

# Smoking and Smoking Cessation

Renee Bittoun

**Director: Smokers' Clinics, SWSAHS.  
Adjunct Associate Professor**

**Director: Smoking Cessation Unit,  
Brain Mind Research Institute,  
University of Sydney.**

**Editor in Chief: The Journal of Smoking Cessation**

**President: AASCP**



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Despite evidence that nicotine dependence is the leading preventable cause of death and morbidity, it remains the most common ***psychiatric disorder.***

*Arch Gen Psychiatry. 2001;58:810-816*

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# ICD-10 Code

(W.H.O. *I*nternational **C**lassification of *D*iseases)

- › **Current Tobacco Use Z 72.0**
- › **Harmful Tobacco Use – non dependent F17.1**
- › **Tobacco Dependence Syndrome – mental and Behavioural Disorders due to Tobacco use F17.2**

W.H.O. World Health Organisation: <http://www.who.int/classifications/icd/en/>

# DSM IV

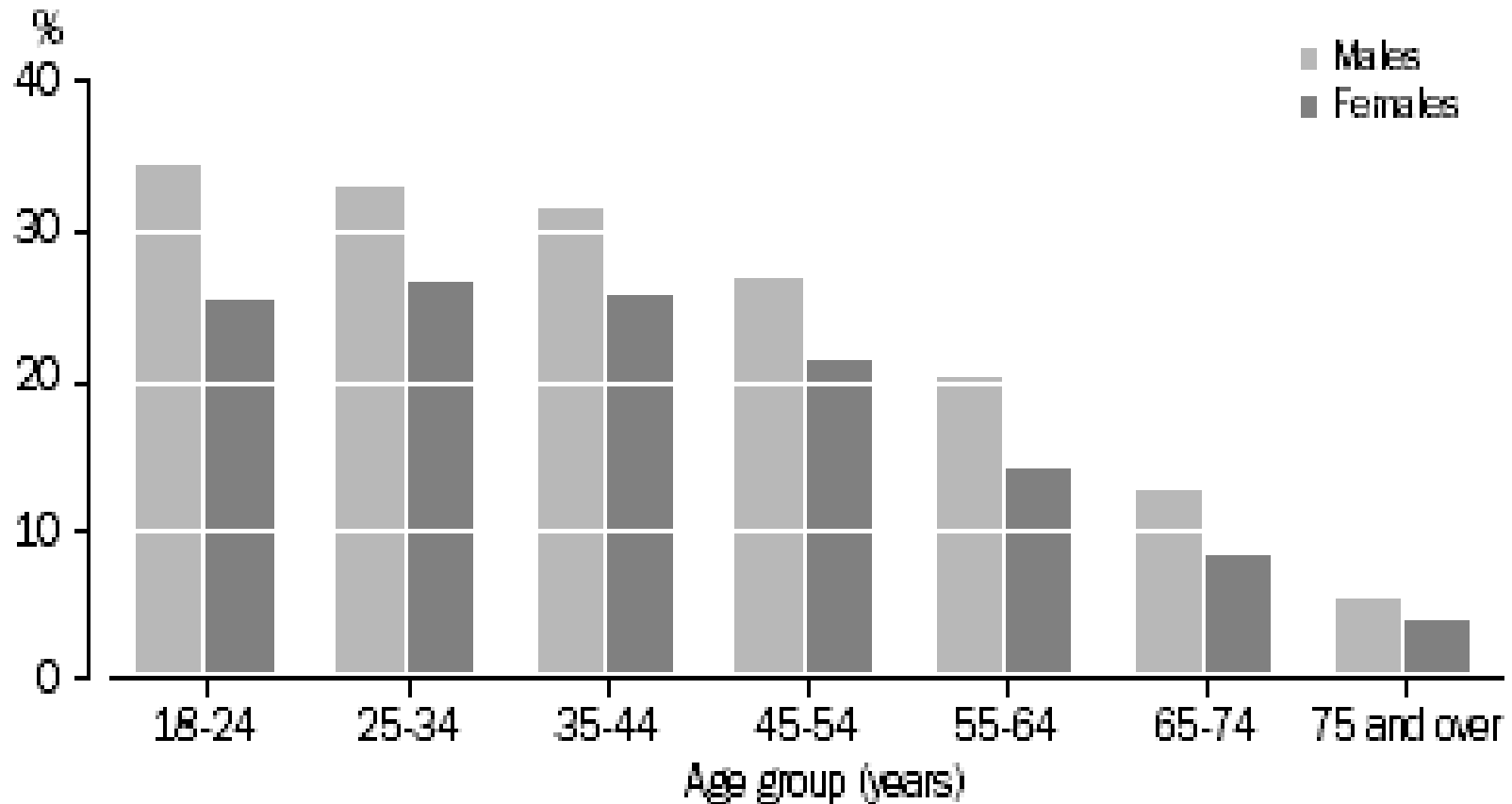
(Diagnostic and Statistical Manual of Mental Disorders –  
American Psychiatric Association)

- › **Nicotine Dependence 305.10**



## Prevalence of Smoking in Australia

Currently, overall 17.8% of Australians smoke,  
Note age and gender.



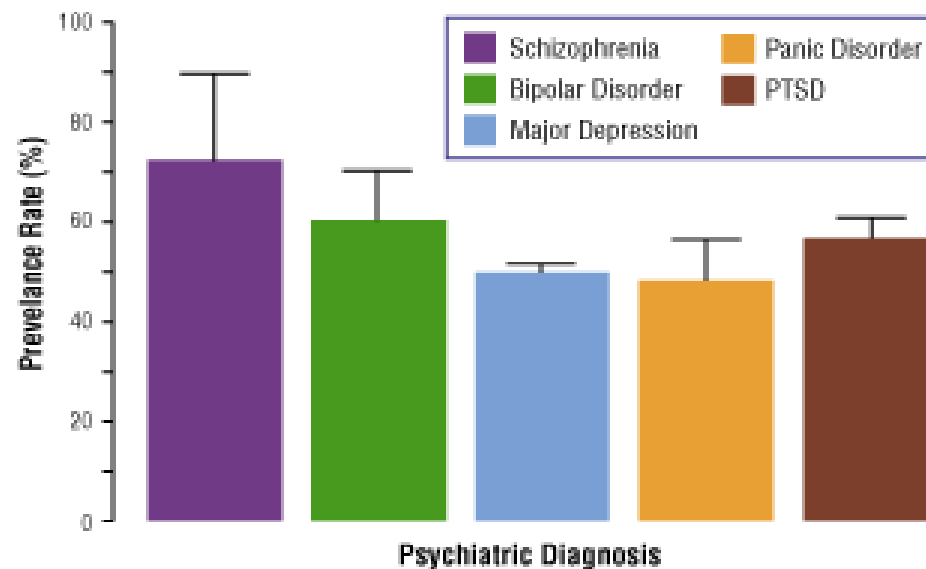
(a) Includes current daily smokers and other current smokers

Source: National Health Survey: Summary of Results 2004-05 (ABS cat no 4364.0)



Figure

### Prevalence Rates\* of Tobacco Use in Psychiatric Disorders



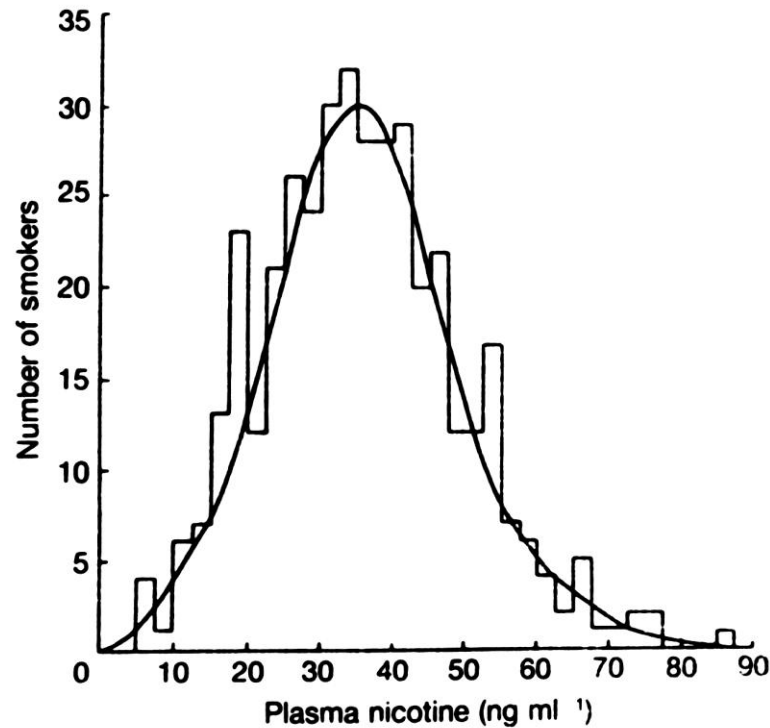
\*Average prevalence rates ( $\pm$ SD) from published studies of tobacco use in patients with schizophrenia (n=13), bipolar disorder (n=2), major depression (n=3), panic disorder (n=2) and posttraumatic stress disorder (PTSD) (n=2).

Source: George TP (2000)

- › Nicotine: no nicotine = no smoking
  - • behaviour 2<sup>nd</sup> to biology
- › nACh receptors have many sub-types
- › Natural ligand for these receptors is Acetyl Choline
- › Nicotine is short acting ( $\cong$  40 mins  $\frac{1}{2}$  life,  $\pm$  20Hrs whole life),
- › Is odourless and colourless
- › Low levels in cigarettes  $\rightarrow$  compensatory smoking
- › Fewer cigarettes/day  $\rightarrow$  compensatory smoking
- › Smokers titrate v. accurately
- • Numbers per day less important in dependence
  - TTFC ( Time to first cigarette) very important

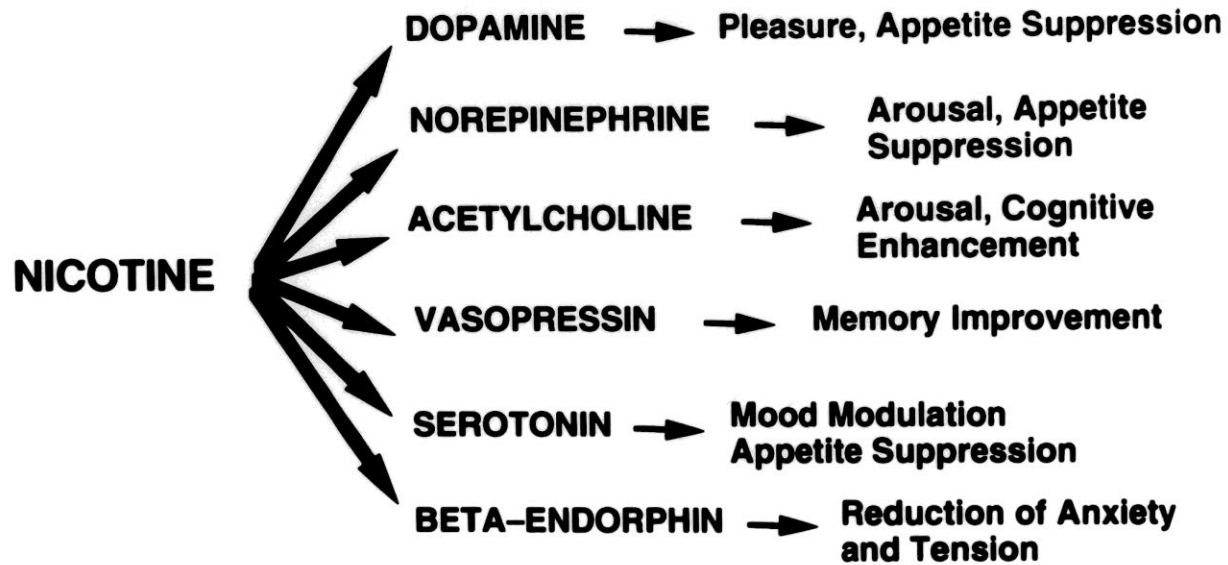


# Plasma levels of Nicotine 2 mins post cigarette (unrelated to numbers or strength of cigarettes).



Russell, Benowitz (1980s)

Levels are higher in schizophrenics,  
Olinic et al, Biol Psych 1997



Benowitz, Neal

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- › URGES ( cravings no longer used, “habit” out of the lexicon)
- › ANXIETY
- › AGGRESSION
- › INCREASE IN APPETITE
- › INABILITY TO CONCENTRATE
- › SLEEPLESSNESS/SLEEPINESS
- › DEPRESSION
- › MOUTH ULCERS
- › CONSTIPATION

***Do not confuse nicotine withdrawals with nicotine toxicity OR overdose  
(toxicity and overdose are EXTREMELY rare)***

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## What has been learnt about metabolizing Nicotine?

- › Genetic (racial) variations of the liver enzyme P450 CYP2A6 \* ranging from fast to slow:
- › fast metabolizers smoke more/slow smoke less
- › Fast are more addicted
- › Slow are less addicted
- › Fast at risk of Ca of the Lung
- › Fast do not do well on NRT  
(Benowitz, Tyndale, et al 2000s)
- › Fast inhale deeper→higher CO readings (Bittoun, 2008)

**NCI Phenotypes and Endophenotypes: Foundation for Genetic Studies of Nicotine Use and Dependence, Nov. 2009**

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## Nicotine Dependence:-

- › Varies in intensity (e.g. like Alcohol Dependence) (Benowitz, 2007)
- › Is highly heritable >50% (Ho,2007)
- › Is lifelong (Tyndale,2009)

## Nicotine blood levels:-

- › Range (10-80ng/ml) (Russell, Fagerstrom 1980s)
- › Schizophrenic patients have higher blood levels (Olinicy, 1997)

## Treatment (Rx):-

- › Responses to Rx vary (Hajek,Tyndale 2009)
  - › Response to Rx may be heritable (David, 2007)
-

- › differences in response to nicotine
- › differences in responsiveness of the various neurotransmitter pathways
- › behavioural traits such as novelty or sensation seeking, impulsivity, hostility, or harm avoidance
- › comorbid psychiatric disorders can predispose a smoker to begin or persist in smoking.
- › the more severe the dependence, the greater the likelihood of psychiatric disorders

NCI Phenotypes and Endophenotypes:

Foundation for Genetic Studies of Nicotine Use and Dependence, Nov. 2009

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- › Genetic vulnerability to initiation to smoking, nicotine dependence, failure to quit, DSM1V (withdrawals)
- › Reinforcement value of nicotine may be due to endophenotype (dopamine D2 receptor,  $\alpha 4$   $\beta 2$  Achr types)
- › Variations in responses to Rx are genetic (eg Bupropion)
- › LTUQ (Lifetime Tobacco Use Questionnaire)
- › Genetic pleiotropy, eg serotonin transporter gene 5HTT associated with anxiety-alcohol consumption-smoking
  
- › \* Gambling

NCI Phenotypes and Endophenotypes: Foundation for Genetic Studies of Nicotine Use and Dependence, Nov. 2009

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- › Polycyclic aromatic hydrocarbons (PAHs) in smoking *any* organic material are potent inducers (stimulators) of hepatic cytochrome P-450 (CYP) isoenzymes.
- › Three inducible CYP1 family genes (A1, A2 and B1).
- › Hepatic CYP1A2 is functionally most important
- › Note: expression also in lung of P-450 isoenzymes

Murray, JoSC, 2011

Smoking (PAHs) greatly effects other liver enzyme activity:

**Smokers need more** Insulin, Pain relievers, anesthetics, Anti-psychotics (clozapine, fluoxetine, clozapine, olanzapine, fluvoxamine, haloperidol, Anti-coagulants, heparin, warfrin, methadone

- › Caffeine intake is double in smokers
- › Caffeine toxicity is common in withdrawals
- › Alcohol intake is double in smokers
- › Tolerance to alcohol drops in withdrawal

**Quitters need less** Insulin, Pain relievers, Anti-psychotics, Anti-coagulants *and must be monitored* -see pharmacist -MIMS

(Benowitz, Zevin, et al 1990s)

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Heparin	<ul style="list-style-type: none"> <li>▪ Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects.</li> <li>▪ Smokers may need ↑ dosages due to PK and PD interactions.</li> </ul>
Insulin, subcutaneous	<ul style="list-style-type: none"> <li>▪ Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance.</li> <li>▪ PK &amp; PD interactions likely not clinically significant; smokers may need ↑ dosages.</li> </ul>
Insulin, inhaled (Exubera)	<ul style="list-style-type: none"> <li>▪ Systemic exposure is greatly increased in smokers; greater maximal insulin concentrations (3–5 fold) and faster (by 20-30 minutes) ; ↑AUC 2–3 fold</li> <li>▪ Contraindicated in smokers and those who have discontinued smoking for less than 6 months.</li> </ul>
Mexiletine (Mexitil)	<ul style="list-style-type: none"> <li>▪ ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).</li> </ul>
Olanzapine (Zyprexa)	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%).</li> <li>▪ Dosage modifications not routinely recommended but smokers may require ↑ dosages.</li> </ul>
Propranolol (Inderal)	<ul style="list-style-type: none"> <li>▪ ↑ Clearance (77%; via side chain oxidation and glucuronidation)</li> </ul>
Tacrine (Cognex)	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower.</li> <li>▪ Smokers may need ↑ dosages.</li> </ul>
Theophylline (Theo Dur, etc.)	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%).</li> <li>▪ Levels should be monitored if smoking is initiated, discontinued, or changed.</li> <li>▪ ↑ Clearance with second-hand smoke exposure.</li> <li>▪ Maintenance doses are considerably higher in smokers.</li> </ul>
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	<ul style="list-style-type: none"> <li>▪ Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.</li> </ul>

## When does this take effect?

- › Half life of CYP1A2 activity decrease ~38 hrs (27-54)
- › Stepwise decrease dose (of caffeine or *other drugs* )reduction of 10% over 4 days
- › Care with medications with hospitalisation and discharge!

Faber 2004

Murray, JoSC, 2011

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- › Nicotine is concentrated in the foetus
  - › Nicotine is poorly metabolised by foetal liver – more so post-partum
  - › Nicotine is concentrated in breast milk-but dose to newborn is oral
  - › Nicotine neuronal receptors (nAchr) upregulated in foetus
  
  - › Bittoun, Femia 2010
-

- › Neonatal withdrawal syndrome: dose related excitability, distress signs (Law, Paediatrics 2003)
  - › Neurobiological Teratogenicity (Slotkin, J Phara Exper Therap 1998; Cohen, 2005)
  - › Childhood conduct disorder and behavioural problems (Wackschlag, Ach Gen Psych 1997;Kandel, JAdol 1998)
  - › Increased risk of child developing childhood cancers  
(Stjernfelt, Lancet 1986)
-

Children of mothers who smoked while pregnant have long-lasting:-

- › cognitive impairment (Butler,1973)
- › learning deficits (Fried,1989)
- › impaired attention (Picone, 1982)
- › poor impulse control (Kristjansson,1989)

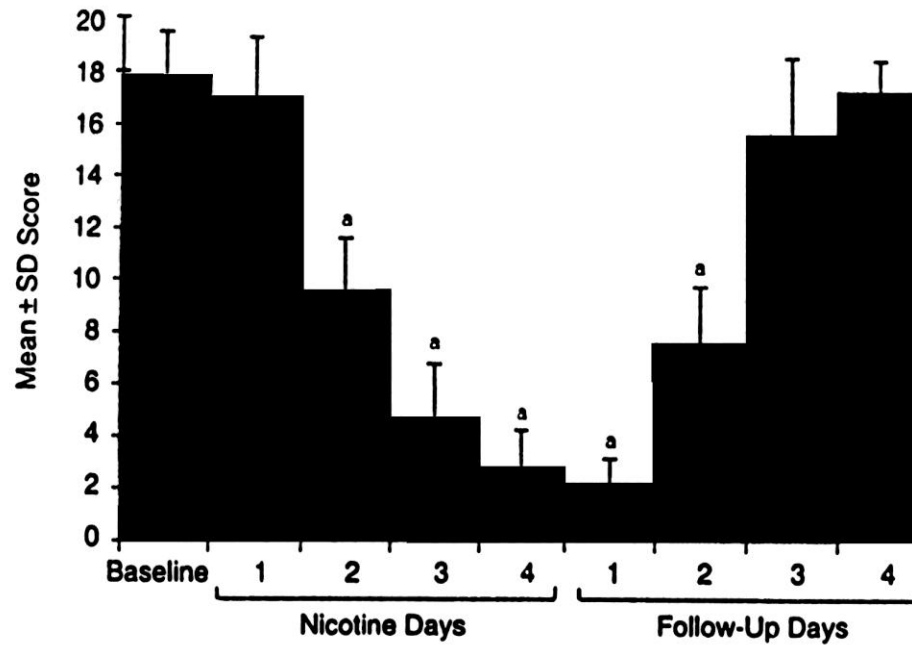
*All dose-response* (Fried, 1992)

**“Hooked from the very first cigarette”, DiFranza, 2008**

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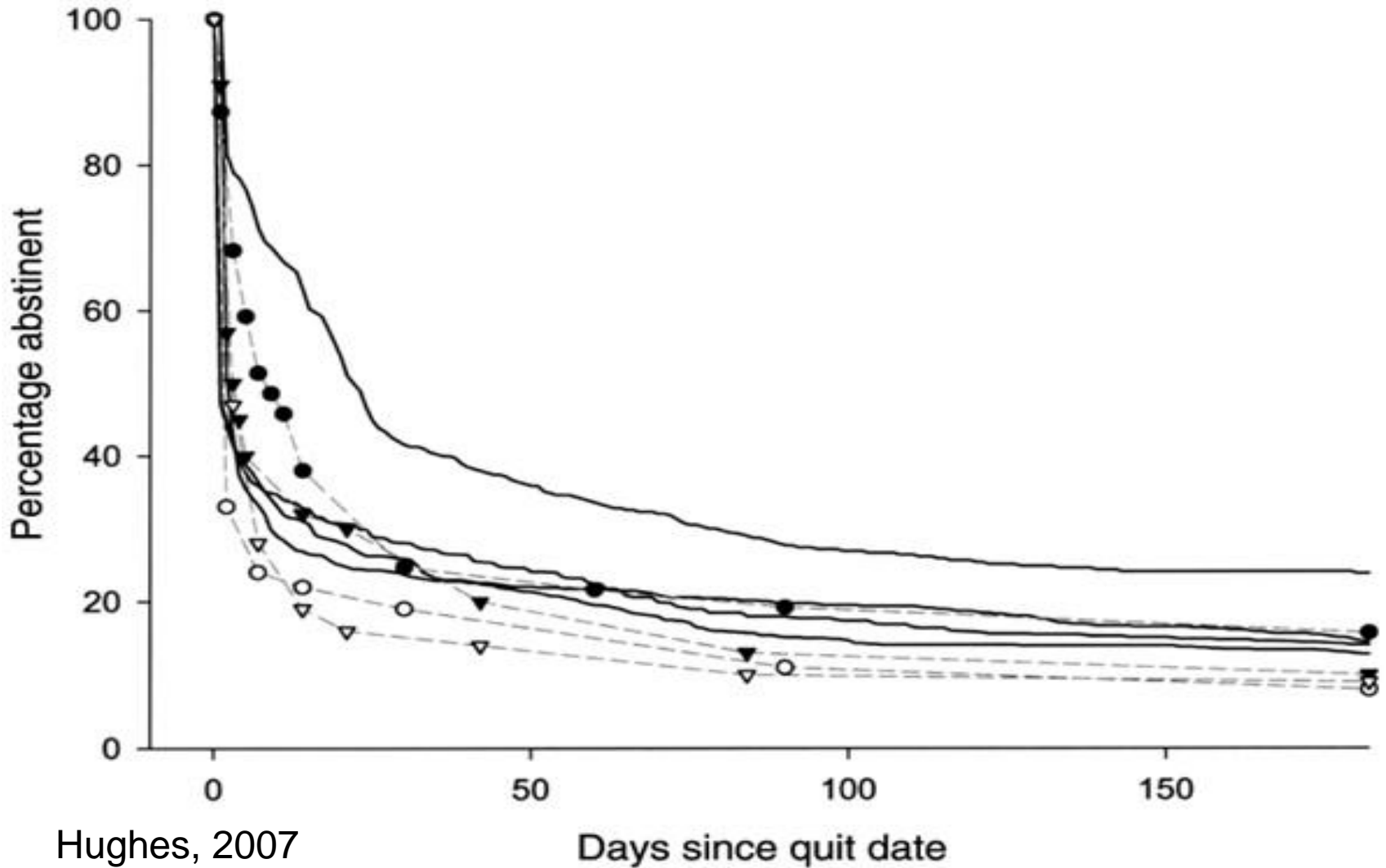


Figure 2. HAM-D (10 Items) Ratings of 10 Depressed Patients Before, During, and After Administration of Nicotine Patches\*



Salin-Pascual, 1996.

- › Psychiatric Illness (Hughes,1986)
- › Familial traits in the above (Hughes,1988)
- › Depression → smoking → depression (Breslau,1991)
- › Smoking and Depression (Glassman, 1993)
- › Adolescents and mood disorders (Kendler,1993)
- › *½ of all cigarettes smoked in US are smoked by depressed people (same in Australia, Jorm etal, 2000)*



# Treatment



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## AT TWELVE MONTHS

› 5% SPONTANEOUS QUITTING

› PHARMACOTHERAPIES RANGE

15 – 50% ABSTINENCE- FREQUENCY/INTENSITY DEPENDENT

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### Nicotine plasma levels

1 CIGARETTE = ~ 40ng/ml (range 10-80) N.B. unrelated to brand concentration or numbers smoked.

- › 1 x 2mg nicotine gum/lozenge/sublingual tab = 7ng/ml
  - › 1 x 4 mg nicotine/lozenge gum = 15ng/ml
  - › 1 x 21mg nicotine patch = 10ng/ml
-

- › Patches may take hours to peak
  - › No evidence that weaning off is required (Garvey, 1998)
  - › No evidence to start on lower doses
  - › Evidence that combination is better (Bittoun, 2007, Shiffman, 2008 etc)
  - › Smoking while using NRT is safe and is a gateway to quitting (Fagerstrom,2000)
-

# What have we learnt about Varenicline?

- › Developed to target  $\alpha 4\beta 2$  subunit only
  - › Good odds ratio (best?) for quitting
  - › There are more than one type of nACh receptor subtype ( $\alpha 4\beta 2$ ) responding to nicotine—eg  $\alpha 7$  a slow responder, increasingly more important (Rose, 2009)
  - › Not *all* patients do well on Varenicline, why not?
  - › Not *all* patients do well on Varenicline alone
  - › Do not confuse nicotine withdrawals with medication side-effects
-

- › Combining Varenicline and NRT is valid (Ebbert, 2009)
  - › Combining Varenicline and NRT is effective (Bittoun, 2009)
  - › Combining Varenicline and bupropion is valid and effective ( Ebbert, 2009)
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- › Use a “medical model” for cessation to diagnose and treat tobacco dependence
  - › Ask: How soon after waking do you smoke?
  - › Ask: Have you had trouble quitting in the past?
  - › Say: New medications are very effective
  - › Advise: Always smoke outside (car included)
  - › Reduce caffeine and alcohol intake
-



# Benefits of using NRT for Temporary Abstinence

- › Relief of craving and other withdrawal symptoms
  - › Reduced cigarette consumption and prevention of compensatory smoking
  - › Reduce harm
  - › Gateway to quitting
-

# Conclusion

Adopt a *Medical Model* of Disease in this group of Patients

As deaths related to smoking are so (1:2) this impels an

- › Ethical
- › Moral
- › Legal Duty of Care to help smokers quit, to do otherwise is negligent

Bittoun, Fagerstrom et al JSC 5.1, 2010