

**Baker TB, Piper ME, Stein JH, and 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. PMID: 26813210**

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**Design:** Randomized clinical trial

**Objective:** To compare the effectiveness of varenicline, combination nicotine replacement therapy (nicotine patch + nicotine lozenge), and the nicotine patch for 26-week quit rates of smoking.

**Population /sample size/setting:**

- A total of 1086 smokers including 566 females and 520 males, (mean age 48 years) were recruited between May 2012 and November 2015 via 2 sources: (1) by contacting participants in an ongoing longitudinal study of smokers, the Wisconsin Smokers Health Study, and (2) via media and community outreach in Milwaukee and Madison, Wisconsin.
- Participants were randomized to one of three 12-week open-label smoking cessation pharmacotherapy groups: (1) nicotine patch only (n = 241); (2) varenicline only n = 424); and, (3) combination nicotine replacement therapy (C-NRT= nicotine patch + nicotine lozenge; n = 421).
- Inclusion criteria included smoking  $\geq 5$  cigarettes per day, at least 17 years old, ability to read and write English, desire to quit smoking but not engaged in smoking treatment, willingness to use the tested cessation treatments, and not use e-cigarettes, telephone access, and use of suitable birth control.
- Exclusion criteria included exhaled carbon monoxide value of less than 4 ppm, end-stage renal disease, prior suicide attempts within the last 5 years or current suicidal ideation, diagnosis of or treatment for psychoses within the last 10 years, moderately severe depression, untreated hypertension of greater than 200/100 mm Hg, current use of bupropion, hospitalization for stroke, myocardial infarction, congestive heart failure, or diabetes within the last year, exclusionary incidental findings from study health assessments or interview, or use of other forms of tobacco more than twice in the past week.

**Methods/Interventions/Outcome Measures:**

- Study design was a randomized, intention-to-treat clinical trial with one year of follow-up.
- Randomization to treatment was computer-based, and treatment assignment was unblinded. Computer-based randomization was stratified by site (city) and by sex and race (nonwhite or white) within each site.

- Baseline visits included physiological assessments, and questionnaires which targeted smoking history, tobacco dependence, and affective and psychiatric symptoms.
- All 3 treatment interventions continued for 12 weeks and also involved counseling during 5 treatment visits and one telephone call. Each intensive counseling session was 10 to 20 minutes in length and comprised motivational, supportive, and skill training elements. Visits also included dispensing of study medications, and assessment of nicotine withdrawal, carbon monoxide levels, adverse events/safety, and medication adherence. Participants were also contacted at weeks 26 and 52 for telephone follow-up assessments of smoking status and use of other nicotine products and cessation aids. These follow-up telephone assessments were intended to be blinded, but treatment assignment was often revealed.
- Pharmacotherapy dosages were titrated over the 12 weeks for all 3 interventions. Varenicline started at 0.5mg daily and was titrated to 1 mg twice daily. Nicotine patches started at 21 mg and tapered to 7 mg patches by 8 weeks. The C-NRT group received the same tapering of nicotine patches plus five 2 mg or 4 mg lozenges daily depending on smoking history.
- The primary outcome was self-reported 7-day point prevalence abstinence at 26 weeks with biochemical confirmation via exhaled carbon monoxide. Biochemical confirmation of abstinence required a carbon monoxide level of 5 ppm or lower which distinguishes smokers from nonsmokers. The primary comparisons were of either varenicline or C-NRT versus the nicotine patch alone.
- By design, the sample sizes for varenicline, C-NRT, and nicotine patch interventions were to comprise approximately 38.5%, 38.5%, and 23% of the total sample size. This sample size strategy gave enhanced power for the varenicline vs C-NRT comparison, which was hypothesized to yield a smaller effect size, and yielded good power for all other targeted comparisons.
- The power calculation analyses assumed a 10-percentage point between the primary comparisons. A 26-week abstinence rate of 24% was hypothesized for the nicotine patch control intervention (sample size = 227), and greater than 34%, for the varenicline and C-NRT interventions (sample size = 387 for both groups), yielding a power of greater than 80% with a significance level of  $P \leq 0.05$ . There was also 80% power to show greater than a 9-percentage-point difference between the varenicline and C-NRT treatments (e.g. 34% vs 44%).

## Results:

- Baseline demographic characteristics and smoking-related variables appeared to be similar among the 3 groups, but specific significance levels or P values for any differences were not reported. The longitudinal study-recruited cohort (n = 169) and the community-recruited cohort (n = 917) differed significantly on multiple characteristics, including race, age, income, years of smoking, and prior use of cessation medication.
- Sixty-seven percent of participants were white, the average number of cigarettes smoked per day was 17, average number of years of smoking was 28.6, and 84% or 917 participants provided 12 month follow-up data.
- For the primary outcome measure of self-reported 7-day point prevalence abstinence rate at 26 weeks with biochemical confirmation of exhaled carbon monoxide, no significant differences were found between the 3 groups. The 7-day point prevalence abstinence

rates at 26 weeks were 23.6% for varenicline, 26.8% for C-NRT, and 22.8% for the nicotine patch only. Odds ratios for all 3 two by two comparisons of the primary outcome measure did not differ from the null value of one, thus confirming no difference between groups.

- In addition, no significant treatment effects between groups were found for biochemically confirmed 7-day point-prevalence abstinence at weeks 4, 12, or 52. Odds ratios for all 3 two by two comparisons at weeks 4, 12, or 52 did not differ from the null value of one, thus confirming no difference between groups at these 3 additional time-points. Quit rates at 52 weeks decreased to around 20% in all 3 groups.
- At week 1 of the study, medication adherence rates were 75.1% for the patch-only, 78.1% for varenicline, and 76% (patch) and 71% (lozenge) for the C-NRT group. By week 8, medication adherence rates had declined significantly and were 45.2% for the patch-only, 49.3% for varenicline, and 49.6% (patch) and 43.0% (lozenge) for the C-NRT group.
- All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion.

#### **Authors' conclusions:**

- Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 or 52 weeks.
- At 26 and 52 weeks, the 3 pharmacotherapy interventions were essentially equivalent in their point-prevalence abstinence rates.
- The superior effectiveness of varenicline and C-NRT compared with the nicotine patch was not evident in the current findings. Furthermore, varenicline and C-NRT did not differ from one another in their effects on 26-or 52-week abstinence.
- This study showed that the nicotine patch, varenicline, or C-NRT are all effective in helping motivated smokers to quit smoking over a period of one year.
- The results of this study raise questions about the relative effectiveness of intense smoking pharmacotherapies.

#### **Comments:**

- This study supports the conclusion that all 3 pharmacotherapeutic interventions used for 12 weeks appear to be equally effective in assisting motivated smokers to quit smoking over a period of one year.
- The treatment effect sizes were relatively small in this study. As in some other studies, adherence to the medication was somewhat low in this study around 45% at 8 weeks, which could have affected results and explained the small effect sizes. It is also possible that stronger treatment effects might have been found had the sample comprised a greater proportion of heavier or more highly dependent smokers as in the past. In general, smokers are smoking fewer cigarettes per day now than they did in the past.
- All pharmacotherapeutic approaches to quitting appear to be similarly effective when combined with structured support and follow-up. Even though the quit rates in this study are not that good, they appear to be similar to previous studies.

- Strengths of this study included the inclusion of a comparable control group (nicotine patch only), long term follow-up, sample size calculation, an appropriate randomization description, and a clearly designated primary outcome.
- It was astute of the authors to not generalize their findings to all smokers, but to limit their results to only individual smokers that are highly motivated to quit. The low participation rate (34.5%) among the recruited smokers certainly confirms the inclusion of only more highly motivated study participants. Therefore, the results of this study may overestimate the effects of the tested medications compared to what would normally occur in regular clinical practice.
- Even though the open-label design of the study tested the 3 interventions under conditions (no blinding) that would be expected to favor varenicline, the results of the study still did not show that varenicline was superior or worked any better compared with the other 2 interventions.
- The authors failed to include P values to show if there were any significant differences between the 3 groups in the baseline demographic and smoking related variables.
- The results of this study call into question the alleged superiority of varenicline and nicotine replacement combination therapy over the nicotine patch alone.

#### **Assessment:**

This adequate study provides some evidence that among adults motivated to quit smoking, 12 weeks of open-label treatment with the nicotine patch alone, varenicline, or combination nicotine replacement therapy (nicotine patch + nicotine lozenge) are equally effective in assisting motivated smokers to quit smoking over a period of one year.