# *NICOTINE*
# *in the Context of Mental Health*


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(Cambridge University Press)


**NO CONFLICT OF INTEREST**


<u>Population</u>
Australia 25 million
Belgium 11.5 million
<u>% Smoking</u>
Australia 11% (-6%)
Belgium 15%

# What has helped to drive down smoking prevalence in Australia?





- Fewer venues to smoke
- Graphic warnings on packaging
- Social marketing campaigns
- Restriction of sales to minors
- Moving tobacco products out of sight
- Heavily subsidised pharmacotherapies for ALL
- Made smoking socially unacceptable
- Strong media campaigns-including radio and television (talk-back radio and promotional television competitions)
- Strong price rises-Heavy Taxation (expensive)
- Very graphic multimedia campaigns
- National Quitline smoking helpline
- No tobacco grown in Australia since 2000

- Doctor and allied-health **ALWAYS** ASK ABOUT SMOKING

# Who is still smoking in Australia today?

Smokers with:

- High dependence
- Mental health concerns MI
- Drug & alcohol comorbidities
- Diseases related to their smoking
- Multiple unsuccessful attempts
- Multiple life stressors
- Aboriginal and Torres Strait Islanders
- Indigenous pregnant women

***Low socio-economic status is common amongst these groups***

# Background

- People with Mental Illness (MI) alcohol and other substance use disorders (SUDs) have higher rates of tobacco smoking and e cigarette use
- Individuals with MI are motivated to quit smoking (Cost a major motive)
- The same interventions that are successful for the general public are successful for those with MI.
- These include the use of nicotine replacement therapy (NRT) and other pharmacotherapies, education around smoking, and smoking cessation counselling.
- Evidence suggests that tobacco cessation interventions initiated for patients receiving inpatient treatment for MI and alcohol and other substance use disorders (SUDs) improve smoking abstinence.
- There is no evidence that providing such interventions affects abstinence from alcohol and other substances or exacerbates MI

# Nicotine is not benign

- Nicotine changes neurotransmission
- Nicotine receptors are upregulated with *speed* of nicotine delivery
- Mood and anxiety disorders, suicidal ideation, depressive symptoms and negatively perceived mental health are all associated with smoking AND e-cigarette use
- These symptoms occur more so when ”quitting” smoking using e cigarettes vs not using e cigarettes to quit
- There is no improvement in mental health when vaping

# Nicotine Intake

- Lung delivery of nicotine is the ideal manner to get nicotine quickly into the brain

(better than sniffed, chewed, transdermal)

- This inhaled arterial delivery has quicker access to the brain as it bypasses the venous system entirely.
- Speed of delivery into the arterial blood via the lungs is essential to the neuropharmacological brain “reward” and dependence.
- The “flux” of nicotine, mgs/puff/sec coming out of vapes depends on the apparatus.
- Current technology allows for a finer, quicker, higher delivery of nicotine.

*This technology has been intentionally developed to make vapes more rewarding and improve the smokers experience to transition from combustible tobacco*

# Overview of nicotine interactions

- The manner in which nicotine is self- administered either smoked, inhaled as vape, chewed or transdermal delivery has a profound hierarchical effect on nicotinic receptor activity, dependence and interaction with other substances in the brain.
- Inhaled nicotine as a vape is currently the most efficient and faster manner of nicotine delivery to the brain such that nicotine receptors, which interact with other substances, are acutely stimulated and upregulated.

# Stress, stressors, distress and nicotine

- Smokers/vapers tend to view smoking as way of improving dysphoric symptoms, without recognizing that this improvement may actually be due to treatment of nicotine withdrawal (Stress paradox)
- Nicotine has an acute anxiolytic effect
- Nicotine has an acute antidepressant effect
- Nicotine has a very short half-life ( 40 mins→2 hrs) and wears off
- Nicotine wearing off → acute anxiety and depression (withdrawals)
- Smokers “manage” stressors better when on NRT and pharmacotherapies
- After cessation smokers are “calmer”, less volatile, less “reactive” to stressor.
- This is a learned process and takes time→ 3 months to adapt

# Nicotine metabolism or NMR (Nicotine Metabolic Rate)

Genetic (racial) variations of the liver enzyme P450 CYP2A6 * ranging from fast to slow:

- Fast metabolisers smoke/vape, more/slow metabolisers smoke/vape less
- Fast are more addicted need to smoke/vape straight away on waking **TTFC/TTFV**
- Slow are less addicted to nicotine
- Fast at risk of cancer of the lung in smokers (yet to be determined with vaping)
- Fast do not do well on one form of NRT (nicotine replacement therapy)
- Fast inhale deeper → higher expired CO readings in smokers
- Fast metabolisers at risk of COPD

# Other critically important liver effects

Smoking (anything) → Polycyclic Aromatic Hydrocarbons (PAHs) which greatly effect other liver enzyme inductions→ CYP1A2, 2D6→

***SO***

- Caffeine intake is at least double in smokers
- Caffeine toxicity is common in nicotine withdrawals and mimics symptoms (watch for caffeine withdrawals)
- Alcohol intake is at least double in smokers
- Tolerance to caffeine drops, alcohol drops in withdrawal and abstinence

***and***

***Smokers need more*** Insulin, Pain relievers, Anti-psychotics, Anti-coagulants, Caffeine, Alcohol , Methadone

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

## *This are NOT a nicotine effect*

*Important to factor in during hospital admissions and discharges.*

# Barriers to change

- A major barrier to the implementation of the Smoke/ Vape Free Policies is attitudes and beliefs around smoking, MI and the ability to quit, in patients with MI, SUDs and staff in mental health and drug detox units.
- This includes, the need to smoke/vape to self-medicate/alleviate symptoms of mental illness, smoking is a right, smoking as a form of control, and the belief that they are unable to quit
- There is also apprehension by the staff on whether they are educated in providing adequate support for smoking and nicotine cessation.
- Fear of an increase in aggression or violence despite there being evidence of no increase in violence or aggression following smoking bans in psychiatric inpatient settings

# Important Issues in *Managing* smokers
# "Quit using the word Quit"

- No evidence that cutting down helps– may be worse-smoker/vapers compensate
- No evidence that weaker/mild cigarettes are better—**are** worse-smokers/vapers compensate changing the topography
- No evidence that hypnotherapy/acupuncture/laser/creams help quitting
- Good evidence for combination NRTs →better outcomes
- No serious side-effects from multiple NRTs-- no overdose
- Good evidence that longer use of pharmacotherapies is better (for at least 6 months)
- No serious side-effects from Varenicline– mostly symptoms of nicotine withdrawal
- Good evidence that longer use of Varenicline is better (6 months)
- Good evidence for combining Varenicline ***and*** NRT if needed

# Harm Reduction and Smoking

Smoking Less Cigarettes Per Day

- There is longstanding good evidence that smoking less cigarettes/day may lead to “compensatory smoking”.
- Smokers are know to change the *topography* of their smoking- inhaling deeper, smoking more of the actual cigarette, breath-holding
- This compensatory smoking leads to higher exhaled CO and COHb and inhaled particulate matter.

Smoking Weaker Strength Cigarettes

- There is longstanding good evidence that smoking weaker or light cigarettes may lead to “compensatory smoking”.

# Pharmacotherapies, poor use and under-dosing

# Evidence-based pharmacotherapies for nicotine withdrawals

1ST Line

- Nicotine Replacement Therapy (NRT) of all types
- Combination NRT (oral + patch)
- Varenicline alone or combined with NRT
- Bupropion alone or combined with NRT

2nd Line

- Nortriptyline, Naltrexone – not registered for use as smoking cessation aid in Australia

Effectiveness

- Combined use of pharmacotherapy more effective than single use
- Varenicline most effective

- CYTISINE is coming

# Individual responses to medication

Genetic variations associated with response to therapies

- Varenicline: Nicotine receptors
- Bupropion: Rate of bupropion metabolism (CYP2B6)
- Nicotine Replacement Therapies: Slow nicotine metabolisers respond better (CYP2A6)

# Nicotine Delivery Devices

*In order of speed of delivery, neurological, vascular and dependency effects.*

2021 Electronic Cigarettes

- Cigarette (2007)
- Nasal Spray
- Oral Spray
- Inhalator
- Sublingual Tablet
- Lozenge
- Gum
- Patch

# Nicotine Replacement Therapy (NRT)

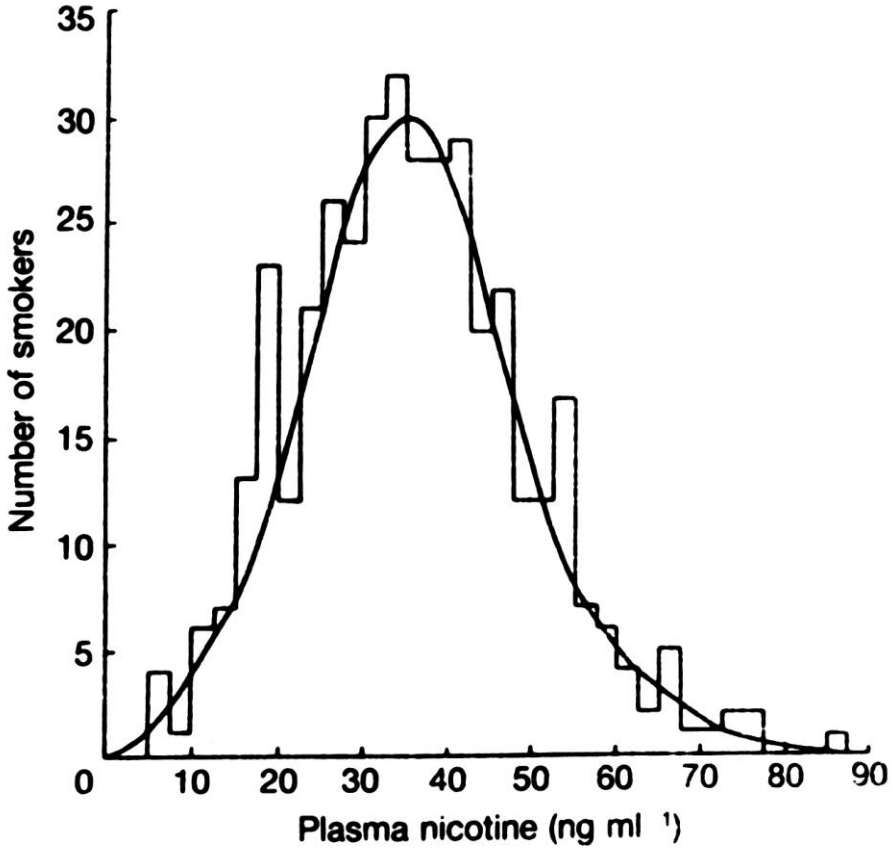
- Works by relieving cravings and withdrawal symptoms
  - replaces some of the nicotine smokers get from tobacco/vaping
- No serious side-effects → mostly due to incorrect use
- SAFE to use NRT and continue smoking (smoking is less reinforcing)
- Stressors  managed better on NRT
- Longer use → better outcome
- Approved by TGA for use in pregnancy
- Compliance with patch easier/better than oral NRT
- No evidence to wean by reducing dose
- Safer than smoking in pregnancy
- **Debunk myths about overdose/toxicity**
- Little to no long term dependence: delivery too slow

# Nicotine plasma levels of commonly used Nicotine products:

- 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 4mg nicotine/lozenge gum = 15ng/ml
- 1 x 21mg nicotine patch = 10ng/ml

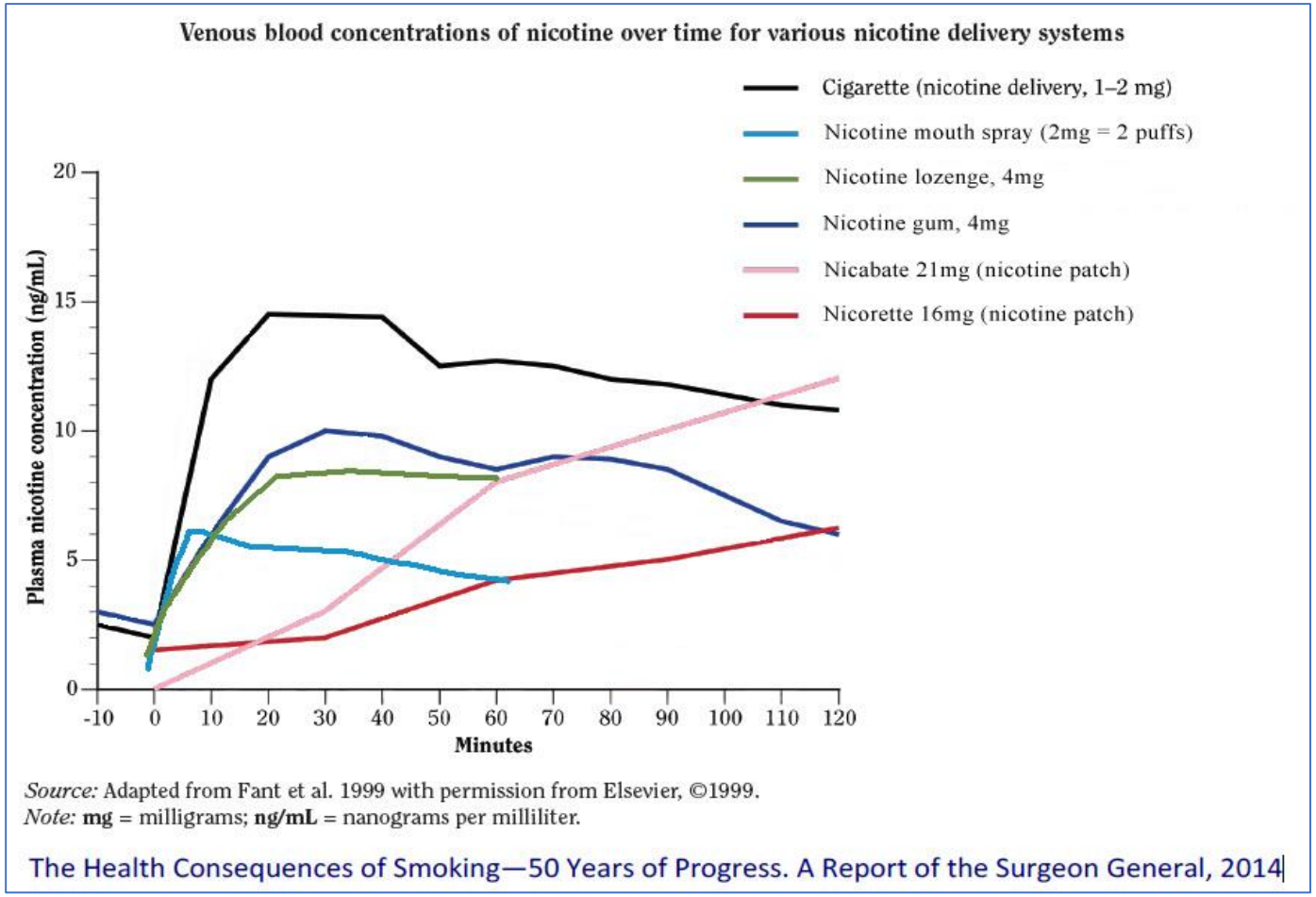
- Vaping delivers similar/higher plasma levels

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




**Levels are higher in**
**Schizophrenia, Depression, Alcohol Dependency and**
**Past history of Alcohol Abuse**

# Blood plasma levels for NRT products vs. cigarettes




*Source:* Adapted from Fant et al. 1999 with permission from Elsevier, ©1999.
*Note:* **mg** = milligrams; **ng/mL** = nanograms per milliliter.

The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General, 2014

# Harm reduction in smoking and the " gateway" to quitting

Cutting down or reducing smoking numbers per se may be counterproductive as

- Smokers/adult vapers accurately titrate their nicotine plasma levels and compensate for the lack of nicotine intake by inhaling deeper
- Smoke more of the actual cigarette and change the "topography" of their smoking (Bittoun, 2008). This occurs in Vaping

Smoking concomitantly with nicotine replacement therapy (NRT) is safer

- Reduces nicotine intake from cigarettes
- Reduces inhaled Carbon Monoxide (CO) and particulate matter (Benowitz, 2008)
- Nicotine Replacement Therapy (NRT) and combined smoking-reduction interventions increase long-term cessation among smokers who are not ready to quit smoking (Asfar, 2011, Hughes 2013).

# Benefits of using NRT and Smoking

## Temporary Abstinence : Gateway to quitting

- Relief of craving and other withdrawal symptoms
- Reduced cigarette consumption and prevention of compensatory smoking
- Smokers may learn that they can manage without tobacco for several hours → ↑ motivation to quit
- nAchReceptor down-regulation occurs as cigarettes are less rewarding
- Most patients unaware of strategies like Cut Down to Quit, e.g. alternating NRT with smoking or safety of patch plus smoking- TGA approved in 2009
- Fear of overdose/continuation of addiction needs to be debunked
- Mental health patients very receptive to this strategy

This strategy allows the smoker to regain autonomy

# Background- Mental Health Facilities

Implementation of smoke-free environment fraught with concerns:

- Staff conflicting imperatives-policy vs civil liberties
- How should policy be implemented: strictly (discharges) vs leniently?
- Poor staff experiences with previous policy implementations
- Poor implementation of policy—not on “the same page”—staff split
- Poor understanding of nicotine addiction and treatments
- *Under-dosing* of NRTs
- Both mandatory and voluntary patients had conflicting information about policy.

# Protocol

- In-servicing (teaching) all staff about nicotine addiction and treatment—multiple training session to cover all staff.
- Explanation to all staff re protocol and non-punitive strategies
- Informing all intending patients about policy..non-judgmental and non-punitive
- Nicotine addiction assessment of all patients on admission, including Expired CO and TTFC/TTFV
- Encouragement of adequate NRT when needed and on demand
- Encourage “health literacy” in patients-biofeedback

# Our Experience in Adapting Mental Health services

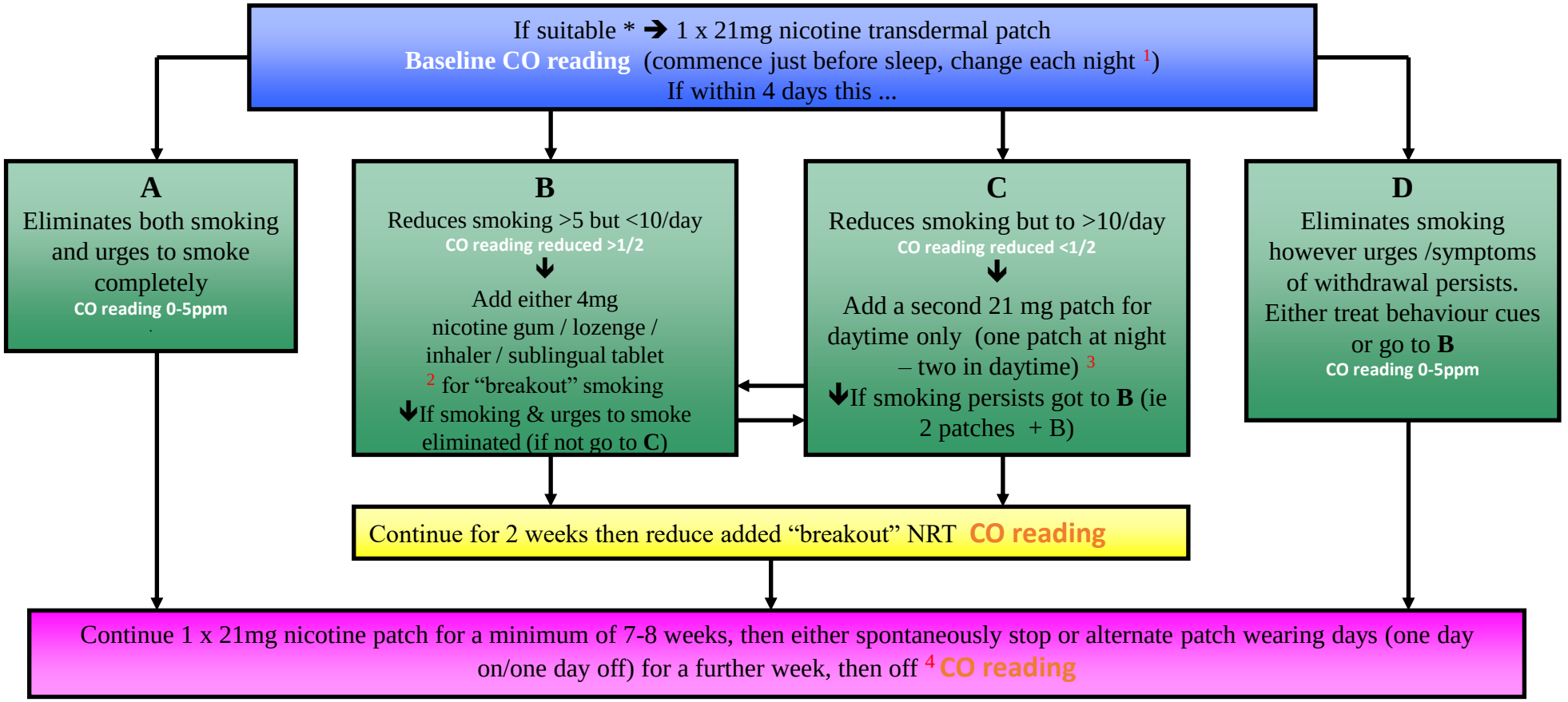
Peer-based forum motivates patients to attend:-

- Comparisons of CO readings
- Comparisons of Fagerstrom nicotine dependence questionnaire outcomes
- Patients appreciate the education re their drug interactions and smoking
- Patients previously resistant to NRT learnt from each other and more acceptant
- Patients accept that nicotine is addictive and should be addressed at an Addiction Treatment Centre

# How addicted are our smokers/vapers? Assess

- Time to first cigarette (TTFC) or Time to first vape TTFV
- How old were you when you started? (Not why)
- Ethnicity-fast or slow metabolisers (Mediterranean rim faster)
- Numbers per day – compensatory smoking when smoking is limited
- Previous “quit” attempts
- Experiences with NRT—massive underdosing = smoked while using
- Experiences with Varenicline?
- Always ask about caffeinated drinks→ reduce them (not eliminate)

# Bittoun Combination Nicotine Replacement Therapy Algorithm#




* KEEP IN MIND CONTRAINDICATIONS: 1) PREGNANCY OR LIKELIHOOD (all NRT OK but not Patch)
2) RECENT CARDIOVASCULAR EVENT (48hrs)

1 Applying patch last thing before sleep allows the slow rise of nicotine overnight - the likelihood of 1st cigarette of the day "urge" is strongly diminished.

2 Either 4mg nicotine gum or lozenge depending on patient choice. Inhaler or sublingual tablet recommended over the others if patient needs faster reinforcement.

3 No evidence in our experience of toxicity. Consider reducing concentrations if nausea occurs.

4 There is no evidence for weaning (or reduction) of patch strengths

Bittoun, Combination Therapy in the Hard to Treat, JSC, 1:1, 2006

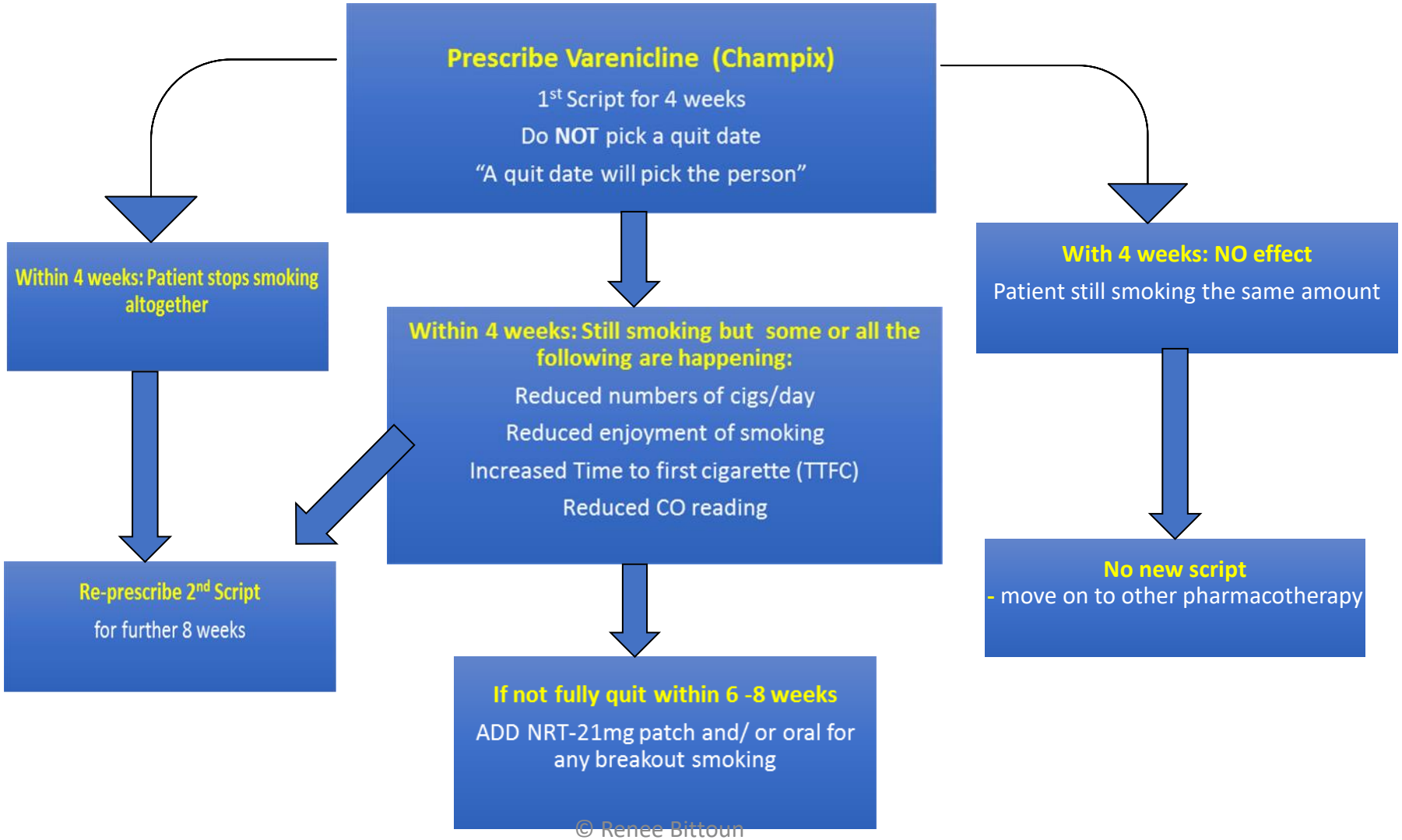
# Practice Quit Attempt (PQA)
# Evidence-based alternative strategy that does not intimidate:

- Provide Nicotine Replacement Therapy (NRT) for a “try-out”
- Hours or “just for one day” only use
- Positive effects from a “practice” rather than a “permanent” goal
- Don’t nag → counterproductive
- Biofeedback such as expired CO or Cotinine

# Varenicline- APO

- **Best odds ratio of all treatment**
- **No known drug interactions**
- **Mechanism of action**
  - Partial Nicotine Receptor Agonist/Antagonist
- reduces cravings and pleasurable effects of tobacco products
- **Doesn't work for everyone**
  - response genetically determined by brain cell types
  - younger age (< 55) and women do better
  - not best choice for non-daily smoker
- **Longer use = better outcome** - withdrawals may re-appear after cessation of treatment
- **SAFE in Mental Illness**

# Varenicline Algorithm



# In-Patient/Outpatient Activities and biofeedback

- Frequent  meetings for patients..comparing CO readings etc to motivate attendance
- Group meetings (2 weekly) with 5 set topics. Nicotine Addiction, Weight Gain, Heart and Lung Effects, Medications for Smoking, Relapse Prevention Strategies, Other Substance Use
- Exercise bikes for short bouts for cravings
- Occupations that distract and engage: painting, cooking
- *Jelly beans-glucose for acute cravings*

# Successful adaptations of these protocols- individuals as outpatients

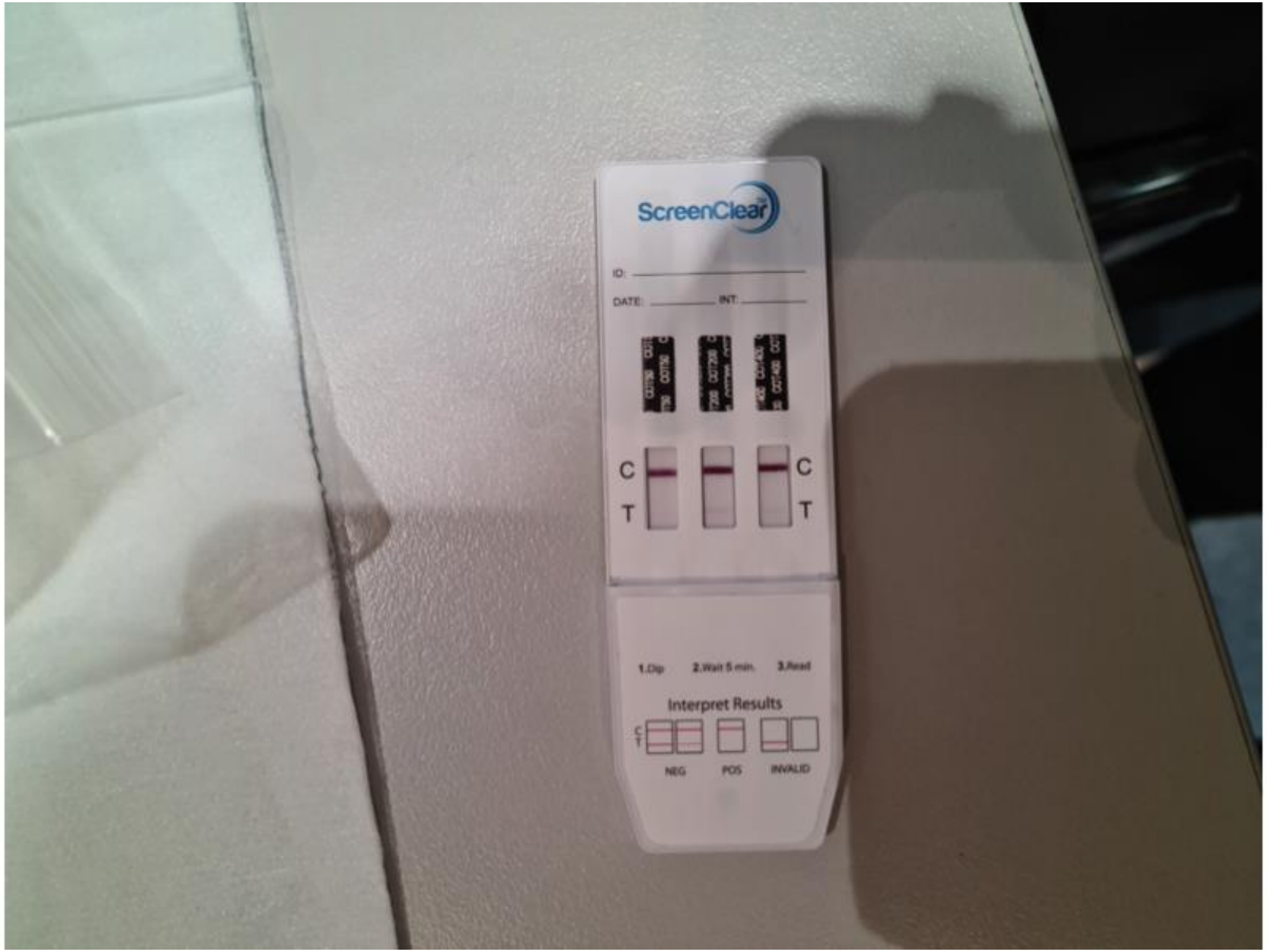
- Depression
- Schizophrenia
- Paranoid Scizophrenia
- Chronic Depression
- PTSD
- Alcohol Dependence
- Gambling

# Expired CO

What is the Smokelyzer?

- A smokelyzer is essentially like a breathalyzer, but instead of measuring your BAC (Blood alcohol content) it measures the CO in your breath
- You measure CO in PPM (Parts per million) and ranges from 0-100 PPM

# Urine Cotinine Dip-Stick measured within 5 minutes



Saliva Cotinine measured within 5 minutes

# Vaping or E Cigarettes in Australia since October 2021

- *Prescription* required for all nicotine containing E cigarettes or devices
- Sales of all nicotine containing E cigarettes or Vapes in shops illegal
- Sales in shops of flavoured vapes is only legal for adults (no nicotine)
- Doctors are not keen on prescribing – concerns about engagement with the tobacco industry, “one stop shop” doctors, concerns about long-term abuse and medical consequences
- All forms of NRT are available without a prescription: some very cheap.
- Pharmacotherapies are heavily subsidized

# Food for thought
# Relationships: Nicotine in the brain and mental health

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# Thank You

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