NICOTINE

A RANDOMIZED CLINICAL TRIAL

BACKGROUND

The single most preventable cause of death in the United States is cigarette smoking. In the United States, most people who smoke want to quit smoking. But a chemical found in cigarettes can make it very difficult to quit. This chemical, *nicotine* (nick-a-teen), is found in tobacco plants and it is very addictive. When someone has an addiction, the person is *dependent* on the substance. People who are addicted can become so dependent on a substance, that they have difficulty functioning if they stop taking the substance.

Nicotine occurs naturally in tobacco plants which are used to make cigarettes. When cigarettes are smoked, many harmful chemicals, including nicotine, are released into the body. When the human brain is exposed to nicotine, receptors in the brain cells are activated or stimulated. This happens because nicotine has a shape like one of the brain's own chemicals, called a *neurotransmitter* (nur-ro-trans-mit-ter).

Neurotransmitters are chemicals the brain uses to communicate between cells. The nicotine tricks the brain cells. This causes the brain to release another neurotransmitter called *dopamine* (doe-pah-meen). When dopamine is released, it creates a feeling of pleasure. But dopamine's affects do not last long, so more nicotine is needed to release more dopomine. This pattern or cycle contributes to dependency on or addiction to cigarettes.

Nicotine addiction is hard to overcome. The drug *varenicline* (vah-REH-ni-klen) has been shown to help smokers quit. The standard directions for taking varenicline has smokers take it for one week prior to quitting (pre-quit) and then for 11 additional weeks (post-quit). Less than 50% of smokers who completed the full 12 weeks of vareniclne treatment are successful. After one year, less than 25% are still not smoking. Even though previous studies show not everyone is able to quit smoking after using varenicline, scientists began to wonder if increasing the length of the pre-quit time from one week to four weeks would help people be more successful to quit smoking.

METHOD

In this study the researchers designed an experiment to test whether changing the pre-quit use of varenicline from one week to four weeks would decrease smoking rates. The study was a randomized clinical trial. Study participants were randomly divided into two groups. By randomly assigning participants to groups, biases (buy-us-es) and unrelated variables are reduced. The randomly divided participants do not know whether they are getting the medicine or a placebo (plah-see-bow). A placebo is a substance that looks the same as the actual medication but does not contain any medicine. The scientists decided to use a **double blind** RCT instead of a **single blind** RCT. In a single blind RCT, the scientists would know which participants are receiving the placebo. In a double blind RCT, neither the scientists nor the participants know who is receiving the medicine or the placebo.

The group receiving the placebo is referred to as the **standard group**. During the four week pre-quit period, the standard group received a placebo for three weeks and varenicline for one week. This means they received the standard pre-quit dosage of varenicline. The group that received varenicline for the entire four week period is known as the **extended group**. Both the standard group and the extended group started treatment at the same time.

The entire study took 16 weeks to complete and was divided into three stages. During the first stage, study participants were selected and randomized into either the standard group or the extended group. Stage two of the study consisted of the four week pre-quit time period. During this time, extended group participants took

varenicline for the entire pre-quit period while the standard group took the placebo for three weeks and varenicline for final week of the pre-quit period. In the third stage, all participants took varenicline for the entire 11 week post-quit period.

DATA

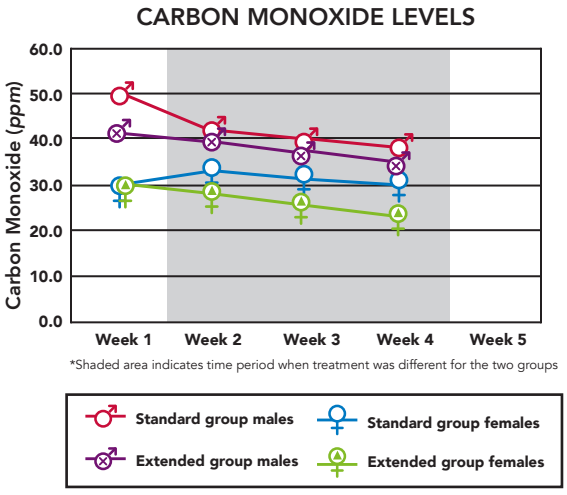
Data was collected in four categories: cigarettes smoked per day, carbon monoxide levels, craving and withdrawal, and cigarette effects. These categories were compared between the extended and standard groups and between genders.

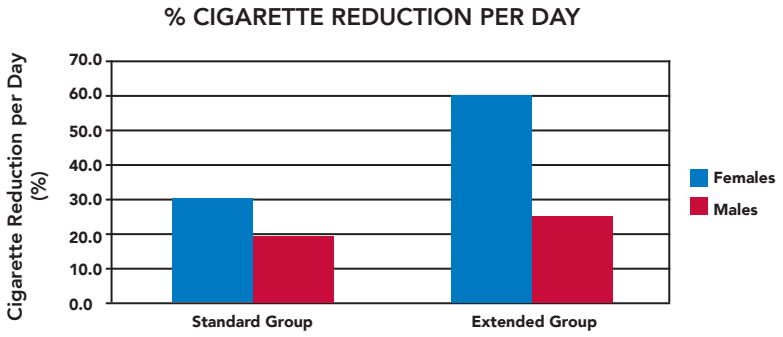
Baseline Measurements (*at start of study*)	Extended Group		Standard Group	
	Male ♂	Female ♀	Male ♂	Female ♀
Participants (n)	14	18	11	17
Weight (kg)	85.6	76.4	85.9	81.0
Years smoking	27.1	26.8	25.3	28.2
Baseline Cigarettes/Day (CPD)	21.4	21.4	23.6	19.4

During the pre-quit period, participants had to report smoking related information for each day. This included how many cigarettes per day, craving, mood, and tobacco withdrawal. This was monitored with a questionnaire completed after every cigarette. It was rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree). Within 15 min after smoking the first cigarette of the day, participants also had to complete a modified version of the questionnaire consisting of ten items rated on a 5-point scale from 1 (not at all) to 5 (extremely).

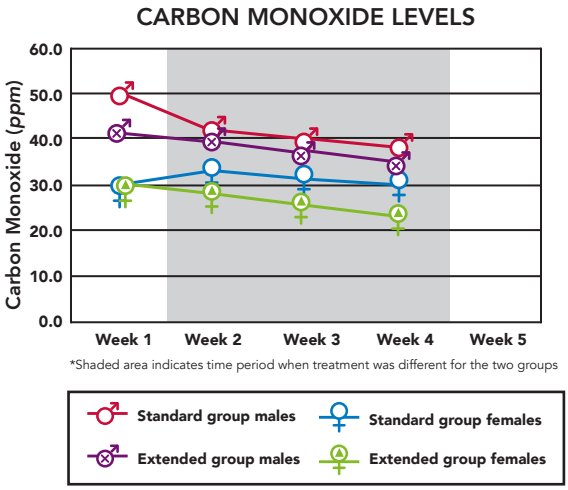
RESULTS

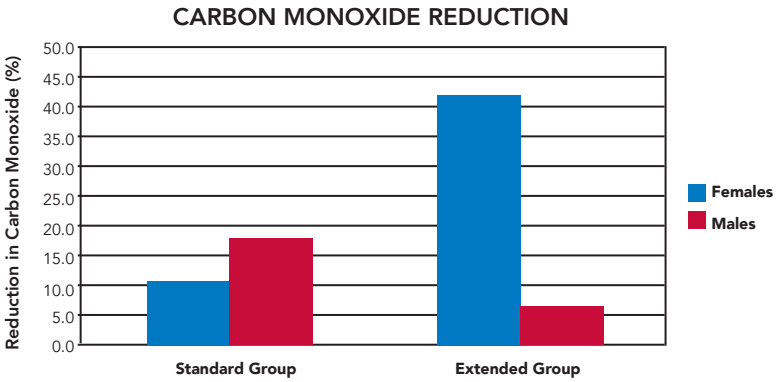
Graphs 1, 2, 3, and 4 represent changes in the number of cigarettes smoked per day and carbon monoxide levels. These are examples of *quantitative data*. Quantitative data is represented by a numerical value or a quantity (an amount). Quantitative data is **objective**, which means data is not affected by personal feelings.





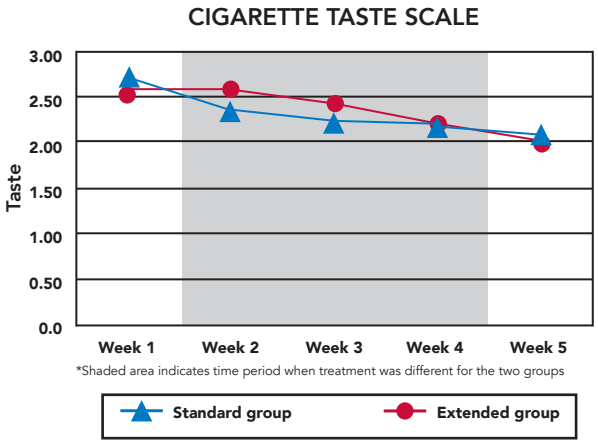
Women in the extended group had a greater reduction in cigarettes per day (CPD) than women in the standard group. Men in the extended group also had a greater reduction in cigarettes per day than those in the standard group. However, for the men in both groups, there was very little difference in the CPD levels. The difference was so small, the data is statistically the same. Overall, women in the extended group continued to show a greater reduction in smoking than any other male/female combinations in either group.

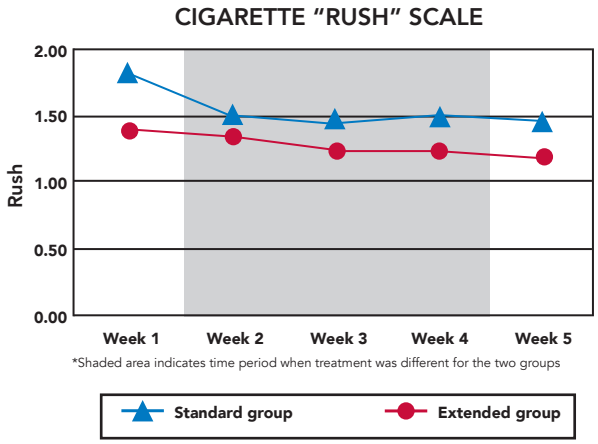




The average carbon monoxide, CO, levels were measured for males and females in both groups throughout the pre-quit period. During the 3-week period when the extended group was on varenicline treatment and the standard group was on placebo (shaded area), women in the extended group had lower CO levels than women in the standard group. The levels of CO for men in the extended group showed only slightly greater reductions than men in the standard group. Interestingly, men in the extended group had higher CO levels than men in the standard group.

Graphs 5 and 6 represent *qualitative* data. Qualitative data is collected when participants share, rate, or describe their attitudes or feelings. Because this type of data cannot be directly measured, it is **subjective**.





In this case, participants self-reported morning cravings and withdrawal symptoms during the pre-quit period. The extended group reported greater reductions in scores for cigarette taste than the standard group. But, there was no significant difference in the qualitative data from both groups regarding cigarette taste during the pre-quit stage.

Both groups responded to a questionnaire item on light headedness called the "rush" scale. The rush is caused by the release of the neurotransmitter dopamine. The extended group reported significant decreases in the rush provided by the first cigarette of the day across the pre-quit period while the standard group showed very little change in their experience of this rush. There were no significant differences in responses of other cigarette effect items for either group or between men and women.

Abstinence rates, not smoking, measured during the final 4 weeks of treatment was higher in the extended group (53%) than in the standard group (40%). Each group was monitored for continuous abstinence rate during the final 4 weeks of the follow-up period (weeks 8-11). For women, the continuous abstinence rate was higher in the extended group (67%) than in the standard group (35%). There were no significant differences in continuous abstinence rates between the extended (36%) and standard (46%) groups in men.

DISCUSSION & CONCLUSION

In this study, scientists evaluated the hypothesis that extending the pre-quit treatment period for varenicline from 1 to 4 weeks would improve a smoker's ability to quit smoking in the long run. They found the extended group showed a greater pre-quit reduction in smoking rate, as well as greater decreases in the taste and "rush" after smoking the first cigarette of the day compared with the standard group. Researchers also found that varenicline is at least as effective as any other major treatment as shown by a 3-month abstinence rate of 40% in the present study. Another recently published clinical trial on varenicline similar to this study also found that pre-quit reductions in cigarettes per day, CO, and cigarette enjoyment as well as 3-month abstinence rates were improved with 4 weeks of pre-quit varenicline as compared with 1 week. After reviewing all of the data, the scientists found that the strategy of increasing the duration of pre-quit varenicline treatment is a strong candidate for further study in larger trials with longer follow-up periods.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

L.W.H.: wrote manuscript, designed and performed research, analyzed data; R.L.A.: wrote manuscript, performed research, analyzed data; S.F.L.: performed research; N.J.L.: performed research; J.D.R.: performed research; S.T.T.: designed research, performed research; J.C.G.: performed research; K.M.C.: designed research; M.C.M.: wrote manuscript, designed and performed research.

Conflict of Interest M.C.M. has served on the speaker's bureau for Pfizer and as the medical director for the NYS Smokers Quit Line. K.M.C. reports receiving consulting fees from Pfizer for work on smoking cessation; consulting fees as an expert witness for plaintiff's attorneys suing tobacco companies; and research contracts from Nabi Biopharmaceuticals. The remaining authors declared no conflict of interest.

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