

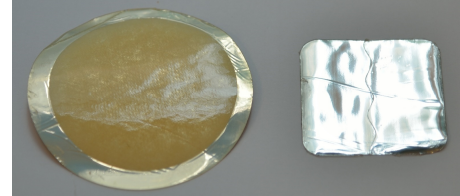
## 戒菸藥物治療：藥物治療常見問題與對策

臺安醫院 吳憲林

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## 尼古丁貼片

- 每天貼一次，方便使用。
- 可與其他尼古丁製劑合併使用。
- 流汗多時貼不住



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介入模式	長期戒菸率(%)
沒介入	3
簡短、隨機勸導	5
簡短、隨機勸導 + NRT	10
專家深度戒菸支持	10
專家深度戒菸支持 + NRT	18

West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;55:987-99.

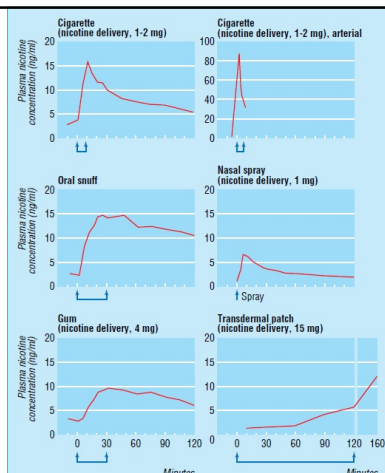
2

## 尼古丁貼片副作用

- 皮膚反應-高達50%的病人有局部發紅。皮膚反應經常輕微且自己會好。每天換貼的部位可以緩解。
- 嚴重時用類固醇藥膏。
- 少於5%的病患因此停止貼片。
- 失眠與/或清楚的夢。



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## 避開會摩擦到的地方



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## 尼古丁貼片特色

- 固定劑量，不能自己調整劑量。
- 藥效在使用後數小時內緩慢增加，血中濃度穩定。
- 使用時不會產生愉悅感，也較不會因濃度下降而出現戒斷症狀。
- 睡眠時也補充尼古丁，劑量過大時睡不著。緩解清晨第一根菸的渴望。

<http://www.nlm.nih.gov/medlineplus/ency/article/007438.htm>

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## 調整劑量

- 持續吸菸，且有明顯戒斷症狀，或常用短效尼古丁，就要增加劑量。
- 易怒、焦慮、挫敗、無法專心、渴望吸菸
- 許多使用貼片無法成功的病人可能是因為劑量不足，而且可能把尼古丁戒斷症狀誤認為是使用貼片的關係而不是藥物劑量不足。
- 假如症狀可用短效尼古丁改善，就不是藥物副作用。尼古丁過量最重要的副作用是噁心。

MICHAEL V. BURKE, EDD; JON O. EBBERT, MD, MSC; AND J. TAYLOR HAYS, MD  
Treatment of Tobacco Dependence *Mayo Clin Proc.* 2004;83(4):479-484

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## 尼古丁貼片劑量

- 21mg 貼片產生血中濃度大約是吸菸者的一半
- Benowitz N. Pharmacodynamics of nicotine: implications for rational treatment of nicotine addiction. *Br J Addict* 1991; 86:495-9
- 突然停止跟逐漸減量成功率一樣。
- Fiore MC, Smith SS, Jorenby DE et al. The effectiveness of the nicotine patch for smoking cessation: a metaanalysis. *JAMA* 1994;271(24):1940-1947.
- Silagy C, Stead LF. Physician advice for smoking cessation (Cochrane Review). In: *The Cochrane Library, Issue 1, 2003. Oxford:Update Software.*

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## 減量

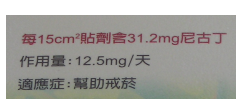
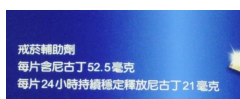
- 正確劑量使用4週後，開始減量。
- 每兩週減量7-14毫克。
- 假如不舒服就聯絡我們。這時的劑量就維持，在1-2週內不減量。

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## 尼古丁貼片起始劑量略估

- 劑量略大於每天吸菸數。
- 每天20根菸，就用30號貼片。
- 信東15號劑量12.5毫克
- 諾華30號劑量21毫克



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## 使用注意事項

- 要選擇適當劑量，劑量選錯了，病患自己難修正。
- 劑量過低沒效；過高會心悸、頭暈、頭痛、反胃。

## 尼古丁貼片使用建議

- 使用24小時，每天睡醒更換新貼片。
- 貼在平坦、沒有毛的地方。
- 假如貼貼片造成噩夢不舒服，嘗試睡前移除貼片。
- 每天吸菸量少於10根菸，應從較低劑量開始，例如14毫克。

<http://www.nlm.nih.gov/medlineplus/ency/article/007438.htm>

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## 使用者調整劑量

- 每天多次使用以調整心情。
- 戒菸者可以調整使用劑量。
- 戒菸早期使用劑量不足會降低戒菸率。

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## 尼古丁咀嚼錠、咀嚼錠、吸入劑

- 在口腔吸收。在酸性環境難吸收。喝酸性飲料(如：果汁、汽水、可樂、咖啡、茶)後就要等15分鐘再開始使用。
- 使用後10分鐘內藥效慢慢出現，也慢慢的退。使用者心情像吸菸一樣會起落，只是幅度沒有吸菸來得大。
- 戒菸者像吸菸一樣週期性使用，睡眠時尼古丁濃度下降。

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## 尼古丁咀嚼錠攝取量的研究

- **Determinants of nicotine intake while chewing nicotine polacrilex gum**
- Neal L Benowitz MD\*, Peyton Jacob III PhD and Chin Savanapridi MD
- *Clinical Pharmacology and Therapeutics* (1987) **41**, 467–473

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## 咀嚼錠、口含錠、吸入劑

- 戒菸者可以藉著使用藥物主動控制尼古丁變化有關的心情變化。
- 想抽菸的衝動出現時，可以對應，有能控制的感覺。
- 尼古丁濃度高低起伏，尼古丁可以再敏感化，尼古丁的藥效每天都存在。

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## 研究對象

- 14吸菸者，10男4女，22-62歲(中位數34歲)
- 每天吸菸 $35 \pm 11$  (SD)根菸(20-60)
- 平均吸菸 $20 \pm 12$ 年(7-48年)
- 機器測量尼古丁 $1.1 \pm 0.3$ mg
- 下午血中cotinine $293 \pm 68$  ng/ml (170-437)，這與吸菸族群整體相似。

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### 分組

- 嚼錠時期：9AM-9PM每小時用一顆咀嚼錠 (2mg x 7, 4mg x 7)，每顆嚼20分鐘。
- 3-4天後，兩小時抽一次血。抽血時是開始用嚼錠後40分鐘。
- 吸菸時期：隨意吸菸，2小時到就抽血
- 9AM與3PM更常抽血(使用前、20,40,60分鐘後)，以測量nicotine與cotinine濃度。

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### 吸菸與嚼錠每天攝取量

分組	吸菸			嚼錠		
	根/天	每天攝取尼古丁mg	每根菸攝取尼古丁	每天攝取尼古丁mg	每顆藥攝取尼古丁	嚼錠尼古丁釋出率
2mg n=7	38 ± 7	33.5 ± 9.5	0.91 ± 0.27	10.2 ± 3.9	0.85 ± 0.33	1.07 ± 0.29
	24-48	20.6-46.1	0.51-1.36	4.5-16.8	0.38-1.40	0.62-1.45
4mg n=7	37 ± 21	34.8 ± 13.9	1.11 ± 0.51	14.7 ± 5.5	1.22 ± 0.46	2.87 ± 0.39
	19-80	14.9-56.1	0.31-1.82	10.2-21.9	0.85-1.92	2.30-3.44

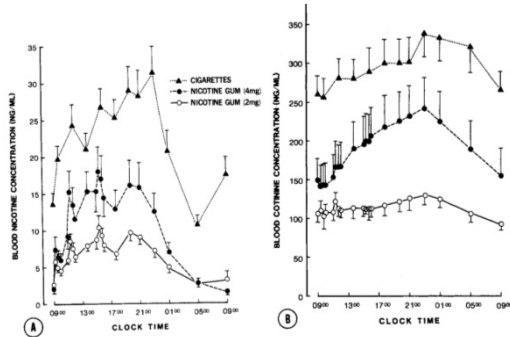
Table 1. Daily intake of nicotine from cigarette smoking and nicotine gum

Group	Cigarette smoking			Gum		
	Cigarettes/day	24-hr nicotine intake (mg)	Nicotine intake per cigarette (mg)	24-hr nicotine intake (mg)	Nicotine intake per piece (mg)	Nicotine extracted per piece* (mg)
2 mg (n = 7)	38 ± 7	33.5 ± 9.5	0.91 ± 0.27	10.2 ± 3.9	0.85 ± 0.33	1.07 ± 0.29
4 mg (n = 7)	37 ± 21	34.8 ± 13.9	1.11 ± 0.51	14.7 ± 5.5	1.22 ± 0.46	2.87 ± 0.39

Clinical Pharmacology and Therapeutics (1987) 41, 467-473

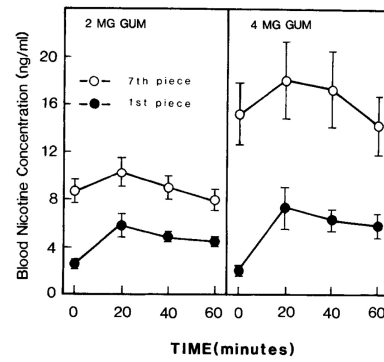
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### 血中尼古丁濃度



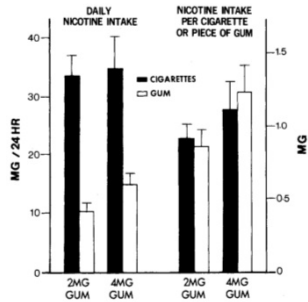
Clinical Pharmacology and Therapeutics (1987) 41, 467-473

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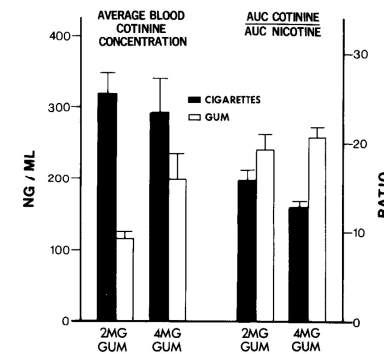
23

### 每天尼古丁攝取量 每根菸或藥吸收量



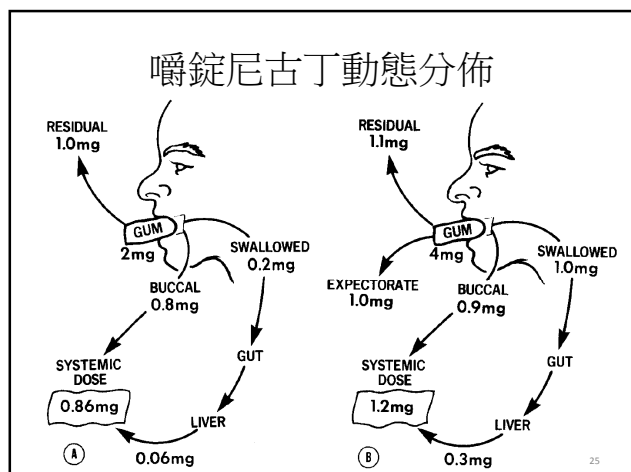
Clinical Pharmacology and Therapeutics (1987) 41, 467-473

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### 嚼錠尼古丁動態分佈



### 嚼錠配合戒菸班

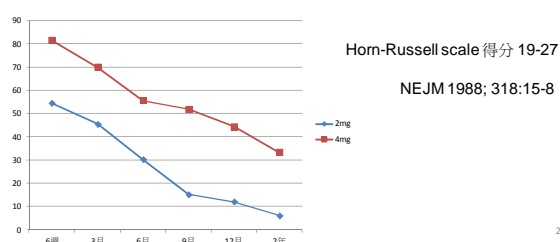
- 173吸菸者，依照Horn-Russell 量表分為高依賴與中低依賴。
- 隨機雙盲研究
- 60高依賴者分配到4mg咀嚼錠(n=27)或2mg(n=33)咀嚼錠
- 113中低依賴者分配到2mg咀嚼錠(n=60)或安慰劑(n=53)
- 所有人都參加戒菸班

- 我們很少單獨使用尼古丁咀嚼錠，經常是建議用 2毫克或 4毫克咀嚼錠配合尼古丁貼片一起用。
- 我們建議病患使用咀嚼錠以對付渴望及戒斷。
- 咬幾下，感到麻辣的味道時，就停幾分鐘
- 習慣咬口香糖的人可能很難不一直咬。
- 一天最多可用20顆，但是大多數的人用太少顆。

MICHAEL V. BURKE, EDD; JON O. EBBERT, MD, MSC, AND J. TAYLOR HAYS, MD  
Treatment of Tobacco Dependence *Mayo Clin Proc.* 2004;83(4):479-484

### 高菸癮者戒菸率

研究開始時間	4mg戒菸人數(%)	2mg戒菸人數(%)	戒菸率差 95% CI
人數	27	33	
6週	81.5%	54.5%	5-49%
12月	44.4%	12.1%	10-54%
24月	33.3%	6.1%	7-47%



- 應建議病患慢慢咬(大約15口)直到辣味或麻的感覺出現。這時應放在臉頰 1-2 分鐘或直到味道消失。重複這樣做30分鐘。
- 建議剛開始時每天至少用 8-12 顆，或固定每個小時一顆。咀嚼錠規則使用較有效。

Smoking Cessation Guidelines  
For Australian General Practice 2004

### 證據與建議

- 每天吸菸20根以上，4mg咀嚼錠比2mg有效。假如要用咀嚼錠的話，應建議吸菸量大的人用4mg。

Smoking Cessation Guidelines  
For Australian General Practice 2004

## 尼古丁口含錠使用方式

- 放在臉頰與牙齦中間，兩邊輪流含。
- 不能咬、不能吞。
- 牙齒不好也能用。
- 有些人不喜歡這種黏黏的感覺。
- 含到太小顆可能會塞在牙縫裡。
- 副作用與咀嚼錠相似，包括：反胃、胸口灼熱。4毫克的口含錠可能導致頭痛。



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- 一年戒菸勝算比 2mg 口含錠是 2.10 (95% CI 1.59 - 2.79)，4mg 口含錠是 2.69 (95% CI 1.69 - 4.29)。
- Shiffman S, Dresler CM, Hajek P et al., Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med.* 2002 Jun 10; 162:1267-76
- 起床30分鐘以內吸第一根菸就用4mg

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- 單獨使用時，第一根菸時間在醒來30分鐘以內建議用4毫克，30分鐘以上建議用2毫克。
- 跟尼古丁貼片一起用時，大多用2毫克。
- 最常見的副作用是頭痛、腹瀉、胸口灼熱、打嗝與噁心。

MICHAEL V. BURKE, EDD; JON O. EBBERT, MD, MSC; AND J. TAYLOR HAYS, MD  
Treatment of Tobacco Dependence *Mayo Clin Proc.* 2004;83(4):479-484

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## 尼古丁吸入劑



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## 尼古丁咀嚼錠或口含錠

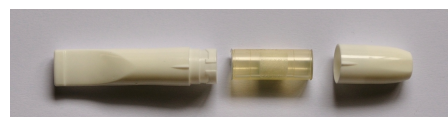
- 有些人較喜歡用，因為可調整劑量。
- 剛開始戒菸時，每小時可使用 1 - 2 顆，但是一天不要超過20顆。
- 慢慢咬，直到它產生辣味，然後放在牙齦與臉頰中間讓它吸收。
- 在6個月內停止使用咀嚼錠或口含錠。
- 在喝咖啡、茶、汽水、果汁等酸飲料之後要等15分鐘再開始使用。
- 每天吸菸25根以上，最好從4毫克開始。

<http://www.nlm.nih.gov/medlineplus/ency/article/007438.htm>

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## 尼古丁吸入劑

- 容易揮發的尼古丁存放在藥匣裡。
- 透過把手持器來吸入。
- 尼古丁會刺激呼吸道，導致咳嗽。淺吸就可以吸收，深吸較會咳嗽。
- 有些人會覺得鼻刺激。



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## 吸入劑使用錯誤

- 很多人把吸入劑當菸來吸。吸入時吸到肺部，導致咳嗽。吸完後嘴巴打開，讓藥流失。
- 吸完後嘴巴一定要閉起來。

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- **NRT**應當使用**8-12週**，但是有少部分的人會用更久(**5%**可能會用到一年)

- Hajek P, McRobbie H, Gillison F. 2007. Dependence potential of nicotine replacement treatments: Effects of product type, patient characteristics, and cost to user. *Preventive Medicine*.

New Zealand  
Smoking Cessation Guidelines 2007

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## 尼古丁吸入劑

- 放尼古丁藥匣進入手持器，然後吸大約**20分鐘**，最多一天**16次**。
- 與咀嚼錠相同，使用吸入劑後藥效來得快，比貼片需要**2-4小時**才有效快多了。
- 吸入劑滿足口慾。
- 大多數的尼古丁蒸氣並未進入肺內的呼吸道。有些人注意到會口腔與喉頭刺激、咳嗽。

<http://www.nlm.nih.gov/medlineplus/ency/article/007438.htm>

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## 尼古丁的特殊考量

- 尼古丁貼片對有心臟血管疾病的人無危險。然而吸菸導致的高密度膽固醇過低只有在尼古丁貼片停止使用後才會改善。
- 孕婦使用尼古丁可能不完全安全，雖然沒有人報告真正的壞處。使用尼古丁時，胎兒心跳較快。

<http://www.nlm.nih.gov/medlineplus/ency/article/007438.htm>

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- **20分鐘**內吸入**80口**可以提供**2毫克**尼古丁。
- 我們用它於吸菸行為與觸覺方面(拿菸、吸菸與咖啡)是重要的吸菸誘發因子。
- 最常見的副作用是嘴與喉嚨刺激，有時會咳嗽。

MICHAEL V. BURKE, EDD; JON O. EBBERT, MD, MSC; AND J. TAYLOR HAYS, MD  
*Treatment of Tobacco Dependence Mayo Clin Proc.* 2004;83(4):479-484

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## 尼古丁合併使用

- 貼片提供穩定尼古丁，想吸菸時再用其他製劑。有統合分析發現，尼古丁合併使用一年戒菸率幾乎是單獨使用的兩倍。
- Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence. Clinical Practice guideline.* Rockville, MD: US Department of Health and Human Services. Public Health Service. June 2000.
- 使用高劑量或合併使用尼古丁應監測是否有劑量過高或過低的症狀。

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For Australian General Practice 2004

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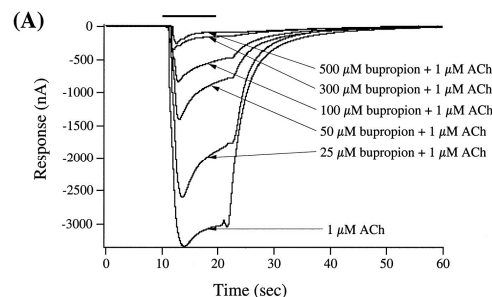
## Bupropion SR

- 是一種單環抗憂鬱劑，抑制多巴胺與正腎上腺素再吸收，但是也直接競爭性抑制作用於尼古丁接受器。
- 戒菸前一週開始用。
- 每天150mg 一次x 3天，然後 150mg 兩次 x 6-12週。
- 直接停，不用減量。

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Treatment of Tobacco Dependence *Mayo Clin Proc.* 2004;83(4):479-484

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## Bupropion 阻斷乙醯膽鹼導致的電流



Slemmer J E, Martin R M, Damaj M I (2000). "Bupropion is a Nicotinic Antagonist".  
*J Pharmacol Exp Ther* 295 (1): 321-327

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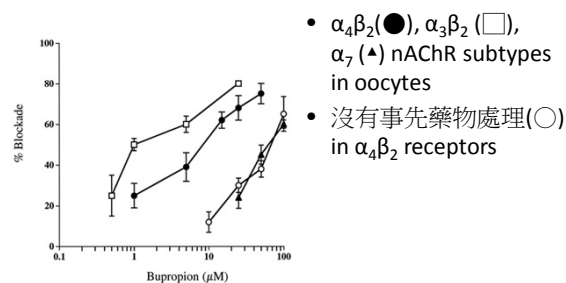
## 抑制慾望藥物

- 可以跟NRT與varenicline合併使用。
- 減少體重增加，可用於在乎體重的人。
- 使用立即釋放型的 bupropion，有飲食異常的病患會出現癲癇症。雖然緩釋型(SR)的風險較低，禁忌症包括曾經有過癲癇症、併有失去知覺的嚴重頭部外傷，使用降低癲癇門檻的藥物，或飲食異常(精神性厭食症或厭食症)
- 主要副作用是失眠與口乾。心血管與性功能副作用不常見。

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## Bupropion 濃度與它抑制各種尼古丁亞型比率



Slemmer J E, Martin R M, Damaj M I (2000). "Bupropion is a Nicotinic Antagonist".  
*J Pharmacol Exp Ther* 295 (1): 321-327

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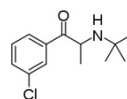
## 阻斷尼古丁接受器

- Bupropion 阻斷 $\alpha_3\beta_2$ ,  $\alpha_4\beta_2$ , 與  $\alpha_7$  神經尼古丁接受器，增加乙醯膽鹼的濃度也不能改善。
- 高濃度的bupropion無法取代腦部 $[^3\text{H}]$ 尼古丁結合位置，代表它抑制 $\alpha_3\beta_2$ 與 $\alpha_4\beta_2$ 接受器可能不是透過阻斷通道打開。
- may explain in part bupropion's efficacy in nicotine dependence. Our present findings suggest that functional blockade of neuronal nAChRs are useful in nicotine dependence treatment.

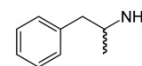
45

## Bupropion ( $\beta$ -Keto-3-chloro-N-tert-butylamphphetamine)

- 抑制正腎上腺素與多巴胺在腦部再吸收。
- 是輕微的興奮劑，常導致失眠(35-40%)。
- 禁忌：癲癇、精神性厭食症。
- 有些人用了血壓會高。



Bupropion



Amphetamine

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## 抗憂鬱劑與癲癇症

- 0.1% at 100–300 mg of bupropion, 0.4% at 300–450 mg, and 2% at 600 mg.
- 普通人 0.0003–0.00084%
- 0.1–0.6% for imipramine, 劑量有關
- 0–0.06% for amitriptyline, 劑量有關
- 0.5% for clomipramine;
- 0.4% for maprotiline;
- 0.2% for fluoxetine and fluvoxamine
  - Pisani F, Oteri G, Costa C, Di Raimondo G, Di Perri R (2002). "Effects of Psychotropic Drugs on Seizure Threshold". *Drug Safety* 25 (2): 91–110
- 長期使用抑制正腎上腺素的抗憂鬱劑普遍增加癲癇機率
  - Ahern TH, Javors MA, Eagles DA, Martelletti J, Mitchell HA, Liles LC, Weinshenker DJ (2006). "The effects of chronic norepinephrine transporter inactivation on seizure susceptibility in mice". *Neuropsychopharmacology* 31 (4): 750–8.
- 憂鬱症本身就有2-7倍癲癇症風險
  - Alper K, Schwartz KA, Kotts RL, Khan A (2007). "Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports". *Biol Psychiatry* 62 (4): 345–54.

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## 抑制CYP2B6的藥物

- Paroxetine(SSRI, Seroxat, 克憂果)
- Sertraline(SSRI, Zoloft, 樂復得)
- fluoxetine(SSRI, Prozac, 百憂解)
- Diazepam(valium)
- Clopidogrel(Plavix, 保栓通)
- Orphenadrine(中樞抗膽鹼、抗組織胺 Tensionlex)

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## 心血管

- 高血壓發生率 1%，與安慰劑並無顯著差異。
- 高血壓的憂鬱症病患，bupropion (400–500 mg/day) 造成血壓上升，但不影響心跳次數
  - Roose SP, Dalack GW, Glasman AH, Woodring S, Walsh BT, Gardina EG (1991). "Cardiovascular effects of bupropion in depressed patients with heart disease". *Am J Psychiatry* 148 (4): 512–6
- 對於沒有心血管疾病的人，300 mg/day對血壓與心跳無顯著影響
  - Aubin HJ (2002). "Tolerability and safety of sustained-release bupropion in the management of smoking cessation". *Drugs* 62 Suppl 2: 45–52
- 有個研究吸菸者因心臟病住院，使用bupropion的這組發生心血管事件的機會有1.5-倍增加(接近統計意義)，但是血壓沒有變化
  - Rigotti NA, Thordike AN, Regan S, McKool K, Pasternak RC, Chang Y, Swartz S, Torres-Finnerty N, Emmons KM, Singer DE (2006). "Bupropion for smokers hospitalized with acute cardiovascular disease". *Am J Med* 119 (12): 1080–7.

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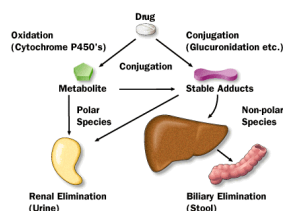
## 增加CYP2B6的藥物

- Carbamazepine(抗癲癇, Tegretol)
- Clotrimazole(抗黴菌, Canesten)
- Rifampicin(抗結核)
- Ritonavir(抗HIV, Norvir)

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## 藥物交互作用CYP2B6

- bupropion 是由cytochrome P450 CYP2B6代謝為 hydroxybupropion 。



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## 藥物交互作用CYP2D6

- Bupropion/Hydroxybupropion抑制CYP2D6 。
- 使用bupropion時，由CYP2D6代謝的藥物濃度顯著增加
- Venlafaxine(SNRI, Effexor)
- Desipramine(三環抗憂鬱劑)
- Dextromethorphan(止咳)

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### 癲癇

- 降低癲癇門檻藥物應避免，如：
- Antipsychotics
- Theophylline
- Steroids
- 某些 tricyclic antidepressants

### Varenicline



### 高血壓

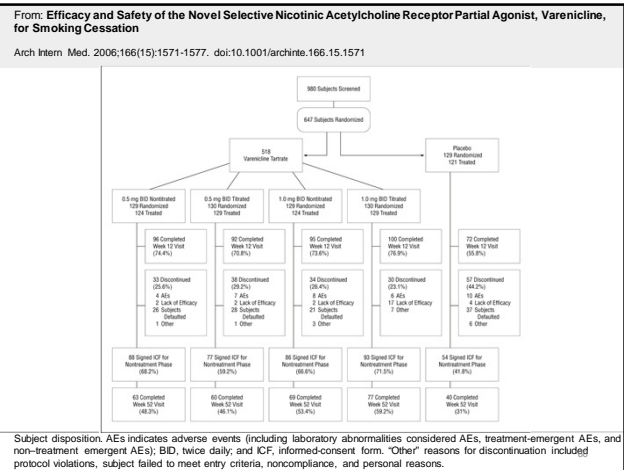
- Nicotine

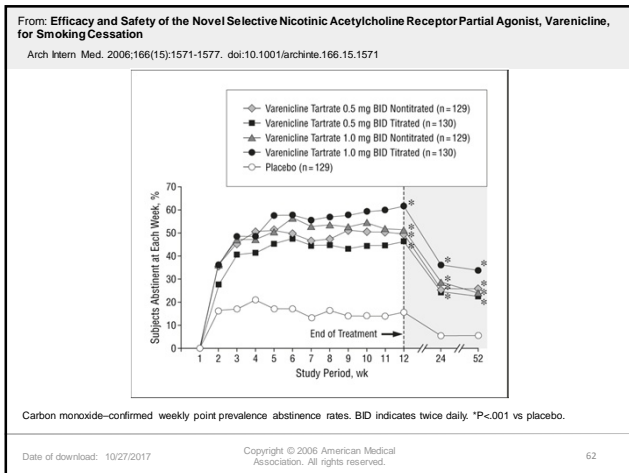
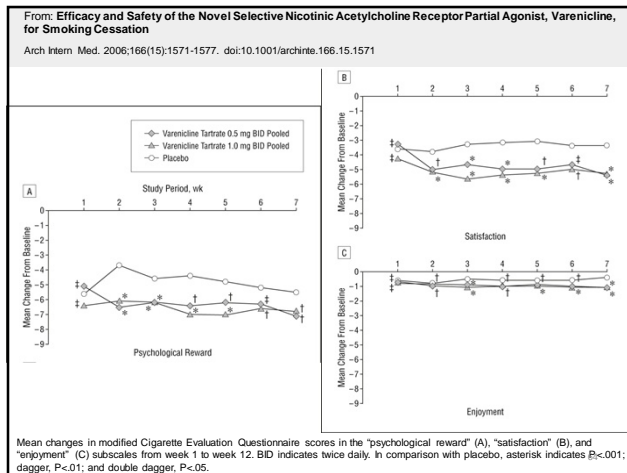
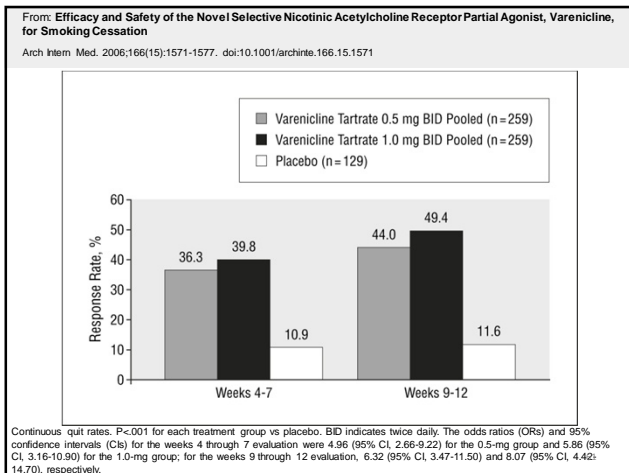
### • Efficacy and Safety of the Novel Selective Nicotinic Acetylcholine Receptor Partial Agonist, Varenicline, for Smoking Cessation

- Cheryl Oncken, MD; David Gonzales, PhD; Mitchell Nides, PhD; et al Stephen Rennard, MD; Eric Watsky, MD; Clare B. Billing, MS; Richard Anziano, MS; Karen Reeves, MD; Varenicline Study Group
- Arch Intern Med. 2006;166(15):1571-1577. doi:10.1001/archinte.166.15.1571

### 喝酒

- 極少數個案，使用bupropion降低對酒的耐受性，且酒降低癲癇門檻。
- GlaxoSmithKline所做的小型研究指出，Bupropion (100 mg)可使人喝少量酒(16–32 ml)之後沒感覺。他們說覺得比較沒有喝醉、腦筋清楚、沒鎮定。
- bupropion (100 mg)又喝酒顯著增加心跳





## mCEQ

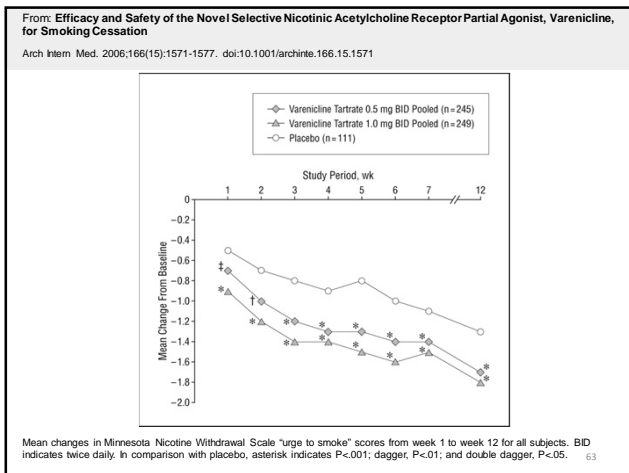
**Table 1**  
Modified Cigarette Evaluation Questionnaire (mCEQ)\*

If you have smoked since you last completed this questionnaire, please mark the number that best represents how smoking made you feel (1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

1.	Was smoking satisfying?
2.	Did cigarettes taste good?
3.	Did you enjoy the sensations in your throat and chest?
4.	Did smoking calm you down?
5.	Did smoking make you feel more awake?
6.	Did smoking make you feel less irritable?
7.	Did smoking help you concentrate?
8.	Did smoking reduce your hunger for food?
9.	Did smoking make you dizzy?
10.	Did smoking make you nauseous?
11.	Did smoking immediately relieve your craving for a cigarette?
12.	Did you enjoy smoking?

\* Items 1, 2, and 12 were presumed or taken to measure "Smoking Satisfaction"; Items 4 through 8 were taken to measure "Psychological Reward"; Items 9 and 10 were taken to measure "Aversion"; Item 3 was taken to measure "Enjoyment of Respiratory Tract Sensations"; and Item 11 was taken to measure "Craving Reduction".

(Cappelleri et al 2007)



From: Efficacy and Safety of the Novel Selective Nicotinic Acetylcholine Receptor Partial Agonist, Varenicline, for Smoking Cessation  
Arch Intern Med. 2006;166(15):1571-1577. doi:10.1001/archinte.166.15.1571

**Table 1. Subject Demographics and Smoking History at Screening\***

Characteristic	Placebo (n = 129)	Varenicline Tartrate			1.0 mg BID Titrated† (n = 130)
		0.5 mg BID Nontitrated (n = 129)	0.5 mg BID Titrated† (n = 130)	1.0 mg BID Nontitrated (n = 129)	
Age, y	43.0 ± 9.4	42.9 ± 10.1	43.5 ± 10.5	43.7 ± 10.0	42.2 ± 10.7
Men	51.9	45.0	53.1	48.8	48.5
White	72.1	85.3	80.8	83.7	80.8
BMI	27.0 ± 4.6	27.1 ± 5.0	26.6 ± 4.5	27.6 ± 5.5	26.6 ± 4.5
Fagerström	5.8 ± 2.3	5.5 ± 2.0	5.4 ± 1.9	5.5 ± 2.0	5.3 ± 2.1
Duration of smoking, y	25.3 ± 8.5	26.0 ± 10.8	25.0 ± 10.8	25.7 ± 10.6	24.0 ± 11.1
Cigarettes smoked per day	20.4 ± 7.2	20.9 ± 8.1	21.3 ± 8.1	20.8 ± 10.1	20.9 ± 7.0
Previous serious quit attempts					
None	8.5	10.1	10.8	6.2	3.8
At least 1	91.5	89.9	89.2	93.8	96.2

Abbreviations: BID, twice daily; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); QD, once daily.  
\*Data are reported as mean ± SD or percentage of subjects.  
†Initial dose of 0.5 mg QD for 7 days then 0.5 mg BID for 11 weeks.  
‡Initial dose of 0.5 mg QD for 3 days, then 0.5 mg BID for 4 d, then 1.0 mg BID for 11 weeks.  
§Fagerström score assesses the severity of nicotine addiction ranging from 0 (minimum dependence) to 10 (maximum dependence).

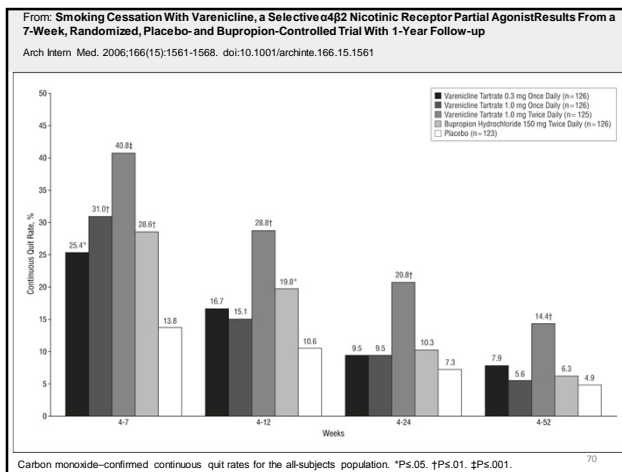
Subject Demographics and Smoking History at Screening\*

From: Efficacy and Safety of the Novel Selective Nicotinic Acetylcholine Receptor Partial Agonist, Varenicline, for Smoking Cessation  
Arch Intern Med. 2006;166(15):1571-1577. doi:10.1001/archinte.166.15.1571

**Table 2. Adverse Events Among Subjects\***

Adverse Event	Treatment Group				
	Placebo (n = 121)	0.5 mg BID Nontitrated (n = 124)	0.5 mg BID Titrated (n = 128)	1.0 mg BID Nontitrated (n = 124)	1.0 mg BID Titrated (n = 129)
Any adverse event	86.3	81.4	90.3	85.3	79.3
Discontinuation due to adverse event	17.4	7.3	14.0	13.7	21.7
Any nausea	14.9	22.6	16.3	41.9	34.9
Mild	11.6	20.2	11.6	23.4	24.8
Moderate	2.5	2.4	3.9	18.5	8.5
Severe	0.8	0	0.8	0	1.6
Discontinuation from nausea	2.5	1.6	0	4.8	3.9
Median nausea duration, dt	4.0	3.0	7.0	9.0	4.0
Insomnia	11.6	33.9	20.9	21.8	37.2
Headache	17.4	27.4	19.4	24.2	22.5
Abnormal dreams	5.0	16.9	11.6	16.9	19.4
Taste perversion	4.1	16.1	7.8	13.7	11.6
Dyspepsia	7.4	8.9	6.2	9.7	14.7
Fatulence	5.8	15.3	6.5	11.3	10.1
Constipation	2.5	6.5	4.7	10.5	10.9
Somnolence	1.7	5.6	5.4	10.5	9.3

Abbreviations: BID, twice daily; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); QD, once daily.  
\*Adverse events were reports of symptoms that began after treatment or were exacerbated by treatment; only adverse events occurring in 10% of subjects or more in any group are listed. Unless otherwise noted, data are reported as percentage of subjects.  
†If more than 1 event occurred, the median duration of the first nausea event was used for the duration calculation.



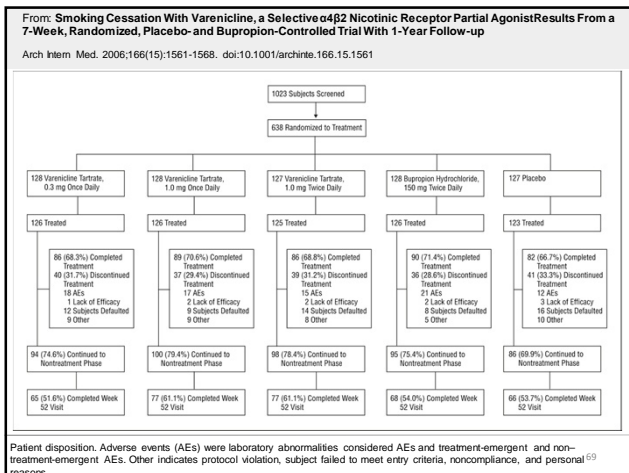
- Smoking Cessation With Varenicline, a Selective  $\alpha 4\beta 2$  Nicotinic Receptor Partial Agonist
- Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up
- Mitchell Nides, PhD; Cheryl Oncken, MD, MPH; David Gonzales, PhD; et al Stephen Rennard, MD; Eric J. Watsky, MD; Rich Anziano, MS; Karen R. Reeves, MD; Varenicline Study Group
- Arch Intern Med. 2006;166(15):1561-1568. doi:10.1001/archinte.166.15.1561

From: Smoking Cessation With Varenicline, a Selective  $\alpha 4\beta 2$  Nicotinic Receptor Partial Agonist Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up  
Arch Intern Med. 2006;166(15):1561-1568. doi:10.1001/archinte.166.15.1561

**Table 1. Demographic Characteristics and Smoking History at Screening**

Characteristic	Varenicline Tartrate			Bupropion Hydrochloride, 150 mg Twice Daily (n = 126)	Placebo (n = 123)
	0.3 mg Once Daily (n = 126)	1.0 mg Once Daily (n = 126)	1.0 mg Twice Daily (n = 126)		
Male, %	50.0	43.7	50.4	45.2	52.0
Age, mean $\pm$ SD, y	41.9 $\pm$ 10.6	42.9 $\pm$ 10.5	41.9 $\pm$ 9.8	40.5 $\pm$ 10.8	41.6 $\pm$ 10.4
White, %	88.1	88.1	85.6	83.3	87.8
Body mass index, mean $\pm$ SD*	25.8 $\pm$ 4.3	25.8 $\pm$ 4.0	25.6 $\pm$ 4.1	26.1 $\pm$ 4.1	26.5 $\pm$ 4.5
Fagerstrom score, mean $\pm$ SD†	5.7 $\pm$ 2.1 (n = 125)	5.5 $\pm$ 2.0 (n = 123)	5.6 $\pm$ 2.0 (n = 122)	5.2 $\pm$ 1.9 (n = 126)	5.5 $\pm$ 2.3 (n = 120)
Smoking history, mean $\pm$ SD, y	24.6 $\pm$ 10.9	25.4 $\pm$ 11.1	23.4 $\pm$ 10.3	23.4 $\pm$ 10.9	23.9 $\pm$ 10.6
No. of cigarettes smoked per day, mean $\pm$ SD	20.3 $\pm$ 7.7	20.1 $\pm$ 7.8	18.9 $\pm$ 6.9	19.5 $\pm$ 6.9	21.5 $\pm$ 8
Previous serious quit attempts, %					
0	6.3	7.1	4.8	9.5	10.6
$\geq 1$	89.6	89.9	95.2	90.5	89.5
Longest period of abstinence in past year, mean $\pm$ SD, d	6.28 $\pm$ 15.2	6.95 $\pm$ 14.6	5.73 $\pm$ 12.1	6.46 $\pm$ 15.0	7.63 $\pm$ 18.5

\*Body mass index is calculated as weight in kilograms divided by the square of height in meters.  
†Fagerstrom Test of Nicotine Dependence assesses the severity of nicotine addiction ranging from 0 (minimum dependence) to 11 (maximum dependence).



From: Smoking Cessation With Varenicline, a Selective  $\alpha 4\beta 2$  Nicotinic Receptor Partial Agonist Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up  
Arch Intern Med. 2006;166(15):1561-1568. doi:10.1001/archinte.166.15.1561

**Table 2. Craving Assessments: Mean Change From Baseline to Weeks 1 to 7\***

Group	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7†
MNWS item 1‡								
Varenicline tartrate								
0.3 mg (n = 126)	2.7	-0.76	-0.73	-1.15	-1.45	-1.53§	-1.66	-1.53
1.0 mg once daily (n = 126)	2.7	-0.97	-1.05§	-1.23§	-1.59§	-1.49	-1.88§	-1.50
1.0 mg twice daily (n = 126)	2.7	-1.14§	-1.19§	-1.57§	-1.61§	-1.98§	-2.04§	-1.61
Bupropion hydrochloride, 150 mg twice daily (n = 126)	2.7	-0.78	-0.88	-1.16	-1.53§	-1.64	-1.70	-1.68
Placebo (n = 123)	2.6	-0.66	-0.73	-0.95	-1.26	-1.23	-1.51	-1.23
OSU-Brief total score¶								
Varenicline tartrate								
0.3 mg (n = 126)	28.8	-5.10	-5.52	-8.08	-10.78	-11.44	-11.59	-11.52
1.0 mg once daily (n = 126)	27.0	-6.30	-9.46§	-10.10§	-11.97	-11.72	-13.04	-13.42
1.0 mg twice daily (n = 126)	28.7	-7.00§	-10.71	-12.73§	-14.09	-13.24§	-14.94	-14.38
Bupropion hydrochloride, 150 mg twice daily (n = 126)	26.9	-5.85	-9.16§	-10.51§	-11.91	-13.22§	-13.98	-14.46
Placebo (n = 123)	29.0	-3.91	-6.22	-7.13	-10.28	-10.21	-11.06	-11.36

Abbreviations: MNWS, Minnesota Nicotine Withdrawal Scale; OSU-Brief, Brief Questionnaire of Smoking Urges.  
\*Mean change is the least squares mean from the analysis of variance model, including baseline value as a covariate and the fixed effects for treatment and center.  
†Varenicline groups were not receiving medication for 1 week at the week 7 visit.  
‡Each item of the MNWS is rated on a 0 to 4 ordinal response scale (0 indicates not at all; 1, slight; 2, moderate; 3, quite a bit; and 4, extreme).  
§P < .05.  
¶P < .001 for comparison with placebo for changes from baseline.  
#In the version of the OSU-Brief used in the present study, subjects rated their strength of agreement with each of the 10 items on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The Total Craving Score is created by averaging all 10 items to provide a total urge score. Higher scores indicate greater intensity of the subject's urge to smoke.

From: Smoking Cessation With Varenicline, a Selective  $\alpha 4\beta 2$  Nicotinic Receptor Partial Agonist Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up  
Arch Intern Med. 2006;166(15):1561-1568. doi:10.1001/archinte.166.15.1561

**Table 3. Modified Cigarette Evaluation Questionnaire Subscale: Mean Change From Baseline to Week 1\***

Group	Satisfaction	Psychological Reward	Enjoyment of Respiratory Tract Sensations	Craving Reduction	Aversion
Varenicline tartrate 0.3 mg (n = 125)					
Baseline	13.0	17.8	2.7	5.1	2.8
Mean change	-3.44	-6.2	-0.51	-1.11	-0.09
1.0 mg once daily (n = 125)					
Baseline	12.6	17.7	2.7	4.9	2.9
Mean change	-3.77	-6.10	-0.74	-1.10	0.42
1.0 mg twice daily (n = 125)					
Baseline	13.1	18.4	2.7	5.2	2.8
Mean change	-4.82†	-6.87	-0.84‡	-1.24	0.82§
Bupropion hydrochloride, 150 mg twice daily (n = 125)					
Baseline	13.1	17.1	2.5	5.1	2.7
Mean change	-4.02	-6.87	-0.60	-1.18	0.00
Placebo (n = 123)					
Baseline	12.9	18.8	2.8	4.9	3.0
Mean change	-3.20	-6.52	-0.55	-1.09	0.03‡

\*The modified version of the Cigarette Evaluation Questionnaire has 12 items that are rated on a 7-point scale ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity of each smoking effect after smoking. Mean change is the least squares mean from the analysis of variance model, including baseline value as a covariate and the fixed effects for treatment and center.  
†P<.001.  
‡P<.05.  
§P<.01 for comparison with placebo for changes from baseline.

Modified Cigarette Evaluation Questionnaire Subscale: Mean Change From Baseline to Week 1\* 73

## 副作用

- 最常見的副作用是噁心，經常是輕微到中度。有人報告出現鮮明的夢。
- 跟食物一起吃可以降低噁心，而不減少藥物可用率。
- FDA警告說，使用varenicline可能與自殺想法、攻擊與異常行為、嗜睡有關。這部分研究仍再進行，臨床工作者應監測病患是否有行為與情緒變化。

MICHAEL V. BURKE, EDD; JON O. EBBERT, MD, MSC; AND J. TAYLOR HAYS, MD  
Treatment of Tobacco Dependence *Mayo Clin Proc.* 2004;83(4):479-484

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From: Smoking Cessation With Varenicline, a Selective  $\alpha 4\beta 2$  Nicotinic Receptor Partial Agonist Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up  
Arch Intern Med. 2006;166(15):1561-1568. doi:10.1001/archinte.166.15.1561

**Table 4. Incidence of Adverse Events (AEs) Occurring in 10% or More of Any Treatment Group**

COSTART Preferred Term	Subjects, %				
	Placebo (n = 123)	Varenicline Tartrate			Bupropion Hydrochloride, 150 mg Twice Daily (n = 126)
		0.3 mg Once Daily (n = 126)	1.0 mg Once Daily (n = 126)	1.0 mg Twice Daily (n = 126)	
Ary AE	87.8	90.5	88.1	92.0	89.7
Discontinuations owing to AEs	9.8	14.3	12.7	11.2	15.9
Nausea	18.7	17.5	37.3	52.0	21.4
Insomnia	22.0	19.8	27.0	35.2	45.2
Headache	25.8	27.0	27.0	24.0	30.2
Abnormal dreams	8.1	7.9	11.1	15.2	11.9
Taste perversion	7.3	8.7	14.3	15.2	11.1
Irritability	9.8	11.9	13.5	12.0	11.1
Respiratory tract infection	25.2	25.4	14.3	12.0	15.9
Asthenia	8.1	10.3	7.9	10.4	7.1
Dyspepsia	7.3	7.9	6.3	8.8	11.1
Increased appetite	5.7	14.3	10.3	8.0	7.1
Constipation	4.1	6.3	6.3	5.6	13.5
Dry mouth	5.7	3.2	8.7	5.6	11.9

Abbreviation: COSTART, Coding Symbols for Thesaurus of Adverse Reaction Terms.

Incidence of Adverse Events (AEs) Occurring in 10% or More of Any Treatment Group 74

## NRT與Varenicline

項目	NRT (n=136)	Varenicline (n=156)	差異(%CI)	調整後差異 (95%CI)
負面情緒平均(SD)	2.30(1.00)	2.29(1.04)	0.01(-0.23-0.25)	0.04(-0.20-0.28)
渴望度平均(SD)	2.90(1.15)	2.57(1.06)	0.34(0.08-0.59)	0.40(0.14-0.66)

1: 完全沒有；6: 極度強烈  
調整基本資料、健康狀態、菸品使用

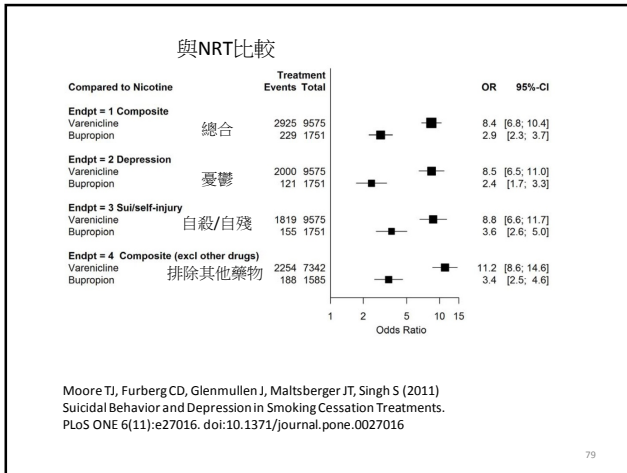
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## FDA 藥物不良反應通報系統

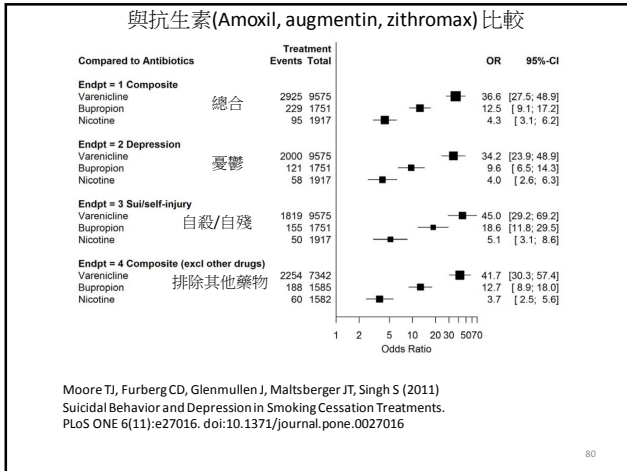
- FDA's Adverse Event Reporting System (AERS) 1998 – 2010
- 美國嚴重個案報告
- Varenicline (n = 9,575)
- Bupropion for smoking cessation (n = 1,751)
- Nicotine replacement products (n = 1,917)

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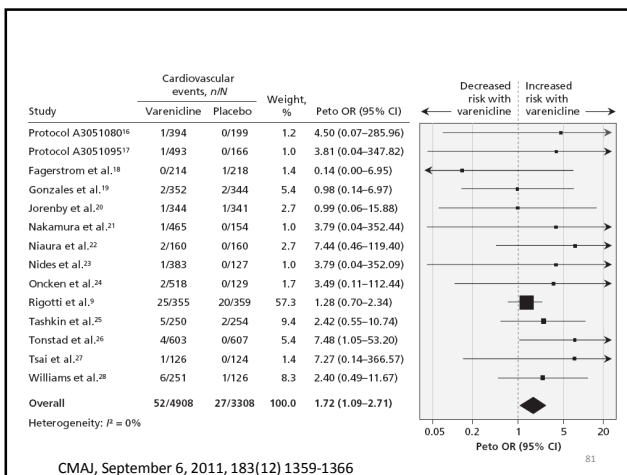


### 戒菸藥物安全性研究

- Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial
- Anthenelli RM, et al.
- Lancet 2016 Apr. 22. pii:S0140-6736(16)30272-0



- 隨機雙盲治療12周，停藥後追蹤12周
- 140中心、16國
- Nov 30, 2011-Jan 13, 2015
- 評估：中重度精神神經症狀、戒菸率
- 8144想戒菸者參加，4116精神患者(4074 安全評估)，4028無精神疾病(3984 安全評估)
- 簡要介入



### 自殺：無精神疾病(N=3984)

Columbia-Suicide Severity Rating Scale (C-SSRS)

	Varenicline	Bupropion	30號貼片	安慰劑
人數	990	989	1006	999
治療中與吃藥30天內				
評估人數	988	983	996	995
自殺	0	0	1(<1%)	1(<1%)*
想自殺	7(1%)	4(<1%)	3(<1%)	6+1(1%)
追蹤(停藥30天之後)				
評估人數	807	816	800	805
自殺	0	1(<1%)	0	0
想自殺	3(<1%)	2(<1%)	3(<1%)	4(<1%)

\*死亡

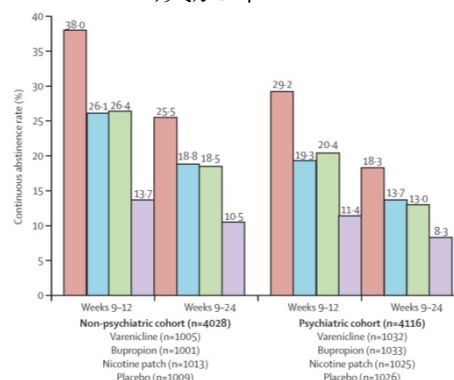
### 自殺：精神疾病(N=4074)

Columbia-Suicide Severity Rating Scale (C-SSRS)

	Varenicline	Bupropion	30號貼片	安慰劑
人數	1026	1017	1016	1015
治療中與吃藥30天內				
評估人數	1017	1012	1006	1006
自殺	0	1(<1%)	0	2(<1%)
想自殺	27(3%)	15(1%)	20(2%)	25(2%)
追蹤(停藥30天之後)				
評估人數	833	836	824	791
自殺	1(<1%)	0	1(<1%)	1(<1%)
想自殺	14(2%)	4(<1%)	9(1%)	11(1%)

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### 戒菸率



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### 精神症狀：非精神疾病 (n=3984)

	Varenicline	Bupropion	30號貼片	安慰劑
精神疾病	32%	34%	30%	26%
怪夢	8%	5%	11%	4%
激動	3%	3%	3%	3%
憤怒	<1%	<1%	<1%	<1%
焦慮	5%	6%	6%	6%
心情低落	3%	1%	3%	3%
憂鬱	2%	1%	1%	2%
失眠	10%	13%	9%	7%
惡夢	1%	1%	3%	1%
恐慌發作	<1%	1%	<1%	<1%
坐立難安	1%	1%	1%	1%
緊張	<1%	1%	<1%	<1%

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### 非戒菸用藥

- 長期使用尼古丁：安全性未確定，不建議使用半年以上。
- 戒菸前使用。

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### 精神症狀：精神疾病 (n=4074)

	Varenicline	Bupropion	30號貼片	安慰劑
精神疾病	39%	43%	41%	35%
怪夢	12%	8%	14%	5%
激動	5%	6%	4%	4%
憤怒	1%	<1%	<1%	<1%
焦慮	8%	10%	9%	6%
心情低落	5%	5%	5%	5%
憂鬱	5%	4%	5%	5%
失眠	9%	12%	10%	7%
惡夢	1%	1%	3%	1%
恐慌發作	1%	2%	1%	1%
坐立難安	2%	2%	1%	1%
緊張	1%	<1%	1%	1%

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### 戒菸前處理與4週戒菸率

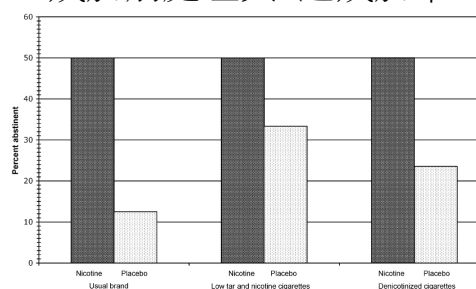
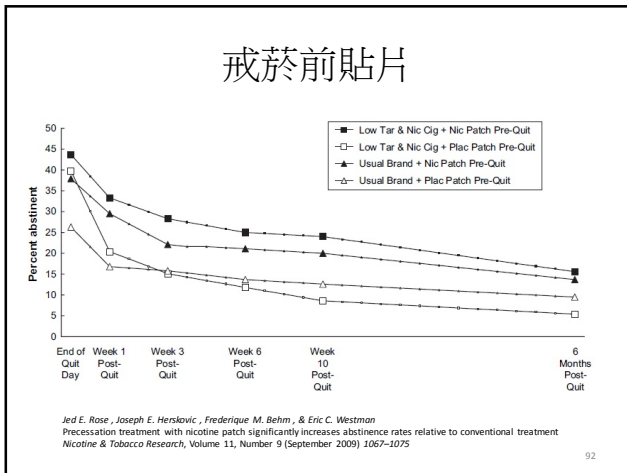
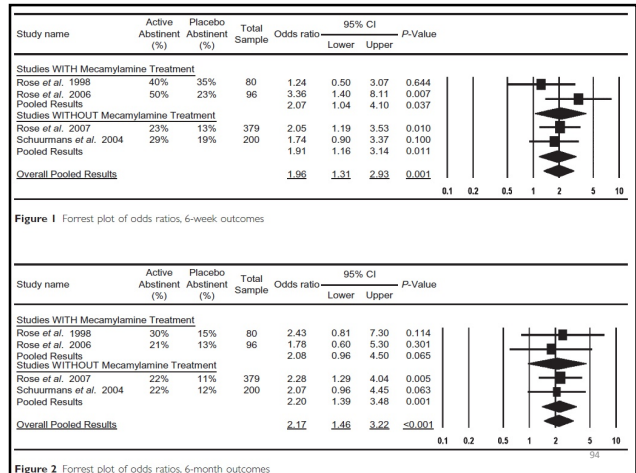
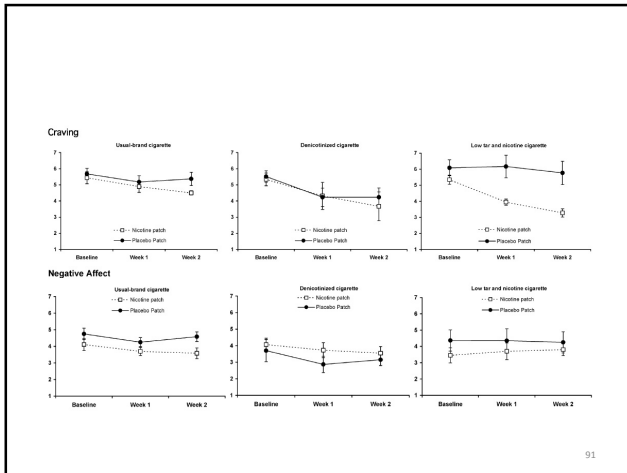


Figure 1. Rates of continuous smoking abstinence (at 4 weeks) in the different experimental conditions.

Jed E. Rose, Frederique M. Behm, Eric C. Westman, Prity Kukovich  
Nicotine & Tobacco Research Volume 8, Number 1 (February 2006) 89-101

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### 綜合分析

研究	貼片人數	對照人數	女性%	平均年齡	吸根/天	平均FTND
Rose 1998	40	40	49%	40.5	29.9	6.4
Schuermans 2004	100	100	44%	43.5	24.8	6.1
Rose 2006	48	48	53%	44.6	28.6	6.5
Rose 2007	191	188	57%	42.0	23.2	6.0

Shiffman, S., & Ferguson, S. G. (2008).  
 Nicotine patch therapy prior to quitting smoking: A meta-analysis.  
*Addiction*, 103, 557-563.

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