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Center for Tobacco Research & Intervention

Using both Varenicline and NRT to Help Smokers Quit: Time for a Recommendation Update?

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2020

Outline

- Varenicline – Mechanism of Action +Effectiveness
- Varenicline in Psychiatric Patients
- Varenicline + NRT – Evidence of Effectiveness
- New American Thoracic Society (ATS) Recommendations
- The Wisconsin QUITS Study
- Varenicline + NRT: Time for a Clinical Recommendation Update?

Varenicline: Mechanism of Action and Effectiveness

Varenicline

- Available Since 2006
- A Selective Alpha$_4$ Beta$_2$ nicotinic acetylcholine receptor partial agonist
- Potential Implications = agonist + antagonist:
  - -Stimulate dopamine release like nicotine
  - -Block nicotine from binding to receptors
- Consistent Evidence of Effectiveness, both versus placebo and versus Nicotine Replacement Therapy

2008 PHS Clinical Practice Guideline: Treating Tobacco Use and Dependence Update

Treatment Recommendations – Medications

Meta-analysis (2008): Effectiveness and abstinence rates for various medications and medication combinations compared to placebo at 6-months post-quit (n = 86 studies)

Medication	Number of arms	Estimated odds ratio (95% C. I.)	Estimated abstinence rate (95% C. I.)
Placebo	**80**	**1.0**	**13.8**
Monotherapies			
Varenicline (2 mg/day)	**5**	**3.1 (2.5, 3.8)**	**33.2 (28.9, 37.8)**
Nicotine Nasal Spray	**4**	**2.3 (1.7, 3.0)**	**26.7 (21.5, 32.7)**
High Dose Nicotine Patch (> 25 mg) (These included both standard or long-term duration)	**4**	**2.3 (1.7, 3.0)**	**26.5 (21.3, 32.5)**
Long-Term Nicotine Gum (> 14 weeks)	**6**	**2.2 (1.5, 3.2)**	**26.1 (19.7, 33.6)**
Varenicline (1 mg/day)	**3**	**2.1 (1.5, 3.0)**	**25.4 (19.6, 32.2)**
Nicotine Inhaler	**6**	**2.1 (1.5, 2.9)**	**24.8 (19.1, 31.6)**
Clonidine	**3**	**2.1 (1.2, 3.7)**	**25.0 (15.7, 37.3)**

2008 PHS Clinical Practice Guideline: Treating Tobacco Use and Dependence Update

Treatment Recommendations

- **Medications**: Varenicline is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

2008 PHS Clinical Practice Guideline: Treating Tobacco Use and Dependence Update

Treatment Recommendations /Medications: Relative Effectiveness

Meta-analysis (2008): Effectiveness and abstinence rates of medications relative to the nicotine patch (n = 86 studies)

Medication	Number of arms	Estimated odds ratio (95% C. I.)
Nicotine Patch (reference group)	32	1.0
Comparison Treatments that were more effective		
Varenicline (2 mg/day)	5	1.6 (1.3, 2.0)
Nicotine Patch + Short Acting NRT	3	1.9 (1.3, 2.7)

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Varenicline in Psychiatric Patients

Varenicline in Psychiatric Patients The Eagles Study*

- **Study Design:**

  -4,116 smokers motivated to quit with psychiatric disorders

  -Randomized to Varenicline, Bupropion, Patch, or Placebo

  -No statistically significant differences in rates of psychiatric symptoms during tx –across the four conditions (4.9% in placebo, 6.5% in varenicline)

- **Abstinence Rates:** Varenicline statistically more effective than bupropion, nicotine patch, and placebo
- **Implications of Eagles**:

  -In the United States, the “Black Box Warning” was removed

- **Implications for Treatment**: Varenicline can be viewed as a first line medication for smoking cessation in patients with a psychiatric history

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Varenicline + NRT: Evidence of Effectiveness

Varenicline + NRT #1
An RCT

Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. Ramon et al. BMC Medicine 2014.

- 341 smokers (20 or more cigs/day) randomized to V+Active Patch or V+Placebo Patch for 12 weeks
- 24 week quit rates of 32.8% (active) versus 28.2% (placebo) was not statistically significant
- Conclusion: V + N did not improve quit rates at 12 or 24 weeks

Varenicline + NRT Study #2 Koegelenberg large RCT

Efficacy of Varenicline combined with NRT vs Varenicline Along for Smoking Cessation. Koegelenberg et al. JAMA 2014

- 446 healthy smokers randomized
- All received V for 12 week, half received active N Patch starting 2 wks pre-quit and continuing for 12 weeks; half received placebo N Patch for the same schedule
- At 24 weeks, V+Active NRT = 43.5%; V+ Placebo NRT = 28.8% (OR = 1.91 [1.28-2.84])
- Conclusion: V+NRT was more effective than V along at 12 and 24 weeks.

Varenicline + NRT Study #3: A Meta-analysis

Combination therapy of varenicline with nicotine replacement therapy is better than varenicline along: a systematic review and meta-analysis of randomized controlled trials. Chang et al, BMC Public Health 2015

- Meta-analysis of 3 RCTs; 904 participants
- Results;: Early OR = 1.50, Late OR = 1.62
- Conclusion: Combination V + NRT is more effective than V alone, especially if pre-ciessation treatment with NRT provided.

Varenicline + NRT Study #4
Pilot of 3 Drugs

Triple Smoking Cessation Therapy with Varenicline, Nicotine Patch, and Nicotine Lozenge: A Pilot study to Assess Tolerability, Satisfaction, and End-of-Treatment Quit Rates. Berg et al, Journal of Smoking Cessation 2017

- 12 week pilot involving 36 smokers of triple therapy – primarily a tolerability study
- Common things happened commonly: insomnia, abnormal dreams, nausea. Typically well tolerated
- High patient satisfaction
- High self-reported quit rates at 12 week (58%)

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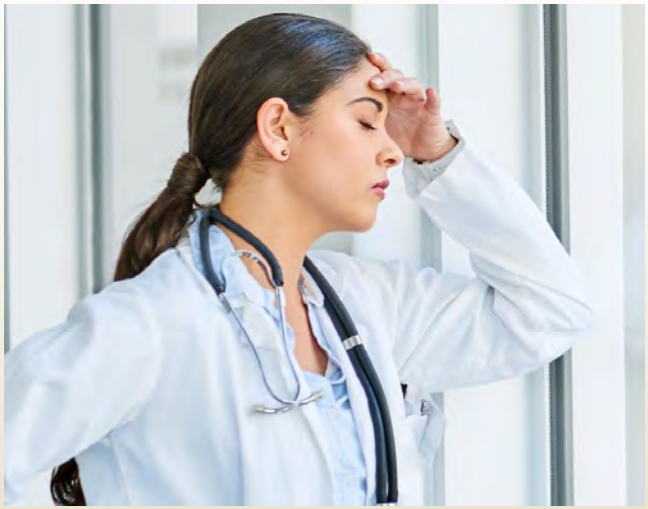
New American Thoracic Society Recommendations regarding Combining Varenicline and NRT for Smoking Cessation

A "Universal" Clinical Path?

	Clinical Question(s)	PICO Question(s)
Initial Medication Choice	Which is the optimal controller medication choice for initiating tobacco dependence treatment?	PICO 1: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with varenicline or nicotine patch? PICO 2: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with bupropion or varenicline?
Potential Modifications	Would combining multiple mechanisms of action improve outcomes?	PICO 3: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with the optimal controller medication (varenicline) plus nicotine replacement therapy or the optimum controller (varenicline) alone?
Important Patient-Level Moderators	What if patients... • aren't interested in approved therapies? • have a mental health or substance use disorder? • remain ambivalent about not smoking?	PICO 4: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with an electronic cigarette or the optimal controller medication? PICO 5: In tobacco-dependent adults who are not ready to discontinue tobacco use, should clinicians begin treatment with the optimal cotroller or wait until they are ready to stop tobacco use? PICO 6: In tobacco-dependent adults with co-morbid psychiatric conditions, including substance use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, in whom treatment is being initiated, should clinicians start with the optimal controller medication identified for patients without psychiatric conditions or use NRT patch?
Maintenance	What is the optimal duration of pharmacologic treatment?	PICO 7: In tobacco-dependent adults for whom treatment is being initiated with a controller, should they be treated with standard duration (6 to 12 weeks) or extended duration (greater than 12 weeks)?



- Reduce choice paralysis
- Emphasize effectiveness
- Minimize perceived impact on workflow

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GRADE EtD - Multiple Outcomes

Alonso-Coello. BMJ 2016;353:i2089
Schünemann. J Clin Epi 2016;76:89–98

- Benefits
- Continuous and PPA
- During treatment and at 6-month follow-up.
- Harms
- SAE as determined by investigators
- Also: Patient Values, Feasibility, Cost, Equity
- Also: PICO-specific outcomes

PICO 1 – Varenicline or Patch?

- Total 14 RCT direct comparison
- 3640-3799 subjects pooled
- 6-mos RR 1.20 (favors varenicline)
- EOT RR 1.40 (favors varenicline)

- 40 Additional Quits/1000 treated
- Strong Recommendation - favors of varenicline over patch
- Moderate Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95%CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Nicotine patch	Relative	Absolute (per 1,000)		
7-Day Point Prevalent Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
11	RCT	not serious	not serious	not serious	not serious	none	1081/3743 (28.9%)	20.2%	**RR 1.20** (1.09 to 1.32)	**40 more** (↑18 to ↑65)	⊕⊕⊕⊕ HIGH	CRITICAL
Point prevalent Tobacco abstinence during the treatment period (follow up: range 10 weeks to 12 weeks; assessed with: Self report + exhaled carbon monoxide)												
9	RCT	not serious	not serious	not serious	not serious	none	1449/3640 (39.8%)	25.4%	**RR 1.40** (1.31 to 1.49)	**101 more** (↑79 to ↑124)	⊕⊕⊕⊕ HIGH	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse events (follow up: range 4 weeks to 3 months)												
10	RCT	not serious	not serious	not serious	serious	none	61/3799 (1.6%)	1.1%	**RR 0.72** (0.52 to 1.00)	**3 fewer** (↓5 to ↓0)	⊕⊕⊕◯ MODERATE	CRITICAL

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** Likely acceptable to pt (black box)*

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PICO 2 – Varenicline or Bupropion?

- Total 7 RCT direct comparison
- 5626-5655 subjects pooled
- 6-mos RR 1.30 (favors varenicline)
- EOT RR 1.41 (favors varenicline)

- 147 Additional Quits/1000 treated
- Strong Recommendation - favors of varenicline over bupropion
- Moderate Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95%CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	varenicline	bupropion	Relative	Absolute (per 1,000)		
7-Day Point Prevalence Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
4	RCT	not serious	not serious	not serious	not serious	none	874/2819 (31.0%)	25.6%	**RR 1.30** (1.19 to 1.42)	**77 more** (↑49 to ↑108)	⊕⊕⊕⊕ HIGH	CRITICAL
7-Day point prevalence Tobacco abstinence during treatment period (follow up: range 8 weeks to 12 weeks; assessed with: Self report + exhaled carbon monoxide concentration verification)												
5	RCT	not serious	not serious	not serious	not serious	none	1206/2834 (42.6%)	35.9%	**RR 1.41** (1.32 to 1.52)	**147 more** (↑115 to ↑187)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: range 7 weeks to 3 months)												
7	RCT	not serious	not serious	not serious	serious [c]	none	54/2954 (1.8%)	1.8%	**RR 0.81** (0.57 to 1.16)	**3 fewer** (↓8 to ↑3)	⊕⊕⊕◯ MODERATE	CRITICAL

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PICO 3 – Varenicline + Patch or Varenicline Alone?

- Total 3 RCT direct comparison
- 776 - 893 subjects pooled
- 6-mos RR 1.36 (favors varenicline)
- EOT RR 1.31 (favors varenicline)
- 105 Additional Quits/1000 treated
- Conditional Recommendation - Suggest varenicline plus patch
- Low Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95%CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	varenicline + nicotine	varenicline alone	Relative	Absolute (per 1,000)		
7-Day point abstinence 6 month or longer (follow up: mean 6 months; assessed with self-report, confirmed with exhaled carbon monoxide)												
2	RCT	not serious	not serious	not serious	not serious	none	154/386 (39.9%)	29.3%	**RR 1.36** (1.07 to 1.72)	**105 more** (↑21 to ↑211)	⊕⊕⊕⊕ HIGH	CRITICAL
7-Day point prevalent abstinence during treatment (assessed with self-report, confirmed with exhaled carbon monoxide)												
2	RCT	not serious	not serious	not serious	not serious	none	184/386 (47.7%)	36.2%	**RR 1.31** (1.11 to 1.54)	**112 more** (↑40 to ↑196)	⊕⊕⊕⊕ HIGH	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse event (follow up: mean 6 months; as reported)												
3	RCT	not serious	not serious	not serious	very serious	none	4/444 (0.9%)	1.4%	**RR 1.06** (0.27 to 4.05)	**1 more** (↓10 to ↑42)	⊕⊕◯◯ LOW	CRITICAL

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PICO 4 – Varenicline or ElectronicCigarette?

- Direct comparisons: 1 conference abstract RCT & 1 obs study
- Network meta-analysis of 8830 subjects in 11 RCT (V vs. N) & 2 RCT (e-cig vs. N)
- 3-mos RR 1.10 (favors varenicline)
- SAE RR 0.32 (favors varenicline)
- 22 Additional Quits/1000 treated
- Conditional Recommendation - Suggest varenicline over e-cig
- Very Low Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95%CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	varenicline	electronic cigarette	Relative	Absolute (per 1,000)		
Point prevalent abstinence 6 month or longer (follow up: mean 24 weeks)												
1	RCT	Serious	not serious	Serious	very serious	none	13/27 (48.1%)	32.5%	**RR 1.44** (0.75 to 2.80)	**143 more** (↓81 to ↑585)	⊕◯◯◯ VERY LOW	CRITICAL
Continuous abstinence 6 month or longer (follow up: mean 1 years; assessed with persistent abstinence from all tobacco)												
1	observational studies	Serious	not serious	not serious	Serious	none	156	200	-	MD **0.046 higher** (↓0.018 to ↑0.11)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse event (follow up: 24 weeks)												
1	RCT	Serious	not serious	Serious	very serious	none	0/27 (0.0%)	0.0%	no estimate		⊕◯◯◯ VERY LOW	CRITICAL

* *EVALI caveat*

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PICO 5 – Pre-treat or Wait for 'Ready'?

- Total 4 RCT direct comparison
- 1250-1360 subjects pooled
- < 6-mos RR 2.49 (favors Pre-treat)
- ≥ 6-mos RR 2.00 (favors Pre-treat)

- 173-308 Additional Quits/1000 treated
- Strong Recommendation - favors of pre-treat over wait
- Moderate Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95%CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-treat varenicline	Wait until patient ready	Relative	Absolute (per 1,000)		
Point abstinence at 6 months or longer (follow up: range 6 months to 1 years; assessed with: Self report + exhaled carbon monoxide concentration verification)												
3	RCT	not serious	not serious	not serious	not serious	none	473/1360 (34.8%)	17.3%	**RR 2.00** (1.70 to 2.35)	**173 more** (↑121 to ↑234)	⊕⊕⊕⊕ HIGH	CRITICAL
Point abstinence during treatment (follow up: 24 weeks; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2	RCT	not serious	not serious	not serious	not serious	none	615/1253 (49.1%)	20.6%	**RR 2.49** (2.09 to 2.98)	**308 more** (↑225 to ↑409)	⊕⊕⊕⊕ HIGH	IMPORTANT
Serious adverse event												
4	RCT	not serious	not serious	not serious	serious	none	34/1369 (2.5%)	17/1046 (1.6%)	**RR 1.75** (0.98 to 3.13)	**12 more** (↓0 to ↑35)	⊕⊕⊕◯ MODERATE	CRITICAL

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PICO 6 – Varenicline or Patch in Behavioral Health Patients?

- Total 2 RCT direct comparison
- 2194 subjects pooled
- 6-mos RR 1.31 (favors varenicline)
- EOT RR 1.78* (? favors
- 36 Additional Quits/1000 treated
- Strong Recommendation - favors varenicline over patch
- Moderate Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95% CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	varenicline	nicotine patch	Relative	Absolute (per 1,000)		
Point prevalent Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2	RCT	not serious	not serious	not serious	not serious	none	275/1109 (24.8%)	11.7%	**RR 1.31** (1.12 to 1.53)	**36 more** (↑14 to ↑62)	⊕⊕⊕⊕ HIGH	CRITICAL
Point prevalent Tobacco abstinence during the treatment period (follow up: 12 weeks; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2	RCT	not serious	not serious	not serious	serious	none	368/1109 (33.2%)	13.9%	**RR 1.78** (0.78 to 4.08)	**108 more** (↓31 to ↑428)	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse events												
2	RCT	not serious	not serious	not serious	serious	none	23/1103 (2.1%)	1.2%	**RR 0.95** (0.54 to 1.67)	**1 fewer** (↓5 to ↑8)	⊕⊕⊕◯ MODERATE	CRITICAL

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PICO 7 – Extended (>12-wk) or Standard (≤ 12-wk) Duration?

- Total 12 RCT direct comparison
- 3711 subjects pooled
- 1 yr RR 1.22 (favors extended)
- 12-18 mos relapse RR 0.43 (favors extended)
- 53 Additional Quits/1000 treated
- Strong Recommendation - favors > 12-wks over ≤ 12-wks Rx
- Moderate Certainty in est effects

Certainty assessment							№ of patients (%)		Effect (95% CI)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	extended duration	standard duration	Relative	Absolute (per 1,000)		
7-day point prevalent abstinence at 1 year (follow up: mean 1 years; assessed with: Self report + exhaled carbon monoxide concentration verification)												
8	RCT	serious	not serious	not serious	not serious	none	751/1935 (38.8%)	24.2%	**RR 1.22** (1.07 to 1.39)	**53 more** (↑17 to ↑94)	⊕⊕⊕◯ MODERATE	CRITICAL
Relapse (follow up: range 12 months to 18 months)												
2	RCT	not serious	not serious	not serious	serious	none	322	333	**HR 0.43** (0.29 to 0.64)	**0 fewer** (0 to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
Serious adverse event												
5	RCT	not serious	not serious	not serious	serious	none	30/1304 (2.3%)	0.8%	**RR 1.37** (0.79 to 2.36)	**3 more** (↓2 to ↑11)	⊕⊕⊕◯ MODERATE	CRITICAL

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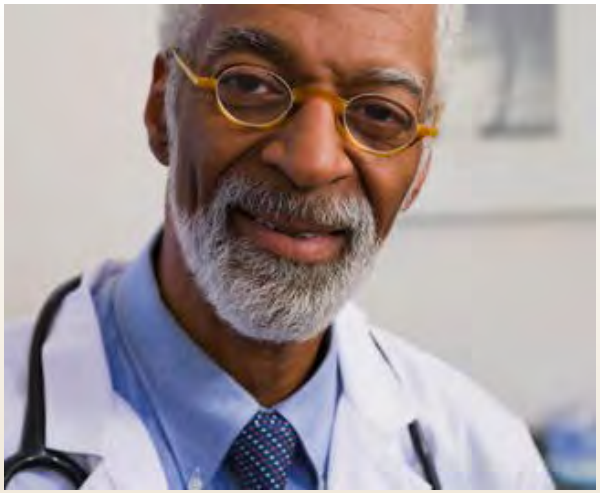
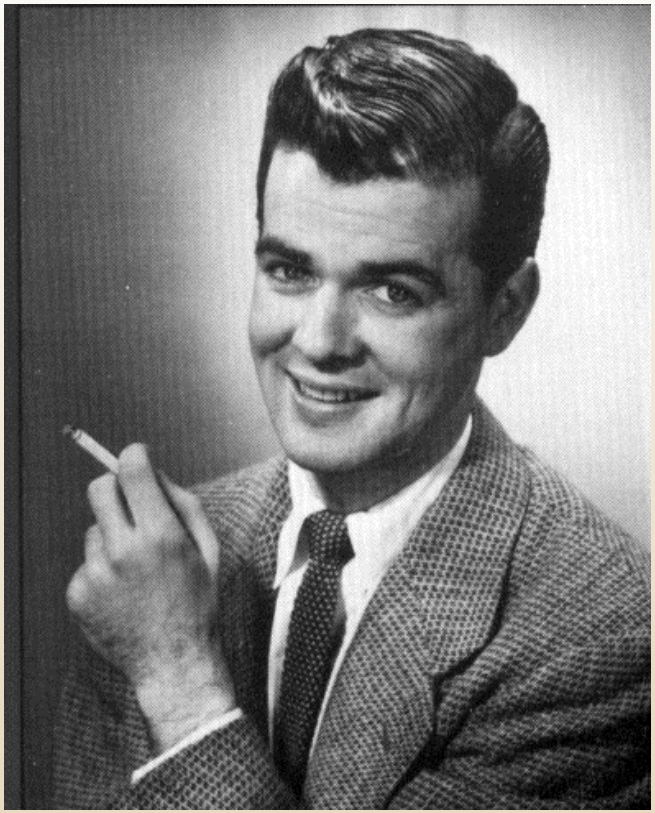
Practical Implications

- *Varenicline as first-line should not require nicotine or bupropion "failure"*
- *Treatment should be available for more than 3 month duration*



- *Treat compulsion before the patient is ready to quit*
- *Nicotine amplifies Varenicline despite proposed mechanism of action*
- *Current / History of BH should not preclude varenicline*

Limitations & Next Steps



- Did not evaluate alternative approaches
- Renal Disease
- What if pt refuses / failed varenicline in past?
- No evaluation of office-based counseling strategies

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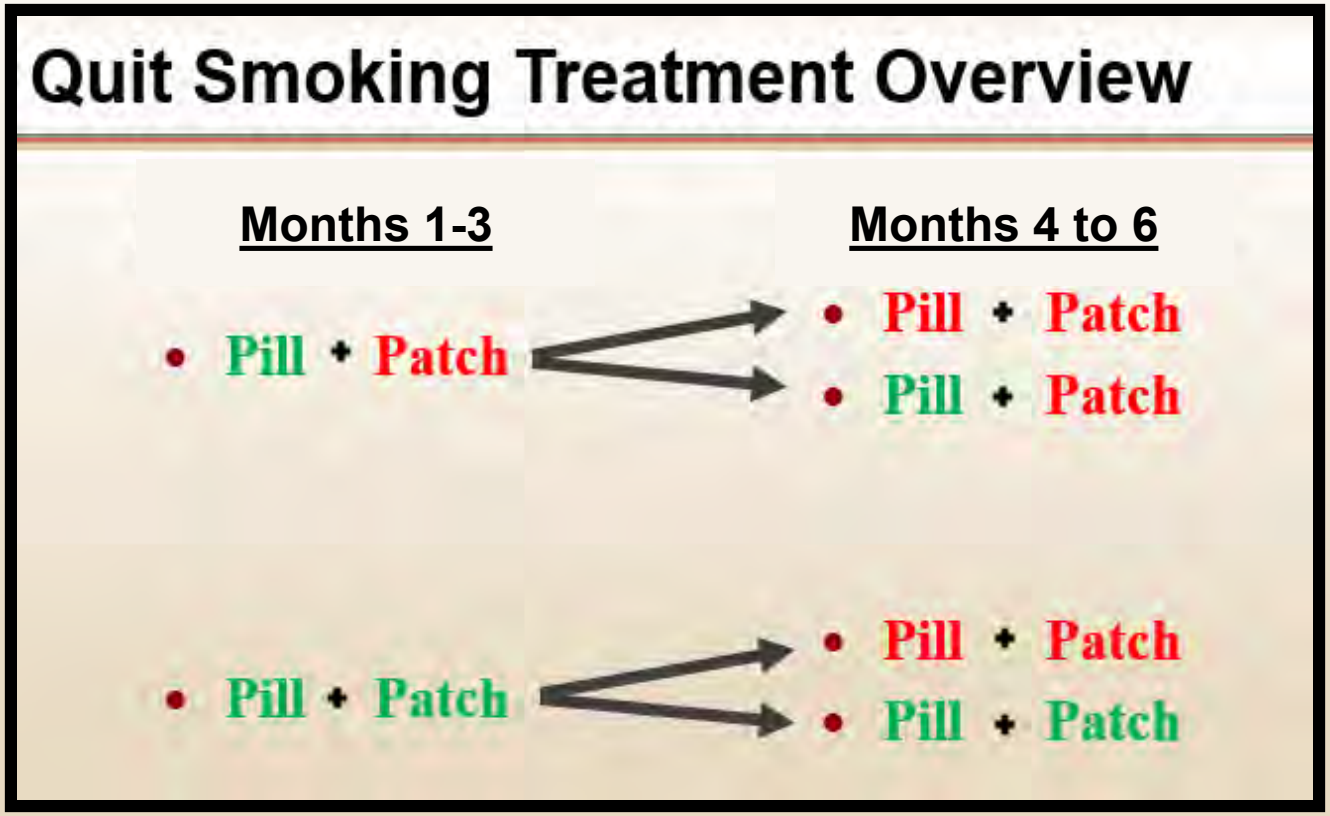
The Wisconsin QUITS Study

The Wisconsin QUITS Study

- PIs: Baker, Stein, Fiore, *University of Wisconsin Center for Tobacco Research and Intervention* (UW-CTRI)
- Funded by NHLBI/NIH
- Sample size: 1,250 Smokers motivated to quit
- Randomized to 4 conditions, double blind
- Assessing both V vs V+N and 12 vs 24 wks of treatment
- Key Outcome – 12 Month Quit Rates

The Wisconsin QUITS Study



GREEN = Active Medication
RED = Placebo Medication

PILL = Varenicline
PATCH = Nicotine Patch 14 mg

Varenicline + NRT: Time for a Clinical Recommendation Update?

Comments/Questions

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