What are the range of abstinence rates for varenicline for smoking cessation? Do they differ based on treatment duration? Are there any studies utilizing 3- 4 months of varenicline treatment?

Background

Varenicline (Chantix®) is a partial neural nicotinic receptor agonist which inhibits the binding of nicotine and reduces the dopamine-mediated reward mechanisms associated with smoking.[1] Varenicline received Food and Drug Administration (FDA)-approval in 2006 as a pharmacotherapeutic aid to smoking cessation for adult patients. For dosing, the manufacturer recommends administration of 0.5 mg once daily for the first 3 days, 0.5 mg twice daily for days 4-7, then the maintenance dose of 1 mg twice daily for 12 weeks. The label also notes that an additional 12 weeks of maintenance therapy may be required to increase the chance of long-term smoking cessation.

Since its approval, varenicline has been recommended as a first-line therapy for smoking cessation in clinical practice guidelines from the United States Preventive Services Task Force (USPSTF) and the United States Public Health Services (USPHS).[2,3] The 2015 update of the USPSTF guideline for tobacco smoking cessation lists varenicline among first-line therapeutic options, stating that there is a high certainty that the net benefit is substantial. Other first-line pharmacotherapeutic options include nicotine replacement therapy (NRT), combinations of NRT, and sustained-release (SR) bupropion. These pharmacologic interventions have been shown to be effective when used alone or in conjunction with behavioral interventions. Though the USPSTF does not specify dosage and administration recommendations for varenicline, it does reference the FDA website for information on dosing and administration. From an internal analysis, the USPSTF estimated a smoking abstinence rate of 28% in those using varenicline, compared to an abstinence rate of approximately 10% for those who use placebo or no therapy at all (p=not reported).

The 2008 update of the USPHS guideline for treatment of tobacco use and dependence also lists varenicline as 1 of the first-line medications to assist with smoking cessation, along with NRT products and bupropion SR.[3] The USPHS performed a meta-analysis of first-line medications and compared the efficacy of each agent to the nicotine patch. Using pooled study results, it was found that varenicline, when administered according to manufacturer recommendations, was significantly more effective than the nicotine patch alone for smoking abstinence at 6 months, with an odds ratio (OR) of 1.6 (95% confidence interval [CI] 1.3 to 2.0). Abstinence rates were also determined for varying doses of varenicline: varenicline at its standard dose was associated with an abstinence rate of approximately 33.2% (95% CI 28.9 to 37.8) and varenicline 1 mg/day was associated with an abstinence rate of approximately 25.4% (95% CI 19.6 to 32.3). Comparatively, placebo was associated with an abstinence rate of 13.8%, with no confidence intervals reported.

Abstinence rates associated with varenicline

A search of Embase was conducted to identify clinical studies evaluating smoking and tobacco abstinence rates associated with varenicline. Two Cochrane reviews were identified, as well as a more recently published randomized controlled trial, comparing varenicline to various NRT agents.

In a 2013 Cochrane review, Cahill et al evaluated the efficacy of pharmacological interventions for smoking cessation.[4] They sought to compare benefits and risks of commonly used smoking cessation aids, through an overview of Cochrane reviews. The authors performed a search of the Cochrane Database of Systematic Reviews in 2012 to identify studies involving generally healthy, non-pregnant adults. They

included Cochrane reviews that involved randomized controlled trials, with a minimum follow-up period of 6 months, and smoking cessation outcomes that had been verified by blood, breath, or urine tests. Interventions included NRT, bupropion, varenicline, and several other agents, such as other antidepressants, anxiolytics, cannabinoid type 1 receptor antagonists, and opioid antagonists. In addition to reviewing these agents, Cahill et al conducted a network meta-analysis to compare NRT, bupropion, and varenicline.

In total, 12 Cochrane reviews were selected, containing 267 trials and 101,804 patients.[4] Of these, 15 placebo-controlled trials of varenicline were assessed; all but 3 used the standard 12-week dosing regimen. The 3 trials which did not use the standard dosing regimen examined lower dosages of varenicline (1 mg daily). Two of the reported trials used a flexible dosing schedule or had flexible quit dates. All studies had a primary outcome of abstinence from smoking for ≥6 months. Varenicline was found to increase the odds of quitting at 6 months compared to placebo, with an OR of 2.88 (95% credible interval [CredI] 2.40 to 3.47). Varenicline was also found to be superior to single forms of NRT, with an OR of 1.57 (95% CredI 1.29 to 1.91), and to bupropion, with an OR of 1.59 (95% CredI 1.29 to 1.96). However, varenicline was not found to be significantly more effective than combination NRT, with an OR of 1.06 (95% CredI 0.75 to 1.48). Of note, the percentage of patients achieving abstinence on any of these interventions was not reported.

In a 2015 Cochrane review, Ebbert et al examined behavioral and pharmacotherapy interventions for smokeless tobacco cessation.[5] The authors performed a search of the Cochrane Tobacco Addiction Group specialized register in 2015 to identify clinical trials with interventions to help adult smokeless tobacco users remain abstinent from tobacco use for a minimum of 6 months. The authors included randomized or pseudo-randomized controlled trials where participants were allocated to receive either a pharmacologic intervention (bupropion , NRT, or varenicline) or placebo, or some form of behavioral intervention or continuation of baseline level of care. A total of 34 trials were selected for analysis, with a population of over 16,000 patients. Two studies assessed the efficacy of varenicline, with a total of 507 patients. Varenicline was administered in accordance with product labeling, for 12-week periods and compared to placebo. Varenicline was found to have a significant effect on tobacco cessation rates at 6 months, with an OR of 1.34 (95% CI 1.08 to 1.68). The most common side effect noted was nausea, ranging from approximately 24% to 33% (results for placebo not reported).

Most recently, Baker et al conducted a randomized open-label examining the effects of nicotine patch monotherapy in comparison to varenicline monotherapy and combination NRT (C-NRT) for smoking cessation.[6] The study recruited generally healthy, non-pregnant adults who smoked at least 5 cigarettes per day. Participants were randomized to 1 of 3 study arms for a total of 12 weeks. The varenicline group used the standard dosing regimen for 12 weeks, the nicotine patch group used the standard step down therapy for 12 weeks, and the C-NRT group used the nicotine patch step down therapy in conjunction with a 2 mg or 4 mg nicotine lozenge – used at least 5 times per day. The primary outcome for this study was self-reported 7-day abstinence at week 26, confirmed by a carbon monoxide (CO) breath test. Secondary outcomes included self-reported and CO breath test-confirmed prolonged abstinence at week 26, as well as week 52. A total of 1086 smokers were selected, with 241 being randomized to the varenicline treatment group. The participants were all recruited from the state of Wisconsin; 52% were female, and 67% were white. The mean age was 48 years and participants used a mean of 17 cigarettes per day for a mean duration of 28.6 years. Abstinence rates at 26 weeks were 22.8% for the nicotine patch group, 23.6% for the varenicline group, and 26.8% for the C-NRT group. Differences among the groups were not statistically significant. The risk difference (RD) for the nicotine patch compared to varenicline at 26 weeks was −0.76 (95% CI −7.4 to 5.9), and the RD for varenicline compared to C-NRT was −3.3

(95% CI: −9.1 to 2.6). At 52 weeks, the 7-day point prevalence abstinence rate for varenicline was 19.1%. Differences compared to the nicotine patch (RD=1.6, 95% CI -4.7 to 8.0) and compared to C-NRT (RD=-1.1, 95% CI -6.4 to 4.3) were not statistically significant.

Effects of treatment duration on abstinence

With regard to duration of therapy, most of the previously identified studies were conducted using the standard 12-week dosing regimen.[4-7] A search of Embase was conducted to identify studies evaluating varenicline administration for longer periods. Two relevant studies were found and are summarized below. Of note, additional studies were identified evaluating extended use of varenicline in patients with other comorbidities (e.g., schizophrenia); however, these were excluded based on potential lack of application to the general population.

In addition to the previous Cochrane review, Ebbert et al conducted a multicenter, multinational, double-blind, randomized controlled trial examining the use of extended maintenance varenicline for 24 weeks compared to placebo for smoking cessation.[7] They included generally healthy, non-pregnant or breastfeeding adults who had been smoking at least 10 cigarettes per day, with no previous abstinence period of greater than 3 months. The participants were randomized in a 1:1 fashion to varenicline or placebo. The primary outcome was self-reported abstinence during weeks 15 through 24, confirmed by a CO breath test. Secondary outcomes included self-reported abstinence at weeks 21 through 24 and 21 through 52, both confirmed by CO breath test. In total, 1510 participants were selected, 55.9% were male, 62.6% were white, and the average age was 44.7 years. Participants smoked an average of 20.6 to 20.8 cigarettes per day for a mean period of 27.4 years. As well, 82.9% of participants had at least 1 previous attempt to quit, with 39.5% having tried at least 3 times. Patients using varenicline were significantly more likely to be abstinent at weeks 15 through 24 (varenicline 32.1% vs placebo 6.9%, RD=25.2%, 95% CI 21.4 to 29.0), as well as weeks 21 through 52 (varenicline 27% vs placebo 9.9%, RD=17.1%, 95%CI, 13.3 to 20.9). The most common adverse events reported for the varenicline group included nausea, vivid dreams, insomnia, constipation, vomiting and weight gain.

In a 2016 Canadian study, Tulloch et al examined the effects of varenicline compared to the nicotine patch and dual-form nicotine therapy (or C-NRT).[8] Eligible participants were generally healthy, non-pregnant adults who smoked more than 10 cigarettes per day. Participants were randomized to 1 of 3 treatment groups. The NRT group received standard-dose nicotine patch therapy for 24 weeks while the C-NRT group received the same patch therapy in conjunction with nicotine gum or inhaler as needed for up to 22 weeks. The varenicline group received the manufacturer-recommended dose for 12 weeks and were offered an additional 12 weeks of therapy at the standard dose (1 mg twice daily) for a total treatment period of 24 weeks. The primary end-point was the CO breath test-confirmed abstinence rate (CAR) from weeks 5-52. Secondary outcomes included CAR from weeks 5-10 and 5-22, as well as 7-day abstinence at weeks 5, 10, 22, and 52. A total of 737 participants were included in the analyses, with a mean age of 48.6 years; 53.6% were male, 91.8% were white. Overall, the study population smoked an average of 23.2 cigarettes per day for an average of 31.0 years and had an average of 4.6 previous attempts to quit. Of those patients, 245 were placed in the NRT group, 245 in the C-NRT group, and 247 in the varenicline group. For weeks 5-52, 15.3% of the varenicline group achieved continuous abstinence, compared with 12.4% of the C-NRT group and 10% of the NRT group. When compared to NRT, varenicline was found to have a non-significant odds of remaining abstinent at 5-52 weeks (OR 1.62 [97.5% CI 0.87 to 3.01]). The varenicline group was found to have significant 7-day point prevalence abstinence rates of 27.1% at week 22 (OR 2.09 [97.5% CI 1.22–3.57]) and 21.7% at week 52 (adjusted OR 1.84 [97.5% CI 1.04-3.26]).

Tulloch et al performed a subpopulation analysis to ascertain abstinence rate differences between patients who chose standard duration varenicline and those who chose the 24-week extended maintenance dosing.[8] The extended dosing group were significantly more likely to remain abstinent in weeks 5–22, with an OR of 2.69 (97.5% CI 1.51 to 4.79). Reviewing abstinence rates for weeks 5-52, rates were highest among those receiving extended varenicline therapy (18.9%, vs. 12.1% non-extended varenicline and 9.4% NRT). With regard to safety concerns, fatigue (17.4%), nausea (56.3%), and sleep disturbances (60.3%) were the most commonly reported adverse events for the varenicline group. These occurred more commonly with varenicline vs. NRT ($p<0.001$ for all 3 types of adverse events). However, patients receiving varenicline were less likely to experience dermatologic reactions, such as rash or skin irritation 4.9% vs. 38.4%, $p<0.001$).

Discussion and conclusion

Smoking cessation and helping patients remain abstinent from is important for improving public health and reducing comorbidities associated with smoking. Current guidelines list varenicline among the first line options potential pharmacological interventions to assist patients with smoking cessation. Varenicline, when used according to the FDA label, appears to be significantly more effective than placebo at maintaining smoking abstinence and at least equally efficacious when compared to other forms of pharmacologic aid.

A search of the literature revealed several studies evaluating the effects of varenicline on smoking and tobacco abstinence. The Cochrane reviews and clinical trials described above were chosen for their potential applicability to the general adult population within the US. All included studies were of strong design and included smoking abstinence as a primary outcome.[4-8] The populations recruited across the studies were similar, with relatively equal gender distribution, similar average age (40s), and similar smoking history (approximately 20 cigarettes smoked per day for mean period of 30 years). Though the trials by Baker et al and Tulloch et al were open-label, active comparators were used. When used as directed by the manufacturer for 12 weeks, varenicline was associated with abstinence rates ranging from 19% to 24% (assessed at weeks 52 and 26, respectively) and was found to be similar to C-NRT. Notably, the guidelines estimate abstinence rates of 28% to 33% with varenicline.[2,3]

Trials directly comparing the effects of different durations of varenicline therapy on smoking abstinence rates are lacking. Based on the reviewed literature, a significant difference was observed between 12 and 24 weeks, favoring longer therapy. These data were collected at weeks 5-22. Longer periods of follow-up may be necessary to conclude effects of therapy on sustained abstinence. Importantly, the manufacturer does state that an additional 12 weeks of maintenance therapy may be required to increase the chance of long-term smoking cessation.

References

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