



## Nicotine replacement therapy and varenicline: A cohort study among low socioeconomic status families

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### Abstract

**Background:** The tobacco epidemic claims 4.9 million lives globally each year with an expected 10 million annual deaths by 2020. Around the globe, 1.3 billion people are tobacco smokers over one-half of whom will die prematurely from a tobacco-related illness.

**Methods:** From April 2022 to January 2023, we conducted a prospective cohort research project at the Institute of Dental Sciences, Bareilly's centre for smoking cessation. Results: From April 2022 to April 2023, 1042 current smokers were monitored at a smoking cessation centre. The study's inclusion criteria were met by 122 subjects, who also volunteered to take part. The rates of abstinence were 36.3% after one year and 61.5% after three months ( $p=0.001$ ). Age, alcohol use, anxiety scale, and exhaled carbon monoxide values were all adjusted for, yet there were no discernible changes in the abstinence rates between the two groups, NRT or VAR. In multivariate analysis, factors associated to a precipitate smoking relapse were presence of anterior previous attempts (HR: 0.10; 95% CI: 0.030-0.328), living with smokers at home (HR: 2.541; 95% CI: 1.019-6.336), having five following visits (HR: 0.091; 95% CI: 0.017-0.500) and having minimal withdrawal syndrome revealed on follow up (HR: 0.23; 95% CI: 0.08-0.662). Whereas, factors associated to quit delay was the use of NRT at the expense of VAR (HR: 4.966; 95% CI: 2.81-8.76).

**Conclusions:** Relapse was not associated to treatment classes, whereas NRT have the benefit of a longer quit duration.

**Keywords:** Tobacco epidemic, nicotine, varenicline, NRT

### Introduction

The tobacco epidemic claims 4.9 million lives globally each year with an expected 10 million annual deaths by 2020 [1]. Around the globe, 1.3 billion people are tobacco smokers over one-half of whom will die prematurely from a tobacco-related illness. Nicotine is the addictive substance in tobacco and is the driver for compulsive tobacco use [2]. Inhaling smoke from combusted tobacco is the quickest route to get nicotine into the brain, which relates in part to how quickly a drug enters the central nervous system. Nicotine affects the neuronal circuits that create "reward." Particularly, nicotine is connected to dopamine release in the brain's mesolimbic pathway, which plays a role in the positive reinforcement of addictive substances [3]. Smoking cessation is linked to numerous health advantages. Former smokers live longer than current smokers, and those who give up smoking before the age of 50 have a reduced risk of passing away within the next 15 years. After ten years, the risk of dying from any cause equals that of a person who has never smoked [4].

There are currently numerous smoking cessation treatments available, including Varenicline (VAR) and Nicotine Replacement Therapy (NRT). The USPHS Clinical Practice Guidelines currently list and suggest seven 'first-line' pharmacotherapies for dealing with tobacco dependence: two non-nicotine drugs, varenicline and bupropion sustained-release (SR), five nicotine replacement therapies, including patches, gum, lozenges, inhalers and nasal sprays. Clonidine and nortriptyline are examples of "second-line" drugs that have not received FDA approval for treating

tobacco dependence. First-line medications should be selected initially because of their well-reported efficacy and favourable side effect profiles [5].

Varenicline is a partial agonist that binds to the nicotinic acetylcholine receptors on 42 neuronal cells with great affinity and specificity.6 Statistics from a pharmacokinetic investigation show that varenicline was associated with a 60-80% (N = 44) reduction in the mean number of cigarettes smoked within 2 to 4 days of beginning, as well as a decrease in the mean plasma nicotine and cotinine concentrations, among smokers who were not advised to quit but continued to smoke while taking it [7]. This has led us to the hypotheses that: 1) varenicline does not completely saturate nicotinic acetylcholine receptors leading to incomplete "reward" response and incomplete blockade of continuing smoking reinforcement; and/or 2) varenicline incompletely replaces the dopaminergic effect of smoking leading to a continued craving to smoke. To avoid underwhelming treatment efficacy outcomes, avoid "Under-replacement" of normal NRT dosages in heavy smokers by changing NRT dose in accordance with number of cigarettes consumed per day. Limited investigations have been done on the impact of these two therapies on heavy smokers. The comparison of smoking cessation success rates and the identification of variables affecting quit and relapse delays were the research's main goals.

### Methodology

From April 15 2022 to April 2023, the study was conducted at the Institute of Dental Sciences' Department of Public

Health Dentistry in Bareilly. The Tobacco Cessation Centre at the Institute of Dental Sciences in Bareilly is staffed by skilled professionals and offers high-quality services and care. Between April 2022 and April 2023, 1,042 active smokers who visited a smoking cessation centre were treated with medication and behavioural treatment. Being HS (smoking more than 19 cigarettes per day), older than 18, motivated to quit, and agreeing to participate in the research with a follow-up assessment every two weeks were the requirements for inclusion. Women who were nursing or pregnant were excluded. A schedule of two visits per week was used for the 24-week period of period follow-up. On May 20, 2022, a survey was taken to determine the status of abstinence. Utilising electronic random sampling (SPSS), patients who attended follow-up appointments and took their medications as directed were paired on treatment NRT vs. VAR for phone interviews.

Participants who had signed up received therapeutic instruction about medication action and management at their initial appointment. The options between NRT and VAR were presented to them. The 24-hour nicotine patch administration technique was utilised in the NRT group to help people stop smoking. For the first four weeks, subjects who smoked 40 cigarettes per day received two nicotine patches at a dose of 21 mg/day, one for each arm. Then, in weeks five to eight, two patches at a dose of 14 mg/day, 21 mg/day in weeks 9 to 12 and lastly 14 mg/day for four weeks before the twentieth week. Nicotine tablet was used when needed to fight cravings. In the VAR group, patients received 0.5 mg/d VAR for three days, followed by 1 mg/d (0.5 mg twice daily) for four days. On day 8, the target quit date, the VAR dose was increased to 1 mg twice daily until 12<sup>th</sup> week.

**Baseline assessments**

We have gathered demographic data (age, gender, educational level), smoking-related data (daily cigarette consumption, prior attempts, other household members who smoke, alcohol use, level of addiction to smoking [measured using the French version of the Fagerström test for nicotine dependence: FTND], and anxiety and depressive behaviour [measured using the French version of the Hospital Anxiety and Depression Scale: HAD]). We frequently measure the quantities of carbon monoxide inhaled.

**Results**

Table 1 shows smokers characteristics at baseline, patients in VAR cohort was younger and more anxious than those treated with NRT. Abstinence rates, were, 61.5% at the latest follow-up visit and 36.3% at one year (p=0.01). Smoking cessation rates, adjusted by age, alcohol consumption, anxiety, and ECM values, at one year were statistically comparable between the two groups NRT or VAR (The quit rates were 46.2% and 26.4% respectively with NRT and VAR at one year (p=0.646; adjusted OR 1.28; CI 95%: 0.44-3.74).

Likewise adverse effects rates were similar in two groups. Urge to smoke and feeling nervous were the most adverse effects, related to quit, described respectively in NRT (25.3%) and VAR cohorts (26.4%) (Table 2). In multivariate analysis, factors associated to smoking relapse at one year were presence of anterior previous attempts (HR: 0.10; 95% CI: 0.030-0.328), living with smokers at home (HR: 2.541; 95% CI: 1.019-6.336), having five following visits (HR: 0.091; 95% CI: 0.017-0.500) and having minimal withdrawal syndrome revealed on follow up (HR: 0.23; 95% CI: 0.08-0.662) (Table 3).

**Table 1:** Participants’ characteristics at baseline.

	VAR (91); n (%)	NRT (91); n (%)	p
Age: more than 40 years	17 (18.9)	52 (57.1)	0
Gender: Male	89 (97.8)	89 (97.8)	1
Education: Bachelor degree and higher	48 (54.5)	41 (45.1)	0.2
Previous attempt	69 (76.7)	67 (73.6)	0.64
Live with home smokers	33 (38.8)	28 (30.8)	0.26
Alcohol use	27 (30.3)	2 (09.5)	0.05
Fagerström scale: 7 and more	57 (62.6)	68 (74.7)	0.08
Anxiety scale: More than 11	19 (22.6)	9 (09.9)	0.02
Depression scale: More than 11	3 (03.6)	0 (00.0)	0.07
Cigarettes consumed per day (%). 20-30	64 (70.3)	58 (63.7)	0.34
31 and more	27 (29.7)	33 (36.3)	
One co-morbidity and more	17(18.7)	21(23.1)	0.47
Have a morning cough	32 (35.2)	24 (26.4)	0.2
Have an effort dyspnea	44 (48.4)	45 (49.5)	0.94
ECM; median, IIQ (ppm)	15 (7.0)	18 (13.0)	0

VAR: Varenicline; NRT: Nicotine Replacement Therapy; ECM: Exhaled Carbon Monoxide; ppm: Particles Per Million

**Assessment**

At follow-up visits and during the phone survey, information about smoking status and negative effects was provided. According to a self-report of smoking in the previous seven days, smoking status was determined. Exhaled carbon monoxide levels (cut off: 8 ppm) were used for biochemical validation to support self-reported

abstinence. The negative side effects comprised both treatment-related side effects (gastric ache, nausea, and cutaneous response) as well as side symptoms associated to quitting (urges to smoke, headaches, feeling nervous, memory impairment, sleep disruption, and increased appetite).

**Table 2:** Quit rates and adverse effects among study participants

Smoking cessation at follow up	Varenicline	NRT	P*
No: n (%)	46 (50.5)	24 (26.4)	0.251*
YES: n (%)	45 (49.5)	67 (73.6)	
<b>Smoking cessation at one year</b>			
No: n (%)	67 (73.6)	49 (53.8)	0.646*
YES: n (%)	24 (26.4)	42 (46.2)	
<b>Adverse effects</b>			
No: n (%)	46 (50.5)	23 (25.3)	
One	23 (30.3)	30 (33.0)	
More than one	22 (28.9)	38 (41.7)	
<b>Adverse effects related to quit</b>			
Urges to smoke	4 (05.5)	23 (25.3)	
Headaches	6 (08.3)	17 (18.7)	
Feeling nervous)	19 (26.4)	2 (02.2)	
Memory impairment	7 (09.7)	1 (01.1)	
Sleep disorder	6 (08.3)	13 (14.3)	
Increased appetite	4 (05.5)	5 (05.5)	
<b>Adverse effects related to treatment</b>			
Gastric ache	24 (33.3)	1 (01.1)	
Dermal Reaction	0	11 (12.1)	

\*: Adjusted on age, Alcohol use, Anxiety scale, Exhaled carbon monoxide values

**Table 3:** Factors associated to relapses delay in a cohort of smokers consuming 20 cigarettes and more in a low income region.

Treatment classes	HR	CI 95%	HR	p
<b>VAR</b>	<b>1</b>			
NRT	0.701	0.392	1.25	0.231
<b>Any previous attempts</b>				
No				
Yes	0.1	0.03	0.33	0
<b>Living with smokers at home</b>				
No	<b>1</b>			
Yes	2.541	1.019	6.34	0.046
<b>number of follow up visits- 0.013</b>				
2	0.214	0.053	0.86	0.03
3	1.38	0.433	4.4	0.585
4	0.198	0.034	1.14	0.069
5	0.091	0.017	0.5	0.006
<b>Number of difficulties during smoking cessation - 0.037</b>				
1	0.23	0.08	0.66	0.006
2	<b>0</b>	0		0.98
3	0.23	0.046	1.15	0.073

Variables included in multivariate model were: Age of first cigarette; Anterior previous attempts, Living with smokers at home, Importance of smoking cessation, self confidence in quitting smoking, treatment classes (NRT/ VAR), number of follow up visits, Number of difficulties during smoking cessation, level of study (baccalaureate).

**Discussion**

At one year, we found that the overall success rate was 36.3% and that the adjusted abstinence rates in the two groups, NRT and VAR, were comparable. Similarly, amongst those who smoke 20 cigarettes or more per day or more, we have found linked factors for quitting and relapsing. The results we obtained show that younger, worried high school smokers have considerably preferred VAR over NRT. Aubin H. J. also noted this preference in his evaluation of the literature.<sup>8</sup> With NRT and VAR, the quit rates were 46.2% and 26.4%, correspondingly (adjusted p=0.646). Our findings agreed with what Aubin HJ had to

say <sup>[8]</sup>. NRT is preferable to VAR, according to Grey KM and Cahill K <sup>[9, 10, 11]</sup>. Kaduri P, Kotz D and Hsueh KC, have revealed higher efficacy of VAR <sup>[12, 13, 14]</sup>. The research's structure, degree of reliance, gender, and racial/ethnic <sup>[15, 16, 17]</sup> disparities in outcomes can all be accounted for. By combining NRT with VAR, Koegelenberg D and Chang PH have established favourable rates <sup>[18, 19]</sup>. Additionally, Ramon JM had shown improved abstinence at 24 weeks amongst smokers who smoked more than 29 cigarettes per day (OR 1.46; 95% CI 1.2-2.8) <sup>[19]</sup>. The abstinence rates among our groups at one year were comparable to Kapaya's with NRT <sup>[20]</sup>.

In the research we conducted, the primary withdrawal symptom associated with NRT was the desire to smoke. Combining oral and dermal NRT may lessen this drawback <sup>[21]</sup>. According to Aubin's analysis, NRT had the best safety and tolerability of the two first-line smoking cessation drugs.<sup>8</sup> Perhaps as a result of its capacity to partially substitute nicotine's reinforcement-enhancing effects, the VAR cohort rarely felt the urge to smoke <sup>[22]</sup>. As a result, when compared to NRT, VAR significantly decreased the craving and withdrawal symptoms <sup>[23]</sup>. The only noticeable drawback among our VAR cohort was feeling anxious, and we haven't noticed any major side effects. Headaches, nausea, and strange dreams were the most typical side effects that were documented in the literature with VAR.<sup>18</sup> There is no evidence, according to Hartmann-Boyce, that trial participants who were randomised to VAR experienced any significantly more serious side events than placebo-controlled people <sup>[24]</sup>. In comparison to one year with two therapies, the abstinence rates were higher at follow-up. By halting the monitoring, former smokers ran the danger of relapsing and were left in an environment that promoted tobacco use. For this reason, we suggest treating tobacco use as a chronic condition and extending a routine follow-up for quitting until one year. In order to prepare smokers to make an effort with the best possibility of success, Fiore MC had advised a smoking-reductions with NRT for a few months <sup>[25]</sup>. In our trial, we changed the trans-dermal nicotine patch's dosing to account for the amount of cigarettes smoked by adding one mg for each cigarette. As a result, we replace our daily intake of 40 cigarettes with two 21 mg patches. With VAR, it's possible that some nicotine receptors are not saturated and won't become accustomed in smokers who use 40 cigarettes per day. Less abstinence rates among subjects who were heavy smokers and received VAR treatment may be due to this "under-dosing."

There are several advantages and disadvantages to our study that should be discussed. We were able to characterize the factors impacting abstinence in the VAR and NRT cohort and those associated with a longer span of stop using rigorous statistical approaches thanks to the utilization of a data cohort research conducted over a two-year research period. We were able to recommend a treatment option for GS in Tunisia because to our analysis. Due to the dearth of female smokers in the research area, particularly those who smoke more than 20 cigarettes per day, we are unable to evaluate gender effects that may affect abstinence rates and choice.

**Conclusion**

Both NRT and VAR can be used to treat highly dependent smokers. The number of negative effects decreased with VAR. NRT lengthen the quit period. We emphasized that by maintaining a routine follow-up for at least a year, we could manage tobacco use as a chronic condition.

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