COPD

Ask: "Are you willing to try quitting?"

YES:

- **S** ...Set a quit date
- **T** ...Tell family & friends
- **A** ...Anticipate challenges
- **R** ...Remove tobacco items
- **T** …Tobacco replacements?

NO:

Here to help if you change your mind

Slide stolen from Adil Virani

Smoking cessation

Physician advice - baseline 2-3% increases it by - 1-3%

"How do you feel about stopping smoking?"; and listening empathetically for just 30-40 seconds)

Abstinence for at least 6 months		
Baseline/placebo	10-15%	
Motivational interviewing	1.27	
Nicotine (overall)	1.58	
Nicotine gum	1.43	2 and 4 mg
Oral lozenges	1.9	1,2, 4 mg
Inhaler	1.9	
Nicotine patch	1.66	7,14, 21 mg 24h patch
Nasal spray	2.02	
Nortriptyline	2.03	10 mg up to 100 mg/day
Bupropion	1.69	150 mg/day **
SSRI	ND	
Nicotine plus bupropion/nortriptyline	ND	
Bupropion vs varenicline	0.66	Varenicline 0.5 mg BID**

likelihood of cessation is greater when motivated, self-referred patients are treated

** different than in CPS

The correct dose for bupropion

Bupropion

Study design

1 year RCT – 742 patients

Dose

Placebo or bupropion SR 100, 150 or 300mg/day for seven weeks

New Engl J Med 1998; 337:1195-202

The correct dose for bupropion is 150 mg daily

Point prevalence smoking cessation rates

Percentage of subjects not smoking -daily dose

	Plac	100mg	150mg	300mg	p value
6 weeks	19.0	28.8*	38.6*	44.2*	< 0.001
3 months	14.4	24.2*	26.1*	29.5*	< 0.001
6 months	15.7	24.2	27.5*	26.9*	0.02
12 months	12.4	19.6	22.9*	23.1*	0.01

* Versus placebo

New Eng J Med 1998; 337:1195-202

CMAJ ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

Oct 4, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Placebo-Controlled Trial of Cytisine for Smoking Cessation

Cytisine (extracted from the seeds of Cytisus laborinum L.)

vs placebo - 25 days - 740 smokers

six 1.5-mg tablets per day (one tablet every 2 hours) for 3 days (days 1 through 3), five tablets per day for 9 days (days 4 through 12), four tablets per day for 4 days (days 13 through 16), three tablets per day for 4 days (days 17 through 20), and two tab- lets per day for the final 5 days (days 21 through 25). The target quit date was scheduled for the fifth day.

Abstinence for 12 months - 8.4% vs 2.4%

Any gastrointestinal event - 14% vs 8%

N Engl J Med 2011; 365:1193-1200

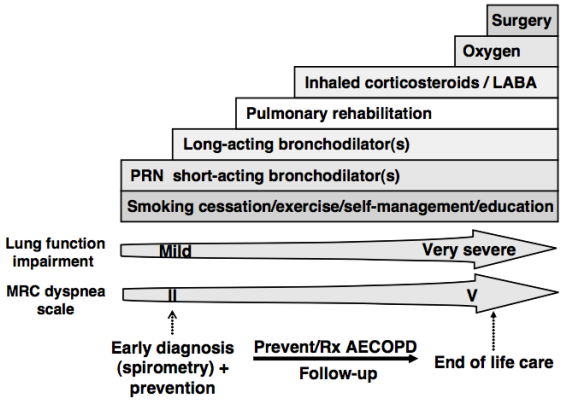
Smoking cessation

	Harm	
Nicotine gum	Dyspepsia (9%), Nausea (9%), Hiccups (10%), Headache (11%), Jaw pain, Denture issues, Throat irritation (5%)	
Nicotine Inhaler	Throat irritation, Sneezing, Coughing, Rhinitis, Pharyngitis	
Nicotine patch	Headache, Disturbed sleep, Site rash	
Nortriptyline	Dry mouth blurred vision, Constipation, Sedation, Confusion, Urinary retention	Least expensive
Bupropion	Insomnia (20%), Dry mouth (10%), Disturbed concentration (9%), Nausea (9%), Constipation (8%), Seizures (1%), Angioedema	
Varenicline	Nausea (30%), Headaches, Abnormal dreams, Constipation, Suicidal ideation?	

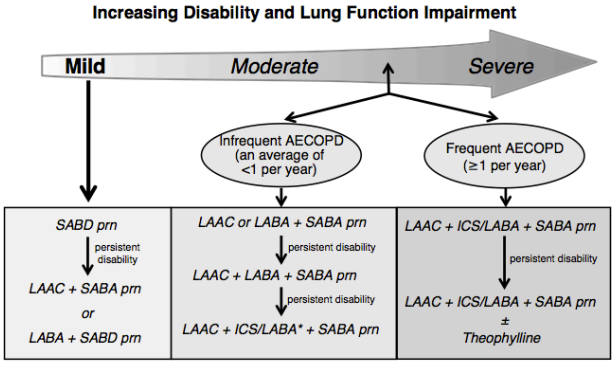
Benefit vs Harm vs Cost vs inconvenience

ACUTE COPD EXACERBATION

	BENEFIT	HARM	Costs (choose least expensive)	Inconvenience
O_2 (but be careful-may need low pO2 to breath)	Immediate relief	SEE ASTHMA		
SABA	Immediate relief			
SAAC	Not many trials comparing SABA and SAAC			
Corticosteroids	Fewer treatment failures - 20% vs 10% 1.5 days less hospitalization			
Methylxanthines	Don't work			
Systemic Antibiotics	If moderate/severe Mortality 14% vs 3% Treatment failure 58% vs 28%	More adverse events 8% vs 22% - diarrhea, skin rash	ABXs used in studies - amoxicillin, amoxicillin/clavulanate, TMP/SMX, ampicillin, penicillin, chloramphenicol, cefaclor, ofloxacin	Oral, IM, IV



Can Respir J Vol 15 Suppl A January/February 2008



Can Respir J Vol 15 Suppl A January/February 2008

Salbutamol is effective for patients with COPD

Beta agonists do produce significant improvements in symptoms of dyspnea and wheezing in patients with moderate to severe COPD

In studies, the risk of dropping out (i.e. treatment failure) when on treatment with placebo was almost twice that of patients on treatment with beta-2 agonists 22% versus 46%

Patients preferred beta-2 agonist therapy more frequently than placebo 57% versus 9%

Main endpoints - usually 1-3 years

	Exacerbations		Mortality	Hospitalized	Pneumonia	ΔSGRQ -100 Δ in score of 4 = small clinical difference	Candidiasis other SE
	Per year	Patients					
Baseline/placebo	1.4	45%	10-15 %	10%	6-7%	≈ 50	1-2%
ICS	0.81 RR	ND	ND	?	?	-1.22	2.49 RR 1.95 Hoarseness
ICS vs LABA	ND	ND	ND	ND	1.42 RR	-0.74 favours ICS	?
ICS/LABA	0.74 RR	ND	0.79 RR	?	1.83 RR	-2.9	5.73 RR
ICS/LABA vs ICS	0.91 RR	ND	0.76 RR	?	ND	-1.3 favours combo	ND
LABA/ICS vs LABA	0.82 RR	ND	ND	ND	1.58 RR	ND	4.28 RR
Tiotropium (LAAC)	?	0.74 RR	ND	0.64 RR	?	-3.28	5.08 RR dry mouth
Add ICS to LAAC/LABA	?	?	?	?	?	?	?
Add ICS/LABA to LAAC	ND	ND	ND	ND	ND	-2.49	?
Pneumococcal vaccine	ND	?	ND	?	?	?	?
Influenza vaccine	0.75 RR	?	ND	?	?	?	12% local reactions
Oral corticosteroids	?	?	?	?	?	?	?
Roflumilast	0.83 RR	?	ND 2%	ND	ND	ND different scale	diarrhea (5%)and weight loss (10%)

Breathlessness (scale of 1-3) - difference of 0.1 to 0.2
Change in SABA puffs a day - typically 1 less per day

? = data not reported
ND - no statistical difference

Minimally important clinical difference "definition"

Change of 4

1. No longer takes a long time to wash or dress, can now walk up stairs without stopping and go out for entertainment.
2. Things no longer seem to require too much effort, no longer has to stop for rests while doing housework and can now carry things upstairs.
3. No longer has to walk more slowly than other people, no longer breathless on getting washed and dressed or on bending over
4. BUT 4 also = slightly effective

Eur Respir J 2002;19:398–404

AVERAGE CHANGE COMPARED TO PLACEBO
Inhaled CS - 1.22
ICS/LABA - 2.9
Tiotropium - 3.3
LABA - 1.3

Other studies

"There is only a modest benefit of ICS in preventing COPD exacerbations, which is not related to the level of baseline lung function on metaregression analysis. The benefits of ICS in preventing COPD exacerbations thus seem to be overstated"

Chest 2010;137:318–325" – 18% relative reduction in exacerbations

"Withdrawal of FP in COPD patients using SFC resulted in acute and persistent deterioration in lung function and dyspnoea and in an increase in mild exacerbations and percentage of disturbed nights. This study clearly indicates a key role for ICS in the management of COPD as their discontinuation leads to disease deterioration, even under treatment with a LABA"
Thorax 2005;60:480–487

Combined salmeterol and fluticasone versus tiotropium in the treatment of COPD (INSPIRE)

Patients

1,323 patients with COPD - mean age 64, male (81%)– smokers (38%), on ICS (50%) - RDBPC, FEV1 39% predicted

Treatment

stopped all therapy (given pred 30mg and salmeterol BID)

randomised to salmeterol/fluticasone BID or tiotropium once daily

Duration

2 years

Am J Respir Crit Care Med 2008;177:19-26

Clinical Endpoints

	Exacer-bations per year	Exacerbations (%)	Hosp for exacerbations (%)	Mortality (%)	Pneumonia (%)	Withdraw from study (%)	Withdraw due to lack of efficacy (%)	SGRQ Δ in score of 4 (Score out of 100)
Salmeterol/ fluticasone	1.28	62	16	3	8	35	5	46
Tiotropium	1.32	59	13	6	4	42	6	48

Colors indicate SS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

"overall mean between-group difference in the SGRQ total score at any time point was 2.7 (95% confidence interval [CI], 2.0 to 3.3) in favor of tiotropium"

"A higher proportion of patients in the tiotropium group than in the placebo group had an improvement of 4 units or more in the SGRQ total scores from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%)

Table 3. Exacerbations of COPD and Related Hospitalizations.*

Variable	Tiotropium	Placebo	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
Exacerbation†				
Per patient-year — no.	0.73±0.02	0.85±0.02	0.86 (0.81–0.91)	<0.001
Leading to hospitalization — no. per patient-year	0.15±0.01	0.16±0.01	0.94 (0.82–1.07)	0.34
Days per patient-year	12.11±0.32	13.64±0.35	0.89 (0.83–0.95)	0.001
Hospitalization days per patient-year	3.17±0.17	3.13±0.17	1.01 (0.87–1.18)	0.86
Patients with exacerbation — no. (%)‡				
Total	2001 (67.0)	2049 (68.2)	NA	0.35
Leading to hospitalization	759 (25.4)	811 (27.0)	NA	0.18

N Engl J Med 2008;359:1543-54

Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations

Terence A. R. Seemungal[1,2*], Tom M. A. Wilkinson[2*], John R. Hurst[2], Wayomi R. Perera[2], Ray J. Sapsford[2], and Jadwiga A. Wedzicha[2]
[1]Department of Clinical Medical Sciences, St. Augustine Campus, University of the West Indies, St. Augustine, Trinidad and Tobago; and [2]Academic Unit of Respiratory Medicine, University College London, London, United Kingdom

250 mg PO BID -12 months
Baseline exacerbations - 2 exacerbations/yr (median)
0.65 RR
Hospitalizations reduced from 11 to 7% - SS?
No difference in side effects

Am J Respir Crit Care Med 2008;178:1139-47

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

250 mg PO BID -12 months
Baseline exacerbations - 1.83 exacerbations/yr
0.73 RR
SGRQ - 2.8 points
Hospitalizations - no difference
Death - no difference
5% increase in audiogram hearing decrement

N Engl J Med 2011;365:689-98

7,376 patients with moderate to very-severe COPD
75% male, 48% smokers, avg age 63 - one year
Tiotropium 18 mcg daily
Salmeterol 50 mcg twice daily

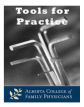
Annual rate of exacerbations
Exacerbation - an increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient's attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospital- ize the patient (criterion for severe exacerbation).

N Engl J Med 2011;364:1093-1103

	Annual rate of exacerbations	% with > 1 exacerbation	% severe exacerbations	% serious adverse events (Resp)
Tiotropium	0.64	34.4	7.1	8.1
Salmeterol	0.72	38.5	9.2	10.0

No difference in mortality

April 30, 2012



Which is the best puffer for initial therapy in COPD?

Clinical Question: Which puffer has the greatest impact on clinical outcomes as the first-line long-acting inhaled treatment for COPD?

Bottom-line: "The available evidence indicates that tiotropium is likely the best initial long-acting therapy for COPD, followed by a LABA (like salmeterol)"

Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease

"There was insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination (LABA plus ICS) therapy. More studies comparing these therapies are needed. The use of triple therapy decreases the number of COPD hospitalizations, improves lung function, and improves the quality of life of patients with moderate-to-severe COPD, compared with tiotropium alone."

Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial

"Participants in the intervention group were trained to detect and treat exacerbations promptly, with ongoing support for 12 months"

"Supported self management had no effect on time to first readmission or death with COPD"

BMJ 2012;344:e1060

Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies

16 RCTs AND 7 OBSERVATIONAL STUDIES - over 3 years - 20-25% INCREASE IN FRACTURES - an NNH of 83

Thorax 2011;66:699-708

The right approach?

FIRST - don't smoke - if you do - nortriptyline low dose - patient ultimately chooses the way however

"At this stage, people with COPD should use the bronchodilator that gives them the most improvement in their symptoms - Cochrane Library 2006

"considering that, historically, the severity of COPD has been classified according to FEV1, which may not correlate directly with symptoms and, consequently, a symptomatic approach to therapy using clinical stages may be more useful, physicians should individualize treatment and try an additional type of drug if the patient symptomatically needs for something else to be tried, and yet stop the additional drug if it does not seem to help" - Chest 2008;134;223-5

If I had COPD I would use a SABA then try either a LABA or tiotropium, then ICS or ABX

Exacerbation - salbutamol, steroids (prednisone), basically any antibiotic