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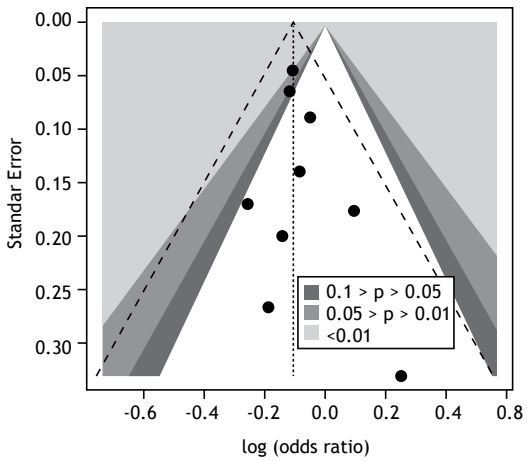
Long-acting muscarinic antagonists vs. long-acting β_2 agonists in COPD exacerbations: a systematic review and meta-analysis

Israel Silva Maia[1], Mariângela Pimentel Pincelli[1], Victor Figueiredo Leite[2], João Amadera[3], Anna Maria Buehler[4]

(((((“Pulmonary Disease, Chronic Obstructive”[Mesh] OR COPD OR Chronic Obstructive Pulmonary Disease OR COAD OR Chronic Obstructive Airway Disease OR Chronic Obstructive Lung Disease OR Airflow Obstruction, Chronic OR Airflow Obstructions, Chronic OR Chronic Airflow Obstructions OR Chronic Airflow Obstruction)) OR (“Lung Diseases, Obstructive”[Mesh] OR Lung Disease, Obstructive OR Obstructive Lung Disease OR Obstructive Lung Diseases OR Obstructive Pulmonary Diseases OR Obstructive Pulmonary Disease OR Pulmonary Disease, Obstructive OR Pulmonary Diseases, Obstructive))) AND ((((“tiotropium” [Supplementary Concept] OR Spiriva OR tiotropium bromide OR 7-((hydroxybis(2-thienyl)acetyl)oxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo(3.3.1.0(2,4))nonane bromide OR BA 679 BR OR BA-679 BR)) OR (“Glycopyrrolate”[Mesh] OR Glycopyrronium Bromide OR Bromide, Glycopyrronium)) OR (“aclidinium bromide” [Supplementary Concept] OR aclidinium bromide))) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] NOT (animals[mh] NOT humans[mh]))

Appendix 1. Search strategy.



Appendix 2. Contour-enhanced funnel plot.

Appendix 3. Quality of evidence measured for the primary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation.[20]

LAMAs vs. LABAs for COPD exacerbations											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With LABAs	With LAMAs		Risk with LABAs	Risk difference with LAMAs
Proportion of patients with at least one exacerbation (follow up: range 12-104 weeks; assessed by number)											
17,120 (9 RCTs)	serious [1,2,3,4,5]	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE	2,944/8,529 (34.5%)	2,679/8,591 (31.2%)	RR 0.91 (0.87 to 0.95)	345 per 1000	31 per 1,000 (45 to 17)
Rate of exacerbation (follow up: range 12-104 weeks; assessed by rate)											
14,488 (6 RCTs)	serious [2,3,5,6,7]	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE					
Hospitalization (follow up: range 12-104 weeks; assessed by number)											
14,740 (8 RCTs)	serious [1,3,5,7]	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE	609/7,345 (8.3%)	474/7,395 (6.4%)	RR 0.77 (0.69 to 0.87)	83 per 1000	19 per 1,000 (26 to 11)

LAMA: long-acting muscarinic antagonists; LABA: long-acting β_2 agonists; and RR: risk ratio. Two studies did not specify the randomization method and allocation concealment.[19,21] 2. One study with per protocol analysis.[26] 3. One open label study; LAMA affecting blinding LAMA.[21] 4. Two studies with possible attrition bias.[23,26] 5. All the studies were sponsored by the industry. 6. One study did not specify the randomization method and allocation concealment.[19] 7. One study with possible attrition bias.[26]