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Addictive Behaviors



Tobacco dependence treatment for hospitalized smokers: A randomized, controlled, pilot trial using varenicline

Michael B. Steinberg^{*}, Jennifer Randall, Shelley Greenhaus, Amy C. Schmelzer, Donna L. Richardson, Jeffrey L. Carson

Division of General Internal Medicine, University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School, New Brunswick, NJ, USA

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ABSTRACT

Objective: The hospital can be an important opportunity for smoking cessation interventions. This is the first randomized, double-blinded, placebo-controlled pilot trial utilizing varenicline and post-discharge, in-person behavioral treatment for hospitalized smokers.

Method: Seventy-nine smokers admitted to a university-based hospital with various diagnoses were enrolled from 2007 to 2009. The primary outcome was biochemically confirmed abstinence at 24 weeks following discharge. Secondary outcomes included withdrawal symptoms, motivation, utilization of treatment, and medical events.

Results: Overall abstinence at 24 weeks was 27% with no difference between varenicline and placebo treatment groups (23% vs. 31%). There were no significant differences in motivation to stop smoking or withdrawal symptoms. Over 40% of all subjects utilized post-discharge behavioral treatment with significantly higher abstinence rates compared with those who did not (53.1% vs. 8.5%, $p < 0.01$). Overall adverse events were similar in both treatment groups with the only significant difference being more nausea in the varenicline group (25% vs. 5%; $p < 0.01$). Twenty-three subjects were re-hospitalized with no significant differences between treatment groups (13 varenicline vs. 10 placebo).

Conclusion: This pilot trial of varenicline in hospitalized smokers demonstrated feasibility of implementation, produced some hypothesis-generating findings, and suggested the potential benefit of face-to-face treatment following discharge.

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1. Introduction

Despite clear reasons to quit smoking, patients with medical illness continue to smoke at alarmingly high rates. For smokers with cardiovascular disease, stopping smoking reduces the risk of recurrent myocardial infarction, restenosis of coronary interventions, and cardiac sudden death by about 36% (Critchley & Capewell, 2003). Patients with diagnoses of cancer who continue to smoke have higher rates of recurrence, additional primary malignancies, less response to treatment, and poorer outcomes than those who quit (Browman et al., 1993; Dikshit et al., 2005; Gritz, 1991). Despite this, up to 50% of smokers admitted for myocardial infarction are smoking again within 6 months (Rigotti, Singer, Mulley, & Thibault, 1991) and over 50% of smokers with a diagnosis of cancer continue using tobacco (Cox, Africano, Tercyak, & Taylor, 2003).

Recent Public Health Service Clinical Guidelines and reviews have demonstrated the efficacy of medications to help smokers quit (Fiore et al., 2008; Hughes, Goldstein, Hurt, & Shiffman, 1999; Silagy, Lancaster, Stead, Mant, & Fowler, 2004). Medically ill, smokers may require intensive efforts to assist them in quitting. However, they often do not receive adequate treatment for tobacco dependence (Critchley & Capewell, 2003), especially pharmacotherapy, as prescribers are cautious of adverse effects with certain conditions, such as cardiac disease, despite numerous studies demonstrating the safety of cessation medications in medically ill smokers (Benowitz, Kuyt, & Jacob, 1984; Fiore et al., 2008; Murray, Bailey, & Daniels, 1996; Steinberg et al., 2009; Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease, 1994). Based on published trials (Gonzales et al., 2006; Jorenby et al., 2006), varenicline can increase cessation and its mechanisms of action may be well suited for treating hospitalized smokers.

Smokers who are hospitalized are at very high risk of continued tobacco-caused morbidity. They are placed in a setting of forced abstinence and feel especially vulnerable thus creating a “teachable moment” yet, tobacco treatment services have been historically underutilized during hospitalization (Emmons et al., 2000; Koplan, Regan, Goldszer, Schneider, & Rigotti, 2009). A recent review reported

^{*} Corresponding author at: Division of General Internal Medicine, University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School, 125 Paterson Street, Suite 2304, New Brunswick, NJ 08903, USA. Tel.: +1 732 235 8219; fax: +1 732 235 7144.

E-mail address: michael.steinberg@umdnj.edu (M.B. Steinberg).

that effective hospital-based interventions require at least a moderate amount of intensity and follow-up and that the link between hospitalization and post-discharge treatment has been the greatest barrier to continued treatment (Rigotti, Munafo, & Stead, 2008). Therefore, intensity of treatment and post-discharge interventions are key factors requiring evaluation. The purpose of this pilot study was to assess the feasibility of a hospital-based intervention utilizing varenicline on withdrawal symptoms, motivation to stop smoking, and abstinence rates.

2. Methods

2.1. Setting and subjects

The study was conducted at a 584-bed university-based hospital in a moderate-sized urban center from August 2007 to March 2009. All protocols were approved by the University Institutional Review Board.

2.2. Eligibility criteria

Patients admitted to the hospital who smoked 10 cigarettes or more per day within the past month, were not being discharged into a setting of forced abstinence (e.g. institutionalized), and could attend a 4-week outpatient follow-up visit (e.g. not moving out of the area) were included. Those who were under the age of 18 years; on dialysis; with mental illness requiring antipsychotic medications; currently using cessation medications (varenicline, bupropion, nortriptyline, or nicotine replacement medications); had previous reaction to varenicline; pregnant; or had active substance abuse, deemed clinically unstable, or life expectancy less than 6 months was excluded.

2.3. Subject recruitment

The hospital computer system identified smoking status for all patients from the admission history and physical examination. Each subject's attending physician agreed to allow approaching the patient to discuss the study, informed consent was obtained, and subjects were assessed and randomly allocated. Patients were generally approached within 24–48 h after admission.

2.4. Data collection and randomization

Data collected by a single research nurse (RN, MPH) at the initial assessment included: age, gender, race/ethnicity, education, employment, current tobacco use, number of years using, previous quit attempts and methods used, Fagerstrom Test for Nicotine Dependence (Fagerström, 1978), environmental tobacco smoke exposure, medical and psychiatric history, admitting diagnosis, Readiness/Importance/Confidence to quit, and the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes, 1992).

A personalized, strong, quit message was given to all subjects, tailored to the subjects' admitting condition where appropriate. Subjects received a printed information sheet on behavioral changes, helpful tips for smoking cessation, and outpatient quit resources, including QuitLine, Quitnet, and the local Tobacco Dependence Program. Subjects were visited briefly by a single study physician (MD, MPH) to discuss benefits and side effects of varenicline.

Subjects were randomized in a 1:1 ratio through a centralized telephone randomization process by the study statistician and hospital research pharmacist. The subject, research nurse, and treatment staff were blinded to treatment assignment. The nurse conducted brief visits to record withdrawal symptoms, changes in motivation, smoking behavior, and any adverse events during hospitalization.

2.5. Medication protocol

Subjects were administered varenicline or placebo following randomization, and continued daily for a total of 12 weeks as per the usual titration recommendations (0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily). Following discharge, subjects were given a 4-week supply of study medications (varenicline or placebo) until they were seen for their 4-week follow-up session at which point they were given the second 4-week supply, and subsequently, their 3rd 4-week supply. Subjects were asked to avoid other cessation medications during the study.

2.6. Counseling/follow-up protocol

All subjects were visited by a single Clinic Coordinator of the local Tobacco Dependence Program (LCSW) during their hospitalization to schedule an appointment at the Program and provide brief (5–10 min) behavioral treatment based on the US Public Health Service Guidelines (Fiore et al., 2008). Subsequent sessions at the Program were generally 15 min in duration and also followed the clinical practice guidelines (i.e. focused on practical problem solving skills and management of withdrawal).

After discharge, subjects attended study data-collection sessions in person at weeks 4, 12, and 24 conducted by the research nurse. These sessions were completely independent of the behavioral treatment conducted by the tobacco treatment specialist. Telephone contact was also made at week 2. At these sessions, subjects were asked about their tobacco use since discharge, nicotine withdrawal symptoms, medication use, adverse medication effects, and any medical complications or symptoms that have occurred since discharge. Exhaled carbon-monoxide (CO) measures were conducted by having the subject hold their breath for 15 s, then exhale into a hand-held CO monitor. A cutoff value of 8 ppm CO discriminates smokers from nonsmokers with 90% sensitivity and 89% specificity, and is a typical standard used in these studies (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). Subjects were given a \$25 gift-card incentive to attend each of the 4, 12, and 24-week follow-up visits. If subjects were not able to attend the data-collection sessions in person, as much information as possible was obtained over the telephone. Follow up data collection regarding medical outcomes were obtained from hospital records, emergency department visits, physician office records, and patient self-report.

2.7. Outcomes

The primary outcome of the study was expired CO confirmed 7-day point abstinence (no smoking for previous week) at 24 weeks following discharge. Secondary outcomes included abstinence at 4 and 12 weeks following discharge; withdrawal symptoms (via the MNWS); motivation (0–10 Likert scale); number of cigarettes smoked during study period; utilization of outpatient treatment (medications, attending treatment at the Tobacco Program) following discharge; and composite medical outcome (re-hospitalization or Emergency Department visit). Adverse events were reported by open-ended subject self-report, and were assessed as to relationship to cessation medications. Predetermined criteria (hospitalization or causing serious medical risk) were utilized for discontinuing a subject based on an adverse event. If a subject could not attend the 24-week session, self-reported information was utilized. Self-reported abstinence is an accepted measure of non-smoking in clinical trials where confirmation is not possible (Hughes et al., 2003; West, Hajek, Stead, & Stapleton, 2005).

2.8. Statistical analysis

Analyses were performed with SPSS (version 17.0). Patient characteristics between the two arms of the trial were compared

using tests for homogeneity of proportions for categorical variables and Student's t-test to test for differences in mean (+ standard deviation). The intervention and control groups were contrasted to test the effectiveness of randomization. The primary statistical analysis tested the hypothesis of no difference between intervention and control groups with respect to tobacco abstinence. The primary outcome was compared using the Mantel–Haenszel chi-square test. The test for differences between intervention and control strategies in the primary outcome was conducted at an overall alpha-level of 0.05. We used an alpha of 0.01 for secondary outcomes to account for multiple outcomes. Adjusted odds ratios and 95% confidence intervals were calculated using standard methods. Logistic regression was used to adjust for differences in other clinical factors including age, sex, race, education, cigarette consumption, time to first cigarette, previous quit attempts, and treatments used. Analysis was conducted on an intent-to-treat basis.

3. Results

3.1. Subject flow

Fig. 1 describes the flow of subjects in the study. Of the 1090 hospital patients assessed for eligibility, 1011 were excluded for various reasons, the most common being clinically unstable condition (376), being discharged within 24 h and leaving prior to assessment (234), not meeting eligibility criteria (125), and actively abusing illicit substances (103).

3.2. Subject characteristics

A total of 79 subjects were enrolled in this pilot study. When subjects relapsed to smoking, they often did not continue returning for follow-up visits. Among all subjects enrolled, 49 (62%) attended the 4-week follow-up visit, 45 (57%) attended the 12 week visit, and

43 (54%) attended the 24 week visit. There was no difference in the number who did not complete follow up between treatment groups (18 in each group).

The characteristics of the study population are shown in Table 1. The mean age was 51 (range of 22–78), 59% were male, 72% were white, and 85% had a high school education or higher. Forty-percent had high dependence as indicated by a Fagerstrom Test for Nicotine Dependence score of 6 or greater, 57% smoked 20 or more cigarettes per day, and 87% smoked their first cigarette within 30 min of waking.

Subjects were admitted for various diagnoses: cardiovascular 57%; orthopedic 14%; pulmonary 13%; and other 16%. Their medical history included heart disease (22%); hypertension (46%); chronic obstructive pulmonary disease (COPD) (25%); asthma (20%); diabetes (22%); any cancer (8%); depression (39%); and hyperlipidemia (14%).

3.3. Abstinence rates

Among all subjects, the overall abstinence rates were 38% at 4 weeks following discharge, 32% at 12 weeks, and 27% at 24 weeks. In univariate analyses, some differences were noted (Table 1). Men tended to have higher abstinence at 24 weeks than women (34% vs. 16%; $p=0.07$); white subjects had higher abstinence rates than African-Americans (26% vs. 8%; $p=0.09$); college graduates had higher abstinence than those subjects with only a high school diploma (67% vs. 24%; $p=0.03$); and those subjects with high dependence (Fagerstrom score of greater than 6) were less likely to be abstinent than those with lower dependence (16% vs. 34%; $p=0.07$). There was no relationship between admitting diagnosis and abstinence.

There was no difference in overall abstinence rates between placebo and varenicline treatment groups (31% placebo vs. 23% varenicline at 24 weeks) (Table 2). The proportion of subjects who were abstinent at all 3 visits was 28% in the placebo group and 20% in the varenicline group.

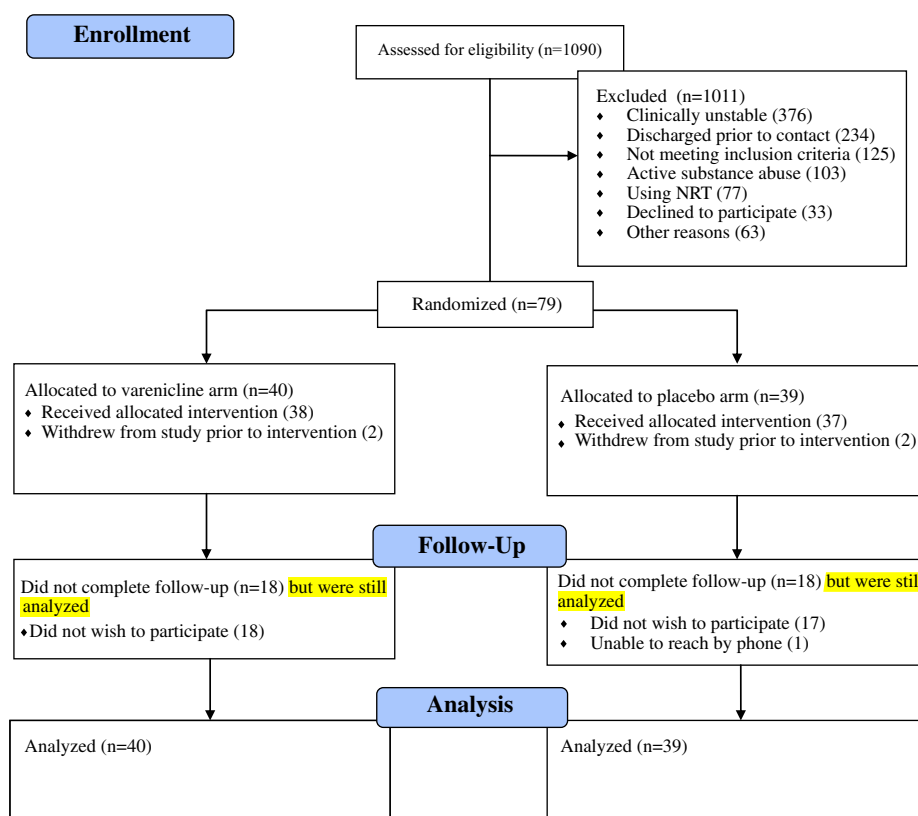


Fig. 1. Subject flow diagram, Robert Wood Johnson University Hospital, 2007–2009.

Table 1
Demographics and tobacco use characteristics by treatment group and overall 24-week abstinence; Robert Wood Johnson University Hospital; 2007–2009.

		Demographics				Abstinence at 24 weeks after discharge ^a	
		Placebo		Varenicline		All subjects	
		n	(%)	n	(%)	n	(%)
Overall		39	(49)	40	(51)	79	(27)
Age	40 and younger	6	(15)	5	(12)	2	(18)
	41–50	13	(33)	9	(22)	7	(32)
	51–59	14	(36)	14	(35)	7	(25)
	60 and older	6	(15)	12	(30)	5	(28)
Gender	Male	23	(59)	24	(60)	16	(34) (p=0.07)
	Female	16	(41)	16	(40)	5	(16)
Race	White	26	(67)	31	(77)	15	(26) (p=0.09)
	African American	7	(18)	5	(12)	1	(8)
	Other	6	(15)	4	(10)	5	(50)
Education	Less than HS graduate	8	(20)	4	(10)	3	(25) (p=0.03)
	HS graduate	14	(36)	19	(47)	8	(24)
	Some college	14	(36)	11	(27)	4	(16)
	College graduate or higher	3	(8)	6	(15)	6	(67)
Fagerstrom Test for Nicotine Dependence	Moderate dependence (<6)	21	(54)	26	(65)	16	(34) (p=0.07)
	High dependence (6+)	18	(46)	14	(35)	5	(16)
Cigarettes per day	Less than 20	18	(46)	16	(40)	9	(26)
	20 or more	21	(54)	24	(60)	12	(27)
Time to first cigarette	More than 30 min	8	(20)	2	(5)	3	(30)
	6–30 min	15	(38)	19	(47)	10	(29)
	Within 5 min	16	(41)	19	(47)	8	(23)
Received any treatment at Tobacco Dependence Program	No treatment	22	(56)	25	(62)	4	(8) (p<0.01)
	Had treatment	17	(44)	15	(37)	17	(53)

^a p-value listed for variable group if less than 0.10. Otherwise, p>0.10.

Logistic regression was performed to control for factors that might influence abstinence rates at 24 weeks. In a model that included age, race, education, level of dependence, and treatment group, none of the variables had statistically different odds of abstinence at 24 weeks. There were non-significant differences in abstinence for highly-dependent subjects (AOR 0.26; 95% CI 0.06–1.02) and for college graduate education level (AOR 6.0; 95% CI 0.89–40.3). The adjusted odds ratio for abstinence was not different between varenicline and placebo (AOR 0.34; 95% CI 0.10–1.23). These findings were similar with full model, forward, and backwards stepwise procedures.

3.4. Medication adherence

Medication adherence (defined as taking 80% or more prescribed tablets) at 1 month was higher in the placebo group compared with varenicline group, although not statistically significant (placebo 78% vs. varenicline 56%; p = 0.12). Among subjects who were adherent to the medication protocol, there was a non-statistically higher abstinence rate at 24-week follow up in the varenicline group compared with placebo (80% vs. 56%; p = 0.2).

3.5. Utilization of face-to-face behavioral treatment

40.5% of all subjects attended treatment at the Tobacco Dependence Program following discharge. Those subjects who attended treatment had significantly higher abstinence rates (53.1%) compared

Table 2
Abstinence rates at 4, 12, and 24 weeks by treatment group; Robert Wood Johnson University Hospital; 2007–2009.^a

	Placebo (n = 39)		Varenicline (n = 40)		Total (n = 79)	
	n	(%)	n	(%)	n	(%)
4 week abstinence	15	(38)	14	(35)	29	(37)
12 week abstinence	13	(33)	12	(30)	25	(32)
24 week abstinence	12	(31)	9	(23)	21	(27)

^a p = not significant between treatment groups at all comparison times.

with those subjects who did not attend treatment (8.5%; p<0.01). In an attempt to determine if subjects who attended follow-up treatment had higher levels of self-reported motivation, the baseline measure of motivation (scale from 0 to 10) was not statistically different (8.3 for those who attended vs. 7.9 for those who did not attend).

3.6. Adverse events

Data regarding adverse events were collected throughout the 24 week study. Table 3 shows the most commonly reported adverse events by treatment group. In general, adverse events were similar between the 2 groups with the exception of nausea.

Table 3
Adverse events, rehospitalization, or emergency department visits; Robert Wood Johnson University Hospital; 2007–2009.

Adverse event	Rate in varenicline group (n = 40)	Rate in placebo group (n = 39)	Significance
	(%)	(%)	
Nausea	27	5	p<0.01
Sleep disturbances	8	8	NS
Depression	5	5	NS
Cardiac related ^a	10	8	NS
Serious adverse events ^b	15	13	NS
Any adverse event	65	51	NS
Rehospitalization or emergency department visits ^c	13 events	10 events	NS

NS = not statistically significant at p = 0.05 level.

^a Cardiac related adverse events included chest pain, palpitations, and tachycardia.

^b Serious adverse events are defined as requiring or prolonging hospitalization or requiring acute medical intervention.

^c Causes for rehospitalization or emergency department visit: in varenicline group – elective surgery/procedure (8), COPD exacerbation (2), congestive heart failure (1), wound debridement (1), and knee pain (1); in placebo group – reinsertion of surgical drain (3), elective surgery/procedure (2), transient ischemic attack (1), COPD exacerbation (1), upper respiratory infection (1), diarrhea (1), and laceration requiring sutures (1).

There were a total of 23 subjects who during the course of the study were re-hospitalized or were treated in the emergency department (Table 3). Of these, 13 occurred in the varenicline group and 10 in the placebo group. None of these events was felt to be related to study treatments. There were no deaths in the study.

3.7. Withdrawal and cravings

There were no statistical differences in cravings as measured by changes in Minnesota Nicotine Withdrawal Scale (MNWS) from baseline to follow-up points. However, at end of treatment (12 weeks), there was a trend toward fewer subjects reporting any cravings in the varenicline group compared with the placebo group (56% varenicline vs. 74% placebo). In addition, at 4 weeks the mean decrease in MNWS was 1.45 points in the varenicline group compared with a 0.11 increase in the placebo group, but this was not significant ($p = 0.5$).

3.8. Environmental factors

Abstinence rates were only 13% among those subjects who live with another smoker compared with 33% for those who did not live with a smoker ($p = 0.04$).

4. Discussion

This pilot study is the first RCT using varenicline in the hospital and did not find a statistically significant increase in abstinence rates at 24 weeks post-discharge. The results did however produce some interesting hypothesis-generating findings. Varenicline has been proven effective in numerous clinical trials (Gonzales et al., 2006; Jorenby et al., 2006) and in co-morbid smokers with cardiovascular disease (Rigotti et al., 2010), COPD (Tashkin, Rennard, Hays, Ma, & Lee, 2009) and various medical and psychiatric conditions (Steinberg et al., 2010). Due to their acute medical illness, it is possible that hospitalized smokers may be less tolerant of adverse effects, and thus less able to successfully initiate this medication regimen. There was a non-significantly lower rate of adherence during the first 4 weeks of treatment (78% placebo vs. 56% varenicline). Among subjects who were adherent to treatment medications, varenicline did seem to have a benefit in 24 week abstinence (80% varenicline vs. 56% placebo), but not significant.

Some previous studies of hospitalized smokers have also failed to find significant results. In 2 separate studies, Campbell, Prescott, and Tjeder-Burton (1991, 1996) assessed the effectiveness of nicotine patch and nicotine gum combined with in-person counseling with no significant effect on smoking cessation rates. Reid et al. (2003) examined a stepped-care intervention including telephone counseling and nicotine patches on hospitalized smokers and found no statistical difference. A recent meta-analysis concluded that adding nicotine replacement therapy to counseling in hospitalized smokers produced a 47% increase in the odds of quitting compared with placebo, although this was not statistically significant (95% CI, 0.92–2.35) (Rigotti et al., 2008). As opposed to these findings, Mohiuddin et al. (2007) found that behavior counseling and individualized pharmacotherapy that included nicotine replacement and/or bupropion had significantly higher quit rates at all follow-up time intervals for both point-prevalence and continuous abstinence analyses (39% intensive-treatment continuous abstinence vs. 9% usual-care at 2-years ($p < 0.0001$)).

An interesting finding in the current trial was the benefit for those subjects attending face-to-face post-discharge treatment at the local tobacco treatment clinic. A substantial barrier for successful hospital-based tobacco interventions has been the link between hospitalization and continued outpatient follow-up (Rigotti et al., 2008). In the current trial, over 40% of hospitalized subjects successfully attended

face-to-face treatment and those subjects had high abstinence rates (53%) at 24 weeks. This rate of treatment adherence and abstinence is similar to that found in other studies (e.g., 42% attending counseling sessions with 53% abstinence rate (Reid et al., 2003)). Many previous trials for hospitalized smokers have utilized telephone follow-up and have had mixed results (Rigotti et al., 2008). However, telephone treatment may not be suited for all settings (Hanssen, Nordrehaug, Eide, & Hanestad, 2009; Sood et al., 2009). For highly dependent, hospitalized smokers, a more intensive face-to-face contact may provide higher quality patient-provider clinical relationships, more accurate assessment of co-morbidities, and allow closer monitoring for adverse effects and withdrawal.

As a feasibility study, this trial illustrated some difficulties in conducting hospital-based interventions. A significant proportion of our screened patients were clinically unstable or actively using other substances. This may be an inherent function of the hospital setting. In addition, many potential subjects were discharged prior to assessment. Future studies could implement other methods to identify, assess, and intervene with potential subjects in a more rapid fashion. Finally, many patients did not meet eligibility criteria. Future studies might explore interventions in smokers of fewer cigarettes per day or in those concurrently using other tobacco products.

4.1. Limitations

This study had some limitations. First, the small sample size in this pilot study did not provide enough power to draw any definitive conclusions, such as treatment effect or the influence of disease and timing. Second, the completion rates were 54% for all subjects at 24 weeks. This rate was similar to that found in other hospital-based tobacco studies (e.g., 50–53% in Campbell et al., 1996). There were no differences in follow-up among treatment groups and we assumed all subjects lost to follow-up were still smoking. Although only 54% attended their follow-up sessions in person, nearly all subjects were contacted by telephone, and reported adverse events in this manner. Third, there was potential bias among subjects who attended post-discharge treatment at the Tobacco Dependence Program (i.e., more highly motivated), thus limiting interpretation of the results. Despite this, the very high abstinence effect in those attending still warrants further investigation in this difficult to treat population.

5. Conclusion

This pilot study represents the first randomized, controlled trial of varenicline in the hospital setting and illustrates some barriers to future trials in this venue. The results suggest the possible benefit of face-to-face treatment following discharge and interventions to improve these follow-up rates may be important in this population. This pilot study is useful in generating hypotheses while larger studies are required to make determinations of effectiveness and safety.

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Contributors

Dr. Steinberg had the overall role of study concept, design, implementation, data analysis, and manuscript preparation; Dr. Randall was involved with literature review and summary, data entry, synthesis, analysis, and manuscript preparation; Ms. Greenhaus was involved in study design and implementation, data collection, and manuscript preparation; Ms. Schmelzer was involved with study design, literature review and summary, data collection, and manuscript preparation; Ms. Richardson was involved with study design, implementation, data collection, and manuscript preparation; and Dr. Carson was involved with study design and manuscript preparation. All of the authors have had access to the data and have had a role in writing and approving the final manuscript.

Conflict of interest

Dr. Steinberg had previously received honoraria for educational programs from Pfizer (2006–2009). The other authors declare that they have no conflicts of interest to disclose.

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