Bupropion and Varenicline

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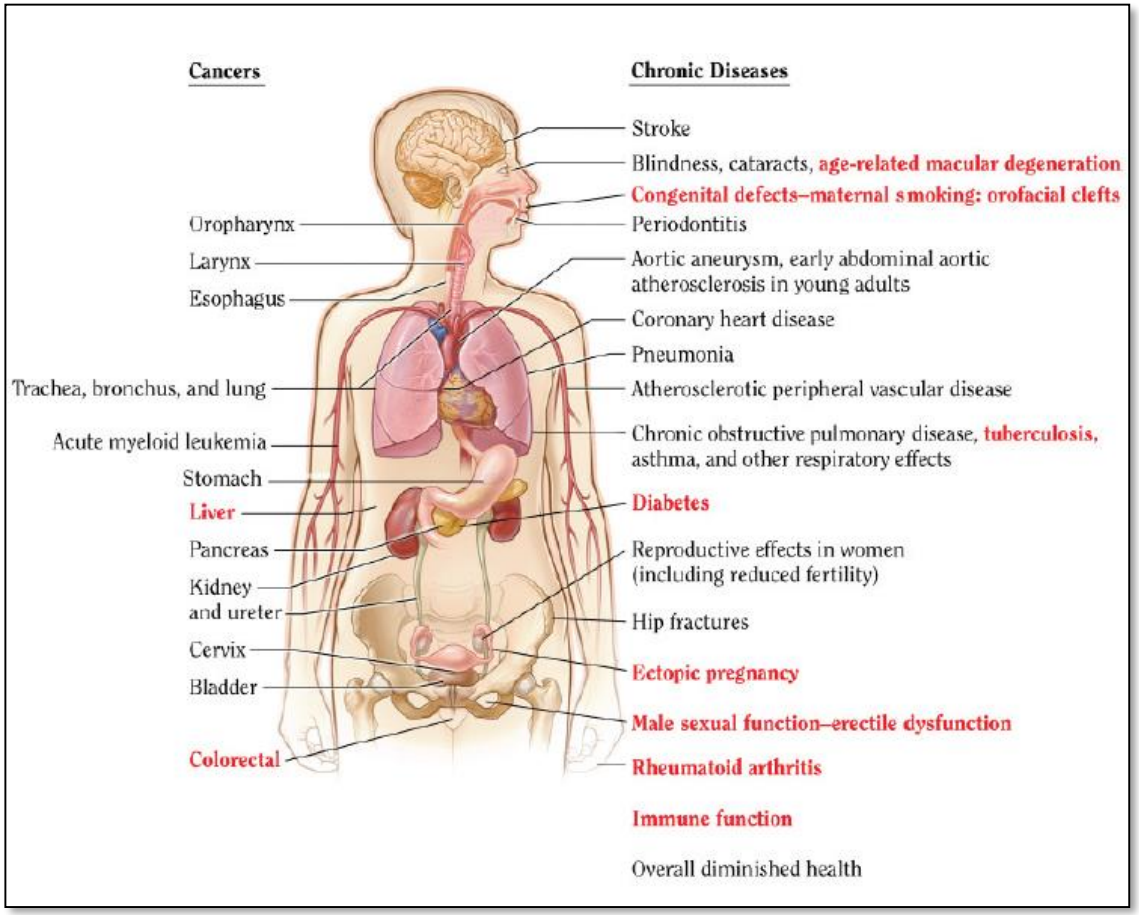
흡연의 건강 결과



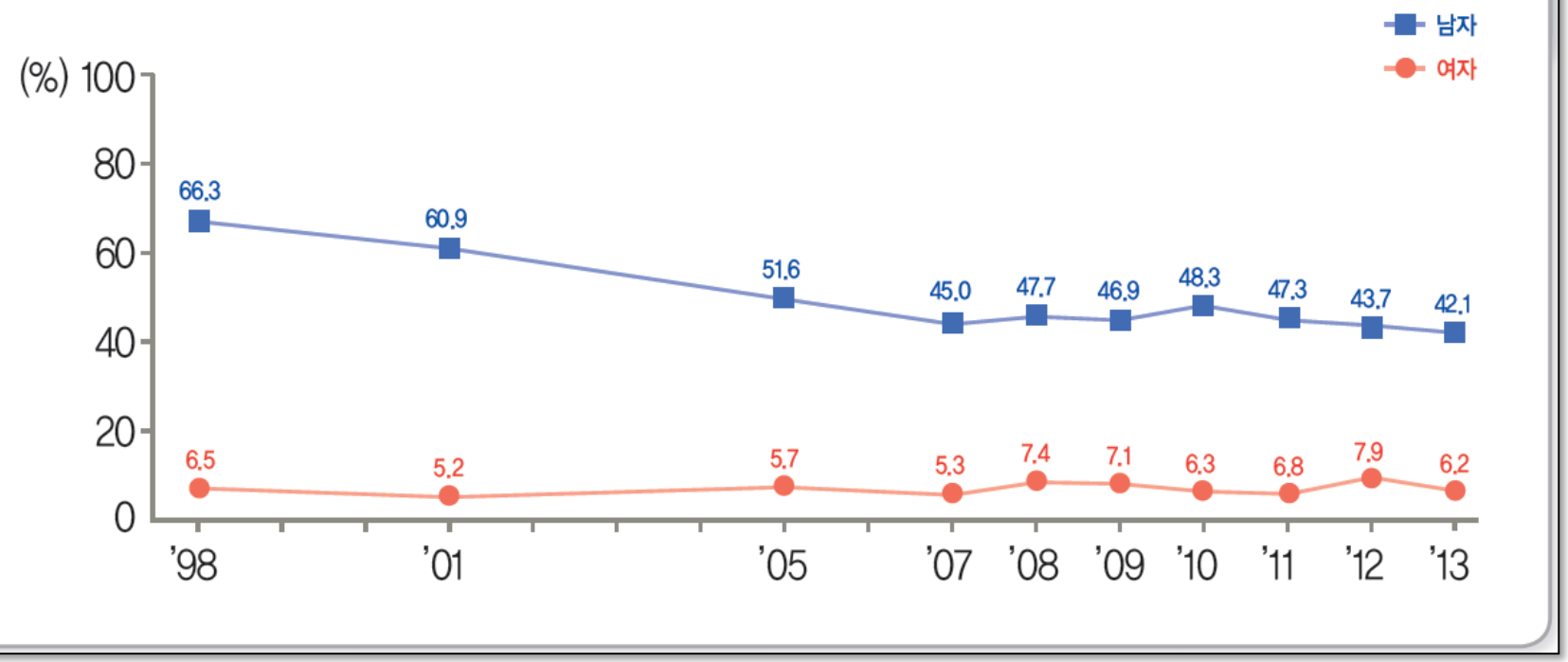
- 암 사망의 1/3
- 평균 수명 11년 단축
- 호흡기, 상부 위장관, 비뇨기계 간암, 대장암, AML
- 황반 변성, 당뇨병, 폐결핵 자궁 외 임신, 남성 성기능 장애 류마티스 관절염, 면역기능 약화

US Department of Health and Human Services. 2014

질병 부담

- 흡연으로 인한 조기 사망 – 600만명 (WHO)
- 흡연의 전체 사망 기여 위험도: 남자 34.7%, 여자 7.2%
- 흡연의 암에 대한 기여 위험도: 남자 41.1%, 여자 5.1%
- 국내 성인 남자 흡연율: 1998년 66.3%, 2013년 42.1%
- 국내 성인 여성 흡연율: 1998년 6.5%, 2013년 6.2%

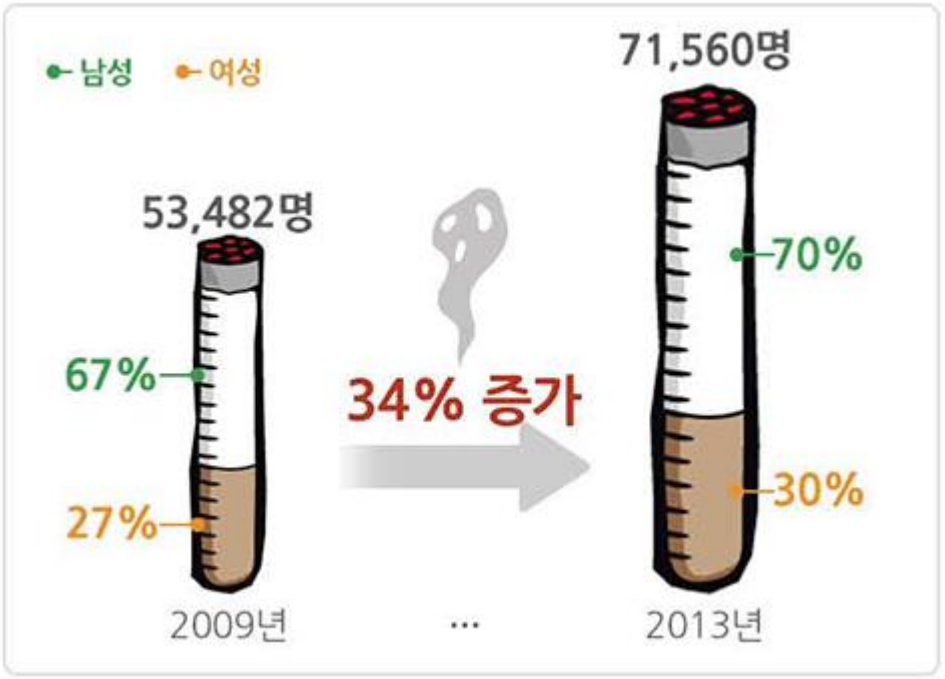
[그림1] 국민건강영양조사 각 년도 (출처 : 보건복지부 질병관리본부 2013 건강행태 및 만성 질환 통계)

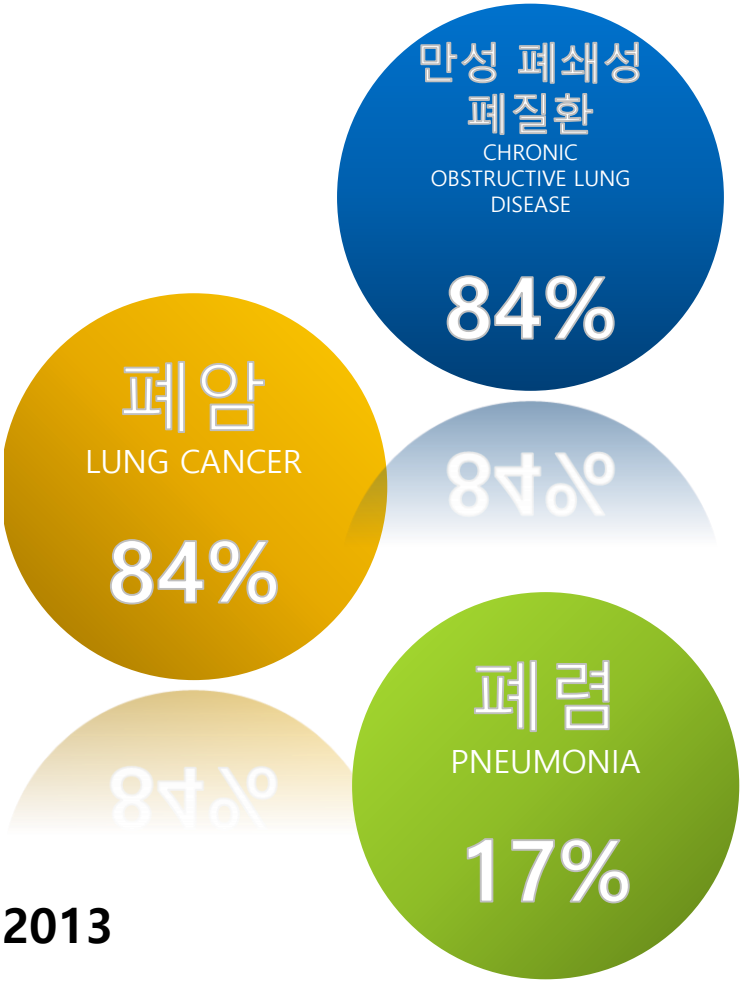


한국보건정보통계학회지 2013;38:36

COPD 발병 위험성의 약 85%가 흡연으로 인한 것입니다.[1)]

< 흡연으로 인한 호흡기 질환 사망률 > [2)]

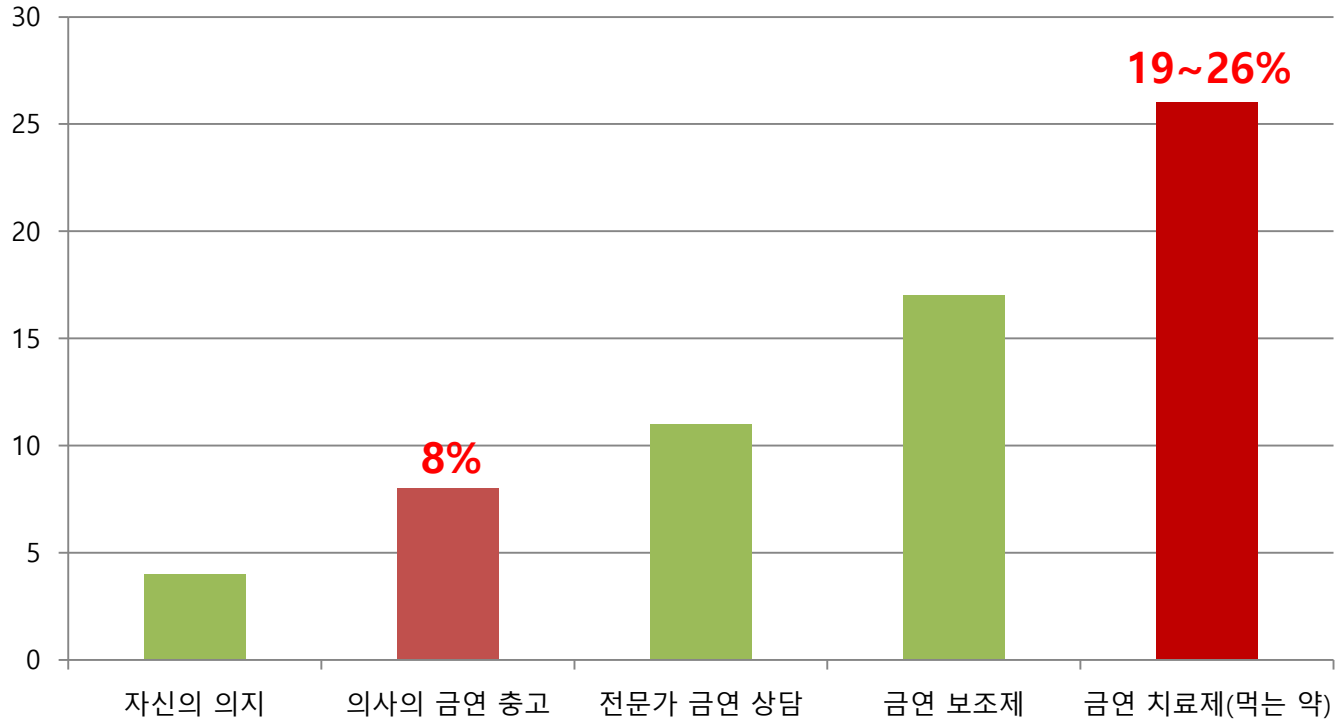




- **폐암으로 진료받은 환자수가 2009년에 비해 2013년에 34% 증가하였습니다.[3)]**

1) Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. Curr Opin Pul Med 1999;5(2):93-101
2) Nicotine addiction in Britain. A report of the Tobacco Advisory Group of The Royal College of Physicians. RCP, London:2000
3) 건강보험심사평가원 2009, 2013

금연 치료 방법별 6개월 이상 금연 성공률



금연 효과

- 91%가 본인 의지만으로 금연을 시도하였습니다.
- 금연 치료제 복용으로 금연을 시도한 흡연자들에서 금연 성공률이 높았습니다.

1) 국립암센터 2010

금연 진료 및 전략 (5As)

흡연 유무 체계적으로 확인
- 빈도, 정도, 과거 금연 유무

금연에 대한 강한 조언
- 명확하게, 강하게, 개별화

금연 의지 파악
- 고려 전 단계 ~행동 단계

담배를 끊도록 실제 도움
- 약물과 상담치료

차기 방문 예약
- 일주 이내 방문 예약

미국 보건부 금연치료 가이드라인 2008

약물 치료 대상자

- 금연을 계획하는 모든 흡연 환자

- 제외 대상
- 임신부
- 경미한 흡연자
- 청소년

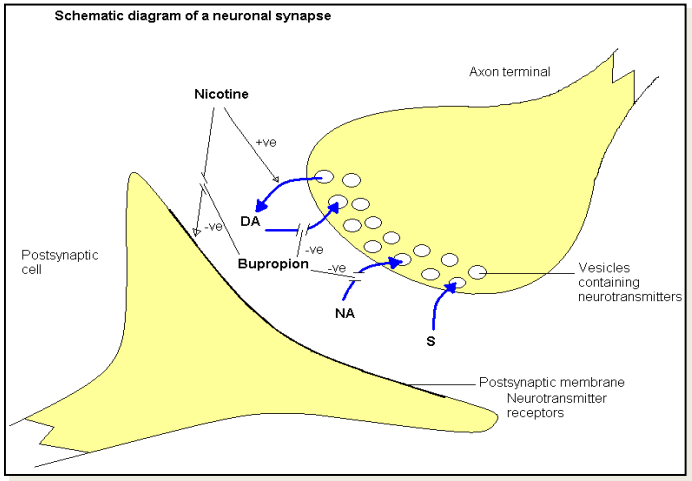
약물 사용

- 하루 10개피 이상 피우는 경우
- 니코틴 의존도가 중등도 이상 (FTND 4점 이상)
- 과거 금연에 여러 번 실패한 경우
- 1차 약물

1) NRT
2) **Bupropion**
3) **Valenicline**

Bupropion sustained release

- 부프로피온: 1997년 FDA에 의해 최초 승인
- 작용 기전: 도파민과 노에피네프린의 재 흡수 차단, nAChR
- 복용 방법:
  - 금연 예정일 1주 전,하루 한 알(150mg)X 3 일 (오전), 다음 날부터 150mg bid
- 혹은 **6일 동안 하루 한번 복용 후 7일째부터 하루 두 번 복용**
- 8시간이 지난 후에 다음 번 약 투여 함, 7주 이상 사용함.
- 장기간 유지요법: 하루 150mg을 금연 후 6개월까지 사용
- 서방정(Sustained Release)이므로 분쇄하거나 씹어서 복용하지 않도록 함



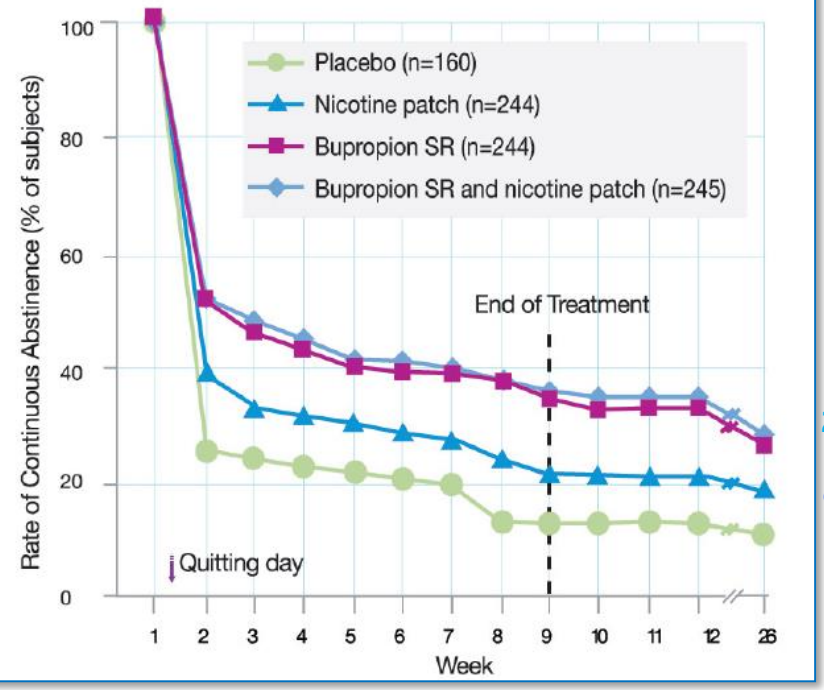
Int J COPD 2008;3:45

A CONTROLLED TRIAL OF SUSTAINED-RELEASE BUPROPION, A NICOTINE PATCH, OR BOTH FOR SMOKING CESSATION

DOUGLAS E. JORENBY, PH.D., SCOTT J. LEISCHOW, PH.D., MITCHELL A. NIDES, PH.D., STEPHEN I. RENNARD, M.D., J. ANDREW JOHNSTON, PHARM.D., ARLENE R. HUGHES, PH.D., STEVENS S. SMITH, PH.D., MYRA L. MURAMOTO, M.D., DAVID M. DAUGHTON, M.S., KIMBERLI DOAN, B.S., MICHAEL C. FIORE, M.D., M.P.H., AND TIMOTHY B. BAKER, PH.D.

- DBRCT NRT vs BP SR vs BP SR+NRT vs Placebo
- 9wks intervention, f/u for 52wks

Rates of Confirmed Continuous Abstinence



22.5%
18.4%
9.8%
5.6%

Point-Prevalence Abstinence Rate**

	Abstinence (at 6month)	Abstinence (at 12month)
Placebo	18.8%	15.6%
Nicotine patch	21.3%	16.4%
Bupropion SR	34.8%	30.3%

**Point – Prevalence Abstinence Rate
: 금연상담 시 이전 7일간 흡연하지 않은 금연자의 비율

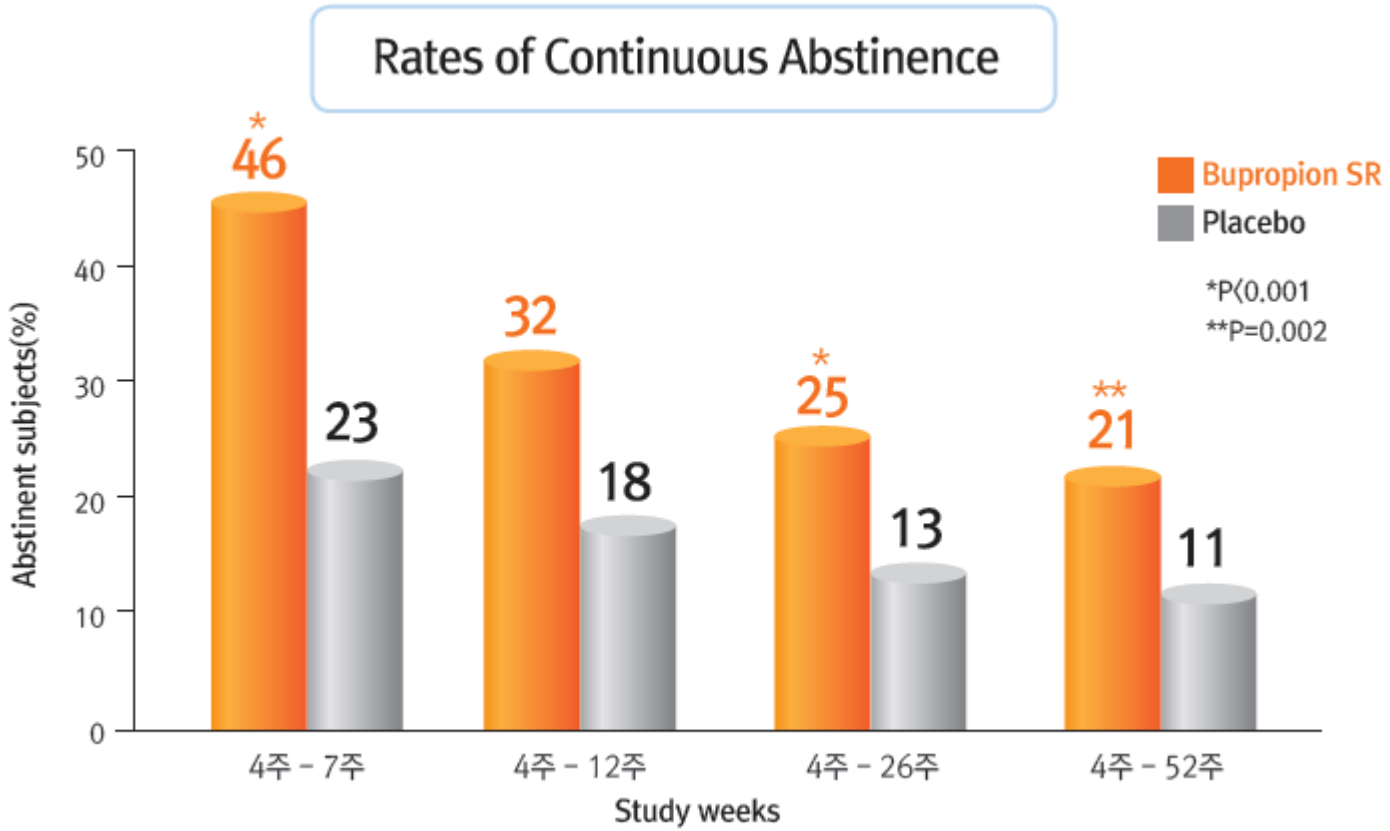
The rates of continuous abstinence during the 12-month period were higher in the bupropion groups than in the nicotine- patch group (P<0.001)

NEJM 1999; 340:685

A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation

P. TØNNESEN[1], S. TONSTAD[2], A. HJALMARSON[3], F. LEBARGY[4], P. I. VAN SPIEGEL[5],

- RCT DB P-Controlled. 707 Smokers an average of 10 cigarettes
- BR with counselling vs PBO (7wks BR and 180 received PBL)
- Outcomes : Seven-week and 12-month abstinence rates

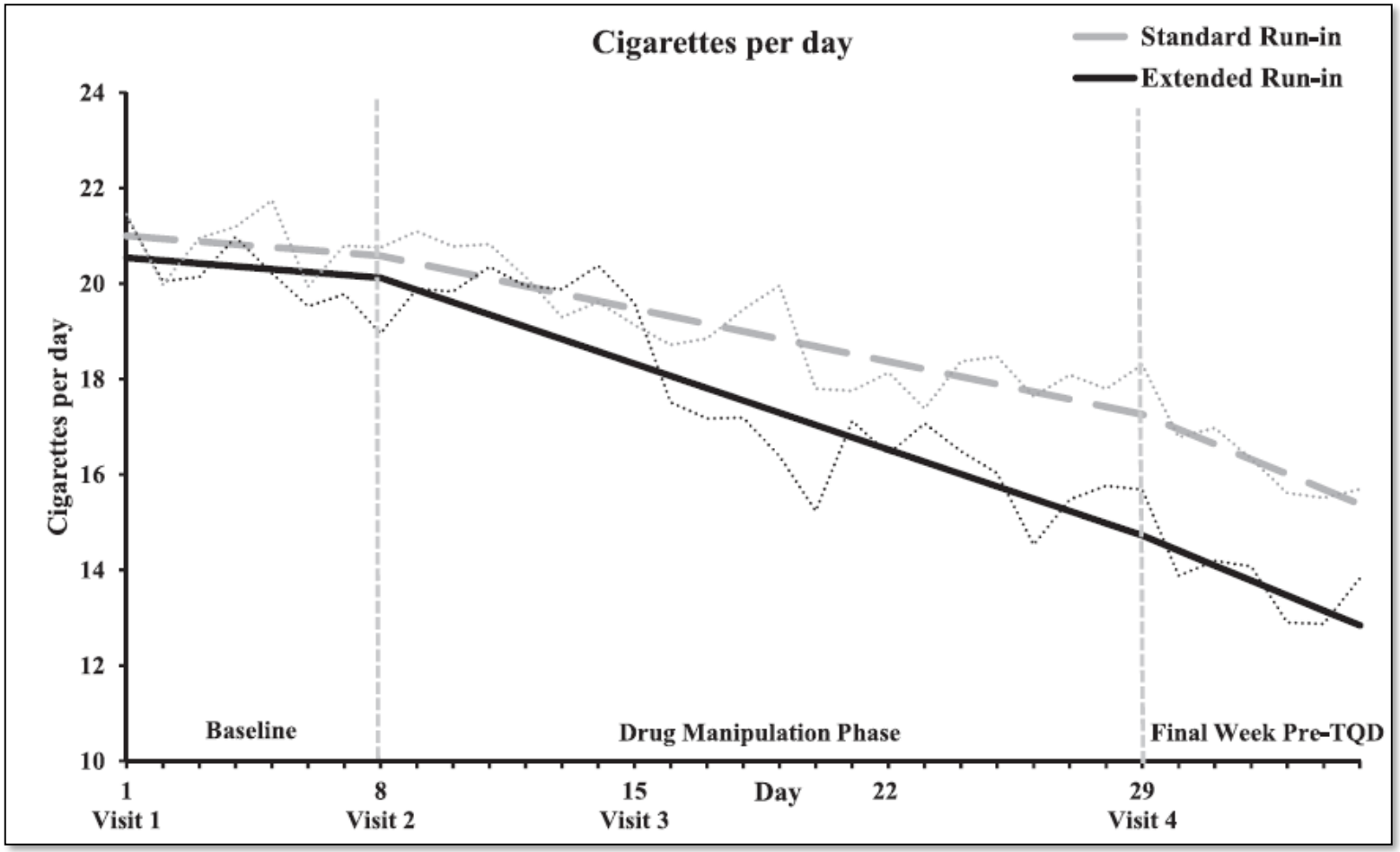


Journal of Internal Medicine 2003; 254:184

Does Extended Pre quit Bupropion Aid in Extinguishing Smoking Behavior?

Larry W. Hawk Jr. PhD[1,2], Rebecca L. Ashare PhD[1,3],

- 4wks of pre quit BR vs standard 1wk
- 7wks BR



P=0.03

Nicotine & Tobacco Research 2015;1

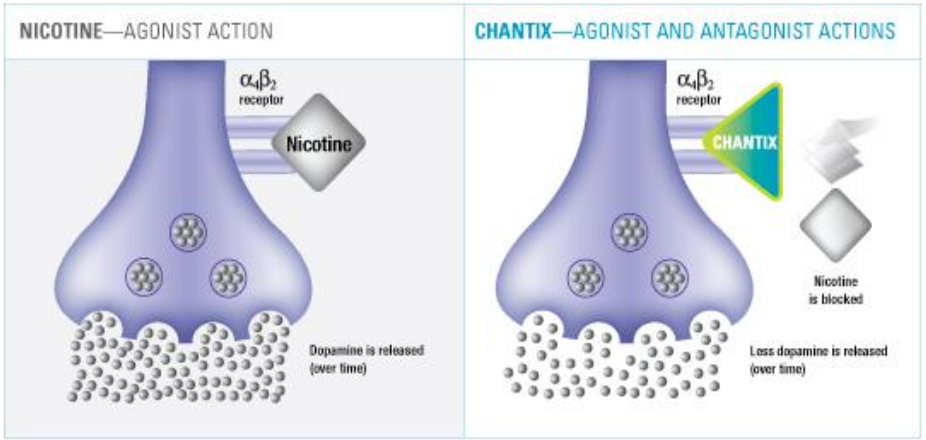
Bupropion sustained release 부작용

- 경련: 용량-의존적 관계. 용량을 초과하지 않도록 주의
- 부작용: 불면 35-40%, 입 마름 10%.
- 불면증이 심한 경우, 오후 약을 일찍 복용. 단 투약간격 8시간 이상 준수.
- 경련: 일반 인구집단에서 0.07-0.09%, 고용량 복용 시 위험성이 증가
- **처방 금기:**
- 경련 질환의 병력
- 중추신경계 종양, 대식증, 신경성 식욕 부진증의 병력
- 알콜 혹은 벤조디아제핀계 신경안정제를 갑작스럽게 중단한 경우, MAOI 동시 투여
- 18세 이하 청소년과 임산부에서는 안전성과 효능이 입증되지 않음
- Enzyme inhibitor로 antidepressant, antiarrthmics, antipsychotics 용량을 줄어야 한다.

Varenicline

- 바레니클린: 2006년 FDA 시판경구용 금연 약물 승인
- 기전: 부분적 항진 및 억제 효과를 통해 금단증상 및 흡연 갈망 감소 (α4β2 nAChRs subtype partial agonist)
- 복용법:

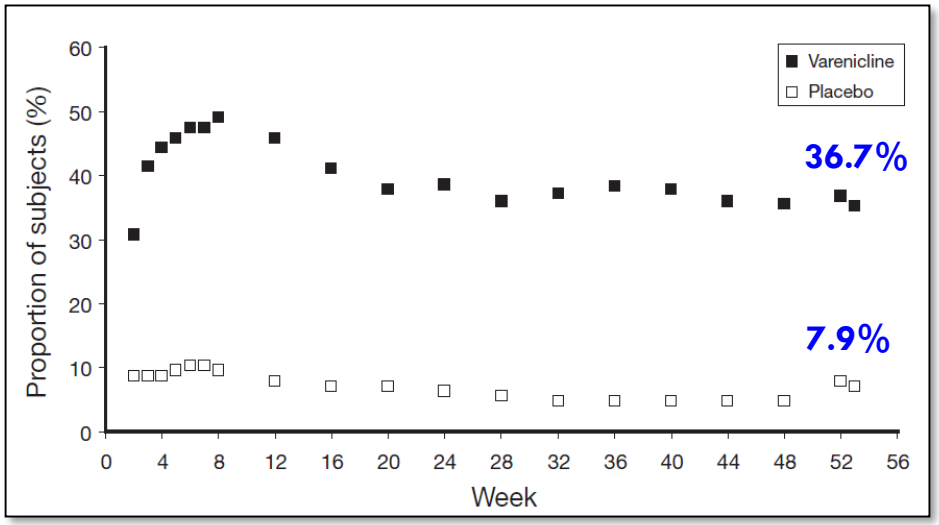
- 금연 예정일 1주 전, 0.5mg qd x 3일 (오전), 다음 4일-7일 째 0.5mg bid, 8일 째 이후 3개월간 1mg을 bid.
- 유지요법으로 6개월~1년까지 연장할 수 있음



A double-blind study evaluating the long-term safety of varenicline for smoking cessation*

- RCT BD multicenter study, average of > 10 cig/day
- Varenicline vs PBO for 52wks medication (n=126)
- Long term safety of VR

Adverse event	Varenicline 1 mg BID (*n* = 251) *n* (%)	Placebo (*n* = 126) *n* (%)
Gastrointestinal disorders		
Nausea	101 (40.2)	10 (7.9)
Dyspepsia	33 (13.1)	3 (2.4)
Constipation	31 (12.4)	9 (7.1)
Flatulence	31 (12.4)	12 (9.5)
Vomiting	17 (6.8)	2 (1.6)
Infections and infestations		
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Sinusitis	17 (6.8)	8 (6.3)
Influenza	15 (6.0)	3 (2.4)
Psychiatric disorders		
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Nervous system disorders		
Dysgeusia	27 (10.8)	3 (2.4)
Dizziness	19 (7.6)	6 (4.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	18 (7.2)	7 (5.6)
Back pain	16 (6.4)	6 (4.8)
All other system organ classes		
Weight increase	17 (6.8)	5 (4.0)
Hypertension	15 (6.0)	5 (4.0)
Increased appetite	13 (5.2)	4 (3.2)

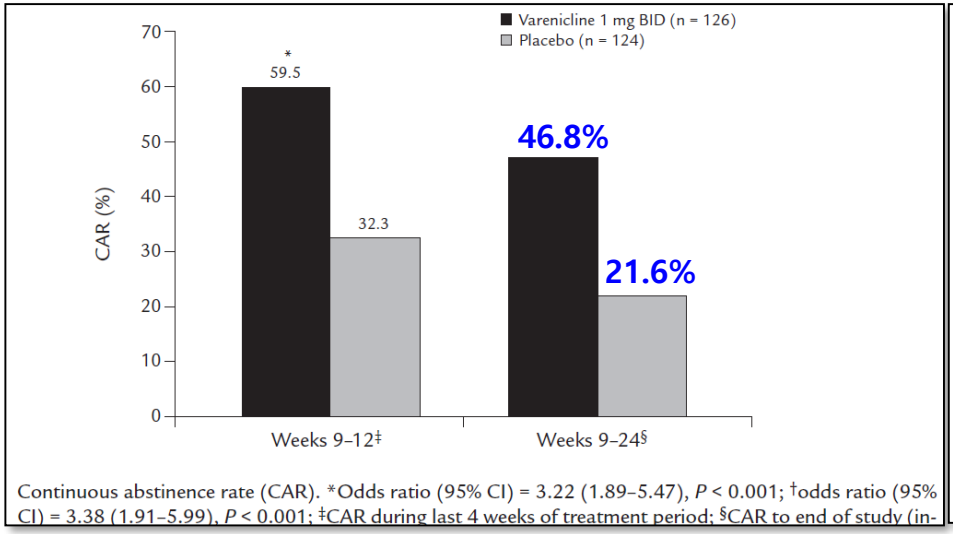


7-Days point prevalence

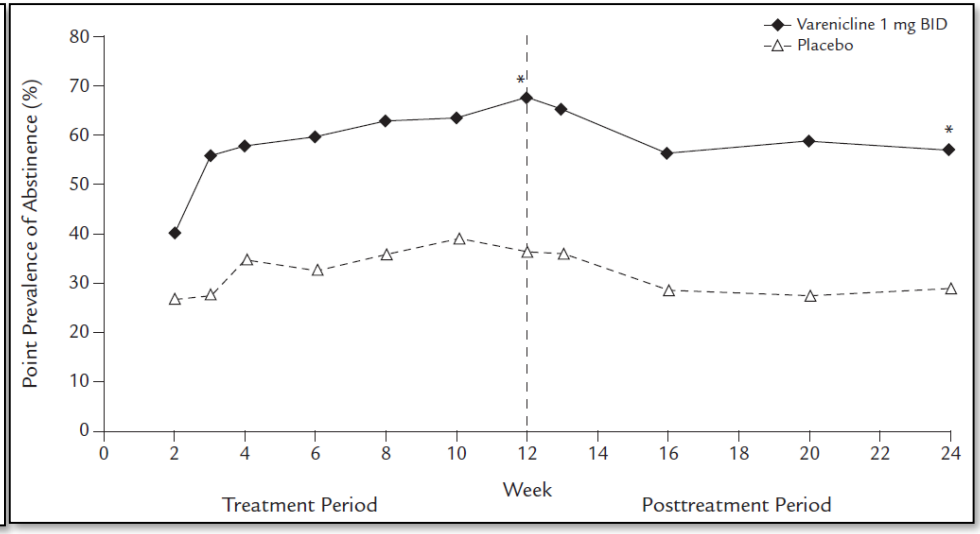
Current Med Resear Opin 2007;23:793

A Randomized, Placebo-Controlled Trial of Varenicline, a Selective $\alpha_4\beta_2$ Nicotinic Acetylcholine Receptor Partial Agonist, as a New Therapy for Smoking Cessation in Asian Smokers

- Efficacy and tolerability of varenicline in **Taiwan and Korea**.
- RCT BD 12wks tx and 12wks f/u (n=126)
- End-Exp CO concentration.



Continuous abstinence rate



7-Day point prevalence of abstinence

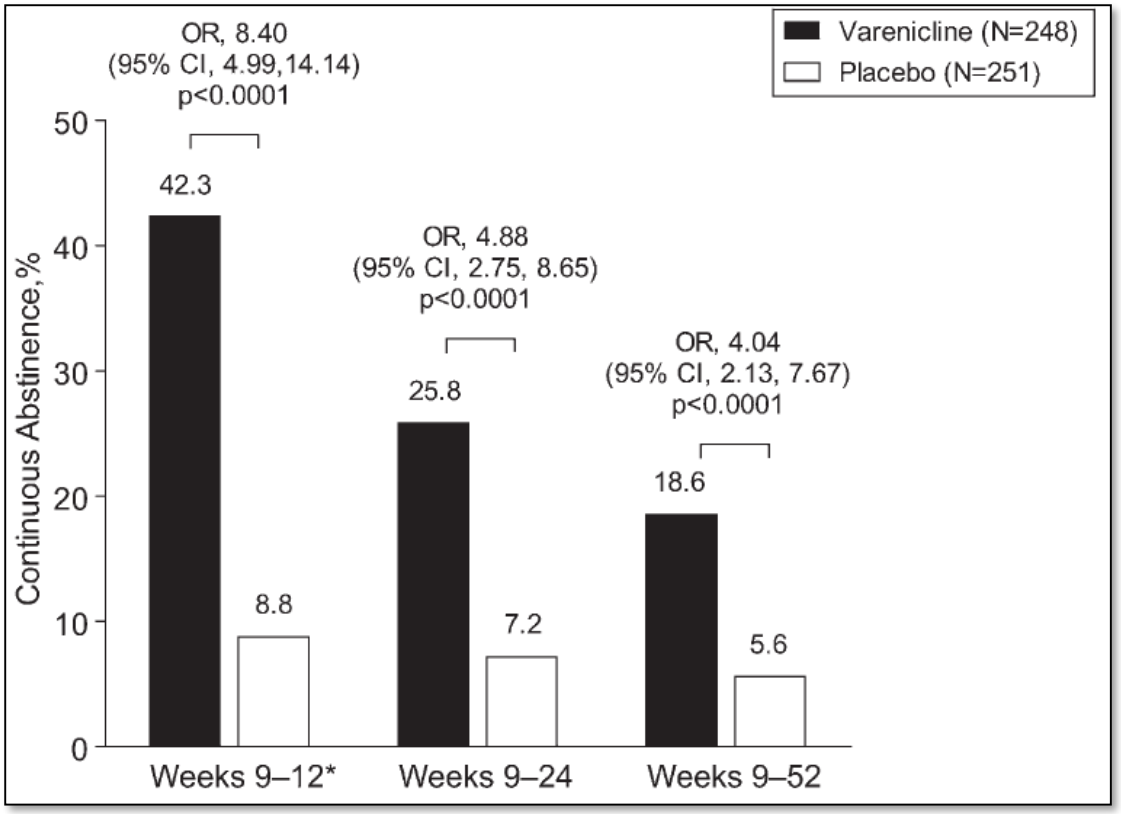
Therapeutics. 2007;29:1027

Effects of Varenicline on Smoking Cessation in Patients With Mild to Moderate COPD

A Randomized Controlled Trial

Donald P. Tashkin, MD, FCCP; Stephen Rennard, MD, FCCP; J. Taylor Hays, MD;

- DB, 504 **mild to mod COPD** (mean post BD FEV1 = 70.0% pred)
- 12wks Tx and 40wks non tx f/u
- End point: CO confirmed CAR



CHEST 2011;139:591

Effects of Varenicline on Smoking Cessation in Patients With Mild to Moderate COPD

A Randomized Controlled Trial

Donald P. Tashkin, MD, FCCP; Stephen Rennard, MD, FCCP; J. Taylor Hays, MD;

Characteristic	Varenicline No.	Varenicline CAR, No. (%)	Placebo No.	Placebo CAR, No. (%)	OR[a]	95% CI[a]	Treatment by Subgroup Interaction *P* Value[b]
COPD Study							
Varenicline (n = 248) / Placebo (n = 251)							
Demographics							
Age, y	57.2 ± 9.1		57.1 ± 9.0				
Male sex	155 (62.5)		156 (62.2)				
White race	203 (81.9)		211 (84.1)				
Smoking history							
Years smoked	40.4 (11-67)[a]		40.6 (18-64)[a]				
Cigarettes/d	25.3 (10-99)[a]		23.6 (10-60)[a]				
Any previous serious quit attempt	205 (82.7)		200 (79.7)				
FTND score[c]	6.2 ± 2.2		5.9[d] ± 2.1				
Smoking cessation rates							
CAR weeks 9-12, %		42.3		8.76			
OR (95% CI)					8.40	(4.99-14.14)	
P Value					< .0001		
CAR weeks 9-24, %		25.8		7.2			
OR (95% CI)					4.88	(2.75-8.65)	
P Value					< .0001		
CAR weeks 9-52, %		18.6		5.6			
OR (95% CI)					4.04	(2.13-7.67)	
P Value					< .0001		
Gonzales et al[15]							
Varenicline (n = 352) / Placebo (n = 344)							
Demographics							
Age, y	42.5 ± 11.1		42.6 ± 11.8				
Male sex	176 (50.0)		186 (54.1)				
White race	280 (79.5)		262 (76.2)				
Smoking history							
Years smoked	24.3 ± 11.5[b]		24.7 ± 12.1[b]				
Cigarettes/d	21.1 ± 9.47[b]		21.5 ± 9.51[b]				
Any previous serious quit attempt	297 (84.4)		288 (83.7)				
FTND score[c]	5.18 ± 2.16		5.38 ± 1.99				
Smoking cessation rates							
CAR weeks 9-12, %		44.0		17.7			
OR (95% CI)					3.85	(2.70-5.50)	
P Value					< .001		
CAR weeks 9-24, %		29.5		10.5			
OR (95% CI)					3.68	(2.42-5.60)	
P Value					< .001		
CAR weeks 9-52, %		21.9		8.4			
OR (95% CI)					3.09	(1.95-4.91)	
P Value					< .001		
Jorenby et al[16]							
Varenicline (n = 344) / Placebo (n = 341)							
Demographics							
Age, y	44.6 ± 11.4		42.3 ± 11.6				
Male sex	190 (55.2)		198 (58.1)				
White race	294 (85.5)		290 (85.0)				
Smoking history							
Years smoked	27.1 ± 11.5[b]		24.4 ± 11.6[b]				
Cigarettes/d	22.5 ± 9.5[b]		21.5 ± 8.7[b]				
Any previous serious quit attempt							
FTND score[c]	5.39 ± 2.21		5.16 ± 2.19				
Smoking cessation rates							
CAR weeks 9-12, %		43.9		17.6			
OR (95% CI)					3.85	(2.69-5.50)	
P Value					< .001		
CAR weeks 9-24, %		29.7		13.2			
OR (95% CI)					2.83	(1.91-4.19)	
P Value					< .001		
CAR weeks 9-52, %		23.0		10.3			
OR (95% CI)					2.66	(1.72-4.11)	
P Value					< .001		

CHEST 2011;139:591

Effect of Maintenance Therapy With Varenicline on Smoking Cessation

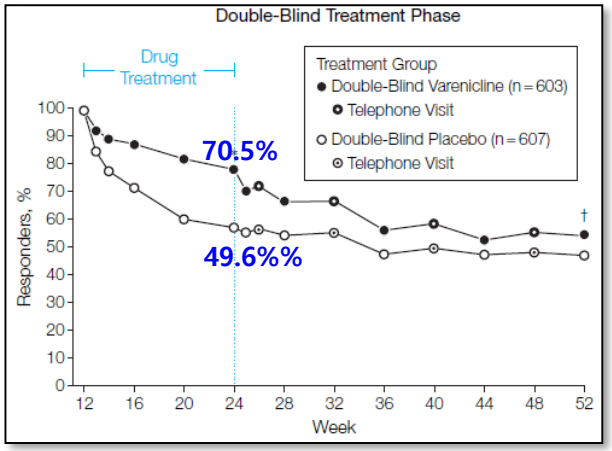
A Randomized Controlled Trial

- After 12wsk open label VR for 12wks (1,927) and additional 12wks of VR
- Did not smoke, use NRT at 12wks
- RDBT (n=1,236)

Table 2. Carbon Monoxide–Confirmed Continuous Abstinence Rate at Clinic Visits

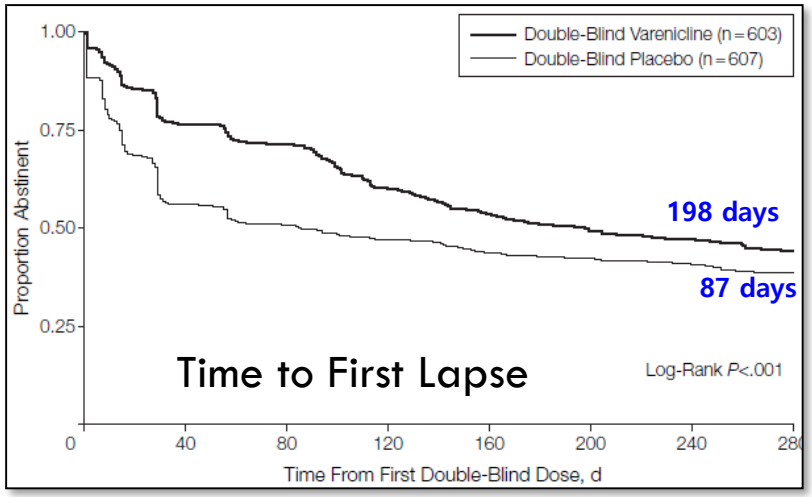
	No. (%) of Participants	
	Double-Blind Varenicline (n = 603)	Double-Blind Placebo (n = 607)
Double-blind treatment phase, wk*		
13	576 (95.5)	537 (88.5)
14	551 (91.4)	476 (78.4)
16	509 (84.4)	413 (68.0)
20	454 (75.3)	331 (54.5)
24	425 (70.5)	301 (49.6)
Nontreatment follow-up phase, wk†		
25	408 (67.7)	293 (48.3)
28	361 (59.9)	282 (46.5)
36	306 (50.7)	257 (42.3)
44	280 (46.4)	239 (39.4)
52	263 (43.6)	224 (36.9)

*Weeks 13-24: odds ratio, 2.48; 95% confidence interval, 1.95-3.16; $P<.001$.
†Weeks 13-52: odds ratio, 1.34; 95% confidence interval, 1.06-1.69; $P = .02$.



7-Day point prevalence

40.6%
36.9%



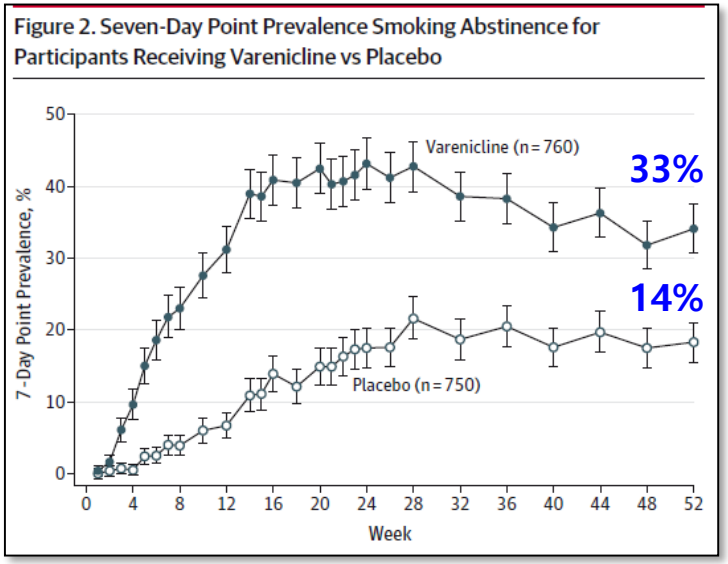
p<.001

JAMA 2006;296:64

Original Investigation

Effect of Varenicline on Smoking Cessation Through Smoking Reduction
A Randomized Clinical Trial

- RCTDB PL-controlled, (n=1,510)
- Varenicline vs placebo for 24wk treatment and 28wks f/u
- 12wks reduction phase, 12wks abstinence phase
- Not willing or able to quit within next month but willing to reduce smoking and quit attempt at 3ms



7-Days Point prevalence

Table 2. Continuous Carbon Monoxide–Confirmed Smoking Abstinence Rates for Periods of the Study[a]

	Continuous Abstinence, No. of Participants (%)			
	Varenicline Group (n = 760)	Placebo Group (n = 750)	Risk Difference, % (95% CI)	Relative Risk (95% CI)
Primary End Point[b]				
Weeks 15-24	244 (32.1)	52 (6.9)	25.2 (21.4-29.0)	4.6 (3.5-6.1)
Secondary End Points[b]				
Weeks 21-24	287 (37.8)	94 (12.5)	25.2 (21.1-29.4)	3.0 (2.4-3.7)
Weeks 21-52	205 (27.0)	74 (9.9)	17.1 (13.3-20.9)	2.7 (2.1-3.5)
Post Hoc End Point[b]				
Weeks 15-52	182 (24.0)	45 (6.0)	18.0 (14.5-21.4)	4.0 (2.9-5.4)

JAMA 2015;313

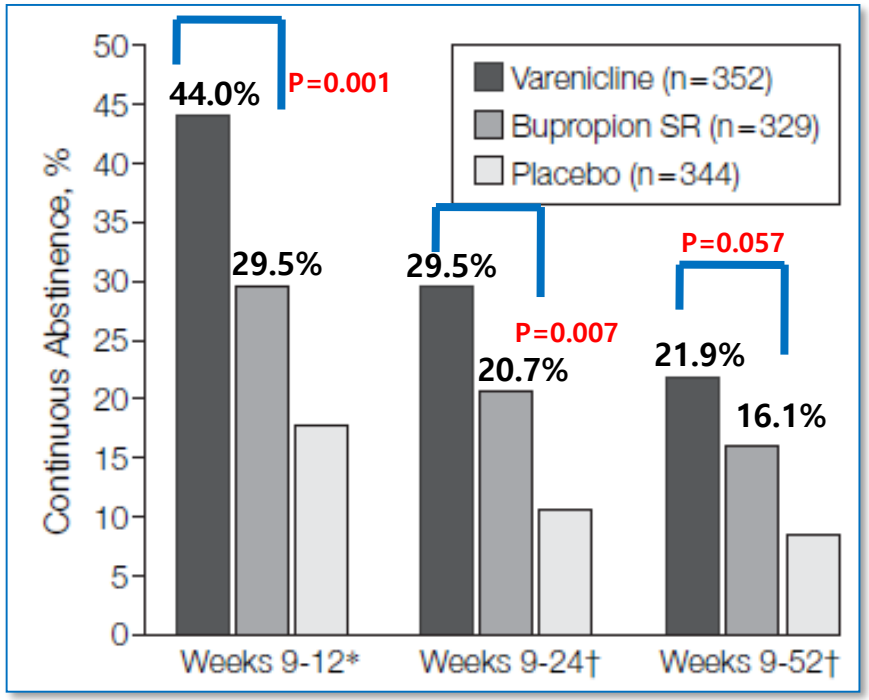
Bupropion SR vs. Varenicline

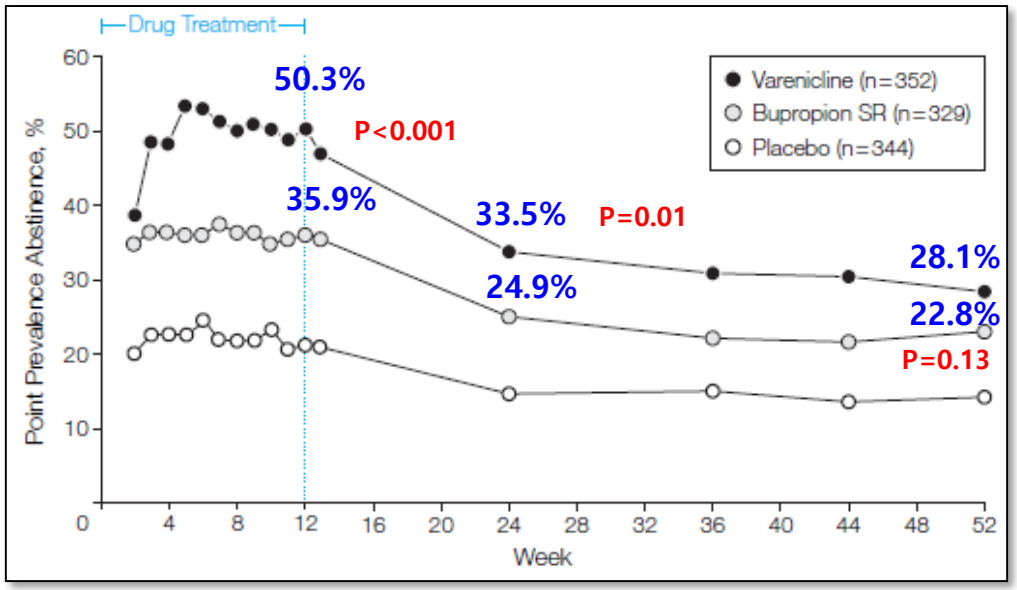
Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release Bupropion and Placebo for Smoking Cessation

A Randomized Controlled Trial

- Assess efficacy and safety of VR vs BR (n= 1,025)
- RDBPCT for 12wks and with 40wks non-drug f/u
- eCO confirmed 4wks ratio of abstinence for wks 9 through 12

OR	Week 9-12	Week 9-24	Week 9-52
VAR vs. Pbo	3.85 (P<0.001)	3.68 (P<0.001)	3.09 (P<0.001)
VAR vs. BUP	1.93 (P<0.001)	1.63 (P=0.007)	1.46 (P=0.057)





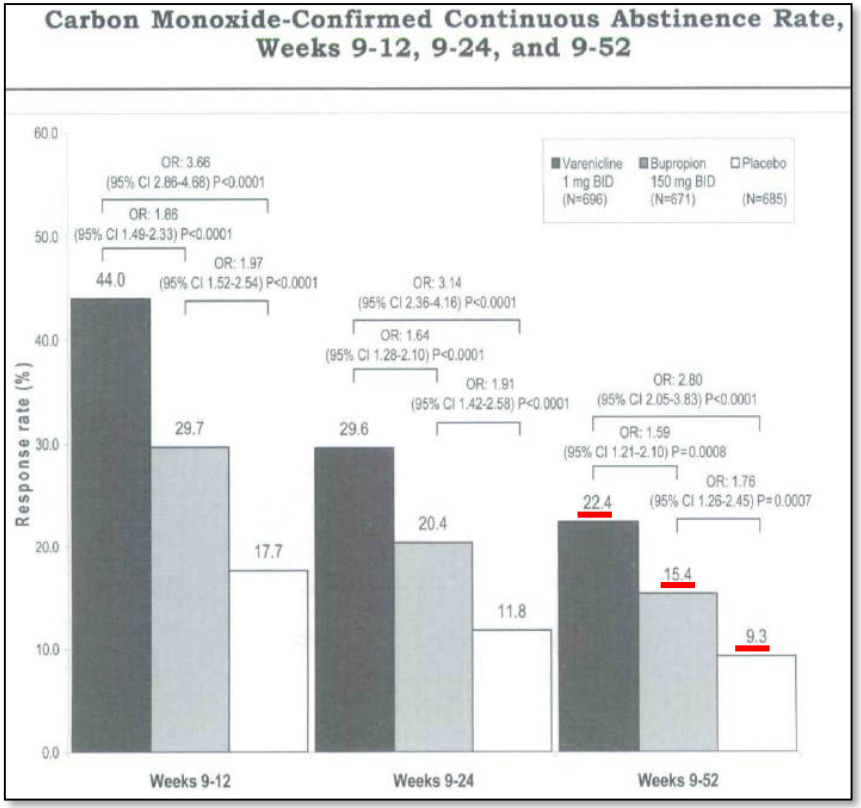
7-Day point prevalence Abstinence

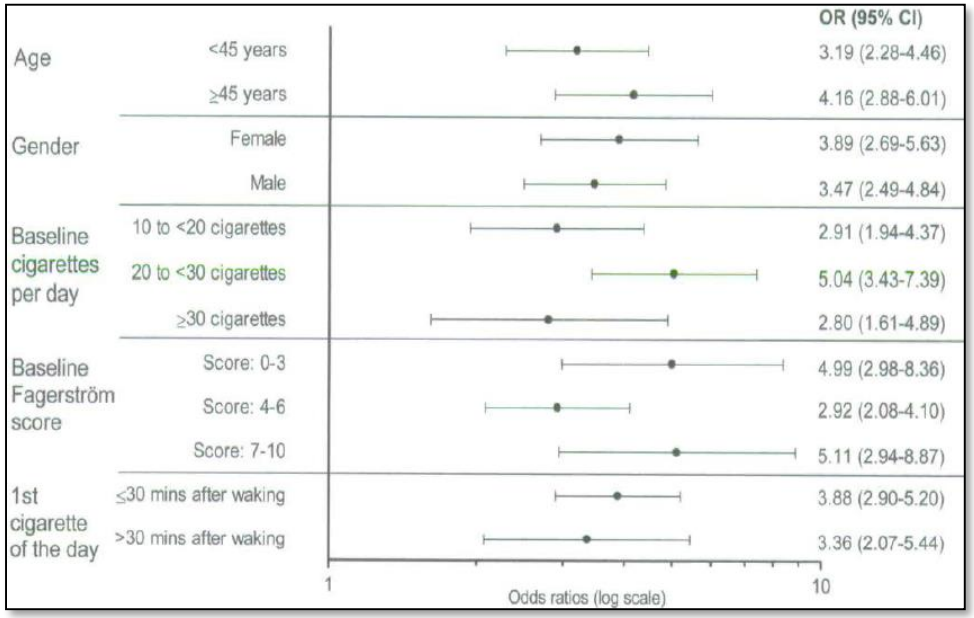
JAMA 2006;296:47

Varenicline Versus Bupropion SR or Placebo for Smoking Cessation: A Pooled Analysis

- At least 10 cigarettes per day
- No period of abstinence 3ms
- 2,052 subjects

OR	Week 9-12	Week 9-24	Week 9-52
VAR vs. Pbo	3.66 (P<0.0001)	3.14 (P<0.0001)	2.80 (P<0.0001)
VAR vs. BUP	1.88 (P<0.0001)	1.64 (P=0.0001)	1.59 (P=0.0008)
BUP vs Pbo	1.97 (P<0.0001)	1.91 (P<0.0001)	1.76 (P=0.0007)





OR for wks 9-12 VR vs PBO (continuous abstinence Rate)

Am J Health Behav 2008;32:64

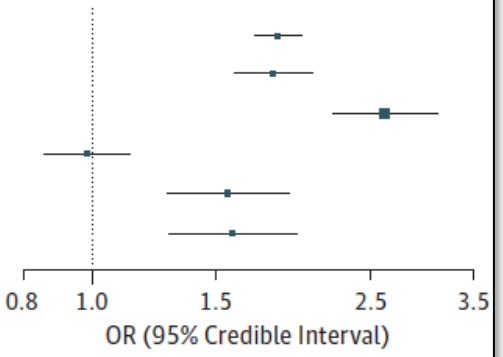
JAMA Clinical Evidence Synopsis

Pharmacological Treatments for Smoking Cessation

- To determine most effective treatment among NRT, Bupropion, Varenicline
- Data from 12 Cochrane reviews of 26 different treatments
- Network meta-analysis

Figure. Odds Ratios for Smoking Abstinence of 6 Months or More

Comparison (Intervention vs Control)	No. of Studies	Total No. of Individuals	Absolute Quit Rates: Intervention n/N (%)	Absolute Quit Rates: Control n/N (%)	Odds Ratio (95% Credible Interval)
NRT vs placebo	119	51225	4704/27258 (17.3)	2464/23967 (10.3)	1.84 (1.71-1.99)
Bupropion vs placebo	36	11440	1214/6409 (18.9)	535/5031 (10.6)	1.82 (1.60-2.06)
Varenicline vs placebo	15	6293	964/3496 (27.6)	332/2797 (11.9)	2.88 (2.40-3.47)
Bupropion vs NRT	8	2581	191/954 (20.0)	375/1627 (23.0)	0.99 (0.86-1.13)
Varenicline vs NRT	0	0	NA	NA	1.57 (1.29-1.91)
Varenicline vs bupropion	3	1622	174/823 (21.1)	111/799 (13.9)	1.59 (1.29-1.96)



JAMA 2014;311:193

Varenicline
부작용

- 부작용: 메스꺼움, 수면장애, 변비, 두통 등.
  - 약물의 용량 점진적 변화, 식후 충분한 양의 물과 함께 복용
- 신장을 통해 배설, GFR<30mL/min나 투석 경우 용량 감소
- 바레니클린이 심혈관계질환과 정신질환을 유발 또는 악화 가능성
  - FDA에서 경고 문구 삽입.(Black box warning)
- 처방 금기

- 우울증, 정신분열증, 자살 충동 환자
- FDA 임신 Class C, 임신 여성에서 그 효과 불확실.

Safety

Table 2 Prevalence of side effects of bupropion SR (range %). Pooled data from trials in Table 1

	Placebo %	Bupropion %
Insomnia[a]	9–21	24–42
Headache	3–33	4–33
Dry mouth[b]	4–24	6–28
Rash/Pruritus	7	15
Rhinitis	12–17	10–14
Nausea/Vomiting	5–6	9–13
Dizziness	1–6	2–11
Anxiety	5–11	5–9
Flu syndrome	6–11	4–9
Taste perversion	5	6
Constipation	1	5–6
Sweating	3	5
Mood disorder	4	4

Bupropion

Table 3. Adverse Events Occurring During Treatment Plus 30 Days in 2% or More of Participants Who Received 1 or More Doses of Study Drug in Either Treatment Group[a]

	No. (%)		
Adverse Events	Varenicline Group (n = 751)	Placebo Group (n = 742)	Risk Difference, % (95% CI)
Nausea	209 (27.8)	67 (9.0)	18.80 (14.99 to 22.61)
Nasopharyngitis	98 (13.0)	89 (12.0)	1.05 (−2.30 to 4.41)
Abnormal dreams	86 (11.5)	43 (5.8)	5.66 (2.83 to 8.49)
Insomnia	80 (10.7)	51 (6.9)	3.78 (0.92 to 6.64)
Upper respiratory tract infection	63 (8.4)	63 (8.5)	−0.10 (−2.92 to 2.72)
Headache	62 (8.3)	54 (7.3)	0.98 (−1.74 to 3.69)
Anxiety	52 (6.9)	65 (8.8)	−1.84 (−4.56 to 0.89)
Fatigue	46 (6.1)	34 (4.6)	1.54 (−0.74 to 3.82)
Irritability	39 (5.2)	30 (4.0)	1.15 (−0.98 to 3.28)
Constipation	38 (5.1)	13 (1.8)	3.31 (1.48 to 5.14)
Increased appetite	37 (4.9)	30 (4.0)	0.88 (−1.22 to 2.98)
Sleep disorder	37 (4.9)	29 (3.9)	1.02 (−1.06 to 3.10)
Dizziness	32 (4.3)	27 (3.6)	0.62 (−1.35 to 2.60)
Vomiting	31 (4.1)	13 (1.8)	2.38 (0.67 to 4.08)

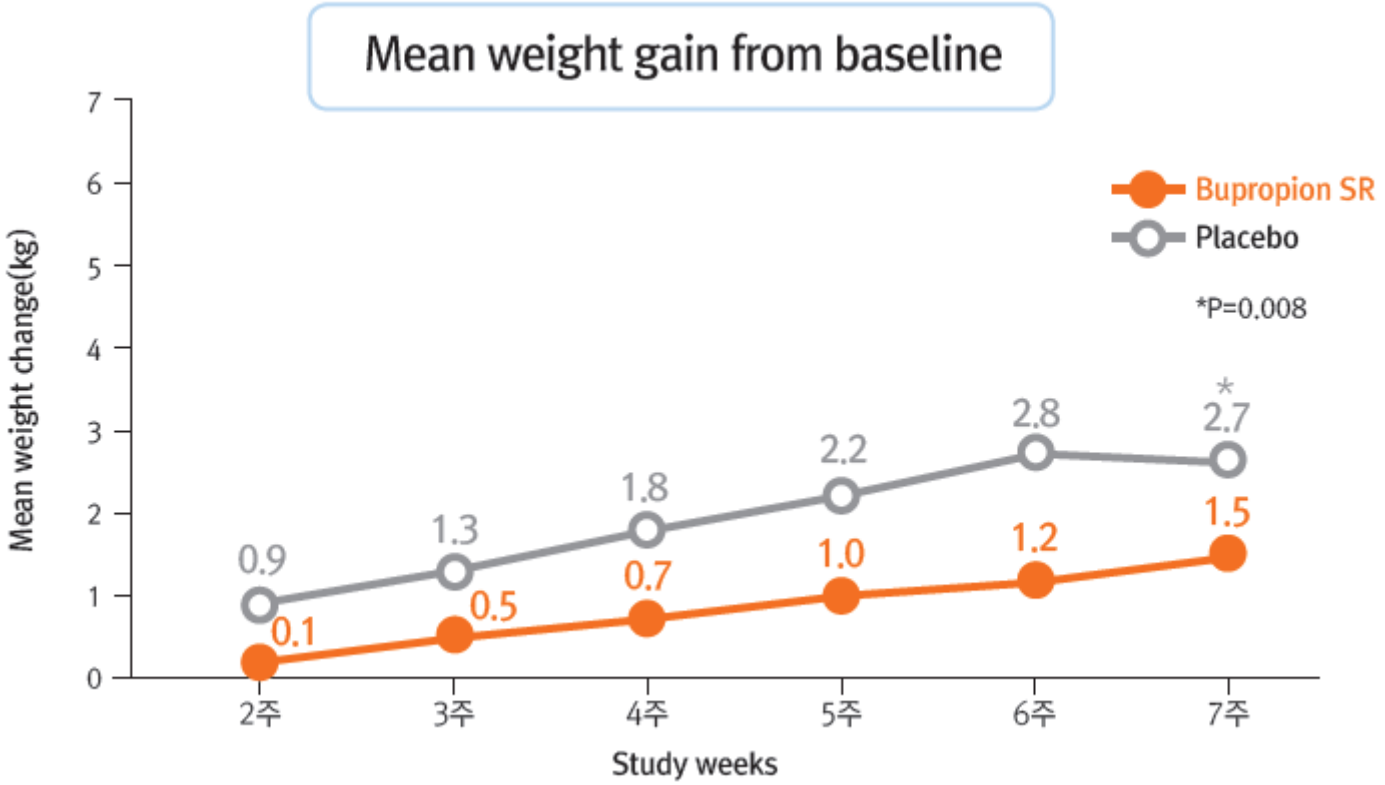
Varenicline

Int J COPD 2008;3:45

A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation

P. TØNNESEN[1], S. TONSTAD[2], A. HJALMARSON[3], F. LEBARGY[4], P. I. VAN SPIEGEL[5],

Weight change



Design : randomized, double-blind, placebo controlled trial
Poulation : 707 Smokers aged >18 years of age who had smoked an average of 10 cigarettes per day on average during the previous 12 months
Methods : randomized in a 3 : 1 ratio to receive bupropion SR 150 mg twice daily or placebo throughout the 7-week treatment phase
Outcomes : Seven-week and 12-month abstinence rates

Journal of Internal Medicine 2003; 254: 184

Interventions for preventing weight gain after smoking cessation (Review)

- 11 Trials for post-cessation wt gain

Analysis 11.1. Comparison 11 Varenicline versus bupropion: weight change, Outcome 1 Mean weight change (kg) at end of treatment.

Review: Interventions for preventing weight gain after smoking cessation

Comparison: 11 Varenicline versus bupropion: weight change

Outcome: 1 Mean weight change (kg) at end of treatment

Study or subgroup	Varenicline N	Mean(SD)	Bupropion N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 AD Gonzales 2006	155	2.37 (2.76)	95	2.12 (1.8)		54.4 %	0.25 [-0.32, 0.82]
2 AD Nides 2006	24	1.96 (2.3)	22	1.68 (1.92)		11.7 %	0.28 [-0.94, 1.50]
2 AD Jorenby 2006	151	2.89 (2.94)	151	1.88 (3.4)		33.9 %	1.01 [0.29, 1.73]
Total (95% CI)	**330**		**268**			**100.0 %**	**0.51 [0.09, 0.93]**

Heterogeneity: $Chi^2 = 2.82$, $df = 2$ ($P = 0.24$); $I^2 = 29\%$

Test for overall effect: $Z = 2.40$ ($P = 0.016$)

In three studies compared bupropion to varenicline, **participants taking bupropion gained significantly less weight** at the end of treatment than those on varenicline (-0.51kg [-0.93kg to -0.09kg]).

Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006219.

Cardiovascular Events Associated With Smoking Cessation Pharmacotherapies

A Network Meta-Analysis

비교군	모든 심혈관 부작용	주요 심혈관 부작용
모든 임상시험		
니코틴대체제 vs 위약	2.29 (1.39–3.82)	1.95 (0.92–4.30)
부프로피온 vs 위약	0.98 (0.54–1.73)	0.45 (0.21–0.85)
바레니클린 vs 위약	1.30 (0.79–1.73)	1.34 (0.66–2.66)
부프로피온 vs 바레니클린	0.76 (0.33–1.73)	0.33 (0.16–0.87)
부프로피온 vs 니코틴대체제	0.43 (0.19–0.91)	0.23 (0.08–0.63)
바레니클린 vs 니코틴대체제	0.56 (0.25–1.27)	0.67 (0.26–1.90)
고위험군		
니코틴대체제 vs 위약	1.31 (0.58–3.32)	1.53 (0.38–6.24)
부프로피온 vs 위약	1.06 (0.59–2.04)	0.48 (0.18–1.21)
바레니클린 vs 위약	0.99 (0.45–1.88)	1.22 (0.44–2.90)
부프로피온 vs 바레니클린	1.09 (0.46–2.92)	0.39 (0.11–1.49)
부프로피온 vs 니코틴대체제	0.81 (0.26–2.26)	0.31 (0.05–1.68)
바레니클린 vs 니코틴대체제	0.92 (0.34–2.19)	0.81 (0.13–4.20)

- To evaluate 3 licened therapies were associated with increased risk of CVD
- 63 RCT

Circulation 2014;129:28

FDA alert (Feb 1, 2008)

- **Black Box warning** (Package Insert Update)

WARNINGS and PRECAUTIONS

Serious neuropsychiatric symptoms have occurred in patients being treated with Varenicline. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. All patients being treated with Varenicline should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior.

- **블랙박스 Warning**

- 시판 후 조사 (PMS: Post-Marketing Surveillance) 결과, 심각하거나 생명을 위협하는 위험에 대해서 명시하도록, 검은색 바탕에 흰색/노란색 글씨로 warning함

Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study

- To compare the risk of suicide, self harm, depression varenicline or BP with NRT
- 349 GP in England. Prospective cohort study with Clinical Practice Research Datalink
- 119,546 subjects,

Smoking cessation product	Total person time (person years)	No of events/No of patients prescribed product	Hazard ratio (95% CI)	
			Basic model*	Fully adjusted model†
Main cohort: treatment initiators				
Fatal and non-fatal self harm				
NRT	19 196	69/78 407	1	1
Bupropion	1622	4/6568	0.62 (0.22 to 1.70)	0.83 (0.30 to 2.31)
Varenicline	7363	19/30 352	0.70 (0.41 to 1.18)	0.88 (0.52 to 1.49)
Treated depression‡				
NRT	10 315	799/42 475	1	1
Bupropion	961	40/3910	0.56 (0.41 to 0.77)	0.63 (0.46 to 0.87)
Varenicline	4435	255/18 386	0.69 (0.60 to 0.80)	0.75 (0.65 to 0.87)
All cause mortality				
NRT	19 947	292/81 496	1	1
Bupropion	1665	5/6740	0.31 (0.13 to 0.74)	0.39 (0.16 to 0.95)
Varenicline	7575	33/31 227	0.37 (0.26 to 0.54)	0.44 (0.30 to 0.63)

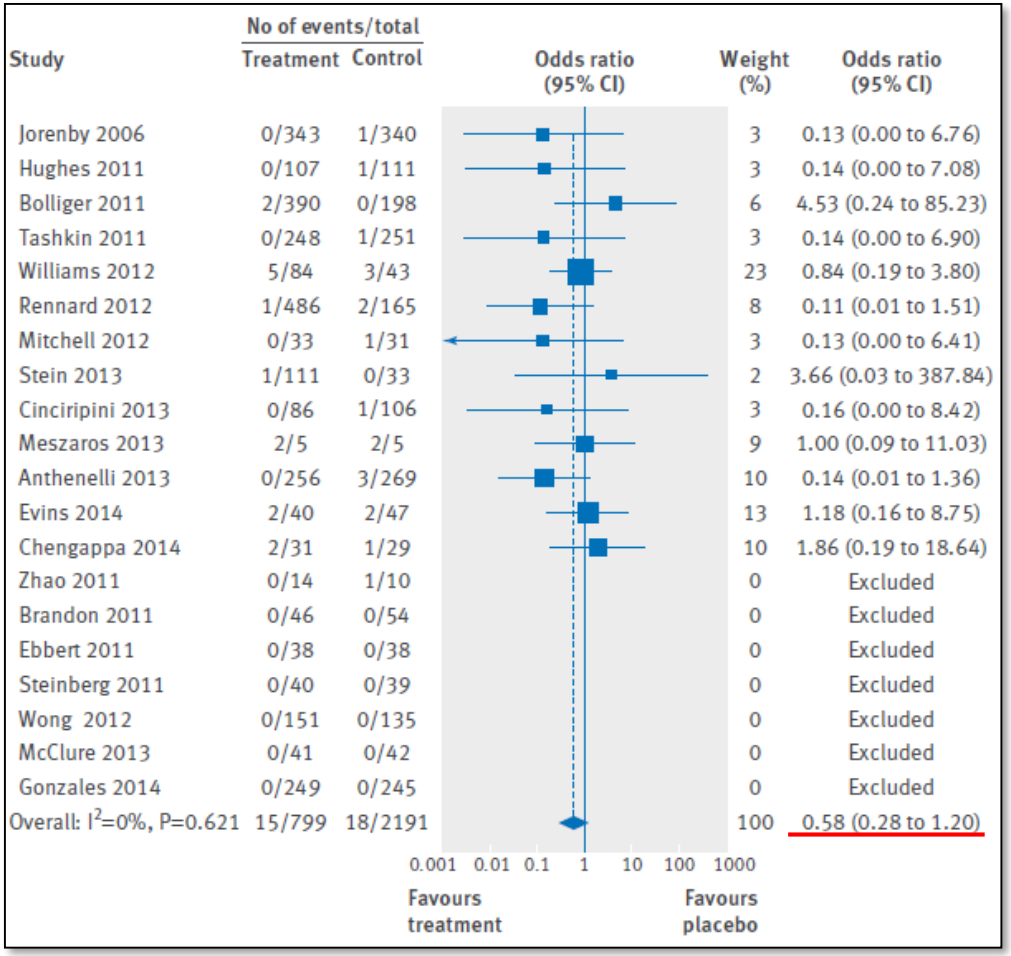
No evidence of an increased risk of fatal or non-fatal self harm or depression in individuals prescribed varenicline or bupropion compared with NRT therapy.

BMJ 2013;347:f5704

Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis

Kyla H Thomas, Richard M Martin, Duleeka W Knipe, Julian P T Higgins, David Gunnell

- To assess risk of neuropsychiatric adverse events compared to placebo
- SR, Meta-analysis
- 39 RCT (10,761 subjects)

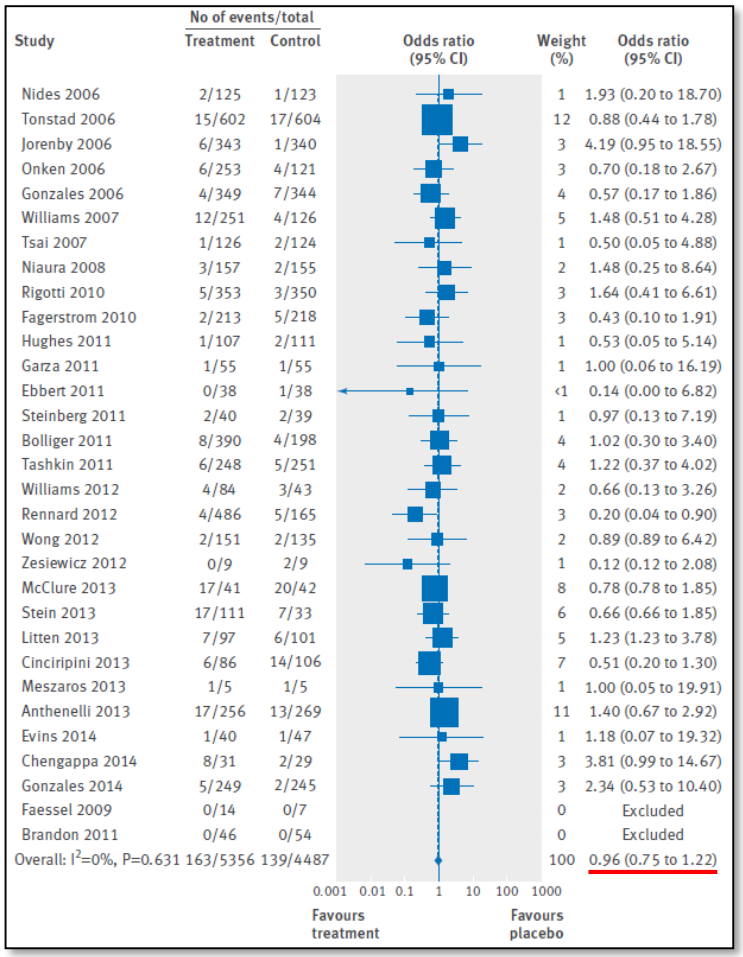


Study	No of events/total: Treatment	Control	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)
Jorenby 2006	0/343	1/340		3	0.13 (0.00 to 6.76)
Hughes 2011	0/107	1/111		3	0.14 (0.00 to 7.08)
Bolliger 2011	2/390	0/198		6	4.53 (0.24 to 85.23)
Tashkin 2011	0/248	1/251		3	0.14 (0.00 to 6.90)
Williams 2012	5/84	3/43		23	0.84 (0.19 to 3.80)
Rennard 2012	1/486	2/165		8	0.11 (0.01 to 1.51)
Mitchell 2012	0/33	1/31		3	0.13 (0.00 to 6.41)
Stein 2013	1/111	0/33		2	3.66 (0.03 to 387.84)
Cinciripini 2013	0/86	1/106		3	0.16 (0.00 to 8.42)
Meszaros 2013	2/5	2/5		9	1.00 (0.09 to 11.03)
Anthenelli 2013	0/256	3/269		10	0.14 (0.01 to 1.36)
Evins 2014	2/40	2/47		13	1.18 (0.16 to 8.75)
Chengappa 2014	2/31	1/29		10	1.86 (0.19 to 18.64)
Zhao 2011	0/14	1/10		0	Excluded
Brandon 2011	0/46	0/54		0	Excluded
Ebbert 2011	0/38	0/38		0	Excluded
Steinberg 2011	0/40	0/39		0	Excluded
Wong 2012	0/151	0/135		0	Excluded
McClure 2013	0/41	0/42		0	Excluded
Gonzales 2014	0/249	0/245		0	Excluded
Overall: I^2=0%, P=0.621	15/799	18/2191		100	0.58 (0.28 to 1.20)

0.001 0.01 0.1 1 10 100 1000

Favours treatment — Favours placebo

Suicidal ideation



Study	No of events/total: Treatment	Control	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)
Nides 2006	2/125	1/123		1	1.93 (0.20 to 18.70)
Tonstad 2006	15/602	17/604		12	0.88 (0.44 to 1.78)
Jorenby 2006	6/343	1/340		3	4.19 (0.95 to 18.55)
Onken 2006	6/253	4/121		3	0.70 (0.18 to 2.67)
Gonzales 2006	4/349	7/344		4	0.57 (0.17 to 1.86)
Williams 2007	12/251	4/126		5	1.48 (0.51 to 4.28)
Tsai 2007	1/126	2/124		1	0.50 (0.05 to 4.88)
Niaura 2008	3/157	2/155		2	1.48 (0.25 to 8.64)
Rigotti 2010	5/353	3/350		3	1.64 (0.41 to 6.61)
Fagerstrom 2010	2/213	5/218		3	0.43 (0.10 to 1.91)
Hughes 2011	1/107	2/111		1	0.53 (0.05 to 5.14)
Garza 2011	1/55	1/55		1	1.00 (0.06 to 16.19)
Ebbert 2011	0/38	1/38		<1	0.14 (0.00 to 6.82)
Steinberg 2011	2/40	2/39		1	0.97 (0.13 to 7.19)
Bolliger 2011	8/390	4/198		4	1.02 (0.30 to 3.40)
Tashkin 2011	6/248	5/251		4	1.22 (0.37 to 4.02)
Williams 2012	4/84	3/43		2	0.66 (0.13 to 3.26)
Rennard 2012	4/486	5/165		3	0.20 (0.04 to 0.90)
Wong 2012	2/151	2/135		2	0.89 (0.89 to 6.42)
Zesiewicz 2012	0/9	2/9		1	0.12 (0.12 to 2.08)
McClure 2013	17/41	20/42		8	0.78 (0.78 to 1.85)
Stein 2013	17/111	7/33		6	0.66 (0.66 to 1.85)
Litten 2013	7/97	6/101		5	1.23 (1.23 to 3.78)
Cinciripini 2013	6/86	14/106		7	0.51 (0.20 to 1.30)
Meszaros 2013	1/5	1/5		1	1.00 (0.05 to 19.91)
Anthenelli 2013	17/256	13/269		11	1.40 (0.67 to 2.92)
Evins 2014	1/40	1/47		1	1.18 (0.07 to 19.32)
Chengappa 2014	8/31	2/29		3	3.81 (0.99 to 14.67)
Gonzales 2014	5/249	2/245		3	2.34 (0.53 to 10.40)
Faessel 2009	0/14	0/7		0	Excluded
Brandon 2011	0/46	0/54		0	Excluded
Overall: I^2=0%, P=0.631	163/5356	139/4487		100	0.96 (0.75 to 1.22)

0.001 0.01 0.1 1 10 100 1000

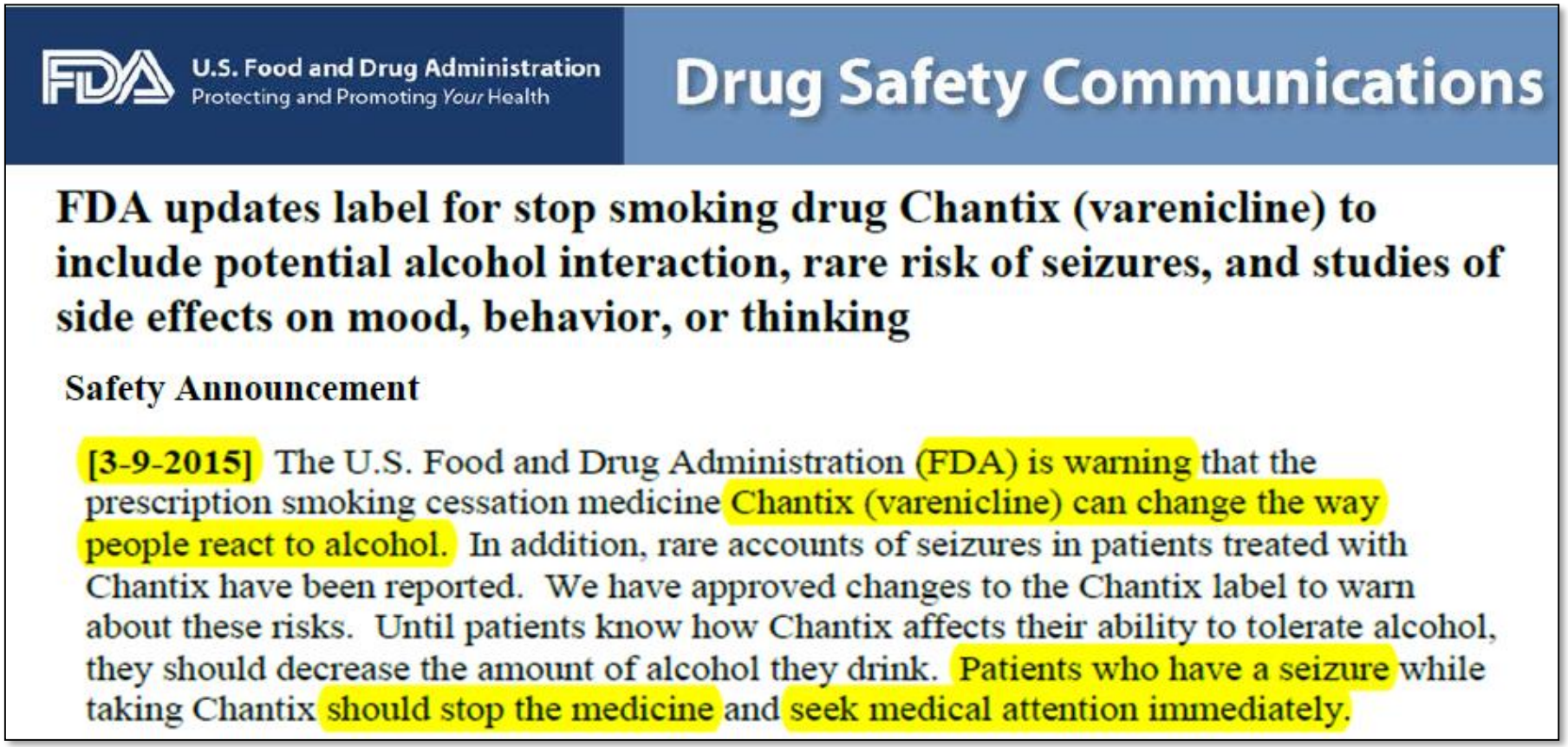
Favours treatment — Favours placebo

Depression

BMJ 2015;350:h1109

KFDA alert (Mar 12, 2015)

- 챔픽스, 알코올 상호작용 및 발작위험 가능성
  - 음주량이 많은 환자에게는 신중 투여



U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

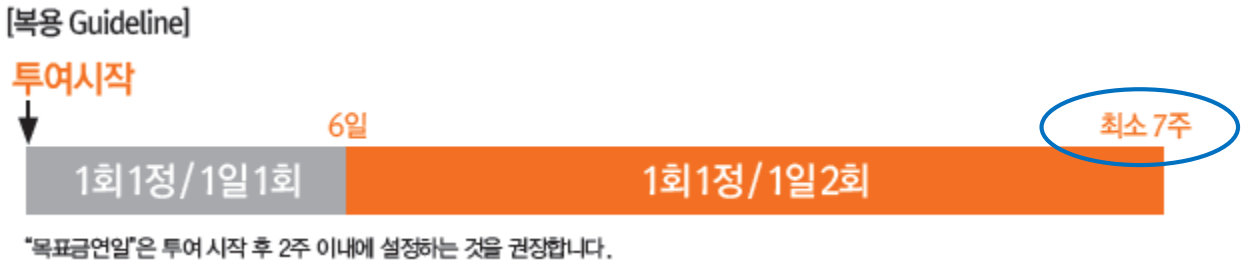
FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking

Safety Announcement

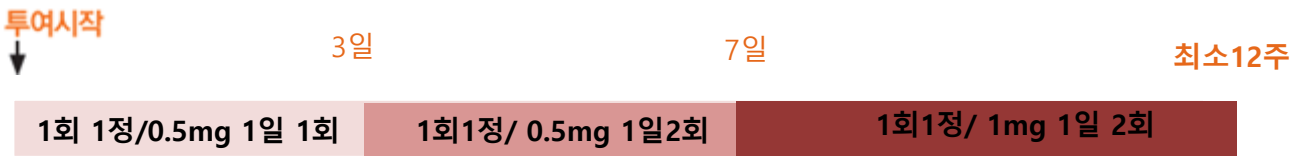
[3-9-2015] The U.S. Food and Drug Administration (FDA) is warning that the prescription smoking cessation medicine Chantix (varenicline) can change the way people react to alcohol. In addition, rare accounts of seizures in patients treated with Chantix have been reported. We have approved changes to the Chantix label to warn about these risks. Until patients know how Chantix affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients who have a seizure while taking Chantix should stop the medicine and seek medical attention immediately.

Regimen : Bupropion SR vs. Varenicline

Bupropion HCl



Varenicline



Simple titration & short term regimen

금연치료의약품 및 금연보조제 지원 기준표

구 분		금연치료의약품		금연보조제	
		부프로피온	바레니클린	니코틴패치	껌, 정제
1일 용법		2정	2정	1일 1장	1일 4~12정
12주 (84일)	공단 사업비 지원 한도	정 당 500원	정 당 1,000원	日 당 1,500원	
	국고 지원 한도액	日 당 1,360원	日 당 3,540원	日 당 2,940원	

[예시 : 12주 기준 금연치료 프로그램 비용]

(단위 : 원)

구분	총비용	건보지원			본인부담		
		소계	상담/약국	의약품/보조제	소계	상담/약국	의약품/보조제
패치 단독 사용 (1일1장, 총84매)	185,700	164,100	50,400	113,700	21,600	21,600	0
부프로피온 (1일2정, 총168정)	186,200	134,400	50,400	84,000	51,800	21,600	30,200
바레니클린 (1일2정, 총168정)	368,900	218,400	50,400	168,000	150,500	21,600	128,900

* 12주 프로그램을 모두 이수한 경우(상담 6회, 약국 방문 6회 기준)

Combination Varenicline and Bupropion SR for Tobacco Dependence Treatment in Cigarette Smokers: A Randomized Trial

- Efficacy of VR+BR vs VR
- 12wks intervention and 52wks f/u
- RCTBD multicenter trial (n=506)
- Primary outcome: abstinence rates at wk 12 (prolonged and point)

		7-Day Point-Prevalence Smoking Abstinence[a]			Prolonged Smoking Abstinence[a]	
	N[b]	No. (%)	OR (95% CI)	*P*	No. (%)	OR (95% CI)	*P*
Overall							
Week 12							
Varenicline+Bupropion SR	249	140 (56.2)	1.36 (0.95, 1.93)	.090	132 (53.0)	1.49 (1.05, 2.12)	.028
Varenicline+Placebo	257	125 (48.6)			111 (43.2)		
Week 26							
Varenicline+Bupropion SR	249	95 (38.2)	1.32 (0.91, 1.91)	.140	91 (36.6)	1.52 (1.04, 2.22)	.031
Varenicline+Placebo	257	82 (31.9)			71 (27.6)		
Week 52							
Varenicline+Bupropion SR	249	91 (36.6)	1.40 (0.96, 2.05)	.077	77 (30.9)	1.39 (0.93, 2.07)	.106
Varenicline+Placebo	257	75 (29.2)			63 (24.5)		

JAMA 2014;311:155

약물 병합 치료

- 바레니클린 + NRT or 부프로피온: 추천되지 않지만, 흡연량이 많거나 니코틴 의존도가 높은 흡연자에서 효과적이었다는 일부 연구들이 발표
- 부작용: 피부 부작용이 많거나(니코틴패치의 병용) 불안, 우울감 등이 더 많았다는(부프로피온과의 병용) 보고가 있어 아직은 제한적으로 사용해보는 것을 추천

약물 선택

- 1차 금연 치료 약물: 부프로피온, 바레니클린이 우선적으로 추천
- 여러 연구를 통해 단독요법으로는 바레니클린> 부프로피온 효과 보고
- 개인이 가지고 있는 유전 형질에 따라 약에 따른 반응 정도도 차이가 있음

- 약제 간의 효과의 차이를 염두에 두면서 (효과 vs 부작용)
- 내담자가 가지고 있는 약물 선호도 (체중 증가, 편리성, 약가)
- 이전 금연 약물 치료의 효과
- 개인 특성(성별, 연령, 사회경제적 요건 등)을 고려하여 약물을 선택하는 것이 일반적인 원칙

Cochrane Database Syst Rev. 2013;5:CD009329
Addiction 2014;109:128