

# RAPID APPRAISAL

**Name of Trial:** Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial

**Reference:** Aubin H-J, Bobak A, Britton JR et al. Thorax 2008;doi:10.1136/thx.2007.090647

**Question:** Does 12 weeks of varenicline treatment compared to 10 weeks of nicotine replacement therapy (patches) provide a better smoking cessation rate during the last four weeks of treatment?

**Summary:** Varenicline demonstrated a significantly better abstinence rate during the final four weeks of treatment with an absolute difference of about 13%. However the 52-week abstinence rate will be of more interest to patients and clinicians and despite a 5.8% benefit for varenicline over nicotine replacement therapy after 52 weeks the effect was not statistically significant.

Compared to nicotine replacement therapy varenicline is more costly, may require longer duration of treatment and, importantly, is associated with a greater incidence of adverse effects.

This study demonstrates that the medium-term (52-week) efficacy of varenicline is not significantly improved compared with nicotine replacement therapy when both are combined with a high level of support and contact. Since greater medium- or long-term efficacy of varenicline over nicotine replacement therapy has not been demonstrated, nicotine replacement therapy should remain the first-line treatment option for patients who are motivated and have expressed a desire to quit smoking.

## ***Did the study ask a clearly focussed question?***

**Yes** — The study compared a 12-week course of varenicline (Champix®▼)<sup>1</sup> to a 10-week course of transdermal nicotine replacement therapy (NRT) (NiQuitin®)<sup>2</sup> as per the product instructions with six weeks at 21 mg / 24 hours, two weeks at 14 mg and two weeks at 7 mg.<sup>3</sup>

## ***Was the study design appropriate?***

**Yes** — It was an open-label, randomised trial comparing varenicline with the generally accepted standard smoking-cessation treatment, NRT in the form of transdermal patches. The primary outcome measure was the rate of continuous abstinence from smoking during the final four weeks of treatment. Abstinence was self-reported but confirmed using carbon monoxide monitoring. Secondary outcome measures included abstinence rates at various time points including 52 weeks. Patients were excluded if they had a history of depression or other psychological disorder, hypertension, renal or hepatic impairment, or if they had used NRT in the previous six months.<sup>3</sup>

The study was sponsored and supported by Pfizer, the manufacturer of Champix®▼.

## ***Were participants appropriately allocated to intervention and control groups?***

**Yes** — Participants were randomised in a 1:1 ratio to treatment with varenicline (n = 378) or NRT (n = 379). Efficacy analyses were based on the number of patients randomised and administered at least one dose of allocated treatment, i.e. the primary analysis population and not the intention-to-treat population.

Efficacy was therefore based on 376 and 370 patients respectively. Treatment groups were well balanced with respect to several demographic characteristics, and their smoking histories.<sup>3</sup>

## ***Were participants, staff and study personnel 'blind' to participants study group?***

**No** — The nature of the treatments used meant that blinding of treatment groups was not practicable. Almost half of the patients in each group had previously tried to quit smoking with the aid of NRT patches and after randomisation three patients refused treatment with NRT.<sup>3</sup> This may bias the results against NRT.

## ***Were all of the participants who entered into the trial accounted for at its conclusion?***

**Yes** — A flowchart accounts for all participants from randomisation to analysis. With respect to the primary outcome measure, which required only 12 weeks of follow-up, < 6% of patients were lost to follow-up during this treatment period although in total 19% discontinued treatment for varying reasons. However by the end of the extended follow-up phase of 52 weeks 36% of patients (more than 1 in 3) were absent with half dropping out during the treatment phase and half dropping out during the extended follow-up phase. Numbers were balanced between groups. A substantial number of patients discontinued during the 12-week treatment phase, most frequently due to a refusal to participate further with 6.6% of varenicline patients and 9.2% of NRT patients discontinuing for this reason. In the same period discontinuation due to adverse effects was 3.5% in the varenicline group and 1.6% in the NRT group.<sup>3</sup>

***Were the participants in all groups followed up and data collected in the same way?***

**No** — Due to the differences in the treatments used it was not possible to follow-up patients in the same way. This difference manifested itself in the duration of active treatment, with varenicline treatment commencing one week before the target quit date and then for 11 weeks after (i.e. weeks 1 to 12), and NRT commencing on the quit date and continuing for 10 weeks (i.e. weeks 2 to 11). Despite these differences patients were followed in both groups for a target of 52 weeks. Following the treatment phase, all patients were requested to make seven more clinic visits which were interspersed with five telephone calls.<sup>3</sup>

***Was the study large enough?***

**Yes** — Based on the sample size and assumptions for the efficacy of NRT the study is reported to have 90% power to detect a difference between varenicline and NRT patches for the last four weeks of treatment and at week 52.<sup>3</sup>

***How are the results presented and what is the main result?***

The primary outcome measures are presented as odds ratios which, although a suitable measure for this type of data, can be misinterpreted as overstating the relative efficacy. For example the four-week continuous abstinence rates for the final four weeks of treatment (i.e. weeks 9 to 12 for varenicline and weeks 8 to 11 for nicotine) were 55.9% with varenicline and 43.2% with NRT patches. This translates to a 12.7% absolute difference, or a 29% relative difference, or an odds ratio of 1.70. Whichever measure is used the difference is statistically significant ( $p < 0.001$ ). At 52 weeks abstinence rates were 26.1% with varenicline and 20.3% with nicotine ( $p = 0.056$ ). This difference does not reach conventional statistical significance however if the results are calculated based on all randomised patients (i.e. intention-to-treat) then the corresponding values are 25.9% and 19.8% respectively ( $p = 0.040$ ).<sup>3</sup>

***How safe were the regimens?***

Overall, 85% of varenicline patients experienced an adverse event during the treatment phase compared to 70% of NRT patients, with severe adverse events affecting 9.8% and 7.3% respectively. The most common adverse events in each group were, varenicline vs. NRT respectively, nausea (37% and 10%), insomnia (21% and 19%), headache (19% and 10%), abnormal dreams (12% and 8%), constipation (8% and 2%) and dizziness (7% and 4%). During the course of the study two varenicline-treated patients experienced psychological disturbances consisting of depression and suicidal ideation.<sup>3</sup>

More details concerning the safety of varenicline are provided in the updated New Drug Evaluation on varenicline.<sup>4</sup>

***How precise are the results?***

The study was specifically designed with planned efficacy outcomes based upon the primary analysis population and not the intention-to-treat population. Therefore results other than those based on the primary analysis population should be interpreted cautiously. Confidence intervals are only stated for the odds ratios and not the actual effects observed. Nonetheless the confidence intervals are relatively narrow and the results can be considered to be fairly precise.<sup>3</sup>

***Can the results be applied to the local population?***

**Possibly** — Nearly a third of the trial population were recruited from the UK and the demographic characteristics of the whole study population do not indicate any obvious anomalies. Patients had a mean age of 43 years, about half were male, mostly white, and smokers for more than 25 years on average at a mean of 22 to 23 cigarettes per day. Over 86% had attempted to quit previously with nearly half having used NRT patches and nearly a fifth bupropion. The authors state that a significant treatment-by-country interaction was observed although no details are provided.<sup>3</sup>

The level of support and contact provided, which in the varenicline group consisted of 19 clinic visits and six telephone calls and in the NRT group consisted of 18 visits and six calls, over 52 weeks may be greater than is provided in practice.<sup>3,4</sup>

***Does 12 weeks of varenicline treatment compared to 10 weeks of nicotine replacement therapy (patches) provide a better smoking cessation rate during the last four weeks of treatment?***

**Yes** — The absolute difference is about 13% in favour of varenicline. However the 52-week abstinence rate will be of more interest to patients and clinicians and despite a 5.8% benefit for varenicline over NRT patches after 52 weeks the effect was not statistically significant.<sup>3</sup> This translates to a number needed-to-treat of 18 (i.e. 18 patients will need to be treated with varenicline instead of NRT to ensure one additional quitter after 52 weeks). The incremental cost is estimated at £1,155 per patient.

Varenicline is more costly, may require longer duration of treatment and is associated with a greater incidence of adverse effects than NRT.

This study demonstrates that the medium-term (52-week) efficacy of varenicline is not significantly improved compared with NRT patches, when both are combined with a high level of support and contact. Since greater medium- or long-term efficacy of varenicline over NRT has not been demonstrated, NRT should remain as the first-line treatment option for patients who are motivated and have expressed a desire to quit smoking.<sup>5</sup>

## REFERENCES

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