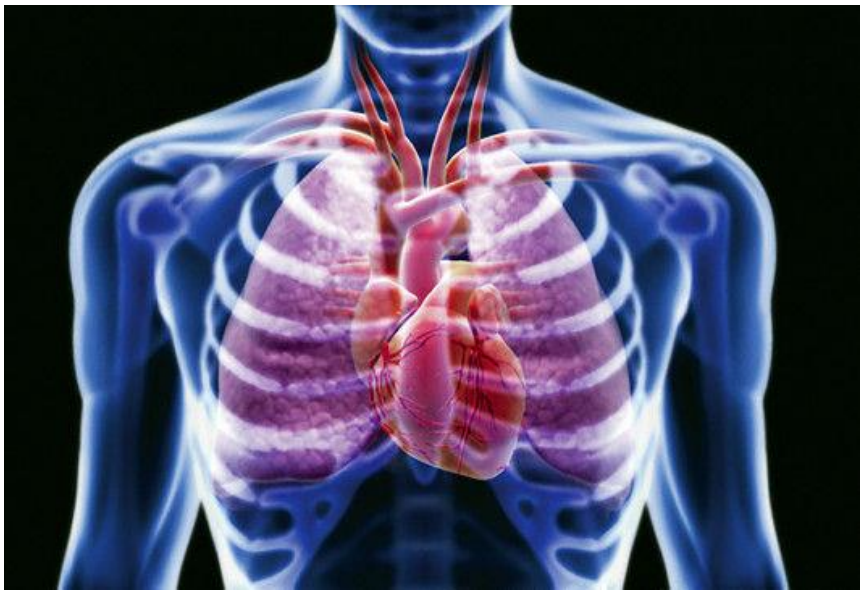
Inhaled Anticholinergic Therapy and Cardiovascular Safety



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Learning Objectives

1. Describe the pathophysiology of chronic obstructive pulmonary disease (COPD).
2. Based on the 2014 GOLD guidelines, discuss treatment options for management of stable COPD, including the role of inhaled anticholinergic therapy.
3. Explain the proposed mechanism for cardiovascular adverse effects associated with inhaled anticholinergic therapy.
4. Evaluate the evidence describing cardiovascular risk with use of inhaled anticholinergic therapy.

Chronic Obstructive Pulmonary Disease (COPD)

1. What is COPD?[1]
    a. Persistent airflow limitation
        i. Progressive: preventable and treatable disease
        ii. Chronic inflammatory response to noxious stimuli
            1. Leads to structural changes and narrowing of the small airways
                a. Decrease in forced expiratory volume in one second (FEV_1)
            2. Structural changes – loss of alveolar attachments and decreased elastic recoil
        iii. Overall severity determined by exacerbations and comorbidities
        iv. Airflow limitation consists of two parts
        (Contribution of each part to overall disease is different between persons)
            1. **Obstructive bronchiolitis** – small airway disease
                a. Defined by cough and sputum production for ≥ three months
                    i. Due to structural changes plus mucous hyper-secretion
            2. **Emphysema** – parenchymal destruction
                a. Destruction of the gas-exchanging surfaces of the lung
                    i. Leads to hypoxemia/hypercapnia

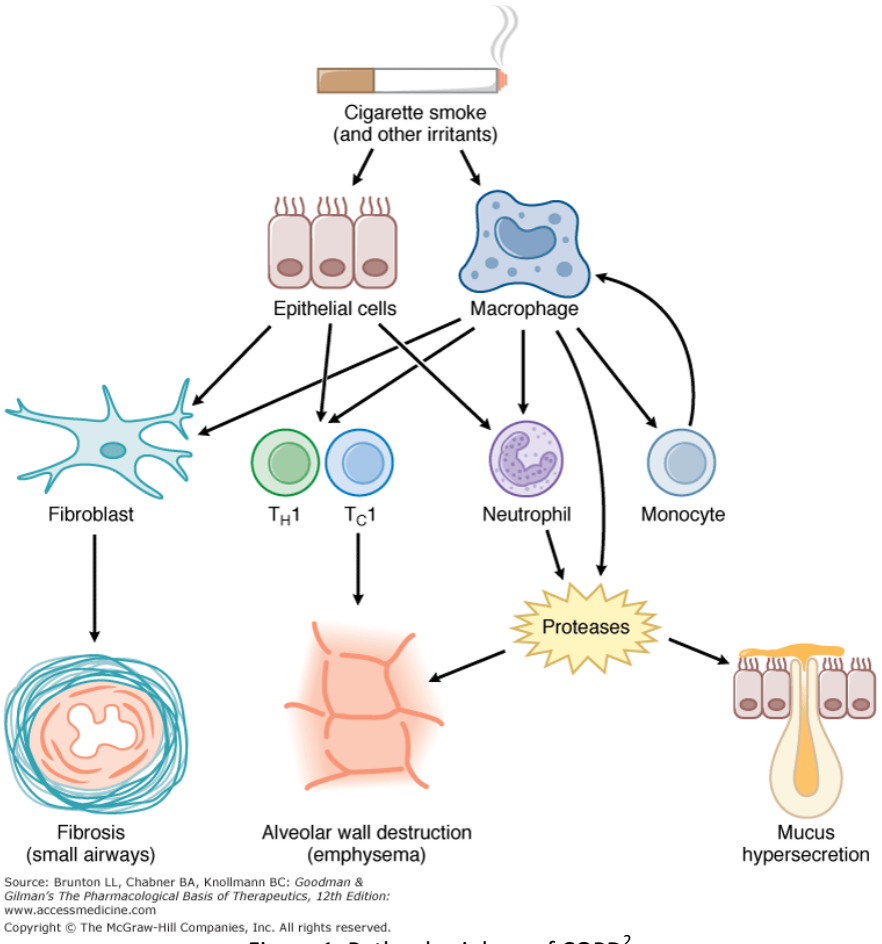


Figure 1: Pathophysiology of COPD[2]

b. Risk (Influencing) Factors[1]
    i. Gene-environment interaction
        1. Severe hereditary deficiency of alpha-1 antitrypsin
            a. Inhibitor of serine proteases
    ii. Environment – exposure to noxious particles
        1. Cigarette smoking
        2. Pollution – indoor and outdoor
        3. Occupational exposures – chemicals, dust
    iii. Age and gender
        1. Aging cells in the lungs mimic structural changes that occur in COPD
    iv. Lung growth and development
c. Prevalence[3]
    i. 14.8 million people diagnosed with COPD in 2010 in the United States (US)
    ii. Estimated 12 million people undiagnosed with COPD

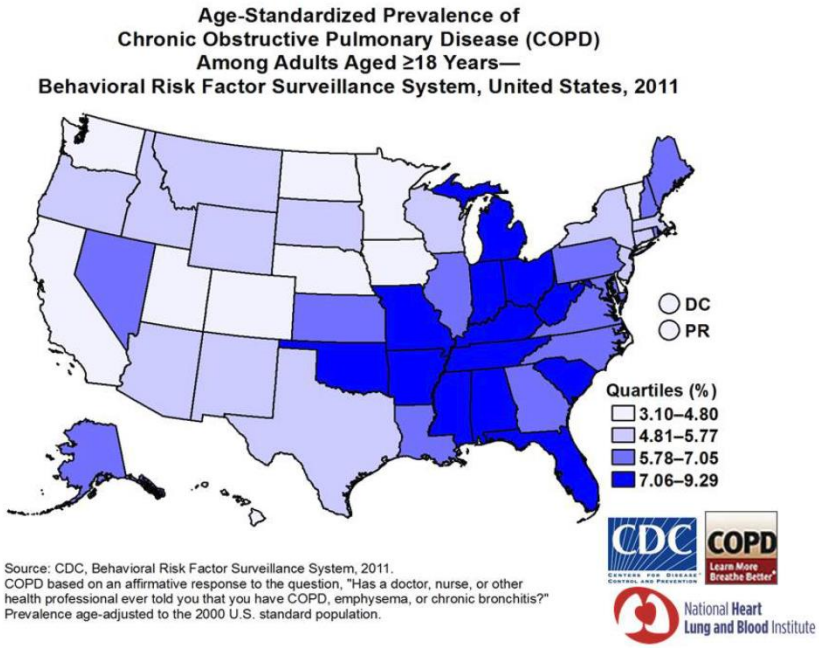


Figure 2: Map COPD prevalence in the US[4]

d. Morbidity and Mortality
    i. Third leading cause of death in world in 2012[5]
    ii. Third leading cause of death after heart disease and malignant neoplasm in United States[6]
    iii. Number of deaths from COPD are increasing from 1950 to 2008[3]
        1. Other causes of death, including heart disease and stroke, are stable or declining
    iv. COPD accounts for more than half of all deaths from lung disease
e. Economic Burden[3]
    i. COPD was second in number of inpatient hospital care days
    ii. Annual cost of COPD estimated at $30 billion in the United States

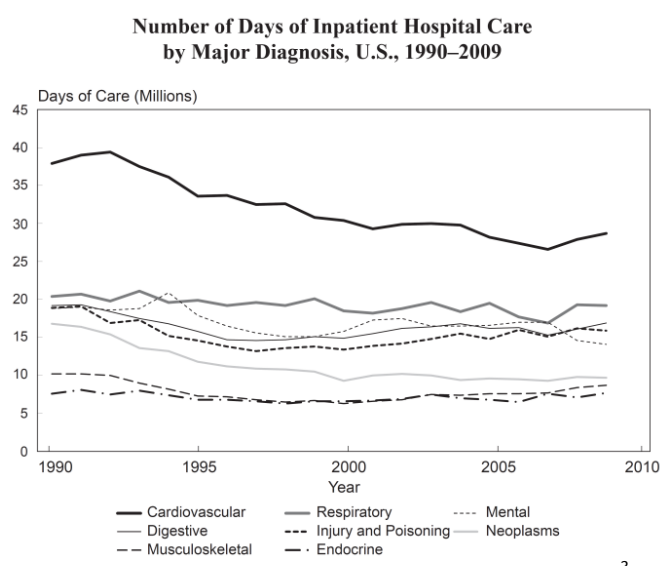


Figure 3: Number of hospital days by major diagnosis[3]

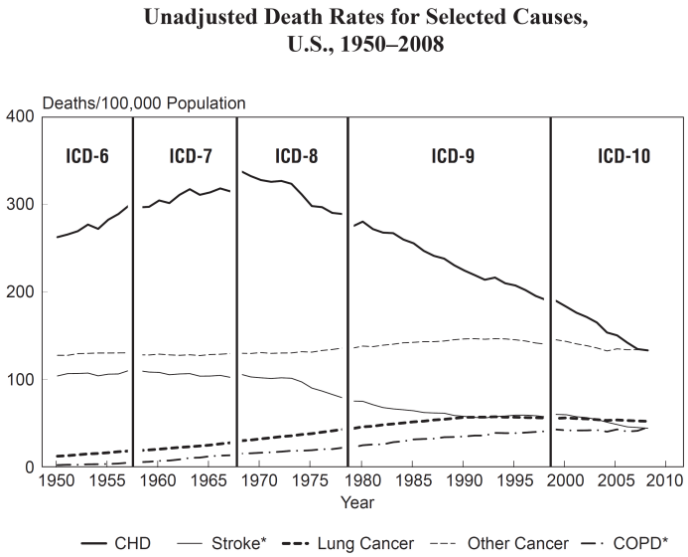
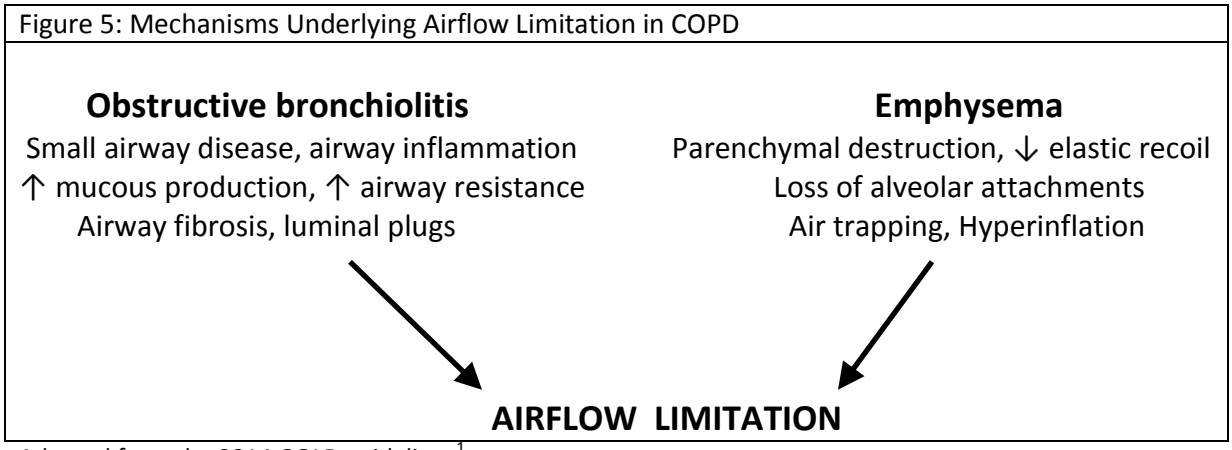


Figure 4: Death rates for leading causes[3]

Diagnosis of COPD

Figure 5: Mechanisms Underlying Airflow Limitation in COPD



Adapted from the 2014 GOLD guidelines[1]

1. Symptoms[1]
    a. Dyspnea: persistent, progressive, worse with exercise
    b. Chronic cough: can be intermittent and non-productive
    c. Chronic sputum production
    d. Exposure to risk factors
        i. Tobacco smoke
        ii. Smoke from domestic sources (cooking and heating fuels)
        iii. Occupational dusts and chemicals
        iv. Family history of COPD
2. Assessment of Disease[1]
    a. Determine severity of disease
        i. Current symptoms (appendix 1)
            1. COPD Assessment Test (CAT)
            2. COPD Control Questionnaire (CCQ)
            3. Modified British Medical Research Council (mMRC)

ii. Spirometric abnormality: classifies airflow severity in COPD
iii. Exacerbation risk
    1. Hospitalizations for AECOPD associated with increased risk of death
iv. Presence of comorbidities
    1. Comorbidities often have significant impact on quality of life, exacerbation frequency, and survival[7]
    2. Cardiovascular disease is a leading cause of morbidity and mortality in COPD[8]

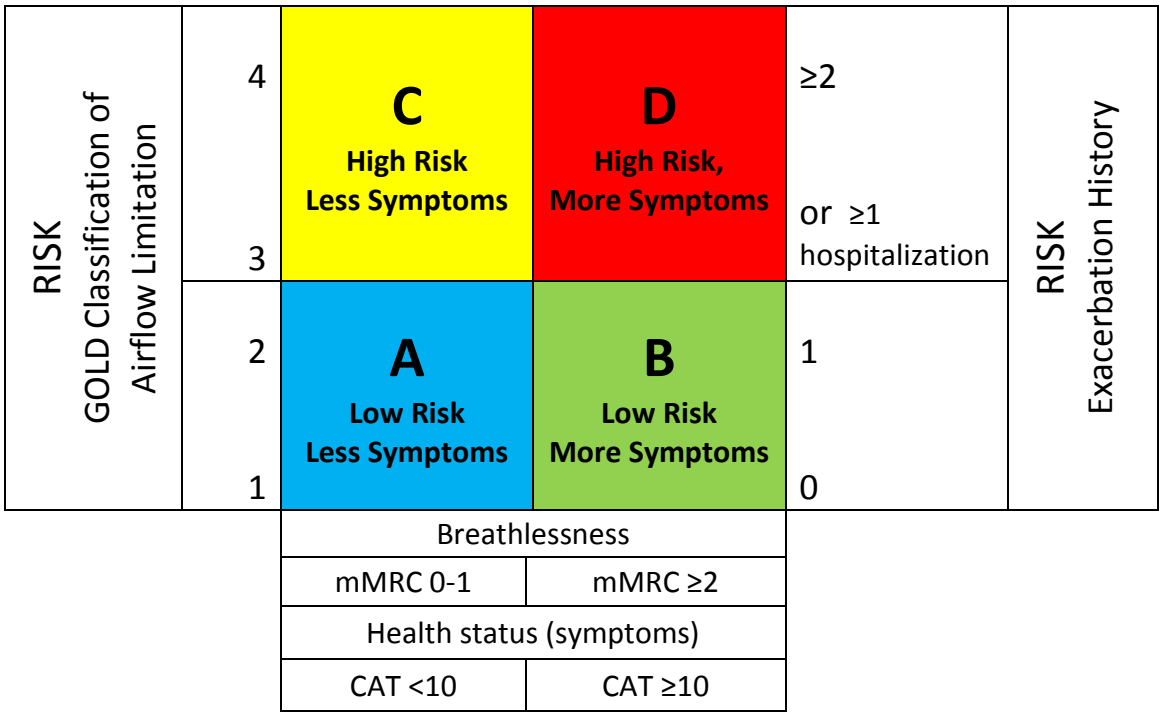
3. Spirometry[1]
    a. Persistent airflow limitation (COPD) defined by post-bronchodilator $FEV_1/FVC < 0.70$ (Table 1)
    b. Objective measurement that can be reproduced

Table 1: Classification of Severity of Airflow Limitation (Based on Post-Bronchodilator FEV_1)	
In patients with $FEV_1/FVC < 0.70$	
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

Adapted from 2014 GOLD guidelines[1]

4. Risk Assessment[1]
    a. Use measurement of symptoms, classification of airflow limitation, and exacerbation history to determine risk
        i. Choose highest risk score for airflow limitation and exacerbation history

Figure 6: Combined COPD Assessment. Adapted from the 2014 GOLD guidelines[1]



Management of Stable COPD

I. Goals of stable COPD treatment[1,9]
   a. Reduce symptoms: reduce symptoms, increase exercise tolerance, improve health status
   b. Reduce risk: decrease mortality, prevent acute exacerbation, slow disease progression

II. Overview of Pharmacologic Therapy[1]
   a. Bronchodilators
      i. Use
         1. Mainstay therapy for symptom management
         2. Indicated in all COPD patients either as-needed basis or scheduled
         3. Demonstrated to decrease COPD exacerbation rates
      ii. $Beta_2$-agonists
         1. Short acting beta2-agonists (SABA)
            a. albuterol, levalbuterol
         2. Long acting beta2-agonists (LABA)
            a. formoterol, aformoterol, salmeterol, indacaterol
      iii. Anticholinergics
         1. Short acting anticholinergics (SAAC)
            a. ipratropium
         2. Long acting anticholinergics (LAAC)
            a. tiotropium, aclidinium
      iv. Methylxanthines
         1. aminophylline, theophylline
      v. Combination bronchodilators
         1. albuterol/ipratropiuum
   b. Corticosteroids
      i. Use
         1. Indicated in COPD patients with FEV_1 <60% predicted
         2. Maintenance treatment improves symptoms, lung function, and QOL, and reduces exacerbation frequency
         3. Does not change the long-term decline of FEV_1 or mortality
      ii. Inhaled corticosteroids (ICS)
         1. fluticasone, budesonide, beclomethasone
         2. Combination ICS with SABA, LABA
      iii. Systemic
         1. prednisone, methylprednisolone
   c. Phosphodiesterase-4 (PDE-4) Inhibitor: roflumilast
      i. Use
         1. MOA: decreases inflammation by inhibiting breakdown of cyclic AMP
         2. Reduces risk of exacerbations in patients with severe COPD based on airflow limitation (FEV_1 <50% predicted), chronic bronchitis, and history of exacerbations
         3. Should always be used in combination with a long-acting bronchodilator

III. Treatment Selection

Table 2: Initial Pharmacologic Management of COPD

Patient Group	Recommended	Alternate Choice
A	• SABA prn • SAAC prn	• LAAC • LABA • SABA + SAAC
B	• LABA • LAAC	• LABA + LAAC
C	• ICS + LABA • LAAC	• LABA + LAAC • LAAC + PDE4 • LABA + PDE4
D	• ICS + LABA • LAAC • ICS + LABA + LAAC	• ICS + LABA + LAAC • ICS + LABA + PDE4 • LABA + LAAC • LAAC + PDE4

SABA = short-acting beta$_2$ agonist; SAAC = short-acting anti-cholinergic;
LABA = long-acting beta$_2$ agonist; LAAC = long-acting anti-cholinergic;
ICS = inhaled corticosteroid; PDE4 = Phosphodiesterase-4 inhibitor

Adapted from the 2014 GOLD guidelines[1]

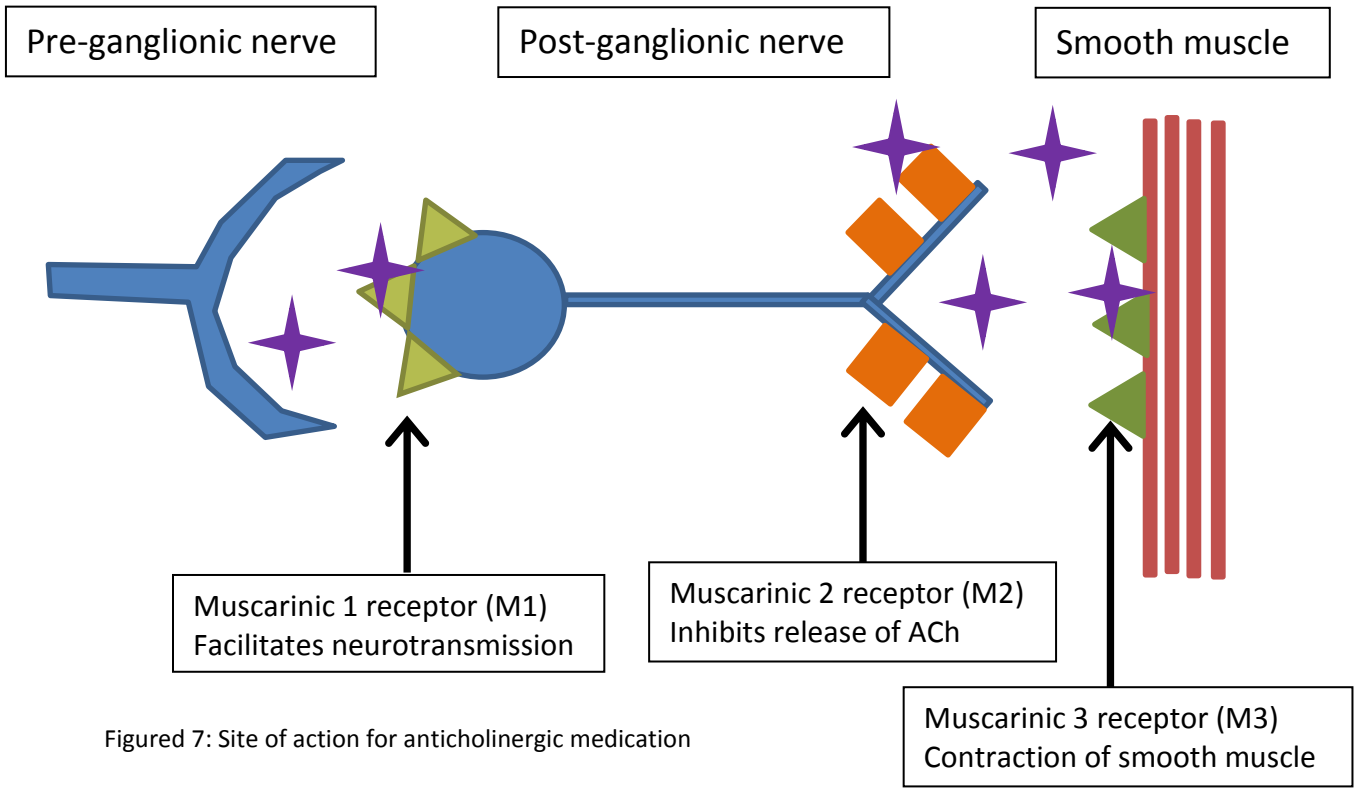
Role of Inhaled Anticholinergics

I. Inhaled anticholinergic treatment options
   a. Short-acting
      i. Atrovent (ipratropium)
   b. Long-acting
      i. Spiriva (tiotropium) via Handihaler®
      ii. Spiriva (tiotropium) via Respimat®
      iii. Tudorza™ Pressair™ (aclidinium)
   c. Class side effects[10]
      i. Precautionary/warning labeling
         1. May worsen bladder neck obstruction, narrow angle glaucoma, and urinary retention
         2. Anticholinergic side effects in renal impairment (creatinine clearance ≤50mL/min)
      ii. Side effects
         1. Common: xerostomia ~16%, pharyngitis ~11%, urinary tract infection ~7%
   d. Efficacy

Table 3: Efficacy of inhaled anticholinergic treatment in COPD[1,11]

	FEV_1	Improved Lung Function	Decreased Hospitalizations	Improved symptoms	QOL	Decreased exacerbation rate
SAAC (ipratropium)	X					
LAAC (tiotropium)		X	X	X	X	X

e. Mechanism of action (MOA)[10,12]
   i. Ipratropium – block acetylcholine from binding to M1, M2, and M3
   ii. Tiotropium – block acetylcholine from binding to M1 and M3
   iii. Aclidinium – block acetylcholine from binding to M1-M5



Figured 7: Site of action for anticholinergic medication

II. Chemical structures[13-16]

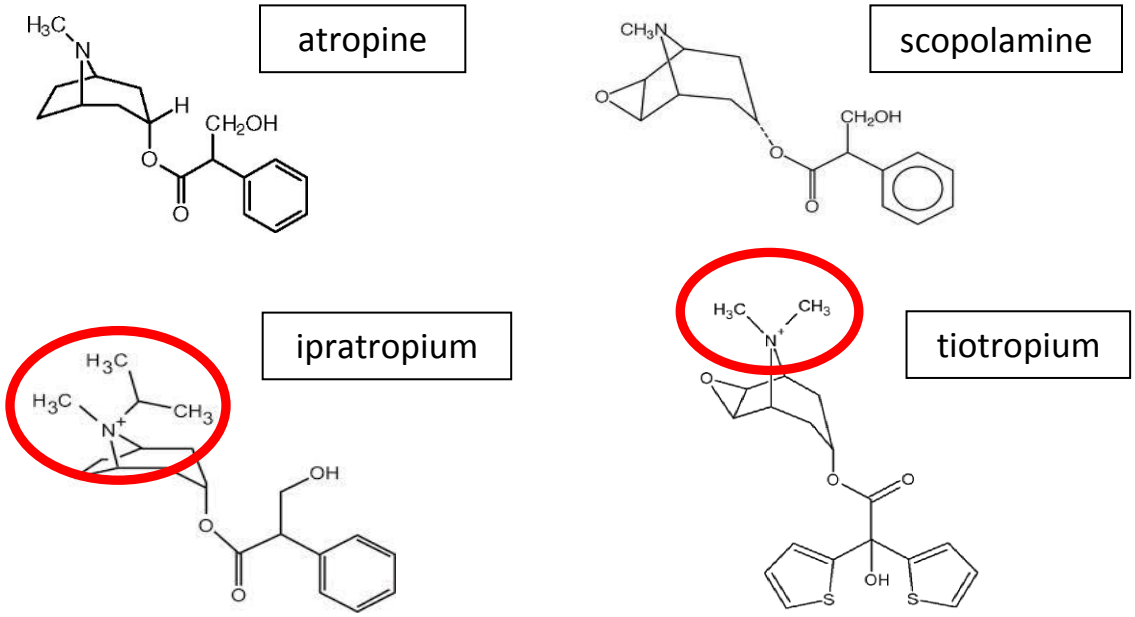


Figure 8: Chemical structures of atropine, scopolamine, ipratropium, and tiotropium

III. Pharmacokinetics
   a. Absorption[10,12,17]
      i. Tiotropium Respimat® – 33%
      ii. Tiotropium Handihaler® – 19.5%
      iii. Ipratropium – 7%
      iv. Aclidinium – 6%
   b. Renal excretion[10]
      i. Respimat® – 18.6% unchanged
      ii. Handihaler® – 14% unchanged
      iii. Tiotropium intravenous – 74% unchanged

Controversy over Use of Inhaled Anticholinergic Agents

I. Controversy arises from potential cardiovascular (CV) side effects from inhaled anticholinergic affecting the vagus nerve negative feedback loop.
II. Evidence of systemic absorption of inhaled anticholinergic therapies
   a. Pharmacokinetic evidence
   b. Side effect profile and precautions support biologic plausibility of systemic effects

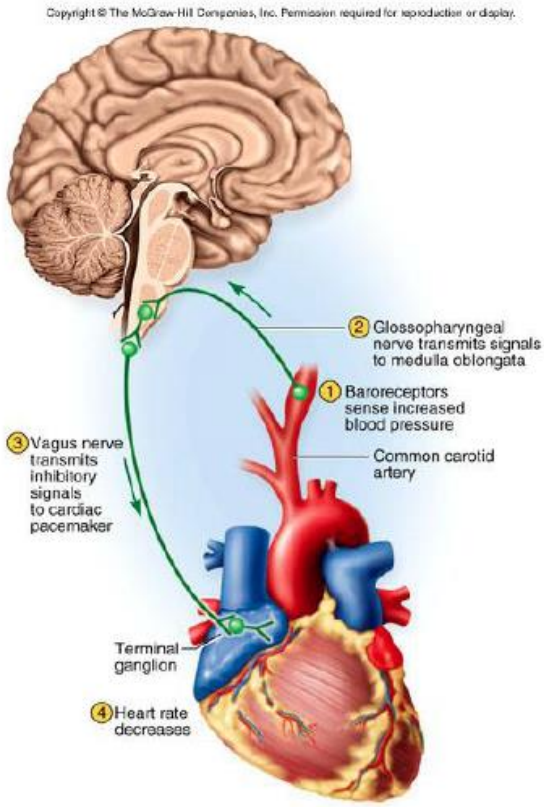


Figure 9: Vagus nerve negative feedback loop[18]

III. Clinical questions
   a. Is use of anticholinergic therapy in patients with COPD associated with increased CV mortality?
   b. Should patients be stratified by CV risk before deciding to use inhaled anticholinergic therapy when treating COPD?

Timeline

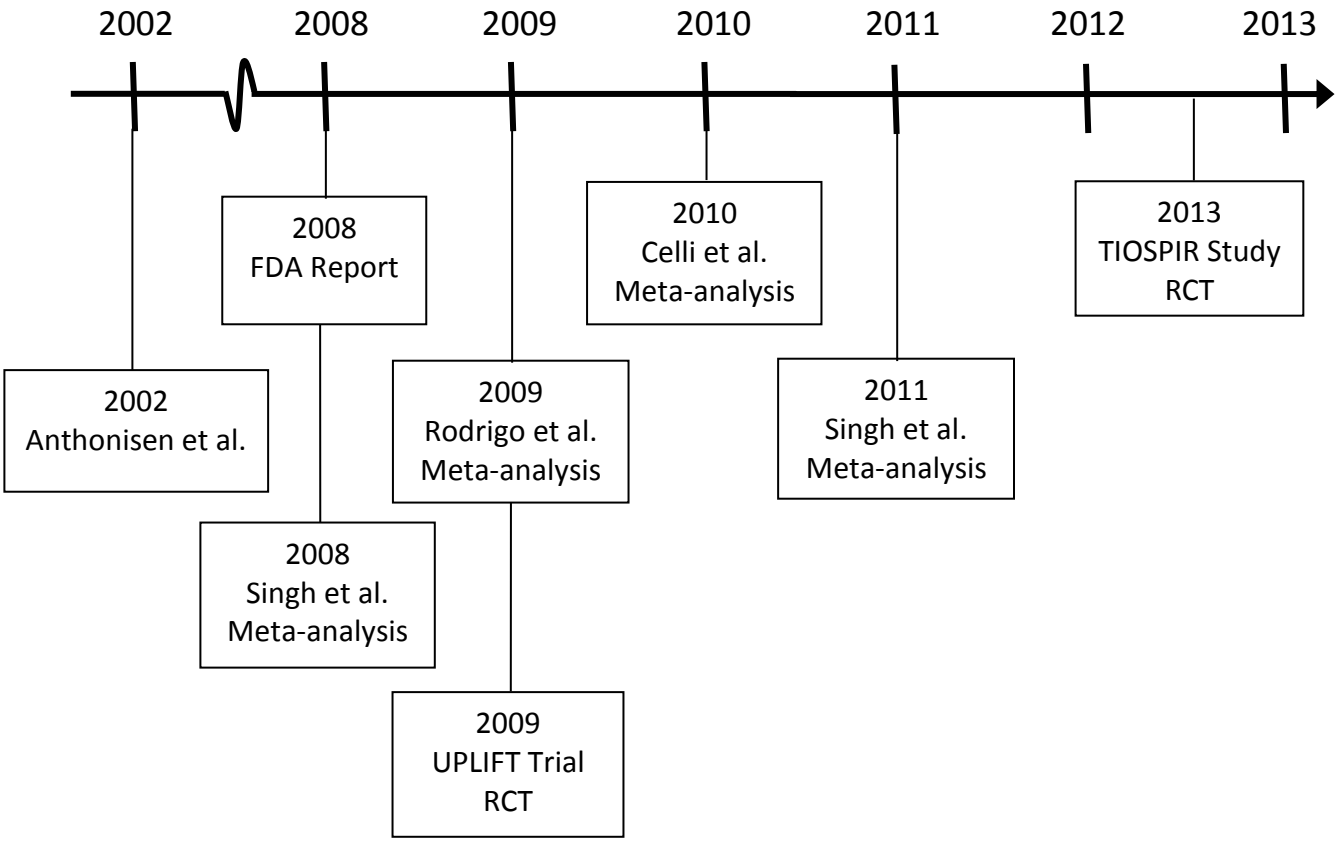


Figure 10: Timeline of anticholinergic studies discussed below

<table>
<tr><td colspan="2">Table 4
2002 Anthonisen et al.[19] – Hospitalizations and mortality in the Lung Health Study (LHS)</td></tr>
<tr><td>Study design</td><td>Randomized, controlled trial (RCT), five-year</td></tr>
<tr><td>Number</td><td>5,887</td></tr>
<tr><td>Objective</td><td>Compare the rates of hospitalization and mortality in the LHS</td></tr>
<tr><td>Inclusion</td><td>• Age 35-60 years old
• Current smoker</td></tr>
<tr><td>Exclusion</td><td>• Myocardial infarction (MI) or stroke in past two years
• Other important medical condition (e.g., hypertension)
• Binge drinker or >25 drinks/week</td></tr>
<tr><td>Treatment</td><td>Ipratropium + smoking intervention (n=1,961)
Placebo + smoking intervention (n=1,962)
No intervention (n=1,964)</td></tr>
<tr><td>Outcomes</td><td>Secondary: incidence of respiratory and CV morbidity and mortality</td></tr>
<tr><td>Statistics</td><td>Differences between group pairs were not adjusted for multiple comparisons
All tests were two sided
Cox regression used with adjustment for baseline covariates to estimate relative hazards associated with treatment group, smoking status, and inhaler use</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Ipratropium + smoking intervention</th><th>Placebo + smoking intervention</th><th>No intervention</th><th>p value</th></tr>
<tr><td>CV death</td><td>18 (0.92%)</td><td>7 (0.36%)</td><td>12 (0.61%)</td><td>0.084</td></tr>
</table>
p=0.027 between ipratropium vs placebo group (unadjusted)
</td></tr>
<tr><td>Author’s Conclusion</td><td>There were no significant differences in CV morbidity and mortality between groups. There was an association found for coronary and CV disease to be more common in the ipratropium group compared to placebo.</td></tr>
<tr><td>Take Home Points</td><td>• Mortality was a secondary outcome
• Presence of COPD was not required for inclusion
• No differences reported in baseline groups or smoking behavior
• No dose effect on CV outcomes were seen between groups (compliance did not correlate with CV events)
• 6/9 patients with supraventricular tachycardia reported high adherence at time of hospitalization (compared to entire group)
• Follow-up analysis[20] showed increase CV events concentrated among patients randomized to ipratropium who were not adherent</td></tr>
</table>

Table 5 2008 Singh et al.[21] – Inhaled anticholinergics and risk of major CV events in COPD	
Study design	Meta-analysis (17 trials)
Number	14,783 participants
Objective	Determine CV risks associated with long-term use of inhaled anticholinergics in patients with COPD
Inclusion	• RCT of any inhaled anticholinergic with >30 days follow-up • Any severity of COPD • Inhaled anticholinergic vs control (active or placebo) • Report data on CV adverse events (MI, stroke, CV death)
Exclusion	None
Treatment	12 trials compared tiotropium vs control 5 trials compared ipratropium vs control 9 trials compared either anticholinergic vs placebo
Outcomes	Primary: composite CV event (CV death, MI, stroke) Secondary: all-cause mortality
Statistics	Statistical heterogeneity between studies tested by I^2 statistic Fixed-effects models used if no substantial heterogeneity present Sensitivity analysis done using random effects model
Results	**Primary** <u>Composite CV event (CV death, MI, stroke)</u> • 17 trials: RR 1.58 (1.21-2.06), p<0.001, I^2 = 0%; NNH=167 • 5 trials (>6 months): RR 1.73 (1.27-2.36), I^2 = 0%, p<0.001; NNH=91 <u>CV Death</u> • 12 trials: RR 1.80 (1.17-2.77), p=0.008, I^2 = 0%; NNH=233 <u>Myocardial Infarction</u> • 11 trials: RR 1.53 (1.05-2.23), p=0.03, I^2 = 0%; NNH=239 **Secondary** <u>All-cause mortality</u> • 17 trials: RR 1.26 (0.99-1.61), p=0.06, I^2 = 2%
Author's Conclusion	Inhaled anticholinergics significantly increase the risk of CV events in patients with COPD.
Take Home Points	• First meta-analysis to investigate anticholinergics and CV outcomes • Two trials were the driving force for the outcomes • Excluded 2 trials that reported no events between groups • Study results adjusted after publication based on double counting patients • Risk of possible CV side effects versus benefits (NNT=21 for prevention of COPD exacerbations; NNT=20 for prevention of COPD-related hospitalization) • No difference in all-cause mortality between groups • Reporting of CV events may not have been complete • Eight of the studies included had ≤2 CV events reported in the trial • Included placebo controlled trials that had higher drop-out rates; selection bias against inhaled anticholinergic treatment (i.e., severe patients more likely to discontinue placebo than patients with less severe symptoms)

Table 6
2009 Rodrigo et al.[22] – Evaluation of tiotropium HandiHaler® safety

Study design	Meta-analysis (19 randomized controlled trials)
Number	18,111 participants
Objective	Evaluate the safety of tiotropium HandiHaler® in patients with COPD
Inclusion	• >35 years old • Stable COPD per GOLD diagnostic criteria • Inhaled tiotropium vs control - control: placebo, LABA, or LABA + ICS • Study of >4 weeks duration • RCT
Exclusion	Only had to meet inclusion criteria
Treatment	• Tiotropium vs placebo (15 trials) • Tiotropium vs control (4 trials) – 2 trials compared tiotropium vs salmeterol/fluticasone – 1 trial compared tiotropium vs salmeterol – 1 trial compared tiotropium vs salmeterol vs placebo • Trial duration – 7 long-term trials (28 weeks – 2 years) – 12 short-term trials (8 weeks – 24 weeks)
Outcomes	Baseline characteristics: mean age 65 years; mean FEV_1 41% Primary: Composite CV event (MI, stroke, CV death), individual CV events Secondary: All-cause mortality
Statistics	Heterogeneity between studies tested by two separate methods. If no substantial heterogeneity found then fixed-effects model used
Results	**Primary**

	tiotropium	active-control	RR (95% CI)	I^2 statistic
Composite CV	3.6%	4.0%	0.96 (0.82-1.12)	6%
CV death	1.7%	1.9%	0.93 (0.73-1.20)	1%
MI	1.6%	2.0%	0.84 (0.64-1.09)	0%
Stroke	1.8%	1.8%	1.04 (0.78-1.39)	0%
All-cause			0.97 (0.86-1.09)	20%

Withdrawal rate lower in tiotropium (25.4% vs 31.1%; p=0.0001)

Author's Conclusion	No significant increase in CV events with tiotropium when compared to placebo. Correlation seen with higher incidence of major CV events with ≥55 smoking pack-years.
Take Home Points	• Removal of largest weighted study did not change results • Most studies compared tiotropium vs placebo -No change in mortality when compared to placebo • Authors had no financial support from manufacturer • Different from Singh et al.[21] - Focused only on a comparison of tiotropium vs placebo - Included 9 new RCT in meta-analysis in addition to previous tiotropium data - Accounted for patients used in multiple trials

Table 7
2009 Post-hoc evaluation of the UPLIFT trial[11] – Mortality of tiotropium in COPD over 4 years

Study design	Post-hoc evaluation of double blind RCT
Number	5,993 participants
Objective	Analyze all-cause mortality in patients with COPD treated with tiotropium versus placebo
Inclusion	• COPD diagnosis • ≥40 years old • ≥10 year pack history • FEV_1 ≤70% predicted
Exclusion	• Asthma history • COPD exacerbation or respiratory infection in last 4 weeks • History pulmonary resection • Supplemental O_2 for >12 hours a day
Treatment	Tiotropium: n=2,987 (36.2% drop-out rate); 18 ug daily via HandiHaler® Placebo: n=3,006 (44.6% drop-out rate)
Outcomes	All-cause mortality
Statistics	All patients that received medication were included in mortality analysis (ITT) Sensitivity analysis performed for mortality based on three separate timeframes Events considered on-treatment if occurred within 30 days of stopping drug
Results	Baseline characteristics: mean age 65 years, 30% active smokers <u>All-cause mortality</u> See table below <u>Mortality by system organ class, cardiac</u> On-treatment (per protocol): hazard ratio (HR) 0.86 (0.75-0.99) Intent to treat (ITT): HR 0.81 (0.48 – 1.01)
Author's Conclusion	Tiotropium given over a four-year period decreased mortality when compared to placebo. Follow-up beyond treatment period showed a decrease in the observed benefit.
Take Home Points	• Measured overall mortality for secondary outcome - Not specifically CV mortality • Higher drop-out rate in placebo group, which would potentially select for higher mortality in tiotropium - Placebo participant could drop out and then start active drug • Smoking may attenuate the all-cause mortality benefit of tiotropium - Increased HR in current smokers versus ex-smokers

	Control	Tiotropium		Tiotropium vs. Control	
	N (%)	N (%)	ΔRates (%)	HR (95% CI)	*P* Value
On-treatment	411 (13.7)	381 (12.8)	0.9	0.84 (0.73–0.97)	0.016
Day 1,440	491 (16.3)	430 (14.4)	1.9	0.87 (0.76–0.99)	0.034
Day 1,470	495 (16.5)	446 (14.9)	1.6	0.89 (0.79–1.02)	0.086
All	514 (17.1)	467 (15.6)	1.5	0.89 (0.78–1.00)	0.058

Table 8
2010 Celli et al.[23] – Cardiovascular Safety of Tiotropium

Study design	Meta-analysis (30 trials) from manufacturer database
Number	19,545
Objective	Determine if specific adverse events are at increased or decreased risk with tiotropium use
Inclusion	• Double-blind, placebo-controlled trials • Age ≥40 years, COPD diagnosis, smoking ≥10 pack-years
Exclusion	• Diagnosis of asthma • Cardiac arrhythmia requiring drug therapy • Heart failure hospitalization in previous one or three years (varied by study) • MI in previous 6 or 12 months (varied by study)
Treatment	Tiotropium: n=10,846 (22% drop-out rate) Placebo: n=8,699 (31% drop-out rate)
Outcomes	Primary: CV events (adverse, serious adverse, or fatal event), composite CV events (MI, stroke, CV death) Secondary: All-cause mortality
Statistics	Exposure to drug included time 30 days after discontinuation Heterogeneity between trials tested by Zelen test Discrepancies in adverse event data reconciled prior to lock/unblinding Statistical significance determined by alpha of <0.05
Result	Baseline characteristics: mean age 65 years, mean FEV_1 41% predicted, 34% active smoker

	tiotropium	placebo	RR (95% CI)	Zelen test
Adverse CV event	8.0%	9.1%	0.91 (0.83-1.01)	p=0.71
Serious CV event	4.3%	5.5%	0.83 (0.73-0.94)	p=1.00
Fatal CV event	1.2%	0.9%	0.77 (0.58-1.03)	p=1.00
Composite CV event			0.83 (0.71-0.98)	

Author's Conclusion	Tiotropium is associated with decreased CV mortality, CV events, and all-cause mortality. This may be due to an association of reduced respiratory events.
Take Home Points	• Higher risk patients excluded • Included UPLIFT trial data • Included 14 of 19 trials from Rodrigo et al.[22] • Largest meta-analysis comparing tiotropium and placebo • Authors have financial ties with manufacturer of tiotropium

Table 9
2011 Singh et al.[24] – Mortality risk with tiotropium Respimat® delivery device

Study design	Meta-analysis (5 RCT; single sponsor; same trials submitted to FDA)
Number	6,522
Objective	Determine if tiotropium delivered via Respimat® is associated with increased mortality when compared to placebo
Inclusion	• RCT, parallel-group • COPD treatment • Treatment for ≥30 days • Provided numerical data on mortality
Treatment	Tiotropium Respimat®: n=3686 Placebo: n=2836 – 2 trials were short-term (12 weeks) – 3 trials were long-term (12 months) – 4 trials included tiotropium 10mcg group
Outcomes	Primary: All-cause mortality Secondary post-hoc: CV mortality (MI, stroke, cardiac death, sudden death)
Statistics	Statistical heterogeneity assessed with I^2 statistic Statistical significance: two-sided alpha of 0.05 Fixed-effect model used; random-effects model for sensitivity analysis Sensitivity analysis on different doses of tiotropium
Results	Baseline characteristics: mean age ~65 years; mean FEV1 ~40%; ~37% current smokers

	tiotropium	placebo	RR (95% CI)	I^2 statistic	p-value
All-cause mortality	2.4%	1.7%	1.52 (1.06-2.16)	I^2=0%	p=0.02
CV mortality	0.8%	0.5%	2.05 (1.06-3.99)	I^2=0%	p=0.03

Author's Conclusion	Tiotropium Respimat® was associated with an increased risk of all-cause mortality and CV mortality when compared to placebo. There may also be a tiotropium dose-dependent increase of mortality risk.
Take Home Points	• First meta-analysis of tiotropium Respimat® and mortality • PK study[25] showed increase systemic absorption with Respimat® when compared to HandiHaler® • Small sample sizes for events • Patients treated with placebo were more closely followed than in previous trials, improving the ability to capture events in the placebo group

Table 10
2013 TIOSPIR trial[26] – Comparison of tiotropium mortality between Respimat® vs HandiHaler® devices.

Study design	Randomized, double-blind, parallel-group, active controlled
Number	17,135
Objective	Compare safety and efficacy of Respimat® vs HandiHaler®
Inclusion	• Age ≥40 years, COPD, smoking ≥10 pack-years
Exclusion	• MI previous 6 months • HF hospitalization or unstable arrhythmia last 12 months • Moderate to severe renal impairment
Treatment	Respimat 2.5 ug daily (n=5730) Respimat 5.0 ug daily (n=5711) Handihaler 18 ug daily (n=5694)
Outcomes	Primary: All-cause mortality Secondary: Exacerbations, moderate or severe exacerbation, major CV event
Statistics	One-sided p value of 0.025 used for noninferiority Mortality analysis included all patients who received at least one dose All patients followed to study completion even if discontinued early Sensitivity analysis done 30 days after discontinuation of study drug
Results	Baseline characteristics: MI ~6.0%, arrhythmia ~10.5%, mean FEV_1 48%; smoker 38%; history of IHD or coronary artery disease ~15%

	R 2.5	R 5	HH	HR (95% CI) R 2.5 vs HH	HR (95% CI) R 5 vs HH
Death					
-ITT	7.7%	7.4%	7.7%	1.00 (0.87-1.14)	0.96 (0.84-1.09)
-Per protocol	6.3%	5.7%	6.3%	1.00 (0.86-1.16)	0.91 (0.79-1.06)
Exacerbation	49.4%	47.9%	48.9%	1.02 (0.96-1.07)	0.98 (0.93-1.03)
CV death	2.1%	2.0%	1.8%	1.17 (0.90-1.53)	1.11 (0.85-1.45)
Major CV event	3.9%	3.9%	3.6%	1.11 (0.91-1.34)	1.10 (0.91-1.33)
CV death with previous arrhythmia	13.1%	10.6%	12.9%	1.02 (0.74-1.39)	0.81 (0.58-1.12)

R 2.5=Respimat® 2.5 ug daily, R 5.0= Respimat® 5.0 ug daily, HH = HandiHaler® 18 ug daily

Rates and severity of COPD exacerbations similar for 3 groups.
77.1% continued study drug for trial duration (similar between groups)
Vital status known for 99.7% patients at end of study

Author's Conclusion	Tiotropium Respimat® at a dose of 2.5 or 5 mcg daily had a safety profile and exacerbation efficacy similar to tiotropium HandiHaler® at a dose of 18 mcg daily. Tiotropium HandiHaler® may be associated with reduced mortality among patients with coexisting cardiac conditions.
Take Home Points	• Powered for mortality • Patients enrolled similar to other Respimat® studies • Respimat® is not worse than HandiHaler® in regards to mortality - Low percentage of study population had high risk cardiac history - Excluded patients with moderate to severe renal impairment • Respimat® is not worse than HandiHaler® in regards to exacerbations • Respimat® is as safe and efficacious as HandiHaler®

Conclusion and Recommendations

I. Summary

a. Tiotropium is effective for the management of COPD
    i. Decreases COPD exacerbations and COPD related hospitalizations, improves symptom control, health-related quality of life, and exercise tolerance.
b. Studies difficult to perform with more severe patients since placebo groups have high drop-out rates
c. Studies may not include patients who have higher cardiac risk or have kidney dysfunction
    i. Limited evidence in these patient populations to support clinical assessment of risk
d. Updated information within last 6 months
    i. More pharmacokinetic data and changes in prescribing information

II. Clinical questions

a. Is use of anticholinergic therapy in patients with COPD associated with increased CV mortality?
    i. Studies really focus on tiotropium over ipratropium ever since tiotropium came on market
        1. Tiotropium used for maintenance whereas ipratropium is rescue therapy
    ii. Pharmacokinetic studies found inhaled anticholinergics are systemically absorbed
        1. Tiotropium is renally excreted with increased exposure in kidney dysfunction
        2. Tiotropium has higher bioavailability compared to other inhaled anticholinergics
        3. Respimat® has higher bioavailability than HandiHaler®
            a. Despite initial association of an increased risk with Respimat® vs HandiHaler® there was no evidence found for increased CV mortality when comparing Respimat® 5 ug daily versus HandiHaler® 18 ug daily
    iii. Relationship between use of anticholinergic agents and CV events
        1. Patients with more severe COPD also have a higher risk of CV disease
        2. Most data support no increased risk of CV mortality with use of tiotropium
        3. Use of ipratropium may be associated with increased CV events

b. Should patients be stratified by CV risk before deciding to use inhaled anticholinergic therapy when treating COPD?
    i. Most studies did not include patients at higher risk for CV events
        1. However, limited data exist in patients with CV comorbidities or renal dysfunction
        2. CV risk with inhaled anticholinergics potentially different in patients with pre-existing CV comorbidities or renal dysfunction
        3. Not sure which CV comorbidities might put someone more at risk, if at all (e.g., unstable ischemic heart disease, recent MI, heart failure, or arrhythmias)
    ii. Recommend that CV risk does NOT need to be taken into account when starting inhaled anticholinergic therapy due to overwhelming benefit to patient with treatment and risk for CV side effect relativity low.
        1. NNT to prevent a COPD exacerbation with both tiotropium HandiHaler® and Respimat® 5 ug ranges from 7-29
        2. NNH for one CV event with both tiotropium HandiHaler® and Respimat® for the populations in the meta-analyses ranged from 91-333
    iii. It would be prudent to monitor for systemic anticholinergic side effects (e.g., urinary retention) when using an inhaled anticholinergic for maintenance therapy
        1. Consider using HandiHaler® or change in drug therapy (after weighing benefits/risks) if patient experiences systemic effects

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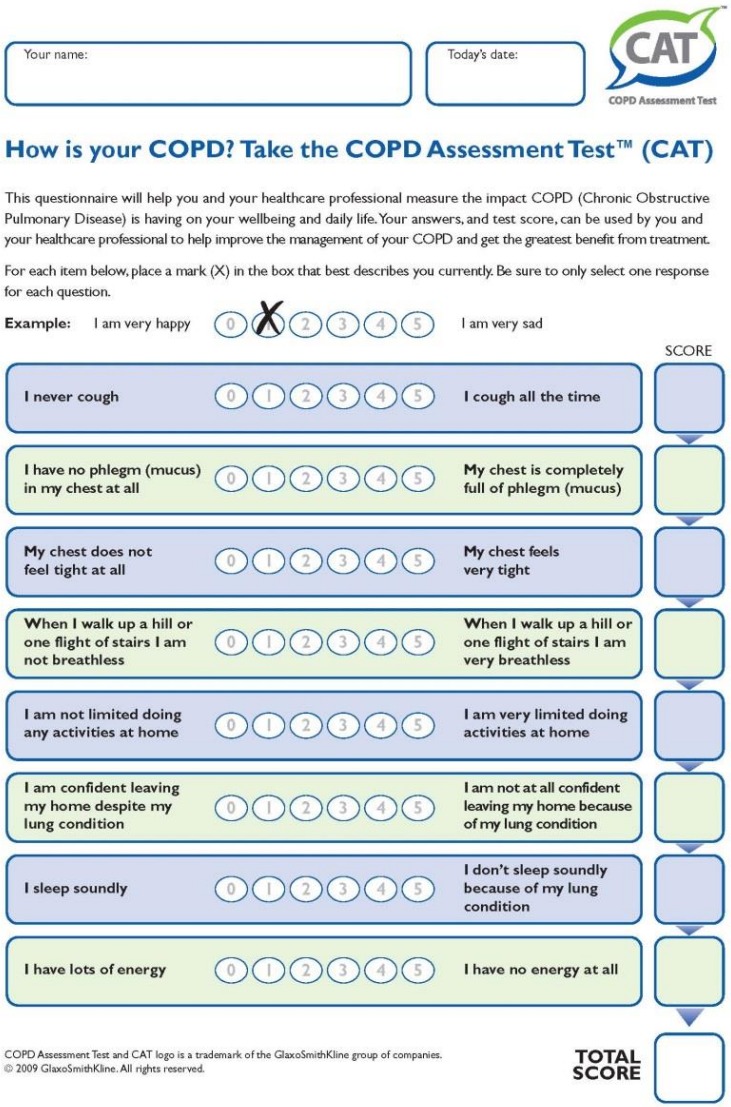
Appendix 1: Assessment of COPD symptoms



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 (X) 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

CLINICAL COPD QUESTIONNAIRE

Please **circle** the number of the response that best describes how you have been feeling during the **past week**.
(Only **one** response for each question).

On average, **during the past week**, how often did you feel:	never	hardly ever	a few times	several times	Many Times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical Activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past week**, how much of the time:							
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past week**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. **Moderate physical activities** (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. **Daily activities at home** (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. **Social activities** (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

Image accessed from: http://bcrt.ca/wp-content/uploads/2011/03/CATest.jpg
Image accessed from: http://openi.nlm.nih.gov/detailedresult.php?img=156640_1477-7525-1-13-1&req=4