A Breath of Fresh Air or A Sigh of Exasperation? Use of Glycopyrronium in COPD

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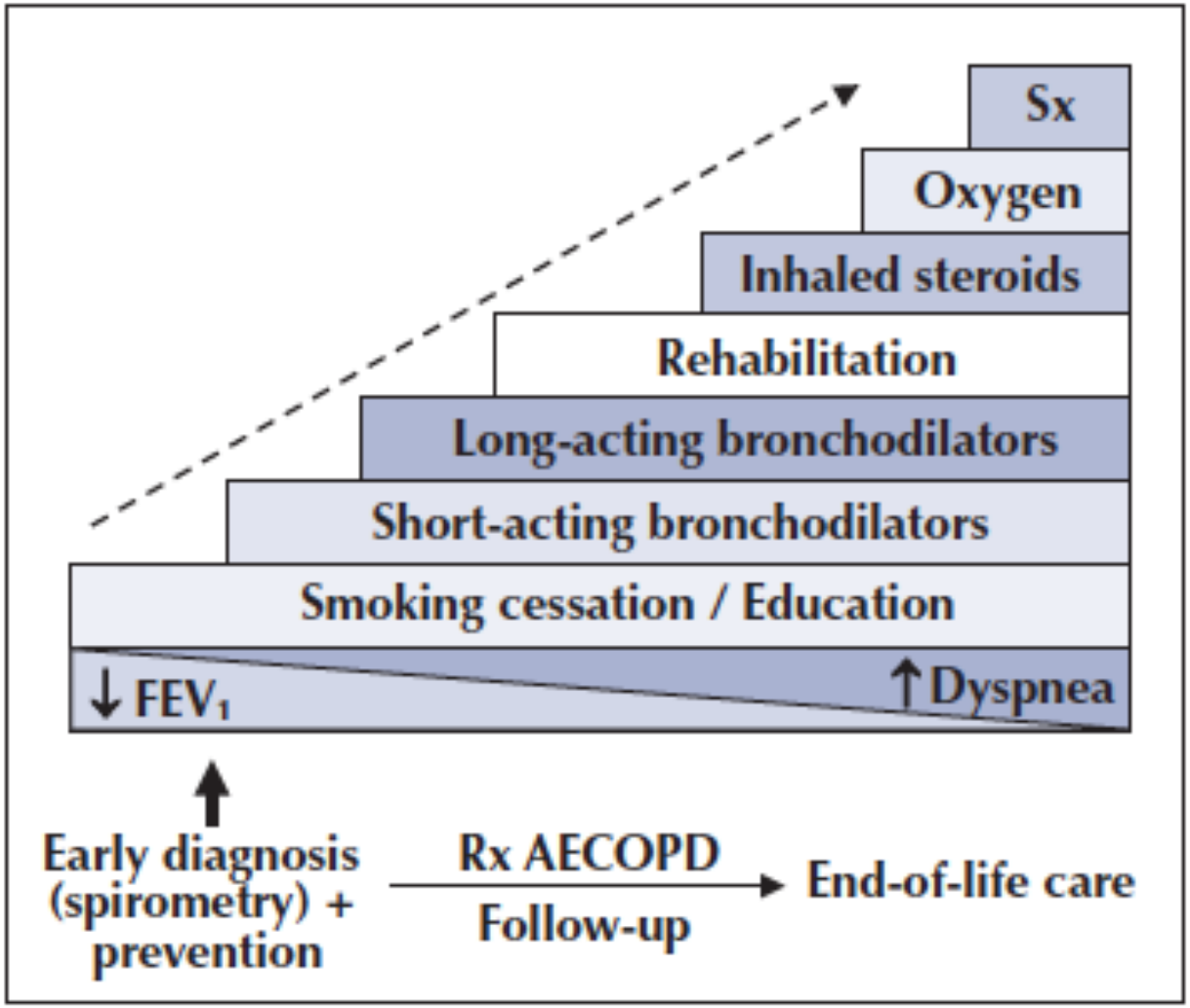
October 17th, 2013

Chronic Obstructive Pulmonary Disease

- A progressive pulmonary condition characterized by airflow limitation that is not fully reversible
- Affects ~4% of Canadians
- Goals of therapy:
  - Improve symptoms
  - Normalize/improve surrogate markers
  - Prevent/treat exacerbations
  - Improve quality of life
  - Prevent progression of disease
  - Prevent/treat complications
  - Delay mortality

International Journal of COPD 2012; 7: 729-741
Statistics Canada

COPD Treatment Algorithm



Can Respir J Vol 14 Suppl B September 2007

Long-Acting Muscarinic Antagonists

- Tiotropium
  - Canadian market - 2002
- Glycopyrronium
  - NOC: 2012-10-16
- Aclidinium
  - NOC: 2013-07-29

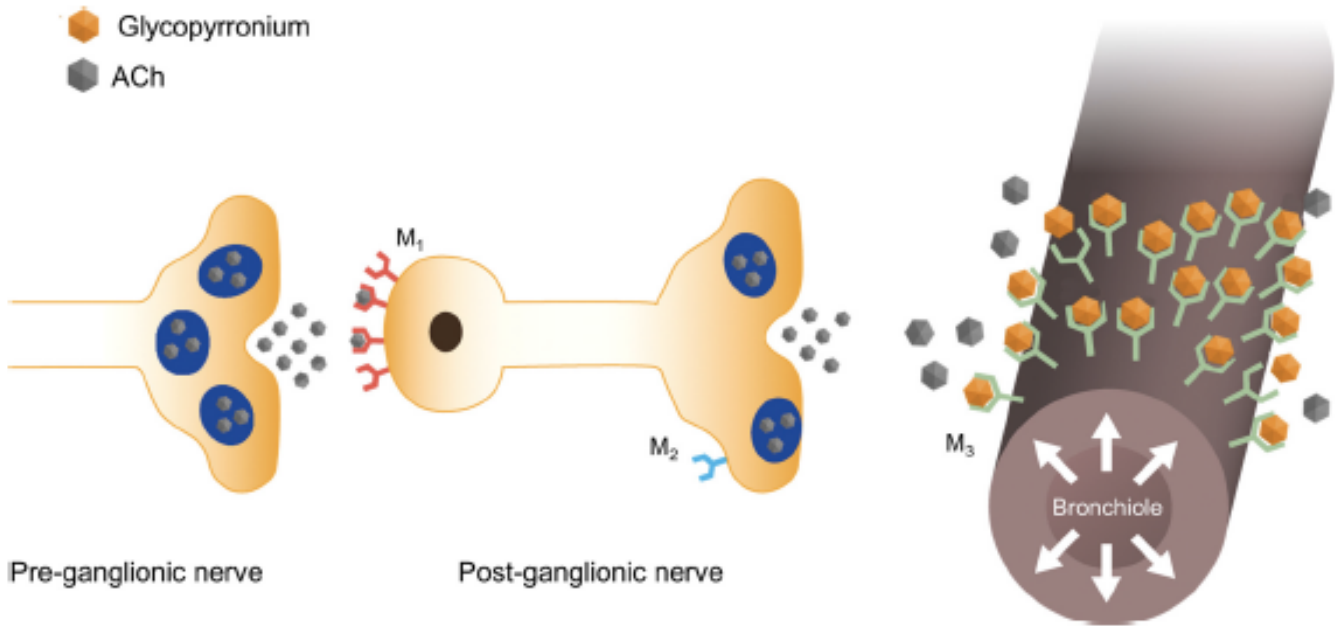
Health Canada Drug Product Database – accessed Oct 2013

Evidence for Tiotropium

	Tiotropium	Placebo	p-value
Mean FEV1 decline	40mL/yr	42mL/yr	0.21
# of Exacerbations (per pt. yr.)	0.73	0.85	<0.001
SGRQ	Mean difference between groups = -2.7		<0.001
Mortality	14.9%	16.5%	0.09

NEJM 2008;359:1543-54

Long-Acting Muscarinic Antagonists



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Clinical Question

- Is glycopyrronium a safe and effective alternative long-acting muscarinic antagonist for the management of COPD?
  - Symptomatic control
  - Required use of SABA
  - Rate of exacerbations
  - Quality of life
  - ADR profile

Search Strategy

Databases	PubMed, EMBASE, International Pharmaceutical Abstracts, Google Scholar
Keywords	Chronic obstructive pulmonary disease, Glycopyrronium, NVA237, Tiotropium, Ipratropium
Limits	Humans, English
Results	- 0 RCTs (glycopyrronium vs. tiotropium) - 3 RCTs (glycopyrronium vs. placebo) - 1 network MA (aclidinium vs. tiotropium and glycopyrronium)

GLycopyrronium in COPD AirWays

Glow 1 Study

D	26 week randomized, double-blind, placebo-controlled study
P (n=822)	- Adults ≥ 40 years of age with moderate-to-severe COPD - Smoking history ≥ 10 pack-years - Post-bronchodilator FEV1 < 80% and FEV1 /FVC ratio < 0.70
I	Glycopyrronium 50mcg inhaled once daily
C	Placebo
O	**Primary**: - trough FEV1 at week 12 **Secondary**: - time to first moderate or severe COPD exacerbation - mean daily rescue medication use - breathlessness on the transition dyspnea index (TDI) - health-related quality of life (SGRQ)

D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

- Trough FEV1

	Day 1	***Week 12***	Week 26
Glycopyrronium	1.414 ± 0.0075 L	1.408 ± 0.0105 L	1.387 ± 0.0112 L
Placebo	1.309 ± 0.0099 L	1.301 ± 0.0137 L	1.275 ± 0.0150 L
DIfference	0.105 ± 0.0109 L	0.108 ± 0.0148 L	0.113 ± 0.0165 L
p-value	<0.001	<0.001	<0.001

D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

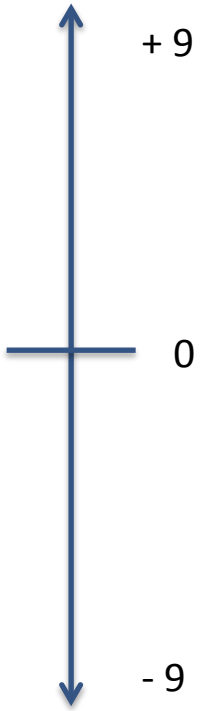
- Time to first moderate to severe exacerbation
  - Glycopyrronium reduced the risk of exacerbations by 31% compared with placebo (HR 0.69, p = 0.023)
- Mean daily rescue inhaler use
  - Significantly lower in the glycopyrronium group (between group difference of 0.46 puffs/day, p = 0.005)

D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

- Transition Dyspnea Index

	Week 26
Glycopyrronium	1.84
Placebo	0.80
Difference	1.04
p-value	<0.001



D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

- St. George's Respiratory Questionnaire

	Week 26
Glycopyrronium	39.50
Placebo	42.31
DIfference	-2.81
p-value	0.004

D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

- Safety

	NVA237 50 µg (n = 550)	Placebo (n = 267)
Patients with adverse events, n (%)	317 (57.5)	174 (65.2)
COPD worsening	111 (20.2)	73 (27.3)
Nasopharyngitis	28 (5.1)	21 (7.9)
Cough	26 (4.7)	13 (4.9)
Upper respiratory tract infection	23 (4.2)	20 (7.5)
Dyspnoea	18 (3.3)	10 (3.7)
Pyrexia	17 (3.1)	13 (4.9)
Upper respiratory tract infection, bacterial	17 (3.1)	12 (4.5)
Headache	14 (2.5)	10 (3.7)

D'Urzo et al. Respiratory Research 2011, 12:156

GLOW 1 – Results

- Safety

	NVA237 n=550	Placebo n=267
Patients with serious adverse events*, n (%)	46 (8.4)	24 (9.0)
COPD worsening	9 (1.6)	11 (4.1)
Pneumonia	4 (0.7)	2 (0.7)
Upper respiratory tract infection, bacterial	3 (0.5)	2 (0.7)
Atrial fibrillation	3 (0.5)	0
Dyspnoea	2 (0.4)	0
Respiratory failure	2 (0.4)	0
Cardiac failure congestive	2 (0.4)	0
Myocardial infarction	2 (0.4)	1 (0.4)
Lung neoplasm	2 (0.4)	0
Syncope	2 (0.4)	0
Upper respiratory tract infection	0	2 (0.7)
Myocardial ischaemia	0	2 (0.7)
Deaths**, n (%)	3 (0.5)	3 (1.1)
Discontinuations due to adverse events, n (%)	32 (5.8)	19 (7.1)

D'Urzo et al. Respiratory Research 2011, 12:156

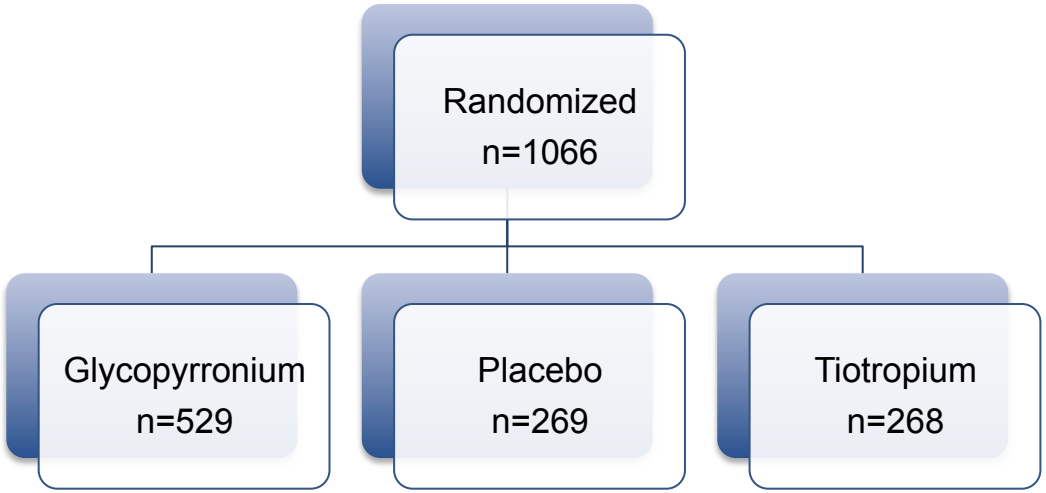
GLOW 1 – Critique

Limitations	- Excluded patients with alpha-1 antitrypsin deficiency - ~80% of study participants – male gender - No details provided on concomitant COPD medication use - Recall bias – patients self-reported symptoms/use of rescue inhaler using an electronic diary - Discussion is centered around comparison against tiotropium - Majority of authors employed by Novartis

GLycopyrronium in COPD AirWays

Glow 2 Study

D	52 week multicenter, randomized, placebo-controlled, parallel study
P	- Adults ≥ 40 years of age with moderate-to-severe COPD - Smoking history ≥ 10 pack-years - Post-bronchodilator FEV1 < 80% and FEV1 /FVC ratio < 0.70



Eur Respir J 2012; 40: 1106–1114

GLycopyrronium in C**O**PD Air**W**ays

Glow 2 Study

O	**Primary**: - Trough FEV1 at week 12 **Secondary**: - Time to first moderate or severe COPD exacerbation and rate of exacerbations - Mean daily rescue medication use over 52 weeks - Breathlessness on the transition dyspnea index at week 26 - Health-related quality of life at week 52

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Trough FEV1

	Day 1	***Week 12***	Week 26	Week 52
Glycopyrronium vs. placebo	0.091 L	0.097 L	0.134 L	0.108 L
Tiotropium vs. placebo	0.083 L	0.083 L	0.084 L	0.089 L

*p<0.001 for all treatment differences at all time points

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Time to first moderate to severe exacerbation
  - Glycopyrronium reduced the risk of exacerbations by 34% compared with placebo (HR 0.66, p = 0.001, NNT 13.27)
  - Tiotropium reduced the risk of exacerbations by 39% compared with placebo (HR 0.61, p = 0.001, NNT 10.04)

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Rate of moderate to severe exacerbations
  - A 34% reduction was observed in the glycopyrronium group compared to placebo (0.54 vs. 0.80 per year, rate ratio 0.66, p = 0.003)
  - The effect of tiotropium was not statistically different from placebo (rate ratio 0.80, p = 0.179)

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Mean daily rescue inhaler use
  - Significantly lower with glycopyrronium vs. placebo (between group difference of 0.37 puffs/day, p = 0.039)
  - Significantly lower with tiotropium vs. placebo (between group difference of 0.63 puffs/day, p = 0.003)

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Transition Dyspnea Index

	Week 26		Week 26
Glycopyrronium	2.13	**Tiotropium**	NR
Placebo	1.32	**Placebo**	NR
Difference	0.81	**Difference**	0.94
p-value	0.002	**p-value**	0.002

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- St. George's Respiratory Questionnaire

	Week 52
Glycopyrronium vs. placebo	-3.32 ($p<0.001$)
Tiotropium vs. placebo	-2.84 ($p=0.014$)

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Results

- Safety

	NVA237 n=525	Placebo n=268	Tiotropium n=267
Patients with adverse events	402 (76.6)	205 (76.5)	198 (74.2)
COPD worsening*	191 (36.4)	116 (43.3)	90 (33.7)
Upper respiratory tract infection	57 (10.9)	33 (12.3)	30 (11.2)
Nasopharyngitis	47 (9.0)	15 (5.6)	21 (7.9)
Sinusitis	28 (5.3)	14 (5.2)	10 (3.7)
Upper respiratory tract infection, bacterial	28 (5.3)	28 (10.4)	21 (7.9)
Back pain	25 (4.8)	10 (3.7)	12 (4.5)
Headache	25 (4.8)	14 (5.2)	12 (4.5)
Lower respiratory tract infection	23 (4.4)	9 (3.4)	10 (3.7)
Bronchitis	22 (4.2)	10 (3.7)	12 (4.5)
Cough	21 (4.0)	13 (4.9)	12 (4.5)
Hypertension	21 (4.0)	12 (4.5)	14 (5.2)
Dry mouth	16 (3.0)	5 (1.9)	4 (1.5)
Dyspnoea	14 (2.7)	13 (4.9)	6 (2.2)
Pneumonia	14 (2.7)	12 (4.5)	7 (2.6)
Urinary tract infection	14 (2.7)	8 (3.0)	16 (6.0)
Peripheral oedema	9 (1.7)	6 (2..2)	8 (3.0)
Upper respiratory tract infection viral	9 (1.7)	13 (4.9)	11 (4.1)

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GLOW 2 – Results

- Safety

	NVA237 n=525	Placebo n=268	Tiotropium n=267
Patients with serious adverse events	66 (12.6)[¶]	43 (16.0)	41 (15.4)[¶]
COPD worsening[#]	19 (3.6)	16 (6.0)	13 (4.9)
Pneumonia	7 (1.3)	7 (2.6)	4 (1.5)
Atrial fibrillation	4 (0.8)	0	0
Dehydration	4 (0.8)	2 (0.7)	0
Syncope	3 (0.6)	1 (0.4)	0
Transient ischemic attack	3 (0.6)	1 (0.4)	0
Bronchitis	3 (0.6)	1 (0.4)	0
Deaths	3 (0.6)[+]	2 (0.7)	2 (0.7)
Discontinuation due to adverse events	42 (8.0)	31 (11.6)	20 (7.5)
Electrocardiographic abnormalities			
Total notable	23 (4.4)	16 (6.0)	14 (5.3)
QTc >500 ms	2 (0.4)	2 (0.7)	0
Increase from baseline of 30–60 ms	83 (15.8)	39 (14.6)	43 (16.2)
Increase from baseline of >60 ms	1 (0.2)	1 (0.4)	0

Eur Respir J 2012; 40: 1106–1114

GLOW 2 – Critique

Limitations	- Not powered to detect a difference between glycopyrronium and tiotropium - Open-label tiotropium arm may have influenced the results of the patient reported outcomes or use of rescue inhalers - Majority of authors employed by Novartis

Conclusion

- Glycopyrronium vs. placebo

	Statistically significant?	Clinically significant?
Trough FEV1	✔	✔
Use of rescue inhaler	✔	?
Rate of exacerbations	✔	?
Symptomatic control	✔	?
Quality of life	✔	✗

Questions?