Mini-CAT Draft Name Arianne Díaz

Clinical Question: *Brief description of patient problem/setting (summarize the case very briefly)*
44 y/o M w/ PMHx HTN, T2DM, obesity, MDD for four years and a 20-pack -year smoking history presents to clinic seeking information on interventions to help him achieve his smoking cessation goals.

PICO Search Question: *Clearly state the question (including outcomes or criteria to be tracked)*
In adult smokers seeking to quit, how does nicotine replacement therapy compare to varenicline in terms of smoking cessation rates/long-term abstinence?

PICO Search terms:

Population	Intervention	Comparison	Outcome
Adult smokers	Nicotine replacement therapy	Pharmacologic therapy	Smoking cessation
Adults who smoke cigarettes	Nicotine patches	Varenicline	Successful smoking cessation
	Nicotine gum		Long-term abstinence
	Nicotine lozenges		

Search tools and strategy used:
Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Database	Terms	Filter	Articles
Wiley Online Library	Adult smokers AND nicotine replacement therapy AND varenicline AND smoking cessation	Open access articles published within the last ten years	116
Cochrane Library (Wiley)	Adult smokers AND nicotine replacement therapy AND varenicline AND smoking cessation	Cochrane Trials published within the last ten years	79
PubMed	Adult smokers AND nicotine replacement therapy AND varenicline AND smoking cessation	Systematic reviews published within the last ten years Meta-analysis published within the last ten years Randomized Control Trials published within the last ten years	15 9 36
UpToDate	Efficacy of varenicline in smoking cessation	Looked at relevant articles in the references section of *Pharmacotherapy for smoking cessation in adults*	23
JAMA	Adult smokers AND varenicline AND smoking cessation	Research articles published within the last ten years	56

TRIP Database	Adult smokers AND nicotine replacement therapy AND varenicline AND smoking cessation	Research articles published within the last ten years	25
ScienceDirect	Adult smokers AND nicotine replacement therapy vs varenicline AND smoking cessation	Open access & open archive research articles published within the last ten years	90

Results found: 449 results

Explain how you narrow your choices to the few selected articles.

I narrowed down my searches to focus on articles of the highest level of evidence that were published within the last ten years. I wanted to include systematic reviews, meta-analysis, and randomized control trials conducted in the United States. For searches that generated a lot of results such as the Wiley Online Library, Cochrane Library, and ScienceDirect, I scrolled through the first three pages to determine whether I could use any articles and while I found nothing useful on the Wiley and ScienceDirect databases, I was able to find one relevant study in the Cochrane database. Majority of my articles were found on PubMed and, surprisingly, I came across more randomized control trials than systematic reviews and meta-analysis.

Articles Chosen:

Article #1

CITATION	Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;2013(5):CD009329. Published 2013 May 31. doi:10.1002/14651858.CD009329.pub2
ABSTRACT	**Background:** Smoking is the leading preventable cause of illness and premature death worldwide. Some medications have been proven to help people to quit, with three licensed for this purpose in Europe and the USA: nicotine replacement therapy (NRT), bupropion, and varenicline. Cytisine (a treatment pharmacologically similar to varenicline) is also licensed for use in Russia and some of the former socialist economy countries. Other therapies, including nortriptyline, have also been tested for effectiveness. **Objectives:** How do NRT, bupropion and varenicline compare with placebo and with each other in achieving long-term abstinence (six months or longer)? How do the remaining treatments compare with placebo in achieving long-term abstinence? How do the risks of adverse and serious adverse events (SAEs) compare between the treatments, and are there instances where the harms may outweigh the benefits? **Methods:** The overview is restricted to Cochrane reviews, all of which include randomised trials. Participants are usually adult smokers, but we exclude reviews of smoking cessation for pregnant women and in particular disease groups or specific settings. We cover nicotine replacement therapy (NRT), antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), clonidine, lobeline, dianicline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines, and silver acetate. Our outcome for benefit is continuous or prolonged abstinence at least six months from the start of treatment. Our outcome for

	harms is the incidence of serious adverse events associated with each of the treatments. We searched the Cochrane Database of Systematic Reviews (CDSR) in *The Cochrane Library*, for any reviews with 'smoking' in the title, abstract or keyword fields. The last search was conducted in November 2012. We assessed methodological quality using a revised version of the AMSTAR scale. For NRT, bupropion and varenicline we conducted network meta-analyses, comparing each with the others and with placebo for benefit, and varenicline and bupropion for risks of serious adverse events. **Conclusions:** NRT, bupropion, varenicline and cytisine have been shown to improve the chances of quitting. Combination NRT and varenicline are equally effective as quitting aids. Nortriptyline also improves the chances of quitting. On current evidence, none of the treatments appear to have an incidence of adverse events that would mitigate their use. Further research is warranted into the safety of varenicline and into cytisine's potential as an effective and affordable treatment, but not into the efficacy and safety of NRT.
LINK/PDF	https://pubmed.ncbi.nlm.nih.gov/23728690/ **PDF POSTED ON BLACKBOARD**

Article #2

CITATION	Wu L, Sun S, He Y, Zeng J. Effect of Smoking Reduction Therapy on Smoking Cessation for Smokers without an Intention to Quit: An Updated Systematic Review and Meta-Analysis of Randomized Controlled. *Int J Environ Res Public Health*. 2015;12(9):10235-10253. Published 2015 Aug 25. doi:10.3390/ijerph120910235
ABSTRACT	**Objective**: Effective strategies are needed to encourage smoking cessation for smokers without an intention to quit. We systematically reviewed the literature to investigate whether smoking reduction therapy can increase the long-term cessation rates of smokers without an intention to quit. **Methods**: PubMed, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched for randomized controlled trials (RCTs) on the effect of smoking reduction therapy on long-term smoking cessation in smokers without an intention to quit. The primary outcome was the cessation rate at the longest follow-up period. A random effects model was used to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs). **Results**: Fourteen trials with a total of 7981 smokers were included. The pooled analysis suggested that reduction support plus medication significantly increased the long-term cessation of smokers without an intention to quit compared to reduction support plus placebo (RR, 1.97; 95% CI, 1.44–2.7; I2, 52%) or no intervention (RR, 1.93; 95% CI, 1.41–2.64; I2, 46%). In a subgroup of smokers who received varenicline or nicotine replacement therapy (NRT), the differences were also statistically significant. This suggests the safety of using NRT. The percentage of smokers with serious adverse events who discontinued because of these events in the non-NRT group was slightly significantly different than in the control group.

	Insufficient evidence is available to test the efficacy of reduction behavioral support in promoting long-term cessation among this population. **Conclusions**: The present meta-analysis indicated the efficacy of NRT- and varenicline-assisted reduction to achieve complete cessation among smokers without an intention to quit. Further evidence is needed to assess the efficacy and safety of reduction behavioral support and bupropion.
LINK/PDF	https://pubmed.ncbi.nlm.nih.gov/26308034/ **PDF POSTED ON BLACKBOARD**

Article #3

CITATION	Cinciripini PM, Kypriotakis G, Green C, et al. The effects of varenicline, bupropion, nicotine patch, and placebo on smoking cessation among smokers with major depression: A randomized clinical trial. *Depress Anxiety*. 2022;39(5):429-440. doi:10.1002/da.23259
ABSTRACT	**Importance:** Improving treatment outcomes for smokers with Major Depressive Disorder (MDD) can have significant public health implications. **Objective:** To evaluate the safety and efficacy of smoking cessation pharmacotherapy among smokers with MDD. **Design:** Secondary analysis of a randomized, double-blind, active- (nicotine patch) and placebo- controlled trial of 12 weeks of either varenicline or bupropion with 12-week follow-up. **Participants:** Community volunteers 18-75 years of age; smoke 10+ cigarettes/day; with clinically stable MDD(N=2635) or no psychiatric disorder(N=4028), from 140 sites in 16 countries. **Intervention:** 12 weeks of pharmacotherapy (placebo, PLA; nicotine replacement therapy, NRT; bupropion, BUP; varenicline, VAR) plus brief cessation counseling. **Results:** 6,653 participants (56% female; 39% MDD) ~47 years old. Risk of NPSAEs did not differ by medication for MDD. MDD had higher risk ($p<0.0001$) for NPSAEs than the non-psychiatric cohort (NPC). Efficacy (6,653; intent-to-treat): CA rates for MDD vs. NPC respectively were 31.2% vs. 38.0% VAR; 23.0% vs 26.1% BUP; 22.6% vs 26.4% NRT; and 13.4% vs. 13.7% PLA but no differential treatment effect was noted within the cohorts. All active treatments differed from PLA but VAR showed the largest effect. **Conclusions:** Results suggest that for MDD smokers, inclusive of those with recurrent episodes (RE), varenicline plus counseling may be the best pharmacological option for the treatment of smoking given its greater efficacy effect size and similar risk of NPSAEs.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9705120/ **PDF POSTED ON BLACKBOARD**

Article #4

CITATION AMA FORMAT	Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA*. 2016;315(4):371-379. doi:10.1001/jama.2015.19284

ABSTRACT	**Importance:** Smoking cessation medications are routinely used in healthcare; it is vital to identify medications that most effectively treat this leading cause of preventable mortality. **Objective:** Compare the efficacies of varenicline, combination nicotine replacement (C-NRT), and the nicotine patch on 26-week quit rates. **Design, Setting, Participants:** 3-group randomized clinical trial occurring from 5/22/2012 – 11/18/2015, using the intention-to-treat principle. Among 1086 smokers who were randomized (52% women, 67% White, mean age 48 years, mean of 17 cigarettes smoked/day), 917 (84%) provided 12 month follow-up data. Recruitment was in the Madison WI and Milwaukee WI communities and 65.5% of smokers offered the study (2687/4102) refused participation prior to randomization. **Interventions**: Three open-label smoking cessation pharmacotherapies for 12 weeks: 1) nicotine patch only (n=241); 2) varenicline only (including 1 pre-quit week; n=424); and 3) C-NRT (nicotine patch + nicotine lozenge; n=421). 6 counseling sessions were offered. **Results**: Treatments did not differ on any abstinence outcome measure at 26 or 52 Weeks, including point-prevalence abstinence at 26 Weeks (nicotine patch: 22.8% [55/241]; varenicline: 23.6% [100/424]; and C-NRT: 26.8% [113/421] or 52 weeks (nicotine patch: 20.8% [50/214]; varenicline: 19.1% [81/424]; and C-NRT: 20.2% [85/421]). At 26 weeks the risk differences for abstinence were: patch versus varenicline (−0.76, 95% CI: −7.4 to 5.9), patch versus C-NRT (−4.0, 95%CI: −10.8 to 2.8), and varenicline versus C-NRT (−3.3, 95% CI: −9.1 to 2.6). All medications were well tolerated, but varenicline produced greater adverse event rates than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion. **Conclusions and Relevance**: Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or combination nicotine replacement produced no significant differences in confirmed rates of smoking abstinence at 26 weeks. The results raise questions about both the relative effectiveness of intense smoking pharmacotherapies in today's smokers and when such therapies should be used.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4824537/ **PDF POSTED ON BLACKBOARD**

Article #5

CITATION AMA FORMAT	Chang PH, Chiang CH, Ho WC, Wu PZ, Tsai JS, Guo FR. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. Published 2015 Jul 22. doi:10.1186/s12889-015-2055-0
ABSTRACT	**Background:** Smoking is a major preventable cause of morbidity and premature death worldwide. Both varenicline and nicotine replacement therapy (NRT) help achieve smoking cessation. However, limited evidence exists regarding whether combination of varenicline and NRT is more effective than either alone. The aim of this research was to investigate the efficacy and safety of varenicline combined with NRT. **Methods**: A systematic search of MEDLINE, EMBASE, ClinicalTrial.gov, and Cochrane Library was conducted in November 2014. Two authors independently reviewed and selected randomized controlled trials. The quality of the studies was evaluated by the Jadad score. We carried out meta-analysis of both early (abstinence rate assessed before or at the end of treatment) and late (assessed after the end of the treatment) outcomes.

	Results: Three randomized controlled trials with 904 participants were included in this meta-analysis. All three were comparing combination therapy with varenicline therapy alone. The late outcomes were assessed in 2 of the 3 trials. Both the early and late outcomes were favorable for combination therapy (OR = 1.50, 95 % CI 1.14 to 1.97; OR = 1.62, 95 % CI 1.18 to 2.23, respectively). However, this significance diminished after eliminating a study with pre-cessation treatment using nicotine patch. The most common adverse events were nausea, insomnia, abnormal dreams, and headache. One study reported more skin reactions (14.4 % vs 7.8 %; p = 0.03) associated with combination therapy. **Conclusions**: Combination therapy is more effective than varenicline alone, especially if pre-cessation treatment of nicotine patch is administrated. Adverse events of combination therapy are similar to mono-therapy except for skin reactions.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508997/ **PDF POSTED ON BLACKBOARD**

Summary of the Evidence:

Article #1:

Author (Date): Cahill K, Stevens S, Perera R, Lancaster T

Level of Evidence: Meta-Analysis

Sample/Setting (#of subjects/studies, cohort definition, etc.)

- Authors searched the Cochrane Database of Systematic Reviews, particularly focusing on reviewing that included "smoking" in the title
- 12 Cochrane reviews were selected, each focusing on different methods to manage smoking cessation. 267 trials were reviewed between 2008 and 2012, all of which were randomized controlled trials comparing active treatment with placebo.
- The AMSTAR measurement tool was used to assess the quality of each review. This is a critical appraisal tool used to evaluate the methodological quality of systematic reviews.
- Inclusion criteria: participants were selected based on their eligibility to receive pharmacotherapy. Authors selected studies containing adult smokers of either gender and of any nationality and ethnicity.
- Exclusion criteria: smokers with mental health issues or pregnant women.
- Abstinence was defined as prolonged, sustained, or continuous abstinence over the course of 6 or more months

Outcome(s) studied

- The primary beneficial outcome for this study is sustained smoking cessation defined as smoking cessation for ≥ 6 months. Secondary beneficial outcomes include reduction of withdrawal symptoms and cravings.
- The primary harmful outcome for this study is any serious/life-threatening adverse event which might be attributed to the pharmacologic intervention. Outcomes include depression, anxiety, suicidal ideation, and seizures.
- Secondary harmful outcomes include GI disorders, cardiovascular problems, insomnia/other sleep disorders, skin disorders, and allergic or hypersensitivity reactions.
- Each trial had their own studied outcomes: one trial measured abstinence at 6 months, three trials at 12 months, and one trial defined success as a reduction of ≥ 85% from baseline smoking rate at 18 months.

Key Findings

- This study focuses on five main interventions that can be used for smoking cessation: nicotine replacement therapy, bupropion, nortriptyline, varenicline, and cystisine. Authors also briefly went over other medications used for smoking cessation such as clonidine, lobeline, dianicline, mecamylamine, nicobrevin, silver acetate, and opioid antagonists.
- In 70% of trials in which participants were manage with nicotine replacement therapy there was sustained abstinence, including continuous abstinence with "not even a slip since quit day" during the 6-month follow-up. In patients taking bupropion versus placebo as well as nicotine receptor partial agonists (such as varenicline) vs placebo, majority of studies reported an outcome of sustained abstinence. Lobeline was more effective at smoking reduction. Participants who used lobeline were not able to fully abstain from smoking.

- Both nicotine replacement therapy and bupropion are similar in efficacy compared with placebo. Varenicline is more effective than NRT or bupropion when compared to placebo. In fact, varenicline is superior to any single type of NRT and to bupropion.
- Ultimately, NRT, bupropion, varenicline, and cystine are more efficacious than other interventions at helping participants with smoking cessation. Combination nicotine replacement therapy and varenicline are equally effective as quitting aids compared to nicotine replacement therapy alone.

Limitations and Biases

- The bupropion review selected by articles only covers trials available to 2009.
- Most trials in which anxiolytics were studied as smoking cessation aids did not report methods in sufficient detail to assess the quality of randomization.
- Studies in which CB1 receptor antagonists such as rimonabant were used were not peer reviewed.
- There were no details of randomization or clear definition of abstinence in trials where clonidine was used for smoking cessation.
- Studies which used mecamylamine for smoking cessation were too small to be conclusive.

Article #2

Author (Date): Lei Wu, Samio Sun, Yao He, and Jing Zeng

Level of Evidence: Systematic Review and Meta-Analysis

Sample/Setting (#of subjects/studies, cohort definition, etc.)

- Authors searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Search terms included "tobacco reduction, cigarette, reduction, reduce smoking, smoking reduction, unwilling to, not willing, not ready, uninterest, and unmotivated". No language restrictions were imposed.
- Inclusion criteria: randomized control trials focused on adult smokers who were not ready to quit, were unwilling to quit, or had no intention to quit smoking. Participants used cessation therapies such as nicotine replacement therapy, varenicline, or bupropion to promote reduction.
- Exclusion criteria: duplicated reports with other included studies, reports with no data on outcome of interest, any study **not** an RCT, study did not refer to smoking reduction, any study containing participants <18 years old, intervention on smokeless tobacco use
- 14 trials including 7,981 smokers were included in the study.

Outcome(s) studied

- The primary outcome was the cessation rate at the longest follow-up period (6 months)
- The secondary outcome included serious and non-serious adverse events that were reported in he included trials. Only 11 of the included trials reported information on adverse events.

Key Findings

- Studies were groups into four comparisons: reduction support plus medication versus reduction support plus placebo, reduction support plus medication versus no intervention, reduction support plus medication versus other support plus medication, and reduction support versus no intervention.
- Reduction support is defined as behavioral interventions of self-help materials to increase reduction; soking cessation medications are not incorporated in this definition.
- A combination of reduction support (nicotine replacement therapy) and medication (varenicline) are effective at achieving complete cessation

Limitations and Biases

- Various definitions and time frames were used to define an intention to quit in the included trials. According to the authors, "future studies should follow a common definition"
- Treatment duration and follow-up time varied between trials, particularly treatment duration ranged from 2-18 months and follow-up time ranged from 6-60 months
- Most trials reported point of prevalence as opposed to sustained abstinence rates
- Several trials did not report the frequency or intensity of baseline and follow-up behavioral counseling

Article #3

Author (Date): Paul M. Cinciripini, George Kypriotakis, Charles Green, David Lawrence, Robert M. Anthenelli, Jennifer Minnix, Janice A. Blalock, Diane Beneventi, Chad Morris, Maher Karam-Hage

Level of Evidence: Randomized Clinical Trial

Sample/Setting (#of subjects/studies, cohort definition, etc.)

- This study was designed based on EAGLES: Evaluating Adverse Events in a Global Smoking Cessation Study. This study was a 24-week double blind RCT characterizing "the neuropsychiatric safety and efficacy of varenicline and bupropion"
- The sample for this analysis consists of 6,653 randomized smokers, 2,635 of which have a primary diagnosis of major depressive disorder and 4,208 of which have no lifetime psychiatric disorder.
- Subjects were randomized to 12 weeks of varenicline 1 mg BID, bupropion 150 mg BID, a nicotine replacement patch 21 mg/daily w/ tapering, or placebo. All participants received at least 10 minutes of behavioral counseling during each follow-up visit.
- Inclusion criteria: smoking >10 cigarettes/day in the previous year, interest in quitting, exhaled carbon monoxide of ≥ 10 parts per million at screening

Outcome(s) studied

- The primary safety outcome was the occurrence of ≥ 1 treatment-emergent, all-causality, moderate to severe neuropsychiatric adverse event consisting of 16 event components.
- The main efficacy endpoint was carbon monoxide confirmed continuous abstinence during the final 4-week treatment.
- The secondary cessation outcome was carbon monoxide confirmed continuous abstinence at 6-months.

Key Findings

- Abstinence at 9-12 weeks for recurrent episodes of depression was lower compared to abstinence at 9-12 weeks in patients who experienced a single episode of depression across all medications except varenicline. Varenicline outperformed bupropion and nicotine replacement therapy in the recurrent depression group. There were no treatment differences in the single episode of depression group.
- Varenicline combined with smoking cessation behavioral counseling is the best treatment for smokers with major depressive disorder.
- Smokers in the recurrent vs single episode of major depression cohort reported more frequent neuropsychiatric adverse events but the difference was not significant and did not differ by medication.
- Participants with major depressive disorder who experienced recurrent episodes of major depressive disorder were less likely to remain abstinent.

Limitations and Biases

- Smokers with major depressive disorder were required to be psychiatrically stable at baseline, hence the findings may not be appliable to smokers with unstable or more severe major depressive disorder
- Combination nicotine replacement therapy was not included among the treatments so its efficacy could not be evaluated. This is the standard therapy that is implemented for smoking cessation
- The study did not detect differences in outcomes for the major depressive disorder cohort compared to the other subgroups.

Article #4

Author (Date): Timothy B. Baker, Megan E. Piper, James H. Stein, Stevens S. Smith, Daniel M. Bolt, David L. Fraser, and Michael C. Fiore

Level of Evidence: Randomized Control Trial

Sample/Setting (#of subjects/studies, cohort definition, etc.)

- Participants were recruited via an ongoing longitudinal study of smokers and via media/community outreach. Of 1,086 participants, 52% were women, 67% were white, and participants smoked an average of 17 cigarettes/day
- Inclusion criteria: adults > 17 years old who smoke ≥ 5 cigarettes/day, able to read and write English, having a desire to quit but not engaged in smoking treatment. Patients were not allowed to use e-cigarettes to help with smoking cessation.
- Exclusion criteria: exhaled carbon monoxide, ESRD, diagnosis or treatment for psychoses within the last 10 years, moderate to severe depression via the Patient Health Questionnaire-9, untreated hypertension of >200/100 mm Hg, current use of bupropion, previous history of being hospitalized for stroke, heart attack, congestive heart failure, or diabetes within the last year, > 60% carotid artery stenosis, third degree heart block, or using other forms of tobacco more than twice in the past week.

- Baseline Visit 1 focused on determining patient's smoking history, dependence, and affective/psychiatric domain symptoms.
- Baseline Visit 2 involved counseling in five treatment visits and one phone call. Counseling lasted 20 minutes for the first three visits, and 10 minutes during the last two visits including the phone call. Medications were dispensed during the first four visits. Medications dispensed include Varenicline, nicotine patch plus nicotine lozenge, or nicotine patch alone

Outcome(s) studied

- Primary outcome measured was carbon monoxide confirmed self-reported 7-day point-prevalence abstinence at 26 weeks
- Secondary outcomes were carbon monoxide confirmed self-reported initial abstinence at 26 weeks, and point prevalence abstinence at weeks 1, 4, and 52.

Key Findings

- This study suggested that nicotine replacement therapy is effective in those who are highly dependent on tobacco, the nicotine patch has been shown to reduce dependence
- Among those who smoked more than 30 minutes after waking as opposed to within 30 minutes of waking, abstinence rates were 19.1% and 25.3% respectively.
- At week 8, medication adherence rates were 45.2% in those who opted for the nicotine patch, 49.3% in those who used varenicline, and 43% in those who used the lozenge.
- Authors concluded that more research must be done to determine the effectiveness of pharmacotherapy in smoking cessation

Limitations and Biases

- According to the authors, "the results may overestimate the effects of the tested medications as they would occur in clinical practice"
- Effects of the pharmacotherapies may be diluted – participants were allowed to attend 6 counseling sessions

Article #5

Author (Date): Ping-Hsun Chang, Chien-Hsieh Chiang, Wei-Che Ho1, Pei-Zu Wu1, Jaw-Shiun Tsai, and Fei-Ran Guo

Level of Evidence: Systematic Review and Meta-Analysis

Sample/Setting (#of subjects/studies, cohort definition, etc.)

- Authors searched MEDLINE, EMBASE, clinicaltrial.gov, and the Cochrane library. Three randomized control trials consisting of 904 participants were selected. The authors used search terms such as "varenicline, nicotine replacement therapy (including nicotine patch, gum, inhaler, nasal spray, lozenge)". Authors also combined "varenicline" and "nicotine replacement therapy" by the Boolean operator.
- Inclusion criteria: smokers > 18 years old, not breastfeeding or pregnant, and with no current psychiatric condition or serious conditions.
- Exclusion criteria: non-randomized control trials, trials without outcome measurements, trials using smoking cessation medications but not aiming to stop cigarette smoking, articles where full-text was not available

Outcome(s) studied

- Early outcome defined as the quit rate assessed before or at the end of treatment completion.
- Late outcome defined as quit rate assessed for a period after the end of treatment completion, mainly at 24 weeks or more.
- Abstinence rates with biochemical verification, safety profile, or tolerability of therapy.

Key Findings

- Authors identified three smoking cessation trials which compared varenicline combined with nicotine patch versus varenicline combined with placebo patch. There were no trials comparing combination therapy with nicotine replacement therapy alone that met the inclusion criteria.
- In patients where a pre-cessation nicotine patch was utilized there is increased rate of abstinence at 6 weeks compared to when no pre-cessation nicotine patch was used. This is believed to be because varenicline on its own does not completely saturate the nicotinic acetylcholine receptors nor does it replace the dopaminergic effect of smoking. There are those who argue, however, that a single dose of 0.5 mg varenicline could saturate nicotinic receptors in the human brain.
- Patients primarily developed adverse skin reactions similar to that seen in nicotine patch mono-therapy.

- Combination therapy is more effective than varenicline alone, especially when a pre-cessation nicotine patch is implemented prior to initiation of pharmacologic therapy.

Limitations and Biases

- Authors did not thoroughly search for "grey" literature, meaning that there may have been lesser-known trials that were not included in the study
- The strength of the research was compromised by the small number of trials. The largest randomized control trial had the greatest influence on the results. It was different from the other trials in terms of demographics.
- Funnel plot and tests of publication bias possess low power to detect a potential bias.

Conclusion(s):

Briefly summarize the conclusions of each article, then provide an overarching conclusion.

Article #1:

Smoking is associated with a myriad of adverse health outcomes including cancer, cardiovascular and lung diseases, and other conditions such as peripheral artery disease, age-related macular degeneration, and T2DM. According to the centers for disease control and prevention, approximately 28.3 million adults in the United States currently smoke cigarettes. Despite declining by 20.9% in the past two decades, smoking continues to impose significant healthcare costs, straining the healthcare system. This article goes over various treatments that have been implemented to help adult smokers who wish to achieve long-term abstinence. Authors discuss the efficacy of five main interventions which are commonly used to assist people with smoking cessation such as nicotine replacement therapy, bupropion, nortriptyline, varenicline, and cystisine. Authors concluded that while nicotine replacement therapy alone may not be as effective at maintaining long-term abstinence, using nicotine replacement therapies in combination with other pharmacologic interventions is effective at assisting adult smokers with smoking cessation and maintaining abstinence.

Article #2:

According to the authors of this study, for smoking cessation therapies to be successful they must help patients achieve reduction in cigarette consumption and maintain abstinence. Authors of this study focused randomized control trials comparing varenicline versus placebo, nicotine replacement therapy versus placebo, and bupropion versus placebo. Authors also included trials which assessed the efficacy of self-help materials rather than behavior reduction support to assist in reduction, trials testing the efficacy of reduction support combined with smoking cessation medication. It was concluded that smokers who received reduction support combined with medication had significant increased smoking abstinence compared to the other groups.

Article #3

Major depressive disorder is defined as a loss of interest or pleasure in most activities or depressed mood lasting at least two weeks. To meet criteria for major depressive disorder, patients must have at least four SIG E CAPS. The SIG E CAPS criteria is as follows: sleep changes, lack of interest, guilt, lack of energy, impairment in cognition/concentration, appetite changes, psychomotor agitation or retardation, or suicidal thoughts/attempts. According to the authors of this study, "smoking rates among those with major depressive disorder are 1.5 times higher than those without major depressive disorder". This psychiatric illness is very common and associated with nicotine dependence, higher rates of release, and more frequent and sustained periods of withdrawal. Because of this, it is important to develop a regimen for smokers with MDD that helps them achieve long-term abstinence. Risk of moderate to severe neuropsychiatric adverse events in this patient population did not drastically differ compared to those without MDD being treated with varenicline, bupropion, or nicotine replacement therapy. Varenicline combined with smoking cessation counseling was most effective at helping patients maintain achieve complete smoking cessation.

Article #4

Although all three interventions were effective at helping participants initiate smoking cessation, neither was overly effective than the other at maintaining abstinence. According to the authors, at week 8, medication adherence rates were 45.2% in those who opted for the nicotine patch, 49.3% in those who used varenicline, and 43% in those who used the lozenge. Although varenicline proved to be the most successful, it was not by a grand margin. Additionally, authors of this study concluded that overall, nicotine replacement therapy was superior to pharmacologic management for smoking cessation, and that more research must be performed before determining the role that smoking cessation drugs play in helping patients quit.

Article #5

Combination of varenicline with nicotine replacement therapy (nicotine patch) yielded favorable early and late outcomes. Patients who used a pre-cessation nicotine patch were more likely to maintain abstinent compared to those who did not use a pre-cessation nicotine patch. This results were consistent with previous studies which indicate that only 40-50% of patients on varenicline monotherapy remained abstinent by the 6-week mark.

Overarching Conclusion

Of all treatment modalities discussed in these studies, the most efficacious pharmacological monotherapy was varenicline. Three of the article I selected determined that varenicline was superior to other smoking cessation drugs such as bupropion, nortriptyline, clonidine, lobeline, dianicline, mecamylamine, nicobrevin, silver acetate, and opioid antagonists. The authors of these studies concluded that a combination of varenicline and nicotine replacement therapy was the most effective at initiating smoking cessation and maintaining abstinence. One article determined that nicotine replacement therapy, particularly nicotine patches and lozenges, were more efficacious than pharmacologic intervention and that this modality required further research before determining their role in smoking cessation. Another study suggested that a pre-cessation nicotine patch in conjunction with varenicline would help patients quit smoking more effectively than varenicline alone.

PICO Question:
In adult smokers seeking to quit, how does nicotine replacement therapy compare to varenicline in terms of smoking cessation rates/long-term abstinence?

Clinical Bottom Line:

Varenicline is a nicotinic receptor partial agonist used to help patients quit smoking. It functions by competitively inhibiting the ability to nicotine to bind to and activate the alpa-4-beta-2 receptor. Binding to these nicotinic receptors helps ease withdrawal symptoms in patients who may want to cut down on how much they smoke or quit altogether. On the other hand, nicotine replacement therapy is a type of treatment that delivers nicotine to patients without the harmful chemicals contained in cigarettes or other products containing tobacco. Nicotine replacement therapy helps reduce cravings so that, in theory, patients are less compelled to smoke. Based on the information gathered, I would recommend that my patient try varenicline with a nicotine replacement adjunct. I would also recommend some type of smoking cessation counseling. His history of major depressive disorder makes him more susceptible to relapsing and to achieve complete smoking cessation, I would like to start him on therapy that would increase his chances of remaining abstinent.

Weight of the Evidence (With Rank and Explanation)

1 Ping-Hsun Chang, Chien-Hsieh Chiang, Wei-Che Ho1, Pei-Zu Wu1, Jaw-Shiun Tsai, and Fei-Ran Guo →

I ranked this article as my first. This article directly addressed my intervention and comparison while also acknowledging the efficacy of combining varenicline and nicotine replacement therapy. The authors provided a table which summarizes the demographics, number of participants, and outcome measurements of their study. They also provided a flowchart which details the process by which studies were selected. The inclusion and exclusion criteria were clearly defined as well as the limitations of the study. Authors systematically addressed the early and late outcomes of varenicline plus nicotine patch versus varenicline plus placebo patch.

2 Cahill K, Stevens S, Perera R, Lancaster T. →

I ranked this article as my second. I like that the authors looked at multiple interventions for smoking cessation including the two that I focused on for my PICO search question, nicotine replacement therapy and varenicline. The authors included a chart which addressed the limitations of each selected study which helped me with the information I needed to include in my summary of evidence. Additionally, each intervention contains its own dedicated section which addresses the participants, interventions and comparisons, and outcomes. Ultimately, I do not rank this as my first because the authors do not explicitly state what the inclusion and exclusion criteria are. To retrieve this information, I had to extrapolate from the information provided in the “objectives” section.

3 Lei Wu, Samio Sun, Yao He, and Jing Zeng →

I ranked this article as my third. The authors include two tables displaying the main characteristic of each included trial and outcome data which were helpful for highlighting the main points of each study. It was written in plain language that I could easily understand. They also provided a flow diagram of the trials which illustrates the selection process from beginning to end and includes the exclusion criteria. There was a dedicated section on limitations that I included in my summary of evidence that was concise and comprehensive. Ultimately, I do not rank this article higher because it only focuses on adult smokers with no intention of quitting. My scenario involves a patient who does want to quit so I am not sure how the results of this study would apply to my patient.

4 Paul M. Cinciripini, George Kypriotakis, Charles Green, David Lawrence, Robert M. Anthenelli, Jennifer Minnix, Janice A. Blalock, Diane Beneventi, Chad Morris, Maher Karam-Hage →

I ranked this article as my fourth. The authors used plain language to discuss their methods, results, discussions, and conclusion. Their simplified points allowed me to better understand the findings discussed and helped me write my key points for my summary of evidence. Authors ultimately concluded that a combination of varenicline and smoking cessation psychotherapy was most effective for patients with recurrent episodes of major depression. These patients had a higher likelihood of relapsing and resuming smoking with monotherapy. In patients with single episodes of major depression, there was no difference in efficacy between the interventions discussed: bupropion, varenicline, nicotine replacement therapy all in conjunction with smoking cessation psychotherapy.

5 Timothy B. Baker, Megan E. Piper, James H. Stein, Stevens S. Smith, Daniel M. Bolt, David L. Fraser, and Michael C. Fiore →

I ranked this article as my fifth. This article is an open-label study meaning that the risk of bias is very high. Results of the study may have been influenced by participants and researchers alike. The evidence provided in this article is drastically different from the information I gathered in my previous four articles. I included this article anyway because I wanted to see what conclusions the authors came up with while conducting their research.

Magnitude of Effects:

1 Ping-Hsun Chang, Chien-Hsieh Chiang, Wei-Che Ho1, Pei-Zu Wu1, Jaw-Shiun Tsai, and Fei-Ran Guo →

- The combination therapy of varenicline with nicotine replacement therapy is more effective than varenicline alone in smoking cessation. This effect is more evident if pre-cessation treatment of nicotine patch is administrated. Both the early and late outcomes were favorable for combination therapy (OR = 1.50, 95 % CI 1.14 to 1.97; OR = 1.62, 95 % CI 1.18 to 2.23, respectively).

2 Cahill K, Stevens S, Perera R, Lancaster T. →

- Varenicline was more effective than nicotine patch (OR 1.51; 95% CredI 1.22 to 1.87), than nicotine gum (OR 1.72; 95% CredI 1.38 to 2.13), or other NRT (inhaler, spray, tablets, lozenges; OR 1.42; 95% CredI 1.12 to 1.79), but was not more effective than combination NRT (OR 1.06; 95% CredI 0.75 to 1.48).

3 Lei Wu, Samio Sun, Yao He, and Jing Zeng →

- The combination of nicotine replacement therapy with varenicline significantly increased long-term and CO-confirmed (by exhaled carbon monoxide) smoking cessation rates by a factor of 2.66. The results suggested that varenicline is an effective treatment option for smokers without an intention to quit.

4 Paul M. Cinciripini, George Kypriotakis, Charles Green, David Lawrence, Robert M. Anthenelli, Jennifer Minnix, Janice A. Blalock, Diane Beneventi, Chad Morris, Maher Karam-Hage →

- Few neuropsychiatric adverse effects were rated as severe (range .6% in SE NRT and placebo, to 2.5% in patients with MDD with recurrence on NRT). Neither the main effect of Treatment ($p = 0.751$) or the Treatment by Group (RE/SE/NPC) interaction ($p = 0.203$) was significant. Varenicline is superior to bupropion and nicotine replacement therapy in patients with recurrent episodes of major depression but there was no difference in efficacy between the interventions for patients who had single episodes.

5 Timothy B. Baker, Megan E. Piper, James H. Stein, Stevens S. Smith, Daniel M. Bolt, David L. Fraser, and Michael C. Fiore →

- Compared to the nicotine patch, both varenicline and C-NRT significantly reduced withdrawal and craving symptoms over the early post-TQD period. varenicline, C-NRT, and the nicotine patch yielded model-estimated abstinence rates of 33%, 37% and 23% at ≥ 5 months post-TQD, respectively

Clinical Significance:

In conclusion, varenicline in combination with nicotine replacement therapy is the most effective way of initiating smoking cessation and maintaining abstinence in those with/without intentions of quitting.

Other Considerations:

- The limitations acknowledged in each of my articles should be addressed in other studies to determine whether other interventions can be implemented to help adult smokers quit smoking.