National PBM Drug Monograph

Varenicline (Chantix™)

December 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Efficacy

- Varenicline is a new class of drug, an α4β2 neuronal nicotinic acetylcholine receptor partial agonist that binds in the central nervous system and produces low to moderate levels of dopamine, mimicking nicotine's effect and reducing withdrawal symptoms.
- It also acts as an antagonist, blocking the binding of nicotine and therefore the positive reinforcement obtained through smoking.
- In two identical double-blind trials comparing varenicline to both bupropion sustained-release and placebo, varenicline produced statistically significant increases in continuous abstinence rates during the final 4 weeks of the trial.
- In a trial assessing the usefulness of maintenance therapy with varenicline for an additional 12 weeks if patients were successful in obtaining abstinence by week 12 of initial therapy, varenicline maintenance reduced relapse rates at the end of weeks 24 and 52 compared to placebo.

Safety

- Varenicline was well tolerated. The most common adverse events were nausea, headache, abnormal dreams, constipation, and vomiting
- Nausea occurred in up to 30% of patients, was generally mild to moderate and lasted less than 12 days, although it did last for several months in some patients.
- Initial titration of the varenicline dose appears to be useful in limiting some of the nausea.
- Dropouts due to adverse events accounted for 8-12% of patients in the large clinical trials.

Cost

- Varenicline costs almost twice that of nicotine patches and almost 3 times the price of bupropion SR for one year quit rates of approximately 28-30% versus 23% with bupropion SR; maintenance therapy increases quit rates to 43% and doubles the price.

Recommendations

- Varenicline should not be used as first-line therapy. It is effective in young healthy patients but there is few data in patients like those we serve.
- It should be restricted to use in patients who have failed on NRT and/or bupropion or in whom bupropion is contraindicated.
- The unresolved question is if it is more effective than bupropion and by how much.
- Monitor serum creatinine levels. As renal function decreases (as seen in elderly patients), dose reductions may be necessary.

Outcomes and adverse events in the VA population should be evaluated prospectively as our population was not highly represented in clinical trials.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating varenicline for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Varenicline is a synthetic derivative from the plant alkaloid cytisine. It acts as a partial agonist at the α4β2 neuronal nicotinic acetylcholine receptor. The α4β2 neuronal nicotinic acetylcholine receptor releases dopamine in the central nervous system, and activation is thought to mediate dependence, including reinforcement, tolerance, and sensitization of the receptor. As a partial agonist, varenicline binds to the receptor and produces low to moderate levels of dopamine release that reduces craving and withdrawal symptoms. At the same time, varenicline acts as an antagonist, blocking the binding and positive reinforcement effects of smoked nicotine.

Table #1 Pharmacokinetic Parameters

Parameter	Drug
Metabolism	Minimal; 92% excreted unchanged
Elimination	Primarily renal via glomerular filtration and tubular secretion
Half-life	24 hours
Protein Binding	PPB ≤20%
Bioavailability	Virtually complete and unaffected by food or time of day

Special Populations:
Renal Impairment- Pharmacokinetic were unchanged in patients with mild renal impairment (creatinine clearance >50 mL/min and ≤80 mL/min). In patients with moderate renal impairment (creatinine clearance ≥30 mL/min and ≤50 mL/min), exposure to varenicline increased 1.5 fold compared to patients with normal renal function. Exposure rates in patients with creatinine clearances <30 mL/min were increased 2.1 fold. Patients receiving varenicline 0.5mg every day while on hemodialysis three times a week had exposure rates increased 2.7 fold. Varenicline is removed by hemodialysis.

Geriatric- Pharmacokinetics in 16 smoking but healthy elderly patients for single dose or multidose studies for 7 days found pharmacokinetic parameters similar to younger patients.

Pediatric: The safety and efficacy of varenicline in pediatric patients has not been studied. Single dose pharmacokinetic studies in 22 pediatric patients aged 12-17 found proportional pharmacokinetics between the 0.5mg and 1mg doses. Area under the curve and clearance of varenicline were comparable to those found in adults.

Hepatic impairment- Varenicline pharmacokinetics should not be affected by hepatic insufficiency because of an absence of significant hepatic metabolism.

FDA Approved Indication(s) and Off-label Uses

Varenicline is approved as an aid to smoking cessation treatment.

Current VA National Formulary Alternatives

Nicotine patches (restricted to VA/DoD Clinical Practice Guidelines)
Nicotine gum (restricted to VA/DoD Clinical Practice Guidelines)
Nicotine lozenge (restricted to patients unable to use or tolerate gum and to VA/DoD Clinical Practice Guidelines)
Bupropion IR

Dosage and Administration

Varenicline should be taken after a meal with a full glass of water.

The recommended dose titration is as follows:

Days 1-3	0.5 mg once a day
Days 4-7	0.5 mg twice a day
Days 8-end of therapy	1 mg twice a day

Doses may be lowered temporarily or permanently in patients who cannot tolerate adverse effects of varenicline therapy.

Treatment should continue for 12 weeks. An additional 12 weeks of therapy may be considered for those patients who have successfully stopped smoking by week 12.

Dosing in Impaired renal function: No adjustments needed for mild or moderate renal impairment. For patients with severe renal impairment, the starting dose is 0.5mg once daily, titrated up to 0.5 mg twice a day. In patients on hemodialysis, the maximum dose is 0.5mg once a day as tolerated.

Dosing in elderly patients and patients with impaired hepatic function: No adjustments needed for impaired hepatic function. Elderly patients may have decreased renal function so care should be taken in selecting a dose, and renal function should be monitored regularly.

Efficacy

Efficacy Measures

Primary Outcomes:
1. Continuous abstinence weeks 9-12 of study treatment
2. Continuous abstinence for any 4 weeks of a 7 week trial
3. Continuous abstinence weeks 13-24 of maintenance therapy

Secondary Outcomes:
1. Continuous abstinence weeks 9-24 and weeks 9-52
2. 7 day point prevalence abstinence rates at weeks 12, 24, and 52
3. Continuous abstinence rates weeks 13-52 with maintenance therapy

Summary of efficacy findings[3,4,5,6,7]

- There were six clinical trials evaluating the efficacy of varenicline in smoking cessation.
- The first trial was a six week dose finding trial.
- The sixth study evaluated the maintenance therapy in relapse prevention.
- Abstinence was determined by patients self-report and verified by exhaled carbon monoxide.
- In all studies, patients were provided written educational material and up to 10 minutes of smoking cessation counseling at each visit.
- A target quit date was set and treatment started 1 week prior to that date.
- Equal numbers of males and females were enrolled; 79-96% of patients were white; the average age was 43, and on average patients smoked about 21 cigarettes per day.
- The primary outcome for studies 2-5 was continuous abstinence for weeks 9-12 of the 12 week treatment cycle.
- Secondary outcomes were continuous abstinence weeks 9-24 and weeks 9-52.

- 7-day point prevalence abstinence rates were reported in order to facilitate comparisons with existing smoking cessation literature.

Table #2 Continuous Abstinence Weeks 9-12

	Varenicline 0.5mg BID	Varenicline 1mg BID	Varenicline Flexible	Bupropion SR 150mg BID	Placebo
Study 2 (95%CI)	45% (39, 51)	51% (44 ,57)			12% (6, 18)
Study 3 (95%CI)			40% (32, 48)		12% (7, 17)
Study 4 (95%CI) OR 95%CI P		44% (38, 49) 3.85* 2.7, 5.50 <0.001		30% (25, 35) 2.00** 1.38, 2.89 <0.001	17% (13, 22)
Study 5 (95%CI) OR 95%CI P		44% (38, 49) 3.85 2.69, 5.50 <0.001		30% (25, 35) 1.9 1.38, 2.62 <0.001	18% (14, 22)

*varenicline versus placebo; ** varenicline versus bupropion

Table #3 Continuous Abstinence Weeks 9-52

	Varenicline 0.5mg BID	Varenicline 1mg BID	Varenicline Flexible	Bupropion SR 150mg BID	Placebo
Study 2 (95%CI)	19% (14, 24)	23% (18, 28)			4% (1, 8)
Study 3 (95%CI)			22% (16, 29)		8% (3, 12)
Study 4 (95%CI) OR 95%CI P		21% (17, 26) 3.09* 1.95, 4.91 <0.001		16% (12, 20) 1.46** 0.99, 2.17 0.057	8% (5, 11)
Study 5 (95%CI) OR 95%CI P		22% (17, 26) 2.66 1.72, 4.11 <0.001		14% (11, 18) 1.77 1.19, 2.63 0.004	10% (7, 13)

*varenicline vs placebo; **varenicline vs bupropion

Table #4 Seven-Day Abstinence Point Prevalence

	Varenicline 1mg BID	Bupropion SR 150mg BID	Placebo
Study 4			
Week 12	50.3%	35.9%	21.2%
P	<0.001*	<0.001**	
Week 24	33.5%	24.9%	14.5%
P	<0.001	0.01	
Week 52	28.1%	22.8%	14%
P	<0.001	0.13	
Study 5			
Week 12	50.3%	36.3%	20.8%
OR vs placebo	4.06	2.21	
95%CI	2.88, 5.73	1.56, 3.13	
P	<0.001	<0.001	
OR vs bupropion	1.84		
95%CI	1.34, 2.51		
P	<0.001		
Week 24	35.2%	26.3%	17.9%
OR vs placebo	2.59	1.67	
95%CI	1.8, 3.72	1.15, 2.42	
P	<0.001	0.007	
OR vs bupropion	1.56		

95%CI	1.11, 2.17		
P	0.009		
Week 52	30.5%	23.4%	17.3%
OR vs placebo	2.14	1.46	
95%CI	1.48, 3.09	1.00, 2.14	
P	<0.001	0.03	
OR vs bupropion	1.46		
95%CI	1.04, 2.06		
P	0.05		

*varenicline vs placebo; **varenicline vs bupropion

- Study 6 assessed the efficacy of an additional 12 weeks of varenicline therapy on long term abstinence
- All patients received varenicline for 12 weeks; only those who had stopped smoking by Week 12 were then randomized to 12 additional weeks of varenicline or placebo.

Table #5 Continuous Abstinence with Maintenance Therapy

	Varenicline	Placebo
Week 13	95.5%	88.5%
Week 24	70.5%	49.6%
OR weeks 13-24	2.48	
95%CI	1.95, 3.16	
P	<0.001	
Week 25	67.7%	48.3%
Week 52	43.6%	36.9%
OR weeks 13-52	1.34	
95%CI	1.06, 1.69	
P	0.02	

- On the Minnesota Nicotine Withdrawal scale, patients in studies 4 and 5 receiving varenicline or bupropion reported statistically significant decreases on the "urge to smoke" item compared to placebo.
- On the Brief Questionnaire of Smoking Urges, varenicline and bupropion treated patients reported statistically significantly lower scores compared to placebo.
- On the Smoking Reinforcement-Modified Cigarette Evaluation Questionnaire use in patients who reported smoking cigarettes while on therapy, varenicline blocked the pleasurable affects of nicotine in both studies 4 and 5. Bupropion blocked some of the satisfaction from smoking in one study but not in the other study.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Adverse Events (Safety Data)

Table #6: Common Treatment Emergent Adverse Events (%) from fixed-dose, placebo controlled trials

Organ System	Varenicline 0.5mg BID N=129	Varenicline 1mg BID N=821	Placebo N=805
Gastrointestinal			
Nausea	16	30	10
Abdominal pain	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
Constipation	5	8	3
GERD	1	1	0
Dry mouth	4	6	4
Psychiatric Disorders			
Insomnia	19	18	13
Abnormal dreams	9	13	5

Sleep disorder	2	5	3
Nightmare	2	1	0
Nervous System			
Headaches	19	15	13
Dysguesia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
General			
Fatigue, malaise, asthenia	4	7	6
Respiratory			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper respiratory tract disorder	7	5	4
Skin			
Rash	1	3	2
Pruritis	0	1	1
Metabolism			
Increased appetite	4	3	2
Decreased appetite/anorexia	1	2	1

Common Adverse Events
Nausea, sleep disturbance, headache, abnormal dreams, constipation, flatulence, vomiting

Tolerability
Varenicline was discontinued due to adverse events in approximately 8% of patients in clinical trials; this was similar to placebo and less than in bupropion treated patients.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Precautions/Contraindications

Precautions
1. General
Nausea was the most common adverse event in varenicline clinical trials. It was described as mild or moderate and generally transient (≤12 days), although it lasted several months for some patients. The incidence rate was dose related, and initial titration of the dose was helpful in decreasing the rate of nausea. Approximately 3% of patients discontinued varenicline treatment due to nausea. For intolerable nausea, a dose reduction can be considered.

2. Effect of smoking cessation
Smoking cessation can cause physiologic changes that alter the pharmacokinetics or pharmacodynamics of some drugs, especially drugs affected by liver enzyme metabolism (e.g. theophylline, warfarin, and insulin).

3. Carcinogenesis, Mutagenesis, Fertility
Carcinogenesis was not demonstrated in mice receiving varenicline up to 2 years. In male rats, brown fat tumors developed at an increased incidence when given doses 23-67 times the maximum human dose. This was not seen in female rats. The clinical relevance in humans is unknown.
Mutagenesis was not demonstrated in standard assays or *in vivo* in rat marrow or *in vitro* in human lymphocytes.
No evidence of impaired fertility was seen in either male or female rats. A decrease in fertility was seen in the offspring of pregnant rats given varenicline at doses 36 times the maximum human dose, but was not evident in offspring of female rats treated at doses 9 times the maximum human dose.

4. Pregnancy Category: C

5. Nonteratogenic effects

Varenicline, when given to pregnant rabbits caused reduced fetal weights at doses 50 times the maximum human dose but did not reduce fetal weights at doses 23 times the maximum human dose. The offspring of pregnant rats and in increase in auditory startle response at doses 36 times the maximum human dose.

6. Nursing Mothers
It is not known if varenicline is excreted in human breast milk, but it has been transferred to nursing pups.

7. Pediatric Use
Safety and efficacy has not been established in patients under the age of 18.

8. Geriatric Use
A single and multidose pharmacokinetic study in 16 healthy elderly adult smokers found not pharmacokinetic parameters similar those of younger subjects. No differences in efficacy or safety were demonstrated in clinical trials, but cannot be ruled out.
Because varenicline is excreted by the kidney and the elderly are more likely to have impaired renal function, the risk of adverse events might be greater in these patients. Care should be taken in dose selection; careful monitoring of renal function may be useful.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
LA/SA for generic name varenicline:
LA/SA for trade name Chantix:

Drug Interactions

Drug-Drug Interactions

No meaningful drug drug interactions have been identified. Varenicline interactions have been studied with digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin.

Metformin: varenicline did not alter steady state pharmacokinetics of metformin, a substrate of OCT2. Metformin did not affect varenicline pharmacokinetics.
Cimetidine: cimetidine increased varenicline exposure in 12 smokers by 29% due to reduction in renal clearance.
Digoxin: Varenicline did not alter digoxin pharmacokinetics in 18 smokers.
Warfarin: Varenicline did not alter single dose warfarin pharmacokinetics or INR.

Bupropion: Varenicline did not alter the pharmacokinetics of bupropion in 46 smokers. Safety of the combination has not been studied.
Nicotine replacement therapy (NRT): Varenicline did not affect nicotine pharmacokinetics, but co-administration produced higher rates of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue.

Data Compilation Tables

Table # 7 Seven-Day Point Prevalence for Abstinence

Drug	Estimated Abstinence Rate (6 months)	Estimated Odds Ratio vs placebo (95%CI)
Varenicline	35%	2.59 (1.8, 3.72)
Nicotine patch	17.7%	1.9 (1.7, 2.2)
Nicotine gum	23.7%	1.5

		(1.3, 1.8)
Bupropion SR	30.5%	2.1 (1.5, 3.0)

Acquisition Costs

Table #8 Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/4 weeks/patient ($)	Cost/12 weeks/patient ($)
Varenicline	0.5mg -1mg twice a day	2.40	67.06	201.18
Bupropion SR	150mg BID	0.92	25.76	77.28
Bupropion IR	50mg TID	0.42	11.76	35.28
Nicotine patch	21mg/ day	1.48	41.44	124.32
Nicotine gum	4mg	2.72	76.16	228.48
Nicotine lozenge	2-4 mg	6.56	183.68	551.04

Pharmacoeconomic Analysis

There are no published pharmacoeconomic models for varenicline therapy. A model developed by Pfizer examined the costs of using smoking cessation drugs and included costs for smoking-related diseases. Their model found that varenicline was more cost effective than nicotine replacement therapy or branded or generic bupropion due to cost offsets from decreased health care costs within 2-5 years.

Conclusions

Efficacy

- In two identical double-blind studies comparing varenicline to placebo and bupropion in healthy adult smokers, varenicline treated patients had a higher abstinence rate for weeks 9-12 of therapy compared to both bupropion and placebo.
- Odds ratios for continuous abstinence for weeks 9-52 were statistically higher for varenicline versus both bupropion and placebo in one trial, but the confidence intervals for the varenicline group and bupropion group had some overlap. The odds ratio between varenicline and bupropion in the second trial did not reach statistical significance.
- Drop-out rates in both trials were high, but similar to other smoking cessation trials. In the varenicline group, 65% of patients completed the entire follow-up. This was higher than in the other groups and may have biased the results in favor of varenicline as all drop outs are treated as relapses.
- In patients who were abstinent by week 12 of an open-label trial, maintenance therapy with 12 more weeks of varenicline produced higher continuous abstinence rates at week 24 and a smaller but statistically significant difference at week 52 than in patients who received placebo maintenance therapy.
- Generalizability of the data is made difficult by the numerous inclusion and exclusion criteria that limited enrollment to relatively healthy smokers.

Safety

- The most common adverse event reported was nausea in up to 30% of patients. The median duration was less than or equal to 12 days, but the upper range includes several months of mild to moderate nausea. Initial titration of the dose may be helpful in limiting the extent of nausea.
- Headache and abnormal (vivid) dreams were more likely in the varenicline group.

- The numbers of serious adverse events in each group was small and one patient developed atrial fibrillation attributed to varenicline.
- No deaths occurred during the two identical phase III trials.

Cost

- Varenicline costs almost twice that of nicotine patches and approximately 3 times that of generic bupropion SR.
- At the end of 1 year, 7-day point prevalence rates for abstinence in 2 clinical trials found that varenicline produces long term quit rates in approximately 28-30% of patients compared to 23% in the bupropion SR group. Adding 12 more weeks of maintenance therapy would increase quit rates to 43% at a cost 4 times that of nicotine patches and 6 times that of generic bupropion SR.

Recommendations and Place in Therapy

- Varenicline should not be used as first-line therapy. It is effective in young healthy patients but there is few data in patients like those we serve.
- It should be restricted to use in patients who have failed on NRT and/or bupropion or in whom bupropion is contraindicated.
- The unresolved question is if it is more effective than bupropion and by how much.
- Monitor serum creatinine levels. As renal function decreases (as seen in elderly patients), dose reductions may be necessary.

Outcomes and adverse events in the VA population should be evaluated prospectively as our population was not highly represented in clinical trials.

References

[1] Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. Int J Clin Prac 2006;60: 571-76.

[2] Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, Huang J, et al. Varenicline: an α4β2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005; 48:3474-3477.

[3] Nides M, Oncken C, Gonzalez D, Rennard S, Watsky EJ, Anziano R, reeves KR. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with a 1-year follow-up. Arch Intern Med 2006; 166:1561-68.

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[5] Gonzales D, Rennard S, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296:47-55.

[6] Jorenby DE, Hays JR, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an αβ2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled tria. JAMA 2006; 296:56-63.

[7] Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves, KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006; 296:64-71.

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Appendix: Clinical Trials

Include a brief description of the methods used to perform the literature search (database, period, search strategy), inclusion criteria for studies, and sources of any other pertinent information on clinical trials (e.g., review of reference lists, manufacturer's formulary and AMCP dossier, medical reviews and transcripts on FDA Web site; conference abstracts—last resort if information is lacking or abstract is of major importance, etc.) This paragraph is optional. For example:

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms <generic name> and <trade name>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Insert text here.

A summary of relevant clinical trials is presented in this section utilizing the example chart formats below. Randomized, placebo-controlled, blinded trials (Grade A evidence) should be reviewed in detail. If available, head-to-head trials against formulary or standard treatments are desired. Trials of low evidence (i.e. open-label, non-comparative, abstract form) should be mentioned with brief synopsis without going into great detail. For reviews including multiple trials a table or chart outlining level of evidence, results of primary efficacy measures and safety data is recommended for easier visual comparison.

Appendix Table #1: Varenicline Clinical Trials

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Jorenby 2006 R, DB, PC Continuous abstinence during last 4 weeks of treatment(Primary) and thru follow up (secondary) Varenicline Phase 3 Group Funding by Pfizer	Inclusion criteria 1. ≥10 cigarettes/d in past year 2. No abstinence >3 mos in past year 3. Age 18-75 Exclusion criteria 1. Previous use of bupropion 2. contraindication to bupropion (seizure history, eating disorder, MAOI in past 14 days, hepatic or renal impairment, diabetes requiring insulin, oral hypoglycemics) 3. Serious or unstable disease in past 6 months 4. Clinically significant CV disease in recent 6 mos 5. Uncontrolled hypertension 6. Baseline systolic >150 or diastolic >95 7. Severe COPD 8. History of cancer 9. Clinically significant allergic reactions 10. BMI <15 or >38 11. weight <45kg 12. History of alcohol or drug abuse in previous 12 mos 13. Treatment for major depression in past 12 mos 14. History or current panic disorder, psychosis, or bipolar disorder 15. Use of NRT,	Varenicline 1mg p.o. twice a day or Bupropion SR 150mg twice a day (initial dose titration to full strength during 1st week for both drugs) or Placebo twice a day For 12 weeks	V 344 / B 342 / P 341 M%: 55.2 / 60.2 / 58.1 Age: 44.6 / 42.9 / 42.3 Race White%: 85.5 / 82.7 / 85 Cigs/d: 22.5 / 21.8 / 21.5 Fagerstrom Score (0-10): 5.39 / 5.39 / 5.16	N_R = 1027 V N=343 / B N=340 / PBO N=340 Wk 12 7-d abstinence Point prev%: 50.3 / 36.3 / 20.8 OR 1 95%CI P1 (v pbo): 4.06 2.88,5.73 <0.001 / 2.21 1.56,3.13 <0.001 OR 2 95%CI P2 (v bup): 1.84 1.34,2.51 <0.001 Wk 24 7-d abstinence Point prevalence%: 35.2 / 26.3 / 17.9 OR 1 95%CI P1 (v pbo): 2.59 1.8,3.72 <0.001 / 1.67 1.15,2.42 0.007 OR 2 95%CI P2 (v bup): 1.56 1.11,2.17 0.009 Wk 52 7-d abstinence Point prev%: 30.5 / 23.4 / 17.3 OR 1 95%CI P1 (v pbo): 2.14 1.48,3.09 <0.001 / 1.46 1.00,2.14 0.03 OR 2 95%CI: 1.46 1.04,2.06	Serious Adverse Events During 12 weeks of therapy 1. Varenicline Cancer, acute coronary syndrome, chest pain, dehydration, periorbital cellulitis, acute psychosis, emotional lability, worsening vertigo, elevated blood pressure, chest pain 2. Bupropion Ectopic pregnancy, angioedema, gunshot wound to left shoulder, post-op bleeding, right leg pain below the knee, breast cancer Serious Adverse Events during follow-up. 1. Varenicline Staph cellulitis, acute psychosis 2. Bupropion Occlusion coronary artery, fatal motorcycle accident, miscarriage Discontinuation # of patients discontinuing therapy by treatment assignment: Varenicline: 83 Bupropion: 100 Placebo: 118

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
	nortriptyline, clonidine in previous month 16. Pregnancy				

P2 (v bup)	0.05		

Continuous Abstinence

	V (vs B)	V (vs PBO)	B (vs PBO)
Wk 9-12 OR 95%CI P	1.9 1.38,2.62 <0.001	3.85 2.69,5.50 <0.001	2.02 1.4,2.92
Wk 9-24 OR 95%CI P	1.69 1.19,2.42 0.003	2.83 1.91,4.19 <0.001	
Wk 9-52 OR 95%CI P	1.77 1.19,2.63 0.004	2.66 1.72,4.11 <0.001	1.5 0.94,2.39 0.08

Discontinuation

	Var	Bup	PBO
Treatment Phase (no.)	83	100	118
Follow-up Phase (no.)	20	19	18
Completed study	240	221	222

Withdrawal Symptoms & Craving Wks 1-7

	Difference in symptoms compared to placebo 95%CI	P value

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results			Safety Results
				Minnesota Nicotine Withdrawal Scale Varenicline			
				Urge	-0.48	<0.001	
				Neg Affect	-0.13	0.001	
				Restless	-0.1	0.05	
				↑appetite	-0.07	0.22	
				Insomnia	0.10	0.07	
				BupropionSR			
				Urge	-0.38	<0.001	
				Neg Affect	-0.13	0.001	
				Restless	-0.07	0.16	
				↑appetite	-0.07	0.23	
				Insomnia	0.20	<0.001	
				Brief Questionnaire of smoking urges Varenicline			
				Total craving	-0.44	<0.001	
				F1-Pleasure	-0.56	<0.001	
				F2 Neg affect relief	-0.27	<0.001	
				Bupropion			
				Total craving	-0.34	<0.001	
				F1-Pleasure	-0.42	<0.001	
				F2 Neg affect relief	-0.21	<0.001	
				Modified Cigarette Evaluation Varenicline			
				-Satisfaction	-0.44	<0.001	
				-Psy reward	-0.32	<0.001	
				-Resp Tract	-0.22	0.01	
				-↓Craving	-0.25	0.04	

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results

-Aversion	0	0.96
Bupropion		
-Satisfaction	-0.32	<0.001
-Psy reward	-0.28	<0.001
-Resp Tract	-0.13	0.14
-↓Craving	-0.15	0.21
-Aversion	0.10	0.21

Mean Weight Gain in 12 weeks
Varenicline: 2.29kg
Placebo: 1.52kg
Bupropion: 1.32kg

Gonzales 2006
R, DB, parallel-group, PC, Phase III

Carbon monoxide-confirmed 4 week abstinence for weeks 9-12 (primary)
Continuous abstinence weeks 9-24 and from weeks 9-52(secondary)

Varenicline Phase III Study Group

Funding by Pfizer

Recruitment via media advertising
Inclusion:
1. 18-75yo
2. ≥10 cigarettes/day
3. < 3months of abstinence in past year
4. Motivated to stop smoking

Exclusion:
1. Serious or unstable disease w/I 6 months
2. Seizure risk
3. Diabetes requiring treatment
4. hepatic or renal impairment
5. Clinically significant CV disease w/i 6 months
6. uncontrolled hypertension
7. Severe COPD
8. H/o cancer
9. H/d clinically significant allergic reactions
10. Major depression requiring treatment in past

1. Varenicline titrated over 1 week to 1 mg twice a day through week 12
2. Bupropion SR titrated over 1 week to 150mg twice a day through week 12
3. Placebo twice a day

Smoking cessation self-help guide, telephone visit 3 days post quit date, weekly visits with brief counseling during 12 weeks of therapy

	V N=352	B N=329	P N=344
Age	42.5	42	42.6
Men%	50	58.4	54.1
White%	79.5	80.2	76.2
Yrs smoked	24.3	24.1	24.7
Cigs/d	21.1	21	21.5
Fagerstrom Score (0-10)	5.18	5.19	5.38
≥1 prior attempt %	84.4	86.3	83.7
-with NRT	48.3	45.9	43.9

N=1025
Continuous Abstinence

	Var vs B	Var vs P	Bup vs P
Week 9-12			
OR	1.93	3.85	2.00
95%CI	1.4, 2.68	2.7, 5.5	1.38, 2.89
P	<0.001	<0.001	<0.001
Week 9-24			
OR	1.63	3.68	
95%CI	1.14,2.33	2.42,5.6	
P	0.007	<0.001	
Week 9-52			
OR	1.46	3.09	
95%CI	.99, 2.17	1.95,4.91	
P	0.057	<0.001	

7-day Point Prevalence

	Var	Bup	PBO
Week 12 prev %	50.3	35.9	21.2
P(vs p)	<0.001		
P(vs B)	<0.001		
Week 24 prev%	33.5	24.9	14.5
P(vs p)	<0.001		

Serious Adverse Events during first 12 weeks:
Varenicline: abdominal pain, atrial fibrillation, pneumonia, possible stroke

Bupropion: cholecystitis and septic shock, headache, grand mal seizure

Placebo: lung cancer, acute myocardial infarction, schizophrenia exacerbation, chest pain, urinary tract infection, atrial fibrillation, chest pain

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results

year
11. H/o panic disorder, psychosis, bipolar disorder, or eating disorder
12. Alcohol or drug abuse/dependency in past year
13. Use of tobacco products other than cigarettes
14. Use of nicotine replacement, clonidine, or nortriptyline w/i month prior to enrollment
15. BMI <15 or >38 or weight less than 45.5kg
16. Prior exposure to bupropion
17. Pregnancy, nursing, or not using effective contraception

P(vs B)	0.01		
Week 52 prev% P(vs p) P(vs B)	28.1 <0.001 0.13	22.8	14

Discontinuation

	Var	Bup	PBO
Treatment Phase (no.)	90	104	129
Follow-up Phase (no.)	46	41	28
Completed Study	213	184	187

Craving, Withdrawal, Satisfaction

	Difference vs placebo	P value
Minnesota Nicotine Withdrawal Scales		
Varenicline		
-Urge	-0.54	<0.001
-Neg affect	-0.19	<0.001
-Restless	-0.14	<0.01
-↑appetite	0.12	0.04
-Insomnia	0.05	0.36
Bupropion		
-Urge	-0.24	<0.001
-Neg affect	-0.16	<0.001
-Restless	-0.09	0.08
-↑appetite	-0.04	0.56
-Insomnia	0.11	0.048
Brief		

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results

Questionnaire of smoking urges		
Varenicline	-0.45	<0.001
Bupropion	-0.21	0.001

Smoking Reinforcement-Modified Cigarette Evaluation Questionnaire

	Difference vs placebo	P value
Varenicline		
-Satisfaction	-0.60	<0.001
-Psy reward	-0.50	<0.001
-Resp tract	-0.34	<0.001
-↓craving	-0.52	<0.001
-Aversion	-0.18	0.53
Bupropion		
-Satisfaction	-0.13	0.18
-Psy reward	-0.23	0.004
-Resp tract	0.04	0.67
-↓craving	0.00	0.98
-Aversion	-0.17	0.056

Mean Weight Gain Weeks 1-12
Varenicline: 2.37kg
Bupropion: 2.12kg
Placebo: 2.92kg

Tonstad 2006
R,DB,PC
Effect of maintence therapy on relapse

Primary Outcome: CO-confirmed continuous abstinence from week 13-24

Inclusion:
1. Age 18-75
2. ≥10 cigarettes/d
3. no abstinence >3 months in previous year
4. motivated to quit
5. use of effective contraception if woman of child-bearing potential

Exclusion:
1. serious or unstable

12 week open label treatment with varenicline 1mg twice a day

Patients continually abstinent for at least the last 7 days of that period were randomized to:

Varenicline 1mg twice

	Open	Double-Blind	
	Var N=1927	Var N=603	PBO N=607
Age	44.2	45.4	45.3
Male%	48.8	50.2	48.3
White%	96.2	96.7	97
Fagerstrom Score (1-10)	5.55	5.43	5.35
Cigs/day	21.6	20.7	20.7
Prev attempts %			

N=1210 Randomized
Continuous Abstinence

	Var %	PBO %
DB Week		
13	95.5	88.5
24	70.5	49.6
OR	2.48	
95%CI	1.95, 3.16	
P	<0.001	
DB Week		
25	67.7	48.3
52	43.6	36.9

Adverse Events leading to discontinuation in 11.9% during open label phase: nausea, headache, depression, fatigue
Nausea: median onset: 8 days
Median duration: 20 days

Three patient died; none were considered related to

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Secondary: continuous abstinence weeks 13-52 The Varenicline Phase 3 Study Group Funding by Pfizer	disease within past 6 months 2. depression requiring treatment in past 12 months 3. history of or current panic disorder, psychosis, or bipolar disease 4. Severe COPD 5. History of cancer 6. History of severe allergic reactions 7. laboratory abnormalities 8. CV disease within the past 6 months 9. uncontrolled hypertension 10. history of drug or alcohol abuse or dependence in past 12 months 11. Use of a smoking cessation drug in the past 12 months 12. use of tobacco products other than cigarettes 13. BMI less than 15 or more than 38 14. Used any of the following:NRT, antidepressants, antipsychotics, mood stabilizers/anticonvulsants, naltrexone, steroids, or insulin	a day for another 12 weeks Or Placebo for another 12 weeks With each visit patients received 10 minutes of smoking cessation counseling	0: 17.7 / 14.6 / 14.7 ≥1: 82.3 / 85.4 / 85.3	OR 1.34; 95%CI 1.06, 1.69; P 0.02 7-day Point Prevalence Week 24: OR 2.82; 95%CI 2.18, 3.64; P <0.001 Week 52: OR 1.33; 95%CI 1.06, 1.67; P 0.01 Minnesota Nicotine Withdrawal Scales: Withdrawal symptoms tended to be slight or not at all. Mean urge to smoke scores were higher in the placebo group at both week13 and week 25. Mean weight gain baseline to week 24 for those who remained abstinent weeks 13-24: Varenicline: 3.62 kg; Placebo: 4.07 kg Mean weight gain baseline to 24 weeks for all participants: Varenicline: 3.41 kg; Placebo: 3.53 kg	varenicline: 1. patient with a h/o depression not revealed at entry died 27 days after completing double-blind portion 2. patient died of complications of lung cancer 3. Patient discontinued therapy during day 25 of open label due to back pain died on day 197 after stopping varenicline due to rectal sarcoma.
Supporting Trials					
Nides 2006 R, DB, parallel group, active controlled, phase II	Inclusion: 1. age 18-65 2. general good health (medical history, limited physical exam, ECG, labs)	Randomized to one of 5 regimens: 1. varenicline 0.3mg once daily 2. varenicline 1mg	Varenicline 0.3 / Varenicline 1 / Varenicline 1 twice / B 150 / P M%: 50 / 43.7 / 50.4 / 45.2 / 52	V 0.3 126; V 1 126; V 2 125; B 150 126; PBO 123 4 week	Discontinuation rates due to AEs were lowest in the placebo group and highest in the bupropion group. In the varenicline group,

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Primary outcome: continuous quit rate for any 4 weeks in a 7 week trial Secondary: CO-confirmed 4 week quit rate for weeks 4-7, 4-12, 4-24m 4-52 The Varenicline Study Group Funding by Pfizer	3. average of 10 cigarettes/day for previous year 4. no abstinence greater than 3 months in past year Exclusion: 1. major depression requiring treatment within past year 2. history of panic disorder, psychosis, or bipolar disorder 3. history of anorexia or bulimia 4. treatment with bupropion in past year 5. history of seizures or CV disease 6. uncontrolled hypertension 7. history of clinically significant allergic, hematologic, renal, endocrine, pulmonary, hepatic, GI, or neurologic disease 8. alcohol or other drug abuse within past year	daily 3. varenicline 1mg twice a day 4. bupropion SR 150mg twice a day 5. placebo Weekly visits included up to 10 minutes of standardized individual smoking cessation counseling After 7 weeks, follow-up until week 52	Age 42 43 42 41 42 BMI 26 26 26 26 27 Wh% 88 88 86 83 88 Fager. Score 5.7 5.5 5.6 5.2 5.5 Cig/d 20 20 19 20 22	CQR % 28.6 37.3 48 33.3 17.1 OR 1.97 2.97 4.71 2.53 95%CI 1.07, 3.65 1.63, 5.4 2.6, 8.53 1.38, 4.63 P .03 <.001 <.001 .002 CO con-Firmed CQR Wk 4-7 % 25.4 31 40.8 28.6 13.8 P ≤.05 ≤.01 ≤.001 ≤01 CO CQR Wk 4-12 % 16.7 15.1 28.8 19.8 10.6 P ≤.01 ≤05 CO CQR Wk 4-24 % 9.5 9.5 20.8 10.3 7.3 P ≤.01 CO CQR Wk 4-52 % 7.9 5.6 14.4 6.3 4.9 P ≤.01 Discontinuation of Therapy Varenicline 0.3: 31.7%; 18AEs Varenicline 1/d: 29.4%; 17AEs Varenicline 1/twice a day: 31.2%; 15AEs Bupropion SR: 28.6%; 21AEs Placebo: 33.3%; 12AEs	discontinuation due to AEs did not appear to be dose related. Most frequent AEs in varenicline: nausea, insomnia, headache, abnormal dreams, taste perversion. Higher doses of varenicline had higher incidences of AEs except for headache. Nausea: mild to moderate in severity and transitory (med duration ≤12 days) Only 1 patient in the varenicline 1mg twice a day group had a serious AE versus 4 in the bupropion group.
Oncken 2006 R, DB, PC Primary Outcome: CO-confirmed 4	Inclusion: 1. 18-65 2. at least 10 cigarettes per day 3. healthy smokers	Randomized to one of 5 regimens for 12 weeks: 1. Varenicline 0.5mg twice daily nontitrated	PBO / Varenicline .5N .5T 1N 1T Age 43 43 44 44 42 M% 52 45 53 49 49 W% 72 85 81 84 81	N_R=647 CQR W 4-7 % 36.3 39.8 10.9 OR 4.96 5.86 Var 0.5 / Var 1 / PBO	Most common AEs: Neurologic: headache, insomnia, abnormal dreams, and/or somnolence

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
week CQR for weeks 4-7 and weeks 9-12 and continuous abstinence weeks 9-52 Secondary: CO-confirmed 7 day point prevalence abstinence, changes in Minnesota Nicotine Withdrawal Scale and the modified Cigarette Evaluation Questionnaire, and 7 day point prevalence for abstinence at weeks 24 and 52 The Varenicline Study Group Funding by Pfizer	Exclusion: 1. treatment with an investigational drug during past year 2. major depression within past year 3. panic disorder, psychosis, or bipolar disease 4. use of nicotine replacement or bupropion within previous 3 months 5. CV disease 6. drug or alcohol abuse or dependence within past year 7. use of tobacco products other than cigarettes or marijuana in past month	2. Varenicline 0.5mg twice daily titrated 3. Varenicline 1mg twice daily nontitrated 4. Varenicline 1mg twice daily titrated 5. Placebo	Fag Score 5.8 5.5 5.4 5.5 5.3 Cig/d 20 21 21 21 21	95%CI 2.66, 9.22 3.16,10.9 P <0.001 <0.001 CQR W9-12 % 44 49.4 11.6 OR 6.32 8.07 95%CI 3.47,11.5 4.42,14.7 P <0.001 <0.001 CQR W 9-52 % 18.5 22.4 3.9 P <0.001 <0.001 7 day Point Prevalence for abstinence Week 12: significantly higher for all varenicline (p<0.001). Week 24 and 52: rates decreased to 1/3 to 1/2 of week 12 rates, but still significantly higher than placebo. Measures of withdrawal were mild on the Minnesota scale. Varenicline reduced the urge to smoke versus placebo to statistical significance. In patients who continued to smoke on therapy, varenicline reduced the reinforcing effects based on the Cigarette Evaluation Questionnaire.	GI: nausea, dyspepsia, constipation, and/or flatulence Nausea rates were higher in the 1mg groups versus placebo (p<0.001) The rates of nausea were reduced by titration of the dose. Serious AEs were reported in 2 placebo patients and 9 varenicline patients. No deaths occurred during the study.

N_R, Number randomized; R=randomized; DB=double-blinded; PC=placebo controlled; MAOI=monoamine oxidase inhibitor; CV=cardiovascular; COPD=chronic obstructive pulmonary disease; BMI=body mass index; p.o.=orally; V=varenicline; B=bupropion SR; P or PBO=placebo; OR=odds ratio; CI=confidence interval; CQR=continuous quit rate