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IMPACT OF SYMPTOMS EXPERIENCED BY VARENICLINE USERS ON TOBACCO TREATMENT IN A REAL WORLD SETTING

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Abstract

This paper examines reported symptoms, nonsmoking rates, and medication use among 1018 smokers using varenicline in a randomized trial comparing three forms of behavioral support for smoking cessation (phone, web, or phone + web). One month after beginning varenicline, 168 people (17%) had discontinued the medication. Most (53%) quit due to side-effects and other symptoms. The most common side-effect among all users was nausea (reported by 57% of users). At one month post medication initiation, those not taking varenicline were more likely to report smoking than those who continued the medication (57% vs. 16%, p<.001). Women reported more symptoms but did not discontinue medication at higher rates. Participants who received any telephone counseling (n=681) were less likely to discontinue their medication than those with web support only (15% vs. 21%, p<.01). Counseling may improve tolerance of this medication and reduce the rate of discontinuation due to side-effects. (149 words)

Keywords

Varenicline; smoking cessation; tobacco dependence treatment

1. Introduction

Varenicline (Chantix®) is the first in a promising new class of medications for treating tobacco dependence. The drug's unique mechanism as a partial α2β4 nicotinic acetylcholine receptor agonist serves to reduce nicotine withdrawal symptoms when quitting while its high affinity binding mitigates the reinforcing effects of smoking. In clinical trials, which all included a behavioral treatment component, varenicline demonstrated superior efficacy for maintaining abstinence from smoking compared with both placebo and bupropion, with continuous

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abstinence rates ranging from 28–44% at 12 weeks and 21–30% at 24 weeks (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Oncken et al., 2006).

While side effects from varenicline are common, most appear to be mild and resolve within the first few weeks of treatment. In the fixed-dose, placebo-controlled studies, adverse effects more frequently experienced by active treatment vs. placebo group trial participants included nausea (30% vs. 10%), insomnia (19% vs. 13%), headache (19% vs. 13%), abnormal dreams (13% vs. 5%), constipation (8% vs. 3%) and abdominal pain (7% vs. 5%) (Pfizer Labs, 2006). Looking at both Phase 2 and 3 trials, 9–28% of subjects discontinued medication due to such symptoms, compared with 7–17% of placebo controls. (Jorenby et al., 2006; Nides et al., 2006; Oncken et al., 2006; Williams, Reeves, Billing, Pennington, and Gong, 2007).

No studies have been published to date that report on treatment-emergent symptoms among varenicline users in a real-world setting or among smokers who have not been extensively screened for eligibility. This is important since smokers in the 'real world' may differ in meaningful ways from participants in the original, well-controlled clinical trials. As such, examining treatment response under more real-world conditions is important for understanding the safety and effectiveness of this new medication. This paper examines reported symptoms, smoking pattern, and medication use among 1018 participants in a randomized trial comparing the effectiveness of three forms of behavioral support for smoking cessation (phone counseling, web-based intervention, or phone + web intervention) when used in conjunction with varenicline.

2. Methods

2.1 Setting

This trial is a collaborative study conducted by SRI International (SRI), Free & Clear, Inc. (F&C), and Group Health (GH). SRI is a non-profit independent research organization, F&C is the U.S.'s largest vendor of tobacco quitline services, and GH is a non-profit, mixed-model integrated healthcare system in the Pacific Northwest. The study was conducted in GH's staff-model health plan.

This study was reviewed and approved by the following Institutional Review Boards (IRB): Western Institutional Review Board (WIRB) on October 4th, 2006 for Free & Clear, Group Health Human Subjects Review Committee on October 17, 2006, and SRI's Human Subjects Committee on October 27, 2006.

2.2 Recruitment & Eligibility

Recruitment occurred over a 12-month period from October 18, 2006 to October 2, 2007. Information about the study was included in publications mailed to GH members and staff, and in brochures distributed to GH-owned primary care clinics. GH providers were encouraged to refer eligible patients to the study. GH members calling to enroll in cessation services provided by Free & Clear were also invited to be screened for the study.

Interested volunteers were screened over the telephone and were considered eligible to participate if they were at least 18 years old, willing to stop smoking in the next 4–6 weeks, able to read and speak English, enrolled in and planning to remain enrolled in the health plan for the next 6 months, and eligible for smoking cessation services (smokers who had not used their insurance benefit in the previous 12 months). Additional criteria included having smoked an average of at least 10 cigarettes per day over the past year and at least 5 or more cigarettes per day within the past week, as well as dependable access to a telephone and the Internet, and comfort using the Internet.

Participants were excluded from the study due to: current/planned pregnancy or breast feeding; self-report of poor health (on a four point scale ranging from poor to excellent); severe heart disease or COPD (requiring hospitalization or oxygen); on dialysis or with certain kidney diseases; current self-reported diagnosis of or treatment for bipolar disorder, schizophrenia, or mania; current use of bupropion, nicotine replacement therapy or illicit drugs; current high use of alcohol; or current use of drugs that were considered to potentially interfere with the renal clearance of varenicline (cimetidine, metformin, phenformin, pindolol or procainamide) (Leabman et al., 2003). Because all study medication was provided by mail with no in-person medical visit and the medication was new to market, our IRB's required that the exclusionary criteria be slightly more stringent than was currently recommended in the prescribing instructions. However, the exclusions were less extensive than in the Phase 3 clinical trials.

2.3 Treatment

Enrolled participants (n = 1202) were randomly assigned to one of three behavioral treatment groups: Web-based (WB), proactive telephone-based (TB), or combined telephone- and web-based (TWB). All three included brief practical coaching and support for smoking cessation augmented with cognitive-behavioral counseling and motivational interviewing techniques provided over the phone, the Internet, or both. Participants all received varenicline along with education about proper medication use and side-effect management, both verbally (by telephone) and through mailed written materials. Medication protocol followed recommended dosing for varenicline consisting of a one-week titration period (0.5 mg QD for 3 days followed by 0.5 mg BID for 4 days) followed by 11 weeks of 1.0 mg BID. Participants were told to stop smoking after taking the medication for one week.

2.4 Assessment

Participants were interviewed over the telephone by trained research assistants approximately 28 days after beginning medication (21 days after their target quit day). They were asked if they had experienced a range of symptoms in the last month that included probable varenicline side effects and common nicotine abstinence or withdrawal effects (Hughes, 2007) (see Table 2). For each reported symptom, participants rated their experience as very mild to very severe on a five-point Likert scale. Participants were also asked to indicate their actual quit date, smoking pattern since this date, if they took any varenicline, if they were still taking it and, if not, the reasons for stopping.

2.5 Data analysis

The analytic sample included all participants who completed the 28-day follow-up survey (n = 1018). Overall and pair-wise group differences on frequency of symptoms were examined using the chi-square test of association (SAS Institute Inc., 2002). To account for multiple comparisons, P values for pair-wise comparisons were adjusted using the false discovery rate method of Benjamini and Hochberg (Benjamini & Hochberg, 1995). Gender comparisons were done using the chi-square test of association for categorical variables or t-tests for continuous variables.

3. Results

3.1 Sample characteristics

Of the 1202 participants randomized to treatment, 43 did not set a target quit date and were not sent any medication. Since the follow-up assessments were timed from the target quit date, these individuals were also excluded from the 28-day interview. An additional 118 participants were not able to be reached for the interview and 23 refused participation. In the remaining sample (n= 1018), participants were on average 48 years of age, high school graduates with

two years of college, and smoked 20 cigarettes per day. Ninety percent were White, and approximately two-thirds were women, married, and rated their overall health as 'good' (Table 1). Compared to men, women in this study smoked fewer cigarettes per day (18.7 vs. 21.3, p<.0001) and were less likely to be married (59% vs. 76%, p<.0001). There were no differences between those who did and did not complete the interview in terms of gender, race, education, overall health rating, amount smoked, or treatment group assignment. However, those who completed the interview were older (47.6 vs. 45.6, p=.017) and more likely to be married (65.1% vs. 56.0%, p=.02).

3.2 Reported symptoms and their severity

Symptoms reported by participants, in total and by gender, are shown in Table 2. Similar to the clinical trials, nausea was the most frequently reported side effect thought to be associated with varenicline, with 57% of total participants answering yes to this survey question. Most of the symptoms believed to be associated with varenicline use, including nausea and vomiting, were reported at higher rates by women.

Of the symptoms considered related to withdrawal of nicotine, desire to smoke or craving was by far the most common, reported by over three-quarters of both women and men (79%). Less than a quarter reported depression (23%) and less than half reported other neuropsychiatric symptoms such as tension/agitation (46%) and irritability/anger (43%). Only anxiety and tension/agitation were more frequently reported by women, compared with men.

Overall, most of those who experienced symptoms in either category reported them to be very mild to moderate (range 67.0%–96.6%), and a smaller percentage very severe or severe (3.4%–33.0%). Women generally rated their symptoms as more severe. (Data not shown)

3.3 Medication use

Participants were asked if they were still taking the medication and if not, to indicate why they stopped. Of the 168 people (17%) who reported that they had discontinued varenicline by the time of the interview, half (53%) reported it was due to side effects or other symptoms attributed to varenicline use, 17% stopped because they felt they did not need it, 11% because they felt it was not working and 15% because they ran out of pills and did not seek a refill. One-third (33%) reported "other" reasons, but many of these (43%) also indicated at least one of the four reasons above. An additional 32 subjects reported they had not taken any varenicline.

Participants were thus categorized into four medication use groups (Table 3): those who stopped because of symptoms or side effects (SS; n=89); those who stopped for any other reason (SO; n=79); those who were continuing to take varenicline at the time of the survey (CT; n=817); and those who never took the medication (NT; n=32). There were no overall or pair-wise differences in baseline characteristics for the four groups with one exception; those who never took the medication had fewer years of formal education than those who continued to take it (13.2 vs. 14.2 years; p<.02). In terms of behavioral treatment groups, those with web support only were more likely to have discontinued medication for any reason than those in the telephone counseling and combined groups (22% vs. 15%, p<.01).

3.4 Symptom experience and medication use

Overall, subjects in the four medication use groups differed in their reporting of all symptoms considered to be varenicline side effects except constipation, and only two of the symptoms commonly attributed to nicotine withdrawal (anxiety and difficulty concentrating), as seen in Table 3. In general, those in the group who stopped the medication due to symptoms or side effects tended to report the highest frequency of probable varenicline symptoms, although only two of these (vomiting and retching) were reported at higher rates among those who said they

stopped due to side effects compared with those who continued to take the medication. Not surprisingly, those who never took varenicline reported the least amount of symptoms related to medication use, but a higher rate of withdrawal symptoms than the other groups.

3.5 Smoking pattern

At the time of the survey, 42% of all participants reported not smoking since their quit date, 33% had smoked at least one cigarette since their quit date but were not smoking currently, 9% had relapsed to smoking and 15% had not quit. Table 4 shows the smoking pattern for each of the medication use groups separately and combined. Of all subjects who were not taking varenicline at the time of the interview, 57% were currently smoking, compared with 16% of those who were still taking varenicline ($p<.001$).

3.6 Neuropsychiatric events

After the 28-day follow-up survey but still during the active treatment phase, one participant experienced suicidal ideation and was hospitalized by his physician for a major depressive episode. This participant had a history of bipolar disorder with prior suicide attempt (>10 years ago) that was not disclosed during eligibility screening as he was not currently being treated for this condition. No other incidents of suicide attempts or severe psychiatric symptoms requiring treatment were reported by participants in the trial, although one other person discontinued varenicline due to a sudden, unexplainable onset of self-described depression and her symptoms resolved after stopping the medication.

Discussion

This study confirms published clinical trial findings that side effects from varenicline are relatively common and, while generally mild to moderate in severity, can be associated with discontinuation of medication in a substantial portion of users, especially those who experience more severe symptoms. Our results additionally show a strong relationship between discontinuation of medication and relapse to smoking in the early weeks after beginning treatment, with over half of those who had discontinued varenicline found to be smoking 28 days after beginning the medication.

Although women reported varenicline side effects more frequently and at greater severity levels than men, they were no more likely to discontinue medication. Interestingly, despite previous studies demonstrating women's experience of greater nicotine withdrawal symptoms while quitting without pharmacotherapy (Leventhal et al., 2007) or with NRT (Wetter et al., 1999), no difference in craving/desire to smoke, irritability/anger or depressed mood was seen in this trial, supporting an equal benefit from the partial nicotinic receptor agonist properties of varenicline. This is consistent with the varenicline clinical trials showing equivalent long-term abstinence rates among women and men (Schnoll, Patterson, and Lerman, 2007).

While participants were not asked which symptom specifically caused them to stop taking their medication, nausea was the most commonly reported medication side effect among those who discontinued, reported by over two-thirds of those who stopped due to symptoms of any kind. Additionally, retching or vomiting were the only two symptoms reported more frequently by those who discontinued their medication than those who continued to take it, suggesting that among potential side effects, those causing gastrointestinal distress are the least bearable for smokers using varenicline.

From a clinical perspective, it appears that identifying patients who are experiencing such symptoms early in their treatment and focusing more aggressively on measures to ameliorate them may improve tolerance and thus continuation of medication. These could include

reinforcing instructions to consistently take varenicline with food and water, temporarily or permanently reducing dosage, or prescribing concurrent anti-nausea or anti-emetic medications. Other factors that may predict more severe nausea or dyspepsia, such as concomitant smoking or pre-existing dyspepsia or gastro-esophageal reflux disease (GERD), should also be further explored and addressed.

Study participants who received any telephone counseling were less likely to discontinue their medication compared with those who were randomized to the web-only group. Although all participants received the same medication use instructions, including information about possible side effects and how to manage them, those assigned to the telephone counseling groups were called proactively, asked if they were experiencing any problems, and had an opportunity to discuss their questions or concerns about their treatment with a trained counselor. Those in the web only group were able to post queries on a discussion forum or call one of the study counselors, but did not receive individualized symptom management unless they took the initiative to call. This suggests that personalized support and counselors' monitoring of symptom experience during the quitting process may improve medication compliance and success in achieving abstinence.

Along with the strengths of this study, which include a large sample size with a relatively high response rate and a "real world" setting, there are several limitations that must be considered. First of all, since this study is primarily an effectiveness trial of different types of behavioral support for treating tobacco dependence, there is no control condition in which participants did not receive varenicline, nor was there a baseline survey of symptoms before beginning the medication. Therefore, causality cannot be established between symptoms and medication discontinuation, nor can we determine the role symptom experience plays in the high rate at which those who stop the medication return to smoking. There is evidence that not completing other approved cessation pharmacotherapies is associated with relapse to smoking (Toll, McKee, Martin, Jatlow, and O'Malley, 2007), and it is plausible that symptoms would contribute to this outcome, but also possible that return to smoking may precede symptoms or discontinuation of medication, or that patients have other reasons for failure to quit or remain abstinent.

Second, the results only examine reported symptoms, medication use, and smoking during the first month of varenicline treatment. However, since relapse most often occurs during the first few weeks of treatment, preventing discontinuation of medication during this critical period is likely to have a positive benefit on cessation. Third, patients were proactively asked about specific symptoms at the time of the survey, thus reporting rates of these symptoms are likely to be higher than if collected passively or via more general questions, while other symptoms that were common among clinical trial participants, such as headache, were not included on the list, and thus may have been underreported.

Fourth, while there were fewer medical exclusions for this study compared with the Phase 3 clinical trials, participants were screened for conditions related to poor health status and also excluded if unable to access the Internet and therefore may not represent all patients under general care, especially those who are more seriously ill. Finally, in light of recent FDA advisories regarding potential varenicline effects on mood and behavior, closer attention should be paid to the occurrence and impact of depression and other neuropsychiatric conditions on tobacco users trying to quit. While we only detected one serious psychiatric event requiring hospitalization out of over 1,000 participants in this trial, careful monitoring of patients on varenicline, especially those with prior diagnosis of mood disorders, is critical.

In summary, while varenicline was generally well-tolerated by most participants, medication side-effects and potential nicotine withdrawal symptoms were associated with discontinuation

of the medication and smoking in the early weeks of treatment. Smokers who continued to take the medication had lower smoking rates and those who received proactive phone counseling in conjunction with the medication were more adherent to medication use. The results suggest that smokers may benefit from proactive assistance managing varenicline side-effects and symptoms of nicotine withdrawal, which in turn could enhance their success quitting smoking. Additional research on how to best help patients avoid or deal with treatment-related symptoms and side-effects is warranted.

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Table 1

Baseline characteristics

Characteristic	Overall (n=1018)
Women, No. (%)	679 (67)
Age, mean (SD), y	48 (11)
White race, No. (%)	903 (90)
Married/living with partner, No. (%)	660 (65)
Education, mean (SD) y	14 (2)
Health rating	
Excellent, No. (%)	133 (13)
Good, No. (%)	666 (65)
Fair, No. (%)	219 (22)
Cigarettes per day, mean (SD)	20 (8)
Treatment Group	
Web only, No. (%)	336 (33)
Phone only, No. (%)	343 (34)
Combined, No. (%)	339 (33)

Table 2

Symptom experience at the 21-day follow-up interview overall and by gender

Symptom experience in last month	Overall (n=1018) No. (%)	By Gender Males (n=339) No. (%)	By Gender Females (n=679) No. (%)	*P* value
Probable varenicline side effects				
Nausea	579 (57)	148 (44)	431 (64)	<.001
Flatulence	553 (55)	159 (47)	394 (58)	<.001
Changes in dreaming	565 (56)	175 (52)	390 (58)	.08
Change in appetite	484 (48)	144 (43)	340 (50)	.02
Dysgeusia	462 (46)	132 (39)	330 (49)	.002
Difficulty sleeping	429 (43)	128 (38)	301 (45)	.04
Constipation	322 (32)	78 (23)	244 (36)	<.001
Retching	100 (10)	21 (6)	79 (12)	.009
Vomiting	100 (10)	15 (4)	85 (13)	<.001
Probable nicotine withdrawal symptoms				
Desire to smoke	795 (78)	266 (79)	529 (78)	.90
Tension/agitation	465 (46)	137 (41)	328 (49)	.01
Irritability/anger	432 (43)	133 (39)	299 (44)	.13
Anxiety	351 (35)	102 (30)	249 (37)	.03
Difficulty concentrating	289 (29)	89 (26)	200 (30)	.28
Depression	234 (23)	69 (20)	165 (24)	.16
Confusion	146 (14)	47 (14)	99 (15)	.74
“Other”	252 (25)	72 (21)	180 (27)	.07

Table 3

Symptom experience at the 21-day follow-up interview by medication use group

Symptom experience in last month	Medication use group: Stopped Side Effects SS (n=89) No. (%)	Stopped Other Reasons SO (n=79) No. (%)	Never Took NT (n=32) No. (%)	Continued to Take CT (n=817) * No. (%)	Overall *P* value
Probable medication side effects					
Nausea[a,b,e,f]	62 (70)	34 (43)	7 (23)	475 (58)	<.001
Flatulence[b,f]	53 (60)	35 (44)	8 (26)	456 (56)	.001
Changes in dreaming[b,d,f]	48 (55)	40 (51)	6 (20)	471 (58)	<.001
Change in appetite[a,e]	46 (52)	25 (32)	12 (39)	401 (49)	.01
Dysgeusia[b,f]	44 (50)	27 (34)	5 (16)	385 (48)	<.001
Difficulty sleeping[b]	46 (52)	26 (33)	7 (23)	350 (43)	.01
Constipation	28 (31)	23 (29)	5 (16)	266 (33)	.25
Retching[a,c]	24 (27)	6 (8)	2 (6)	68 (8)	<.001
Vomiting[a,c]	19 (21)	3 (4)	2 (6)	76 (9)	<.001
Probable nicotine withdrawal symptoms					
Desire to smoke	64 (72)	64 (81)	27 (87)	639 (79)	.27
Tension/agitation	46 (53)	36 (46)	15 (48)	368 (45)	.53
Irritability/anger	40 (46)	34 (43)	13 (42)	345 (42)	.93
Anxiety[c,f]	44 (50)	28 (35)	17 (55)	262 (32)	<.001
Difficulty concentrating[c]	39 (44)	21 (27)	7 (23)	222 (27)	.007
Depression	27 (30)	15 (19)	9 (29)	183 (23)	.22
Confusion	21 (24)	8 (10)	4 (13)	113 (14)	.05
"Other"[a,b'c]	31 (35)	10 (13)	3 (10)	208 (26)	<.001

* One person responded "don't know" when asked if still taking varenicline.

Overall p-value for chi-square comparing the four medication use groups on each symptom. Significant pairwise comparisons, after adjustment for multiple comparisons:

[a] SS vs. SO;

[b] SS vs. NT;

[c] SS vs. CT;

[d] SO vs. NT;

[e] SO vs. CT;

[f] NT vs. CT.

Table 4

Smoking pattern since quit and current smoking, by medication use

		Medication use group			
Smoking pattern since target quit day	**Overall (n=1018)**	**Stopped Side Effects (SS) (n=89)**	**Stopped Other Reasons (SO) (n=79)**	**Never Took (NT) (n=32)**	**Continued to Take (CT) (n=817)**
Not smoked, %	42	30	27	6	46
Slipped/not smoking, %	34	17	19	16	38
Relapsed/smoking, %	9	28	23	16	5
Did not quit, %	15	25	32	62	11
Current smoking		**Not currently taking varenicline (Combined SS, SO and NT) (n=200)**			**Currently taking (CT) (n=817)**
Currently not smoking, %*	76		43		84
Currently smoking, %**	24		57		16

* Currently not smoking = participants who reported not smoking in the past 7 days (point prevalence abstinence)

** Currently smoking = participants who smoked in the past seven days