COMPARATIVE EFFICACY OF INHALED MEDICATIONS (ICS/LABA, LAMA, LAMA/LABA AND SAMA) IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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INTRODUCTION & OBJECTIVE

- The Agency for Care Effectiveness (ACE) is the national health technology assessment (HTA) agency in Singapore to guide health policy, drive appropriate use of treatments and inform technology subsidy decisions.
- COPD is a global health problem that causes substantial morbidity and mortality.
- Our objective was to assess the comparative efficacy of short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists (LAMA), LAMA in combination with long-acting beta-agonists (LAMA/LABA) and inhaled corticosteroids in combination with LABA (ICS/LABA) for the maintenance treatment of COPD in Singapore.

METHOD

- Two independent reviewers identified all RCTs using electronic databases (up to Nov 2017) including the following interventions: SAMA (ipratropium [IPRA]); LAMA (glycopyrronium [GLYCO], tiotropium 5mcg and 18mcg [TIO5 and TIO18], umeclidinium [UMEC]); LAMA/LABA (glycopyrronium/indacaterol [INDA/GLYCO], tiotropium/olodaterol [TIO/OLO], umeclidinium/vilanterol [UMEC/VIL]); and ICS/LABA (salmeterol/fluticasone [SFC], formoterol/budesonide [BUDE/FORM]).

- Due to a lack of head-to-head trials directly comparing all relevant interventions and comparators, a network meta-analysis (NMA) was conducted to examine the change from baseline in trough forced expiratory volume in 1 second (FEV_1) at weeks 12 and 24 using a random effects model. A frequentist framework (performed with mvmeta package in Stata 15 statistical software) allowed statistical inferences and comparisons to be made based on significance testing using p-values.
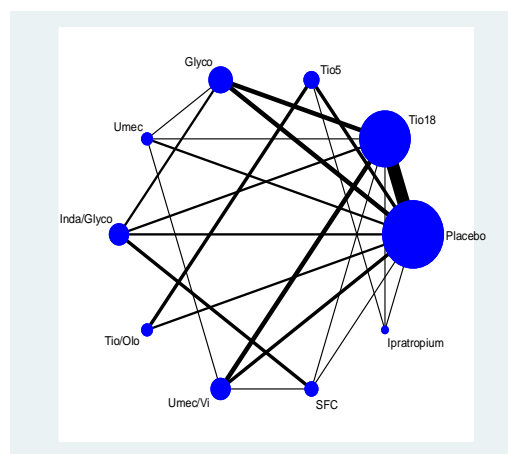

Figure 1: Network plot of available evidence on FEV_1 at week 12

RESULTS

- Forty seven studies comprising 55,515 patients were included in the NMA, with 38 studies reporting results at week 12 and 29 studies at week 24.

- Inconsistency models were not statistically significant (week 12: p=0.0584, week 24: p=0.0728).

- All LAMAs, LAMA/LABAs and ICS/LABAs led to significantly greater improvement in trough FEV_1 compared to SAMA at weeks 12 and 24.

- All LAMA/LABAs led to greater statistically significant improvements in FEV_1 than LAMAs and ICS/LABAs at weeks 12 and 24, for all comparisons except TIO/OLO versus UMEC.

- Among the LAMAs, UMEC showed statistically significant improvement in trough FEV_1 at week 12 compared to TIO18 and GLYCO, but the results were not clinically significant. There were no significant differences in trough FEV_1 for all LAMA-LAMA comparisons at week 24.

- Among the LAMA/LABAs, there were no significant differences in FEV_1 at weeks 12 and 24.

						FEV_1 at week 24					
	BUDE/FORM	-32.09 (-71.43,7.25)	-105.12 (-142.35,-67.88)	-88.25 (-135.06,-41.45)	-111.15 (-147.28,-75.03)	-45.50 (-95.75,4.75)	-40.15 (-74.23,-6.06)	-29.19 (-63.89,5.51)	-31.09 (-62.67,0.48)	131.06 (74.43,187.68)	79.44 (50.26,108.63)
	NA	**SFC**	-73.03 (-107.14,-38.92)	-56.17 (-101.02,-11.31)	-79.06 (-98.97,-59.16)	-13.41 (-61.70,34.88)	-8.06 (-35.97,19.85)	2.90 (-29.11,34.92)	1.00 (-25.92,27.92)	163.15 (108.97,217.32)	111.53 (85.15,137.92)
	NA	-64.90 (-92.53,-37.27)	**UMEC/VIL**	16.86 (-25.51,59.23)	-6.04 (-35.81,23.74)	59.62 (19.63,99.60)	64.97 (37.19,92.75)	75.93 (47.33,104.53)	74.02 (51.66,96.39)	236.17 (184.20,288.14)	184.56 (161.45,207.67)
	NA	-42.65 (-83.27,-2.04)	22.25 (-15.96,60.46)	**TIO/OLO**	-22.90 (-64.50,18.71)	42.76 (-11.67,97.18)	48.11 (7.83,88.39)	59.07 (27.76,90.38)	57.16 (19.76,94.57)	219.31 (159.36,279.26)	167.70 (131.12,204.28)
FEV_1 at week 12	NA	-72.39 (-94.33,-50.45)	-7.49 (-34.89,19.91)	-29.73 (-69.23,9.76)	**INDA/GLYCO**	65.66 (20.20,111.11)	71.01 (48.76,93.25)	81.97 (54.55,109.38)	80.06 (58.91,101.21)	242.21 (190.72,293.69)	190.60 (169.32,211.88)
	NA	-20.78 (-54.66,13.10)	44.12 (14.58,73.66)	21.88 (-19.80,63.55)	51.61 (19.08,84.13)	**UMEC**	5.35 (-38.72,49.42)	16.31 (-28.21,60.83)	14.41 (-27.00,55.81)	176.55 (113.96,239.15)	124.94 (84.04,165.85)
	NA	10.57 (-16.85,37.99)	75.47 (50.49,100.45)	53.22 (16.30,90.14)	82.95 (58.38,107.53)	31.35 (3.59,59.10)	**GLYCO**	10.96 (-14.26,36.18)	9.06 (-9.11,27.22)	171.20 (120.80,221.61)	119.59 (102.00,137.19)
	NA	9.01 (-29.36,47.37)	73.91 (38.12,109.69)	51.66 (24.58,78.75)	81.39 (44.20,118.59)	29.79 (-9.65,69.22)	-1.56 (-35.86,32.74)	**TIO5**	-1.91 (-22.35,18.54)	160.24 (109.10,211.39)	108.63 (89.87,127.39)
	NA	17.17 (-7.00,41.34)	82.07 (62.10,102.04)	59.82 (25.10,94.54)	89.56 (67.14,111.97)	37.95 (11.63,64.27)	6.60 (-11.62,24.82)	8.16 (-23.67,39.99)	**TIO18**	162.15 (115.18,209.11)	110.54 (98.50,122.57)
	NA	112.75 (69.18,156.32)	177.65 (136.32,218.99)	155.41 (109.32,201.50)	185.14 (142.55,227.73)	133.53 (88.92,178.15)	102.19 (61.99,142.38)	103.75 (61.40,146.09)	95.58 (58.49,132.67)	**IPRA**	-51.61 (-100.13,-3.09)
	NA	120.94 (95.69,146.19)	185.84 (164.74,206.94)	163.59 (131.16,196.03)	193.33 (169.90,216.75)	141.72 (114.93,168.51)	110.37 (92.04,128.71)	111.93 (82.66,141.21)	103.77 (90.07,117.47)	8.19 (-28.80,45.17)	**Placebo**

Table 1. Treatment effects on FEV_1 at week 12 (lower triangle) and week 24 (upper triangle) Comparisons between treatments should be read from left to right. The mean difference (MD) in millilitres with 95% confidence interval (95%CI) are shown in the cell. MD more than 0 favours the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**.
NA: results not available.

CONCLUSION

- LAMA/LABAs showed greatest improvement in lung function at weeks 12 and 24 compared with other inhaled drug classes; SAMA showed least improvement.

- Results from our analysis may assist clinicians make evidence-based treatment decisions and inform policy makers when making subsidy decisions.

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