day for 8 weeks. Then you will use the nose spray less often for the next 4 to 6 weeks.

Nicotine lozenge

You will suck on a lozenge 9 or more times a day for 6 weeks. Then you will use one less often for the next 6 weeks.

Bupropion

You will take one pill a day for 3 days then one pill twice a day. You can start the pill up to 2 weeks before you quit smoking. You will take the pills for at least 7 weeks. You may keep taking the pills longer. Bupropion can also be used to help people with depression or seasonal affective disorder.

Varenicline

You will take one pill a day for 3 days then one pill twice a day. You will start the pill a week or more before you quit smoking. You will take the pills for 12 weeks. You may keep taking the pills longer.

FAQ 2: Will it help me quit smoking?

No treatment

Only **10** out of 100 smokers (10%) quit smoking and continue to not smoke at 6 months.

Counseling (talking with a coach)

15 out of 100 smokers (15%) quit smoking and continue to not smoke at 6 months. Talking to your coach more times may increase your chances of quitting.

Nicotine gum

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Nicotine patch

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Nicotine inhaler

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Nicotine nose spray

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Nicotine lozenge

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Bupropion

17 out of 100 smokers (17%) quit smoking and continue to not smoke at 6 months.

Varenicline

23 out of 100 smokers (23%) quit smoking and continue to not smoke at 6 months.

FAQ 3: What are the side effects?

No treatment

Some symptoms happen without taking medicine. Knowing these symptoms can help you compare to taking medicine. Of 100 people, symptoms without medicine may include:

- nausea in **6** (6%)
- headache in **10** (10%)
- trouble sleeping in **7** (7%)
- strange dreams in **4** (4%)
- dry mouth in **3** (3%)
- dizziness in **3** (3%)

Counseling (talking with a coach)

There are no side effects from counseling. Some symptoms happen without taking medicine. Knowing these symptoms can help you compare to taking medicine. Of 100 people, symptoms without medicine may include:

- nausea in **6** (6%)
- headache in **10** (10%)
- trouble sleeping in **7** (7%)
- strange dreams in **4** (4%)
- dry mouth in **3** (3%)
- dizziness in **3** (3%)

Nicotine gum

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth.

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **13** (13%)
- trouble sleeping in **9** (9%)
- strange dreams in **11** (11%)
- dry mouth in **3** (3%)
- dizziness in **4** (4%)

Nicotine patch

Nicotine may increase your heart rate. You may have some redness, itching, or discomfort where the patch touches your skin.

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **13** (13%)
- trouble sleeping in **9** (9%)
- strange dreams in **11** (11%)
- dry mouth in **3** (3%)
- dizziness in **4** (4%)

Nicotine inhaler

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth or throat.

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **13** (13%)
- trouble sleeping in **9** (9%)
- strange dreams in **11** (11%)
- dry mouth in **3** (3%)
- dizziness in **4** (4%)

Nicotine nose spray

Nicotine may increase your heart rate. You may have some itching or discomfort in your nose.

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **13** (13%)
- trouble sleeping in **9** (9%)
- strange dreams in **11** (11%)
- dry mouth in **3** (3%)
- dizziness in **4** (4%)

Nicotine lozenge

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth.

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **13** (13%)
- trouble sleeping in **9** (9%)
- strange dreams in **11** (11%)
- dry mouth in **3** (3%)
- dizziness in **4** (4%)

Bupropion

Of 100 people, side effects may include:

- nausea in **9** (9%)
- headache in **9** (9%)
- trouble sleeping in **13** (13%)
- strange dreams in **5** (5%)
- dry mouth in **7** (7%)
- dizziness in **5** (5%)

Bupropion may not be the best choice for someone who has seizures or is at increased risk of having a seizure, such as people who have had a serious head injury or have an eating disorder. Bupropion may make seizures more likely for these people.

Varenicline

Of 100 people, side effects may include:

- nausea in **25** (25%)
- headache in **12** (12%)
- trouble sleeping in **10** (10%)
- strange dreams in **8** (8%)
- dry mouth in **3** (3%)
- dizziness in **3** (3%)

Early on, there was some worry about whether varenicline might increase a person's risk for a heart attack or a serious mood problem, including committing suicide. However, evidence looking into this does not suggest an increase in risk.

FAQ 4: Is a generic version available?

No treatment
Does not apply.

Counseling (talking with a coach)
Does not apply.

Nicotine gum
Yes, there is a generic version.

Nicotine patch
Yes, there is a generic version.

Nicotine inhaler
No, there is no generic version.

Nicotine nose spray
No, there is no generic version.

Nicotine lozenge
Yes, there is a generic version.

Bupropion
Yes, there is a generic version.

Varenicline
No, there is no generic version.

FAQ 4 (United States variant): What will it cost?

No treatment

Does not apply.

Counseling (talking with a coach)

It may cost hundreds of dollars. Your insurance may help. You can spend this much on cigarettes in about 2 months.

Nicotine gum

It may cost $100 to $200. Your insurance or coupons may help. You can spend this much on smoking in about 1 month.

Nicotine patch

It may cost about $100. Your insurance or coupons may help. You can spend this much on smoking in about 3 weeks.

Nicotine inhaler

It may cost $1500 to $1700. Your insurance or coupons may help. You can spend this much on smoking in 8 to 9 months.

Nicotine nose spray

It may cost $1500 to $1700. Your insurance or coupons may help. You can spend this much on smoking in 8 to 9 months.

Nicotine lozenge

The medication may cost about $300. Your insurance or coupons may help. You can spend this much on smoking in about 2 months.

Bupropion

It may cost about $20. Your insurance or coupons may help. You can spend this much on smoking in about 3 days.

Varenicline

It may cost about $1,300. Your insurance or coupons may help. You can spend this much on smoking in 6 to 7 months.

FAQ 5: Will it affect my weight?

No treatment

You may gain some weight when you quit smoking.

Counseling (talking with a coach)

You may gain some weight when you quit smoking.

Nicotine gum

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Nicotine patch

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Nicotine inhaler

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Nicotine nose spray

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Nicotine lozenge

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Bupropion

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Varenicline

You may gain some weight when you quit smoking. You might gain less weight with a medicine, but the difference may be small.

Search Summary

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	125	9
2nd-round (Systematic review searches)	280	2
3rd-round (Original article searches)	255	0
4th-round (Citation tracing)	0	0
Total	*660*	*11*

* Number shown is after deduplication

	Articles selected for evaluation (Author Year)
Systematic reviews (8)	Cahill 2016, Hartmann-Boyce 2018, Hsieh 2019, Hughes 2014, Lancaster 2017, Lindson 2019, Mottillo 2009, Sun 2018
Randomized, controlled trials (3)	Anthenelli 2016, Benowitz 2018, Tulloch 2016
Other article types (0)	None

Results – Synthesis Details

FAQ 1: What does the treatment involve?

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

No treatment

You will stop smoking without help from medicines or counseling.

Counseling (talking with a coach)

You will talk with a skilled guide or coach about ways to help you quit.

Nicotine replacement with gum

You will chew gum in place of your cigarettes. You will chew gum 9 or more times a day for 6 weeks. Then you will chew gum less often for the next 6 weeks.

Nicotine replacement with patch

You will use a skin patch in place of your cigarettes. You will wear the patch all day for 8 to 10 weeks. The dose of the patch will be changed at times.

Nicotine replacement with inhaler

You will breathe from a puffer in place of your cigarettes. You will use the puffer for 20 minutes at a time. You will use the puffer 6 to 16 times a day for 3 weeks. Then you will use the puffer less often for the next 9 weeks.

Nicotine replacement with nose spray

You will use a nose spray in place of your cigarettes. You will use the nose spray 8 to 40 times a day for 8 weeks. Then you will use the nose spray less often for the next 4 to 6 weeks.

Nicotine replacement with lozenge

You will suck on a lozenge in place of your cigarettes. You will use one 9 or more times a day for 6 weeks. Then you will use one less often for the next 6 weeks.

Bupropion

You will take a pill to make it easier to quit smoking. You can start the pill up to 2 weeks before you quit smoking. You will take one pill a day for 3 days then one pill twice a day. You will take the pills for at least 7 weeks. You may keep taking the pills longer. Bupropion can also be used to help people with depression or seasonal affective disorder.

Varenicline

You will take a pill to make it easier to quit smoking. You will start the pill a week or more before you quit smoking. You will take one pill a day for 3 days then one pill twice a day. You will take the pills for 12 weeks. You may keep taking the pills longer.

(DynaMed 2019-2020)

FAQ 2: Will it help me quit smoking?

Evidence Review

Continuous abstinence rates at 6 months (closest approximation)

Intervention vs. Comparator	Source (number of trials; number of participants)	Control group event rate (%)	Relative effect estimate	Certainty
Individual counselling vs. minimal contact control*	Lancaster 2017 (33; 13,762)	7.7%	RR 1.48 (95% CI 1.34 to 1.64)	Moderate (inconsistency)[1]
NRT vs. placebo†	Hartmann-Boyce 2018 (131; 64,640)	10.45%	RR 1.55 (95% CI 1.49 to 1.61)	High
Bupropion vs. placebo	Hughes 2014 (17; 3,862)	12.0%	RR 1.69 (95% CI 1.45 to 1.97)	High
Bupropion vs. placebo, non-psychiatric group	Anthenelli 2016/EAGLES trial (1; 2,010)	10.5%	OR 2.00 (95% CI 1.54 to 2.59) RR 1.81 (95% CI 1.46 to 2.22)‡	High
Bupropion vs. placebo, overall group	Anthenelli 2016/EAGLES trial (1; 4,069)	9.4%	OR 1.89 (95% CI 1.56 to 2.29) RR 1.74 (95% CI 1.48 to 2.04)‡	High
Varenicline vs. placebo	Cahill 2016 (25; 12,304)	12.4%	RR 2.25 (95% CI 2.08 to 2.44)	High
Bupropion vs. NRT (abstinence at 6 months or more)	Hughes 2014 (8; 4,086)	25.4%	RR 0.96 (95% CI 0.85 to 1.09)	Moderate (risk of bias)[2]
Bupropion vs. NRT, non-psychiatric group	Anthenelli 2016/EAGLES trial (1; 2,014)	18.5%	OR 1.02 (95% CI 0.81 to 1.28) RR 1.02 (95% CI 0.84 to 1.22)‡	Moderate (imprecision)
Bupropion vs. NRT, overall group	Anthenelli 2016/EAGLES trial (1; 4,072)	15.7%	OR 1.04 (95% CI 0.88 to 1.24) RR 1.03 (95% CI 0.90 to 1.19)‡	Moderate (imprecision)
Varenicline vs. nicotine patch (point prevalence abstinence)	Cahill 2016 (8; 6,264)	18.9%	RR 1.25 (95% CI 1.14 to 1.37)	High
Varenicline vs. nicotine patch	Tulloch 2016 (1; 466)	15.8%	OR 2.01 (95% CI 1.20 to 3.36)	Moderate (risk of bias)[2]
Varenicline vs. bupropion	Cahill 2016 (5; 5,877)	17.1%	RR 1.39 (95% CI 1.25 to 1.54)	High

*Although beyond scope of the present evidence report, we also note Lancaster 2017 also found that more intensive counseling may be better than less intensive counseling (RR 1.29, 95% CI 1.09 to 1.53; Low certainty).

†No significant evidence of differences in efficacy among different forms of NRT identified across placebo-controlled comparisons in systematic review (Hartmann-Boyce 2018) or among any direct comparisons in 9 randomized trials in systematic review (Lindson 2019, Moderate certainty)

‡Estimated from the reported OR and the control group risk in the standard fashion

[1]Heterogeneity

[2]High attrition rates (and no trial without high attrition rates)

Evidence Synthesis Process

Outcome for all is "quit smoking and remain quit at 6 months"

Option	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
No treatment	Does not apply	Does not apply	**Use control group event rate from largest meta-analysis** (Hartmann-Boyce 2018)**.** This control group event rate (10.45%) rounds down to 10%. The placebo and minimal contact control event rates range from 7.7% to 12.4% across the evidence. The midpoint of this range is 10%, and the mean and median of all the estimates are 10.4% and 10.5%, respectively. For ease of understanding, we use 10% as a reference point for a common control event rate.	**Without treatment, 10 out of 100 smokers (10%) can quit smoking and remain quit at 6 months.**
Counseling	**Use meta-analysis** (Lancaster 2017) **already done.**	**Counseling may increase the likelihood of sustained abstinence at 6 months** (Moderate certainty), with RR 1.48. Although beyond scope, we also note more intensive counseling may be better than less intensive counseling (Low certainty)	**Calculate using effect estimate from meta-analysis and common control group event rate.** 10% x 1.48 = 14.8%. **Include qualitative statement that more counseling may be better.**	**With counseling, 15 out of 100 smokers (15%) can quit smoking and remain quit at 6 months. Talking to your coach more times may be better.**

Nicotine replacement therapy	**Use meta-analysis** (Hartmann-Boyce 2018) **already done.** Use the same estimate for all NRT forms because there is no evidence of differences.	**Nicotine replacement increases the likelihood of sustained abstinence at 6 months** (High certainty), with RR 1.55.	**Calculate using effect estimate from meta-analysis and common control group event rate.** 10% x 1.55 = 15.5%. **Replace with rate for bupropion.** The evidence supports equivalence in efficacy for NRT and bupropion, so selection of one of these rates for both options is considered more accurate than suggesting minor differences in efficacy based on subtle differences in sample populations in different trials used for effect estimates. The higher rate (17%) is selected to emphasize the difference from placebo (10%).	**With nicotine replacement, 17 out of 100 smokers (17%) can quit smoking and remain quit at 6 months.**
Bupropion	**Use meta-analysis** (Hughes 2014) **already done.** The estimate is not substantially different than the estimate provided by the subsequent EAGLES trial.	**Bupropion increases the likelihood of sustained abstinence at 6 months** (High certainty), with RR 1.69.	**Calculate using effect estimate from meta-analysis and common control group event rate.** 10% x 1.69 = 16.9%.	**With bupropion, 17 out of 100 smokers (17%) can quit smoking and remain quit at 6 months.**
Varenicline	**Use meta-analysis** (Cahill 2016) **already done.** Efficacy estimate is higher than NRT and bupropion. This is supported by direct comparisons in Cahill 2016 (including the EAGLES trial) and Tulloch 2016.	**Varenicline increases the likelihood of sustained abstinence at 6 months** (High certainty), with RR 2.25.	**Calculate using effect estimate from meta-analysis and common control group event rate.** 10% x 2.25 = 22.5%. We round up to 23 for parallelism with how the results for nicotine replacement and bupropion are presented.	**With varenicline, 23 out of 100 smokers (23%) can quit smoking and remain quit at 6 months.**

Evidence Synthesis Results

No treatment

Without treatment, 10 out of 100 smokers (10%) quit smoking and remain quit at 6 months. (based on systematic review: Hartmann-Boyce 2018)

Counseling (talking with a coach)

With counseling, 15 out of 100 smokers (15%) quit smoking and remain quit at 6 months. (Moderate certainty; based on 1 systematic review: Lancaster 2017) **Talking to your coach more times may be better.** (Low certainty; based on 1 systematic review: Lancaster 2017)

Nicotine replacement with gum

With nicotine gum, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hartmann-Boyce 2018)

Nicotine replacement with patch

With nicotine patch, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hartmann-Boyce 2018)

Nicotine replacement with inhaler

With nicotine inhaler, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hartmann-Boyce 2018)

Nicotine replacement with nose spray

With nicotine nose spray, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hartmann-Boyce 2018)

Nicotine replacement with lozenge

With nicotine lozenges, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hartmann-Boyce 2018)

Bupropion

With bupropion, 17 out of 100 smokers (17%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Hughes 2014)

Varenicline

With varenicline, 23 out of 100 smokers (23%) quit smoking and remain quit at 6 months. (High certainty; based on 1 systematic review: Cahill 2016)

FAQ 3: What are the side effects?

Evidence Review

Side effects with significant differences for at least one drug

Side effect	Source (number of trials; number of participants)	Placebo rate (%)	NRT rate (%)	Bupropion rate (%)	Varenicline rate (%)	Certainty (NRT/Bupropion/ Varenicline)
Nausea	Anthenelli 2016/EAGLES trial (1; 3,984)*	6.3%	9.4%	9.1%	24.5%	High/Moderate[1]/High
	Cahill 2016 (32; 14,963)	8.5%			27.8%	High
Insomnia	Anthenelli 2016/EAGLES trial (1; 3,984)*	7.3%	9.0%	12.7%	9.6%	Low[1]/High/Low[1]
	Cahill 2016 (29; 14,447)	8.3%			12.4%	High
Abnormal dreams	Anthenelli 2016/EAGLES trial (1; 3,984)*	3.9%	11.0%	4.8%	8.4%	High/Very low[1]/High
	Cahill 2016 (26; 13,682)	5.7%			12.1%	High
Headache	Anthenelli 2016/EAGLES trial (1; 3,984)*	9.5%	12.8%	8.8%	11.7%	High/Very low[1]/Low[1]
	Cahill 2016 (25; 13,835)	10.2%			11.9%	High
Dizziness	Anthenelli 2016/EAGLES trial (1; 3,984)*	2.8%	3.8%	5.2%	3.3%	Low[1]/High/Low[1]
Dry mouth	Anthenelli 2016/EAGLES trial (1; 3,984)*	2.6%	3.1%	7.1%	2.9%	Low[1]/High/Low[1]
Major adverse cardiovascular events	Benowitz 2018/EAGLES trial (1; 8,058)†	0.1%	0.4%	0.3%	0.4%	High
Serious cardiac adverse events	Cahill 2016 (21; 8,587)	0.9%			1.2% (not significant)	Moderate[1]
Chest pains and palpitations	Hartmann-Boyce 2018 (15; 11,074)	1.4%	2.5%			Moderate[2]
Application-site pruritus	Anthenelli 2016/EAGLES trial (1; 3,984)*	Not applicable	5.1% with patch	Not applicable	Not applicable	High

* Specific adverse events extracted limited to those showing an increase in adverse event meta-analyses in Cahill 2016 Cochrane review (which evaluated varenicline) or > 2% absolute increase over placebo Anthenelli 2016

†This is a separate publication of the data from the EAGLES trial program that focused on cardiovascular safety. Unlike Anthenelli 2016 in which we limited results to the non-psychiatric cohort, results reported for Benowitz 2018 included both psychiatric and non-psychiatric cohorts.

[1]Due to degree of imprecision

[2]Due to risk of bias with unclear risk of bias assessments for key contributing trials

Anthenelli 2016 also found no significant differences in neuropsychiatric events, severe neuropsychiatric events, or suicidal behavior or ideation for varenicline, bupropion, or NRT compared to placebo (additional detail is in Critical Appraisal).

Evidence Synthesis Process

For side effects with rates reported in all treatment options in Anthenelli 2016 (EAGLES trial), these rates will be reported directly because they are derived from a common representative group and provide the best-available evidence for direct comparisons across all options. Evidence available from Cahill 2016 is consistent. Per Scoping, we will use the data for the nicotine patch (the NRT studied in the EAGLES trial) to estimate the adverse event rates for the other NRT options in the absence of compelling evidence for substantively different adverse event rates.

For major adverse cardiovascular events and serious cardiac adverse events, Benowitz 2018 (EAGLES trial) and Cahill 2016 support no significant risk differences across treatment options.

A singular finding regarding systemic side effects (but not available for all options) is noted in Hartmann-Boyce 2018, which suggests a small but statistically significant increase in the risk for "chest pains and palpitations" with nicotine compared to placebo. Review of drug information for nicotine (IBM Micromedex) notes multiple studies establishing no additive effect of nicotine through prescribed methods on risks for clinical or research-measured cardiac ischemia, in addition to the risks clearly documented with cigarette smoking. Nicotine by all routes of administration produces tachycardia. This will be noted descriptively for the nicotine summaries.

Consistent with Scoping, site-of-application side effects for nicotine formulations will be derived from drug monographs (DynaMed 2019-2020) and reported descriptively. For example, although Anthenelli 2016 reports 5.1% rate of application-site pruritus with nicotine patch, the review of drug information for nicotine (IBM Micromedex) notes mild skin irritation in 97%, moderate irritation in 36%, severe reactions in 12%, intense erythema with edema in 7%, and transient itching in 29%. With such data coming from single reports, the number of manifestations of local irritation, and the uncertainty in accuracy and precision of the reported rates, approaching the concept of local irritation descriptively rather than quantitatively seems a more prudent approach.

Evidence Synthesis Results

No treatment

Some symptoms happen without taking medicine. Knowing these symptoms can help you compare to taking medicine. Of 100 people who do not take medicine to help quit smoking, symptoms may include:

- **nausea in 6 (6%)**
- **headache in 10 (10%)**
- **trouble sleeping in 7 (7%)**
- **strange dreams in 4 (4%)**
- **dry mouth in 3 (3%)**
- **dizziness in 3 (3%)**

(Based on 1 randomized trial: Anthenelli 2016)

Counseling (talking with a coach)

There are no side effects from counseling. Some symptoms happen without taking medicine. Knowing these symptoms can help you compare to taking medicine. Of 100 people who do not take medicine to help quit smoking, symptoms may include:

- **nausea in 6 (6%)**
- **headache in 10 (10%)**
- **trouble sleeping in 7 (7%)**
- **strange dreams in 4 (4%)**
- **dry mouth in 3 (3%)**
- **dizziness in 3 (3%)**

(Based on 1 randomized trial: Anthenelli 2016)

Nicotine replacement with gum

Of 100 people who use nicotine gum to quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 13 (13%)**
- **trouble sleeping in 9 (9%)**
- **strange dreams in 11 (11%)**
- **dry mouth in 3 (3%)**
- **dizziness in 4 (4%)**

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth.

(High certainty for nausea, abnormal dreams, headache; Low certainty for insomnia, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016)

Nicotine replacement with patch

Of 100 people who use nicotine patches to quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 13 (13%)**
- **trouble sleeping in 9 (9%)**
- **strange dreams in 11 (11%)**
- **dry mouth in 3 (3%)**
- **dizziness in 4 (4%)**

Nicotine may increase your heart rate. You may have some redness, itching, or discomfort where the patch touches your skin.

(High certainty for nausea, abnormal dreams, headache; Low certainty for insomnia, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016)

Nicotine replacement with inhaler

Of 100 people who use a nicotine inhaler to quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 13 (13%)**
- **trouble sleeping in 9 (9%)**
- **strange dreams in 11 (11%)**
- **dry mouth in 3 (3%)**
- **dizziness in 4 (4%)**

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth or throat.

(High certainty for nausea, abnormal dreams, headache; Low certainty for insomnia, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016)

Nicotine replacement with nose spray

Of 100 people who use nicotine nose spray to quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 13 (13%)**
- **trouble sleeping in 9 (9%)**
- **strange dreams in 11 (11%)**
- **dry mouth in 3 (3%)**
- **dizziness in 4 (4%)**

Nicotine may increase your heart rate. You may have some itching or discomfort in your nose.

(High certainty for nausea, abnormal dreams, headache; Low certainty for insomnia, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016)

Nicotine replacement with lozenge

Of 100 people who use nicotine lozenges to quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 13 (13%)**
- **trouble sleeping in 9 (9%)**
- **strange dreams in 11 (11%)**
- **dry mouth in 3 (3%)**
- **dizziness in 4 (4%)**

Nicotine may increase your heart rate. You may have some itching or discomfort in your mouth.

(High certainty for nausea, abnormal dreams, headache; Low certainty for insomnia, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016)

Bupropion

Of 100 people who use bupropion to help quit smoking, side effects may include:

- **nausea in 9 (9%)**
- **headache in 9 (9%)**
- **trouble sleeping in 13 (13%)**
- **strange dreams in 5 (5%)**
- **dry mouth in 7 (7%)**
- **dizziness in 5 (5%)**

Bupropion may not be the best choice for someone who has seizures or is at increased risk of having a seizure, such as people who have had a serious head injury or have an eating disorder. Bupropion may make seizures more likely for these people.

(High certainty for insomnia, dizziness, dry mouth; Moderate certainty for nausea; Very low certainty for abnormal dreams, headaches; based on 1 randomized trial: Anthenelli 2016; certainty not rated for qualitative statement about use of bupropion in people with or at risk for seizures)

Varenicline

Of 100 people who use varenicline to help quit smoking, side effects may include:

- **nausea in 25 (25%)**
- **headache in 12 (12%)**
- **trouble sleeping in 10 (10%)**
- **strange dreams in 8 (8%)**
- **dry mouth in 3 (3%)**
- **dizziness in 3 (3%)**

Early on, there was some worry about whether varenicline might increase a person's risk for a heart attack or a serious mood problem, including committing suicide. However, evidence looking into this does not suggest an increase in risk.

(High certainty for nausea, abnormal dreams; Low certainty for insomnia, headaches, dizziness, dry mouth; based on 1 randomized trial: Anthenelli 2016; certainty not rated for qualitative statement about early cardiovascular and neuropsychiatric concerns surrounding use of varenicline)

FAQ 4: Is a generic version available?

No treatment
Does not apply.

Counseling (talking with a coach)
Does not apply.

Nicotine gum
Yes, there is a generic version.

Nicotine patch
Yes, there is a generic version.

Nicotine inhaler
No, there is no generic version.

Nicotine nose spray
No, there is no generic version.

Nicotine lozenge
Yes, there is a generic version.

Bupropion
Yes, there is a generic version.

Varenicline
No, there is no generic version.

(DynaMed 2019-2020)

FAQ 4: What will it cost? (United States variant)

Estimates of the acquisition cost in the United States are based on the National Average Drug Acquisition Cost (NADAC). Comparisons to the cost of smoking are based on the average price of cigarettes in the United States and assuming someone smokes 1 pack of cigarettes per day. Such estimates may not hold outside the United States. Given the common sources used to provide answers to this FAQ for all the pharmaceutical options, a single reference is provided at the end of this section rather than after each option.

Based on an assumed cigarette consumption of 1 pack per day (consistent with recent estimates from the United States Centers for Disease Control and Prevention) and an average cost of $6.28 for a pack of cigarettes in the United States (based on estimates from the National Cancer Institute of the National Institutes of Health), the following costs can be estimated:

Duration	Cost
1 week	$44
1 month	$188
6 months	$1,146
1 year	$2,292
10 years*	$30,213*

*Based on prices increasing by 6%/year. Note the estimates offered at smokefree.gov using the same parameters make the mistake of calculating this figure over 11 years, not 10 years.

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

No treatment

Does not apply.

Counseling (talking with a coach)

It may cost hundreds of dollars. Your insurance may help. You can spend this much on cigarettes in about 2 months.

Nicotine replacement with gum

- dosing information
  - dose used (2 mg or 4 mg) depends on time to first cigarette upon awakening; cost calculations will assume 4 mg dose
    - 4 mg used for smokers who smoke their first cigarette within 30 minutes of waking up
    - 2 mg used for smokers who smoke their first cigarette more than 30 minutes after waking up
  - a full course of treatment typically amounts to a tapered 12-week regimen
    - weeks 1 to 6: 1 piece every 1 to 2 hours; maximum 24 pieces/day (10 pieces/day used for cost calculations)
    - weeks 7 to 9: 1 piece every 2 to 4 hours (7 pieces/day used for cost calculations)
    - weeks 10 to 12: 1 piece every 4 to 8 hours (4 pieces/day used for cost calculations)
  - assumptions used for cost calculations
    - weeks 1 to 6 = 10 pieces/day (thus 10*7*6 = 420 pieces for first 6 weeks)
    - weeks 7 to 9 = 6 pieces/day (thus 7*7*3 = 147 pieces for weeks 7 to 9)
    - weeks 10 to 12 = 4 pieces/day (thus 4*7*3 = 84 pieces for weeks 10 to 12)
    - total amount needed for 12-week course with taper: 420 + 147 + 84 = 651 pieces
- 4 mg dose (broad search for *nicotine* with filter for "NDC Description" > "Contains" > *4 mg chewing gum*) has numerous entries (different National Drug Codes [NDCs]), but all have a NADAC of 0.23669 (for 2 mg, NADAC is 0.21194 for all entries)
- Nicotine gum available in 100-unit packages, so base assumption $23.67 per 100-unit package
- estimated cost: 7 packages x $23.67/package = $165.69

It may cost $100 to $200. Your insurance or coupons may help. You can spend this much on smoking in about 1 month.

Nicotine replacement with patch

- dosing information (cost calculations will assume use of Nicoderm CQ brand for smoker who smokes 20 cigarettes/day)
  - strength used depends on amount of cigarette consumption (>10 cigarettes/day vs. ≤10 cigarettes/day)
  - full course for someone smoking >10 cigarettes/day using Nicoderm CQ
    - 21 mg/day patch for first 6 weeks
    - 14 mg/day patch for weeks 7 and 8
    - 7 mg/day patch for weeks 9 and 10
  - full course for someone smoking >10 cigarettes/day using Habitrol
    - 21 mg/day patch for first 4 weeks
    - 14 mg/day patch for weeks 5 and 6
    - 7 mg/day patch for weeks 7 and 8
  - full course for someone smoking <10 cigarettes/day using Habitrol or Nicoderm CQ
    - 14 mg/day patch for 6 weeks

        - 7 mg/day patch for 2 weeks
- NADACs for different patch strengths (broad search for *nicotine* with filter for "NDC Description" > "contains" > *[dose] mg/24hr patch*)
    - each dose had numerous entries (different National Drug Codes [NDCs])
    - 21 mg/day: 1.68515 (all entries)
    - 14 mg/day: 1.59152 (all entries)
    - 7 mg/day: 1.61725 (all entries)
- estimated cost:
    - of first 6 weeks = 1.68515*6*7 = 70.7763
    - of weeks 7 and 8 = 1.59152*2*7 = 22.28128
    - of weeks 9 and 10 = 1.61725*2*7 = 22.6415
    - overall: 70.7763 + 22.28128 + 22.6415 = 115.69908
    - if person instead smoked ≤10 cigarettes/day, the estimated cost would be: (1.59152*6*7) + (1.61725*2*7) = 89.48534
- total estimated cost ≈ $116

It may cost about $100. Your insurance or coupons may help. You can spend this much on smoking in about 3 weeks.

Nicotine replacement with inhaler

- dosing information
    - 6 to 16 cartridges/day for "up to" 12 weeks
    - labeling says use beyond 6 months not recommended
    - no specific tapering suggested, but can either gradually reduce dose over 6 to 12 weeks or stop abruptly
    - calculations will assume a 12-week regimen using the midpoint of the cartridge range initially (i.e., 11 cartridges per day) and ~50% taper at set intervals (roughly informed by tapering for nicotine patch and gum)
        - weeks 1 to 6: 11*7*6 = 462 cartridges
        - weeks 7 to 9: 6*7*3 = 126 cartridges
        - weeks 10 to 12: 3*7*3 = 63 cartridges
        - thus 462 + 126 + 63 = 651 cartridges
- NADAC for Nicotrol cartridge inhaler is 2.49976
    - have to search by brand name; no generic
- estimated cost: 651*2.49976 = 1,627.34376
- total estimated cost ≈ $1,627

It may cost $1500 to $1700. Your insurance or coupons may help. You can spend this much on smoking in 8 to 9 months.

Nicotine replacement with nose spray

- dosing information
  - 1 to 2 doses/hour, then "adjust dose as needed based on patient response"
    - each dose = 1 spray in each nostril (so 2 sprays altogether)
    - each dose delivers 1 mg nicotine
  - 1 dose/hour = 24 doses (48 sprays, or 24 mg nicotine)/day
  - Minimum for initial dosing 8 times/day
  - maximum of 5 doses (10 sprays) per hour and 40 doses (80 sprays)/day
  - maximal duration of use is 3 months (12 weeks)
  - no specific tapering suggested, but can either gradually reduce dose over 4 to 6 weeks or patient may stop abruptly
  - cost calculations will assume
    - midpoint of dosing frequency range 8 to 40 doses/day (so 24 doses/day or 48 sprays/day or 24 mg/day)
    - 12-week regimen with roughly 50% reduction starting week 7 and again starting week 10
  - Cumulative mg dose needed for 12-week regimen
    - weeks 1 to 6: 24 mg/day = 24*7*6 = 1,008 mg needed
    - weeks 7 to 9: 12 mg/day = 12*7*3 = 252 mg needed
    - weeks 10 to 12: 6 mg/day = 6*7*3 = 126 mg needed
    - total needed = 1,008 + 252 + 126 = 1,386 mg
    - given 10 mg/mL, one would need 138.6 mL ≈ 140 mL (using 10 mL spray bottles)
- NADAC for Nicotrol nasal spray 10 mg/mL is 10.9871
  - have to search by brand name; no generic
- estimated cost: 140 mL*10.9871/mL = 1,538.194
- total estimated cost ≈ $1,538

It may cost $1500 to $1700. Your insurance or coupons may help. You can spend this much on smoking in 8 to 9 months.

Nicotine replacement with lozenge

- dosing information
  - dose used (2 mg or 4 mg) depends on time to first cigarette upon awakening; cost calculations will assume 4 mg dose
    - 4 mg used for smokers who smoke their first cigarette within 30 minutes of waking up
    - 2 mg used for smokers who smoke their first cigarette more than 30 minutes after waking up
  - a full course of treatment typically amounts to a tapered 12-week regimen
    - weeks 1 to 6: 1 lozenge every 1 to 2 hours; maximum 5 lozenges/6 hours and 20 lozenges/day (14 lozenges/day used for cost calculations)
    - weeks 7 to 9: 1 lozenge every 2 to 4 hours (7 lozenges/day used for cost calculations)
    - weeks 10 to 12: 1 lozenge every 4 to 8 hours (4 lozenges/day used for cost calculations)
  - assumptions used for cost calculations
    - weeks 1 to 6 = 14 lozenges/day (thus 14*7*6 = 588 lozenges for first 6 weeks)
    - weeks 7 to 9 = 7 lozenges/day (thus 7*7*3 = 147 lozenges for weeks 7 to 9)
    - weeks 10 to 12 = 4 lozenges/day (thus 4*7*3 = 84 lozenges for weeks 10 to 12)
    - total amount needed for 12-week course with taper: 588 + 147 + 84 = 819 lozenges
- 4 mg nicotine lozenge (broad search for *nicotine* with filter for "NDC Description" > "Contains" > *4 mg lozenge*) has numerous entries (different National Drug Codes [NDCs]), but all have a NADAC of 0.36794 (for 2 mg, the NADAC is 0.3659 for all entries)
  - each of these doses also has a "mini" lozenge version (e.g., filter as above, but for "Contains", enter *4 mg mini lozenge*)
    - for 4 mg, the "mini lozenge" version has a NADAC of 0.39472 for all entries, and for 2 mg, the "mini lozenge" version has a NADAC of 0.38441 for all entries
    - for both doses, the mean, median, and mode of the NADAC data for the "general" lozenge and "mini" lozenge considered together all favor using the NADAC for the "general" lozenge
- Nicotine lozenges available in 108-unit packages, so base assumption $39.74 per 108-unit package
- estimated cost: 8 packages x $39.74/package = $317.92

The medication may cost about $300. Your insurance or coupons may help. You can spend this much on smoking in about 2 months.

Bupropion

- dosing information
  - day 1 to 3: bupropion SR 150 mg once daily
  - days 4 and beyond: bupropion SR 150 mg twice daily
  - full treatment course less explicitly defined than with varenicline, but often continues for at least 7 to 12 weeks
    - some people remain on it much longer, and efficacy is noted up to 1 year out; additionally, it is important to note patients may wish to remain on this medication for its possible benefit in other domains, perhaps most notably depression (but this is beyond the scope of estimating cost strictly for smoking cessation)
  - calculations here will assume 12 weeks of treatment
- there are numerous entries (different National Drug Codes [NDCs]) for "bupropion HCl SR 150 mg tablet", but majority (89.7%) have NADAC of 0.11903 (the remainder have a NADAC of 0.35225)
  - mean, median, and mode all favor using 0.11903
- for a 12-week (84-day) treatment course, person would need 3 + (2*81) = 165 tablets
- estimated cost: 165*0.11903 = 19.63995
  - if one instead used 0.35225 for the NADAC, total would be 58.12125
- total estimated cost ≈ $20

It may cost about $20. Your insurance or coupons may help. You can spend this much on smoking in about 3 days.

Varenicline

- dosing information
  - day 1 to 3: 0.5 mg once daily
  - day 4 to 7: 0.5 mg twice a day
  - day 8 and beyond: 1 mg twice a day
  - full treatment course lasts 12 weeks
- first 4 weeks (28 days)
  - the person would need:
    - 11 x 0.5 mg tablets (first 7 days)
    - 42 x 1 mg tablets (remaining 21 days)
    - total of 53 tablets
  - NADAC for Chantix starting month box is 8.00598
    - have to search by brand name; no generic
  - first 4 weeks thus estimated at 8.00598*53 = 424.31694
- remaining 8 weeks (56 days)
  - the person would need 112 x 1 mg tablets
  - could use Chantix continuing month box, for which NADAC is 7.57298
    - have to search by brand name; no generic
    - NADAC for Chantix 1 mg tablet not as part of a continuing month box is identical
  - remaining 8 weeks thus estimated at 7.57298*112 = 848.17376
- estimated cost: 424.31694 + 848.17376 = 1,272.4907
- total estimated cost (per NADAC information) ≈ $1,272

It may cost about $1,300. Your insurance or coupons may help. You can spend this much on smoking in 6 to 7 months.

(DynaMed 2019-2020, Centers for Medicare & Medicaid Services 2020, National Cancer Institute nd)

FAQ 5: Will it affect my weight?

As noted in Scoping, for the options of no treatment and counseling, we will provide a qualitative statement that, on average, people gain some weight when they quit smoking (based on Aubin 2012 and Tian 2015). For the other options, we conducted systematic evidence review and appraisal, as presented below.

Evidence Review

Effect of smoking cessation therapies vs. placebo on weight change during treatment (in kg)*

Intervention (Source)†	Mean difference (95% CI)		Certainty (reason for downgrade)
	Pairwise meta-analysis	Network meta-analysis	
Bupropion 300 mg (Hsieh 2019)	**-1.25 (-2.23 to -0.27)**	**-1.04 (-1.64 to -0.43)**	Moderate (risk of bias)[1,2]
Nicotine inhaler (Hsieh 2019)	-1.10 (-2.43 to +0.23)	-1.10 (-2.63 to +0.43)	Moderate (risk of bias)[1,2]
Nicotine lozenge (Hsieh 2019)	Not available	**-1.20 (-2.39 to -0.02)**	Low (risk of bias, indirectness)[1,2]
Nicotine gum (Hsieh 2019)	**-0.61 (-1.13 to -0.10)**	**-0.59 (-1.17 to -0.01)**	Moderate (risk of bias)[1,2]
Nicotine patch 14 mg (Hsieh 2019)	**-0.47 (-0.76 to -0.18)**	-0.43 (-0.95 to +0.10)	Moderate (risk of bias)[1,2]
Nicotine patch 21 mg (Hsieh 2019)	-0.43 (-1.29 to +0.44)	**-0.56 (-1.12 to 0.00)**	Moderate (risk of bias)[1,2]
Nicotine spray (Hsieh 2019)	**-2.80 (-5.03 to -0.57)**	**-2.80 (-5.16 to -0.44)**	Moderate (risk of bias)[1,2]
Varenicline 2 mg (Hsieh 2019)‡	-0.30 (-1.37 to +0.77)	-0.30 (-1.61 to +1.01)	Moderate (risk of bias)[1,2]
Varenicline 2 mg (Sun 2018)§	-0.29 (-0.46 to -0.12)	Not applicable	Moderate (risk of bias)[2,3]

*Differences < 0 suggest less weight gain with the intervention compared to with placebo. **Statistically significant differences are bolded**.
†In most instances, it is not clear how many studies/people contributed to a given estimate. An exception is varenicline, which is handled separately.
‡Based on 1 trial totaling 139 people
§Based on 8 trials totaling 3,627 people
[1]Only 2 of 31 randomized trials across the entire series of meta-analyses were assessed as having clear allocation concealment.
[2]No concern for imprecision with confidence interval width <5 kg suggesting absence of moderate or larger effects, regardless of statistical significance.
[3]Insufficient assessment of risk of bias (use of Jadad scale)

Evidence Synthesis Process

The evidence for this question comes from 2 systematic reviews: Hsieh 2019 and Sun 2018. Sun 2018 only provides estimates for varenicline vs. placebo, so for all other estimates, the evidence comes from Hsieh 2019. For the estimate of varenicline vs. placebo, we rely on Sun 2018, which is more comprehensive despite having an earlier date of publication.

Pairwise meta-analysis estimates and network meta-analysis estimates were consistent in all cases so we use pairwise meta-analysis for all options where available, and we use the network meta-analysis estimate for nicotine lozenge where no pairwise meta-analysis estimate is available.

Every effect estimate, regardless of specific medication with the exception of nicotine spray, is consistent in the following ways:

1) The point estimate is a negative value, meaning the point estimate is consistent with less weight gain with the medication than with placebo.
2) The point estimate is a small value, ranging from -0.29 kg to -1.25 kg. Although the minimal clinically important difference (MCID) is not easy to establish in this situation as it will differ for every person and there are different ways to estimate an MCID (Germeroth 2018), a difference of 1.25 kg or less is reasonably considered unimportant by most people.
3) The upper bound of the confidence intervals, whether statistically significant or not, is not greater than +0.44 kg, suggesting no reasonable expectation for an important increase in weight gain with any medication.
4) The lower bound of the confidence intervals is no lower than -2.43 kg, a difference that is still reasonably considered unimportant by most people.

The effect estimate for nicotine spray is -2.80 kg (95% CI -5.03 kg to -0.57 kg). Although it is plausible that some people may consider the lower half of this confidence interval to include a MCID the overall confidence interval is wide and includes absence of important differences from placebo and thus from any of the other medications. This wider confidence interval and overlap with absence of important differences does not support conclusions or suggestions that nicotine spray is particularly effective or more effective than other options for mitigating weight gain with smoking cessation.

Because the precision suggested by data with hundredths of a kilogram would not be meaningful for reporting results to patients we use qualitative descriptions of these concepts and provide a similar response for all options.

Although the certainty was reported as Low with nicotine lozenge (based on absence of pairwise meta-analysis), the results are so consistent with all other options we consider Moderate certainty for this finding in the overall evidence synthesis.

Descriptive Summary and Evidence Synthesis Results

No treatment

On average, people gain some weight when they quit smoking.

(Aubin 2012, Tian 2015 [certainty not assessed for this descriptive summary response])

Counseling (talking with a coach)

On average, people gain some weight when they quit smoking.

(Aubin 2012, Tian 2015 [certainty not assessed for this descriptive summary response])

Nicotine replacement with gum

On average, people gain some weight when they quit smoking. People might gain less weight if they use nicotine gum, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Nicotine replacement with patch

On average, people gain some weight when they quit smoking. People might gain less weight if they use nicotine patches, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Nicotine replacement with inhaler

On average, people gain some weight when they quit smoking. People might gain less weight if they use nicotine inhalers, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Nicotine replacement with nose spray

On average, people gain some weight when they quit smoking. People might gain less weight if they use nicotine nose spray, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Nicotine replacement with lozenge

On average, people gain some weight when they quit smoking. People might gain less weight if they use nicotine lozenges, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Bupropion

On average, people gain some weight when they quit smoking. People might gain less weight if they use bupropion, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Hsieh 2019)

Varenicline

On average, people gain some weight when they quit smoking. People might gain less weight if they use varenicline, but the difference may be small.

(Moderate certainty, based on 1 systematic review: Sun 2018)

Evidence report for smoking cessation

Search and Selection

Prepared by EBSCO Information Services

February 22, 2020
Revised March 2, 2020 to add FAQ5 Will it affect my weight?
Updated March 14, 2020 for search currency

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

First-round searching will consist of searching DynaMed summaries pertinent to the topic. The search starts with DynaMed because DynaMed content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Fourth-round searching will involve citation tracing from sources found in the preceding rounds of searching. This may be done to identify additional evidence sources if the results from the preceding rounds of searching are insufficient.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

FAQ 1: What does the treatment involve?

FAQ 2: Will it help me quit smoking?

FAQ 3: What are the side effects?

FAQ 4: Is a generic version available? (US variant: What will it cost?)

FAQ 5: Will it affect my weight?

Results

First-round searching – DynaMed

DynaMed subsection	Number of article citations	Number of unique references included
Counseling for Tobacco Cessation topic, General Efficacy section (February 17, 2020) (last searched March 14, 2020)	12	2 (Lancaster 2017, Mottillo 2009)
Treatment for Tobacco Use topic, Bupropion section (February 17, 2020) (last searched March 14, 2020)	15	1 (Hughes 2014)
Treatment for Tobacco Use topic, Varenicline section (February 17, 2020) (last searched March 14, 2020)	21	1 (Cahill 2016)
Nicotine Replacement Therapy for Tobacco Cessation topic, Overall Efficacy and Safety section (February 17, 2020) (last searched March 14, 2020)	20	1 (Hartmann-Boyce 2018)
Nicotine Replacement Therapy for Tobacco Cessation topic, Transdermal Nicotine Patch section (February 17, 2020) (last searched March 14, 2020)	14	1 (Lindson 2019)*
Nicotine Replacement Therapy for Tobacco Cessation topic, Nicotine Gum section (February 17, 2020) (last searched March 14, 2020)	7	0*†

Nicotine Replacement Therapy for Tobacco Cessation topic, Nicotine Lozenge section (February 17, 2020) (last searched March 14, 2020)	8	0*†
Nicotine Replacement Therapy for Tobacco Cessation topic, Nicotine Oral Inhaler or Spray section (February 17, 2020) (last searched March 14, 2020)	6	0*
Nicotine Replacement Therapy for Tobacco Cessation topic, Nicotine Nasal Spray section (February 17, 2020) (last searched March 14, 2020)	5	0*†
Treatment for Tobacco Use topic, Comparative Efficacy and Safety section (February 18, 2020) (last searched March 14, 2020)	16	3 (Anthenelli 2016, Benowitz 2018, Tulloch 2016)‡
Treatment for Tobacco Use topic, Other Management section, Preventing and treating weight gain subsection (March 2, 2020) (last searched March 14, 2020)	1	0

*Hartmann-Boyce 2018 captured in prior searching
†Lindson 2019 captured in prior searching
‡Cahill 2016 and Hughes 2014 captured in prior searching

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of unique references included
PubMed February 22, 2020 (last searched March 14, 2020)	bupropion AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2013/11/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] child*[ti])	63	0*
PubMed February 22, 2020 (last searched March 14, 2020)	varenicline AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2016/03/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	39	0†
PubMed February 22, 2020 (last searched March 14, 2020)	(nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal)) AND (smoking OR smokers OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2018/03/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	34	0‡
PubMed February 22, 2020 (last searched March 14, 2020)	(counseling[tiab] OR counselling[tiab] OR behavior[tiab] OR behaviour[tiab] OR behavioral[tiab] OR behavioural[tiab]) AND (smoking[tiab] OR tobacco[tiab] OR nicotine[tiab]) AND (quit*[tiab] OR cessation[tiab] OR stop[tiab]) AND (systematic[sb] OR meta-analysis[ti]) AND ("2017/01/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR child*[ti])	132	0§
PubMed March 4, 2020 (last searched March 14, 2020)	(bupropion OR varenicline OR (nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal))) AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND weight NOT (pediatric[ti] OR paediatric[ti] child*[ti])	12	2 (Hsieh 2019, Sun 2018)

*Cahill 2016 and Hughes 2014 captured in prior searching

†Cahill 2016 captured in prior searching

‡Hartmann-Boyce 2018 captured in prior searching

§Lancaster 2017 captured in prior searching; Denison 2017 was potentially eligible (SR of 21 randomized trials of cognitive therapies for smoking cessation) but only 1 of the included trials had a population, comparator and outcome assessment timeframe matching our scope (McCarthy 2008) and this trial was included in Lancaster 2017

PARSE Mapping

PARSE Name	Search string	Number of search results	Number of new references selected for inclusion
EvRep Smoking cessation second round string #1	bupropion AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2013/11/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] child*[ti])	62 (on February 22, 2020) 63 (on March 8, 2020) 63 (on March 14, 2020)	0
EvRep Smoking cessation second round string #2	varenicline AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2016/03/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	37 (on February 22, 2020) 39 (on March 8, 2020) 39 (on March 14, 2020)	0
EvRep Smoking cessation second round string #3	(nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal)) AND (smoking OR smokers OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND ("2018/03/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	32 (on February 22, 2020) 34 (on March 8, 2020) 34 (on March 14, 2020)	0
EvRep Smoking cessation second round string #4	(counseling[tiab] OR counselling[tiab] OR behavior[tiab] OR behaviour[tiab] OR behavioral[tiab] OR behavioural[tiab]) AND (smoking[tiab] OR tobacco[tiab] OR nicotine[tiab]) AND (quit*[tiab] OR cessation[tiab] OR stop[tiab]) AND (systematic[sb] OR meta-analysis[ti]) AND ("2017/01/01"[PDAT]: "3000/01/01"[PDAT]) NOT (pediatric[ti] OR child*[ti])	130 (on February 22, 2020) 132 (on March 8, 2020) 132 (on March 14, 2020)	0
EvRep Smoking cessation second round string #5	(bupropion OR varenicline OR (nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal))) AND (smoking OR smokers OR nicotine OR tobacco) AND (systematic[sb] OR meta-analysis[ti]) AND weight NOT (pediatric[ti] OR paediatric[ti] child*[ti])	12 (on March 4, 2020) 12 (on March 8, 2020) 12 (on March 14, 2020)	0

Third-round searching – searches for original evidence reports

Note: Based on data available from systematic reviews additional inclusion criteria were applied of either including sample size ≥ 200 or findings suggesting additional side effects

Database	Search string	Number of search results	Number of unique references included
PubMed February 22, 2020 (last searched March 14, 2020)	bupropion AND (smoking OR smokers OR nicotine OR tobacco) AND (randomized controlled trial[pt]) AND ("2013/05/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	64	0*†
PubMed February 22, 2020 (last searched March 14, 2020)	varenicline AND (smoking OR smokers OR nicotine OR tobacco) AND (randomized controlled trial[pt]) AND ("2015/03/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	97	0*‡
PubMed February 22, 2020 (last searched March 14, 2020)	(nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal)) AND (smoking OR smokers OR tobacco) AND (randomized controlled trial[pt]) AND ("2017/05/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	94	0*

*Anthenelli 2016 and Benowitz 2018 captured in prior searching
†Stapleton 2013 included in Hughes 2014
‡Baker 2016 included in Cahill 2016, Tulloch 2016 captured in prior searching

PARSE Mapping

PARSE Name	Search string	Number of search results	Number of new references selected for inclusion
EvRep Smoking cessation third round string #1	bupropion AND (smoking OR smokers OR nicotine OR tobacco) AND (randomized controlled trial[pt]) AND ("2013/05/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	62 (on February 22, 2020) 64 (on March 8, 2020) 64 (on March 14, 2020)	0
EvRep Smoking cessation third round string #2	varenicline AND (smoking OR smokers OR nicotine OR tobacco) AND (randomized controlled trial[pt]) AND ("2015/03/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	96 (on February 22, 2020) 96 (on March 8, 2020) 97 (on March 14, 2020)	0
EvRep Smoking cessation third round string #3	(nicotine AND (replacement OR gum OR lozenge OR patch OR transdermal OR inhaler OR nasal OR intranasal)) AND (smoking OR smokers OR tobacco) AND (randomized controlled trial[pt]) AND ("2017/05/01"[EDAT]: "3000/01/01"[EDAT]) NOT (pediatric[ti] OR paediatric[ti] OR child*[ti])	92 (on February 22, 2020) 93 (on March 8, 2020) 94 (on March 14, 2020)	0

Fourth-round searching – citation tracing

Source	Tracing	Number of unique references included
Not needed in this review		

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	125	9
2nd-round (Systematic review searches)	280	2
3rd-round (Original article searches)	255	0
4th-round (Citation tracing)	0	0
Total	*660*	*11*

* Number shown is after deduplication

	Articles selected for evaluation (Author Year)
Systematic reviews (8)	Cahill 2016, Hartmann-Boyce 2018, Hsieh 2019, Hughes 2014, Lancaster 2017, Lindson 2019, Mottillo 2009, Sun 2018
Randomized, controlled trials (3)	Anthenelli 2016, Benowitz 2018, Tulloch 2016
Other article types (0)	None

Evidence report for smoking cessation

Critical Appraisal

Prepared by EBSCO Information Services

February 24, 2020

Revised March 8, 2020 to add Hsieh 2019 and Sun 2018 for FAQ5

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

FAQ 1: What does the treatment involve?

FAQ 2: Will it help me quit smoking?

FAQ 3: What are the side effects?

FAQ 4: Is a generic version available? (US variant: What will it cost?)

FAQ 5: Will it affect my weight?

Results

Characteristics and Results of Critically Appraised Studies/Sources

ANTHENELLI 2016 (EAGLES trial)
Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet. 2016 Jun 18;387(10037):2507-20. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** stratified, randomized controlled trial
  - strata defined based on presence/absence of psychiatric comorbidity
  - conducted at 140 centers in 16 countries
- **Population:** adult smokers motivated to quit
- **Intervention and Comparator:** 4-arm trial comparing varenicline 1 mg twice a day, bupropion 150 mg twice a day, nicotine patch 21 mg/day with taper, and placebo
  - all patients also received brief counseling at each visit
- **Study inclusion criteria:**
  - participants with a psychiatric diagnosis had to be considered stable and not at high risk of self-injury or suicidal behavior
  - randomized between November 30, 2011, and January 13, 2015
- **Number of participants:** 8,144 overall
  - 4,116 in psychiatric cohort, 4,028 in non-psychiatric cohort
  - psychiatric cohort
    - varenicline n=1,032
    - bupropion n=1,033
    - nicotine patch n=1,025
    - placebo n=1,026
  - non-psychiatric cohort
    - varenicline n=1,005
    - bupropion n=1,001
    - nicotine patch n=1,013
    - placebo n=1,009
- **Duration of follow-up:** 24 weeks
  - 12-week treatment phase followed by a 12-week non-treatment phase

- **Results and certainty:**

Continuous abstinence rates (9-24 weeks) comparing bupropion vs. placebo or nicotine replacement*

Population	Bupropion rate	Placebo rate	Rate difference	Odds ratio (95% CI)	Certainty (reason for downgrade)
Bupropion vs. placebo					
Non-psychiatric cohort (n=2,010)	18.8%	10.5%	8.3%	2.00 (1.54 to 2.59)	High[1]
Overall cohort (n=4,069)	16.2%	9.4%	6.8%	1.89 (1.56 to 2.29)	High[1]
Bupropion vs. NRT					
Non-psychiatric cohort (n=2,014)	18.8%	18.5%	0.3%	1.02 (0.81 to 1.28)	Moderate (imprecision)[1]
Overall cohort (n=4,072)	16.2%	15.7%	0.5%	1.04 (0.88 to 1.24)	Moderate (imprecision)[1]

*Results only provided for bupropion vs. placebo or NRT because efficacy results for other comparisons from this trial are included in other systematic reviews included in this report

[1] Attrition rates 22% overall; however, because rates and reasons were similar across all treatment groups and because attrition bias would be a bias against finding a treatment effect, we do not consider this to downrate our certainty

Risks of specific adverse events* in the non-psychiatric cohort

Outcome	Intervention	Event rate (%)	Risk difference vs. placebo	Certainty (reason for downgrade)
Nausea	varenicline	24.5% (243/990)	18.2%	High
	bupropion	9.1% (90/989)	2.8%	Moderate (imprecision)[1]
	nicotine patch	9.4% (95/1,006)	3.1%	High
	placebo	6.3% (63/999)	Not applicable	Not applicable
Insomnia	varenicline	9.6% (95/990)	2.3%	Low (serious imprecision)[2]
	bupropion	12.7% (126/989)	5.4%	High
	nicotine patch	9.0% (91/1,006)	1.7%	Low (serious imprecision)[2]
	placebo	7.3% (73/999)	Not applicable	Not applicable
Abnormal dreams	varenicline	8.4% (83/990)	4.5%	High
	bupropion	4.8% (47/989)	0.9%	Very low (very serious imprecision)[3]
	nicotine patch	11.0% (111/1,006)	7.1%	High
	placebo	3.9% (39/999)	Not applicable	Not applicable
Headache	varenicline	11.7% (116/990)	2.2%	Low (serious imprecision)[2]
	bupropion	8.8% (87/989)	-0.7%	Very low (very serious imprecision)[3]
	nicotine patch	12.8% (129/1,006)	3.3%	High
	placebo	9.5% (95/999)	Not applicable	Not applicable
Dizziness	varenicline	3.3% (33/990)	0.5%	Low (serious imprecision)[2]
	bupropion	5.2% (51/989)	2.4%	High
	nicotine patch	3.8% (38/1,006)	1.0%	Low (serious imprecision)[2]
	placebo	2.8% (28/999)	Not applicable	Not applicable
Dry mouth	varenicline	2.9% (29/990)	0.3%	Low (serious imprecision)[2]
	bupropion	7.1% (70/989)	4.5%	High
	nicotine patch	3.1% (31/1,006)	0.5%	Low (serious imprecision)[2]
	placebo	2.6% (26/999)	Not applicable	Not applicable
Application-site pruritus	varenicline	1.1% (11/990)	0%	Not applicable
	bupropion	0.6% (6/989)	-0.5%	Not applicable
	nicotine patch	5.1% (51/1,006)	0.5%	High
	placebo	1.1% (11/999)	Not applicable	Not applicable

* Specific adverse events extracted limited to those showing an increase in adverse event meta-analyses in Cahill 2016 Cochrane review (which evaluated varenicline) or > 2% absolute increase over placebo Anthenelli 2016.

[1]Lower bound of 95% confidence interval for absolute risk difference between 0% and 0.5%

[2]Lower bound of 95% confidence interval for absolute risk difference includes decrease between -2% and 0%

[3]Lower bound of 95% confidence interval for absolute risk difference includes substantial decrease < -2%

- **Other considerations pertaining to adverse events:**
  - no significant increases in neuropsychiatric adverse events with varenicline (1.3%), bupropion (2.2%), or nicotine patch (2.5%) compared to placebo (2.4%)
  - no significant increases in severe neuropsychiatric adverse events with varenicline (0.1%), bupropion (0.4%), or nicotine patch (0.3%) compared to placebo (0.5%)
  - no significant differences in suicidal behavior and/or ideation (1% or lower in all groups)

BENOWITZ 2018 (EAGLES trial)
Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. JAMA Intern Med. 2018 May 1;178(5):622-631. PubMed

Relevant to FAQ3

This is a secondary analysis of the EAGLES trial described in Anthenelli 2016. The incidence of cardiovascular events during treatment and extended follow-up was low (< 0.8% overall) and did not differ significantly by treatment.

- Rates of major adverse cardiovascular events during treatment or within 30 days
  - < 0.1% with varenicline (1 event)
  - 0.1% with bupropion (2 events)
  - 0.1% with NRT (2 events)
  - 0.2% with placebo (4 events)
- Rates of major adverse cardiovascular events by end of study (at least 24 weeks for 8,058 EAGLES trial participants and additional 28 weeks for 4,595 participants who agreed to be followed in extension study)
  - 0.1% with varenicline (3 events)
  - 0.4% with bupropion (9 events)
  - 0.3% with NRT (6 events)
  - 0.4% with placebo (8 events)
- Rates of major adverse cardiovascular events or any intervention for peripheral vascular disease at end of study
  - 0.5% with varenicline (10 events)
  - 0.7% with bupropion (15 events)
  - 0.5% with NRT (10 events)
  - 0.6% with placebo (12 events)

CAHILL 2016
Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016 May 9;(5):CD006103. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** adult smokers
- **Intervention:** varenicline
  - also considered other selective nicotine receptor partial agonists (e.g., cytisine), but this is beyond scope, so we only consider the trials of varenicline in this summary
- **Comparison:** placebo
  - also included comparisons with bupropion and nicotine patches where available
- **Study inclusion criteria:**
  - search window to May 2015
  - reported rate of smoking cessation at six months or later after starting treatment
- **Number of studies:** 39

- **Number of participants:** 25,290 in overall systematic review
  - 11,801 took varenicline
  - 7,109 took placebo
  - 2,935 took bupropion
  - 3,445 took nicotine replacement therapy (patch form)
- **Duration of follow-up:** outcomes reported at 3 months, 24 weeks, 6 months, 12 months, and longest follow-up (24+ weeks)

Results and Certainty:

Comparing varenicline vs. placebo*

Outcome	No. of patients (studies)	Control group % (events/sample size)	Risk ratio (95% CI)	Certainty (reason for downgrade)
Continuous or sustained abstinence at longest follow-up (24+ weeks)	12,625 (27)	11.1% (668/5,993)	2.24 (2.06 to 2.43)	High
Abstinence at six months	12,304 (25)	12.4% (726/5,832)	2.25 (2.08 to 2.44)	High
Nausea	14,963 (32)	8.5% (596/7,034)	3.27 (3.00 to 3.55)	High
Insomnia	14,447 (29)	8.3% (562/6,777)	1.49 (1.35 to 1.65)	High
Abnormal dreams	13,682 (26)	5.7% (365/6,393)	2.12 (1.88 to 2.38)	High
Headache	13,835 (25)	10.2% (668/6,531)	1.17 (1.07 to 1.29)	High
Depression	16,189 (36)	2.4% (184/7,652)	0.94 (0.77 to 1.14)	Moderate (imprecision)[1]
Suicidal ideation	11,193 (24)	0.7% (37/5,288)	0.68 (0.43 to 1.07)	Moderate (imprecision)[1]
Serious cardiac adverse events	8,587 (21)	0.90% (35/3,891)	1.36 (0.91 to 2.04)	Moderate (imprecision)[1]

* varenicline dose was 1.0 mg twice/day
[1]CI includes both clinically important differences and no effect

Comparing varenicline vs. bupropion*

Outcome	No. of patients (studies)	Control group % (events/sample size)	Risk ratio (95% CI)	Certainty (reason for downgrade)
Continuous or sustained abstinence at 24 weeks/6 months	5,877 (5)	17.1% (503/2,933)	1.39 (1.25 to 1.54)	High
Continuous abstinence at 52 weeks	1,618 (3)	13.9% (111/797)	1.52 (1.22 to 1.88)	High

*varenicline dose was 1.0 mg twice/day; bupropion dose was 150 mg twice/day

Comparing varenicline vs. nicotine patch*

Outcome	No. of patients (studies)	Control group % (events/sample size)	Risk ratio (95% CI)	Certainty (reason for downgrade)
Point prevalence abstinence at 24 weeks	6,264 (8)	18.9% (575/3,037)	1.25 (1.14 to 1.37)	High†

*varenicline dose was 1.0 mg twice/day where reported (not specifically mentioned for 3 trials)
†3 trials included in this analysis were open-label, but inspection of forest plot does not suggest they substantially bias the effect estimate. A sensitivity analysis removing these 3 trials gives RR 1.34 (95% CI 1.19 to 1.50), and the estimate from the large and rigorous EAGLES trial (Anthenelli 2016) is RR 1.39 (95% CI 1.22 to 1.58). Therefore, the overall effect estimate is, if anything, more conservative, but the 95% CIs of these estimates overlap substantially. Therefore, we did not downgrade for risk of bias.

Other considerations:

- Researchers used sustained cessation rates in preference to point prevalence
- Researchers preferred biochemically verified rates to rates based on self-report of quitting
- Participants lost to follow-up were treated as continuing smokers

HARTMANN-BOYCE 2018

Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. Cochrane Database Syst Rev. 2018 May 31;5:CD000146. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized and quasi-randomized trials
- **Population:** people who smoke and are willing to make attempt to quit
  - majority of trials conducted in adults; 2 small trials limited to adolescents did not contribute substantially
  - people enrolled in the studies typically smoked ≥ 15 cigarettes a day at the start of the trials
- **Intervention:** nicotine replacement therapy (NRT)
  - included gum, transdermal patch, nose spray, inhaler (inhalator) and oral lozenge
- **Comparison:** placebo or no NRT
- **Study inclusion criteria:**
  - minimal 6 months follow-up
  - trial reported cessation rates
  - search window close date July 2017
  - studies that randomized therapists, rather than smokers, to offer NRT or a control, were included if the specific aim of the trial was to examine the effect of NRT on smoking cessation
- **Number of studies:** 136
  - 133 contributed to primary comparison of any type of NRT vs. placebo or non-NRT control group on smoking cessation rate

- **Number of participants:** 64,640 included in primary comparison
- **Duration of follow-up:** minimum of 6 months

- **Results and certainty:**

Effects vs. placebo/no NRT control on smoking cessation at ≥ 6 months follow up*

NRT type and total combined	No. of patients (studies)	Risk ratio (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
Gum	22,581 (56)	1.49 (1.40 to 1.60)	16.3% (1,732/10,596)	10.0% (1,196/11,985)	High[1]
Patch	25,754 (51)	1.64 (1.53 to 1.75)	15.7% (2,160/13,773)	9.4% (1,131/11,981)	High[1]
Inhaler/Inhalator	976 (4)	1.90 (1.36 to 2.67)	17.1% (84/490)	9.1% (44/486)	High
Nose spray	887 (4)	2.02 (1.49 to 2.73)	23.9% (107/448)	11.8% (52/439)	Moderate (risk of bias)[2]
Tablets/lozenges	4,439 (8)	1.52 (1.32 to 1.74)	21.0% (488/2326)	12.9% (273/2113)	High[3]
Any NRT (including combinations and patient choice)	64,640 (131)	1.55 (1.49 to 1.61)	16.9% (5,574/32,918)	10.45% (3,315/31,722)	High[1]

*smoking cessation outcome based on strictest available criteria used to define abstinence in each trial

[1] although most studies were judged to have high or unclear risk of bias by Cochrane review authors, analysis for the overall combined effect estimate restricted to 12 studies at low risk of bias did not significantly change the results

[2] all 4 trials had at least one high or unclear risk of bias assessment by Cochrane review authors, including unclear allocation concealment in all 4 trials (none reported method used, if any, to conceal allocation) and unclear risk of bias from incomplete outcome data in 3 of the trials (because of limited reporting in the trial publications)

[3] although the analysis had a high degree of heterogeneity the inconsistency was based on one trial (Fraser 2014) having a substantially lower effect estimate consistent with no effect. Fraser 2014 studied the intervention of a 2-week free "starter pack" of nicotine lozenges while all other trials studied nicotine lozenge replacement therapy as 12 weeks or more of prescribed intervention. For this reason, we do not downgrade our certainty of efficacy based on one trial that is arguably not appropriate to include in the meta-analysis.

- adverse effects
    - minor adverse events related to site through which product is administered
        - skin irritation from patches
        - irritation to inside of mouth from gum and tablets
    - attempts to quantitatively synthesize the incidence of various adverse effects hindered by extensive variation in reporting nature, timing, and duration of symptoms
    - serious adverse events were extremely rare
    - pooled estimates reported for chest pains and palpitations
        - odds ratio 1.88 (95% CI 1.37 to 2.57)
            - based on analysis of 15 trials with 11,074 participants (including trials excluded from efficacy analysis)
            - chest pains and palpitations were rare in both groups
                - rate with NRT 2.47% (165/6,673)
                - rate with placebo 1.41% (62/4,401)
        - Certainty: **Moderate** (due to risk of bias with unclear risk of bias assessments for key trials contributing to this meta-analysis)

HSIEH 2019

Hsieh MT, Tseng PT, Wu YC, Tu YK, Wu HC, Hsu CW, et al. Effects of different pharmacologic smoking cessation treatments on body weight changes and success rates in patients with nicotine dependence: A network meta-analysis. Obes Rev. 2019 Jun;20(6):895-905. PubMed

Relevant to FAQ5

- **Study design:** systematic review with pairwise (direct) and network meta-analysis of randomized trials
- **Population:** smokers
- **Intervention:** any pharmacologic treatment for smoking cessation
- **Comparison:** placebo or active control
- **Study inclusion criteria:**
    - search window to October 6, 2018
    - reported changes in body weight before and after pharmacologic treatment
- **Number of studies:** 31
- **Number of participants:** 5,650
- **Duration of follow-up:** duration of treatment varied
    - 2 to 13 weeks with nicotine replacement therapy (16 trials)
    - 12 to 26 weeks with bupropion (4 trials)
    - 12 weeks with varenicline (1 trial)

- **Results and Certainty:**

Effect of smoking cessation therapies vs. placebo on weight change during treatment (in kg)*

Intervention	Mean difference (95% CI)		Certainty (reason for downgrade)
	Pairwise meta-analysis	Network meta-analysis	
Bupropion 300 mg	**-1.25 (-2.23 to -0.27)**	**-1.04 (-1.64 to -0.43)**	Moderate (risk of bias)[1,2]
Nicotine inhaler	-1.10 (-2.43 to +0.23)	-1.10 (-2.63 to +0.43)	Moderate (risk of bias)[1,2]
Nicotine lozenge	Not available	**-1.20 (-2.39 to -0.02)**	Low (risk of bias, indirectness)[1,2]
Nicotine gum	**-0.61 (-1.13 to -0.10)**	**-0.59 (-1.17 to -0.01)**	Moderate (risk of bias)[1,2]
Nicotine patch 14 mg	**-0.47 (-0.76 to -0.18)**	-0.43 (-0.95 to +0.10)	Moderate (risk of bias)[1,2]
Nicotine patch 21 mg	-0.43 (-1.29 to +0.44)	**-0.56 (-1.12 to 0.00)**	Moderate (risk of bias)[1,2]
Nicotine spray	**-2.80 (-5.03 to -0.57)**	**-2.80 (-5.16 to -0.44)**	Moderate (risk of bias)[1,2]
Varenicline 2 mg	-0.30 (-1.37 to +0.77)	-0.30 (-1.61 to +1.01)	Moderate (risk of bias)[1,2]

*Differences < 0 suggest less weight gain with the intervention compared to with placebo. **Statistically significant differences are bolded**.

[1] Only 2 of 31 randomized trials across the entire series of meta-analyses were assessed as having clear allocation concealment.

[2] No concern for imprecision with confidence interval width <5 kg suggesting absence of moderate or larger effects, regardless of statistical significance.

HUGHES 2014

Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014 Jan 8;(1):CD000031. doi: 10.1002/14651858.CD000031. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** adult smokers
- **Intervention:** bupropion
  - also considered other antidepressants (e.g., nortriptyline), but this is outside of scope, so we only consider the trials of bupropion in this summary
- **Comparison:** placebo
  - also included comparisons with nicotine replacement therapy (NRT) and varenicline where available
- **Study inclusion criteria:**
  - search window to 2013
  - reported rate of smoking cessation at six months or later after starting treatment
- **Number of studies:** 66 trials evaluated bupropion
- **Number of participants:** varies by outcome (see table below)
- **Duration of follow-up:** outcomes were reported at 6 months and at 12 months
  - per Scoping, we have focused on the 6-month outcome data over an outcome based on mixed follow-up times

- **Results and Certainty:**

Efficacy outcomes (Bupropion versus comparator) for smoking cessation

Outcome	No. of patients (studies)	Control group % (events/sample size)	Risk ratio (95% CI)	Certainty (reason for downgrade)
Bupropion versus placebo/control Abstinence at 6 months follow-up*	3,862 (17)	12.0% (200/1,660)	1.69 (1.45 to 1.97)	High[1,2]
Bupropion versus NRT*† Abstinence at 6 months or greater follow-up	4,086 (8)	25.4% (658/2,591)	0.96 (0.85 to 1.09)	Moderate (risk of bias)[1]

*bupropion dose was 300 mg/day where mentioned (not specifically mentioned for 1 trial in bupropion vs. NRT comparison)

†Results for bupropion vs. individual types of NRT (e.g., patch, lozenge) were consistent so we only present the results for any NRT as comparator

[1]Cochrane authors considered loss to follow-up rates < 50% as low risk of bias. We disagree with this threshold and consider the high attrition rates (about 30%) across this evidence base to be a serious concern for risk of bias.

[2]We evaluated the 4 largest trials contributing to this assessment (Ahluwalia 2002, Aubin 2004, Collins 2004, Cox 2012). Loss to follow-up rates in these trials were 32%, 27%, 6% and 30%, respectively. Overall this would lead to a downrating for risk of bias. However, the one trial at low risk of bias (Collins 2004 with a 6% rate of loss to follow-up) was completely consistent with the overall effect estimates. With losses to follow-up being counted as failure of cessation all the other trials show consistent relative estimates of efficacy and proportionately lower absolute rates.

Other considerations:

- Hughes 2014 also includes a comparison of bupropion versus varenicline, but we do not include those data here because:
  - Cahill 2016 is more current than Hughes 2014 and includes the very large and rigorous EAGLES trial (Anthenelli 2016).
  - Hughes 2014 defined outcomes differently than Cahill 2016, with Cahill 2016 representing a better match to Scoping (Hughes 2014 used the timepoint of 6 months or more while Cahill 2016 used the timepoint of 6 months)
  - Despite the above differences, Cahill 2016 and Hughes 2014 are consistent with each other, finding that varenicline seems better than bupropion for rates of smoking cessation (Cahill 2016, varenicline versus bupropion: RR 1.39, 95% CI 1.25 to 1.54; Hughes 2014, bupropion versus varenicline: RR 0.68, 95% CI 0.56 to 0.83).
- Hughes 2014 also includes a tabulated description of various side effects from individual trials without any quantitative synthesis, but we do not include those data here because we specified in Scoping a preference for direct comparisons (head-to-head trials), which are available via the EAGLES trial (Anthenelli 2016).

LANCASTER 2017

Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev. 2017 Mar 31;3:CD001292. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized and quasi-randomized trials
- **Population:** people who smoke and are willing to make attempt to quit
  - any smokers were included with exception of pregnant women (addressed by separate Cochrane review)
- **Intervention:** face-to-face individual counselling from a healthcare worker trained in assisting smoking cessation and not involved in routine clinical care
  - all trial interventions involved $\geq$ 1 face-to-face counselling sessions lasting $\geq$ 10 minutes, although the duration was typically much longer
  - many trial interventions included further telephone contact for additional support
  - trials that evaluated the effect of counselling as an addition to pharmacotherapy were included
- **Comparison:**
  - minimal contact control
    - including usual care, brief advice, or self-help materials
    - this comparison included here within our scope for this Evidence Review
  - different counselling model of similar intensity
    - This comparison not included here, except to note absence of clear evidence of effect difference by counseling model

- **Study inclusion criteria:**
  - minimal 6 months follow-up
  - reported cessation rates
    - sustained abstinence used where available
  - search window close date May 2016
  - interventions or comparisons that were excluded
    - interventions
      - counselling delivered by doctors and nurses as part of clinical care
      - motivational interviewing
      - interventions that address multiple risk factors in addition to smoking
    - comparisons
      - combined counselling with provision of pharmacotherapy vs. brief support
      - individual counselling vs. behavioral therapy conducted in groups

- **Number of studies:** 49
  - 33 trials compared individual counselling vs. minimal contact control
    - 27 trials had no adjuvant pharmacotherapy
    - 6 trials had adjuvant pharmacotherapy
  - 11 trials compared more intensive counselling vs. less intensive counselling
  - 5 trials compared different counselling approaches that were similar in intensity of contact
- **Number of participants:** about 19,000
- **Duration of follow-up:** minimum of 6 months

- **Results and certainty:**

Individual counselling vs. minimal contact control

Outcome/subgroup	No. of patients (studies)	Risk ratio (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
Smoking cessation at longest follow-up (≥ 6 months)*	13,762 (33)	1.48 (1.34 to 1.64)	11.4% (765/6,715)	7.7% (546/7,047)	Moderate (inconsistency)[1]
No systematic pharmacotherapy	11,100 (27)	1.57 (1.40 to 1.77)	10.9% (604/5,519)	7.0% (392/5,581)	Moderate (inconsistency) [1]
Pharmacotherapy offered to all participants	2,662 (6)	1.24 (1.01 to 1.51)	13.5% (161/1,196)	10.5% (154/1,466)	Moderate (imprecision)

***** Subgroup results are reported below because test for subgroup difference detected a difference between subgroups with and without pharmacotherapy.

[1] Significant heterogeneity

More intensive vs. less intensive counselling

Outcomes	No. of patients (studies)	Risk ratio (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
Smoking cessation at longest follow-up (≥ 6 months)	2,920 (11)	1.29 (1.09 to 1.53)	16.8% (252/1,499)	12.7% (181/1,421)	Low (inconsistency, imprecision)[1,2]
No systematic pharmacotherapy	872 (4)	1.42 (0.98 to 2.06)	13.0% (58/446)	9.2% (39/426)	Moderate (imprecision)
Pharmacotherapy offered to all participants	2,048 (8)	1.26 (1.04 to 1.52)	18.4% (194/1,053)	14.3% (142/995)	Low (inconsistency, imprecision) [1,3]

[1]Significant heterogeneity
[2]Despite statistical significance of the pooled estimate only 3 studies (with relatively little weight) have substantially higher effect estimates than the pooled estimate, so the overall precision is less certain
[3]Despite statistical significance of the pooled estimate only 2 studies (with relatively little weight) have substantially higher effect estimates than the pooled estimate, so the overall precision is less certain

- no significant differences in 5 trials that compared different counselling models of similar intensity

LINDSON 2019
Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2019 Apr 18;4:CD013308. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** patients of any age motivated to quit smoking
- **Intervention:**
  - any type, delivery, dose, duration, and schedule of NRT
  - this summary limits to comparison of different types of NRT
- **Comparison:**
  - any other type, dose(s), duration(s), schedule(s) of NRT use
  - this summary limits to comparison of different types of NRT

- **Study inclusion criteria:**
  - included cluster-randomized trials and quasi-randomized trials
  - studies that randomized therapists, rather than smokers, were included if the specific aim of the trial was to examine the effect of different types of NRT on smoking cessation
  - minimal 6 months follow-up
  - trial reported cessation rates
  - search window close date 30 April 2018

- **Number of studies:** 63
- **Number of participants:** 41,509
- **Duration of follow-up:** minimum of 6 months

- **Results and certainty:**

Fast-acting NRT vs. patch on smoking cessation at ≥ 6 months follow up

No. of patients (studies)	Risk ratio (95% CI)	Fast-acting NRT group event rate (%)	Patch group event rate (%)	Certainty (reason for downgrade)
3,319 (8)*	0.90 (0.77 to 1.05)	14.7% (244/1,661)	16.4% (272/1,658)	Moderate (imprecision)

* Among the 8 included trials, the following specific comparisons were included: inhaler vs. patch in 1 trial with 222 patients; nose spray vs. patch in analysis of 2 trials with 1,272 patients; lozenge vs. patch in analysis of 3 trials with 1,707 patients; gum vs. patch in analysis of 2 trials with 118 patients. The RR for each specific comparison showed no significant difference between groups with wide CIs.

- no significant differences between groups comparing oral spray vs. gum vs. inhaler in one 3-armed trial with 100 participants
- cardiac adverse events analyzed for fast-acting NRT vs. patch, but only 1 trial identified with only 38 participants and 0 events, so no meaningful data for specific adverse events for NRT formulation comparisons

MOTTILLO 2009

Mottillo S, Filion KB, Bélisle P, Joseph L, Gervais A, O'Loughlin J, Paradis G, Pihl R, Pilote L, Rinfret S, Tremblay M, Eisenberg MJ. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J. 2009 Mar;30(6):718-30. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** patients motivated to quit smoking
  - healthy populations evaluated in 22 trials
  - 'at-risk' populations evaluated in 28 trials
    - included pregnant women or diabetic patients, and miscellaneous populations corresponding to various age, sex, socioeconomic, or ethnic groups

- **Intervention:**
  - individual counselling
    - defined as ≥ 1 face-to-face encounters of ≥ 15 minutes between a smoker and a trained smoking cessation counsellor not involved in routine clinical care
  - group counselling
    - defined as ≥ 2 behavioral therapy meetings in which at least two smokers were present
    - smokers received advice from counsellors and were encouraged to discuss their problems with the group
  - telephone counselling
    - provision of telephone calls to aid in smoking cessation
    - trials evaluating both pro-active telephone counselling (counsellor initiates calls) and reactive telephone counselling (counsellor responds to calls from smokers)
  - minimal clinical intervention
    - defined as brief advice from healthcare worker to stop smoking delivered in < 20 minutes during a single consultation
    - included routine counselling, discussions, or recommendations that physicians or nurses (not trained in smoking cessation) provide their patients at regular clinical visit
- **Comparison:**
  - minimal clinical intervention
    - used as control for evaluating effects of 3 other more intensive counselling options
  - usual care intervention consisting of only self-help materials or no treatment
    - used as control for evaluating effects of minimal clinical intervention
    - considered co-intervention in evaluating effects of 3 more intensive counselling options vs. minimal clinical intervention

- **Study inclusion criteria:**
  - only trials that verified smoking abstinence outcomes by means of biochemical validation were included
  - recorded smoking cessation at 6 or 12 months
    - 12 months preferred if both time points reported
  - only trials that randomized individual patients were included
    - trials that randomized physicians, therapists, or centers rather than patients were excluded

- **Number of studies:** 50
- **Number of participants:** 26,927
- **Duration of follow-up:** minimum of 6 months

- **Results and certainty**

Effects of counselling interventions on smoking cessation at 6 or 12 months

Comparison	No. of patients (studies)	Odds ratio (95% credible interval)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
Minimal clinical intervention vs. usual care intervention	6,456 (9)	1.50 (0.84 to 2.78)	8.7% (275/3,173)	6.9% (227/3,268)	Very low (risk of bias [unclear] , imprecision, inconsistency)[1,2]
Individual counselling vs. minimal clinical intervention	8,646 (23)	1.49 (1.08 to 2.07)	10.4% (542/5,214)	7.9% (457/5,788)	Low (risk of bias, inconsistency) [1,2]
Group counselling vs. minimal clinical intervention	3,600 (12)	1.76 (1.11 to 2.93)	13.0% (245/1,883)	9.6% (165/1,717)	Low (risk of bias, inconsistency) [1,2]
Telephone counselling vs. minimal clinical intervention	8,225 (10)	1.58 (1.15 to 2.29)	10.3% (412/4,019)	7.0% (294/4,204)	Low (risk of bias, inconsistency) [1,2]

[1] Risk of bias was assessed using modified version of Jadad scale which included only randomization and dropouts, and results of these assessments were reported only as average overall score across all trials with no reporting of individual RoB domains for each trial (ie, RoB assessments reported only as follows: "The average quality assessment score of all 50 RCTs was 2.14 on a scale of 3, suggesting that most of the RCTs had medium-to-low probability of bias.")

[2] Downgrade for heterogeneity for all comparisons because for each forest plot some trials showed a clearly significant benefit and others showed no between group difference. Although no heterogeneity statistics were reported, it is likely that if they had been there would be significant heterogeneity in all analyses because credible intervals for several studies do not have overlap in all forest plots.

- **Other considerations**
  - in addition to the concerns noted in the Certainty downgrades, other issues which make this systematic review sub-optimal for our purposes include the following
    - indirectness in that 12-month outcomes preferentially used and our intended scope is 6-month outcomes
    - outcomes pooled using Bayesian approach to inference with 95% credible interval reported rather than confidence interval
      - it is unclear
        - whether selection of Bayesian approach in preference to classical meta-analysis (which is standard approach using in Cochrane Tobacco Addiction Group SRs) has been justified
        - whether methodologic benefits of this approach over the classical meta-analysis (if any) compensate for the additional challenges this approach poses to interpretability (for the reader of our Evidence Report)

SUN 2018
Sun Y, Duan W, Meng X, Li H, Jia C. Varenicline is associated with a modest limitation in weight gain in smokers after smoking cessation: a meta-analysis. J Public Health (Oxf). 2018 Jun 1;40(2):e126-e132. PubMed

Relevant to FAQ5

- **Study design:** systematic review and meta-analysis
- **Population:** smokers
- **Intervention:** varenicline 2 mg/day
- **Comparison:** placebo (6 studies) or active control (4 studies)
- **Study inclusion criteria:**
  - search window 2006 to 2016
  - randomized trials and cohort studies were eligible
- **Number of studies:** 10 (9 randomized trials and 1 cohort study)
- **Number of participants:** 5,007
  - 2,458 randomized to varenicline, 409 to nicotine replacement therapy, 329 to bupropion, and 1,811 to placebo
  - in placebo-controlled trials, 1,816 were randomized to varenicline and 1,811 to placebo
- **Duration of follow-up:** timepoint of weight measurement varied
  - 12 weeks in 9 studies
  - 52 weeks in 2 studies (1 also reported at 12 weeks)
  - 60 weeks in 1 study (also reported at 12 weeks)
- **Certainty: Moderate**
  - **Risk of bias:** risk of bias assessment was limited (use of Jadad score does not cover allocation concealment or intention-to-treat analysis); although observational studies were eligible, the 1 included cohort study did not contribute to the analysis of varenicline vs. placebo
  - **Indirectness**: 1 study included patients with COPD, but had very little weight in contribution to meta-analysis
  - **Inconsistency**: no serious concern; I^2 is reported at 60%, but this measure can be overly sensitive when used with absolute measures (especially as sample size increases), and the possible signal of statistical heterogeneity in this case does not correspond with differences reaching clinical importance
  - **Imprecision: no serious concern**
  - **Publication bias**: no serious concern
- **Results:**
  - Varenicline associated with modestly less weight gain compared to placebo in meta-analysis of 9 comparisons from 8 trials (weighted mean difference -0.29 kg, 95% CI -0.46 kg to -0.12 kg)

TULLOCH 2016
Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. BMC Med. 2016 Jun 7;14:80. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** randomized controlled trial, stratified by psychiatric status
- **Population:** adult smokers willing to quit
  - 59% met criteria for lifetime psychiatric diagnosis
- **Intervention and Comparator:** 3-arm trial comparing
  - nicotine replacement therapy (NRT) with nicotine patch 7-21 mg/day tapered over 10 weeks
  - nicotine replacement therapy (NRT+) with nicotine patch and additional nicotine (gum or inhalers) with dose titrated by withdrawal symptoms for up to 22 weeks
  - varenicline 1 mg twice daily for 12 weeks (lower ramp-up dosing in first week) and option to continue for up to 24 weeks
- **Number of participants:** 737 overall
  - 245 NRT
  - 245 NRT+
  - 247 varenicline
- **Duration of follow-up:** 22 weeks and 52 weeks
  - Attrition rates at 22 weeks 37.6% with NRT and 29.6% with varenicline
- **Results and certainty:**

Comparing NRT vs. varenicline

Outcome	NRT rate	Varenicline rate	Odds ratio (95% CI)*	Certainty (reason for downgrade)
Continuous abstinence weeks 5 to 52	10% (23/230)	12.4% (29/236)	1.62 (0.87 to 3.01)	Low (risk of bias, imprecision)[1]
Continuous abstinence weeks 5 to 22	15.8% (38/230)	24.5% (59/236)	2.01 (1.20 to 3.36)	Moderate (risk of bias)[1]
Digestive adverse events (eg nausea, diarrhea)	19.6% (48/245)	56.3% (139/247)	Not reported	High
Sleep disturbance (eg abnormal dreams, insomnia)	37.6% (92/245)	60.3% (149/247)	Not reported	High
Fatigue	3.7% (9/245)	17.4% (43/247)	Not reported	High
Skin adverse events	38.4% (94/245)	4.9% (12/247)	Not reported	High

*Results reported with NRT as comparator and varenicline as intervention.

[1] Attrition rates > 25%, lacking full intention-to-treat analysis

Note: Adverse events not progressed to Evidence Synthesis because the rates were much higher than other evidence reports and the sample size was considerably lower.

Evidence report for smoking cessation

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