How can there be a warning regarding concomitant use of varenicline with nicotine replacement therapy yet patients can be on varenicline and smoke concurrently?
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The United States (US) Preventive Services Task Force and the Department of Health and Human Services (DHHS) recommend use of varenicline and nicotine replacement therapy (NRT), individually, as first-line agents for the treatment of tobacco dependence.[1,2] Both organizations also recommend usage of selected medications in combination for treatment of tobacco dependence and describe several combinations (e.g., nicotine patch with other forms of NRT as needed, nicotine patch with bupropion). However, varenicline with NRT is not included in these recommendations.

Varenicline, also known by the brand name Chantix®, is a medication approved by the Food and Drug Administration (FDA) for the cessation of smoking.[3] It acts as a partial agonist on the neuronal alpha-4-beta-2 nicotinic acetylcholine receptors. Although it stimulates these receptors, it does so at a significantly lower level compared to nicotine, while also blocking the binding of nicotine to these receptors. This interrupts the stimulation of the mesolimbic dopamine system, which is responsible for the reinforcement and reward associated with smoking. According to the varenicline manufacturer's prescribing recommendations, adults should be treated with an initial dose of 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, and then finally a maintenance dose of 1 mg twice daily for a total of 12 weeks. Varenicline should be started 1 week before the patient's quit date, though it has also been shown to be effective when patients set a quit date between day 8 and day 35 after beginning varenicline. Potential side effects can include headache, insomnia, nausea, abnormal dreams, depression, and suicidal thoughts. NRT, an alternative form of nicotine that patients use in place of tobacco, is another aid to smoking cessation. NRT acts to replace cigarettes with other sources of nicotine, including transdermal patches, gums, inhalers, nasal sprays, and lozenges. The dose of these products is gradually titrated downward over time in order to reduce tobacco dependence.

While varenicline can be initiated while a person continues to smoke, the manufacturer states that there is a potential interaction between varenicline and NRT.[3] Co-administration of varenicline and transdermal nicotine for 12 days may lead to increased risk of adverse effects (including nausea, headache, vomiting, and dizziness) and, in a study, was associated with higher treatment discontinuation rates compared to NRT alone. Similar effects may be observed with concurrent usage of tobacco and varenicline.

A search of the literature revealed that there are few published studies that evaluate the use of varenicline in combination with NRT in the treatment of nicotine dependence in adults.[4-6] One such study by Ramon et al evaluated the efficacy of varenicline with NRT in a randomized placebo-controlled clinical trial.[4] Participants were recruited from an outpatient smoking cessation clinic in Spain between February 2012 and December 2013. Included in the study were adults aged 18 years or older who smoked ≥20 cigarettes per day over the 6 months prior to study initiation. Smoking had to be continuous, with no period of smoking abstinence longer than 3 months over the past year. Excluded were patients with psychotic disorders or a history of psychotic disorders, a history of suicide attempts, or current or past alcoholism. Also excluded were patients who used NRT patches or varenicline in the past 6 months. Participants in both groups were started on varenicline 1 week before their target quit day (TQD).[4] Varenicline was dosed according to prescribing guidelines at 0.5 mg once daily for 3 days,

then 0.5 mg twice daily for 4 days, and then finally 1 mg twice daily for 11 weeks. In terms of NRT patches, patients in the treatment group received 21 mg/24 hours Nicotinell® patches in addition to varenicline, while a placebo patch was given to patients in the control group. NRT and placebo patches were initiated on the TQD. The primary endpoint of this study was continuous abstinence, which was defined as not smoking from week 2 through 12. Secondary endpoints included continuous abstinence rates from week 12 through 24 and adverse events.

A total of 341 eligible patients were enrolled in the study: 170 patients in the treatment group and 171 patients in the control group.[4] Baseline characteristics were similar for both groups. With regard to the primary endpoint, a higher number of patients maintained abstinence in the treatment group (39.1%) compared to the control group (31.8%), but the difference was not significant (odds ratio [OR] 1.24; 95% confidence interval [CI] 0.8-2.6) after 12 weeks. Similar results were observed at 24 weeks (32.8% vs. 28.2%); however the difference noted between groups was also not significant (OR 1.17; 95% CI 0.4-1.9).

Ramon et al also assessed safety of varenicline in combination with the nicotine patch by looking at adverse events.[4] Adverse events were reported for 39.7% of participants in the control group, compared to 41.3% of participants in the treatment group; the difference was not statistically significant (P=0.79). The main adverse events reported for both groups (treatment vs. control) were insomnia (17.3% vs. 13.2%, P=0.35), abnormal dreams (17.4% vs. 15.1%, P=0.64), and nausea (18.3% vs. 19.1%, P=0.88). Though less frequently reported, headache was slightly more prevalent in the treatment group (4.1% vs. 2.6%), but not at a rate that was significantly different (P=0.35). While no serious adverse events were reported, 5 patients in the treatment group and 4 patients in the placebo group discontinued treatment due to adverse events.

Overall, Ramon et al concluded that the combination of varenicline with nicotine patches does not improve smoking cessation rates when compared to varenicline alone.[4] Although adverse events were reported, the difference between the 2 groups was not statistically significant, and there were no serious events reported. There are some limitations to note. One limitation acknowledged by the authors is that different therapists were employed as part of the non-pharmacologic treatment of patients in the study. There were 3 therapists involved, and although the personnel were trained in standardization protocols and no differences were observed, this could have been a source of bias in the study. Another potential limitation is that this study was conducted in Spain, which could possibly limit its applicability to patients in the US and other countries. Notably, the doses used were consistent with those recommended in the US product labeling.[3,4] Lastly, the fact that the only form of NRT evaluated was the patch limits the applicability of the study to other forms of NRT.[4]

Koegelenberg et al evaluated the use of varenicline in combination with NRT patches in another randomized, double-blind, placebo-controlled trial.[5] They evaluated the efficacy and safety of varenicline in combination with the nicotine patch. The study took place in South Africa from April 2011 to October 2012. Included in the study were patients aged 18-75 years old, smoked ≥10 cigarettes per day throughout the previous year and the month prior to screening, and had no period of smoking abstinence longer than 3 months in the past year. Exclusion criteria included current depression or a history of depression, treatment with an antidepressant within the past 12 months, current or past psychiatric disorders, severe chronic obstructive pulmonary disease, and clinically significant cardiovascular disease, neurological disorders, or endocrine or gastrointestinal disorders in the past 6 months. Two weeks before their TQD, patients were randomized into 1 of 2 arms: a treatment group to

receive 15 mg/16 hour nicotine patches or a control group to receive placebo patches. Participants were initiated on varenicline 1 week before their TQD. Varenicline was dosed at 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, followed by 1 mg twice daily through week 12. Varenicline was then tapered off and discontinued fully at week 13. The primary endpoint was continuous abstinence from smoking. Secondary endpoints included continuous abstinence rates from week 12 through 24 and adverse events.

A total of 446 patients were enrolled in the study: 222 patients in the treatment group and 224 in the control group.[5] Baseline characteristics were similar in both groups and did not vary significantly. In terms of the primary endpoint, significantly higher abstinence rates were seen in the treatment group (55.4%) compared to the control group (40.9%) after 12 weeks of therapy (P=0.007). Similar results were also observed at 24 weeks (49% vs 32.6%), and this, too, was statistically significant (P=0.004).

Koegelenberg et al also assessed safety of varenicline in combination with nicotine patches.[5] Adverse events were noted if they were reported by at least 2% of participants in either group. Adverse events reported that were numerically more prevalent in the treatment group were nausea (27.3% vs. 24.7%, P=0.53), insomnia (19.9% vs. 15.1%, P=0.18), constipation (4.1% vs 2.7%, P=0.42), and depression (2.3% vs. 1.4%, P=50). The only statistically significant adverse event that was more prevalent in the treatment group was skin reactions (14.4% vs. 7.8%, P=0.03). A total of 7 serious adverse events were reported: 4 among patients in the treatment group and 3 in the control group. Of these serious adverse events, only 1 was considered to be potentially related to treatment with varenicline (teratogenic effect).

Overall, Koegelenberg et al concluded that the combination of varenicline with nicotine patches was associated with a statistically significant increase in continuous abstinence rates. Safety was assessed and it was determined that there was no statistically significant increase in adverse effects with combination therapy except in regards to skin reactions. There are some limitations to note. One limitation was that only 62.3% of randomized participants completed the study, which could potentially affect study results. Another limitation was the extensive exclusion criteria, limiting the study population to relatively healthy smokers. This could potentially limit the applicability of the study. Also, varenicline was tapered off after 12 weeks of therapy before being discontinued, which is not following with usual dosing recommendations.[3] Lastly, only 1 form of NRT was investigated: the patch. The use of only 1 form of NRT limits the applicability of the study to other forms of NRT. Additionally, the dosage used in the study (15 mg/16 hours) is not available in the US.[6]

Hajek et al also conducted a double-blind, randomized, controlled study evaluating the use of varenicline in combination with NRT patches.[7] Participants were recruited for this trial in London, England in April 2011. Included in the study were adults aged 18 years or older. Excluded from the study were patients with current psychiatric illness or other serious illness. All study participants were initiated on varenicline 1 week before their TQD. Varenicline was dosed at 0.5 mg/day for 3 days, then 1 mg/day for 4 days, followed by 2 mg/day for the rest of the 12-week treatment course. On their TQD, patients were randomized into 1 of 2 arms: a treatment group to receive 15 mg/16 hour nicotine patches or a control group to receive placebo patches. The primary endpoint for this study was abstinence from smoking. Other endpoints were urge to smoke (assessed using the Mood and Physical Symptoms Scale [MPSS] – a 5-point scale) and adverse events.

A total of 117 patients were enrolled in the study: 58 patients in the treatment group and 59 patients in the control group.[7] Baseline characteristics between the 2 groups were similar and did not vary significantly. Regarding abstinence rates at 12 weeks, a higher number of patients maintained abstinence in the treatment group (36%) compared to the control group (29%). This difference, however, was not statistically significant (P=0.39). In terms of urge to smoke, there was no statistically significant difference between the treatment and control groups at 1 week post TQD (2.7 vs 3.0, P=0.15) or at 4 weeks post TQD (2.1 vs 2.2, P=0.78).

Hajek et al also assessed safety by looking at adverse events.[7] Adverse events were noted if they were reported by >5% of participants either arm. The main adverse events reported for both groups (treatment vs. control) were abnormal dreams (20.7% vs. 8.5%, P=0.06), headache (10.3% vs. 6.8%, P=0.49), insomnia (19% vs. 18.6%, P=0.97), and nausea (56.9% vs. 44.1%, P=0.17). Overall there were more events reported in the treatment group, but the difference between the treatment and control groups for each type of adverse event reported was not statistically significant. Only 1 serious adverse event was reported during the study, but it was reported in the placebo group (musculoskeletal injury).

Overall, Hajek et al concluded that the addition of nicotine patches to therapy with varenicline had no significant effect on abstinence rates, urge to smoke, or adverse effects.[7] Hajek et al stated that although the number of reported adverse effects such as abnormal dreams was greater in the treatment group, the safety of combining the 2 treatments was not concerning. While this is promising, there were a few limitations that should be acknowledged. One limitation is the small sample size. The authors acknowledge this limitation, stating that subtle effects, although unlikely, might possibly be seen in a larger sample. Another limitation is the use of only 1 form of NRT: the patch. This limits the applicability of the study to other forms of NRT. Additionally, the dosage used in the study (15 mg/16 hours) is not available in the US.[6]

In conclusion, there is currently inadequate evidence to support the concomitant use of varenicline with NRT. There are few studies published on the concomitant use of varenicline and NRT, and those published use the patch as the only form of NRT. Additionally, the data are conflicting. When looking at the studies outlined above by Ramon et al and Hajek et al,[4,7] it would seem as though there is a lack of benefit to combination therapy, as there was not a statistically significant increase in abstinence rates in the groups being treated with concomitant varenicline and NRT patches. The study by Koegelenberg et al, however, contradicts this, suggesting there might be a benefit to combination therapy. Overall, these 3 studies demonstrate that there is no significantly increased risk for most adverse events with combination therapy; only the study by Koegelenberg et al showed a statistically significant risk of skin reactions. In the end however, more studies are needed in order to support such findings. Thus, based on the reviewed literature, a definitive answer as to whether or not concomitant treatment with varenicline and all forms of NRT produces an increased risk of adverse events cannot be provided.

References:

1. Siu AL; US Preventative Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2015;163(8):622-634.
2. Tobacco use and Dependence Guideline Panel. Treating tobacco use and dependence: 2008 Update. Rockville, MD: US Department of Health and Human Services; 2008.

3. Chantix® [package insert]. New York, NY: Pfizer, Inc,; 2016
4. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Med*. 2014;12:172.
5. Koegelenberg CFN, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014;312(2):155-161.
6. Varenicline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc. [updated 03/16/17; accessed 04/10/17]. http://online.lexi.com/lco/action/doc/retrieve/docid/fc_dfc/5549495.
7. Hajek P, Smith KM, Dhanji AR, McRobbie H. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. *BMC Med.* 2013;11:140.