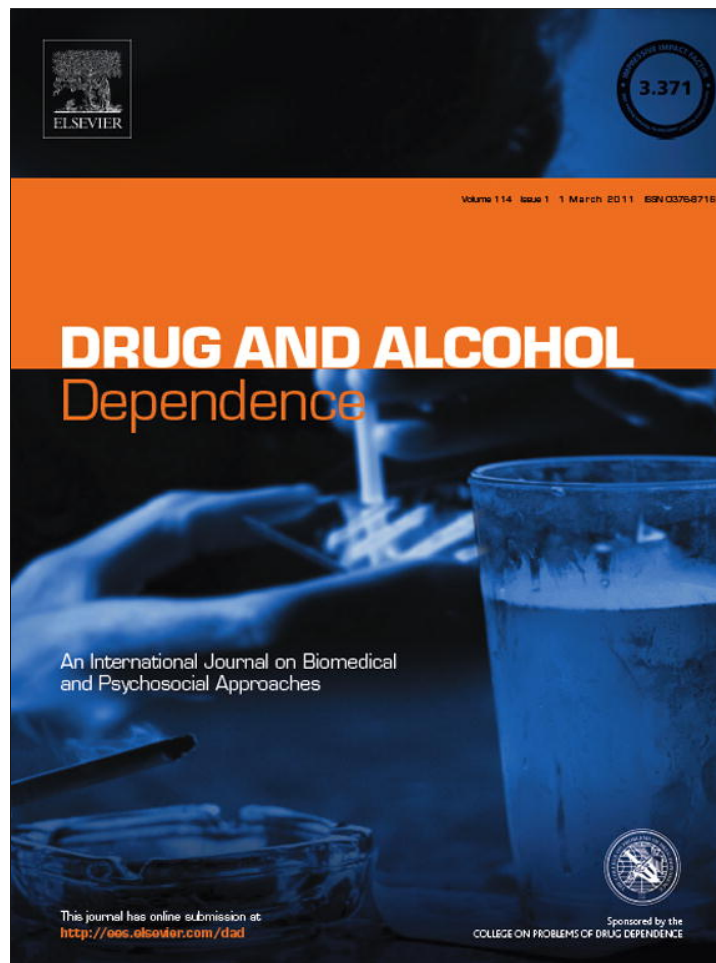


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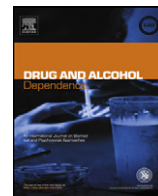
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Short communication

Abstinence and psychological distress in co-morbid smokers using various pharmacotherapies

Michael B. Steinberg^{a,b,*}, Michelle T. Bover^b, Donna L. Richardson^b, Amy C. Schmelzer^b, Jill M. Williams^{a,b}, Jonathan Foulds^{b,a}^a Division of General Internal Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, 125 Paterson Street, Suite 2300, New Brunswick, NJ 08903, USA^b Tobacco Dependence Program, University of Medicine and Dentistry of New Jersey-School of Public Health, 317 George Street, Suite 210, New Brunswick, NJ 08901, USA

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ABSTRACT

Background: Existing trials of varenicline have typically excluded smokers with concurrent medical and psychiatric illnesses and no data exist comparing effectiveness of varenicline with combination pharmacotherapy. This study evaluated abstinence and psychiatric outcomes of various tobacco dependence medications, including varenicline.

Methods: Retrospective cohort of 723 smokers, most with significant medical and psychiatric comorbidity, was evaluated at the UMDNJ-Tobacco Dependence Clinic from 2006 to 2008. Demographics, measures of tobacco dependence and co-morbidities, and a validated instrument measuring psychological distress (Kessler-6) were obtained. Primary outcome was 7-day point abstinence at 6 months after target quit date.

Results: Cessation medications used included combination pharmacotherapy (39%), single nicotine replacement therapy (NRT) or bupropion (29%), and varenicline (23%), with 9% using no medications. Overall, 23% of patients were abstinent at 6 months. In an adjusted regression model, smokers using varenicline or combination medications were more likely abstinent at 6 months than those using no medications (adjusted odds ratio = 2.99; 95% confidence interval = 1.20–7.47 and 2.80; 1.15–6.82, respectively), but not statistically higher than those using single medications (AOR = 1.70). Age, gender, education, marital status, cigarettes per day, time to first cigarette, night smoking, and menthol smoking were not significantly related to abstinence. Varenicline or combination medications did not significantly increase serious psychological distress over the treatment period compared to other medication options.

Conclusions: Both varenicline and combination pharmacotherapy were effective and did not increase psychological distress for up to 6 months in smokers with co-morbidities treated at a specialty clinic.

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1. Introduction

Tobacco dependence treatments significantly increase long-term abstinence, typically in the 20–30% range for 6-month quit rates (Fiore et al., 2008). Currently, 7 tobacco treatment medications are approved by the U.S. Food and Drug Administration (FDA), with varenicline being the first new non-nicotine pharmacotherapy in over 12 years. Early efficacy trials have shown varenicline's superiority to placebo and bupropion (Gonzales et al., 2006; Jorenby et al., 2006). Non-randomized studies also appear to

show benefit compared with single nicotine replacement therapy (NRT) (Stapleton et al., 2008; Aubin et al., 2008), with an acceptable side effect profile up to 24 weeks (Tonstad et al., 2006) and even up to 1 year of use (Williams et al., 2007). Evidence from other studies supports the comparative benefit of varenicline and combination medications over other therapies (Fiore et al., 2008; Cahill et al., 2009; Nides et al., 2008; Steinberg et al., 2009; Piper et al., 2009).

However, numerous case reports of serious adverse events led to boxed-warnings for both varenicline and bupropion regarding potential neuropsychiatric effects (US FDA, 2008). In contrast to these case reports, clinical trials of varenicline have not demonstrated adverse effects on mood, behavior, or suicidality (Tonstad et al., 2010). Relying primarily on trial data alone has limitations in evaluating effectiveness. Smokers with complicated psychiatric and medical conditions are typically excluded from these studies. Practicing clinicians must reconcile the lack of adverse events in clinical trials with the reports in post-marketing use. This study

* Corresponding author at: University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School Division of General Internal Medicine, 125 Paterson Street, Suite 2300, 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).

presents data from a specialized clinic treating smokers with co-occurring conditions and focuses on the effectiveness and adverse psychological events of tobacco dependence treatments, including varenicline.

2. Methods

2.1. Design and setting

This study is a retrospective cohort analysis of 723 smokers treated at the UMDNJ-Tobacco Dependence Clinic from 2006 to 2008 and was approved by the University's Institutional Review Board.

2.2. Participants

842 smokers presenting for treatment were assessed and set a quit date between 7/1/06 and 6/30/08. Of those, 723 patients (86%) entered treatment and were contacted 4 weeks after their quit date. Medication use data were systematically recorded at this 4-week point. As the purpose of the study was to evaluate the effects of medications the patients actually used instead of what they initially planned to use, those who were not contacted at 4 weeks (and whose medication use was therefore unclear) were excluded from the analysis. Nearly all of the excluded patients were only seen for one encounter, so no further data were available on them. Of those who initiated treatment and were contacted 4 weeks, 579 patients (80%) were contacted at 6 months for follow-up. Initial assessment data were collected in-person, 4-week follow-up data were collected in-person, by mail or telephone and 6-month by telephone or mail. For analyses, patients not reached at 6 months were assumed to be smoking.

2.3. Measures

Data collected during the initial assessment included demographics, tobacco use, dependence, medical and psychiatric history, motivation, and treatment preferences for the current quit attempt. In addition, the Kessler-6 (K-6) instrument was used to measure recent psychological distress. Six questions assess psychological distress (nervous, restless, hopeless, everything was an effort, worthless, and sad) with a total score from 0 to 24. Scores above 12 indicate likely serious psychological distress. The K-6 has been used in the U.S. National Health Interview Survey (Pratt et al., 2007), has excellent internal consistency and reliability (Cronbach's $\alpha = 0.89$), has consistent psychometric properties across major socio-demographic sub-samples, and strongly discriminates between community cases and non-cases of DSM IV/SCID disorders (Kessler et al., 2002, 2003; Hagman et al., 2008) making it one of the most reliable screening instruments for psychological distress and mental illness (Cairney et al., 2007).

Follow-up data were collected at 4-weeks and 6-months with the primary outcome being 7-day point abstinence rates (no smoking during the previous 7 days). Exhaled CO levels were measured in all participants seen in-person as confirmation of abstinence (Bedfont-Smokerlyzer-Micro-III). A cutoff value of 10 parts-per-million CO discriminates smokers from nonsmokers with 88% sensitivity and 84% specificity (Jarvis et al., 1987). Among those subjects who attended follow-ups in-person and claimed to be abstinent, 99% had an expired CO less than 10 ppm (Steinberg et al., 2006).

2.4. Treatment

Clinical treatment was based on the US Public Health Service Guidelines (Fiore et al., 2008) and addressed nicotine withdrawal symptoms and behavioral change. A 60-min initial assessment included an individualized treatment plan, setting a quit-date typically within 2 weeks, and evaluation by the medical director who prescribed all medications. All FDA-approved medications were described to the patient, whose self-selected choice was based on dependence, preferences, and medical co-morbidities. Patients were encouraged, but not required, to use medications and attend no-cost counseling sessions designed to enhance motivation, prevent relapse, and encourage problem solving.

Patients used single medications (NRT, bupropion, or varenicline alone) or combination medications (patch and/or bupropion plus spray/inhaler/gum/lozenge) at standard doses. Patients were advised not to reduce medications until experiencing 14 consecutive days without significant cravings, withdrawal symptoms, or lapses to smoking. Thus, short-acting medications were often utilized for extended periods of time, even at minimal doses.

2.5. Statistical methods

Data were analyzed using SPSS Software (Version 16.0). Frequencies of demographic variables are reported. Chi square analyses were used to determine differences between categorical variables, Student's *t*-tests were used to determine differences between continuous variables, and logistic regression was used to calculate adjusted odds ratios with 95% confidence intervals for the primary outcome of tobacco abstinence. Significance was defined as *p*-value <0.05.

3. Results

3.1. Demographics

Characteristics of patients in the study are shown in Table 1. Patients had a mean age of 45 (range 16–78), smoked a mean of 19 cigarettes per day and 52% reported a history of medical problems.

3.2. Treatment characteristics

Ninety-one percent of subjects used cessation pharmacotherapy; most commonly combination pharmacotherapy (39%), followed by single NRT or bupropion (29%), and varenicline (23%). Subjects who were African-American or Hispanic, single, less educated, unemployed, did not have private insurance, and smoked less than 20 cigarettes and at night, were less likely to receive varenicline. Additionally, those who had previous behavioral health treatment were less likely to receive varenicline (28 vs. 20%) and those who met K-6 criteria for serious psychological distress at baseline received combination medications (41%), single NRT (37%), or varenicline (12%). There were no differences in medication groups by other characteristics.

3.3. Abstinence rates – unadjusted

Abstinence rates at 6 months are displayed in Table 1. Overall, 23% of patients were abstinent at 6 months with the remainder reporting continued smoking or if lost to follow-up, classified as smoking. Patients who were older, white, more educated, employed, married, had less behavioral health co-morbidities, and longer time-to-first-cigarette tended towards higher abstinence rates. Abstinence rates by medication used were varenicline 30%, combination medications 25%, single NRT 19%, and bupropion 6%. The most common reason reported for relapse was general stress (17%).

3.4. Abstinence rates – adjusted

Logistic regression was performed for 6-month abstinence (Table 2). In a model controlling for demographic factors, factors of dependence, and factors significantly related to abstinence in univariate analysis, smokers using varenicline or combination medications were more likely abstinent at 6 months than those using no medications (adjusted odds ratio (AOR) = 2.99; 95% confidence-interval (CI) = 1.20–7.47 and 2.80; 1.15–6.81, respectively). In addition, African-American smokers, unemployed, and disabled smokers were less likely to quit (AOR = 0.39; 0.21–0.72; AOR = 0.45; 0.25–0.80; AOR = 0.43; 0.21–0.89, respectively). Similar results were obtained with backward and forward stepwise procedures.

3.5. Assessment of psychological distress

As anticipated, psychological distress at baseline was related to difficulty quitting. The mean baseline K-6 score for smokers who were able to quit at 6 months was significantly lower than those who were not abstinent (mean score = 6.0 vs. 7.0, respectively; $p < 0.05$). Overall among the entire sample, K-6 scores improved from baseline to follow up (mean overall baseline score 6.7 ± 5.4 ; 4-week follow-up 5.0 ± 4.9 ; 6-month follow-up 4.5 ± 5.0). Those patients who used varenicline had similar changes in K-6 scores compared to smokers using other medications (1.6 point improvement for varenicline; 1.8 for other single medications; 2.1 for combination medications; 0.4 for subjects using no medications). Abstinence rates among those with previous behavioral health treatment were generally lower for most medication groups except

Table 1
Demographic characteristics and 6-month abstinence rates; UMDNJ-Tobacco Dependence Clinic; 2006–2008.

Characteristic	No of sample	(% of sample)	6-month abstinence		Significance for 6-month abstinence (univariate analysis)
			n	(%)	
Overall	723	(100)	166	(23)	
Age					NS
<25	37	(5)	7	(19)	
25–39	191	(26)	34	(18)	
40–64	451	(62)	113	(25)	
65+	44	(6)	12	(27)	
Gender					NS
Female	381	(53)	92	(24)	
Male	338	(47)	74	(22)	
Race					P < 0.01
White	423	(59)	115	(27)	
African-American	165	(23)	23	(14)	
Latino	99	(14)	18	(18)	
Other	34	(5)	10	(29)	
Education					NS
Less than High School Diploma	89	(13)	17	(19)	
High School Diploma	197	(28)	49	(25)	
Some College	248	(35)	55	(22)	
College or Graduate Degree	168	(24)	44	(26)	
Employment					P < 0.01
Full	298	(42)	87	(29)	
Unemployed	93	(13)	12	(13)	
Disabled	156	(22)	27	(17)	
Other	156	(22)	38	(24)	
Marital status					P = 0.01
Married/partner	297	(43)	85	(29)	
Divorced/separated	184	(26)	41	(22)	
Single/never	215	(31)	38	(18)	
Cigarettes per day					NS
Less than 20	326	(45)	81	(25)	
20 or more	397	(55)	85	(21)	
Time to first cigarette upon waking					P = 0.08
Within 5 min	352	(49)	70	(20)	
6–30 min	260	(36)	63	(24)	
Greater than 30 min	111	(15)	33	(30)	
Wake up at night to smoke					P < 0.01
Yes	324	(46)	58	(18)	
No	386	(54)	106	(28)	
Smoke menthol					P = 0.06
Yes	331	(48)	66	(20)	
No	361	(52)	94	(26)	
Current diagnosis of					
Depression	210	(29)	42	(20)	NS
Anxiety	149	(21)	32	(21)	NS
Schizophrenia	39	(5)	5	(15)	NS
Bipolar disorder	65	(9)	12	(18)	NS
Substance dependence	114	(16)	15	(13)	P < 0.05
Heart disease	85	(12)	25	(29)	NS
Hypertension	167	(23)	42	(25)	NS
Diabetes	91	(13)	22	(24)	NS
High cholesterol	181	(25)	55	(30)	P = 0.01
Ever treated for behavioral health problem	374	(53)	78	(21)	NS
Ever treated for substance abuse problem	215	(31)	37	(17)	P = 0.01
Meets K-6 criteria for serious psychological distress at baseline	98	(15)	15	(15)	P < 0.01
Medications used					P < 0.01
No medications	65	(9)	7	(11)	
Single NRT	192	(27)	37	(19)	
Bupropion alone	16	(2)	1	(6)	
Varenicline alone	168	(23)	51	(30)	
Combination medications*	278	(39)	70	(25)	

NS, no significant statistical difference between subgroups.

* Combination medications include multiple NRT's or NRT plus bupropion (e.g. patch and/or bupropion plus spray/inhaler/gum/lozenge).

varenicline (36% with previous behavioral treatment vs. 26% with no previous behavioral treatment). Abstinence rates among those who met criteria as K-6 cases (score > 12) were lower in most medication groups except for the varenicline group (33% cases vs. 32% non-cases).

There were a total of 19 cases of subjects who did not meet criteria for serious psychological distress at baseline but met criteria at the 4-week follow-up. Of those, 1 (1.5% of those using) used no med-

ications; 1 (1.5%) used bupropion; 8 (3.8%) used single NRT; 3 (1.8%) used varenicline; and 6 (1.4%) used combination medications. There was no distinct pattern for becoming severely psychologically distressed at 4-weeks based on medication treatments used.

4. Discussion

This study suggests that varenicline and combination pharmacotherapies (multiple NRTs and NRT plus bupropion) are

Table 2
Adjusted odds ratios for 6-month Abstinence; UMDNJ-Tobacco Dependence Clinic; 2006–2008.

Variable	Adjusted odds ratio	95% Confidence interval
Age		
Less than 25	Referent	
25–39	0.85	0.31–2.28
40–64	1.46	0.54–3.92
65 and older	1.49	0.41–5.39
Gender		
Male	Referent	
Female	1.39	0.93–2.10
Race		
White	Referent	
African-American	0.39	0.21–0.72
Latino	0.65	0.33–1.27
Other	1.18	0.45–3.10
Marital status		
Married/partner	Referent	
Divorced/separated	1.00	0.61–1.64
Single/never	0.87	0.52–1.46
Education		
Less than High School Diploma	Referent	
High School Diploma	1.31	0.64–2.71
Some College	0.90	0.43–1.86
College/Graduate Degree	0.84	0.39–1.79
Employment		
Full	Referent	
Unemployed	0.45	0.25–0.80
Disabled	0.43	0.21–0.89
Other	0.80	0.48–1.34
Cigarettes per day		
Less than 20	Referent	
20 or more	0.74	0.48–1.15
Time to first cigarette upon waking		
Within 5 min	Referent	
6–30 min	1.25	0.80–1.95
Greater than 30 min	1.42	0.79–2.57
Night smoking		
No	Referent	
Yes	0.80	0.51–1.24
Smoke menthol products		
No	Referent	
Yes	1.02	0.66–1.58
Medication used		
No medications	Referent	
Single NRT or Bupropion alone	1.70	0.68–4.26
Varenicline alone	2.99	1.20–7.47
Combination medications*	2.80	1.15–6.82

Regression model included: age, gender, race, education, cigarettes per day, time to first cigarette, employment, marital status, night smoking, and menthol smoking. Results were similar with forward and backward stepwise procedures.

* Combination medications include multiple NRT's or NRT plus bupropion (e.g. patch and/or bupropion plus spray/inhaler/gum/lozenge).

effective treatments over 6-month-follow-up in smokers presenting to a tobacco treatment clinic and found no evidence of adverse psychological effects for either treatment during the study period. As both varenicline and combination medications had non-statistically higher adjusted odds ratios than other single medications (AOR = 2.99 and 2.80 vs. 1.70), our findings support current recommendations to consider varenicline and combination pharmacotherapy as first line treatments, especially among highly dependent smokers (Fiore et al., 2008).

Concerns remain regarding the potential risk from neuropsychiatric adverse events for varenicline despite recent reports from large cohorts of primary care patients indicating no significant evidence of increased suicide (Hazard ratio (HR) = 1.12; 95% CI = 0.67–1.88) or depression (HR = 0.88; 0.77–1.00) in smokers prescribed varenicline compared with NRT (Gunnell et al., 2009). Confounding the issue of psychological distress and quitting smoking are the effects of cessation itself on mood. When smokers abstain from nicotine they experience a group of nicotine

withdrawal symptoms including unpleasant mood states (irritability, anxiety, depression, restlessness) but also poor concentration, hunger and sleep disturbance. The severity of these symptoms typically peaks in the first week and returns to baseline within 4 weeks (Hughes, 2007). Studies have found that stopping smoking causes clinically significant psychological distress in untreated smokers (Hughes, 2006). Considering that depressed mood is a chief nicotine withdrawal symptom, a follow-up plan is essential for all smokers attempting to quit, regardless of the medication used (Fiore et al., 2008). This is consistent with the understanding that tobacco dependence is a chronic condition which prescribers should treat as they do other conditions, such as diabetes and hypertension (Steinberg et al., 2008).

The characteristics of this sample make our findings useful for the practicing clinician by including smokers with significant psychiatric and medical co-morbidity. The results show that smokers using varenicline or combination medications did not have any worsening of psychological distress as measured by a standardized instrument. Our study has some limitations. First, we only had uniform medication data at week 4, thus limiting our subject inclusion. Although the study achieved an 80% follow-up rate on these subjects (69% overall), it is unclear what neuropsychiatric effects that those who were lost to follow up by 6 months may have experienced. It should be noted that few subjects who were taking varenicline at 4 weeks were lost to follow-up at 6 months (approximately 3%). Second, our abstinence rates were largely determined by self-report at 6 months. As previously published, we have found a 99% consistency between self-reported abstinence and CO-confirmation among subjects attending appointments at our clinic (Steinberg et al., 2006). However, we acknowledge the possibility of lower concordance with telephone follow-ups. Finally, as this was a clinical service, patients received medications based on clinical criteria and were not randomly allocated to treatment. Therefore, some of the observed effects could have been due to differences in medication treatment groups that were not controlled for.

Tobacco dependence represents the leading cause of preventable death in our society and this study supports previous findings that varenicline and combination pharmacotherapies are effective treatments in smokers with co-morbidities. Regardless of the treatment utilized, all smokers seeking assistance should have adequate screening for medical and psychiatric issues and appropriate follow-up that includes monitoring of mood and behavior.

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Conflict of interest

All authors have indicated their status as consultants or contractors for any company that is involved in cessation pharmacotherapy within the past 3 years below: MS has conducted clinical research supported in part by various organizations including Pfizer and has previously served on a speakers' bureau for Pfizer (2006–2008); JF was previously on a speakers' bureau for Pfizer and has previously worked as a paid consultant for pharmaceutical companies (Pfizer, Novartis, GSK, Celtic Pharma). He currently serves on the nicotine dependence advisory committee for Pfizer and Novartis (without personal compensation); JW has conducted clinical research supported in part by Pfizer and is consultant for Novartis and BeBetter Inc.; All other authors declare that they have no conflicts to report.

Contributors

M.S., M.B., J.F. designed the study protocol and analyses; M.S., D.R., J.F., J.W. conducted data collection; M.S., M.B., A.S., J.F. were involved in data analyses; M.S., A.S., J.F. were involved in literature searches and summary; All authors were involved in manuscript writing and revisions.

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