Initiating Pharmacologic Treatment of Tobacco Dependence:

An Official ATS Clinical Practice Guideline

(Running Title: ATS Tobacco Treatment Guideline)

Online Data Supplement

Questions 1-3

MEDLINE via PubMed Strategy
((((((((((tobacco* OR nicotine* OR cigarette OR cigarettes OR cigar OR cigars) AND (quit OR quitting OR cessation OR cessations OR dependence OR dependent OR "giving up" OR disorder OR disorders OR abstain OR abstinence OR abstinent OR addict OR addicts OR addiction)))) OR "Smoking Cessation"[Mesh]) OR "Smokers"[Mesh]) OR "Tobacco Use"[Mesh]) OR "Tobacco Use Disorder"[Mesh]) OR ((smoker OR smokers OR smoking))) OR (("tobacco use" OR "cigarette use" OR "nicotine use")))) AND ((((("Varenicline"[Mesh] OR varenicline OR chantix OR champix))) AND ((((("Bupropion"[Mesh] OR (bupropion OR zyban OR wellbutrin OR buproban)))) OR ((((nicotine OR NRT) AND (gum OR gums OR inhaler OR inhalers OR inhalator OR inhalators OR inhalant OR inhalants OR spray OR spays OR tablet OR tablets OR microtab OR microtabs OR lozenge OR lozenges OR patch OR patches OR polacrilex OR polacrilices)) OR (nicorette OR "NicoDerm CQ" OR nicotrol OR habitrol) OR ("nicotine replacement" OR C-NRT OR NRT) OR ((quitting OR cessation) AND (aid OR aids OR product OR products)) OR "Nicotine Chewing Gum"[Mesh] OR "Tobacco Use Cessation Products"[Mesh]))))

Questions 1-3

Embase Search Strategy	
#1	tobacco* OR nicotine* OR cigarette OR cigarettes OR cigar OR cigars
#2	quit OR quitting OR cessation OR cessations OR dependence OR dependent OR 'giving up' OR disorder OR disorders OR abstain OR abstinence OR abstinent OR addict OR addicts OR addiction
#3	#1 AND #2
#4	'smoking cessation'/exp
#5	'tobacco use'/exp
#6	'tobacco dependence'/exp
#7	smoker OR smokers OR smoking
#8	'tobacco use' OR 'cigarette use' OR 'nicotine use'
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	'varenicline'/exp
#11	varenicline
#12	chantix OR champix
#13	#10 OR #11 OR #12
#14	'amfebutamone'/exp
#15	bupropion OR zyban OR wellbutrin OR buproban
#16	#14 OR #15
#17	nicotine OR nrt
#18	gum OR gums OR inhaler OR inhalers OR inhalator OR inhalators OR inhalant OR inhalants OR spray OR spays OR tablet OR tablets OR microtab OR microtabs OR lozenge OR lozenges OR patch OR patches OR polacrilex OR polacrilices
#19	#17 AND #18
#20	nicorette OR 'nicoderm cq' OR nicotrol OR habitrol
#21	'nicotine replacement' OR 'c nrt' OR nrt
#22	quitting OR cessation
#23	aid OR aids OR product OR products
#24	#22 AND #23
#25	'nicotine gum'/exp
#26	'nicotine replacement therapy'/exp
#27	#19 OR #20 OR #21 OR #24 OR #25 OR #26
#28	#16 OR #27
#29	#13 AND #28
#30	#9 AND #29

Question 4: Adult smoker AND e-cig AND varenicline

MEDLINE via PubMed Strategy
(((((((tobacco* or nicotine* OR cigarette OR cigarettes OR cigar OR cigars) AND (quit OR quitting OR cessation OR cessations OR dependence OR dependent OR “giving up” OR disorder OR disorders OR abstain OR abstinence OR abstinent OR addict OR addicts OR addiction)) OR smoker OR smokers OR smoking OR “tobacco use” OR “cigarette use” OR “nicotine use” OR "Smoking Cessation"[Mesh] OR "Smokers"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Disorder"[Mesh]))) AND (“electronic cigarette” OR “electronic cigarettes” OR e-cigarette OR e-cigarettes

OR e-cig OR "Electronic Nicotine Delivery Systems"[Mesh] OR "Vaping"[Mesh] OR e-cigs OR “Electronic Nicotine Delivery System” OR “Electronic Nicotine Delivery Systems” OR ENDS OR “electronic non-nicotine delivery system” OR “electronic non-nicotine delivery systems” OR ENNDS OR vape OR vapes OR vaping OR vaper OR vapers OR vapor OR vapors OR vaporize OR vaporise OR vaporizing OR vaporising OR electronic cigar OR electronic cigars OR e-cigar OR electronic nicotine OR e-nicotine OR juul OR juuling OR iQOS OR mod OR pen)) AND (((Varenicline OR Chantix OR Champix OR "Varenicline"[Mesh]))))) AND (((((("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh])))) OR ((((((((("Cohort Studies"[Mesh]) OR cohort*[tw]) OR "Controlled Clinical Trial"[Publication Type]) OR ("Epidemiologic Methods"[Mesh:noexp] AND ("1966/01/01"[PDat] : "1989/12/31"[PDat]))) OR "Case-Control Studies"[Mesh]) OR (case*[tw] AND control*[tw])) OR (case*[tw] AND series[tw])) OR "Case Reports"[Publication Type]) OR (case*[tw] AND report*[tw])) OR (case*[tw] AND stud*[tw])))

Question 5: tobacco dependent adults who are not ready to discontinue tobacco use AND best controller/varenicline

Run search with RCT filter

MEDLINE via PubMed Search Strategy
((((((tobacco* OR nicotine* OR cigarette OR cigarettes OR cigar OR cigars) AND (quit OR quitting OR quitter OR cessation OR cessations OR dependence OR dependent OR “give up” OR “giving up” OR disorder OR disorders OR abstain OR abstinence OR abstinent OR discontinue OR addict OR addicts OR addiction OR stop OR stopping)) OR smoker[tiab] OR smokers[tiab] OR smoking[tiab] OR “tobacco use” OR “cigarette use” OR “nicotine use” OR "Smoking Cessation"[Mesh] OR "Smokers"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR “Smoking”[Mesh]))) AND ("Motivation"[Mesh] OR unwilling OR “not willing” OR “not yet willing” OR “no intention” OR “no intentions” OR “without intention” OR “without intentions” OR “not interested” OR “uninterested” OR unmotivated OR “not motivated” OR “no motivation” OR “no motive” OR “without motivation” OR “not trying” OR “not currently trying” OR “no plan” OR “no plans” OR “not planning” OR “not currently planning” OR “not ready” OR “not able” OR “non-treatment seeking” OR “non-therapy seeking” OR “no desire” OR “no immediate desire” OR “do not wish” OR “no wish” OR reluctant OR reluctance OR readiness OR satisfaction OR satisfying OR pleasure OR pleasurable OR enjoyment OR enjoy OR enjoying OR “ad lib” OR crave OR craves OR craving OR cravings OR prequit OR “pre quit” OR preloading OR preload OR “pre load” OR “pre loading” OR “quit attempt” OR “quit attempts” OR “reduce to quit” OR “induction phase” OR “cessation induction” OR “smoking induction”)) AND ((Varenicline OR Chantix OR Champix OR "Varenicline"[Mesh]))
RCT Filter: (("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh]))

Question 5

Embase Search Strategy	
#1	('tobacco*':ti,ab,kw OR 'nicotine*':ti,ab,kw OR 'cigarette':ti,ab,kw OR 'cigarettes':ti,ab,kw OR 'cigar':ti,ab,kw OR 'cigars':ti,ab,kw) AND ('quit':ti,ab,kw OR 'quitting':ti,ab,kw OR 'quitter':ti,ab,kw OR 'cessation':ti,ab,kw OR 'cessations':ti,ab,kw OR 'dependence':ti,ab,kw OR 'dependent':ti,ab,kw OR 'give up':ti,ab,kw OR 'giving up':ti,ab,kw OR 'disorder':ti,ab,kw OR 'disorders':ti,ab,kw OR 'abstain':ti,ab,kw OR 'abstinence':ti,ab,kw OR 'abstinent':ti,ab,kw OR 'discontinue':ti,ab,kw OR 'addict':ti,ab,kw OR 'addicts':ti,ab,kw OR 'addiction':ti,ab,kw OR 'stop':ti,ab,kw OR 'stopping':ti,ab,kw)
#2	'smoker':ti,ab,kw OR 'smokers':ti,ab,kw OR 'smoking':ti,ab,kw
#3	'tobacco use':ti,ab,kw OR 'cigarette use':ti,ab,kw OR 'nicotine use':ti,ab,kw

#4	'smoking cessation'/exp
#5	'smoking'/exp
#6	'tobacco use'/exp
#7	'tobacco dependence'/exp
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	'varenicline':ti,ab,kw OR 'chantix':ti,ab,kw OR 'champix':ti,ab,kw
#10	'varenicline'/exp
#11	#9 OR #10
#12	'motivation'/exp
#13	'unwilling':ti,ab,kw OR 'not willing':ti,ab,kw OR 'not yet willing':ti,ab,kw OR 'no intention':ti,ab,kw OR 'no intentions':ti,ab,kw OR 'without intention':ti,ab,kw OR 'without intentions':ti,ab,kw OR 'not interested':ti,ab,kw OR 'uninterested':ti,ab,kw OR 'unmotivated':ti,ab,kw OR 'not motivated':ti,ab,kw OR 'no motivation':ti,ab,kw OR 'no motive':ti,ab,kw OR 'without motivation':ti,ab,kw OR 'not trying':ti,ab,kw OR 'not currently trying':ti,ab,kw OR 'no plan':ti,ab,kw OR 'no plans':ti,ab,kw OR 'not planning':ti,ab,kw OR 'not currently planning':ti,ab,kw OR 'not ready':ti,ab,kw OR 'not able':ti,ab,kw OR 'non-treatment seeking':ti,ab,kw OR 'non-therapy seeking':ti,ab,kw OR 'no desire':ti,ab,kw OR 'no immediate desire':ti,ab,kw OR 'no wish':ti,ab,kw OR 'reluctant':ti,ab,kw OR 'reluctance':ti,ab,kw OR 'readiness':ti,ab,kw OR 'satisfaction':ti,ab,kw OR 'satisfying':ti,ab,kw OR 'pleasure':ti,ab,kw OR 'pleasurable':ti,ab,kw OR 'enjoyment':ti,ab,kw OR 'enjoy':ti,ab,kw OR 'enjoying':ti,ab,kw OR 'ad lib':ti,ab,kw OR 'crave':ti,ab,kw OR 'craves':ti,ab,kw OR 'craving':ti,ab,kw OR 'cravings':ti,ab,kw OR 'prequit':ti,ab,kw OR 'pre quit':ti,ab,kw OR 'preloading':ti,ab,kw OR 'preload':ti,ab,kw OR 'pre load':ti,ab,kw OR 'pre loading':ti,ab,kw OR 'quit attempt':ti,ab,kw OR 'quit attempts':ti,ab,kw OR 'reduce to quit':ti,ab,kw OR 'induction phase':ti,ab,kw OR 'cessation induction':ti,ab,kw OR 'smoking induction':ti,ab,kw
#14	#12 OR #13
#15	random*
#16	factorial*
#17	(crossover* OR cross) AND over* OR 'cross over*'
#18	placebo
#19	doubl* NEXT/1 blind*
#20	singl* NEXT/1 blind*
#21	assign*
#22	allocat*
#23	volunteer*
#24	'crossover procedure'/exp
#25	'double blind procedure'/exp
#26	'randomized controlled trial'/exp
#27	'single blind procedure'/exp
#28	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	#8 AND #11 AND #14
#30	#28 AND #29

Question 6: tobacco dependent adults AND psychiatric conditions AND best controller

Best controller as varenicline; Run with RCT filter

MEDLINE via PubMed Search Strategy
Varenicline only: ((((((tobacco* OR nicotine* OR cigarette OR cigarettes OR cigar OR cigars) AND (quit OR quitting OR cessation OR cessations OR dependence OR

dependent OR “giving up” OR disorder OR disorders OR abstain OR abstinence OR abstinent OR addict OR addicts OR addiction)) OR smoker[tiab] OR smokers[tiab] OR smoking[tiab] OR “tobacco use” OR “cigarette use” OR “nicotine use” OR "Smoking Cessation"[Mesh] OR "Smokers"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR “Smoking”[Mesh]))) AND (("Substance-Related Disorders"[Mesh] OR "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Bipolar Disorder"[Mesh] OR "Schizophrenia"[Mesh] OR alcoholic[tiab] OR alcoholism[tiab] OR ((drug[tiab] OR drugs[tiab] OR substance[tiab] OR substances[tiab] OR heroin[tiab] OR alcohol[tiab] OR drinking[tiab] OR cocaine[tiab] OR marijuana[tiab] OR amphetamine[tiab] OR amphetamines[tiab] OR opioid[tiab] OR opioids[tiab] OR morphine[tiab] OR phencyclidine[tiab] OR opium[tiab] OR inhalant[tiab]) AND (disorder[tiab] OR disorders[tiab] OR abuse[tiab] OR abuses[tiab] OR dependence[tiab] OR dependent[tiab] OR addict[tiab] OR addicts[tiab] OR addiction[tiab] OR addicted[tiab] OR habituation[tiab] OR binge[tiab])) OR depression[tiab] OR depressions[tiab] OR ((depressive[tiab] OR neurotic[tiab]) AND (disorder[tiab] OR disorders[tiab] OR symptom[tiab] OR symptoms[tiab] OR neuroses[tiab] OR neurosis[tiab] OR syndrome[tiab] OR syndromes[tiab])) OR melancholia[tiab] OR melancholias[tiab] OR psychoses[tiab] OR psychosis[tiab] OR psychotic[tiab] OR paraphrenia[tiab] OR paraphrenias[tiab] OR “dysthymic disorder”[tiab] OR dysthymia[tiab] OR anxiety[tiab] OR anxieties[tiab] OR nervousness[tiab] OR agoraphobia[tiab] OR psychoneuroses[tiab] OR neurosis[tiab] OR neuroses[tiab] OR “obsessive compulsive disorder”[tiab] OR “obsessive compulsive disorders”[tiab] OR “panic disorder”[tiab] OR “panic disorders”[tiab] OR “panic attack”[tiab] OR “panic attacks”[tiab] OR “phobic disorder”[tiab] OR “phobic disorders”[tiab] OR claustrophobia[tiab] OR claustrophobias[tiab] OR bipolar[tiab] OR “manic state”[tiab] OR “manic states”[tiab] OR “manic disorder”[tiab] OR “manic disorders”[tiab] OR schizophrenia[tiab] OR schizophrenias[tiab] OR schizophrenic[tiab] OR “shared paranoid disorder”[tiab] OR schizoaffective[tiab]))) AND ((Varenicline OR Chantix OR Champix OR "Varenicline"[Mesh]))

Question 6

Embase Search Strategy	
#1	('tobacco*':ti,ab,kw OR 'nicotine*':ti,ab,kw OR 'cigarette':ti,ab,kw OR 'cigarettes':ti,ab,kw OR 'cigar':ti,ab,kw OR 'cigars':ti,ab,kw) AND ('quit':ti,ab,kw OR 'quitting':ti,ab,kw OR 'cessation':ti,ab,kw OR 'cessations':ti,ab,kw OR 'dependence':ti,ab,kw OR 'dependent':ti,ab,kw OR 'giving up':ti,ab,kw OR 'disorder':ti,ab,kw OR 'disorders':ti,ab,kw OR 'abstain':ti,ab,kw OR 'abstinence':ti,ab,kw OR 'abstinent':ti,ab,kw OR 'addict':ti,ab,kw OR 'addicts':ti,ab,kw OR 'addiction':ti,ab,kw)
#2	'smoker':ti,ab,kw OR 'smokers':ti,ab,kw OR 'smoking':ti,ab,kw
#3	'tobacco use':ti,ab,kw OR 'cigarette use':ti,ab,kw OR 'nicotine use':ti,ab,kw
#4	'smoking cessation'/exp
#5	'smoking'/exp
#6	'tobacco use'/exp
#7	'tobacco dependence'/exp
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	'drug dependence'/exp
#10	'depression'/exp
#11	'anxiety disorder'/exp
#12	'bipolar disorder'/exp
#13	'schizophrenia'/exp
#14	'alcoholic':ti,ab,kw OR 'alcoholism':ti,ab,kw
#15	'drug':ti,ab,kw OR 'drugs':ti,ab,kw OR 'substance':ti,ab,kw OR 'substances':ti,ab,kw OR 'heroin':ti,ab,kw OR 'alcohol':ti,ab,kw OR 'drinking':ti,ab,kw OR 'cocaine':ti,ab,kw OR 'marijuana':ti,ab,kw OR 'amphetamine':ti,ab,kw OR 'amphetamines':ti,ab,kw OR 'opioid':ti,ab,kw OR 'opioids':ti,ab,kw OR 'morphine':ti,ab,kw OR 'phencyclidine':ti,ab,kw OR 'opium':ti,ab,kw OR 'inhalant':ti,ab,kw
#16	'disorder':ti,ab,kw OR 'disorders':ti,ab,kw OR 'abuse':ti,ab,kw OR 'abuses':ti,ab,kw OR 'dependence':ti,ab,kw OR 'dependent':ti,ab,kw OR 'addict':ti,ab,kw OR 'addicts':ti,ab,kw OR 'addiction':ti,ab,kw OR 'addicted':ti,ab,kw OR 'habituation':ti,ab,kw OR 'binge':ti,ab,kw
#17	#15 AND #16
#18	'depression':ti,ab,kw OR 'depressions':ti,ab,kw
#19	'depressive':ti,ab,kw OR 'neurotic':ti,ab,kw
#20	'disorder':ti,ab,kw OR 'disorders':ti,ab,kw OR 'symptom':ti,ab,kw OR 'symptoms':ti,ab,kw OR 'neuroses':ti,ab,kw OR 'neurosis':ti,ab,kw OR 'syndrome':ti,ab,kw OR 'syndromes':ti,ab,kw
#21	#19 AND #20
#22	'melancholia':ti,ab,kw OR 'melancholias':ti,ab,kw OR 'psychoses':ti,ab,kw OR 'psychosis':ti,ab,kw OR 'psychotic':ti,ab,kw OR 'paraphrenia':ti,ab,kw OR 'paraphrenias':ti,ab,kw OR 'dysthymic disorder':ti,ab,kw OR 'dysthymia':ti,ab,kw OR 'anxiety':ti,ab,kw OR 'anxieties':ti,ab,kw OR 'nervousness':ti,ab,kw OR 'agoraphobia':ti,ab,kw OR 'psychoneuroses':ti,ab,kw OR 'neurosis':ti,ab,kw OR 'neuroses':ti,ab,kw OR 'obsessive compulsive disorder':ti,ab,kw OR 'obsessive compulsive disorders':ti,ab,kw OR 'panic disorder':ti,ab,kw OR 'panic

	disorders':ti,ab,kw OR 'panic attack':ti,ab,kw OR 'panic attacks':ti,ab,kw OR 'phobic disorder':ti,ab,kw OR 'phobic disorders':ti,ab,kw OR 'claustrophobia':ti,ab,kw OR 'claustrophobias':ti,ab,kw OR 'bipolar':ti,ab,kw OR 'manic state':ti,ab,kw OR 'manic states':ti,ab,kw OR 'manic disorder':ti,ab,kw OR 'manic disorders':ti,ab,kw OR 'schizophrenia':ti,ab,kw OR 'schizophrenias':ti,ab,kw OR 'schizophrenic':ti,ab,kw OR 'shared paranoid disorder':ti,ab,kw OR 'schizoaffective':ti,ab,kw
#23	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #17 OR #18 OR #21 OR #22
#24	'varenicline':ti,ab,kw OR 'chantix':ti,ab,kw OR 'champix':ti,ab,kw
#25	'varenicline'/exp
#26	#24 OR #25
#27	random*
#28	factorial*
#29	(crossover* OR cross) AND over* OR 'cross over*'
#30	placebo
#31	doubl* NEXT/1 blind*
#32	singl* NEXT/1 blind*
#33	assign*
#34	allocat*
#35	volunteer*
#36	'crossover procedure'/exp
#37	'double blind procedure'/exp
#38	'randomized controlled trial'/exp
#39	'single blind procedure'/exp
#40	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#41	#8 AND #23 AND #26 AND #40

Question 7: tobacco dependent adults AND controller AND duration

Run search with RCT filter

MEDLINE via PubMed Search Strategy
((((((tobacco* OR nicotine* OR cigarette OR cigarettes OR cigar OR cigars) AND (quit OR quitting OR quitter OR cessation OR cessations OR dependence OR dependent OR “give up” OR “giving up” OR disorder OR disorders OR abstain OR abstinence OR abstinent OR discontinue OR addict OR addicts OR addiction OR stop OR stopping)) OR smoker[tiab] OR smokers[tiab] OR smoking[tiab] OR “tobacco use” OR “cigarette use” OR “nicotine use” OR "Smoking Cessation"[Mesh] OR "Smokers"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR “Smoking”[Mesh]) AND (Varenicline OR Chantix OR Champix OR "Varenicline"[Mesh] OR "Bupropion"[Mesh] OR bupropion OR zyban OR wellbutrin OR buproban OR “NicoDerm CQ” OR nicotrol OR habitrol OR ((nicotine OR NRT OR nicotinic) AND (patch OR patches)))))) AND (("length of treatment"[tiab] OR “standard treatment”[tiab] OR “extended treatment”[tiab] OR “standard course”[tiab] OR “standard courses”[tiab] OR “extended course”[tiab] OR “extended courses”[tiab] OR “maintenance therapy”[tiab] OR “maintenance treatment”[tiab] OR “maintenance pharmacotherapy”[tiab] OR duration[tiab] OR period[tiab] OR periods[tiab] OR week[tiab] OR weeks[tiab] OR month[tiab] OR months[tiab] OR day[tiab] OR days[tiab]))
RCT Filter: (("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh]))

Question 7

Embase Search Strategy	
#1	('tobacco*':ti,ab,kw OR 'nicotine*':ti,ab,kw OR 'cigarette':ti,ab,kw OR 'cigarettes':ti,ab,kw OR 'cigar':ti,ab,kw OR 'cigars':ti,ab,kw) AND ('quit':ti,ab,kw OR 'quitting':ti,ab,kw OR 'quitter':ti,ab,kw OR 'cessation':ti,ab,kw OR 'cessations':ti,ab,kw OR 'dependence':ti,ab,kw OR 'dependent':ti,ab,kw OR 'give up':ti,ab,kw OR 'giving up':ti,ab,kw OR 'disorder':ti,ab,kw OR 'disorders':ti,ab,kw OR 'abstain':ti,ab,kw OR 'abstinence':ti,ab,kw OR 'abstinent':ti,ab,kw OR 'discontinue':ti,ab,kw OR 'addict':ti,ab,kw OR 'addicts':ti,ab,kw OR 'addiction':ti,ab,kw OR 'stop':ti,ab,kw OR 'stopping':ti,ab,kw)
#2	'smoker':ti,ab,kw OR 'smokers':ti,ab,kw OR 'smoking':ti,ab,kw
#3	'tobacco use':ti,ab,kw OR 'cigarette use':ti,ab,kw OR 'nicotine use':ti,ab,kw
#4	'smoking cessation'/exp
#5	'smoking'/exp
#6	'tobacco use'/exp
#7	'tobacco dependence'/exp
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	'varenicline':ti,ab,kw OR 'chantix':ti,ab,kw OR 'champix':ti,ab,kw
#10	'varenicline'/exp
#11	'bupropion':ti,ab,kw OR 'zyban':ti,ab,kw OR 'wellbutrin':ti,ab,kw OR 'buproban':ti,ab,kw
#12	'amfebutamone'/exp
#13	'nicoderm cq':ti,ab,kw OR 'nicotrol':ti,ab,kw OR 'habitrol':ti,ab,kw
#14	('nicotine':ti,ab,kw OR 'nrt':ti,ab,kw OR 'nicotinic':ti,ab,kw) AND ('patch':ti,ab,kw OR 'patches':ti,ab,kw)
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#8 AND #15
#17	'length of treatment':ti,ab,kw OR 'standard treatment':ti,ab,kw OR 'extended treatment':ti,ab,kw OR 'standard course':ti,ab,kw OR 'standard courses':ti,ab,kw OR 'extended course':ti,ab,kw OR 'extended courses':ti,ab,kw OR 'maintenance therapy':ti,ab,kw OR 'maintenance treatment':ti,ab,kw OR 'maintenance pharmacotherapy':ti,ab,kw OR 'duration':ti,ab,kw OR 'period':ti,ab,kw OR 'periods':ti,ab,kw OR 'week':ti,ab,kw OR 'weeks':ti,ab,kw OR 'month':ti,ab,kw OR 'months':ti,ab,kw OR 'day':ti,ab,kw OR 'days':ti,ab,kw
#18	#16 AND #17
#19	random*
#20	factorial*
#21	(crossover* OR cross) AND over* OR 'cross over*'
#22	placebo
#23	doubl* NEXT/1 blind*
#24	singl* NEXT/1 blind*
#25	assign*
#26	allocat*
#27	volunteer*
#28	'crossover procedure'/exp
#29	'double blind procedure'/exp
#30	'randomized controlled trial'/exp
#31	'single blind procedure'/exp
#32	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	#18 AND #32

PICO 1: In tobacco-dependent adults, should treatment be started with varenicline or nicotine patch?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Nicotine patch	Relative (95% CI)	Absolute (95% CI)		
7-Day Point Prevalent Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
11 [1,2,3,4,5,6,7,8,9,10,11]	randomised trials	not serious [a]	not serious	not serious	not serious	none	1081/3743 (28.9%)	20.2%	RR 1.20 (1.09 to 1.32)	40 more per 1,000 (from 18 more to 65 more)	⨁⨁⨁⨁ 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 concentration verification)												
9 [1,2,3,4,6,7,9,10]	randomised trials	not serious [b]	not serious	not serious	not serious	none	1449/3640 (39.8%)	25.4%	RR 1.40 (1.31 to 1.49)	101 more per 1,000 (from 79 more to 124 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse events (follow up: range 4 weeks to 3 months)												
10 [1,2,4,6,7,9,10,12,13]	randomised trials	not serious [c]	not serious	not serious	serious [d]	none	61/3799 (1.6%)	1.1%	RR 0.72 (0.52 to 1.00)	3 fewer per 1,000 (from 5 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Tobacco use relapse measured at the end of the follow-up (follow up: range 8 weeks to 6 months)												
2 [4,12]	randomised trials	serious [e]	not serious	not serious	serious [f]	none	0/491 (0.0%)	0/314 (0.0%)	HR 0.93 (0.78 to 1.11)	-	⨁⨁◯◯ LOW	IMPORTANT
Other substance abuse-**Alcohol (follow up: 6 months; assessed with: alcohol test (breath alcohol ≤ 0.02 g/dl))**												
1 [7]	randomised trials	serious [g]	not serious	not serious	very serious [h]	none	8/49 (16.3%)	29.0%	RR 0.56 (0.24 to 1.30)	128 fewer per 1,000 (from 221 fewer to 87 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Other substance abuse-any drug (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Nicotine patch	Relative (95% CI)	Absolute (95% CI)		
1 [7]	randomised trials	serious [g]	not serious	not serious	very serious [h]	none	18/49 (36.7%)	25.8%	RR 1.42 (0.71 to 2.87)	108 more per 1,000 (from 75 fewer to 483 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Severity of withdrawal - MNWS total (follow up: 12 weeks; assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome)												
1 [8]	randomised trials	serious [i]	not serious	not serious	very serious [j]	none	14	14	-	MD 0.08 higher (1.98 lower to 2.14 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Severity of withdrawal - MNWS-Urge to smoke (follow up: range 7 weeks to 12 weeks; assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome; Scale from: 0 to 4)												
2 [1,8]	randomised trials	serious [k]	serious [l]	not serious	not serious	none	381	380	-	MD 0.32 lower (0.33 lower to 0.31 lower)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; HR: Hazard Ratio

Explanations

a. The estimate was similar to the low risk of bias study Anthenelli 2016. But being influenced by high risk of bias studies (mostly due to open label nature), the lower limit of the pooled estimate was closer to 1.
b. The estimate was based on 9 studies. Though some of them were open label studies, studies with high risk of bias show similar estimates with the low risk of bias studies (Anthenellie 2016, Lerman 2015, and Rohsenow 2017).
c. Though most of the studies were open label studies, the estimate was largely based on Anthenelli 2016 and Lerman 2015, two low risk of bias studies.
d. The confidence interval is 0.52 to 1.00, suggesting varenicline does not increase risk of serious adverse events compared with nicotine patch. But this confidence interval does not support varenicline will decrease risk of serious adverse events.
e. Baker 2016 was an open label trial.
f. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of varenicline will be different.
g. Because of lost to follow up, the substance abuse outcomes were compared in an unbalanced manner in Rohsenow 2017 (49 in Varenicline group vs 31 in nicotine replacement therapy group).
h. The estimate is based on a very small total number of events. The confidence interval includes 1.
i. Tsukahara 2010 was an open label study. This study did not report baseline measurement of withdrawal symptoms, and patients in varenicline group had higher symptom scores from Week 2 to Week 12, although patients in varenicline group improved more.
j. We have no estimate of clinical minimal important difference. However, the confidence interval includes 0. Considering the lower or the upper limits of the confidence interval, varenicline may or may not be considered as beneficial in the withdrawal symptom score, compared with nicotine patch.
k. Two studies reported this outcome (Aubin 2008 and Tsukahara 2010). Both studies were open label.
l. Aubin 2008 reported the changes from baseline and suggested varenicline reduced withdrawal symptoms further than nicotine patch. While Tsukahara 2010 did not report baseline measurement, and patients in varenicline group had higher withdrawal symptom scores than those in the nicotine patch group from Week 2 to Week 12, although patients in varenicline group improved more. We did not pool the estimates, and the effect estimate was based on Aubin 2008.

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Evidence to Decision

QUESTION

Should Varenicline vs. Nicotine patch be used for Tobacco-dependent adults?	
POPULATION:	Tobacco-dependent adults
INTERVENTION:	Varenicline
COMPARISON:	Nicotine patch
MAIN OUTCOMES:	7-Day Point Prevalent Tobacco abstinence at 6 months; Point prevalent Tobacco abstinence during the treatment period; Quality of life; Serious adverse events; Tobacco use relapse measured at the end of the follow-up; Other substance abuse-Alcohol; Other substance abuse-any drug; Severity of withdrawal – Minnesota Nicotine Withdrawal Scale (MNWS) total; Severity of withdrawal - MNWS-Urge to smoke.
SETTING:	Outpatient
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and disease in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking. (1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with nicotine patch	Risk difference with varenicline
7-Day Point Prevalent Tobacco abstinence at 6 months assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 6 months	7362 (11 RCTs)[1,10,11,2,3,4,5,6,7,8,9]	⨁⨁⨁⨁ HIGH[a]	**RR 1.20** (1.09 to 1.32)	202 per 1,000	**40 more per 1,000** (18 more to 65 more)
Point prevalent Tobacco abstinence during the treatment period assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 10	7153 (9 RCTs)[1,10,2,3,4,6,7,9]	⨁⨁⨁⨁ HIGH[b]	**RR 1.40** (1.31 to 1.49)	254 per 1,000	**101 more per 1,000** (79 more to 124 more)

	weeks to 12 weeks					
	Quality of life - not reported	-	-	-	-	-
	Serious adverse events follow up: range 4 weeks to 3 months	7487 (10 RCTs)[1,10,12,13,2,4,6,7,9]	⊕⊕⊕◯ MODERATE[c,d]	**RR 0.72** (0.52 to 1.00)	11 per 1,000	**3 fewer per 1,000** (5 fewer to 0 fewer)
	Tobacco use relapse measured at the end of the follow-up follow up: range 8 weeks to 6 months	805 (2 RCTs)[12,4]	⊕⊕◯◯ LOW[e,f]	**HR 0.93** (0.78 to 1.11)	-	-
	Other substance abuse-Alcohol assessed with: alcohol test (breath alcohol ≤ 0.02 g/dl) follow up: 6 months	80 (1 RCT)[7]	⊕◯◯◯ VERY LOW[g,h]	**RR 0.56** (0.24 to 1.30)	290 per 1,000	**128 fewer per 1,000** (221 fewer to 87 more)

Other substance abuse-any drug follow up: 6 months	80 (1 RCT)[7]	⨁◯◯◯ VERY LOW[g,h]	**RR 1.42** (0.71 to 2.87)	258 per 1,000	**108 more per 1,000** (75 fewer to 483 more)	
Severity of withdrawal - MNWS total assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome follow up: 12 weeks	28 (1 RCT)[8]	⨁◯◯◯ VERY LOW[i,j]	-	-	MD **0.08 higher** (1.98 lower to 2.14 higher)	
Severity of withdrawal - MNWS-Urge to smoke assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome Scale from: 0 to 4 follow up: range 7 weeks to 12 weeks	761 (2 RCTs)[1,8]	⨁⨁◯◯ LOW[k,l]	-	-	MD **0.32 lower** (0.33 lower to 0.31 lower)	

References

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l. Two studies reported this outcome (Aubin 2008 and Tsukahara 2010). Both studies were open label.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
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ADDITIONAL CONSIDERATIONS

concentration verification follow up: 6 months						
Point prevalent Tobacco abstinence during the treatment period assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 10 weeks to 12 weeks	7153 (9 RCTs)[1,10,2,3,4,6,7,9]	⊕⊕⊕⊕ HIGH[b]	**RR 1.40** (1.31 to 1.49)	254 per 1,000	**101 more per 1,000** (79 more to 124 more)
Quality of life - not reported	-	-	-	-	-
Serious adverse events follow up: range 4 weeks to 3 months	7487 (10 RCTs)[1,10,12,13,2,4,6,7,9]	⊕⊕⊕◯ MODERATE[c,d]	**RR 0.72** (0.52 to 1.00)	11 per 1,000	**3 fewer per 1,000** (5 fewer to 0 fewer)

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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, less-frequent side effects and prevention of weight gain; however, acceptability (i.e., over-the-counter) and the cost are less important compared with efficacy and safety.**(10, 19, 3, 8, 14, 9) **Efficacy is an important consideration for those who choose smoking cessation options.** Most people were willing to pay for more effective treatment.(10, 20) Compared with reduction, people prefer to quit completely.(21, 16) People also claimed they quit smoking for general health or long-term health.(22, 23, 4, 24) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Over eighty percent of users (81.2% of nicotine patch users and 89.7% of varenicline users) stated that the reason to accept the treatment was “to quit smoking or avoid relapse”.(3) “To deal with withdrawal” was chosen by 79.5% and 76.0% of the nicotine patch and varenicline respectively. “To deal with craving” is also important for 69.4% nicotine patch and 71.1% varenicline users; followed by “to deal with stress”, chosen by 34.6% nicotine patch and 22.1% varenicline users.(3) “To deal with situations or places where cannot smoke” is also important, but mostly for nicotine patch users (34.0%), compared with 31.3% varenicline users.(3, 9) **"No effects" plays an important role in stopping use.**(19, 3) Etter et al. reported that 41.6% of current nicotine patch users and 18.2% varenicline users chose “failing to stop smoking/relapse” as the reason to discontinue use; 29.2% nicotine patch users and 11.7% varenicline users chose “having craving or withdrawal” as the reason.(3)	There may be gender-specific priorities; for example, women might worry about weight gain and appearance, and this may impact on their decision. Overall health is a priority. Preference will change depending on where you’re at in your life and quit journey

	Safety is also an important consideration. (25, 26, 19, 3, 27, 9) People who chose unassisted cessation stated that their main concern was side effects.(9) If current users stop using the treatment, side effects would be the reason for 23.3% of nicotine patch users and 42.9% varenicline users.(3) Specifically for nicotine replacement therapy, people interviewed stated their concern over dependence on nicotine replacement therapy.(3, 5) Cost is important,(7, 8) but less important compared with side effects.(9) In a willingness to pay study, it was estimated that people were willing to pay $538 for a quit.(10) **In general, respondents are more willing to use nicotine replacement therapy than to use varenicline.**(11, 6, 12, 7, 3, 13, 14, 15, 16, 17) Most users (81.2% nicotine patch and 88.7% varenicline users) would recommend their treatment to a friend, and would consider using it again (66.7% nicotine patch and 73.0% varenicline users).(3) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) compared with light smokers (16.0%). But still, nicotine patch is the most preferred option (25.2% for moderate to heavy smokers and 29.2% for light smokers).(15) Most people who failed to quit would like to quit again, and they would prefer combination treatment.(12, 18) **Variability exists for the preference.**(6, 28, 14, 20). Included studies reported that several factors that may influence people's willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, being employed, having children, and higher education level may increase the willingness to use pharmacotherapy. (6, 14) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (such as childbirth), concerns about others' health, concerns about smoking on their image and appearance.(4) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles (the currently available options are not effective or safe as users expected). The willingness to pay for the medications is lower than the market price. (6)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake of varenicline is lower as compared to nicotine patch.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline, and 25% the nicotine patch. Other nicotine replacement therapy had a lower prescription rate: 16% for nicotine gum, 9% for nicotine lozenge, 5% for nicotine inhaler, and 3% for nicotine spray.(29) Muilenburg et al. reported similar results: nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the most frequently implemented treatment was nicotine patch, which was used with an average of 2.10 adolescents. Varenicline was used with an average of 0.22 adolescents.(30) Though nicotine patch is in general acceptable,(31) primary care physicians were less confident to prescribe nicotine replacement therapy in pregnancy and uncertain about the safety of nicotine replacement therapy for smokers in pregnancy.(32)	Past evidence including black box warning, favored "probably no" however with the emergence of recent data (EAGLES trial) the trend with stakeholders is leaning towards "probably yes". When the black box was lifted in Sept 2017 the trend headed towards "probably yes". There is inductive evidence that this intervention is acceptable.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. Compared with the nicotine patch, varenicline is the less available option.** Availability of varenicline could be a barrier. Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested that all programs offered nicotine replacement therapy, with patches or gum as the primary options. But fewer programs provided varenicline.(33) In addition, pregnant smokers supported nicotine replacement therapy being offered of pregnant smokers.(34) According to Muilenburg et al., nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, nicotine patch was available for 25 of 63 (39.68%) counsellors. Only 10.17% of the counsellors had varenicline. (30) Cost, especially greater out-of-pocket payment for varenicline was associated with suboptimal adherence to varenicline and less refilling.(35) May et al. conducted semi-structured interviews with healthcare professionals and concluded that financial implications, lack of knowledge and safety issues were barriers for hospital-based nicotine replacement therapy as a secondary prevention strategy in the acute cardiac setting.(36) Patient willingness may be a barrier too. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and smoking cessation program in hospital, a still very high proportion (30.3%) of patients hospitalized for COPD exacerbation were unwilling to quit smoking following the evidence-based recommendation.(37) **However, quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(38)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **recommends** offering varenicline over NRT patch **(strong recommendation based on moderate certainty in the evidence about effects).**
Remarks: To promote adherence to pharmacologic therapy, providers should be prepared to counsel patients about the relative safety and efficacy of varenicline treatment compared to nicotine patches.

Justification

The panel concluded that 1) varenicline is superior in achieving continuous long-term abstinence when compared to nicotine patch and 2) varenicline is associated with fewer AE than the nicotine patch. On balance, the panel concluded that the clinical superiority of varenicline outweighs its higher price. While there was unanimity about the preferred intervention, two panelists (HJF, PF) departed from panel consensus and advocated that the recommendation be conditional rather than strong, arguing that some patients may prefer to initiate treatment with nicotine patch due to concerns of out of pocket costs, over-the-counter availability, and perceptions of non-severe adverse effects, and that escalation of therapy can be considered on follow-up if the nicotine patch is not effective as initial pharmacotherapy.

Subgroup considerations

None

Implementation considerations

Although Varenicline is probably appropriate for the majority of patients, some patients may choose nicotine patch. A shared decision-making approach involving a discussion with the patient about the potential benefits, harms, and cost of the alternatives may be a way for implementing this recommendation into practice.
Policymakers need to support the use of varenicline as a first-line pharmacotherapeutic choice, without nicotine failure prerequisite.

Monitoring and evaluation

None

Research priorities

Clinical trials to assess the long-term efficacy and relapse prevention capabilities of both the intervention and comparator were limited. Future research should consider measuring QOL outcomes given the paucity of evidence on this outcome. More research is needed to evaluate effective strategies for using varenicline in relapse prevention and management. Behavioral and social science investment in strategies for improving uptake of varenicline is warranted. An assessment of the potentially negative consequences of over-the-counter availability of pharmacotherapy would also be useful in directing future policy.

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PICO 2: In tobacco-dependent adults, should treatment be started with varenicline or bupropion?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Bupropion	Relative (95% CI)	Absolute (95% CI)		
7-Day Point Prevalence Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
4 [1,2,3,4]	randomised trials	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 per 1,000 (from 49 more to 108 more)	⨁⨁⨁⨁ 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 [1,2,3,4,5]	randomised trials	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 per 1,000 (from 115 more to 187 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Quality of life-self-control (follow up: 12 months; assessed with: Smoking cessation quality of life; higher score indicates better outcome)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Bupropion	Relative (95% CI)	Absolute (95% CI)		
2 [2,3,6]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	448	398	-	effect size 0.17 higher	⨁⨁◯◯ LOW	CRITICAL
Quality of life-health transition (follow up: 12 months; assessed with: Smoking cessation quality of life; lower score indicates better outcome)												
2 [2,3,6]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	451	401	-	effect size 0.18 lower	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow up: range 7 weeks to 3 months)												
7 [1,2,3,4,5,7,8]	randomised trials	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 per 1,000 (from 8 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Tobacco use relapse measured at the end of follow up - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	
Other substance abuse - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	
Withdrawal symptom-Urge to smoke (follow up: 12 weeks; assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome; Scale from: 0 to 4)												
3 [2,3,7]	randomised trials	not serious	not serious	not serious	serious [d]	none	798	772	-	MD 0.3 lower (0.43 lower to 0.17 lower) [e]	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal symptom-QSU-brief total Craving Score (follow up: 12 weeks; assessed with: The Brief Questionnaire of Smoking Urges (QSU-brief); lower score indicates better outcome)												
3 [2,3,7]	randomised trials	not serious	not serious	not serious	serious [d]	none	797	772	-	MD 0.23 lower (0.37 lower to 0.09 lower) [e]	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Hays 2012 was a reanalysis of two trials with identical study design: Jorenby 2006 and Gonzales 2006. The comparison of quality of life was subjected to high risk of bias because a large and unequal proportion of participants did not provide data on quality of life. Thus the comparison was unbalanced.
b. The effect size is considered small in general (about 0.2; in general, effect size of 0.5 will be considered as medium effect).
c. The confidence interval includes 1, ranges from 0.57 to 1.16. This indicates that varenicline could largely decrease the risk of serious adverse events, if the lower limit of the confidence interval represents the true effect; or increase the risk of serious adverse events, if the upper limit is true. However, the sample size is large, and we are confident that the risk of serious adverse events is low.
d. We have no estimate of clinical minimal important difference. However, considering the lower or the upper limits of the confidence interval, the benefit of varenicline may or may not be considered as a large effect.

e. The estimate is based on one single study, Gonzales 2006. Two other studies, Jorenby 2006 and Nides 2006 also reported the outcome, suggesting a similar trend on benefit on this outcome. But we are unable to pool due to inconsistent and incomplete data reporting.

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Evidence to Decision

QUESTION

Should Varenicline vs. Bupropion be used for Tobacco-dependent adults?	
POPULATION:	Tobacco-dependent adults
INTERVENTION:	Varenicline
COMPARISON:	Bupropion
MAIN OUTCOMES:	7-Day Point Prevalence Tobacco abstinence at 6 months; 7-Day point prevalence Tobacco abstinence during treatment period; Quality of life-self-control; Quality of life-health transition ; Serious adverse events; Tobacco use relapse measured at the end of follow up; Other substance abuse; Withdrawal symptom-Urge to smoke; Withdrawal symptom-QSU-brief total Craving Score;
SETTING:	Outpatient
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and disease in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking. (1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ● Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bupropion	Risk difference with varenicline
7-Day Point Prevalence Tobacco abstinence at 6 months assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 6 months	5626 (4 RCTs)[1,2,3,4]	⨁⨁⨁⨁ HIGH	**RR 1.30** (1.19 to 1.42)	256 per 1,000	**77 more per 1,000** (49 more to 108 more)
7-Day point prevalence Tobacco abstinence during treatment period assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 8	5655 (5 RCTs)[1,2,3,4,5]	⨁⨁⨁⨁ HIGH	**RR 1.41** (1.32 to 1.52)	359 per 1,000	**147 more per 1,000** (115 more to 187 more)

ADDITIONAL CONSIDERATIONS

	weeks to 12 weeks					
	Quality of life-self-control assessed with: Smoking cessation quality of life; higher score indicates better outcome follow up: 12 months	846 (2 RCTs)[2,3,6]	⨁⨁◯◯ LOW[a,b]	-	-	effect size **0.17 higher**
	Quality of life-health transition assessed with: Smoking cessation quality of life; lower score indicates better outcome follow up: 12 months	852 (2 RCTs)[2,3,6]	⨁⨁◯◯ LOW[a,b]	-	-	effect size **0.18 lower**

	Serious adverse events follow up: range 7 weeks to 3 months	5892 (7 RCTs)[1,2,3,4,5,7,8]	⨁⨁⨁◯ MODERATE[c]	**RR 0.81** (0.57 to 1.16)	18 per 1,000	**3 fewer per 1,000** (8 fewer to 3 more)	
	Tobacco use relapse measured at the end of follow up - not measured	-	-	-	-	-	
	Other substance abuse - not measured	-	-	-	-	-	
	Withdrawal symptom-Urge to smoke assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome Scale from: 0 to 4 follow up: 12 weeks	1570 (3 RCTs)[2,3,7]	⨁⨁⨁◯ MODERATE[d]	-[e]		MD **0.3 lower** (0.43 lower to 0.17 lower)[e]	
	Withdrawal symptom-QSU-brief total Craving Score assessed with: The	1569 (3 RCTs)[2,3,7]	⨁⨁⨁◯ MODERATE[d]	-[e]		MD **0.23 lower** (0.37 lower to 0.09 lower)[e]	

Brief Questionnaire of Smoking Urges (QSU-brief); lower score indicates better outcome follow up: 12 weeks						

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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bupropion	Risk difference with varenicline
7-Day Point Prevalence Tobacco abstinence at 6 months assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 6 months	5626 (4 RCTs)[1,2,3,4]	⨁⨁⨁⨁ HIGH	**RR 1.30** (1.19 to 1.42)	256 per 1,000	**77 more per 1,000** (49 more to 108 more)
7-Day point prevalence Tobacco abstinence during treatment period assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 8 weeks to 12 weeks	5655 (5 RCTs)[1,2,3,4,5]	⨁⨁⨁⨁ HIGH	**RR 1.41** (1.32 to 1.52)	359 per 1,000	**147 more per 1,000** (115 more to 187 more)

ADDITIONAL CONSIDERATIONS

Quality of life-self-control assessed with: Smoking cessation quality of life; higher score indicates better outcome follow up: 12 months	846 (2 RCTs)[2,3,6]	⨁⨁◯◯ LOW[a,b]	-	-	effect size **0.17 higher**	
Quality of life-health transition assessed with: Smoking cessation quality of life; lower score indicates better outcome follow up: 12 months	852 (2 RCTs)[2,3,6]	⨁⨁◯◯ LOW[a,b]	-	-	effect size **0.18 lower**	
Serious adverse events follow up: range 7 weeks to 3 months	5892 (7 RCTs)[1,2,3,4,5,7,8]	⨁⨁⨁◯ MODERATE[c]	**RR 0.81** (0.57 to 1.16)	18 per 1,000	**3 fewer per 1,000** (8 fewer to 3 more)	
Tobacco use relapse measured at the end of follow up - not measured	-	-	-	-	-	

Other substance abuse - not measured	-	-	-	-	-
Withdrawal symptom-Urge to smoke assessed with: Minnesota Nicotine Withdrawal Scale (MNWS); lower score indicates better outcome Scale from: 0 to 4 follow up: 12 weeks	1570 (3 RCTs)[2,3,7]	⨁⨁⨁◯ MODERATE[d]	-[e]		MD **0.3 lower** (0.43 lower to 0.17 lower)[e]
Withdrawal symptom-QSU-brief total Craving Score assessed with: The Brief Questionnaire of Smoking Urges (QSU-brief); lower score indicates better outcome follow up: 12 weeks	1569 (3 RCTs)[2,3,7]	⨁⨁⨁◯ MODERATE[d]	-[e]		MD **0.23 lower** (0.37 lower to 0.09 lower)[e]

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	quality of life was subjected to high risk of bias because a large and unequal proportion of participants did not provide data on quality of life. Thus the comparison was unbalanced. b. The effect size is considered small in general (about 0.2; in general, effect size of 0.5 will be considered as medium effect). c. The confidence interval includes 1, ranges from 0.57 to 1.16. This indicates that varenicline could largely decrease the risk of serious adverse events, if the lower limit of the confidence interval represents the true effect; or increase the risk of serious adverse events, if the upper limit is true. However, the sample size is large, and we are confident that the risk of serious adverse events is low. d. We have no estimate of clinical minimal important difference. However, considering the lower or the upper limits of the confidence interval, the benefit of varenicline may or may not be considered as a large effect. e. The estimate is based on one single study, Gonzales 2006. Two other studies, Jorenby 2006 and Nides 2006 also reported the outcome, suggesting a similar trend on benefit on this outcome. But we are unable to pool due to inconsistent and incomplete data reporting.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, less-frequent side effects and prevention of weight gain; however, accessibility (i.e., over-the-counter) and the cost are less important.**(7, 18, 3, 5, 12, 6) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for more effective treatment.(7, 17) Compared with reduction, people prefer to quit completely.(19, 14) People also claimed they quit smoking for general health or long-term health.(20, 21, 22, 23) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Over eighty percent users (89.7% of varenicline users and 80.6% of bupropion users) stated that the reason to accept the treatment was "to quit smoking or avoid relapse".(3) "To deal with withdrawal" was chosen by 76.0% and 61.2% of the varenicline and bupropion users. "To deal with craving" is also important for 71.1% varenicline and 55.2% bupropion users; followed by "to deal with stress", chosen by 22.1% varenicline and 29.8% bupropion users.(3) "To deal with situations or places where cannot smoke" is also important, 31.3% varenicline users and 23.3% bupropion users chose this.(3) **"No effects" plays an important role in stopping use.**(18, 3) Etter et al. reported that 18.2% varenicline users and 25.6% bupropion users chose "failing to stop smoking/relapse" as the reason to discontinue use; 11.7% varenicline users and 25.6% bupropion chose "having craving or withdrawal" as the reason.(3) Safety is also an important consideration.(24, 25, 18, 3, 26) People who chose unassisted cessation stated that their main concern was side effects.(6) While if current users stop using the treatment, side effects would be the reason for 42.9% varenicline users and 23.1% bupropion users.(3) Cost is important,(4, 5) but less important compared with side effects.(6) In a willingness to pay study, it was estimated that people were willing to pay $538 for a quit.(7) **In general, respondents are willing to use pharmacotherapy.**(8, 9, 10, 4, 3, 11, 12, 13, 14, 15) Most users (76.1% bupropion and 88.7% varenicline users) would recommend their treatment to a friend, and would consider using it again (62.6% bupropion and 73.0% varenicline users).(3) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) compared with light smokers (16.0%). A similar preference was reported for bupropion (9.9% for moderate to heavy smokers versus 7.5% for light smokers).(13) **Variability exists for the preference.**(9, 16, 12, 17) Included studies reported that several factors that may influence people's willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, being employed, having children, and higher education level may increase the willingness to use pharmacotherapy.(9, 12) Reid et al. reported that females were more likely to be	

	motivated to quit by experiencing a life change (such as childbirth), concerns about others' health, concerns about smoking on their image and appearance.(22) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles (the currently available options are not effective or safe as users expected). The willingness to pay for the medications is lower than the market price.(9)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake is low for varenicline and bupropion.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline and 11% prescribed bupropion.(27) Muilenburg et al. reported that compared with the nicotine patch, the most available option, bupropion and varenicline was less implemented. In this cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the nicotine patch was used with an average of 2.10 adolescents. While bupropion and varenicline were used with an average of 0.48 and 0.22 adolescents, respectively.(28)	The panel made important observations related to varenicline access. A qualitative interview study of the Veterans Health Administration (VHA) substance abuse program staff reported that all programs offered nicotine replacement therapy (NRT), some provided bupropion, but few provided varenicline. This pattern is unlikely to be unique to the VHA; payer costs appear to form barriers to availability, despite favorable cost-effectiveness

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. Varenicline is less available compared with bupropion.** Availability of varenicline could be a barrier to implementation. Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested that all programs offered nicotine replacement therapy, with patches or gum as the primary options. Most programs provided bupropion, but fewer programs provided varenicline.(29) In addition, pregnant smokers supported nicotine replacement therapy being offered to pregnant smokers.(30) According to Muilenburg et al., nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, nicotine patch was available for 25 of 63 (39.68%) counsellors. Only 10.17% of the counsellors had varenicline.(28) Cost, especially greater out-of-pocket payment for varenicline was associated with suboptimal adherence to varenicline and less refilling.(31) Patient willingness could be a barrier. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and smoking cessation program in hospital, a still very high proportion (30.3%) of patients hospitalized for COPD exacerbation were unwilling to quit smoking following the evidence-based recommendation.(32) **However, quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(33)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **recommends** offering varenicline over bupropion **(strong recommendation based on moderate certainty in the evidence about effects).**
Remarks: Caution is needed for pregnant women since currently there is no evidence on this population.

Justification

The panel concluded that 1) varenicline showed significant benefit in achieving abstinence compared to bupropion and 2) varenicline treatment resulted in similar risk of AE as bupropion. As a result, the panel recommended varenicline rather than bupropion for the treatment of tobacco dependence. The panel chose to make a strong recommendation based on high certainty in the estimates of benefit and moderate certainty in the estimates of AE.

Subgroup considerations

None

Implementation considerations

Policymakers need to support the use of varenicline as a first-line pharmacotherapeutic option, without bupropion failure prerequisite.

Monitoring and evaluation

None

Research priorities

Future trials are necessary to evaluate the relative clinical effect of varenicline and bupropion in uniquely at-risk populations, such as pregnant women, adolescents, and patients with a history of treatment unresponsiveness. The relative cost-effectiveness of these agents should be further evaluated in the contexts of both relapse prevention and re-treatment following relapse.

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PICO 3: In tobacco-dependent adults, should treatment be started with the optimal controller medication plus nicotine replacement therapy or the best controller alone?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline plus Nicotine Replacement Therapy	Varenicline	Relative (95% CI)	Absolute (95% CI)		
7-Day point abstinence 6 month or longer (follow up: mean 6 months; assessed with: self report, confirmed with exhaled carbon monoxide)												
2 [1,2]	randomised trials	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 per 1,000 (from 21 more to 211 more)	⨁⨁⨁⨁ HIGH	CRITICAL
7-Day point prevalent abstinence during treatment (assessed with: self report, confirmed with exhaled carbon monoxide)												
2 [1,2]	randomised trials	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 per 1,000 (from 40 more to 196 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse event (follow up: mean 6 months; assessed with: as reported)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [a]	none	4/444 (0.9%)	1.4%	RR 1.06 (0.27 to 4.05)	1 more per 1,000 (from 10 fewer to 42 more)	⨁⨁◯◯ LOW	CRITICAL
Relapse - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Other substance use - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Withdrawal - Composite symptoms rating (follow up: mean 4 weeks; assessed with: Mood and Physical Symptoms Scale; Lower change score indicates better outcome; Scale from: 2 to 12)												
1 [3]	randomised trials	serious [b]	not serious	not serious	very serious [c,d]	none	35	34	-	MD 0.04 lower	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal - craving (follow up: mean 4 weeks; assessed with: Wisconsin Withdrawal Symptom Scale; Lower score indicates better outcome; Scale from: 0 to 4)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline plus Nicotine Replacement Therapy	Varenicline	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	serious [e]	not serious	not serious	serious [c,f]	none	110	87	-	MD 0.1 **higher** (0.19 lower to 0.39 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The estimate was based on a very small number of events.
b. In Hajek 2013, a large proportion of participants did not provide information. At week 4, 35 in the combination group and 35 in the varenicline monotherapy group reported the withdrawal symptoms.
c. Though we do not have the minimum important clinical difference, the difference between groups is unlikely to be clinical significant.
d. The measurement of this continuous outcome is based on a very small sample size.
e. In Koegelenberg 2014, only those who abstained from smoking during the preceding 7 days were compared, and this was not a balanced between group comparison.
f. The 95% confidence interval included 0.

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1. Ramon, , M., J., Morchon, , S., , Baena, , A., , al, et. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. NLM.
2. Koegelenberg, , N., C.,F., Noor, , F., , Bateman, , D., E., al, et. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: A randomized clinical trial.
3. Hajek, , P., , Smith, , M., K., Dhanji, , R., A., al, et. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. NLM.

Evidence to Decision

QUESTION

Should Varenicline plus Nicotine Replacement Therapy vs. Varenicline be used for tobacco-dependent adults?	
POPULATION:	tobacco-dependent adults
INTERVENTION:	Varenicline plus Nicotine Replacement Therapy
COMPARISON:	Varenicline
MAIN OUTCOMES:	7-Day point abstinence 6 month or longer; 7-Day point prevalent abstinence during treatment; Quality of life; Serious adverse event; Relapse; Other substance use; Withdrawal - Composite symptoms rating; Withdrawal - craving;
SETTING:	outpatients
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and disease in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking.(1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with varenicline	Risk difference with varenicline plus nicotine replacement therapy
7-Day point abstinence 6 month or longer assessed with: self report, confirmed with exhaled carbon monoxide follow up: mean 6 months	776 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH	**RR 1.36** (1.07 to 1.72)	293 per 1,000	**105 more per 1,000** (21 more to 211 more)
7-Day point prevalent abstinence during treatment assessed with: self report, confirmed with	776 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH	**RR 1.31** (1.11 to 1.54)	362 per 1,000	**112 more per 1,000** (40 more to 196 more)

exhaled carbon monoxide						
Quality of life - not measured	-	-	-	-	-	
Serious adverse event assessed with: as reported follow up: mean 6 months	893 (3 RCTs)[1,2,3]	⨁⨁◯◯ LOW[a]	**RR 1.06** (0.27 to 4.05)	14 per 1,000	**1 more per 1,000** (10 fewer to 42 more)	
Relapse - not measured	-	-	-	-	-	
Other substance use - not measured	-	-	-	-	-	
Withdrawal - Composite symptoms rating assessed with: Mood and Physical Symptoms Scale; Lower change score indicates better	69 (1 RCT)[3]	⨁◯◯◯ VERY LOW[b,c,d]	-	-	MD **0.04 lower**	

outcome Scale from: 2 to 12 follow up: mean 4 weeks						
Withdrawal - craving assessed with: Wisconsin Withdrawal Symptom Scale; Lower score indicates better outcome Scale from: 0 to 4 follow up: mean 4 weeks	197 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	-	MD **0.1 higher** (0.19 lower to 0.39 higher)	

References

1. Ramon, , M., J., Morchon, , S., , Baena, , A., , al, et. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. NLM.
2. Koegelenberg, , N., C.,F., Noor, , F., , Bateman, , D., E., al, et. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: A randomized clinical trial.
3. Hajek, , P., , Smith, , M., K., Dhanji, , R., A., al, et. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. NLM.

Explanations

a. The estimate was based on a very small number of events.
b. In Hajek 2013, a large proportion of participants did not provide information. At week 4, 35 in the combination

group and 35 in the varenicline monotherapy group reported the withdrawal symptoms.

c. Though we do not have the minimum important clinical difference, the difference between groups is unlikely to be clinical significant.

d. The measurement of this continuous outcome is based on a very small sample size.

e. In Koegelenberg 2014, only those who abstained from smoking during the preceding 7 days were compared, and this was not a balanced between group comparison.

f. The 95% confidence interval included 0.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with varenicline	Risk difference with varenicline plus nicotine replacement therapy
7-Day point abstinence 6 month or longer assessed with: self report, confirmed with exhaled carbon monoxide	776 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH	**RR 1.36** (1.07 to 1.72)	293 per 1,000	**105 more per 1,000** (21 more to 211 more)

	follow up: mean 6 months					
	7-Day point prevalent abstinence during treatment assessed with: self report, confirmed with exhaled carbon monoxide	776 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH	**RR 1.31** (1.11 to 1.54)	362 per 1,000	**112 more per 1,000** (40 more to 196 more)
	Quality of life - not measured	-	-	-	-	-
	Serious adverse event assessed with: as reported follow up: mean 6 months	893 (3 RCTs)[1,2,3]	⨁⨁◯◯ LOW[a]	**RR 1.06** (0.27 to 4.05)	14 per 1,000	**1 more per 1,000** (10 fewer to 42 more)
	Relapse - not measured	-	-	-	-	-
	Other substance use - not measured	-	-	-	-	-

	Withdrawal - Composite symptoms rating assessed with: Mood and Physical Symptoms Scale; Lower change score indicates better outcome Scale from: 2 to 12 follow up: mean 4 weeks	69 (1 RCT)[3]	⨁◯◯◯ VERY LOW[b,c,d]	-	-	MD **0.04 lower**
	Withdrawal - craving assessed with: Wisconsin Withdrawal Symptom Scale; Lower score indicates better outcome Scale from: 0 to 4 follow up: mean 4 weeks	197 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	-	MD **0.1 higher** (0.19 lower to 0.39 higher)

References

	1. Ramon, , M., J., Morchon, , S., , Baena, , A., , al, et. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. NLM. 2. Koegelenberg, , N., C.,F., Noor, , F., , Bateman, , D., E., al, et. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: A randomized clinical trial. 3. Hajek, , P., , Smith, , M., K., Dhanji, , R., A., al, et. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. NLM. Explanations a. The estimate was based on a very small number of events. b. In Hajek 2013, a large proportion of participants did not provide information. At week 4, 35 in the combination group and 35 in the varenicline monotherapy group reported the withdrawal symptoms. c. Though we do not have the minimum important clinical difference, the difference between groups is unlikely to be clinical significant. d. The measurement of this continuous outcome is based on a very small sample size. e. In Koegelenberg 2014, only those who abstained from smoking during the preceding 7 days were compared, and this was not a balanced between group comparison. f. The 95% confidence interval included 0.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, less-frequent side effects and prevention of weight gain; however, accessibility (i.e., over-the-counter) and the cost are less important.**(10, 19, 3, 8, 14, 9) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for more effective treatment.(10, 20) Compared with reduction, people prefer to quit completely.(21, 16) People also claimed they quit smoking for general health or long-term health.(22, 23, 4, 24) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Over eighty percent users (81.2% of nicotine patch users and 89.7% of varenicline users) stated that the reason to accept the treatment was “to quit smoking or avoid relapse”.(3) “To deal with withdrawal” was chosen by 79.5% and 76.0% of the nicotine patch and varenicline users. “To deal with craving” is also important for 69.4% nicotine patch and 71.1% varenicline users; followed by “to deal with stress”, chosen by 34.6% nicotine patch and 22.1% varenicline users.(3) “To deal with situations or places where cannot smoke” is also important, but mostly for nicotine patch users (34.0%),compared with 31.3% varenicline users.(3, 9) **"No effects" plays an important role in stopping use.**(19, 3) Etter et al. reported that 41.6% of current nicotine patch users and 18.2% varenicline users chose “failing to stop smoking/relapse” as the reason to discontinue treatment; 29.2% nicotine patch users and 11.7% varenicline users chose “having craving or withdrawal” as the reason.(3)	Most people who quit like to try combination therapy after trying single interventions.

	Safety is also an important consideration.(25, 26, 19, 3, 27) People who chose unassisted cessation stated that their main concern was side effects.(9) While if current users stop using the treatment, side effects would be the reason for 23.3% of nicotine patch users and 42.9% varenicline users.(3) Specifically for nicotine replacement therapy, people interviewed stated their concern over dependence on nicotine replacement therapy.(3, 5) Cost is important,(7, 8) but less important compared with side effects.(9) In a willingness to pay study, it was estimated that people were willing to pay $538 for a quit.(10) **In general, respondents are willing to use pharmacotherapy.**(11, 6, 12, 7, 3, 13, 14, 15, 16, 17) Most users (81.2% nicotine patch and 88.7% varenicline users) would recommend their treatment to a friend, and would consider using it again (66.7% nicotine patch and 73.0% varenicline users).(3) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) compared with light smokers (16.0%).(15) **Most people who failed to quit would like to quit again, and they would prefer combination treatment.**(12, 18) **Variability exists for the preference.**(6, 28, 14, 20) Included studies reported that several factors that may influence people's willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, being employed, having children, and higher education level may increase the willingness to use pharmacotherapy.(6, 14) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (such as childbirth), concerns about others' health, concerns about smoking on their image and appearance.(4) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles (the currently available options are not effective or safe as users expected). The willingness to pay for the medications is lower than the market price.(6)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considered the mall number of studies and low certainty of evidence.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**There are no studies on the uptake of the combination of nicotine replacement therapy and varenicline. However, the uptake of varenicline is lower as compared to nicotine patch.** Rothrauff et al. conducted a study with counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results suggested that 16% of programs prescribed varenicline, and 25% the nicotine patch. Other nicotine replacement therapy had a lower prescription rate: 16% for nicotine gum, 9% for nicotine lozenge, 5% for nicotine inhaler, and 3% for nicotine spray.(29) Muilenburg 2015 reported similar results: nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the most frequently implemented treatment was nicotine patch, which was used with an average of 2.10 adolescents. Varenicline was used with an average of 0.22 adolescents. (30) Though nicotine patch is in general acceptable,(31) primary care physicians were less confident to prescribe nicotine replacement therapy in pregnancy and uncertain about the safety of nicotine replacement therapy for smokers in pregnancy.(32)	Smokers who were unsuccessful at quitting using first line therapy find receiving combination therapy acceptable. Highly dependent patients might find combination therapy more acceptable. In general, two medications may be less acceptable for patients with concerns including nausea and burden.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. Nicotine replacement therapy is the most available option for smoking cessation. The availability of Varenicline is limited.** Gifford et al. reported an interview on staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested all programs offered nicotine replacement therapy, with patches or gum as the primary options. But fewer programs provided varenicline.(33) According to Muilenburg et al., nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, nicotine patch was available for 25 of 63 (39.68%) counsellors. Only 10.17% of the counsellors had varenicline. (30) Cost, especially greater out-of-pocket payment for varenicline was associated with suboptimal adherence to varenicline and less refilling.(34) May et al. conducted semi-structured interviews with healthcare professionals and concluded that financial implications, lack of knowledge and safety issues were barriers for hospital-based nicotine replacement therapy as a secondary prevention strategy in the acute cardiac setting.(35) Patient willingness may be a barrier too. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and smoking cessation program in hospital, a still very high proportion (30.3%) of patients hospitalized for COPD exacerbation were unwilling to quit smoking following the evidence-based recommendation.(36) **However, a quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(37)	Combination of two medications might have reduced feasibility.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **suggests** offering varenicline plus nicotine replacement therapy patch over using varenicline alone **(conditional recommendation based on low certainty in the evidence about effects).**

Remarks:

Original question is that should Varenicline plus a reliever or varenicline alone be used in patients who are initiating treatment. We did not find any direct evidence on the original research question but found existing evidence on varenicline and nicotine patch combination. The panel therefore decided to make an alternative recommendation on varenicline and nicotine patch combination versus Varenicline alone. Given the differences in pharmacokinetics between nicotine patch and other delivery forms, the panel did not feel that a conclusion regarding the effectiveness of other forms of nicotine replacement could be made at this time.

Justification

The panel concluded 1) varenicline plus nicotine patch showed benefit compared to varenicline alone in smoking abstinence and 2) combination therapy had similar risk of adverse events as varenicline alone. As a result, the panel recommended varenicline plus nicotine patch rather than varenicline alone for treatment of tobacco dependence. The panel chose to make a conditional recommendation because the low certainty in estimated adverse events limited confidence in the overall certainty of the evidence.

Subgroup considerations

None

Implementation considerations

While combination therapy was considered feasible to implement, the panel remained concerned that prescriber and/or payer reluctance might affect feasibility. Initiating two medications may complicate instructions, affect adherence, or limit patient agreement with the recommendation. While the panel considered both interventions to be acceptable to stakeholders, combination therapy might be most acceptable if introduced sequentially, particularly if the patient experienced monotherapy or significant withdrawal symptoms in the past.
Although nicotine patch and varenicline combination is probably appropriate for the majority of patients, for mild smokers, it might not be feasible. A shared decision-making approach involving a discussion with the patient about the potential benefits, harms and cost, severity, and coverage perspective of the alternatives may be a way for implementing this recommendation into practice.

Monitoring and evaluation

None

Research priorities

Randomized clinical trials are needed on the effects of varenicline plus any type of reliever, in particular on the outcomes including serious adverse events, adverse events, relapse outcomes after stopping the treatment.
Cost-effectiveness studies are also needed on this question.

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PICO 4: In tobacco-dependent adults, should treatment be started with the optimal controller medication or an electronic cigarette?

Evidence Profile (for direct comparison evidence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Electronic cigarette	Relative (95% CI)	Absolute (95% CI)		
Point prevalent abstinence 6 month or longer (follow up: mean 24 weeks)												
1 [1]	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	13/27 (48.1%)	32.5%	RR 1.44 (0.75 to 2.80)	143 more per 1,000 (from 81 fewer to 585 more)	⨁◯◯◯ VERY LOW	CRITICAL
Continuous abstinence 6 month or longer (follow up: mean 1 years; assessed with: persistent abstinence from all tobacco)												
1 [2]	observational studies	serious [d,e]	not serious	not serious	serious [f,g]	none	156	200	-	MD 0.046 higher (0.018 lower to 0.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Point abstinence during treatment - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse event (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [h]	none	0/27 (0.0%)	0.0%	not estimable [h]	-	⨁◯◯◯ VERY LOW	CRITICAL
Relapse (follow up: 1 years; assessed with: Relapser with Cigarettes only, cigarettes + electronic nicotine delivery systems, or cigarettes + other)												
1 [2]	observational studies	serious [d]	not serious	not serious	serious [g]	none	156	200	-	MD 0.065 higher	⨁◯◯◯ VERY LOW	IMPORTANT
Other substance use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Withdrawal - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The full methodological details of this study are not available. We were uncertain of the risk of bias. Furthermore, the numbers of abstinence were not reported. We estimated the numbers based on the sample size, 1:1 randomization, and proportion of abstinence. We could not reproduce the proportion of abstinence reported (48.1% of varenicline versus 33.3% of e-cigarette users in our estimation, compared with 47.3% of varenicline versus 32.5% of e-cigarette users reported in the conference abstract).
b. This study was on the smokers with a history of acute coronary syndrome, rather than adult smokers in general.
c. The sample size of this study was 54 in total. The total number of events (abstinence) was less than 30.
d. This study used two waves of survey; the researchers compared the tobacco use status at Wave 1 and Wave 2, and had no control over the use of cessation aid. The adherence to the cessation aid at Wave 1 was unclear.
e. The abstinence outcome was a self reported outcome, and was not confirmed with objective measurement.
f. The confidence interval includes 0, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of varenicline compared with e-cigarette will be different.
g. Small sample size (n < 400).
h. Zero events.

References

1. Ioakeimidis, N., Vlachopoulos, C., Georgakopoulos, C., Abdelrasoul, M., Skliros, N., Katsi, V., Vaina, S., Tousoulis, D.. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. European heart journal; 2018.
2. Benmarhnia, Tarik, Pierce, John P., Leas, Eric, White, Martha M., Strong, David R., Noble, Madison L., Trinidad, Dennis R.. Can E-Cigarettes and Pharmaceutical Aids Increase Smoking Cessation and Reduce Cigarette Consumption? Findings From a Nationally Representative Cohort of American Smokers. American Journal of Epidemiology; 2018.

Evidence to Decision

QUESTION

Should Varenicline vs. Electronic cigarette be used for Tobacco-dependent adult - Indirect?	
POPULATION:	Tobacco-dependent adult - Indirect
INTERVENTION:	Varenicline
COMPARISON:	Electronic cigarette
MAIN OUTCOMES:	Point abstinence 6 month or longer (indirect comparison results); Point abstinence during treatment (indirect comparison results); Quality of life; Serious adverse event (indirect comparison results); Other substance use; Withdrawal ; Relapse;
SETTING:	Outpatient (NMA)
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and diseases in the United States and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking.(1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Electronic cigarette	Risk difference with Varenicline
Point prevalent abstinence 6 month or longer follow up: mean 24 weeks	54 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	**RR 1.44** (0.75 to 2.80)	325 per 1,000	**143 more per 1,000** (81 fewer to 585 more)
Continuous abstinence 6 month or longer assessed with: persistent abstinence from all tobacco follow up: mean 1 years	356 (1 observational study)[2]	⨁◯◯◯ VERY LOW[d,e,f,g]	-	-	MD **0.046 higher** (0.018 lower to 0.11 higher)
Point abstinence during treatment - not measured	-	-	-	-	-
Quality of life - not reported	-	-	-	-	-
Serious adverse event follow up: 24 weeks	54 (1 RCT)	⨁◯◯◯ VERY LOW[a,b,h]	not estimable[h]	-	-

Relapse assessed with: Relapser with Cigarettes only, cigarettes + electronic nicotine delivery systems, or cigarettes + other follow up: 1 years	356 (1 observational study)[2]	⊕◯◯◯ VERY LOW[d,g]	-	-	MD **0.065 higher**
Other substance use - not reported	-	-	-	-	-
Withdrawal - not reported	-	-	-	-	-

References

1. Ioakeimidis, N., Vlachopoulos, C., Georgakopoulos, C., Abdelrasoul, M., Skliros, N., Katsi, V., Vaina, S., Tousoulis, D.. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. European heart journal; 2018.
2. Benmarhnia, Tarik, Pierce, John P., Leas, Eric, White, Martha M., Strong, David R., Noble, Madison L., Trinidad, Dennis R.. Can E-Cigarettes and Pharmaceutical Aids Increase Smoking Cessation and Reduce Cigarette Consumption? Findings From a Nationally Representative Cohort of American Smokers. American Journal of Epidemiology; 2018.

Explanations

a. The full methodological details of this study are not available. We were uncertain of the risk of bias. Furthermore, the numbers of abstinence were not reported. We estimated the numbers based on the sample size, 1:1 randomization, and proportion of abstinence. We could not reproduce the proportion of abstinence reported (48.1% of varenicline versus 33.3% of e-cigarette users in our estimation, compared with 47.3% of varenicline versus 32.5% of e-cigarette users reported in the conference abstract).
b. This study was on the smokers with a history of acute coronary syndrome, rather than adult smokers in general.
c. The sample size of this study was 54 in total. The total number of events (abstinence) was less than 30.
d. This study used two waves of survey; the researchers compared the tobacco use status at Wave 1 and Wave 2, and had no control over the use of cessation aid. The adherence to the cessation aid at Wave 1 was unclear.
e. The abstinence outcome was a self reported outcome, and was not confirmed with objective measurement.
f. The confidence interval includes 0, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of varenicline compared with e-cigarette will be different.
g. Small sample size (n < 400).
h. Zero events.

Estimates of effects, credible intervals, and certainty of the evidence for treatment of tobacco dependence

Bayesian NMA-SoF table

BENEFITS

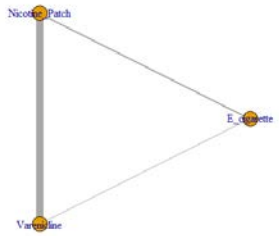
Patient or population: Adult smokers

Interventions: Varenicline, nicotine replacement therapy

Comparator (reference): e-cigarette

Outcome: 7 day point prevalent abstinence at 6 months

Setting: Outpatient



Geometry of the Network*

Total studies: 13 RCT[1,2,3,4,5,6,7,8,9,10,11,12] Total Participants: 8830	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Interpretation of Findings
		Without intervention	*With* intervention	Difference		
Varenicline (11 RCTs;[1,2,3,4,5,6,7,8,9,10] 7362 participants)	RR 0.85 (0.65 to 1.10) Network estimate	282 per 1000[1]	240 per 1000	42 fewer per 1000 (99 fewer to 28 more)	⨁◯◯◯ Very low Due to risk of bias, indirectness, and imprecision[1,2,3,]	-

NMA-SoF table definitions

* Lines represent direct comparisons

** Estimates are reported as risk ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (7) since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The indirect comparison between varenicline versus e-cigarette is estimated by the comparisons between varenicline versus nicotine patch, and nicotine replacement therapy versus e-cigarette. Two trials (Bullen 2013 and Hajek 2019) consisted of the comparison between nicotine replacement therapy versus e-cigarette. But both trials were open label studies.

[2] The estimate for the comparison between varenicline and e-cigarette was based on indirect comparison using nicotine replacement therapy as the common comparator. For the comparison between varenicline and nicotine replacement therapy, the 11 included studies used nicotine patch. While for the comparison between e-cigarette and nicotine replacement therapy, Hajek 2019 (the study with the larger sample size of the two included studies) used patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs. Because of the difference in nicotine replacement therapy, there was concern on the transitivity assumption. In our sensitivity analysis of including the conference abstract of direct comparison between varenicline and e-cigarette, the estimate of RR for point prevalent abstinence at 6 months or longer would be 0.90 (95% confidence interval: 0.71 to 1.1), and it would lead to 32 fewer abstinence per 1,000 patients (from 94 fewer to 33 more, while assuming 32.5% abstinence in the e-cigarette group). We did not consider this direct comparison in our reference case analysis, because the full methodological details of this study are not available. We were uncertain of the risk of bias. The numbers of abstinence were not reported. We estimated the numbers based on the sample size, 1:1 randomization, and proportion of abstinence. We could not reproduce the proportion of abstinence reported (48.1% of varenicline versus 33.3% of e-cigarette users in our estimation, compared with 47.3% of varenicline versus 32.5% of e-cigarette users reported in the conference abstract).

[3] The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the effect of varenicline compared with e-cigarette will be different.

BENEFITS

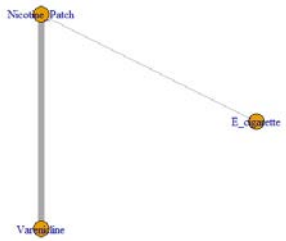
Patient or population: Adult smokers

Interventions: Varenicline, nicotine replacement therapy

Comparator (reference): e-cigarette

Outcome: 7 day point prevalent abstinence during treatment

Setting: Outpatient



Geometry of the Network*

Total studies: 10 RCT[1,3,4,5,6,7,9,10,11,12] Total Participants: 7737	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Interpretation of Findings
		Without intervention	*With* intervention	Difference		
Varenicline (9 RCTs[1,3,4,5,6,7,9,10]; 7153 participants)	RR 1.1 (0.73 to 1.6) Network estimate	215 per 1000[1]	237 per 1000	22 more per 1000 (58 fewer to 129 more)	⨁◯◯◯ Very low Due to risk of bias, indirectness, and imprecision[1,2,3]	-

NMA-SoF table definitions

* Lines represent direct comparisons

** Estimates are reported as risk ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (7) since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

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Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The indirect comparison between varenicline versus e-cigarette is estimated by the comparisons between varenicline versus nicotine patch, and nicotine replacement therapy versus e-cigarette. Two trials (Bullen 2013 and Hajek 2019) consisted of the comparison between nicotine replacement therapy versus e-cigarette. But both trials were open label studies.

[2] The estimate for the comparison between varenicline and e-cigarette was based on indirect comparison using nicotine replacement therapy as the common comparator. For the comparison between varenicline and nicotine replacement therapy, the 9 included studies used nicotine patch. While for the comparison between e-cigarette and nicotine replacement therapy, Hajek 2019 (the study with the larger sample size of the two included studies) used patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs. Because of the difference in nicotine replacement therapy, there was concern on the transitivity assumption.

[3] The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the effect of varenicline compared with e-cigarette will be different.

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15. NCT01406223.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		Thirteen panelists believe there is a moderate effect. Two panelists (MCP and HJF), believe there is a large effect.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Electronic cigarette	Risk difference with Varenicline
Point prevalent abstinence 6 month or longer follow up: mean 24 weeks	54 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	**RR 1.44** (0.75 to 2.80)	325 per 1,000	**143 more per 1,000** (81 fewer to 585 more)

Continuous abstinence 6 month or longer assessed with: persistent abstinence from all tobacco follow up: mean 1 years	356 (1 observational study)[2]	⨁◯◯◯ VERY LOW[d,e,f,g]	-	-	MD **0.046 higher** (0.018 lower to 0.11 higher)
Point abstinence during treatment - not measured	-	-	-	-	-
Quality of life - not reported	-	-	-	-	-
Serious adverse event follow up: 24 weeks	54 (1 RCT)	⨁◯◯◯ VERY LOW[a,b,h]	not estimable[h]	-	-
Relapse assessed with: Relapser with Cigarettes only, cigarettes + electronic nicotine delivery systems, or cigarettes + other follow up: 1 years	356 (1 observational study)[2]	⨁◯◯◯ VERY LOW[d,g]	-	-	MD **0.065 higher**
Other substance use - not reported	-	-	-	-	-
Withdrawal - not reported	-	-	-	-	-

References

1. Ioakeimidis, N., Vlachopoulos, C., Georgakopoulos, C., Abdelrasoul, M., Skliros, N., Katsi, V., Vaina, S., Tousoulis, D.. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. European heart journal; 2018.

2. Benmarhnia, Tarik, Pierce, John P., Leas, Eric, White, Martha M., Strong, David R., Noble, Madison L., Trinidad, Dennis R.. Can E-Cigarettes and Pharmaceutical Aids Increase Smoking Cessation and Reduce Cigarette Consumption? Findings From a Nationally Representative Cohort of American Smokers. American Journal of Epidemiology; 2018.

Explanations

a. The full methodological details of this study are not available. We were uncertain of the risk of bias. Furthermore, the numbers of abstinence were not reported. We estimated the numbers based on the sample size, 1:1 randomization, and proportion of abstinence. We could not reproduce the proportion of abstinence reported (48.1% of varenicline versus 33.3% of e-cigarette users in our estimation, compared with 47.3% of varenicline versus 32.5% of e-cigarette users reported in the conference abstract).
b. This study was on the smokers with a history of acute coronary syndrome, rather than adult smokers in general.
c. The sample size of this study was 54 in total. The total number of events (abstinence) was less than 30.
d. This study used two waves of survey; the researchers compared the tobacco use status at Wave 1 and Wave 2, and had no control over the use of cessation aid. The adherence to the cessation aid at Wave 1 was unclear.
e. The abstinence outcome was a self reported outcome, and was not confirmed with objective measurement.
f. The confidence interval includes 0, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of varenicline compared with e-cigarette will be different.
g. Small sample size (n < 400).
h. Zero events.

Estimates of effects, credible intervals, and certainty of the evidence for treatment of tobacco dependence

Bayesian NMA-SoF table

HARMS

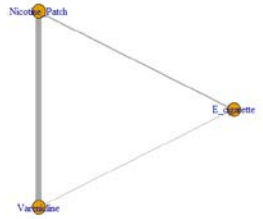
Patient or population: Adult smokers

Interventions: Varenicline, nicotine replacement therapy

Comparator (reference): e-cigarette

Outcome: serious adverse event

Setting: Outpatient



Geometry of the Network*

Total studies: 13 RCT[1,4,5,6,7,9,10,11,12,13,14,15] Total Participants: 8957	Relative effect** (95% CrI)	Anticipated absolute effect*** (95%			Certainty of the evidence	Interpretation of Findings
		Without intervention	*With* intervention	Difference		
Varenicline (10 RCTs;[1,4,5,6,7,9,10,13,14,15] 7487 participants)	RR 0.32 (0.071 to 0.82) Network estimate	77 per 1000[1]	31 per 1000	52 fewer per 1000 (72 fewer to 14 fewer)	⨁◯◯◯ Very low Due to risk of bias, indirectness, and imprecision[1,2,3]	-

NMA-SoF table definitions

* Lines represent direct comparisons

** Estimates are reported as risk ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (7) since a Bayesian analysis has been conducted.

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GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The indirect comparison between varenicline versus e-cigarette is estimated by the comparisons between varenicline versus nicotine patch, and nicotine replacement therapy versus e-cigarette. Two trials (Bullen 2013 and Hajek 2019) consisted of the comparison between nicotine replacement therapy versus e-cigarette. But both trials were open label studies.

[2] The estimate for the comparison between varenicline and e-cigarette was based on indirect comparison using nicotine replacement therapy as the common comparator. For the comparison between varenicline and nicotine replacement therapy, the 11 included studies used nicotine patch. While for the comparison between e-cigarette and nicotine replacement therapy, Hajek 2019 (the study with the larger sample size of the two included studies) used patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs. Because of the difference in nicotine replacement therapy, there was concern on the transitivity assumption. In our sensitivity analysis of including the conference abstract of direct comparison between varenicline and e-cigarette, the estimate for RR of serious adverse events would be 0.30 (95% confidence interval: 0.065 to 0.74), and it would lead to 43 fewer (from 58 fewer to 16 fewer, while assuming 6.2% serious adverse events in the e-cigarette group) serious adverse events. We did not consider this direct comparison in our reference case analysis, because the full methodological details of this study are not available. We were uncertain of the risk of bias. The numbers of abstinence were not reported. We estimated the numbers based on the sample size, 1:1 randomization, and proportion of abstinence. We could not reproduce the proportion of abstinence reported (48.1% of varenicline versus 33.3% of e-cigarette users in our estimation, compared with 47.3% of varenicline versus 32.5% of e-cigarette users reported in the conference abstract).

[3] Small number of events.

UNDESIRABLE OUTCOMES

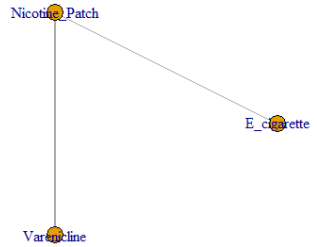
Patient or population: Adult smokers

Interventions: Varenicline, nicotine replacement therapy

Comparator (reference): e-cigarette

Outcome: relapse

Setting: Outpatient



Geometry of the Network*

Total studies: 3 RCT[4,11,14] Total Participants: 1691	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Interpretation of Findings
		Without intervention	*With* intervention	Difference		
Varenicline (2 RCTs;[4,14] 805 participants)	HR 1.1 (0.70 to 1.50) Network estimate	-	-	-	⨁◯◯◯ Very low Due to risk of bias, indirectness, and imprecision[1,2,3]	-

NMA-SoF table definitions

* Lines represent direct comparisons

** Estimates are reported as hazard ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (7) since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The indirect comparison between varenicline versus e-cigarette is estimated by the comparisons between varenicline versus nicotine patch, and nicotine replacement therapy versus e-cigarette. Two trials (Bullen 2013 and Hajek 2019) consisted of the comparison between nicotine replacement therapy versus e-cigarette. But both trials were open label studies.

[2] The estimate for the comparison between varenicline and e-cigarette was based on indirect comparison using nicotine replacement therapy as the common comparator. For the comparison between varenicline and nicotine replacement therapy, the 11 included studies used nicotine patch. While for the comparison between e-cigarette and nicotine replacement therapy, Hajek 2019 (the study with the larger sample size of the two included studies) used patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs. Because of the difference in nicotine replacement therapy, there was concern on the transitivity assumption.

[3] The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the effect of varenicline compared with e-cigarette will be different.

[4] Small number of events.

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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, cause less-frequent side effects and help with the prevention of weight gain; however, accessibility (i.e., availability over-the-counter) and the cost are less important.**(4, 19, 9, 20, 11, 3) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for the more effective treatment.(4, 17) Compared with reduction, people prefer to quit completely.(21, 13) People also claimed they quit smoking for general health or long-term health.(22, 23, 18, 24) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Nearly ninety percent of users (89.7% of varenicline users) stated that the reason to accept the treatment was “to quit smoking or avoid relapse,” while 76.0% chose “to deal with withdrawal,” 71.1% “to deal with craving,” followed by 31.3% "to deal with situations or places where cannot smoke" and 22.1% “to deal with stress.”(9) **"No effects" plays an important role in stopping use of treatment.**(19, 9) Etter et al. reported that 18.2% varenicline users chose “failing to stop smoking/relapse” as the reason to stop and 11.7% varenicline users chose “having craving or withdrawal.”(9) Safety is also an important consideration.(25, 26, 19, 9, 27) People who chose unassisted cessation stated that their main concern was side effects.(3) If current users stop using smoking cessation treatment, side effects would be the reason for 42.9% varenicline users.(9) Cost is an important factor to consider,(8, 28) but less important when compared with side effects.(3) In a willingness to pay study, it was estimated that people were willing to pay $538 for to quit smoking.(4) **In general, respondents are willing to use pharmacotherapy.**(5, 6, 7, 8, 9, 10, 11, 12, 13, 14) Most varenicline users (88.7%) would recommend their treatment to a friend, and 73.% would consider using it again.(9) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) compared with light smokers (16.0%).(12) **Camenga and colleagues conducted focus groups on adolescents and young adults about their perception with e-cigarette as a smoking cessation aid. For participants, positive attributes of e-cigarettes included maintenance of smoking actions, being a "healthier" alternative to cigarettes, and parental approval. Negative attributes include persistence of craving and maintenance of addiction.**(15) **Variability exists for the preference.**(6, 16, 11, 17) Included studies reported that several factors may influence people’s willingness to use pharmacotherapy for tobacco dependence. Factors such as being heavy smokers, male, or employed and having children or a higher education level may increase the willingness to use pharmacotherapy.(6, 11) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (such as childbirth), having concerns about others’ health, or having concerns about smoking on their image and appearance.(18) **Notably, the included studies also suggested that there is a potential demand for improved medication for its efficacy and safety profiles** (the currently available options are not effective or safe as users expected). The willingness to pay for the medications is lower than the market price.(6)	Eight panelists believe there is important uncertainty or variability whereas 6 panelists believe there is possible uncertainty or variability. The reasons for this include that panelists agreed that there are variabilities on patients' preferences of the outcomes (e.g., free of smoking, and addiction) and the intervention since they are different delivery methods. There are also potential variabilities about the continued use of nicotine products.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake is low for varenicline.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline.(29) Muilenburg et al. reported that compared with the nicotine patch, the most available option, varenicline was less implemented. In this cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the nicotine patch was used with an average of 2.10 adolescents. While varenicline was used with an average of 0.22 adolescents, respectively.(30) **E-cigarettes are common and available, but stakeholders may lack knowledge on the evolving evidence about its benefits and harms.** El-Shahawy et al. conducted semi-structured interviews with primary care physicians in the US to explore their beliefs and practices about e-cigarettes. They discovered that discussions focusing on e-cigarettes were common and primary care physicians were willing to support the use of e-cigarettes for their patients, while they lack knowledge on its benefits and harms. Physicians also believed e-cigarettes are a safer alternative to the combustible tobacco product. The researchers underscored the need for the physicians to be informed about the evolving evidence on the benefits and harms of e-cigarettes.(31) Truman and colleagues explored the acceptability of e-cigarettes in hospitals in New Zealand and concluded e-cigarettes was an acceptable way to manage tobacco dependence in the hospital setting for alcohol-dependent patients and heavy smokers.(32)	The panel considered both interventions to be acceptable to stakeholders, with varenicline becoming increasingly feasible since the removal of the boxed warning.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. The evidence suggested the availability of varenicline may be a barrier to implementation.** Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested fewer programs provided varenicline compared with the most available option, nicotine replacement therapy.(33) According to Muilenburg et al., nicotine patch is the most available and most implemented option. In this cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, only 10.17% of the counsellors had varenicline.(30) Cost, especially greater out-of-pocket payment, for varenicline was associated with suboptimal adherence to varenicline and less refilling.(34) Patient willingness could be a barrier too. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and smoking cessation program in hospital, a still very high proportion (30.3%) of patients hospitalized for COPD exacerbation were unwilling to quit smoking following the evidence-based recommendation.(35) **Though e-cigarettes were widely available, there were barriers in the introduction of e-cigarettes in smoking cessation services.** Hsu et al. reported a variety of channels in which users accessed e-cigarettes with vape shops being the most likely channel in 2016.(36) Another report from the perspective of frontline smoking cessation service providers in England suggested that there were barriers to introducing e-cigarettes in smoking cessation services, including availability, concerns about habit and long-term use, and concerns about negative health effects, safety and lack of licensed products, and tension over the profit. Services varied in their attitudes toward "e-cigarette friendly". Some services took active approaches to be e-cigarette friendly, while others did not. Public health leadership played a role in this as well, and there was resistance from the wider public health.(37) **Quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving smoking cessation medication increased from 5% to 18%.(38)	Electronic-cigarettes are unregulated products with the uncertainty of harm and increased risk of higher rates of initiation of smoking, particularly among adolescents. Varenicline is available and becoming increasingly feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important	No important uncertainty or variability			

	JUDGEMENT						
			uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **suggests against offering** electronic cigarettes over varenicline **(conditional recommendation based on very low certainty in the evidence about effects).**

Remarks: The recommendation's strength reflects very low certainty in the effects used to derive the recommendation. After our evidence synthesis, new evidence emerged regarding the serious adverse effects of electronic cigarettes. If these serious adverse effects continue to be reported, the strength of the recommendation should be re-evaluated. Note that this recommendation is intended for the treatment of tobacco dependence under the supervision of a clinician; it should not be extrapolated to unsupervised treatment or recreational use.

Justification

The panel concluded 1) varenicline showed uncertain benefits compared to electronic cigarettes in abstinence or relapse, and 2) varenicline had fewer adverse events than electronic cigarettes. As a result, the panel recommended varenicline rather than electronic cigarettes for treatment of tobacco dependence. The panel chose to make a conditional recommendation because of the very low certainty in the estimated effects limited confidence in these conclusions.

While there was unanimity among the panel regarding the preferred intervention, two panelists (HJF, MCP) advocated for a strong, rather than conditional, recommendation. They were concerned about the safety and effectiveness of electronic cigarettes due to case reports that were not included in the evidence synthesis. They cited reports of deaths or disability due to electronic cigarette or vaping use-associated lung injury (EVALI), burns due to product explosion, acute nicotine poisoning, and seizures, as well as histopathological injuries in laboratory studies. They noted that such concerns have prompted warnings about electronic cigarettes from numerous organizations as described below. Two panelists later joined the dissent (PF, TL), but these panelists were unavailable to participate in the panel discussions of the evidence or the formulation and grading of the recommendation.

Subgroup considerations

None.

Implementation considerations

Although Varenicline is probably appropriate for the majority of patients, some patients may choose to use electronic cigarettes. A shared decision-making approach involving a discussion with the patient about the potential benefits, harms and costs of the alternatives may be a way for implementing this recommendation into practice.

Monitoring and evaluation

None.

Research priorities

In all cases of clinical trials involving electronic cigarettes, we recommend using objective measures of compensatory behaviors and long-term control over dependence, not simply counts of cigarettes consumed. Observational studies that account for the known variability in real-world use patterns when describing the long-term safety outcomes of electronic cigarette use are also needed.

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PICO 5: In tobacco-dependent adults who are not ready to discontinue tobacco use, should clinicians begin treatment with the optimal controller or wait until they are ready to stop tobacco use?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Wait list until patients are ready to stop tobacco use	Relative (95% CI)	Absolute (95% CI)		
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 [1,2,3]	randomised trials	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 per 1,000 (from 121 more to 234 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Point abstinence during treatment (follow up: 24 weeks; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2 [1,3]	randomised trials	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 per 1,000 (from 225 more to 409 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Smoking reduction - Week 4 (follow up: 4 weeks; assessed with: reduction of 50% or more)												
2 [1,4]	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	0/785 (0.0%)	31.1%	OR 1.95 (1.59 to 2.41)	157 more per 1,000 (from 107 more to 210 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Smoking reduction (follow up: range 8 weeks to 3 months; assessed with: 50% or more)[c]												
2 [1,4]	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	0/785 (0.0%)	15.1%	OR 2.03 (1.57 to 2.61)	114 more per 1,000 (from 67 more to 166 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Smoking reduction in number of cigarettes per day												
1 [2]	randomised trials	serious [d]	not serious	serious [b]	serious [e]	none	77	76	-	MD 2.6 higher	⨁◯◯◯ VERY LOW	IMPORTANT
Motivation to quit												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Wait list until patients are ready to stop tobacco use	Relative (95% CI)	Absolute (95% CI)		
3 [2,3,4]	randomised trials	serious [d,f]	not serious [d,f]	serious [b]	serious [g]	none	456/595 (76.6%)	169/270 (62.6%)	RR 1.17 (0.98 to 1.40)	106 more per 1,000 (from 13 fewer to 250 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse event												
4 [1,2,3,4]	randomised trials	not serious	not serious	not serious	serious [h]	none	34/1369 (2.5%)	17/1046 (1.6%)	RR 1.75 (0.98 to 3.13)	12 more per 1,000 (from 0 fewer to 35 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Other substance use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Withdrawal (follow up: range 12 days to 15 days; assessed with: Questionnaire of Smoking Urges-Tonic craving; lower score indicates better outcome; Scale from: 1 to 7)												
1 [5]	randomised trials	serious [i]	not serious	not serious	serious [e]	none	46	54	-	MD 1.54 lower (2.15 lower to 0.93 lower)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal (follow up: range 12 days to 15 days; assessed with: Wisconsin Smoking Withdrawal Scale - Tonic craving; lower score indicates better outcome; Scale from: 0 to 8)												
1 [5]	randomised trials	serious [i]	not serious	not serious	serious [e]	none	46	54	-	MD 1.26 lower (1.34 lower to 1.18 lower)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal (follow up: 2 months; assessed with: Minnesota Nicotine Withdrawal Scale-Total withdrawal; lower score indicates better outcome; Scale from: 0 to 27)												
1 [2]	randomised trials	serious [d]	not serious [d]	not serious	serious [e]	none	77	76	-	MD 0.1 higher	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio

Explanations

a. The pooled estimate was largely based on Ebbert 2015, a low risk of bias study.
b. Smoking reduction or motivation to quit is a surrogate outcome for abstinence.

c. It was defined as 75% or more after Week 8 in Ebbert 2015, and 50% or more in Steinberg 2018.
d. In Hughes 2011, 28% for varenicline group and 32% of placebo group participants were not included in the analysis for this outcome. The high proportion of exclusion from analysis may create an unbalanced comparison.
e. We are unaware of the minimal clinical important difference for this measurement. But empirically the total sample size is too small to provide precise estimate.
f. Steinberg 2018 had a high proportion of loss-to-follow up. In addition, it is unclear the number of participants in the outcome "motivation to quit".
g. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of varenicline will be different.
h. The number of events is small.
i. Brandon 2011, the included study did not specify if they used intention-to-treat analysis or per-protocol. After breaking the blind, it was revealed that greater attrition from assessments 1 to 3 occurred for the varenicline (17.9%) condition compared to the placebo condition (7.4%)

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Evidence to Decision

QUESTION

Should Varenicline vs. Wait list until patients are ready to stop tobacco use be used for tobacco-dependent adults who are not ready to discontinue tobacco use?	
POPULATION:	tobacco-dependent adults who are not ready to discontinue tobacco use
INTERVENTION:	Varenicline
COMPARISON:	Wait list until patients are ready to stop tobacco use
MAIN OUTCOMES:	Point abstinence at 6 months or longer; Point abstinence during treatment; Quality of life; Smoking reduction - Week 4; Smoking reduction; Smoking reduction in number of cigarettes per day; Motivation to quit; Serious adverse event; Relapse; Other substance use; Withdrawal ; Withdrawal; Withdrawal;
SETTING:	outpatient
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and diseases in the United States and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking.(1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with wait list until patients are ready to stop tobacco use	Risk difference with varenicline
Point abstinence at 6 months or longer assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 6 months to 1 years	2387 (3 RCTs)[1,2,3]	⨁⨁⨁⨁ HIGH	**RR 2.00** (1.70 to 2.35)	173 per 1,000	**173 more per 1,000** (121 more to 234 more)
Point abstinence during treatment assessed with: Self report + exhaled carbon monoxide	2169 (2 RCTs)[1,3]	⨁⨁⨁⨁ HIGH	**RR 2.49** (2.09 to 2.98)	207 per 1,000	**308 more per 1,000** (225 more to 409 more)

	concentration verification follow up: 24 weeks					
	Quality of life - not reported	-	-	-	-	-
	Serious adverse event	2415 (4 RCTs)[1,2,3,4]	⨁⨁⨁◯ MODERATE[a]	**RR 1.75** (0.98 to 3.13)	16 per 1,000	**12 more per 1,000** (0 fewer to 35 more)
	Relapse - not reported	-	-	-	-	-
	Other substance use - not reported	-	-	-	-	-
	Withdrawal assessed with: Questionnaire of Smoking Urges-Tonic craving; lower score indicates better outcome Scale from: 1 to 7 follow up: range 12 days to 15 days	100 (1 RCT)[5]	⨁⨁◯◯ LOW[b,c]	-		MD **1.54 lower** (2.15 lower to 0.93 lower)

Withdrawal assessed with: Wisconsin Smoking Withdrawal Scale - Tonic craving; lower score indicates better outcome Scale from: 0 to 8 follow up: range 12 days to 15 days	100 (1 RCT)[5]	⊕⊕◯◯ LOW[b,c]	-		MD **1.26 lower** (1.34 lower to 1.18 lower)
Withdrawal assessed with: Minnesota Nicotine Withdrawal Scale-Total withdrawal; lower score indicates better outcome Scale from: 0 to 27 follow up: 2 months	153 (1 RCT)[2]	⊕⊕◯◯ LOW[c,d]	-		MD **0.1 higher**

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	3. S, Rennard, J, Hughes, M, Cinciripini,P, E, Kralikova, T, Raupach, C, Arteaga, al, et. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. Nicotine Tob Res; 2012. 4. L, Steinberg,M, E, Lu,S, M, Williams,J. Varenicline for smoking reduction in smokers not yet ready to quit: A double-blind, proof-of-concept randomized clinical trial. Addict Behav; 2018. 5. Thomas, Brandon, David, Drobes, Marina, Unrod, Bryan, Heckman, Jason, Oliver, Richard, Roetzheim, al, et. Varenicline effects on craving, cue reactivity, and smoking reward. Psychopharmacology; 2011. Explanations a. The number of events is small. b. Brandon 2011, the included study did not specify if they used intention-to-treat analysis or per-protocol. After breaking the blind, it was revealed that greater attrition from assessments 1 to 3 occurred for the varenicline (17.9%) condition compared to the placebo condition (7.4%) c. We are unaware of the minimal clinical important difference for this measurement. But empirically the total sample size is too small to provide precise estimate. d. In Hughes 2011, 28% for varenicline group and 32% of placebo group participants were not included in the analysis for this outcome. The high proportion of exclusion from analysis may create an unbalanced comparison.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with wait list until patients are ready to stop tobacco use	Risk difference with varenicline
Point abstinence at 6 months or longer assessed with: Self report + exhaled carbon monoxide concentration verification follow up: range 6 months to 1 years	2387 (3 RCTs)[1,2,3]	⨁⨁⨁⨁ HIGH	**RR 2.00** (1.70 to 2.35)	173 per 1,000	**173 more per 1,000** (121 more to 234 more)
Point abstinence during treatment assessed with: Self report + exhaled carbon monoxide	2169 (2 RCTs)[1,3]	⨁⨁⨁⨁ HIGH	**RR 2.49** (2.09 to 2.98)	207 per 1,000	**308 more per 1,000** (225 more to 409 more)

ADDITIONAL CONSIDERATIONS

The panel stated that withdrawal might cause serious adverse events. If so, clinicians can improve the treatment regimen to prevent such serious adverse events.

concentration verification follow up: 24 weeks						
Quality of life - not reported	-	-	-	-	-	
Serious adverse event	2415 (4 RCTs)[1,2,3,4]	⨁⨁⨁◯ MODERATE[a]	**RR 1.75** (0.98 to 3.13)	16 per 1,000	**12 more per 1,000** (0 fewer to 35 more)	
Relapse - not reported	-	-	-	-	-	
Other substance use - not reported	-	-	-	-	-	
Withdrawal assessed with: Questionnaire of Smoking Urges-Tonic craving; lower score indicates better outcome Scale from: 1 to 7 follow up: range 12 days to 15 days	100 (1 RCT)[5]	⨁⨁◯◯ LOW[b,c]	-		MD **1.54 lower** (2.15 lower to 0.93 lower)	

Withdrawal assessed with: Wisconsin Smoking Withdrawal Scale - Tonic craving; lower score indicates better outcome Scale from: 0 to 8 follow up: range 12 days to 15 days	100 (1 RCT)[5]	⨁⨁◯◯ LOW[b,c]	-		MD **1.26 lower** (1.34 lower to 1.18 lower)
Withdrawal assessed with: Minnesota Nicotine Withdrawal Scale-Total withdrawal; lower score indicates better outcome Scale from: 0 to 27 follow up: 2 months	153 (1 RCT)[2]	⨁⨁◯◯ LOW[c,d]	-		MD **0.1 higher**

References

1. Ebbert, , R, Hughes J, J, West R, I, Rennard S, C, Russ, D, McRae T, al, et. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. Jama; 2015.
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	3. S, Rennard, J, Hughes, M, Cinciripini,P, E, Kralikova, T, Raupach, C, Arteaga, al, et. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. Nicotine Tob Res; 2012. 4. L, Steinberg,M, E, Lu,S, M, Williams,J. Varenicline for smoking reduction in smokers not yet ready to quit: A double-blind, proof-of-concept randomized clinical trial. Addict Behav; 2018. 5. Thomas, Brandon, David, Drobes, Marina, Unrod, Bryan, Heckman, Jason, Oliver, Richard, Roetzheim, al, et. Varenicline effects on craving, cue reactivity, and smoking reward. Psychopharmacology; 2011. Explanations a. The number of events is small. b. Brandon 2011, the included study did not specify if they used intention-to-treat analysis or per-protocol. After breaking the blind, it was revealed that greater attrition from assessments 1 to 3 occurred for the varenicline (17.9%) condition compared to the placebo condition (7.4%) c. We are unaware of the minimal clinical important difference for this measurement. But empirically the total sample size is too small to provide precise estimate. d. In Hughes 2011, 28% for varenicline group and 32% of placebo group participants were not included in the analysis for this outcome. The high proportion of exclusion from analysis may create an unbalanced comparison.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, cause less-frequent side effects and help with prevention of weight gain; however, accessibility (i.e., availability over-the-counter) and the cost are less important.**(4, 18, 9, 19, 11, 3) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for more effective treatment.(4, 16) Compared with reduction, people prefer to quit completely.(20, 13) People also claimed they quit smoking for general health or long-term health.(21, 22, 17, 23) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Nearly ninety percent users (89.7% of varenicline users) stated that the reason to accept the treatment was “to quit smoking or avoid relapse,” 76.0% “to deal with withdrawal,” 71.1% “to deal with craving,” 31.3% for “to deal with situations or places where cannot smoke,” and 21.1% for “to deal with stress” (9) **"No effects" plays an important role in stopping use.**(18, 9) Etter et al. reported that 18.2% varenicline users chose “failing to stop smoking/relapse” and 11.7% chose “having craving or withdrawal” as the reason to stop.(9) Safety is also an important consideration.(24, 25, 18, 9, 26) People who chose unassisted cessation stated that their main concern was side effects.(3) While if current users stop using the treatment, side effects would be the reason for 42.9% of varenicline users.(9)	

	Cost is important,(8, 19) but less important compared with side effects.(3) In a willingness to pay study, it was estimated that people were willing to pay $538 to quit.(4) **In general, respondents are more willing to use nicotine replacement therapy than to use varenicline or bupropion.**(5, 6, 7, 8, 9, 10, 11, 12, 13, 14) Most varenicline users (88.7%) would recommend their treatment to a friend, and would consider using it again (73.0%).(9) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) when compared to light smokers (16.0%).(12) **Variability exists for the preference.**(6, 15, 11, 16) Included studies reported that several factors that may influence people's willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, or employed, and having children or a higher education level may increase the willingness to use pharmacotherapy.(6, 11) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (e.g. childbirth), and having concerns about others' health or about the impact of smoking on their image and appearance.(17) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles. The currently available options are not as effective or safe as users expected. The willingness to pay for the medications is lower than the market price.(6)	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake is low for varenicline.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline.(27) Muilenburg 2015 reported that compared with the nicotine patch, the most available option, varenicline was less implemented. In this cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the nicotine patch was used with an average of 2.10 adolescents while varenicline was used with an average of 0.22 adolescents.(28)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. The evidence suggested the availability of varenicline may be a barrier to implementation.** Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested fewer programs provided varenicline compared with the most available option, nicotine replacement therapy.(29) According to Muilenburg et al., nicotine patch is the most available and most implemented option. In this cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, only 10.17% of the counsellors had varenicline.(28) Cost, especially greater out-of-pocket payment for varenicline, was associated with suboptimal adherence to varenicline and less refilling.(30) Patient willingness could be a barrier, too. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and accessing a smoking cessation program in hospital, a still very high proportion (30.3%) of patients hospitalized for COPD exacerbation were unwilling to quit smoking following the evidence-based recommendation.(31) **Quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(32)	The panel determined that starting varenicline directly is more feasible than asking patients to quit immediately.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **recommends** offering treat with varenicline over **waiting until patients are ready** to stop tobacco use **(strong recommendation based on moderate certainty in the evidence about effects)** for tobacco-dependent adults who are not ready to discontinue tobacco use.
Remarks: The initiation of varenicline treatment in smokers not ready to abstain showed a large effect on abstinence with high certainty in the estimated effects, and initiation of pre-treatment showed small increase in adverse events with moderate certainty in the estimated effects.

Justification

The panel concluded that 1) the initiation of varenicline treatment in smokers not ready to abstain showed a large effect on abstinence with high certainty in the estimated effects, and 2) initiation of pre-treatment showed small increase in adverse events with moderate certainty in the estimated effects. The panel considered the potential threat to patient autonomy if the proactive approach is misapplied but recognized that autonomy is preserved when clinicians engage their patients in discussion, encourage pharmacotherapy with continued smoking, and respect their decision to decline treatment. Overall, the panel judged patient values as having important variability, given that individual patients may prioritize relative efficacy, side effects, accessibility and costs differently.

Subgroup considerations

None.

Implementation considerations

Implementing pre-treatment protocols in practice will require clinicians to move their therapeutic focus away from the anticipated behavioral outcome (i.e. smoking), and focus instead on resolving the intermediate *mediator* of smoking (i.e. the compulsion to smoke). The prescriber becomes responsible for reframing the patient's expectations and goals of therapy.

Monitoring and evaluation

None.

Research priorities

Research on the optimal duration of treatment, including methods for determining when continuation is unlikely to derive further benefit, is critical to maximizing impact on outcomes. Future research needs to measure patient-important outcomes such as quality of life and other substance use when conducting trials on patients unready to quit. Studies evaluating the impact of combination pharmacotherapy on treatment outcomes are warranted. Finally, research on sub-group populations with comorbidities should be considered.

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PICO 6: In tobacco dependent adults with co-morbid psychiatric conditions, including substance use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, should clinicians start with the optimal controller medication identified for the non-psychiatric population or use nicotine patch?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Nicotine patch	Relative (95% CI)	Absolute (95% CI)		
Point prevalent Tobacco abstinence at 6 months (follow up: 6 months; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2 [1,2]	randomised trials	not serious	not serious	not serious	not serious [a]	none	275/1109 (24.8%)	11.7%	RR 1.31 (1.12 to 1.53)	36 more per 1,000 (from 14 more to 62 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Point prevalent Tobacco abstinence during the treatment period (follow up: 12 weeks; assessed with: Self report + exhaled carbon monoxide concentration verification)												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [b]	none	368/1109 (33.2%)	13.9%	RR 1.78 (0.78 to 4.08)	108 more per 1,000 (from 31 fewer to 428 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse events												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [c]	none	23/1103 (2.1%)	1.2%	RR 0.95 (0.54 to 1.67)	1 fewer per 1,000 (from 5 fewer to 8 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Tobacco use relapse measured at the end of the follow-up. (At 6 months or longer) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Other substance abuse-alcohol												
1 [2]	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	8/49 (16.3%)	29.0%	RR 0.56 (0.24 to 1.30)	128 fewer per 1,000 (from 221 fewer to 87 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Other substance abuse-any drug												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Nicotine patch	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	18/49 (36.7%)	25.8%	RR 1.42 (0.71 to 2.87)	108 more per 1,000 (from 75 fewer to 483 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Severity of withdrawal - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; HR: Hazard Ratio

Explanations

a. The lower limit of the confidence interval is 1.12, suggesting the benefits could be as low as 14 additional abstinence per 1,000 patients treated.
b. The confidence interval includes 1 and is very wide, ranging from 0.78 to 4.08, indicating a potentially very large benefit (31 additional abstinence) for nicotine patch or a very large benefit (428 more abstinence) for varenicline.
c. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of varenicline will be different.
d. Because of lost to follow up, the substance abuse outcomes were compared in an unbalanced manner in Rohsenow 2017 (49 in Varenicline group vs 31 in nicotine replacement therapy group).
e. The estimate is based on a very small total number of events. The confidence interval includes 1.

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Evidence to Decision

QUESTION

Should Varenicline vs. Nicotine patch be used for tobacco-dependent adults with co-morbid psychiatric conditions?	
POPULATION:	tobacco-dependent adults with co-morbid psychiatric conditions
INTERVENTION:	Varenicline
COMPARISON:	Nicotine patch
MAIN OUTCOMES:	Point prevalent Tobacco abstinence at 6 months; Point prevalent Tobacco abstinence during the treatment period; Quality of life; Serious adverse events; Tobacco use relapse measured at the end of the follow-up. (At 6 months or longer); Other substance abuse-alcohol; Other substance abuse-any drug; Severity of withdrawal;
SETTING:	outpatient; the psychiatric conditions including substance abuse disorder, depression, anxiety, schizophrenia, and/or bipolar disorder
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and diseases in the United States and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking.(1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with nicotine replacement therapy patch	Risk difference with varenicline
Point prevalent Tobacco abstinence at 6 months assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 6 months	2194 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH[a]	**RR 1.31** (1.12 to 1.53)	117 per 1,000	**36 more per 1,000** (14 more to 62 more)
Point prevalent Tobacco abstinence during the treatment period assessed with: Self report + exhaled carbon monoxide concentration verification	2194 (2 RCTs)[1,2]	⨁⨁⨁◯ MODERATE[b]	**RR 1.78** (0.78 to 4.08)	139 per 1,000	**108 more per 1,000** (31 fewer to 428 more)

ADDITIONAL CONSIDERATIONS

The panel agreed that the confidence interval of abstinence during treatment was wide but many additional patients quit at 6 months. Therefore, they judged the desirable effects as large.

follow up: 12 weeks						
Quality of life - not reported	-	-	-	-	-	
Serious adverse events	2179 (2 RCTs)[1,2]	⨁⨁⨁◯ MODERATE[c]	**RR 0.95** (0.54 to 1.67)	12 per 1,000	**1 fewer per 1,000** (5 fewer to 8 more)	
Tobacco use relapse measured at the end of the follow-up. (At 6 months or longer) - not reported	-	-	-	-	-	
Other substance abuse-alcohol	80 (1 RCT)[2]	⨁◯◯◯ VERY LOW[d,e]	**RR 0.56** (0.24 to 1.30)	290 per 1,000	**128 fewer per 1,000** (221 fewer to 87 more)	

Other substance abuse-any drug	80 (1 RCT)[2]	⊕◯◯◯ VERY LOW[d,e]	**RR 1.42** (0.71 to 2.87)	258 per 1,000	**108 more per 1,000** (75 fewer to 483 more)
Severity of withdrawal - not reported	-	-	-	-	-

References

1. Anthenelli, R. M., Benowitz, N. L., West, R., St Aubin, L., McRae, T., Lawrence, D., Ascher, J., Russ, C., Krishen, A., Evins, A. E.. 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. Lancet; Jun 18 2016.
2. Rohsenow, D. J., Tidey, J. W., Martin, R. A., Colby, S. M., Swift, R. M., Leggio, L., Monti, P. M.. Varenicline versus nicotine patch with brief advice for smokers with substance use disorders with or without depression: effects on smoking, substance use and depressive symptoms. Addiction; Oct 2017.

Explanations

a. The lower limit of the confidence interval is 1.12, suggesting the benefits could be as low as 14 additional abstinence per 1,000 patients treated.
b. The confidence interval includes 1 and is very wide, ranging from 0.78 to 4.08, indicating a potentially very large benefit (31 additional abstinence) for nicotine patch or a very large benefit (428 more abstinence) for varenicline.
c. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of varenicline will be different.
d. Because of lost to follow up, the substance abuse outcomes were compared in an unbalanced manner in Rohsenow 2017 (49 in Varenicline group vs 31 in nicotine replacement therapy group).

e. The estimate is based on a very small total number of events. The confidence interval includes 1.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with nicotine replacement therapy patch	Risk difference with varenicline
Point prevalent Tobacco abstinence at 6 months assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 6 months	2194 (2 RCTs)[1,2]	⨁⨁⨁⨁ HIGH[a]	**RR 1.31** (1.12 to 1.53)	117 per 1,000	**36 more per 1,000** (14 more to 62 more)

ADDITIONAL CONSIDERATIONS

The studies do not suggest that patient complexity or potential for loss to follow-up obscured detection. This may require further monitoring in clinical practice.

Point prevalent Tobacco abstinence during the treatment period assessed with: Self report + exhaled carbon monoxide concentration verification follow up: 12 weeks	2194 (2 RCTs)[1,2]	⨁⨁⨁◯ MODERATE[b]	**RR 1.78** (0.78 to 4.08)	139 per 1,000	**108 more per 1,000** (31 fewer to 428 more)
Quality of life - not reported	-	-	-	-	-
Serious adverse events	2179 (2 RCTs)[1,2]	⨁⨁⨁◯ MODERATE[c]	**RR 0.95** (0.54 to 1.67)	12 per 1,000	**1 fewer per 1,000** (5 fewer to 8 more)
Tobacco use relapse measured at the end of the follow-up. (At 6 months or longer) - not reported	-	-	-	-	-

Other substance abuse-alcohol	80 (1 RCT)[2]	⊕◯◯◯ VERY LOW[d,e]	**RR 0.56** (0.24 to 1.30)	290 per 1,000	**128 fewer per 1,000** (221 fewer to 87 more)
Other substance abuse-any drug	80 (1 RCT)[2]	⊕◯◯◯ VERY LOW[d,e]	**RR 1.42** (0.71 to 2.87)	258 per 1,000	**108 more per 1,000** (75 fewer to 483 more)
Severity of withdrawal - not reported	-	-	-	-	-

References

1. Anthenelli, R. M., Benowitz, N. L., West, R., St Aubin, L., McRae, T., Lawrence, D., Ascher, J., Russ, C., Krishen, A., Evins, A. E.. 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. Lancet; Jun 18 2016.
2. Rohsenow, D. J., Tidey, J. W., Martin, R. A., Colby, S. M., Swift, R. M., Leggio, L., Monti, P. M.. Varenicline versus nicotine patch with brief advice for smokers with substance use disorders with or without depression: effects on smoking, substance use and depressive symptoms. Addiction; Oct 2017.

Explanations

a. The lower limit of the confidence interval is 1.12, suggesting the benefits could be as low as 14 additional abstinence per 1,000 patients treated.
b. The confidence interval includes 1 and is very wide, ranging from 0.78 to 4.08, indicating a potentially very large benefit

	(31 additional abstinence) for nicotine patch or a very large benefit (428 more abstinence) for varenicline. c. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of varenicline will be different. d. Because of lost to follow up, the substance abuse outcomes were compared in an unbalanced manner in Rohsenow 2017 (49 in Varenicline group vs 31 in nicotine replacement therapy group). e. The estimate is based on a very small total number of events. The confidence interval includes 1.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, cause less-frequent side effects and help with the prevention of weight gain; however, accessibility (i.e., availability over-the-counter) and the cost are less important.**(11, 19, 6, 10, 5, 3) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for more effective treatment.(11, 20) Compared with	The evidence on preferences were based on misconceptions among both patients and clinicians regarding the nature of varenicline and probability of serious adverse effects. Panel members acknowledged that nicotine self-treatment concerns and the complexity of underlying

	reduction, people prefer to quit completely.(12, 17) People also claimed they quit smoking for general health or long-term health.(21, 22, 7, 23) Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Over eighty percent of users (81.2% of nicotine patch users and 89.7% of varenicline users) stated that the reason to accept the treatment was “to quit smoking or avoid relapse”.(6) “to deal with withdrawal” was chosen by 79.5% and 76.0% of the nicotine patch and varenicline users, respectively. “To deal with craving” is also important for 69.4% nicotine patch and 71.1% varenicline users; followed by “to deal with stress”, chosen by 34.6% nicotine patch and 22.1% varenicline users.(6) “To deal with situations or places where cannot smoke” is also important, but this is more true for nicotine patch users (34.0%),(6, 3) when compared with varenicline users (31.3%).(6) "No effects" plays an important role in stopping use.(19, 6) Etter et al. reported that 41.6% of current nicotine patch users and 18.2% varenicline users chose “failing to stop smoking/relapse” as the reason to stop; 29.2% nicotine patch users and 11.7% varenicline users chose “having craving or withdrawal” as the reason.(6) Safety is also an important consideration.(24, 25, 19, 6, 26) People who chose unassisted cessation stated that their main concern was side effects.(3) Side effects would be the reason for 23.3% of nicotine patch users and 42.9% of varenicline users who are using smoking cessation treatment to stop.(6) Specifically for nicotine replacement therapy, people interviewed stated their concern over dependence on nicotine replacement therapy.(6, 8) Cost is important,(9, 10) but less important compared with side effects.(3) In a willingness to pay study, it was estimated that people were willing to pay $538 to quit.(11) **For people with substance use, maintaining the current treatment for substance abuse is also important.** Specifically, being diverted from their quitting illicit drug use or tapering off methadone maintenance treatment is the concern for smokers with substance use.(12) **In general, respondents are more willing to use nicotine replacement therapy than to use varenicline.**(13, 4, 14, 9, 6, 15, 5, 16, 17, 18) Most users (81.2% nicotine patch and 88.7% varenicline users) would recommend their treatment to a friend, and would consider using it again (66.7% nicotine patch and 73.0% varenicline users).(6) In a cross-sectional survey in the USA, moderate to heavy smokers prefer varenicline more (19.8%) when compared to light smokers (16.0%). But still, nicotine patch is the most preferred option (25.2% for moderate to heavy smokers and 29.2% for light smokers).(16) **Variability exists for the preference.**(4, 27, 5, 20) Included studies reported that several factors may influence people’s willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, or employed and having children or a higher education level may increase the willingness to use pharmacotherapy.(4, 5) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (e.g. childbirth), and concerns about others’ health or the impact smoking on their image and appearance.(7) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles. The currently available options are not as	pharmacotherapeutic regimens may complicate care in this population.

	effective or safe as users expected. The willingness to pay for the medications is lower than the market price.(4)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		There is no evidence or data on quality of life.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake of varenicline is lower when compared to nicotine patches.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the US. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline, and 25% prescribed the nicotine patch. Other nicotine replacement therapy had a lower prescription rate: 16% for nicotine gum, 9% for nicotine lozenge, 5% for nicotine inhaler, and 3% for nicotine spray.(28) Deal et al. reported that providing smoking cessation with nicotine replacement therapy within a substance abuse treatment service is feasible in New Zealand.(29) **Education and training for healthcare providers may be necessary to improve knowledge and awareness.** Two studies, one in the UK setting and(30) another in Iran,(31) reported relatively low levels of knowledge and awareness for smoking cessation services for people with mental health problems. Ratschen et al. reported that support for inpatient smokers may be compromised by low levels of knowledge and awareness of tobacco dependence among mental health	Health care providers needs more education and clinical training in the appropriate management of tobacco dependence.

	professionals.(30) Shakeshaft and colleagues suggested further education and training for primary care physicians may be necessary.(31)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers existed for the introduction of smoking cessation programs. Compared with the nicotine patch, varenicline is the less available option.** Availability of varenicline could be a barrier. Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested that all programs offered nicotine replacement therapy, with patches or gum as the primary options. But fewer programs provided varenicline.(32) In addition, pregnant smokers supported nicotine replacement therapy being offered to pregnant smokers.(33) According to Muilenburg et al., nicotine patches are the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the nicotine patch was available for 25 of 63 (39.68%) counsellors. Comparatively, only 10.17% of the counsellors had access to varenicline.(34) Cost, especially greater out-of-pocket payment for varenicline, was associated with suboptimal adherence to varenicline and less refilling.(35) Specifically for people with mental health problems, low willingness to quit, dual dependence, perceived lack of efficacy of nicotine replacement therapy, and need for intensive support were considered as barriers.(36, 37) In contrast, Knudsen et al. reported that the health insurance coverage will improve the availability of pharmacotherapy for smoking cessation.(38) **The uptake of evidence-based treatment was low in people with mental health problems.** Strong et al. conducted another survey in the US setting and concluded that though smokers were willing to quit and attempted to quit, the uptake of evidence based treatment was low.(39) Himelhoch et al. reported the major barrier was the belief that patients were not willing to quit. They concluded training and education is necessary to overcome this barrier.(40) **However, quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. conducted a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(41)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **recommends** offering varenicline over NRT patch over **(strong recommendation based on moderate certainty in the evidence about effects)** In tobacco dependent adults with co-morbid psychiatric conditions, including substance abuse disorder, depression, anxiety, schizophrenia, and/or bipolar disorder,

Remarks: Patients with psychiatric and/or substance use disorders are more likely to be tobacco dependent, and these patients account for almost 40% of cigarette consumption in the United States. But fewer than half of mental health and substance use treatment facilities in the United States offer evidence-based tobacco dependence treatments. The panel chose to make a strong recommendation given the moderate certainty in estimated effects for critical outcomes.

Justification

When compared to nicotine patches, the panel concluded that varenicline 1) may result in a large benefit and 2) may decrease adverse events, both with moderate certainty in the estimated effects, in patients with substance use or psychiatric disorders. The panel chose to make a strong recommendation given the moderate certainty in estimated effects for critical outcomes.

Subgroup considerations

None.

Implementation considerations

Variation in styles of behavioral therapy and substance use recovery, along with accompanying attitudes regarding pharmacologic support, represent additional potential barriers to implementation unique to this population. Persons with psychiatric illnesses may also have more severe nicotine dependence than the general population, and may require more flexibility in approach, including higher doses, longer duration counseling, or more aggressive combinations of pharmacotherapy.

Substance use disorder clinics need more access to education.

Monitoring and evaluation

None.

Research priorities

More research is needed on the substance use population.
Implementation research is needed to maximize provision of evidence-based treatments for tobacco dependence within this context.

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PICO 7: In tobacco-dependent adults for whom treatment has been initiated with a controller, should they be treated with an extended duration (greater than 12-weeks) or standard duration (6 to 12-weeks) regimen?

Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extended duration (greater than 12-week)	Standard duration	Relative (95% CI)	Absolute (95% CI)		
7-day point prevalent abstinence at 1 year (follow up: mean 1 years; assessed with: Self report + exhaled carbon monoxide concentration verification)												
8 [1,2,3,4,5,6,7,8]	randomised trials	serious [a,b,c,d]	not serious [e]	not serious	not serious	none	751/1935 (38.8%)	24.2%	RR 1.22 (1.07 to 1.39)	53 more per 1,000 (from 17 more to 94 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (follow up: 52 weeks; assessed with: The Short-Form Health Survey (SF-12) (Higher score indicates worse quality of life); Scale from: 12 to 47)												
1 [8]	randomised trials	serious [f]	not serious	serious [g]	serious [h]	none	47	51	-	MD 1.15 lower (3.75 lower to 1.45 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Number of cigarette (follow up: mean 1 years)												
1 [5]	randomised trials	serious [a]	not serious	not serious	serious [i]	none	345	180	-	MD 0.6 lower (1.53 lower to 0.33 higher)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse event												
5 [2,4,6,7,8]	randomised trials	not serious	not serious	not serious	serious [j,k]	none	30/1304 (2.3%)	0.8%	RR 1.37 (0.79 to 2.36)	3 more per 1,000 (from 2 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse (follow up: range 12 months to 18 months)[l]												
2 [2,6]	randomised trials	not serious	not serious	not serious	serious [m]	none	0/322 (0.0%)	0/333 (0.0%)	HR 0.43 (0.29 to 0.64)	-	⨁⨁⨁◯ MODERATE	IMPORTANT
Time to relapse (follow up: 1 years)[o]												
2 [4,5]	randomised trials	serious [a]	serious [p]	not serious	not serious	none	948	787	-	MD 22.03 days more (10.81 more to 33.24 more) [n]	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extended duration (greater than 12-week)	Standard duration	Relative (95% CI)	Absolute (95% CI)		
Other substance use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Withdrawal (follow up: range 13 weeks to 14 weeks; assessed with: craving and urge to smoke; low scores indicates better outcome)[q]												
2 [4,9]	randomised trials	serious [r,s]	serious [t]	not serious	serious [u]	none	601	585	-	SMD 1.54 **lower** (3.94 lower to 0.85 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal (follow up: 25 weeks; assessed with: Minnesota Nicotine Withdrawal Scale, urge to smoke; lower score indicates better outcome; Scale from: 0 to 4)												
1 [4]	randomised trials	serious [s]	not serious	not serious	serious [v]	none	499	468	-	MD 0.27 **lower** (0.44 lower to 0.1 lower)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; HR: Hazard Ratio; SMD: Standardised mean difference

Explanations

a. Schnoll 2015 was an open label trial and no placebo was used.
b. Schlam 2016 was an open label study.
c. It was unclear whether Croghan 2007 was a trial with participants, healthcare personnel, and outcome assessors blinded.
d. If we excluding three studies (Schnoll 2015, Schlam 2016, and Croghan 2007), the lower limit of confidence interval would be 1.02, suggesting only a small benefit of extended treatment. It means if we excluded open label studies, the estimate would be imprecise.
e. The overall I2 was 46.3%. We conducted exploratory subgroup analysis for extended treatment shorter than 12 months and extended treatment of 12 months. The I2 were 0% and 72% for the subgroup of extended treatment shorter than 12 months and the subgroup of extended treatment of 12 months, respectively. It suggested that the duration of extended treatment may explain the variance across estimates, though the estimates were in general similar.
f. In NCT01756885, 47 of 105 participants in the extended treatment group and 51 of 102 in the standard duration group provided the quality of life data. The high proportion of loss to follow up and missing participant data may cause an imbalance in prognosis factors between groups. Furthermore, we have limited information (only from trial registry) to fully assess the risk of bias for this study.
g. This is a study on smoking cancer patients.
h. Small sample size.
i. The confidence interval included 0, indicating the extended treatment may not decrease the number of cigarettes compared with standard duration. Furthermore, the difference may not be clinically important.
j. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of extended treatment will be different.
k. The number of events was small.
l. In Evins 2014, it was unclear how relapse was defined (though their expired CO exceeded 9 ppm was considered as relapse). In Schnoll 2010, relapse was defined as 7 consecutive days of self-reported smoking.
m. The estimate was based on three studies (Evins 2014, Hays 2001, Schnoll 2010), and the pooled estimate was based on two studies (Evins 2014, Schnoll 2010). The total sample size was 662.
n. Those receiving extended treatment had a longer time to relapse compared with those receiving standard duration of treatment.
o. In Schnoll 2015, relapse was defined as 7 consecutive days of self-reported smoking from the cessation date to weeks 24 and 52 after a 2-week grace period, while in Tonstad 2006, relapse was measured by the strict criterion of a single "puff."
p. The estimates of difference in time to relapse between groups were so different between the two studies (Schnoll 2015 and Tonstad 2006): 17 days and 111 days. Schnoll 2015 used nicotine patch while Tonstad 2006 was on varenicline. But it is unclear the type of medication was the reason of inconsistency.
q. In Pomerleau 2003, the craving was measured with a scale of 0 to 5, with 5 indicating the greatest severity. In Tonstad 2006, the urge to smoke was measured with Minnesota Nicotine Withdrawal Scale, with a range of 0 to 4. Lower score indicates better outcomes in both scales.
r. There was no detail reported on the randomization process for Pomerleau 2003.
s. In Tonstad 2006, though this study used intention to treat analysis strategy, the study was considered at high risk of bias for "withdrawal symptom", because the loss to follow up was different between groups (499 in extended treatment group and 468 participants in the control group).

t. Though both suggested extended use of medication can decrease the withdrawal symptom, the two studies (Pomerleau 2003 and Tonstad 2006) showed different effect estimates. The two studies used different measurement tools (craving score and Minnesota Nicotine Withdrawal Scale), and were on different medications (nicotine patch versus varenicline), and used different length of extended treatment. The source of inconsistency was unclear.
u. The confidence interval includes 0, indicating the effect of extended treatment on the withdrawal symptom is inconclusive.
v. The difference between groups was small. Though the minimal clinical important difference is unclear, it was unlikely to be clinically important.

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Evidence to Decision

QUESTION

Should Extended duration (greater than 12-week) vs. Standard duration be used for tobacco-dependent adults for whom treatment has been initiated with a controller?	
POPULATION:	tobacco-dependent adults for whom treatment has been initiated with a controller
INTERVENTION:	Extended duration (greater than 12-week)
COMPARISON:	Standard duration
MAIN OUTCOMES:	7-day point prevalent abstinence at 1 year; Quality of life; Number of cigarette; Serious adverse event; Relapse; Time to relapse; Other substance use; Withdrawal; Withdrawal;
SETTING:	outpatient
PERSPECTIVE:	Individual patient and healthcare professionals
BACKGROUND:	Smoking is a major preventable risk factor for early death and diseases in the U.S. and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 death attributed to second-hand smoking.(1, 2)
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking is a major preventable risk factor for early death and diseases in the United States and worldwide. In 2016, approximately 37.8 million (15.5%) American adults were current cigarette smokers. Over 480,000 Americans die of cigarette smoking annually, with more than 41,000 deaths attributed to second-hand smoking.(1, 2)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard duration	Risk difference with extended duration (greater than 12-week)
7-day point prevalent abstinence at 1 year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: mean 1 years	3609 (8 RCTs)[1,2,3,4,5,6,7,8]	⨁⨁⨁◯ MODERATE[a,b,c,d,e]	**RR 1.22** (1.07 to 1.39)	242 per 1,000	**53 more per 1,000** (17 more to 94 more)
Quality of life assessed with: The Short-Form Health Survey (SF-12) (Higher score	98 (1 RCT)[8]	⨁◯◯◯ VERY LOW[f,g,h]	-	-	MD **1.15 lower** (3.75 lower to 1.45 higher)

indicates worse quality of life) Scale from: 12 to 47 follow up: 52 weeks						
Number of cigarettes follow up: mean 1 years	525 (1 RCT)[5]	⊕⊕◯◯ LOW[b,i]	-	-	MD **0.6 lower** (1.53 lower to 0.33 higher)	
Serious adverse event	2612 (5 RCTs)[2,4,6,7,8]	⊕⊕⊕◯ MODERATE[j,k]	**RR 1.37** (0.79 to 2.36)	8 per 1,000	**3 more per 1,000** (2 fewer to 11 more)	
Relapse follow up: range 12 months to 18 months[l]	328 (3 RCTs)[1,2,6]	⊕⊕⊕◯ MODERATE[m]	**HR 0.43** (0.29 to 0.64)	-	-	
Time to relapse follow up: 1 years[n]	1735 (2 RCTs)[4,5]	⊕⊕◯◯ LOW[b,o]	-[p]	-	MD **22.03 days more** (10.81 more to 33.24 more)[p]	
Other substance use - not reported	-	-	-	-	-	
Withdrawal assessed with: craving and urge to smoke; low	1186 (2 RCTs)[4,9]	⊕◯◯◯ VERY LOW[r,s,t,u]	-	-	SMD **1.54 lower** (3.94 lower to	

scores indicates better outcome follow up: range 13 weeks to 14 weeks[q]					0.85 higher)
Withdrawal assessed with: Minnesota Nicotine Withdrawal Scale, urge to smoke; lower score indicates better outcome Scale from: 0 to 4 follow up: 25 weeks	967 (1 RCT)[4]	⨁⨁◯◯ LOW[u,v]	-	-	MD **0.27 lower** (0.44 lower to 0.1 lower)

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	compared with standard duration. Furthermore, the difference may not be clinically important. j. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of extended treatment will be different. k. The number of events was small. l. In Evins 2014, it was unclear how relapse was defined (though their expired CO exceeded 9 ppm was considered as relapse). In Schnoll 2010, relapse was defined as 7 consecutive days of self-reported smoking. m. The estimate was based on three studies (Evins 2014, Hays 2001, Schnoll 2010), and the pooled estimate was based on two studies (Evins 2014, Schnoll 2010). The total sample size was 662. n. In Schnoll 2015, relapse was defined as 7 consecutive days of self-reported smoking from the cessation date to weeks 24 and 52 after a 2-week grace period, while in Tonstad 2006, relapse was measured by the strict criterion of a single "puff." o. The estimates of difference in time to relapse between groups were so different between the two studies (Schnoll 2015 and Tonstad 2006): 17 days and 111 days. Schnoll 2015 used nicotine patch while Tonstad 2006 was on varenicline. But it is unclear the type of medication was the reason of inconsistency. p. Those receiving extended treatment had a longer time to relapse compared with those receiving standard duration of treatment. q. In Pomerleau 2003, the craving was measured with a scale of 0 to 5, with 5 indicating the greatest severity. In Tonstad 2006, the urge to smoke was measured with Minnesota Nicotine Withdrawal Scale, with a range of 0 to 4. Lower score indicates better outcomes in both scales. r. Though both suggested extended use of medication can decrease the withdrawal symptom, the two studies (Pomerleau 2003 and Tonstad 2006) showed different effect estimates. The two studies used different measurement tools (craving score and Minnesota Nicotine Withdrawal Scale) and were on different medications (nicotine patch versus varenicline), and used different length of extended treatment. The source of inconsistency was unclear. s. The confidence interval includes 0, indicating the effect of extended treatment on the withdrawal symptom is inconclusive. t. There were no details reported on the randomization process for Pomerleau 2003. u. In Tonstad 2006, though this study used intention to treat analysis strategy, the study was considered at high risk of bias	

	for "withdrawal symptom", because the loss to follow up was different between groups (499 in extended treatment group and 468 participants in the control group). v. The difference between groups was small. Though the minimal clinical important difference is unclear, it was unlikely to be clinically important.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Relapse is decreasing the benefits of the treatment and is one of the main concerns of treating smoking cessation.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard duration	Risk difference with extended duration (greater than 12-week)
7-day point prevalent abstinence at 1 year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: mean 1 years	3609 (8 RCTs)[1,2,3,4,5,6,7,8]	⨁⨁⨁◯ MODERATE[a,b,c,d,e]	**RR 1.22** (1.07 to 1.39)	242 per 1,000	**53 more per 1,000** (17 more to 94 more)
Quality of life assessed with: The Short-Form Health Survey (SF-12) (Higher score indicates worse quality of life) Scale from: 12 to 47 follow up: 52 weeks	98 (1 RCT)[8]	⨁◯◯◯ VERY LOW[f,g,h]	-		MD **1.15 lower** (3.75 lower to 1.45 higher)
Number of cigarette follow up: mean 1 years	525 (1 RCT)[5]	⨁⨁◯◯ LOW[b,i]	-		MD **0.6 lower** (1.53 lower to

					0.33 higher)
Serious adverse event	2612 (5 RCTs)[2,4,6,7,8]	⊕⊕⊕◯ MODERATE[j,k]	**RR 1.37** (0.79 to 2.36)	8 per 1,000	**3 more per 1,000** (2 fewer to 11 more)
Relapse follow up: range 12 months to 18 months[l]	328 (3 RCTs)[1,2,6]	⊕⊕⊕◯ MODERATE[m]	**HR 0.43** (0.29 to 0.64)	-	-
Time to relapse follow up: 1 years[n]	1735 (2 RCTs)[4,5]	⊕⊕◯◯ LOW[b,o]	-[p]	**-**	MD **22.03 days more** (10.81 more to 33.24 more)[p]
Other substance use - not reported	-	-	-	-	-
Withdrawal assessed with: craving and urge to smoke; low scores indicates better outcome follow up: range 13 weeks to 14 weeks[q]	1186 (2 RCTs)[4,9]	⊕◯◯◯ VERY LOW[r,s,t,u]	-	-	SMD **1.54 lower** (3.94 lower to 0.85 higher)
Withdrawal assessed with:	967 (1 RCT)[4]	⊕⊕◯◯ LOW[u,v]	-	**-**	MD **0.27 lower** (0.44

Minnesota Nicotine Withdrawal Scale, urge to smoke; lower score indicates better outcome Scale from: 0 to 4 follow up: 25 weeks					lower to 0.1 lower)	

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	patch use in quitters with past abstinence-induced depressed mood. J Subst Abuse Treat; 2003. Explanations a. The overall I2 was 46.3%. We conducted exploratory subgroup analysis for extended treatment shorter than 12 months and extended treatment of 12 months. The I2 were 0% and 72% for the subgroup of extended treatment shorter than 12 months and the subgroup of extended treatment of 12 months, respectively. It suggested that the duration of extended treatment may explain the variance across estimates, though the estimates were in general similar. b. Schnoll 2015 was an open label trial and no placebo was used. c. Schlam 2016 was an open label study. d. It was unclear whether Croghan 2007 was a trial with participants, healthcare personnel, and outcome assessors blinded. e. If we excluding three studies (Schnoll 2015, Schlam 2016, and Croghan 2007), the lower limit of confidence interval would be 1.02, suggesting only a small benefit of extended treatment. It means if we excluded open label studies, the estimate would be imprecise. f. In NCT01756885, 47 of 105 participants in the extended treatment group and 51 of 102 in the standard duration group provided the quality of life data. The high proportion of loss to follow up and missing participant data may cause an imbalance in prognosis factors between groups. Furthermore, we have limited information (only from trial registry) to fully assess the risk of bias for this study. g. This is a study on smoking cancer patients. h. Small sample size. i. The confidence interval included 0, indicating the extended treatment may not decrease the number of cigarettes compared with standard duration. Furthermore, the difference may not be clinically important. j. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of extended treatment will be different. k. The number of events was small. l. In Evins 2014, it was unclear how relapse was defined (though their expired CO exceeded 9 ppm was considered as relapse). In Schnoll 2010, relapse was defined as 7 consecutive days of self-reported smoking.	

	m. The estimate was based on three studies (Evins 2014, Hays 2001, Schnoll 2010), and the pooled estimate was based on two studies (Evins 2014, Schnoll 2010). The total sample size was 662. n. In Schnoll 2015, relapse was defined as 7 consecutive days of self-reported smoking from the cessation date to weeks 24 and 52 after a 2-week grace period, while in Tonstad 2006, relapse was measured by the strict criterion of a single "puff." o. The estimates of difference in time to relapse between groups were so different between the two studies (Schnoll 2015 and Tonstad 2006): 17 days and 111 days. Schnoll 2015 used nicotine patch while Tonstad 2006 was on varenicline. But it is unclear the type of medication was the reason of inconsistency. p. Those receiving extended treatment had a longer time to relapse compared with those receiving standard duration of treatment. q. In Pomerleau 2003, the craving was measured with a scale of 0 to 5, with 5 indicating the greatest severity. In Tonstad 2006, the urge to smoke was measured with Minnesota Nicotine Withdrawal Scale, with a range of 0 to 4. Lower score indicates better outcomes in both scales. r. Though both suggested extended use of medication can decrease the withdrawal symptom, the two studies (Pomerleau 2003 and Tonstad 2006) showed different effect estimates. The two studies used different measurement tools (craving score and Minnesota Nicotine Withdrawal Scale), and were on different medications (nicotine patch versus varenicline), and used different length of extended treatment. The source of inconsistency was unclear. s. The confidence interval includes 0, indicating the effect of extended treatment on the withdrawal symptom is inconclusive. t. There was no detail reported on the randomization process for Pomerleau 2003. u. In Tonstad 2006, though this study used intention to treat analysis strategy, the study was considered at high risk of bias for "withdrawal symptom", because the loss to follow up was different between groups (499 in extended treatment group and 468 participants in the control group). v. The difference between groups was small. Though the minimal clinical important difference is unclear, it was unlikely to be clinically important.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**People would prefer the pharmacotherapy options if they are of higher efficacy, cause less-frequent side effects and help with the prevention of weight gain; however, accessibility (i.e., availability over-the-counter) and the cost are less important.** (9, 20, 5, 8, 13, 3) Efficacy is an important consideration for those who choose smoking cessation options. Most people were willing to pay for more effective treatment.(9, 19) Compared with reduction, people prefer to quit completely.(21, 15) People also claimed they quit smoking for general health or long-term health. (22, 23, 24, 25)	

	Specifically, important outcomes include abstinence, withdrawal, craving, and stress. Over eighty percent of users (81.2% of nicotine patch users, 89.7% of varenicline users, and 80.6% of bupropion users) stated that their reason to accept treatment was “to quit smoking or avoid relapse”.(5) “To deal with withdrawal” was chosen by 79.5%, 76.0%, and 61.2% of the nicotine patch, varenicline, and bupropion users. “To deal with craving” is also important for 69.4% nicotine patch, 71.1% varenicline and 55.2% bupropion users; followed by “to deal with stress”, chosen by 34.6% nicotine patch, 22.1% varenicline, and 29.8% bupropion users.(5) “To deal with situations or places where cannot smoke” is also important, but moreso for nicotine patch users (34.0%),(5, 3) when compared to 31.3% of varenicline users and 23.3% of bupropion users.(5) **"No effects" plays an important role in stopping use.**(20, 5) Etter et al. reported that 41.6% of current nicotine patch users, 18.2% varenicline users, 25.6% bupropion users chose “failing to stop smoking/relapse” as the reason to stop; 29.2% nicotine patch users, 11.7% varenicline users, and 25.6% bupropion chose “having craving or withdrawal” as the reason.(5) Safety is also an important consideration.(26, 27, 20, 5, 28) People who chose unassisted cessation stated that their main concern was side effects.(3) Side effects would be the reason for 23.3% of nicotine patch users, 42.9% varenicline users, and 23.1% bupropion users to stop using smoking cessation treatment.(5) Specifically for nicotine replacement therapy, people interviewed stated their concern over dependence on nicotine replacement therapy.(5, 6) Cost is important,(7, 8) but less important compared with side effects.(3) In a willingness to pay study, it was estimated that people were willing to pay $538 to quit.(9) **In general, respondents are willing to use medication.**(10, 4, 11, 7, 5, 12, 13, 14, 15, 16) **Most people who failed to quit would like to quit again, and they would prefer combination treatment.**(11, 17) **Variability exists for the preference.**(4, 18, 13, 19) Included studies reported that several factors may influence people’s willingness to use pharmacotherapy for tobacco dependence. Being heavy smokers, male, or employed and having children or a higher education level may increase their willingness to use pharmacotherapy.(4, 13) Reid et al. reported that females were more likely to be motivated to quit by experiencing a life change (e.g. childbirth) and concerns about others’ health or the impact of smoking on their image and appearance.(24) Notably, the included studies also suggested there is a potential demand for improved medication for its efficacy and safety profiles. The currently available options are not as effective or safe as users expected. The willingness to pay for the medications is lower than the market price. (4)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**The uptake of evidence based recommendation was low; but the nicotine patch was the most available and implemented option.** Rothrauff et al. conducted a study using counsellor-level data on 658 counsellors from 11 substance abuse treatment programs affiliated with 26 treatment organizations across the USA. The study suggested that most of these substance abuse treatment programs had not adopted evidence-based tobacco cessation medications. The results showed that 16% of programs prescribed varenicline, 11 prescribed bupropion, and 25% for the nicotine patch.(29) Muilenburg 2015 reported similar results: the nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, the most frequently implemented treatment was the nicotine patch, which was used with an average of 2.10 adolescents. Bupropion and varenicline were used with an average of 0.48 and 0.22 adolescents, respectively.(30)	Longer therapy would be acceptable to prescribers/providers. Patients who tolerate short-term therapy seem likely to tolerate continuing therapy. However, there may be reluctance to begin a prolonged therapy due to the burden. Therapy is not usually described as a specific duration, rather it is described as being long as needed. There is no acceptability data for prolonged therapy.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	**Compared with the nicotine patch, bupropion and varenicline are less available.** Gifford et al. conducted interviews with staff from Veterans Health Administration substance use disorder residential treatment programs. This qualitative study suggested	The intervention is not as feasible to implement.

○ Yes ○ Varies ○ Don't know	that all programs offered nicotine replacement therapy, with patches or gum as their primary options. Most programs provided bupropion, but fewer programs provided varenicline.(31) In addition, pregnant smokers supported nicotine replacement therapy being offered of pregnant smokers.(32) According to Muilenburg et al., the nicotine patch is the most available and most implemented option. In a cross-sectional survey on 63 counsellors working in 22 adolescent-only treatment programs, nicotine patches were available for 25 of 63 (39.68%) counsellors. The most available non-nicotine replacement therapy was bupropion (29.63%). Comparatively, only 10.17% of the counsellors had access to varenicline.(30) **Barriers existed for the introduction of smoking cessation programs.** May et al. conducted semi-structured interviews with healthcare professionals and concluded that financial implications, lack of knowledge and safety issues were barriers for hospital-based nicotine replacement therapy as a secondary prevention strategy in the acute cardiac setting.(33) Patient willingness may be a barrier too. Tilea et al. reported that despite precarious physical and psychological health, efficient treatment, and access to smoking cessation programs in hospital, a very high proportion (30.3%) of patients hospitalized for COPD exacerbation were still unwilling to quit smoking following the evidence-based recommendation.(34) Cost, especially greater out-of-pocket payment for varenicline, was associated with suboptimal adherence to varenicline and less refilling.(35) **However, quality improvement project showed the feasibility of improving the uptakes of pharmacotherapy for smoking cessation.** Chen et al. reported a quality improvement project on patients with serious mental illness at community mental health centers. Pre- and post-implementation data from pharmacy and medical records suggested the percentage of patients receiving cessation medication increased from 5% to 18%.(36)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important	No important uncertainty or variability			

	JUDGEMENT						
			uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For tobacco-dependent adults for whom treatment is being initiated, the ATS guideline panel **recommends** offering extended duration **(greater than 12-weeks)** over standard duration of treatment **(6 to 12-weeks) (strong recommendation based on moderate certainty in the evidence about effects).**

Remarks:
Extended, >12 weeks of pharmacotherapy provides a large benefit compared to standard, <12-week treatment courses, with increased abstinence and decreased relapse rates, which is favorable.

Justification

The panel concluded that 1) >12 weeks of pharmacotherapy provides a large benefit compared to standard, <12-week treatment courses, with increased abstinence and decreased relapse rates, and 2) extended duration and standard duration therapy had a similar risk of AE. As a result, the panel made a strong recommendation for extended duration treatment of tobacco dependence beyond 3 months, including regimens of up to 12 months in duration.

Subgroup considerations

None.

Implementation considerations

Medication costs differ significantly based upon drug class and availability of generic alternatives, and these differences create economic barriers to implementation for uninsured populations.

Monitoring and evaluation

None.

Research priorities

Further well designed and large randomized clinical trials are needed comparing extended versus standard treatment. While extended duration therapy for tobacco dependence is effective and safe, the optimal duration of treatment for each drug within specific populations is unknown. Benefits of pharmacotherapy are evident in studies of treatment for up to 12 months, but additional studies of long-term and maintenance therapy are needed.
Studies evaluating the factors influencing long-term adherence could shed light on novel methods for improving maintenance outcomes.

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