

Materials and methods

Search strategy and study eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO, Protocol ID: CRD42020211870), and performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [1]. The relative flow diagram and network nodes are shown in Figure 1A and B. This study satisfied all the recommended items reported by the PRISMA-P checklist (Table S1) [1].

A comprehensive literature search was performed for Phase III randomized controlled trials (RCTs) written in English and evaluating the efficacy and safety of triple combination therapies for the treatment of asthma. In this regard, the PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported [2]. Namely, the "Patient problem" included patients suffering from asthma; the "Intervention" regarded the administration of different triple combination therapies; the "Comparison" was performed across active combination treatments; the assessed "Outcomes" were the risk of moderate to severe asthma exacerbation, lung function, level of asthma control, and risk of serious adverse events (SAEs), specifically with respect to pneumonia and serious cardiovascular adverse events (AEs).

The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science, in order to provide for relevant studies lasting ≥ 24 weeks, and published up to September 23rd, 2020. The research string was as follows: (((Beclomethasone formoterol glycopyrronium) OR (CHF 5993) OR (CHF5993)) OR (fluticasone furoate vilanterol umeclidinium) OR (mometasone indacaterol glycopyrronium OR (QVM149) OR (QVM 149)) OR ((fluticasone propionate salmeterol tiotropium) OR (ICS LABA tiotropium)) OR triple) AND asthma. Citations of previous published reviews were checked to select further pertinent RCTs, if any.

Literature search results were uploaded to Eppi-Reviewer 4 (EPPI-Centre Software. London, UK), a web-based software program for managing and

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analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ≥ 24 weeks, and that included at least one arm assessing the impact of any triple combination therapy in asthma were included in the network meta-analysis. Three reviewers independently examined the studies, and any difference in opinion concerning the selection of relevant Phase III RCTs from literature searches and databases was resolved by consensus.

Data extraction

Data from the RCTs included in this quantitative synthesis were extracted from published papers, and/or supplementary files, and/or the public database ClinicalTrials.gov and/or publically available pharmaceutical companies' clinical databases. Data were checked for study characteristics and duration, number of analysed patients, treatments with doses of medications and regimen of administration, asthma severity and main inclusion criteria, age, gender, asthma duration; forced expiratory volume in the 1st second (FEV₁); level of FEV₁ reversibility; blood eosinophil count at baseline; smoking habit, Asthma Control Questionnaire (ACQ), primary outcomes analysed in every study, Jadad Score [3], and the Cochrane risk of bias [4].

The level of inhaled corticosteroid (ICS) doses (medium-dose [MD] and high-dose [HD]) included in the combinations was ranked in agreement with the current Global Initiative for asthma (GINA) recommendations [5] and the National Institute for Health and Care Excellence (NICE) guidelines [6].

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECIMAL) recommendations [7]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described [8]. Briefly, Cohen's Kappa ≥ 0.80 indicated excellent agreement, coefficients between 0.61 and 0.80 represented substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and <0.41 fair to poor agreement.

Endpoints

Supplementary data

The co-primary endpoints of this network meta-analysis were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe exacerbation in asthmatic patients and the change from baseline in trough FEV₁.

The secondary efficacy endpoint was the comparison across the different triple combination therapies and comparators with respect to the change from baseline in ACQ score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular AEs.

Quality of studies, risk bias, and evidence profile

The summary of the risk of bias for each included Phase III RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [4] and Jadad score [3]. The Jadad score ranges from 1 to 5 (score of 5 being the best score), and the quality of studies was ranked as follows: score ≤2, low quality; score =3, medium quality; score ≥4 high quality. The weighted assessment of the risk of bias was analyzed via the Cochrane RoB 2 [4].

The risk of bias was performed for the co-primary endpoints and it was checked via the normalized consistency/inconsistency analysis, a procedure that allows assessing whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [9]. The inconsistency of evidence was also investigated by quantifying the inconsistency factor, that indicates whether one of the treatments had a different effect when it was compared with the others.

The quality of the evidence was assessed for the co-primary endpoints in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, indicating ++++ for high-quality of evidence, +++ for moderate-quality of evidence, ++ for low-quality of evidence, and + for very low-quality of evidence [10].

Three reviewers independently assessed the quality of studies, risk bias, and evidence profile, and any difference in opinion was resolved by consensus.

Data synthesis and analysis

A network meta-analysis was performed to indirectly compare the impact of the different triple combination therapies and active comparators in asthmatic patients.

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A full Bayesian evidence network was used in the network meta-analysis (chains: 4; initial values scaling: 2.5; tuning iterations: 20.000; simulation iterations: 50.000; tuning interval: 10). The convergence diagnostics for consistency and inconsistency were assessed via the Brooks-Gelman-Rubin method, as previously described [11]. Due to the characteristics of parameters besides the available data, the just proper non-informative distributions specified the prior densities, in agreement with the Bayesian Approaches to Clinical Trials and Health-Care Evaluation [12, 13]. Since the distributions were sufficiently vague, the reference treatment, study baseline effects, and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, via heuristically determining a value for the outcome scale parameter (i.e. outcome scale S) [14, 15]. The posterior mean deviance of data points in the unrelated mean effects model was plotted against their posterior mean deviance in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent [16]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI).

The analysis of the number needed to treat (NNT) was performed on the risk of moderate to severe exacerbations. NNT is the reciprocal of the absolute risk reduction associated with an intervention over a fixed period of time [17-19].

The values of NNT are reported in this study as person-based per year and calculated by analysing the Kaplan-Meyer curves or the Cox proportional hazards model, as previously described [20, 21]. The relative weight of each study resulting from the network meta-analysis was used to calculate the weighted average rate of the investigated treatment arms and to correctly provide NNT values.

Sensitivity analysis was performed in agreement with the patients' characteristics at baseline of each study.

Subset analyses were performed on both moderate or severe exacerbations, and with respect to the different doses of umeclidinium included in the fixed-dose combination (FDC).

Supplementary data

The probability that each intervention arm was the most effective/safe was calculated by counting the proportion of iterations of the chain in which each intervention arm had the best relative effect, and the surface under the cumulative ranking curve analysis (SUCRA), representing the summary of these probabilities [22]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [9].

Software and statistical significance

ImageJ was used to extract data from the figures, when necessary [23], GeMTC [24] software was used to perform the network meta-analysis, GraphPad Prism (CA, US) software to graph the data, GRADEpro GDT to assess the quality of evidence [10], and the robvis visualization software to perform the RoB 2 tool [25, 26]. The statistical significance of the effect estimates resulting from the network meta-analysis was assessed for P<0.05.

Results

Study characteristics

Data obtained from 9535 asthmatic patients (MD ICS/LABA/LAMA FDC: 26.02%; HD ICS/LABA/LAMA FDC: 25.99%; HD ICS/LABA FDC: 23.23%; MD ICS/LABA FDC: 16.76%; HD ICS/LABA FDC + TIO: 8.00%) were selected from 5 Phase III RCTs published between 2019 and 2020.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen's Kappa >0.90). The intra-rater reliability produced a Cohen's Kappa of 1.00 after the learning process.

All the studies included in the network meta-analysis were Phase III RCTs published as full-text papers, with a period of treatment between 24 weeks and 52 weeks.

Supplementary data

Supplementary Tables

Table S1. PRISMA-P Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 main MS
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 main MS
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 main MS
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 main MS
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3-4 main MS; 1 suppl. file
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4 main MS; 1 suppl. file
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	1 suppl. file
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	1 suppl. File; Table S2; Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 main MS; 2 suppl. file
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4 main MS; 2 suppl. file

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Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 main MS; 3 suppl. file
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4 main MS; 3 suppl. file
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5 main MS; 4 suppl. file
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 main MS; 4-5 suppl. file
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 main MS; 3 suppl. file
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4 suppl. file
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 main MS, Figure 1; 5 suppl. file
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5 main MS; Table S3; 5 suppl. file
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 main MS; Figure S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8 main MS; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 main MS; Table 1; Figure 3; Figure S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 main MS; Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 main MS; Table 2, Table 3

Supplementary data

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10 main MS
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11 main MS
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11 main MS
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12 main MS

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed.1000097.

MS: manuscript; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol.

Supplementary data

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this network meta-analysis is reported at step #30. The summary text of the identified records is shown in Appendix 1.

#	Search strategy
1	Beclomethasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
2	Formoterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
3	Glycopyrronium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
4	CHF 5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
5	CHF5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
6	Fluticasone furoate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
7	Vilanterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
8	Umeclidinium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
9	Mometasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
10	Indacaterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
11	QVM149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
12	QVM 149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
13	Fluticasone propionate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
14	Salmeterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
15	Tiotropium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
16	ICS*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
17	LABA*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
18	Triple*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
19	Asthma*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
20	1 and 2 and 3
21	4 or 5
22	6 and 7 and 8
23	3 and 9 and 10
24	11 or 12
25	13 and 14 and 15
26	15 and 16 and 17
27	20 or 21
28	23 or 24
29	18 or 22 or 25 or 27 or 28
30	19 and 29

Supplementary data

Table S3. Patient demographics, baseline, study characteristics, and Jadad score.

Study and year and reference	Trial number Identifier	Study characteristics	Study duration (months)	Number of analyzed patients	Triple FDC therapy (doses and regimen of administration)	Comparator (doses and regimen of administration)	Inhaler device (brand)	Patients characteristics	Age (years)	Male (%)	Duration of asthma (years)	Pre-bronchodilator FEV ₁ (% predicted)	Reversibility (%)	Rate of exacerbation in the previous year	Blood eosinophil count (cells per µL)	Current smokers (%)	ACQ at baseline (score)	Primary outcome	Jadad score
Lee et al., 2020, CAPTAIN [27]	NCT02924688	Phase IIIA, multicentre, randomized, double-blind, active-controlled, parallel-group	12.0	2436	FF/VI/UMECA (100/25/31.25 µg q.d.), FF/VI/UMECA (100/25/62.5 µg q.d.), FF/VI/UMECA (200/25/31.25 µg q.d.), FF/VI/UMECA (200/25/62.5 µg q.d.)	FF/VI (100/25 µg q.d.), FF/VI (200/25 µg q.d.)	FF/VI/UMECA; FF/VI; DPI (Ellipta®)	Inadequately controlled asthma (pre-bronchodilator FEV ₁ ≥30% and <85% predicted; airway reversibility at screening defined as an increase in FEV ₁ ≥12% and ≥200 mL after four inhalations of albuterol or salbutamol; ICS stable use >250 µg per day for ≥6 weeks prior to pre-screening)	53.2	38.0	21.2	58.5	29.9	0.8	228	0.0	2.8	Change in clinic trough FEV ₁ at week 24	5
Kerstjens et al., 2020, IRIDIUM [28]	NCT02571777	Phase III, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	12.0	3092	MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)	MF/IND (80/150 µg q.d.), MF/IND (160/150 µg q.d.), FP/SAL (500/50 µg b.i.d.)	MF/IND/GLY: DPI (Breezhaler®); MF/IND: DPI (Breezhaler®); FP/SAL: DPI (Diskus®)	Symptomatic asthma (pre-bronchodilator FEV ₁ <80% predicted; ≥1 asthma exacerbation requiring medical care from a physician, ER visit, hospitalization, and systemic corticosteroid treatment in the year prior to screening; airway reversibility defined as an increase in FEV ₁ ≥12% and ≥200 mL after inhalation of albuterol or salbutamol; use of ICS/LABA medium- or high-dose for ≥3 months and at stable dose for ≥1 month prior to screening)	52.2	38.0	18.1	54.8	27.7	1.3	NA	NA	2.5	Change in trough FEV ₁ at week 26	5
Gessner et al., 2020 ARGON [29]	NCT03158311	Phase IIIB, multicentre, randomized, non-inferiority, partially-blinded, open-label, active-controlled, parallel-group	5.5	1426	MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)	FP/SAL (500/50 µg b.i.d.) + TIO (5 µg q.d.)	MF/IND/GLY: DPI (Breezhaler®); FP/SAL: DPI (Accuhaler®); TIO: soft mist inhaler (Respirim®)	Symptomatic asthma (pre-bronchodilator FEV ₁ <85% predicted; ≥1 severe asthma exacerbation requiring medical care from a physician, ER visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the year prior to study entry; airway reversibility defined as an increase in FEV ₁ ≥12% and ≥200 mL or historical evidence within the past 5 years of reversibility or positive bronchial provocation test; use of ICS/LABA stable medium- or high-dose prior to screening)	52.5	36.7	20.7	62.9	28.1	1.2	NA	2.2	2.6	Change in AQLQ total score	3
Virchow et al., 2019, TRIMARAN [30]	NCT02676076	Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group	12.0	1150	BDP/FOR/GLY (200/12/20 µg b.i.d.)	BDP/FOR (200/12 µg b.i.d.)	BDP/FOR/GLY: pMDI (NA); BDP/FOR: pMDI (NA)	Uncontrolled asthma (pre-bronchodilator FEV ₁ <80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV ₁ ≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA medium-dose for ≥1 month prior to study entry)	52.6	38.5	25.0	55.5	31.7	1.2	NA	0.0	2.3	Change in trough FEV ₁ at week 26, rate of moderate and severe exacerbations	5

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Virchow et al., 2019 TRIGGER [30]	NCT02676089	Phase III, multicentre, randomized, double-blind (BDP/FOR + TIO group was open-label), active-controlled, parallel-group	12.0	1431	BDP/FOR/GLY (400/120 µg b.i.d.)	BDP/FOR (400/120 µg b.i.d.) + TIO (5 µg q.d.)	BDP/FOR/GLY: pMDI (NA); BDP/FOR: pMDI (NA); TIO: soft mist inhaler (Respimat®)	Uncontrolled asthma (pre-bronchodilator FEV ₁ <80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV ₁ ≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA high-dose for ≥1 month prior to study entry)	52.9	38.7	25.2	51.9	34.0	1.2	NA	0.0	2.4	Change in trough FEV ₁ at week 26, rate of moderate and severe exacerbations	5
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ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BDP: beclomethasone dipropionate; b.i.d.: *bis in die*, twice-daily; DPI: dry powder inhaler; ER: emergency room; FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β₂-adrenoceptor agonist; q.d.: *quaque die*, once daily; MF: momethasone furoate; NA: not available; pMDI: pressurized metered dose inhaler; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.

Supplementary data

Table S4. Definition of moderate and severe asthma exacerbations as reported by the studies included in the network meta-analysis.

Study, year and reference	Study identifier	Definition of asthma exacerbation
Lee et al., 2020, CAPTAIN [27]	NCT02924688	Moderate asthma exacerbation: "deterioration in either asthma symptoms or lung function, or increased rescue bronchodilator use, that required a physician-directed temporary change in maintenance treatment to prevent the exacerbation from becoming a severe exacerbation". Severe asthma exacerbation: "an exacerbation requiring admission to hospital or a visit to an emergency department due to the need for SCSs, or asthma deterioration requiring SCS use (or doubling of the current maintenance SCS dose) for at least 3 days".
Kerstjens et al., 2020 IRIDIUM [28]	NCT02571777	Moderate asthma exacerbation: "the occurrence of two or more of the following: progressive increase of at least one asthma symptom; increased use of rescue medication; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant SCSs for more than 2 days or hospitalization". Severe asthma exacerbation: "an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that requires SCSs for at least 3 consecutive days or a need for an ER visit, hospitalisation owing to asthma, or death due to asthma".
Gessner et al., 2020 ARGON [29]	NCT03158311	Moderate asthma exacerbation: "the occurrence of two or more of the following: 1. progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms were outside the patient's usual range of day-to-day asthma and lasted at least two consecutive days. 2. increased use of "rescue" inhaled bronchodilators defined by: ≥50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured or night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights. 3. deterioration in lung function, which lasted for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalisation. This deterioration was defined by: ≥20% decrease in FEV ₁ from baseline value or ≥20% decrease in morning or evening PEF from baseline on 2 out of any 3 consecutive days compared to baseline or <60% of predicted PEF compared to baseline". Severe asthma exacerbation: "an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that required SCS for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalisation due to asthma or death due to asthma".
Virchow et al., 2019 TRIMARAN [30]	NCT02676076	Moderate asthma exacerbation: "nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV ₁ from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs" (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: "worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)".
Virchow et al., 2019 TRIGGER [30]	NCT02676089	Moderate asthma exacerbation: "nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV ₁ from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs" (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: "worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)".

ATS: American Thoracic Society; ER: emergency room; ERS: European Respiratory Society; FEV₁: forced expiratory flow in the 1st second; PEF: peak expiratory flow; SABA: short-acting β_2 -adrenoceptor agonist; SCS: systemic corticosteroid.

Supplementary data

Table S5. Level of ICS doses in agreement with the daily doses of medications in adults in the Phase III RCTs included in the network meta-analysis as reported by current GINA recommendations [5] and NICE guidelines [6].

Treatment	Regimen of administration	Daily dose	Level of ICS dose
BDP	200 µg b.i.d.	400 µg	MD
	400 µg b.i.d.	800 µg	HD
FF	100 µg q.d.	100 µg	MD ^a
	200 µg q.d.	200 µg	HD ^a
FP	500 µg b.i.d.	1000 µg	HD
MF	80 µg q.d.	80 µg	MD ^b
	160 µg q.d.	160 µg	HD ^b
	320 µg q.d.	320 µg	HD ^b

^aThe dose levels refer to those reported in the NICE guidelines [32].

^bThe MD 80 µg and the HD 160 µg of MF delivered via Breezhaler® device correspond to the MD 400 µg and the HD 800 µg of MF delivered via the approved Twisthaler® formulation [28, 29].

b.i.d.: *bis in die*, twice-daily; BDP: beclomethasone dipropionate; FF: fluticasone furoate; FP: fluticasone propionate; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; HD: high-dose; MD: medium-dose; MF: mometasone furoate; NICE: National Institute for Health and Care Excellence; PD: pharmacodynamics; PK: pharmacokinetic; q.d.: *quaque die*, once-daily; RCT: randomized controlled trials.

Supplementary data

Table S6. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network concerning the relative effects with 95%CrI of the co-primary endpoints.

Comparisons		Sensitivity analysis		
		References for direct comparisons	Moderate to severe asthma exacerbation (RR)	Trough FEV ₁ (mL)
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	[29, 30]	1.01 (0.76 - 1.31)	20.11 (-45.84 - 86.08)
	MD ICS/LABA/LAMA FDC	[28, 29]	0.83 (0.66 - 1.03)	30.99 (-18.79 - 82.46)
	HD ICS/LABA FDC	[28, 30]	0.74 (0.59 - 0.92) *	97.13 (43.71 - 150.47) *
	MD ICS/LABA FDC	[28]	0.66 (0.51 - 0.84) *	98.80 (43.55 - 82.46) *
HD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	[29]	0.83 (0.62 - 1.11)	10.20 (-61.15 - 83.76)
	HD ICS/LABA FDC	[30]	0.73 (0.54 - 0.98) *	76.38 (2.87 - 151.51) *
	MD ICS/LABA FDC	IC	0.65 (0.47 - 0.91) *	80.42 (1.44 - 160.14) *
MD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC	[28]	0.89 (0.69 - 1.12)	65.15 (9.29 - 120.94) *
	MD ICS/LABA FDC	[27, 28, 30]	0.79 (0.63 - 0.99) *	67.55 (16.00 - 118.41) *
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	IC	0.89 (0.69 - 1.15)	1.52 (-56.02 - 62.01)

*P<0.05.

CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting β_2 -adrenoceptor agonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.

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Table S7. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network with respect to the moderate or severe asthma exacerbations.

Comparisons		Moderate asthma exacerbation (RR)	Severe asthma exacerbation (RR)
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	0.86 (0.61 - 1.14)	1.39 (0.85 - 2.36)
	MD ICS/LABA/LAMA FDC	0.95 (0.73 - 1.23)	0.72 (0.48 - 1.09)
	HD ICS/LABA FDC	0.79 (0.60 - 1.01)	0.65 (0.42 - 0.98) *
	MD ICS/LABA FDC	0.74 (0.55 - 0.98) *	0.57 (0.36 - 0.90) *
MD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	1.10 (0.80 - 1.58)	0.52 (0.29 - 0.89) *
	HD ICS/LABA FDC	0.92 (0.67 - 1.32)	0.46 (0.26 - 0.80) *
	MD ICS/LABA FDC	0.85 (0.60 - 1.28)	0.41 (0.22 - 0.75) *
MD ICS/LABA FDC vs.	HD ICS/LABA FDC	0.83 (0.63 - 1.10)	0.89 (0.57 - 1.40)
	MD ICS/LABA FDC	0.77 (0.60 - 1.00) #	0.79 (0.52 - 1.20)
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	0.93 (0.69 - 1.26)	0.88 (0.55 - 1.42)

*P<0.05, #P=0.05.

CrI: credible interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2 -adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

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Supplementary Figures

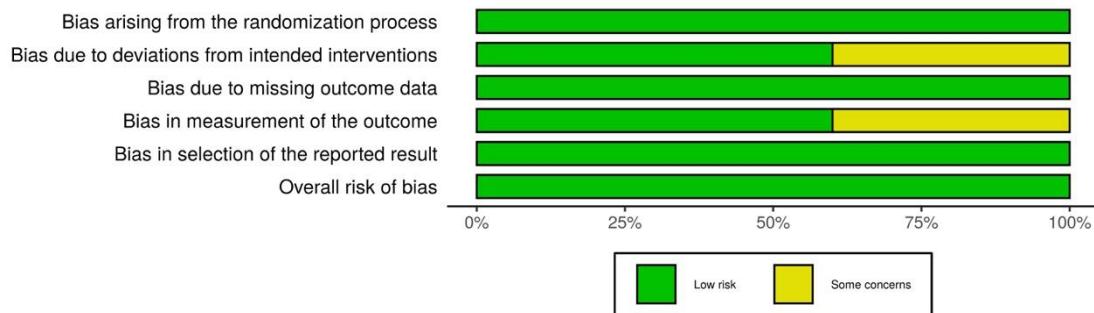


Figure S1. Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=5 Phase III RCTs). RCT: randomized controlled trial; RoB 2: Risk of Bias 2.

Supplementary data

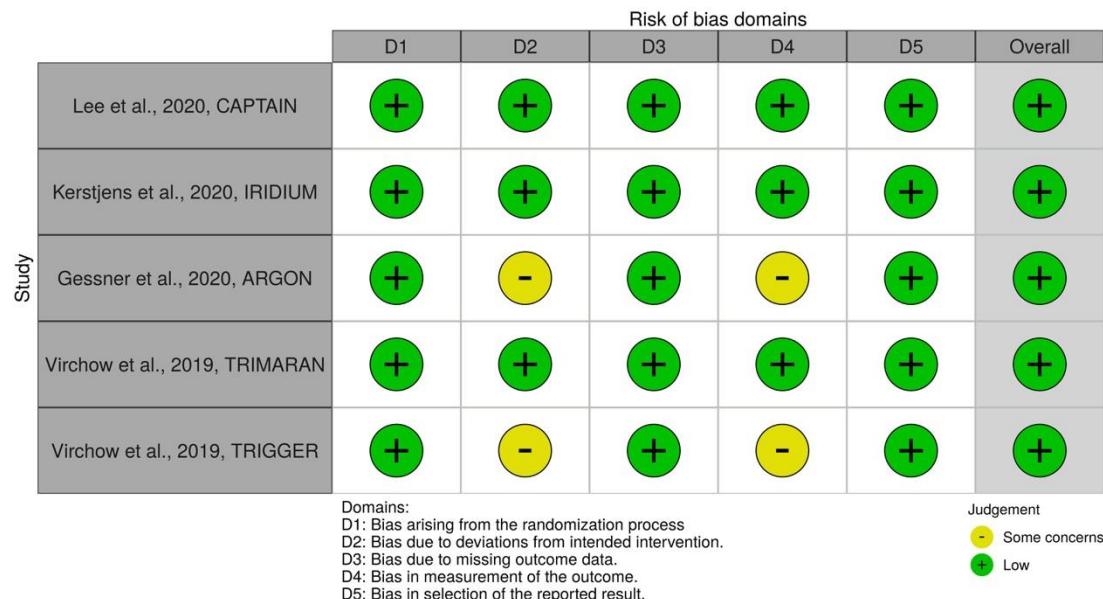


Figure S2. Traffic light plot for assessment of the risk of bias of each included Phase III RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; RCT: randomized controlled trial; RoB: risk of bias; robvis: risk of bias visualization tool. Yellow circle indicates some concerns on the risk of bias and green circle represents low risk of bias.

Supplementary data

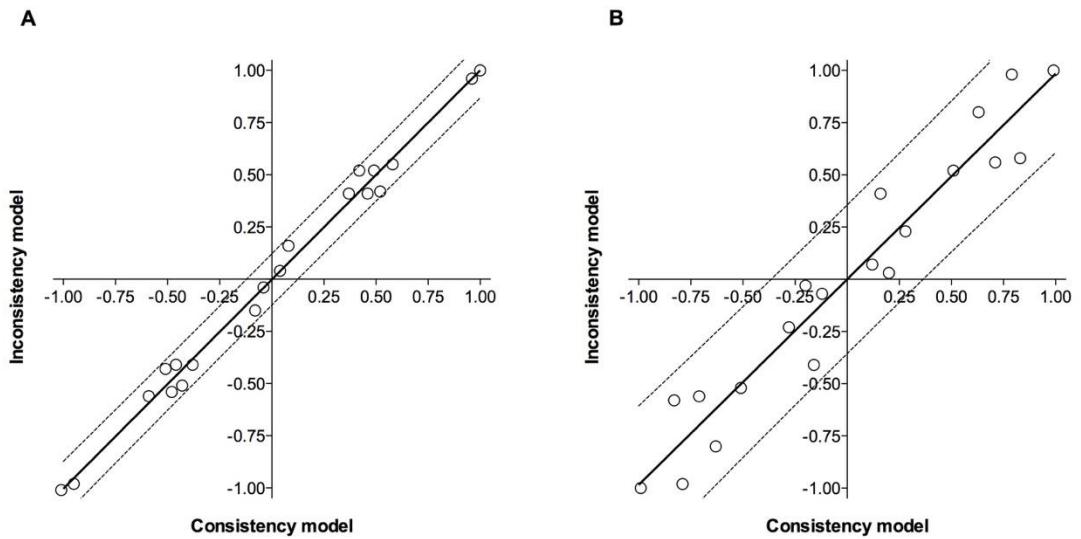


Figure S3. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% prediction bands) of different triple combination therapies and active comparators with respect to the risk of moderate to severe asthma exacerbation (A) and change from baseline in trough FEV₁ (B). FEV₁: forced expiratory volume in the 1st second.

Supplementary data

References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015; 4: 1.
2. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007; 7: 16.
3. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17(1): 1-12.
4. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from <http://www.training.cochrane.org/handbook>. 2019: 205-228.
5. GINA. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Available at: <https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report -final- wms.pdf>. Last accessed September 4, 2020. 2020.
6. NICE. National Institute for Health and Care Excellence (NICE). Inhaled corticosteroid doses for NICE's asthma guideline. Available at: <http://www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781> Last accessed November 26, 2020. 2018.
7. Pedder H, Sarri G, Keeney E, Nunes V, Dias S. Data extraction for complex meta-analysis (DECiMAL) guide. *Systematic reviews* 2016; 5(1): 212.
8. Gianinazzi ME, Rueegg CS, Zimmerman K, Kuehni CE, Michel G, Swiss Paediatric Oncology G. Intra-rater and inter-rater reliability of a medical record abstraction study on transition of care after childhood cancer. *PLoS One* 2015; 10(5): e0124290.
9. Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG. Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis. *COPD* 2017; 14(5): 552-563.
10. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpolh J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64(4): 383-394.
11. Calzetta L, Rogliani P, Ora J, Puxeddu E, Cazzola M, Matera MG. LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. *European Respiratory Review* 2017; 26(143): 160043.
12. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006; 101(474): 447-459.
13. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. John Wiley & Sons, 2004.
14. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012; 3(4): 285-299.
15. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Research synthesis methods* 2016; 7(1): 80-93.
16. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; 33(5): 641-656.
17. Cazzola M. Application of Number Needed to Treat (NNT) as a Measure of Treatment Effect in Respiratory Medicine. *Treat Respir Med* 2006; 5(2): 79-84.
18. Aaron SD, Fergusson DA. Exaggeration of treatment benefits using the "event-based" number needed to treat. *CMAJ* 2008; 179(7): 669-671.
19. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax* 2013; 68(6): 540-543.
20. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *Bmj* 1999; 319(7223): 1492-1495.

Supplementary data

21. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; 317(7168): 1309-1312.
22. Dobler CC, Wilson ME, Murad MH. A pulmonologist's guide to understanding network meta-analysis. *Eur Respir J* 2018; 52(1).
23. Abràmoff MD, Magalhães PJ, Ram SJ. Image processing with ImageJ. *Biophotonics international* 2004; 11(7): 36-42.
24. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods* 2012; 3(4): 285-299.
25. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj* 2019; 366: i4898.
26. McGuinness LA. robvis: An R package and web application for visualising risk-of-bias assessments. 2019 2019/07/01 [cited; Available from: <https://github.com/mcguinlu/robvis>
27. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UME/C/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *The Lancet Respiratory medicine* 2020.
28. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *The Lancet Respiratory medicine* 2020.
29. Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). *Respir Med* 2020; 170: 106021.
30. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet* 2019; 394(10210): 1737-1749.
31. Virchow JC, Backer V, de Blay F, Kuna P, Ljørring C, Prieto JL, Villesen HH. Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement. *Respir Med* 2015; 109(5): 547-556.
32. NICE. National Institute for Health and Care Excellence (NICE). Inhaled corticosteroid doses for NICE's asthma guideline. Available at: <http://www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781> Last accessed January 16, 2020. 2018.

Supplementary data

Appendix

Appendix 1. Summary text of the identified records.

- 1: Miller D, Vaidya S, Jauernig J, Ethell B, Wagner K, Radhakrishnan R, Tillmann HC. Lung function, pharmacokinetics, and tolerability of inhaled indacaterol maleate and acetate in asthma patients. *Respir Res.* 2020 Sep 23;21(1):248. doi: 10.1186/s12931-020-01501-1. PMID: 32967685; PMCID: PMC7513528.
- 2: Table: Correct Use of inhalers for COPD. *Med Lett Drugs Ther.* 2020 Sep 7;62(1606):e150-e154. PMID: 32960876.
- 3: Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UME/CVI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med.* 2020 Sep 9:S2213-2600(20)30389-1. doi: 10.1016/S2213-2600(20)30389-1. Epub ahead of print. PMID: 32918892.
- 4: Sarlus H, Codita A, Wang X, Cedazo-Minguez A, Schultzberg M, Oprica M. Chronic Airway Allergy Induces Pro-Inflammatory Responses in the Brain of Wildtype Mice but Not 3xTgAD Mice. *Neuroscience.* 2020 Sep 8;448:14-27. doi: 10.1016/j.neuroscience.2020.09.005. Epub ahead of print. PMID: 32916195.
- 5: Di Mauro A, Baldassarre ME, Brindisi G, Zicari AM, Tarantini M, Laera N, Capozza M, Panza R, Salvatore S, Pensabene L, Fanelli M, Laforgia N. Hydrolyzed Protein Formula for Allergy Prevention in Preterm Infants: Follow-Up Analysis of a Randomized, Triple-Blind, Placebo-Controlled Study. *Front Pediatr.* 2020 Jul 30;8:422. doi: 10.3389/fped.2020.00422. PMID: 32903747; PMCID: PMC7438860.
- 6: Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). *Respir Med.* 2020 Aug-Sep;170:106021. doi: 10.1016/j.rmed.2020.106021. Epub 2020 May 27. PMID: 32843164.
- 7: Paplinska-Goryca M, Misiukiewicz-Stepien P, Proboscycz M, Nejman-Gryz P, Gorska K, Krenke R. The Expressions of TSLP, IL-33, and IL-17A in Monocyte-Derived Dendritic Cells from Asthma and COPD Patients are Related to Epithelial-Macrophage Interactions. *Cells.* 2020 Aug 22;9(9):E1944. doi: 10.3390/cells9091944. PMID: 32842623.
- 8: Omori T, Nakamori S, Fujimoto N, Ishida M, Kitagawa K, Ichikawa Y, Kumagai N, Kurita T, Imanaka-Yoshida K, Hiroe M, Sakuma H, Ito M, Dohi K. Myocardial Native T₁ Predicts Load-Independent Left Ventricular Chamber Stiffness In Patients With HFrEF. *JACC Cardiovasc Imaging.* 2020 Aug 3:S1936-878X(20)30518-0. doi: 10.1016/j.jcmg.2020.05.030. Epub ahead of print. PMID: 32771571.
- 9: Hong H, Liao S, Chen F, Yang Q, Wang DY. Role of IL-25, IL-33, and TSLP in triggering united airway diseases toward type 2 inflammation. *Allergy.* 2020 Aug 1. doi: 10.1111/all.14526. Epub ahead of print. PMID: 32737888.
- 10: Zhang Q, Chen S, Liu A, Wang Y. Quantification of 10 bioactive components of Yazhangsan in rat plasma by LC-MS/MS and its application. *Biomed Chromatogr.* 2020 Jul 28:e4958. doi: 10.1002/bmc.4958. Epub ahead of print. PMID: 32725639.
- 11: Ait Bamai Y, Goudarzi H, Araki A, Okada E, Kashino I, Miyashita C, Kishi R. Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health. *Environ Int.* 2020 Jul 24;143:105979. doi: 10.1016/j.envint.2020.105979. Epub ahead of print. PMID: 32717646.
- 12: Luz MI, Aguiar R, Morais-Almeida M. The reality of LAMAs for adult asthmatic patients. *Expert Rev Respir Med.* 2020 Jul 20:1-8. doi: 10.1080/17476348.2020.1794828. Epub ahead of print. PMID: 32687426.
- 13: Lipworth B, Chan R, Kuo CR. Systemic Interleukin-6 and Severe Asthma. *Am J Respir Crit Care Med.* 2020 Jul 20. doi: 10.1164/rccm.202006-2354LE. Epub ahead of print. PMID: 32687393.
- 14: Virchow JC. Assessing the benefits of triple versus dual fixed-dose

Supplementary data

combinations for the treatment of severe asthma. *Lancet Respir Med.* 2020 Oct;8(10):937-939. doi: 10.1016/S2213-2600(20)30303-9. Epub 2020 Jul 9. PMID: 32653077.

15: van Zyl-Smit RN, Krüll M, Gessner C, Gon Y, Noga O, Richard A, de Los Reyes A, Shu X, Pethe A, Tanase AM, D'Andrea P; PALLADIUM trial investigators. Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study. *Lancet Respir Med.* 2020 Oct;8(10):987-999. doi: 10.1016/S2213-2600(20)30178-8. Epub 2020 Jul 9. PMID: 32653075.

16: Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P; IRIDIUM trial investigators. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med.* 2020 Oct;8(10):1000-1012. doi: 10.1016/S2213-2600(20)30190-9. Epub 2020 Jul 9. PMID: 32653074.

17: Ghasemi Sakha F, Azimi Saeen A, Moazzeni SM, Etesam F, Vaezi G. A Randomized, Triple-blind Placebo-controlled Trial to Determine the Effect of Saffron on the Serum Levels of MMP-9 and TIMP-1 in Patients with Multiple Sclerosis. *Iran J Allergy Asthma Immunol.* 2020 Jun 23;19(3):297-304. doi: 10.18502/ijaaai.v19i3.3457. PMID: 32615663.

18: Avdeev SN, Aisanov ZR, Belevsky AS, Beeh KM, Vizel AA, Zyryanov SK, Ignatova GL, Kostikas K, Leshchenko IV, Ovcharenko SI, Sinopal'nikov AI, Titova ON, Shmelev EI. [The concept of chronic obstructive pulmonary disease clinical control as a decision - making tool in real clinical practice for optimizing of basic pharmacotherapy]. *Ter Arkh.* 2020 Jan 15;92(1):89-95. Russian. doi: 10.26442/00403660.2020.01.000489. PMID: 32598669.

19: Velázquez-Quesada I, Ruiz-Moreno AJ, Casique-Aguirre D, Aguirre-Alvarado C, Cortés-Mendoza F, de la Fuente-Granada M, García-Pérez C, Pérez-Tapia SM, González-Arenas A, Segura-Cabrera A, Velasco-Velázquez MA. Pranlukast Antagonizes CD49f and Reduces Stemness in Triple-Negative Breast Cancer Cells. *Drug Des Devel Ther.* 2020 May 12;14:1799-1811. doi: 10.2147/DDDT.S247730. PMID: 32494122; PMCID: PMC7229803.

20: Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, Papi A. Extrafine triple therapy in patients with asthma and persistent airflow limitation. *Eur Respir J.* 2020 Sep 24;56(3):2000476. doi: 10.1183/13993003.00476-2020. PMID: 32430414.

21: Chippis B, Mosnaim G, Mathur SK, Shaikh A, Khoury S, Gopalan G, Palli SR, Lamerato L, Casciano J, Dotiwala Z, Settipane R. Add-on tiotropium versus step-up inhaled corticosteroid plus long-acting beta-2-agonist in real-world patients with asthma. *Allergy Asthma Proc.* 2020 Jul 1;41(4):248-255. doi: 10.2500/aap.2020.41.200036. Epub 2020 May 15. PMID: 32414426.

22: Suzuki T, Fairburn-Beech J, Sato K, Kaise T. Clinical characteristics, treatment patterns, disease burden, and persistence/adherence in patients with asthma initiating inhaled triple therapy: real-world evidence from Japan. *Curr Med Res Opin.* 2020 Jun;36(6):1049-1057. doi: 10.1080/03007995.2020.1763937. Epub 2020 May 14. PMID: 32363945.

23: Matera MG, Belardo C, Rinaldi M, Rinaldi B, Cazzola M. New perspectives on the role of muscarinic antagonists in asthma therapy. *Expert Rev Respir Med.* 2020 Aug;14(8):817-824. doi: 10.1080/17476348.2020.1758069. Epub 2020 Apr 26. PMID: 32316778.

24: Matera MG, Belardo C, Rinaldi M, Rinaldi B, Cazzola M. Emerging muscarinic receptor antagonists for the treatment of asthma. *Expert Opin Emerg Drugs.* 2020 Jun;25(2):123-130. doi: 10.1080/14728214.2020.1758059. Epub 2020 Jun 17. PMID: 32312134.

25: Bloom CI, Douglas I, Usmani OS, Quint JK. Inhaled Corticosteroid Treatment Regimens and Health Outcomes in a UK COPD Population Study. *Int J Chron Obstruct Pulmon Dis.* 2020 Apr 2;15:701-710. doi: 10.2147/COPD.S241568. Erratum in: *Int J Chron Obstruct Pulmon Dis.* 2020 Apr 22;15:869. PMID: 32308379; PMCID: PMC7136662.

26: Paplinska-Goryca M, Misiukiewicz-Stepien P, Nejman-Gryz P, Proboszcz M, Mlacki M, Gorska K, Krenke R. Epithelial-macrophage-dendritic cell interactions impact alarmins expression in asthma and COPD. *Clin Immunol.* 2020 Jun;215:108421. doi: 10.1016/j.clim.2020.108421. Epub 2020 Apr 14. PMID:

Supplementary data

32302698.

27: Watz H, Hohlfeld JM, Singh D, Beier J, Diamant Z, Liu J, Hua S, Abd-Elaziz K, Pinot P, Jones I, Tillmann HC. Letter to the editor: indacaterol/glycopyrronium/mometasone furoate compared with salmeterol/fluticasone propionate in patients with asthma: a randomized controlled cross-over study. *Respir Res.* 2020 Apr 15;21(1):87. doi: 10.1186/s12931-020-01349-5. PMID: 32295593; PMCID: PMC7160900.

28: Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, Criner GJ, Donaldson GC, Dreher M, Fan VS, Gershon AS, Han MK, Krishnan JA, Martinez FJ, Meek PM, Morgan M, Polkey MI, Puhan MA, Sadatsafavi M, Sin DD, Washko GR, Wedzicha JA, Aaron SD. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2020 May 1;201(9):e56-e69. doi: 10.1164/rccm.202003-0625ST. Erratum in: *Am J Respir Crit Care Med.* 2020 Sep 15;202(6):910. PMID: 32283960; PMCID: PMC7193862.

29: Li Y, Lim J, Stemkowski S, Kaila S, Renda A, Shaikh A. Initiation of triple therapy maintenance treatment among patients with COPD. *Am J Manag Care.* 2020 Apr 1;26(4):e106-e112. doi: 10.37765/ajmc.2020.42837. PMID: 32270987.

30: Kaplan AG. Inhaled Corticosteroid Treatment in Chronic Obstructive Pulmonary Disease (COPD): Boon or Bane? *J Am Board Fam Med.* 2020 Mar-Apr;33(2):289-302. doi: 10.3122/jabfm.2020.02.190227. PMID: 32179613.

31: Chung S, Lee YG, Karpurapu M, Englert JA, Ballinger MN, Davis IC, Park GY, Christman JW. Depletion of microRNA-451 in response to allergen exposure accentuates asthmatic inflammation by regulating Sirtuin2. *Am J Physiol Lung Cell Mol Physiol.* 2020 May 1;318(5):L921-L930. doi: 10.1152/ajplung.00457.2019. Epub 2020 Mar 11. PMID: 32159972; PMCID: PMC7272736.

32: Knibb RC, Alviani C, Garriga-Baraut T, Mortz CG, Vazquez-Ortiz M, Angier E, Blumchen K, Comberiati P, Duca B, DunnGalvin A, Gore C, Hox V, Jensen B, Pite H, Santos AF, Sanchez-Garcia S, Gowland MH, Timmermans F, Roberts G. The effectiveness of interventions to improve self-management for adolescents and young adults with allergic conditions: A systematic review. *Allergy.* 2020 Aug;75(8):1881-1898. doi: 10.1111/all.14269. PMID: 32159856.

33: Kardos P, Geiss F, Simon J, Franken C, Butt U, Worth H. Duplicate Prescriptions of Inhaled Medications for Obstructive Lung Diseases. *Pneumologie.* 2020 Mar;74(3):149-158. English. doi: 10.1055/a-1083-7961. Epub 2020 Mar 6. PMID: 32143230.

34: Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, Sawai Y, Shimizu T, Tamaki T, Nomura S. Triple Therapy with Budesonide/Glycopyrrolate/Formoterol Fumarate Improves Inspiratory Capacity in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap. *Int J Chron Obstruct Pulmon Dis.* 2020 Feb 5;15:269-277. doi: 10.2147/COPD.S231004. PMID: 32103926; PMCID: PMC7014958.

35: Calabria S, Ronconi G, Dondi L, Piccinni C, Pedrini A, Esposito I, Pistelli R, Martini N. Open triple therapy for chronic obstructive pulmonary disease: Patterns of prescription, exacerbations and healthcare costs from a large Italian claims database. *Pulm Pharmacol Ther.* 2020 Apr;61:101904. doi: 10.1016/j.pupt.2020.101904. Epub 2020 Feb 21. PMID: 32092473.

36: Bousquet J, Farrell J, Illario M; ARIA-MASK study group. Aligning the Good Practice MASK With the Objectives of the European Innovation Partnership on Active and Healthy Ageing. *Allergy Asthma Immunol Res.* 2020 Mar;12(2):238-258. doi: 10.4168/aaair.2020.12.2.238. PMID: 32009320; PMCID: PMC6997284.

37: Ioachimescu OC, Janocko NJ, Ciavatta MM, Howard M, Warnock MV. Obstructive Lung Disease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment. *J Clin Sleep Med.* 2020 Feb 15;16(2):267-277. doi: 10.5664/jcsm.8180. Epub 2020 Jan 13. PMID: 31992433; PMCID: PMC7053033.

38: Matera MG, Rinaldi B, Berardo C, Rinaldi M, Cazzola M. A review of the pharmacokinetics of M₃ muscarinic receptor antagonists used for the treatment of asthma. *Expert Opin Drug Metab Toxicol.* 2020 Feb;16(2):143-148. doi: 10.1080/17425255.2020.1716730. Epub 2020 Jan 30. PMID: 31958237.

39: Vogelberg C, Goldstein S, Graham L, Kaplan A, de la Hoz A, Hamelmann E. A comparison of tiotropium, long-acting β₂-agonists and leukotriene receptor antagonists on lung function and exacerbations in paediatric patients with asthma. *Respir Res.* 2020 Jan 13;21(1):19. doi: 10.1186/s12931-020-1282-9.

Supplementary data

PMID: 31931792; PMCID: PMC6958672.

- 40: Jensen ME, Ducharme FM, Alos N, Mailhot G, Mâsse B, White JH, Sadatsafavi M, Khamessan A, Tse SM, Alizadehfar R, Bock DE, Daigneault P, Lemire C, Yang C, Radhakrishnan D. Vitamin D in the prevention of exacerbations of asthma in preschoolers (DIVA): protocol for a multicentre randomised placebo-controlled triple-blind trial. *BMJ Open*. 2019 Dec 30;9(12):e033075. doi: 10.1136/bmjopen-2019-033075. PMID: 31892662; PMCID: PMC6955525.
- 41: Messinger AI, Luo G, Deterding RR. The doctor will see you now: How machine learning and artificial intelligence can extend our understanding and treatment of asthma. *J Allergy Clin Immunol*. 2020 Feb;145(2):476-478. doi: 10.1016/j.jaci.2019.12.898. Epub 2019 Dec 25. PMID: 31883444; PMCID: PMC7035143.
- 42: LeMessurier KS, Iverson AR, Chang TC, Palipane M, Vogel P, Rosch JW, Samarasinghe AE. Allergic inflammation alters the lung microbiome and hinders synergistic co-infection with H1N1 influenza virus and Streptococcus pneumoniae in C57BL/6 mice. *Sci Rep*. 2019 Dec 18;9(1):19360. doi: 10.1038/s41598-019-55712-8. PMID: 31852944; PMCID: PMC6920369.
- 43: Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and Therapeutics of Bronchodilators Revisited. *Pharmacol Rev*. 2020 Jan;72(1):218-252. doi: 10.1124/pr.119.018150. PMID: 31848208.
- 44: Sulkku J, Janson C, Melhus H, Malinovschi A, Ställberg B, Bröms K, Höglund M, Lisspers K, Hammarlund-Udenaes M, Nielsen EI. A Cross-Sectional Study Assessing Appropriateness Of Inhaled Corticosteroid Treatment In Primary And Secondary Care Patients With COPD In Sweden. *Int J Chron Obstruct Pulmon Dis*. 2019 Nov 5;14:2451-2460. doi: 10.2147/COPD.S218747. PMID: 31806954; PMCID: PMC6842319.
- 45: Lombardi C, Menzella F, Passalacqua G. Long-term responsiveness to mepolizumab after failure of omalizumab and bronchial thermoplasty: Two triple-switch case reports. *Respir Med Case Rep*. 2019 Nov 19;29:100967. doi: 10.1016/j.rmedcr.2019.100967. PMID: 31799113; PMCID: PMC6881682.
- 46: Désirée LL, Margarita FV, Mónica RG, María Del Carmen CS, Jorge Agustín LP, José Antonio OM, Blanca DR, Erika Del Carmen LE, Jade RL, Juan Carlos VG, Jorge SP. An online survey detected knowledge gaps and cost-saving opportunities in asthma maintenance treatment among allergists, pulmonologists, ENTs and primary care. *World Allergy Organ J*. 2019 Nov 19;12(12):100084. doi: 10.1016/j.waojou.2019.100084. PMID: 31768217; PMCID: PMC6872758.
- 47: Gregoriano C, Tschacher A, Grendelmeier P, Cadus C. Inhalative Therapie bei COPD und Asthma [Development of inhaled therapies for COPD and asthma]. *Ther Umsch*. 2019 Nov;76(6):301-310. German. doi: 10.1024/0040-5930/a001103. PMID: 31762413.
- 48: Niimi A, Fukumitsu K, Takeda N, Kanemitsu Y. Interfering with airway nerves in cough associated with asthma. *Pulm Pharmacol Ther*. 2019 Dec;59:101854. doi: 10.1016/j.pupt.2019.101854. Epub 2019 Nov 1. PMID: 31683030.
- 49: Rogliani P, Matera MG, Facciolo F, Page C, Cazzola M, Calzetta L. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide: Synergy of triple combination therapy on human airway smooth muscle ex vivo. *Br J Pharmacol*. 2020 Mar;177(5):1150-1163. doi: 10.1111/bph.14909. Epub 2020 Jan 29. PMID: 31660611; PMCID: PMC7042115.
- 50: Cheng WC, Liao WC, Wu BR, Chen CY, Shen MF, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. Clinical predictors of asthmatics in identifying subgroup requiring long-term tiotropium add-on therapy: a real-world study. *J Thorac Dis*. 2019 Sep;11(9):3785-3793. doi: 10.21037/jtd.2019.09.22. PMID: 31656651; PMCID: PMC6790467.
- 51: Calzetta L, Matera MG, Cazzola M, Rogliani P. Optimizing the Development Strategy of Combination Therapy in Respiratory Medicine: From Isolated Airways to Patients. *Adv Ther*. 2019 Dec;36(12):3291-3298. doi: 10.1007/s12325-019-01119-w. Epub 2019 Oct 25. PMID: 31654332; PMCID: PMC6860506.
- 52: Averell CM, Laliberté F, Duh MS, Wu JW, Germain G, Faison S. Characterizing Real-World Use Of Tiotropium In Asthma In The USA. *J Asthma Allergy*. 2019 Oct 7;12:309-321. doi: 10.2147/JAA.S216932. PMID: 31632091; PMCID: PMC6789414.
- 53: Domingo C, Rello J, Sogo A. As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say? *Drugs*. 2019 Nov;79(16):1729-1737. doi: 10.1007/s40265-019-01202-0. Erratum in: *Drugs*. 2019 Oct 29;: PMID: 31584145.
- 54: FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new

Supplementary data

- option for uncontrolled asthma. *Lancet.* 2019 Nov 9;394(10210):1690-1692. doi: 10.1016/S0140-6736(19)32216-0. Epub 2019 Sep 30. PMID: 31582315.
- 55: Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet.* 2019 Nov 9;394(10210):1737-1749. doi: 10.1016/S0140-6736(19)32215-9. Epub 2019 Sep 30. PMID: 31582314.
- 56: Fens T, van der Pol S, Kocks JWH, Postma MJ, van Boven JFM. Economic Impact of Reducing Inappropriate Inhaled Corticosteroids Use in Patients With Chronic Obstructive Pulmonary Disease: ISPOR's Guidance on Budget Impact in Practice. *Value Health.* 2019 Oct;22(10):1092-1101. doi: 10.1016/j.jval.2019.05.006. Epub 2019 Aug 17. PMID: 31563251.
- 57: Moretz C, Sharpsten L, Bengtson LG, Koep E, Le L, Tong J, Stanford RH, Hahn B, Ray R. Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study. *Int J Chron Obstruct Pulmon Dis.* 2019 Aug 1;14:1721-1737. doi: 10.2147/COPD.S204649. PMID: 31534326; PMCID: PMC6681903.
- 58: Voorham J, Corradi M, Papi A, Vogelmeier CF, Singh D, Fabbri LM, Kerkhof M, Kocks JH, Carter V, Price D. Comparative effectiveness of triple therapy <i>versus</i> dual bronchodilation in COPD. *ERJ Open Res.* 2019 Aug 30;5(3):00106-2019. doi: 10.1183/23120541.00106-2019. PMID: 31497610; PMCID: PMC6715826.
- 59: Moore BJR, Islam B, Ward S, Jackson O, Armitage R, Blackburn J, Haider S, McHugh PC. Repurposing of Tranilast for Potential Neuropathic Pain Treatment by Inhibition of Sepiapterin Reductase in the BH₄ Pathway. *ACS Omega.* 2019 Jul 10;4(7):11960-11972. doi: 10.1021/acsomega.9b01228. PMID: 31460307; PMCID: PMC6682008.
- 60: Cazzola M, Rogliani P, Matera MG. Ultra-LABAs for the treatment of asthma. *Respir Med.* 2019 Sep;156:47-52. doi: 10.1016/j.rmed.2019.08.005. Epub 2019 Aug 12. PMID: 31425937.
- 61: Cazzola M, Puxeddu E, Matera MG, Rogliani P. A potential role of triple therapy for asthma patients. *Expert Rev Respir Med.* 2019 Nov;13(11):1079-1085. doi: 10.1080/17476348.2019.1657408. Epub 2019 Sep 1. PMID: 31422716.
- 62: Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, Halpin DMG, Han MK, Hartley B, Lange P, Lettis S, Lipson DA, Lomas DA, Martinez FJ, Papi A, Roche N, van der Valk RJP, Wise R, Singh D. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *Lancet Respir Med.* 2019 Sep;7(9):745-756. doi: 10.1016/S2213-2600(19)30190-0. Epub 2019 Jul 4. PMID: 31281061.
- 63: Roberts S, Salmon SL, Steiner DJ, Williams CM, Metzger DW, Furuya Y. Allergic Airway Disease Prevents Lethal Synergy of Influenza A Virus-Streptococcus pneumoniae Coinfection. *mBio.* 2019 Jul 2;10(4):e01335-19. doi: 10.1128/mBio.01335-19. PMID: 31266877; PMCID: PMC6606812.
- 64: Wahid B. Successful treatment of HBV, HCV, & HEV, with 12-week long use of tenofovir, sofosbuvir, daclatasvir, and ribavirin: A case report. *J Infect Public Health.* 2020 Jan;13(1):149-150. doi: 10.1016/j.jiph.2019.06.004. Epub 2019 Jun 21. PMID: 31235341.
- 65: Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, Tamaki T, Shimizu T, Nomura S. Effect of triple therapy in patients with asthma-COPD overlap. *Int J Clin Pharmacol Ther.* 2019 Aug;57(8):384-392. doi: 10.5414/CP203382. PMID: 31232275; PMCID: PMC6637394.
- 66: Huang WC, Gu PY, Fang LW, Huang YL, Lin CF, Liou CJ. Sophoraflavanone G from Sophora flavescens induces apoptosis in triple-negative breast cancer cells. *Phytomedicine.* 2019 Aug;61:152852. doi: 10.1016/j.phymed.2019.152852. Epub 2019 Jan 29. PMID: 31035052.
- 67: Almatrafi A, Alfadhli F, Khan YN, Afzal S, Hashmi JA, Ullah A, Albalawi AM, Basit S. A Heterozygous Mutation in the Triple Helical Region of the Alpha 1 (II) Chain of the COL2A1 Protein Causes Non-Lethal Spondyloepiphyseal Dysplasia Congenita. *Genet Test Mol Biomarkers.* 2019 May;23(5):310-315. doi: 10.1089/gtmb.2018.0301. Epub 2019 Mar 30. PMID: 30932712.

Supplementary data

- 68: Gaduzo S, McGovern V, Roberts J, Scullion JE, Singh D. When to use single-inhaler triple therapy in COPD: a practical approach for primary care health care professionals. *Int J Chron Obstruct Pulmon Dis.* 2019 Feb 13;14:391-401. doi: 10.2147/COPD.S173901. PMID: 30863039; PMCID: PMC6388781.
- 69: Ducharme FM, Jensen M, Mailhot G, Alos N, White J, Rousseau E, Tse SM, Khamessan A, Vinet B. Impact of two oral doses of 100,000 IU of vitamin D₃ in preschoolers with viral-induced asthma: a pilot randomised controlled trial. *Trials.* 2019 Feb 18;20(1):138. doi: 10.1186/s13063-019-3184-z. PMID: 30777118; PMCID: PMC6379931.
- 70: Llanos JP, Bell CF, Packnett E, Thiel E, Irwin DE, Hahn B, Ortega H. Real-world characteristics and disease burden of patients with asthma prior to treatment initiation with mepolizumab or omalizumab: a retrospective cohort database study. *J Asthma Allergy.* 2019 Jan 25;12:43-58. doi: 10.2147/JAA.S189676. PMID: 30774390; PMCID: PMC6354698.
- 71: Kaplan A, Chapman KR, Anees SM, Mayers I, Rochdi D, Djandji M, Préfontaine D, McIvor A. Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study. *Int J Chron Obstruct Pulmon Dis.* 2019 Jan 18;14:249-260. doi: 10.2147/COPD.S185485. PMID: 30718952; PMCID: PMC6343749.
- 72: Parmar G, Pundarikakshudu K, Balaraman R. Anti-anaphylactic and antiasthmatic activity of *Euphorbia thymifolia* L. on experimental animals. *J Tradit Complement Med.* 2018 Apr 30;9(1):60-65. doi: 10.1016/j.jtcme.2018.03.002. PMID: 30671367; PMCID: PMC6335472.
- 73: Lee YG, Reader BF, Herman D, Streicher A, Englert JA, Ziegler M, Chung S, Karpurapu M, Park GY, Christman JW, Ballinger MN. Sirtuin 2 enhances allergic asthmatic inflammation. *JCI Insight.* 2019 Feb 21;4(4):e124710. doi: 10.1172/jci.insight.124710. PMID: 30668546; PMCID: PMC6478424.
- 74: Lépine M, Sleno L, Lesage J, Gagné S. A validated liquid chromatography/tandem mass spectrometry method for 4,4'-methylenedianiline quantitation in human urine as a measure of 4,4'-methylene diphenyl diisocyanate exposure. *Rapid Commun Mass Spectrom.* 2019 Mar 30;33(6):600-606. doi: 10.1002/rcm.8380. PMID: 30604511.
- 75: Yang CH, Su CH, Liu SC, Ng LT. Isolation, Anti-Inflammatory Activity and Physico-chemical Properties of Bioactive Polysaccharides from Fruiting Bodies of Cultivated *Cordyceps cicadae* (Ascomycetes). *Int J Med Mushrooms.* 2019;21(10):995-1006. doi: 10.1615/IntJMedMushrooms.2019031922. PMID: 32450036.
- 76: Vanfleteren L, Fabbri LM, Papi A, Petruzzelli S, Celli B. Triple therapy (ICS/LABA/LAMA) in COPD: time for a reappraisal. *Int J Chron Obstruct Pulmon Dis.* 2018 Dec 12;13:3971-3981. doi: 10.2147/COPD.S185975. PMID: 30587953; PMCID: PMC6296179.
- 77: Saito H, Tsuchiya K, Chiba S, Ogata T, Imase R, Yagi T, Mishima Y, Jinta T, Saito K, Taki R, Isogai S, Jin Y, Kawasaki T, Natsume I, Miyashita Y, Takagiwa J, Ishiwata N, Chiaki T, Kishi M, Tsukada Y, Yamasaki M, Inase N, Miyazaki Y. Treatment of asthma in smokers: A questionnaire survey in Japanese clinical practice. *Respir Investig.* 2019 Mar;57(2):126-132. doi: 10.1016/j.resinv.2018.11.001. Epub 2018 Dec 11. PMID: 30552072.
- 78: Watz H, Tetzlaff K, Magnussen H, Mueller A, Rodriguez-Roisin R, Wouters EFM, Vogelmeier C, Calverley PMA. Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM trial. *Respir Res.* 2018 Dec 13;19(1):251. doi: 10.1186/s12931-018-0944-3. PMID: 30545350; PMCID: PMC6293570.
- 79: Hosseini SA, Zilaee M, Shoushtari MH, Ghasemi Dehcheshmeh M. An evaluation of the effect of saffron supplementation on the antibody titer to heat-shock protein (HSP) 70, hsCRP and spirometry test in patients with mild and moderate persistent allergic asthma: A triple-blind, randomized placebo-controlled trial. *Respir Med.* 2018 Dec;145:28-34. doi: 10.1016/j.rmed.2018.10.016. Epub 2018 Oct 19. PMID: 30509713.
- 80: Hamelmann E. Managing Severe Asthma: A Role for the Long-Acting Muscarinic Antagonist Tiotropium. *Biomed Res Int.* 2018 Oct 24;2018:7473690. doi: 10.1155/2018/7473690. Erratum in: *Biomed Res Int.* 2019 Jan 29;2019:8515804. PMID: 30474042; PMCID: PMC6220412.
- 81: Kupczyk M, Kuna P. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide as a combination therapy for chronic obstructive pulmonary disease. *Expert Rev Respir Med.* 2019 Jan;13(1):5-11. doi:

Supplementary data

10.1080/17476348.2019.1548937. Epub 2018 Nov 27. PMID: 30463457.

82: Muller A, Rochoy M. Plongée sous-marine et asthme : revue de littérature [Diving and asthma: Literature review]. Rev Pneumol Clin. 2018 Dec;74(6):416-426. French. doi: 10.1016/j.pneumo.2018.10.002. Epub 2018 Nov 12. PMID: 30442511.

83: Li Y, Li H, Sheng Y, Du X, Yao Y, Luo X, Ma P. Pharmacokinetics of Single and Repeat Doses of Fluticasone Furoate/Umeclidinium/Vilanterol in Healthy Chinese Adults. Clin Pharmacol Drug Dev. 2019 Aug;8(6):721-733. doi: 10.1002/cpdd.626. Epub 2018 Nov 14. PMID: 30427594.

84: Glied SA, Jackson A. How Would Americans' Out-of-Pocket Costs Change If Insurance Plans Were Allowed to Exclude Coverage for Preexisting Conditions? Issue Brief (Commonw Fund). 2018 Nov 1;2018:1-9. PMID: 30387577.

85: Erkman J, Vaynblat A, Thomas K, Segal LN, Levine J, Moy L, Greifer M, Giusti R, Shah R, Kazachkov M. Airway and esophageal eosinophils in children with severe uncontrolled asthma. Pediatr Pulmonol. 2018 Dec;53(12):1598-1603. doi: 10.1002/ppul.24180. Epub 2018 Oct 23. PMID: 30353711.

86: Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. Lancet Respir Med. 2018 Nov;6(11):855-862. doi: 10.1016/S2213-2600(18)30368-0. Epub 2018 Oct 18. PMID: 30343028.

87: Buhl R, FitzGerald JM, Busse WW. Tiotropium add-on to inhaled corticosteroids versus addition of long-acting β_{2} -agonists for adults with asthma. Respir Med. 2018 Oct;143:82-90. doi: 10.1016/j.rmed.2018.08.014. Epub 2018 Aug 29. PMID: 30261998.

88: Shi W, Lin Z, Liao C, Zhang J, Liu W, Wang X, Cai J, Zou Z, Wang H, Norback D, Kan H, Huang C, Zhao Z. Urinary phthalate metabolites in relation to childhood asthmatic and allergic symptoms in Shanghai. Environ Int. 2018 Dec;121(Pt 1):276-286. doi: 10.1016/j.envint.2018.08.043. Epub 2018 Sep 15. PMID: 30223204.

89: Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018 Aug 27;13:2587-2601. doi: 10.2147/COPD.S172240. PMID: 30214177; PMCID: PMC6118265.

90: Hoshino M, Akitsu K, Ohtawa J. Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β_{2} -agonist in patients with asthma. J Asthma. 2019 Sep;56(9):995-1003. doi: 10.1080/02770903.2018.1514047. Epub 2018 Sep 13. PMID: 30212239.

91: Buhl R, Criée CP, Kardos P, Vogelmeier CF, Kostikas K, Lossi NS, Worth H. Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. Int J Chron Obstruct Pulmon Dis. 2018 Aug 24;13:2557-2568. doi: 10.2147/COPD.S169958. PMID: 30197512; PMCID: PMC6113909.

92: Hara J, Kasahara K, Ohkura N, Yamamura K, Sakai T, Abo M, Ogawa N, Saeki K, Koba H, Watanabe S, Uchida Y, Tambo Y, Sone T, Kimura H. A Single Institution Retrospective Study of the Clinical Efficacy of Tiotropium Respimat in Never-Smoking Elderly Asthmatics with Irreversible Airflow Limitation. Drug Res (Stuttg). 2019 Apr;69(4):211-217. doi: 10.1055/a-0665-4379. Epub 2018 Sep 7. PMID: 30193393.

93: Lopez-Campos JL, Navarrete BA, Soriano JB, Soler-Cataluña JJ, González-Moro JMR, Ferrer MEF, Rubio MC. Determinants of medical prescriptions for COPD care: an analysis of the EPOCONSUL clinical audit. Int J Chron Obstruct Pulmon Dis. 2018 Jul 27;13:2279-2288. doi: 10.2147/COPD.S160842. PMID: 30100718; PMCID: PMC6067777.

94: Yao XJ, Liu XF, Wang XD. Potential Role of Interleukin-25/Interleukin-33/Thymic Stromal Lymphopoietin-Fibrocyte Axis in the Pathogenesis of Allergic Airway Diseases. Chin Med J (Engl). 2018 Aug 20;131(16):1983-1989. doi: 10.4103/0366-6999.238150. PMID: 30082531; PMCID: PMC6085861.

95: Cheng WC, Wu BR, Liao WC, Chen CY, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. Clinical predictors of the effectiveness of tiotropium in adults with symptomatic asthma: a real-life study. J Thorac Dis. 2018 Jun;10(6):3661-3669. doi: 10.21037/jtd.2018.05.139. PMID: 30069364; PMCID: PMC6051811.

Supplementary data

- 96: Sposato B, Scalese M, Milanese M, Masieri S, Cavaliere C, Ricci A, Paggiaro P. Should omalizumab be used in severe asthma/COPD overlap? *J Biol Regul Homeost Agents.* 2018 Jul-Aug;32(4):755-761. PMID: 30043557.
- 97: Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? *ERJ Open Res.* 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.
- 98: Bonaventure A, Orsi L, Rudant J, Goujon-Bellec S, Leverger G, Baruchel A, Bertrand Y, Nelken B, Pasquet M, Michel G, Sirvent N, Chastagner P, Ducassou S, Thomas C, Besse C, Hémon D, Clavel J. Genetic polymorphisms of Th2 interleukins, history of asthma or eczema and childhood acute lymphoid leukaemia: Findings from the ESCALE study (SFCE). *Cancer Epidemiol.* 2018 Aug;55:96-103. doi: 10.1016/j.canep.2018.05.004. Epub 2018 Jun 6. PMID: 29883839.
- 99: Hot topics from the Assemblies. *Breathe (Sheff).* 2018 Jun;14(2):157-158. doi: 10.1183/20734735.142118. PMID: 29875836; PMCID: PMC5980479.
- 100: Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost Effectiveness of Pharmacological Treatments for Asthma: A Systematic Review. *Pharmacoeconomics.* 2018 Oct;36(10):1165-1200. doi: 10.1007/s40273-018-0668-8. PMID: 29869050.
- 101: Spergel JM, Aceves SS, Kliwewer K, Gonsalves N, Chehade M, Wechsler JB, Groetch M, Friedlander J, Dellon ES, Book W, Hirano I, Muir AB, Cianferoni A, Spencer L, Liacouras CA, Cheng E, Kottyan L, Wen T, Platts-Mills T, Rothenberg ME. New developments in patients with eosinophilic gastrointestinal diseases presented at the CEGIR/TIGERS Symposium at the 2018 American Academy of Allergy, Asthma & Immunology Meeting. *J Allergy Clin Immunol.* 2018 Jul;142(1):48-53. doi: 10.1016/j.jaci.2018.05.005. Epub 2018 May 24. PMID: 29803797; PMCID: PMC6129859.
- 102: Reiger G, Zwick R, Lamprecht B, Kähler C, Burghuber OC, Valipour A. Phenotypes of COPD in an Austrian population : National data from the POPE study. *Wien Klin Wochenschr.* 2018 Jun;130(11-12):382-389. doi: 10.1007/s00508-018-1347-7. Epub 2018 May 24. PMID: 29797071.
- 103: Chapman KR, Hurst JR, Frent SM, Larbig M, Fogel R, Guerin T, Banerji D, Patalano F, Goyal P, Pfister P, Kostikas K, Wedzicha JA. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am J Respir Crit Care Med.* 2018 Aug 1;198(3):329-339. doi: 10.1164/rccm.201803-0405OC. PMID: 29779416.
- 104: Grozdanovic M, Laffey KG, Abdelkarim H, Hutchinson B, Harijith A, Moon HG, Park GY, Rousslang LK, Masterson JC, Furuta GT, Tarasova NI, Gaponenko V, Ackerman SJ. Novel peptide nanoparticle-biased antagonist of CCR3 blocks eosinophil recruitment and airway hyperresponsiveness. *J Allergy Clin Immunol.* 2019 Feb;143(2):669-680.e12. doi: 10.1016/j.jaci.2018.05.003. Epub 2018 May 17. PMID: 29778505; PMCID: PMC6240402.
- 105: Dedaj R, Unsel L. Case study: A Combination of Mepolizumab and Omaluzimab injections for severe asthma. *J Asthma.* 2019 May;56(5):473-474. doi: 10.1080/02770903.2018.1471706. Epub 2018 Oct 25. PMID: 29733738.
- 106: Suknuntha K, Yubolphan R, Krueaprasertkul K, Srihirun S, Sibmooh N, Vivithanaporn P. Leukotriene Receptor Antagonists Inhibit Mitogenic Activity in Triple Negative Breast Cancer Cells. *Asian Pac J Cancer Prev.* 2018 Mar 27;19(3):833-837. doi: 10.22034/APJCP.2018.19.3.833. PMID: 29582642; PMCID: PMC5980863.
- 107: Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. *JAMA.* 2018 Apr 10;319(14):1473-1484. doi: 10.1001/jama.2018.2757. Erratum in: *JAMA.* 2018 May 8;319(18):1939. PMID: 29554174; PMCID: PMC5876909.
- 108: Hurst JR, Dilleen M, Morris K, Hills S, Emir B, Jones R. Factors influencing treatment escalation from long-acting muscarinic antagonist monotherapy to triple therapy in patients with COPD: a retrospective THIN-database analysis. *Int J Chron Obstruct Pulmon Dis.* 2018 Mar 5;13:781-792. doi: 10.2147/COPD.S153655. PMID: 29551894; PMCID: PMC5842770.
- 109: Mesonzhenik NV, Moskaleva NE, Shestakova KM, Kurynina KO, Baranov PA, Gretskaya NM, Serkov IV, Lyubimov II, Bezuglov VV, Appolonova SA. LC-MS/MS

Supplementary data

Identification and Structural Characterization of Main Biodegradation Products of Nitroproston - A Novel Prostaglandin-based Pharmaceutical Compound. *Drug Metab Lett.* 2018;12(1):54-61. doi: 10.2174/1872312812666180309160927. PMID: 29521215.

110: Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Mar. Report No.: 17(18)-EHC027-EF. PMID: 29741837.

111: Zhang L, Huang G, Jin L, Han S. Therapeutic Effects of a Long-Acting Cholinergic Receptor Blocker, Tiotropium Bromide, on Asthma. *Med Sci Monit.* 2018 Feb 15;24:944-950. doi: 10.12659/msm.907950. PMID: 29446377; PMCID: PMC5822933.

112: Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet.* 2018 Mar 17;391(10125):1076-1084. doi: 10.1016/S0140-6736(18)30206-X. Epub 2018 Feb 9. Erratum in: *Lancet.* 2018 Feb 26;: PMID: 29429593.

113: Zafari Z, Sadatsafavi M, Mark FitzGerald J; Canadian Respiratory Research Network. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. *Cost Eff Resour Alloc.* 2018 Jan 30;16:3. doi: 10.1186/s12962-018-0089-8. PMID: 29422778; PMCID: PMC5789632.

114: Song YD, Li XZ, Wu YX, Shen Y, Liu FF, Gao PP, Sun L, Qian F. Emodin alleviates alternatively activated macrophage and asthmatic airway inflammation in a murine asthma model. *Acta Pharmacol Sin.* 2018 Aug;39(8):1317-1325. doi: 10.1038/aps.2017.147. Epub 2018 Feb 8. PMID: 29417945; PMCID: PMC6289379.

115: Fukumitsu K, Kanemitsu Y, Asano T, Takeda N, Ichikawa H, Yap JMG, Fukuda S, Uemura T, Takakuwa O, Ohkubo H, Maeno K, Ito Y, Oguri T, Nakamura A, Takemura M, Niimi A. Tiotropium Attenuates Refractory Cough and Capsaicin Cough Reflex Sensitivity in Patients with Asthma. *J Allergy Clin Immunol Pract.* 2018 Sep-Oct;6(5):1613-1620.e2. doi: 10.1016/j.jaip.2018.01.016. Epub 2018 Feb 3. PMID: 29408386.

116: Johansson G, Mushnikov V, Bäckström T, Engström A, Khalid JM, Wall J, Hoti F. Exacerbations and healthcare resource utilization among COPD patients in a Swedish registry-based nation-wide study. *BMC Pulm Med.* 2018 Jan 25;18(1):17. doi: 10.1186/s12890-018-0573-0. PMID: 29370846; PMCID: PMC5784707.

117: Padrão E, Araújo D, Todo Bom A, Robalo Cordeiro C, Correia de Sousa J, Cardoso J, Morais-Almeida M, Costa R, Pavão F, Leite RB, Marques A. Asthma-COPD overlap: A Portuguese survey. *Pulmonology.* 2018 Jan 12:S2173-5115(17)30181-1. doi: 10.1016/j.rppnen.2017.11.009. Epub ahead of print. PMID: 29338973.

118: Meltzer EO, Berger WE. A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma. *Allergy Asthma Proc.* 2018 Jan 6;39(1):14-26. doi: 10.2500/aap.2018.39.4103. PMID: 29279056.

119: Dreher M, Müller T. Add-on Therapy for Symptomatic Asthma despite Long-Acting Beta-Agonists/Inhaled Corticosteroid. *Tuberc Respir Dis (Seoul).* 2018 Jan;81(1):1-5. doi: 10.4046/trd.2017.0102. Epub 2017 Dec 13. PMID: 29256220; PMCID: PMC5771741.

120: Corral Gudino L, Borao Cengotita-Bengoa M, Jorge Sánchez RJ, García Aparicio J. El paciente y su travesía entre la atención primaria y la hospitalaria. Revisión sistemática de ensayos clínicos para la implementación de herramientas para la integración en España [The patient and the crossing between Primary and Hospital care. Systematic review of trials for the implementation of tools for integration in Spain]. *An Sist Sanit Navar.* 2017 Dec 29;40(3):443-459. Spanish. doi: 10.23938/ASSN.0119. PMID: 29215657.

121: Casale TB, Bateman ED, Vandewalker M, Virchow JC, Schmidt H, Engel M, Moroni-Zentgraf P, Kerstjens HAM. Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype. *J Allergy Clin Immunol Pract.* 2018 May-Jun;6(3):923-935.e9. doi: 10.1016/j.jaip.2017.08.037. Epub 2017 Nov 22. PMID: 29174062.

122: Meltzer EO, Berger WE. A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma. *Allergy Asthma Proc.* 2017 Nov 6. doi: 10.2500/aap.2017.38.1403. Epub ahead of

Supplementary data

print. PMID: 29108533.

123: Singh D, Corradi M, Spinola M, Papi A, Usmani OS, Scuri M, Petruzzelli S, Vestbo J. Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide. *Int J Chron Obstruct Pulmon Dis.* 2017 Oct;12:2917-2928. doi: 10.2147/COPD.S146822. PMID: 29062229; PMCID: PMC5638574.

124: Lee L, Kerwin E, Collison K, Nelsen L, Wu W, Yang S, Pascoe S. The effect of umeclidinium on lung function and symptoms in patients with fixed airflow obstruction and reversibility to salbutamol: A randomised, 3-phase study. *Respir Med.* 2017 Oct;131:148-157. doi: 10.1016/j.rmed.2017.08.013. Epub 2017 Aug 14. PMID: 28947022.

125: Nandyal S, Suria S, Chogtu B, Bhattacharjee D. Risk of GERD with Diabetes Mellitus, Hypertension and Bronchial Asthma - A Hospital based Retrospective Cohort Study. *J Clin Diagn Res.* 2017 Jul;11(7):OC25-OC29. doi: 10.7860/JCDR/2017/25571.10232. Epub 2017 Jul 1. PMID: 28892957; PMCID: PMC5583783.

126: Kalach N, Bontems P, Raymond J. Helicobacter pylori infection in children. *Helicobacter.* 2017 Sep;22 Suppl 1. doi: 10.1111/hel.12414. PMID: 28891139.

127: Beasley R, Hardy J, Hancox R. Asthma prescribing: Where are we headed? *Respirology.* 2017 Nov;22(8):1487-1488. doi: 10.1111/resp.13159. Epub 2017 Aug 27. PMID: 28845601.

128: Makadia LD, Roper PJ, Andrews JO, Tingan MS. Tobacco Use and Smoke Exposure in Children: New Trends, Harm, and Strategies to Improve Health Outcomes. *Curr Allergy Asthma Rep.* 2017 Aug;17(8):55. doi: 10.1007/s11882-017-0723-0. PMID: 28741144.

129: Sánchez J, Zakzuk J, Cardona R. Evaluation of a Guidelines-Based Approach to the Treatment of Chronic Spontaneous Urticaria. *J Allergy Clin Immunol Pract.* 2018 Jan-Feb;6(1):177-182.e1. doi: 10.1016/j.jaip.2017.06.002. Epub 2017 Jul 12. PMID: 28709817.

130: Mapel D, Laliberté F, Roberts MH, Sama SR, Sundaresan D, Pilon D, Lefebvre P, Duh MS, Patel J. A retrospective study to assess clinical characteristics and time to initiation of open-triple therapy among patients with chronic obstructive pulmonary disease, newly established on long-acting mono- or combination therapy. *Int J Chron Obstruct Pulmon Dis.* 2017 Jun 21;12:1825-1836. doi: 10.2147/COPD.S129007. PMID: 28684905; PMCID: PMC5485896.

131: Aalbers R, Park HS. Positioning of Long-Acting Muscarinic Antagonists in the Management of Asthma. *Allergy Asthma Immunol Res.* 2017 Sep;9(5):386-393. doi: 10.4168/aaair.2017.9.5.386. PMID: 28677351; PMCID: PMC5500692.

132: Jabbal S, Manoharan A, Lipworth BJ. Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma. *Clin Exp Allergy.* 2017 Oct;47(10):1239-1245. doi: 10.1111/cea.12972. Epub 2017 Aug 1. PMID: 28665534.

133: Clarke A, Perry E, Kelly C, De Soyza A, Heesom K, Gold LI, Ollier W, Hutchinson D, Eggleton P. Heightened autoantibody immune response to citrullinated calreticulin in bronchiectasis: Implications for rheumatoid arthritis. *Int J Biochem Cell Biol.* 2017 Aug;89:199-206. doi: 10.1016/j.biocel.2017.06.013. Epub 2017 Jun 24. PMID: 28652209.

134: Miravitles M, Anzueto A, Jardim JR. Optimizing bronchodilation in the prevention of COPD exacerbations. *Respir Res.* 2017 Jun 20;18(1):125. doi: 10.1186/s12931-017-0601-2. PMID: 28633665; PMCID: PMC5477752.

135: Wang G, Wang F, Gibson PG, Guo M, Zhang WJ, Gao P, Zhang HP, Harvey ES, Li H, Zhang J. Severe and uncontrolled asthma in China: a cross-sectional survey from the Australasian Severe Asthma Network. *J Thorac Dis.* 2017 May;9(5):1333-1344. doi: 10.21037/jtd.2017.04.74. PMID: 28616286; PMCID: PMC5465130.

136: Reddel HK, Valenti L, Easton KL, Gordon J, Bayram C, Miller GC. Assessment and management of asthma and chronic obstructive pulmonary disease in Australian general practice. *Aust Fam Physician.* 2017 Jun;46(6):413-419. PMID: 28609599.

137: Kew KM, Carr R, Crossingham I. Lay-led and peer support interventions for adolescents with asthma. *Cochrane Database Syst Rev.* 2017 Apr 19;4(4):CD012331. doi: 10.1002/14651858.CD012331.pub2. PMID: 28421600; PMCID: PMC6478329.

Supplementary data

- 138: Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet.* 2017 May 13;389(10082):1919-1929. doi: 10.1016/S0140-6736(17)30188-5. Epub 2017 Apr 3. PMID: 28385353.
- 139: Glassberg J, Minnitti C, Cromwell C, Cytryn L, Kraus T, Skloot GS, Connor JT, Rahman AH, Meurer WJ. Inhaled steroids reduce pain and sVCAM levels in individuals with sickle cell disease: A triple-blind, randomized trial. *Am J Hematol.* 2017 Jul;92(7):622-631. doi: 10.1002/ajh.24742. Epub 2017 Jun 5. PMID: 28370266; PMCID: PMC5484635.
- 140: Al-Sheyab NA, Khader YS, Shah S, Roydhouse JK, Gallagher R. The Effect of a "Class Smoke Free Pledge" on Breath Carbon Monoxide in Arabic Male Adolescents. *Nicotine Tob Res.* 2018 Apr 2;20(5):568-574. doi: 10.1093/ntr/ntx050. PMID: 28340136.
- 141: Morawska A, Mitchell AE, Burgess S, Fraser J. Fathers' Perceptions of Change Following Parenting Intervention: Randomized Controlled Trial of Triple P for Parents of Children With Asthma or Eczema. *J Pediatr Psychol.* 2017 Aug 1;42(7):792-803. doi: 10.1093/jpepsy/jsw106. PMID: 28339996.
- 142: Morawska A, Mitchell A, Burgess S, Fraser J. Randomized controlled trial of Triple P for parents of children with asthma or eczema: Effects on parenting and child behavior. *J Consult Clin Psychol.* 2017 Apr;85(4):283-296. doi: 10.1037/ccp0000177. PMID: 28333531.
- 143: Cazzola M, Ora J, Rogliani P, Matera MG. Role of muscarinic antagonists in asthma therapy. *Expert Rev Respir Med.* 2017 Mar;11(3):239-253. doi: 10.1080/17476348.2017.1289844. Epub 2017 Feb 9. PMID: 28140686.
- 144: Morawska A, Mitchell AE, Burgess S, Fraser J. Corrigendum to "Effects of Triple P parenting intervention on child health outcomes for childhood asthma and eczema: Randomised controlled trial" [Behav. Res. Ther. 83 (2016) 35-44]. *Behav Res Ther.* 2017 May;92:107. doi: 10.1016/j.brat.2016.12.017. Epub 2017 Jan 24. Erratum for: Behav Res Ther. 2016 Aug;83:35-44. PMID: 28129879.
- 145: Hamelmann E, Vogelberg C, Szefler SJ. Tiotropium for the treatment of asthma in adolescents. *Expert Opin Pharmacother.* 2017 Feb;18(3):305-312. doi: 10.1080/14656566.2017.1285906. Epub 2017 Feb 1. PMID: 28110558.
- 146: Thomson NC. New and developing non-adrenoreceptor small molecule drugs for the treatment of asthma. *Expert Opin Pharmacother.* 2017 Feb;18(3):283-293. doi: 10.1080/14656566.2017.1284794. Epub 2017 Feb 1. PMID: 28099820.
- 147: Araújo D, Padrão E, Morais-Almeida M, Cardoso J, Pavão F, Leite RB, Caldas AC, Marques A. Asthma-chronic obstructive pulmonary disease overlap syndrome - Literature review and contributions towards a Portuguese consensus. *Rev Port Pneumol (2006).* 2017 Mar-Apr;23(2):90-99. doi: 10.1016/j.rppnen.2016.11.005. Epub 2017 Jan 6. PMID: 28089081.
- 148: Irshad S, Flores-Borja F, Lawler K, Monypenny J, Evans R, Male V, Gordon P, Cheung A, Gazinska P, Noor F, Wong F, Grigoriadis A, Fruhwirth GO, Barber PR, Woodman N, Patel D, Rodriguez-Justo M, Owen J, Martin SG, Pinder SE, Gillett CE, Poland SP, Ameer-Beg S, McCaughan F, Carlin LM, Hasan U, Withers DR, Lane P, Vojnovic B, Quezada SA, Ellis P, Tutt AN, Ng T. ROR γ T⁺ Innate Lymphoid Cells Promote Lymph Node Metastasis of Breast Cancers. *Cancer Res.* 2017 Mar 1;77(5):1083-1096. doi: 10.1158/0008-5472.CAN-16-0598. Epub 2017 Jan 12. PMID: 28082403.
- 149: Nejatbakhsh F, Karegar-Borzi H, Amin G, Eslaminejad A, Hosseini M, Bozorgi M, Gharabaghi MA. Squill Oxymel, a traditional formulation from Drimia Maritima (L.) Stearn, as an add-on treatment in patients with moderate to severe persistent asthma: A pilot, triple-blind, randomized clinical trial. *J Ethnopharmacol.* 2017 Jan 20;196:186-192. doi: 10.1016/j.jep.2016.12.032. Epub 2016 Dec 18. PMID: 27998692.
- 150: Hoshino M, Ohtawa J, Akitsu K. Effects of the addition of tiotropium on airway dimensions in symptomatic asthma. *Allergy Asthma Proc.* 2016 Nov;37(6):147-153. doi: 10.2500/aap.2016.37.3991. PMID: 27931291.
- 151: Albertson TE, Chenoweth JA, Adams JY, Sutter ME. Muscarinic antagonists in early stage clinical development for the treatment of asthma. *Expert Opin Investig Drugs.* 2017 Jan;26(1):35-49. doi: 10.1080/13543784.2017.1264388. Epub 2016 Dec 7. PMID: 27927039.

Supplementary data

- 152: Edwards SC, Fairbrother SE, Scowcroft A, Chiu G, Ternouth A, Lipworth BJ. The burden of chronic obstructive pulmonary disease associated with maintenance monotherapy in the UK. *Int J Chron Obstruct Pulmon Dis.* 2016 Nov;22:11:2851-2858. doi: 10.2147/COPD.S109707. PMID: 27920512; PMCID: PMC5125989.
- 153: Tasanarong P, Dechatiwongse Na Ayudhya T, Techanitiswad T, Koontongkaew S. Reduction of viable bacteria in dentinal tubules treated with a novel medicament (Z-Mix). *J Dent Sci.* 2016 Dec;11(4):419-426. doi: 10.1016/j.jds.2016.06.006. Epub 2016 Aug 10. PMID: 30895007; PMCID: PMC6395269.
- 154: Montuschi P, Malerba M, Macis G, Mores N, Santini G. Triple inhaled therapy for chronic obstructive pulmonary disease. *Drug Discov Today.* 2016 Nov;21(11):1820-1827. doi: 10.1016/j.drudis.2016.07.009. Epub 2016 Jul 21. PMID: 27452453.
- 155: Page C, Cazzola M. Bifunctional Drugs for the Treatment of Respiratory Diseases. *Handb Exp Pharmacol.* 2017;237:197-212. doi: 10.1007/164_2016_69. PMID: 27787715.
- 156: Blom RA, Erni ST, Krempaská K, Schaeerer O, van Dijk RM, Amacker M, Moser C, Hall SR, von Garnier C, Blank F. A Triple Co-Culture Model of the Human Respiratory Tract to Study Immune-Modulatory Effects of Liposomes and Virosomes. *PLoS One.* 2016 Sep 29;11(9):e0163539. doi: 10.1371/journal.pone.0163539. PMID: 27685460; PMCID: PMC5042471.
- 157: Halpin DM. Tiotropium in asthma: what is the evidence and how does it fit in? *World Allergy Organ J.* 2016 Sep 14;9(1):29. doi: 10.1186/s40413-016-0119-y. PMID: 27679681; PMCID: PMC5022240.
- 158: Vogelberg C. Tiotropium in the add-on treatment of asthma in adults: clinical trial evidence and experience. *Ther Adv Respir Dis.* 2016 Dec;10(6):525-533. doi: 10.1177/1753465816662571. Epub 2016 Sep 9. PMID: 27612491; PMCID: PMC5933593.
- 159: Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet.* 2016 Sep 3;388(10048):963-73. doi: 10.1016/S0140-6736(16)31354-X. Epub 2016 Sep 1. PMID: 27598678.
- 160: Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, Schmidt H, Engel M, Bateman ED. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. *Respir Med.* 2016 Aug;117:198-206. doi: 10.1016/j.rmed.2016.06.013. Epub 2016 Jun 14. PMID: 27492532.
- 161: Morawska A, Mitchell AE, Burgess S, Fraser J. Effects of Triple P parenting intervention on child health outcomes for childhood asthma and eczema: Randomised controlled trial. *Behav Res Ther.* 2016 Aug;83:35-44. doi: 10.1016/j.brat.2016.06.001. Epub 2016 Jun 3. Erratum in: *Behav Res Ther.* 2017 May;92 :107. PMID: 27295179.
- 162: Zhou T, Zeng D, Zhao T, Yang Y, Liu S, Wu J, Xu L, Tan W. In vivo metabolism study of (R)-bambuterol in humans using ultra high performance liquid chromatography with tandem mass spectrometry. *J Sep Sci.* 2016 Aug;39(15):2896-906. doi: 10.1002/jssc.201600424. Epub 2016 Jun 27. PMID: 27273913.
- 163: Shibata Y. [Role of ICS/LABA on COPD treatment]. *Nihon Rinsho.* 2016 May;74(5):827-32. Japanese. PMID: 27254954.
- 164: Banerji D, Mahler DA, Hanania NA. Efficacy and safety of LABA/LAMA fixed-dose combinations approved in the US for the management of COPD. *Expert Rev Respir Med.* 2016 Jul;10(7):767-80. doi: 10.1080/17476348.2016.1190276. Epub 2016 May 30. PMID: 27223863.
- 165: Mariotti F, Ciurlia G, Spaccapelo L, Muraro A, Acerbi D. A Two-Period Open-Label, Single-Dose Crossover Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Between Cimetidine and Inhaled Extrafine CHF 5993. *Eur J Drug Metab Pharmacokinet.* 2017 Apr;42(2):269-279. doi: 10.1007/s13318-016-0345-2. PMID: 27209586; PMCID: PMC5340825.
- 166: Lichtveld M, Kennedy S, Krouse RZ, Grimsley F, El-Dahr J, Bordelon K,

Supplementary data

- Sterling Y, White L, Barlow N, DeGruy S, Paul D, Denham S, Hayes C, Sanders M, Mvula MM, Thornton E, Chulada P, Mitchell H, Martin WJ 2nd, Stephens KU, Cohn RD. From Design to Dissemination: Implementing Community-Based Participatory Research in Postdisaster Communities. *Am J Public Health.* 2016 Jul;106(7):1235-42. doi: 10.2105/AJPH.2016.303169. Epub 2016 May 19. PMID: 27196662; PMCID: PMC4984744.
- 167: Patra J, Maher YI, Mishra S, Bhatia M, Alam D, Malini DS, Gupta PC, Jha P. Effects of body mass index, tobacco smoking, alcohol drinking and solid fuel use on the risk of asthma: Individual Participant Data (IPD) meta-analysis of 175 000 individuals from 51 nationally representative surveys. *BMJ Open Respir Res.* 2016 Apr 4;3(1):e000121. doi: 10.1136/bmjresp-2015-000121. PMID: 27099758; PMCID: PMC4823466.
- 168: Abdel-Hameed EA, Rouston SD, Ji H, Ulm A, Hetta HF, Anwar N, Sherman KE, Shata MT. Evaluating the Role of Cellular Immune Responses in the Emergence of HCV NS3 Resistance Mutations During Protease Inhibitor Therapy. *Viral Immunol.* 2016 May;29(4):252-8. doi: 10.1089/vim.2015.0093. Epub 2016 Feb 17. PMID: 26885675; PMCID: PMC4860622.
- 169: Busch R, Han MK, Bowler RP, Dransfield MT, Wells JM, Regan EA, Hersh CP; COPDGene Investigators. Risk factors for COPD exacerbations in inhaled medication users: the COPDGene study biannual longitudinal follow-up prospective cohort. *BMC Pulm Med.* 2016 Feb 10;16:28. doi: 10.1186/s12890-016-0191-7. PMID: 26861867; PMCID: PMC4748594.
- 170: Mantuani D, Frazee BW, Fahimi J, Nagdev A. Point-of-Care Multi-Organ Ultrasound Improves Diagnostic Accuracy in Adults Presenting to the Emergency Department with Acute Dyspnea. *West J Emerg Med.* 2016 Jan;17(1):46-53. doi: 10.5811/westjem.2015.11.28525. Epub 2016 Jan 12. PMID: 26823930; PMCID: PMC4729418.
- 171: Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta₂-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev.* 2016 Jan 21;(1):CD011721. doi: 10.1002/14651858.CD011721.pub2. PMID: 26798035.
- 172: Wang K, Tian P, Fan Y, Wang Y, Liu C. Assessment of second-line treatments for patients with uncontrolled moderate asthma. *Int J Clin Exp Med.* 2015 Oct 15;8(10):19476-80. PMID: 26770595; PMCID: PMC4694495.
- 173: Kim SA, Lee JH, Kim EK, Kim TH, Kim WJ, Lee JH, Yoon HI, Baek S, Lee JS, Oh YM, Lee SD. Outcome of Inhaler Withdrawal in Patients Receiving Triple Therapy for COPD. *Tuberc Respir Dis (Seoul).* 2016 Jan;79(1):22-30. doi: 10.4046/trd.2016.79.1.22. Epub 2015 Dec 31. Erratum in: *Tuberc Respir Dis (Seoul).* 2016 Jul;79(3):193. PMID: 26770231; PMCID: PMC4701790.
- 174: Barrecheguren M, Monteagudo M, Ferrer J, Borrell E, Llor C, Esquinas C, Miravitles M. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. *Respir Med.* 2016 Feb;111:47-53. doi: 10.1016/j.rmed.2015.12.004. Epub 2015 Dec 23. PMID: 26758585.
- 175: Covelli H, Pek B, Schenkenberger I, Scott-Wilson C, Emmett A, Crim C. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. *Int J Chron Obstruct Pulmon Dis.* 2015 Dec 18;11:1-12. doi: 10.2147/COPD.S91407. PMID: 26730183; PMCID: PMC4694692.
- 176: Woodfolk JA, Glesner J, Wright PW, Kepley CL, Li M, Hinly M, Muehling LM, Gustchina A, Wlodawer A, Chapman MD, Pomés A. Antigenic Determinants of the Bilobal Cockroach Allergen Bla g 2. *J Biol Chem.* 2016 Jan 29;291(5):2288-301. doi: 10.1074/jbc.M115.702324. Epub 2015 Dec 7. PMID: 26644466; PMCID: PMC4732212.
- 177: Vogelberg C. Emerging role of long-acting anticholinergics in children with asthma. *Curr Opin Pulm Med.* 2016 Jan;22(1):74-9. doi: 10.1097/MCP.000000000000229. PMID: 26606079.
- 178: Pizzichini MM, Kerstjens HA, Pizzichini E. Current role of anticholinergic drugs in the treatment of asthma: key messages for clinical practice. *Pol Arch Med Wewn.* 2015;125(11):859-66. doi: 10.20452/pamw.3168. Epub 2015 Oct 30. Erratum in: *Pol Arch Med Wewn.* 2015;125(12):954. PMID: 26529261.
- 179: Brusselle G, Price D, Gruffydd-Jones K, Miravitles M, Keininger DL, Stewart R, Baldwin M, Jones RC. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis.* 2015 Oct 15;10:2207-17. doi: 10.2147/COPD.S91694. PMID: 26527869; PMCID: PMC4621207.

Supplementary data

- 180: Wechsler ME, Yawn BP, Fuhlbrigge AL, Pace WD, Pencina MJ, Doros G, Kazani S, Raby BA, Lanzillotti J, Madison S, Israel E; BELT Investigators. Anticholinergic vs Long-Acting β -Agonist in Combination With Inhaled Corticosteroids in Black Adults With Asthma: The BELT Randomized Clinical Trial. *JAMA*. 2015 Oct 27;314(16):1720-30. doi: 10.1001/jama.2015.13277. PMID: 26505596.
- 181: Tilp C, Bucher H, Haas H, Duechs MJ, Wex E, Erb KJ. Effects of conventional tobacco smoke and nicotine-free cigarette smoke on airway inflammation, airway remodelling and lung function in a triple allergen model of severe asthma. *Clin Exp Allergy*. 2016 Jul;46(7):957-72. doi: 10.1111/cea.12665. Epub 2016 May 3. PMID: 26502779.
- 182: Trudo F, Kern DM, Davis JR, Tunceli O, Zhou S, Graham EL, Strange C, Williams SA. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. *Int J Chron Obstruct Pulmon Dis*. 2015 Sep 28;10:2055-66. doi: 10.2147/COPD.S90658. PMID: 26451101; PMCID: PMC4592033.
- 183: Hamilton M, Leggett R, Pang C, Charles S, Gillett B, Prime D. In Vitro Dosing Performance of the ELLIPTA® Dry Powder Inhaler Using Asthma and COPD Patient Inhalation Profiles Replicated with the Electronic Lung (eLung™). *J Aerosol Med Pulm Drug Deliv*. 2015 Dec;28(6):498-506. doi: 10.1089/jamp.2015.1225. Epub 2015 Sep 15. PMID: 26372465; PMCID: PMC4685503.
- 184: Barnes PJ. Therapeutic approaches to asthma-chronic obstructive pulmonary disease overlap syndromes. *J Allergy Clin Immunol*. 2015 Sep;136(3):531-45. doi: 10.1016/j.jaci.2015.05.052. PMID: 26343937.
- 185: Bouwmeester C, Kraft J, Bungay KM. Optimizing inhaler use by pharmacist-provided education to community-dwelling elderly. *Respir Med*. 2015 Oct;109(10):1363-8. doi: 10.1016/j.rmed.2015.07.013. Epub 2015 Jul 20. PMID: 26341546.
- 186: Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. *Cochrane Database Syst Rev*. 2015 Aug 24;(8):CD011397. doi: 10.1002/14651858.CD011397.pub2. PMID: 26301488.
- 187: Miravitles M, Alcázar B, Alvarez FJ, Bazús T, Calle M, Casanova C, Cisneros C, de-Torres JP, Entrenas LM, Esteban C, García-Sidro P, Cosio BG, Huerta A, Iribarri M, Izquierdo JL, López-Viña A, López-Campos JL, Martínez-Moragón E, Pérez de Llano L, Perpiñá M, Ros JA, Serrano J, Soler-Cataluña JJ, Torrego A, Urrutia I, Plaza V. What pulmonologists think about the asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis*. 2015 Jul 15;10:1321-30. doi: 10.2147/COPD.S88667. PMID: 26270415; PMCID: PMC4507793.
- 188: Wang Y, Qin F, Xiong Z, Fu X, Ma C. An LC-MS/MS method for simultaneous determination of trantinterol and its major metabolite in rat plasma and its application to a comparative pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2015 Sep 1;1000:163-8. doi: 10.1016/j.jchromb.2015.07.022. Epub 2015 Jul 17. PMID: 26245359.
- 189: Itadani S, Yashiro K, Aratani Y, Sekiguchi T, Kinoshita A, Moriguchi H, Ohta N, Takahashi S, Ishida A, Tajima Y, Hisaichi K, Ima M, Ueda J, Egashira H, Sekioka T, Kadode M, Yonetomi Y, Nakao T, Inoue A, Nomura H, Kitamine T, Fujita M, Nabe T, Yamaura Y, Matsumura N, Imagawa A, Nakayama Y, Takeuchi J, Ohmoto K. Discovery of Gemilukast (ONO-6950), a Dual CysLT1 and CysLT2 Antagonist As a Therapeutic Agent for Asthma. *J Med Chem*. 2015 Aug 13;58(15):6093-113. doi: 10.1021/acs.jmedchem.5b00741. Epub 2015 Jul 22. PMID: 26200813.
- 190: Norman P. Developments in inhaled combination therapies: patent activity 2013-2014. *Expert Opin Ther Pat*. 2015;25(11):1239-45. doi: 10.1517/13543776.2015.1064394. Epub 2015 Jul 2. PMID: 26135360.
- 191: Bood JR, Sundblad BM, Delin I, Sjödin M, Larsson K, Anderson SD, Wheelock CE, Dahlén SE, Dahlén B. Urinary excretion of lipid mediators in response to repeated eucapnic voluntary hyperpnea in asthmatic subjects. *J Appl Physiol* (1985). 2015 Aug 1;119(3):272-9. doi: 10.1152/japplphysiol.00301.2015. Epub 2015 Jun 25. PMID: 26112240.
- 192: Mahler DA, Kerstjens HA, Donohue JF, Buhl R, Lawrence D, Altman P. Indacaterol vs tiotropium in COPD patients classified as GOLD A and B. *Respir Med*. 2015 Aug;109(8):1031-9. doi: 10.1016/j.rmed.2015.05.012. Epub 2015 May 22. PMID: 26094050.

Supplementary data

- 193: Miyazaki M, Nakamura H, Takahashi S, Chubachi S, Sasaki M, Haraguchi M, Terai H, Ishii M, Fukunaga K, Tasaka S, Soejima K, Asano K, Betsuyaku T; Keio COPD Comorbidity Research (K-CCR) group. The reasons for triple therapy in stable COPD patients in Japanese clinical practice. *Int J Chron Obstruct Pulmon Dis.* 2015 Jun;4:10:1053-9. doi: 10.2147/COPD.S79864. PMID: 26082629; PMCID: PMC4461139.
- 194: Kew KM, Evans DJ, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta₂-agonists (LABA) for adults with asthma. *Cochrane Database Syst Rev.* 2015 Jun 2;2015(6):CD011438. doi: 10.1002/14651858.CD011438.pub2. PMID: 26031392; PMCID: PMC6513433.
- 195: Matsuse H, Yamagishi T, Kodaka N, Miura A, Kurose Y, Nakano C, Oshio T. Tiotropium bromide as add-on therapy to inhaled corticosteroids for treating asthma. *Expert Opin Pharmacother.* 2015 Jun;16(9):1403-9. doi: 10.1517/14656566.2015.1045877. PMID: 26001185.
- 196: Quirce S, Dominguez-Ortega J, Barranco P. Anticholinergics for treatment of asthma. *J Investig Allergol Clin Immunol.* 2015;25(2):84-93; quiz 94-5. PMID: 25997301.
- 197: Chen Y, Guo J, Tang Y, Wu L, Tao W, Qian Y, Duan JA. Pharmacokinetic profile and metabolite identification of yuanhuapine, a bioactive component in Daphne genkwa by ultra-high performance liquid chromatography coupled with tandem mass spectrometry. *J Pharm Biomed Anal.* 2015 Aug 10;112:60-9. doi: 10.1016/j.jpba.2015.04.023. Epub 2015 Apr 25. PMID: 25956226.
- 198: McKeage K. Tiotropium Respimat®: A Review of Its Use in Asthma Poorly Controlled with Inhaled Corticosteroids and Long-Acting β₂-Adrenergic Agonists. *Drugs.* 2015 May;75(7):809-16. doi: 10.1007/s40265-015-0393-y. PMID: 25895466.
- 199: Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, Sakamoto W, Adachi M. Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study. *PLoS One.* 2015 Apr 20;10(4):e0124109. doi: 10.1371/journal.pone.0124109. PMID: 25894430; PMCID: PMC4404354.
- 200: Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, Frenzel C, Kurstjens N; Glisten Study Group. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial. *Thorax.* 2015 Jun;70(6):519-27. doi: 10.1136/thoraxjnl-2014-206670. Epub 2015 Apr 3. PMID: 25841237; PMCID: PMC4453631.
- 201: Bernstein JA, Moellman JJ, Collins SP, Hart KW, Lindsell CJ. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor-induced angioedema in the emergency department. *Ann Allergy Asthma Immunol.* 2015 Mar;114(3):245-9. doi: 10.1016/j.anai.2014.12.007. Epub 2015 Jan 16. PMID: 25601538.
- 202: Kankaanranta H, Harju T, Kilpeläinen M, Mazur W, Lehto JT, Katajisto M, Peisa T, Meinander T, Lehtimäki L. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. *Basic Clin Pharmacol Toxicol.* 2015 Apr;116(4):291-307. doi: 10.1111/bcpt.12366. Epub 2015 Jan 22. PMID: 25515181; PMCID: PMC4409821.
- 203: Salmon M, Tannheimer SL, Gentzler TT, Cui ZH, Sorensen EA, Hartsough KC, Kim M, Purvis LJ, Barrett EG, McDonald JD, Rudolph K, Doyle-Eisele M, Kuehl PJ, Royer CM, Baker WR, Phillips GB, Wright CD. The in vivo efficacy and side effect pharmacology of GS-5759, a novel bifunctional phosphodiesterase 4 inhibitor and long-acting β₂-adrenoceptor agonist in preclinical animal species. *Pharmacol Res Perspect.* 2014 Aug;2(4):e00046. doi: 10.1002/prp2.46. Epub 2014 Jun 9. PMID: 25505595; PMCID: PMC4186437.
- 204: Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. *Respir Med.* 2015 Jan;109(1):54-62. doi: 10.1016/j.rmed.2014.09.012. Epub 2014 Oct 2. PMID: 25452139.
- 205: Latorre M, Novelli F, Vagaggini B, Braido F, Papi A, Sanduzzi A, Santus P, Scichilone N, Paggiaro P. Differences in the efficacy and safety among inhaled corticosteroids (ICS)/long-acting beta₂-agonists (LABA) combinations in the treatment of chronic obstructive pulmonary disease (COPD): Role of ICS. *Pulm*

Supplementary data

Pharmacol Ther. 2015 Feb;30:44-50. doi: 10.1016/j.pupt.2014.10.006. Epub 2014 Nov 6. PMID: 25445928.

206: Abadoglu O, Berk S. Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: the real-life data. Clin Respir J. 2016 Jul;10(4):421-7. doi: 10.1111/crj.12230. Epub 2014 Nov 9. PMID: 25335652.

207: Otim ME, Jayasinha R, Forbes H, Shah S. Building evidence for peer-led interventions: assessing the cost of the Adolescent Asthma Action program in Australia. Aust J Prim Health. 2015;21(4):438-43. doi: 10.1071/PY14066. PMID: 25230153.

208: Price D, Fromer L, Kaplan A, van der Molen T, Román-Rodríguez M. Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? NPJ Prim Care Respir Med. 2014 Jul 17;24:14023. doi: 10.1038/npjpcrm.2014.23. PMID: 25030457; PMCID: PMC4373380.

209: Ciprandi G, Schiavetti I, Bellezza Fontana R, Sorbello V, Ricciardolo FL. Overweight and obesity as risk factors for impaired lung function in patients with asthma: A real-life experience. Allergy Asthma Proc. 2014 Jul-Aug;35(4):e62-71. doi: 10.2500/aap.2014.35.3773. PMID: 24992544.

210: Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β -agonists. Appl Health Econ Health Policy. 2014 Aug;12(4):447-59. doi: 10.1007/s40258-014-0107-8. Erratum in: Appl Health Econ Health Policy. 2016 Feb;14(1):119-25. PMID: 24974107.

211: Tan C, Gao D, Zhang C, Fu Y, Wang BK, Zhu Q, Wang YP. [Research on correlation between lung and large intestine based on meridian and acupoint palpation in patients with bronchial asthma]. Zhongguo Zhen Jiu. 2014 Feb;34(2):145-8. Chinese. PMID: 24796049.

212: Novelli F, Costa F, Latorre M, Malagrinò L, Celi A, Vagaggini B, Paggiaro P. Tiotropium: a new therapeutic option in asthma. Monaldi Arch Chest Dis. 2013 Sep-Dec;79(3-4):109-15. doi: 10.4081/monaldi.2013.5208. PMID: 24761528.

213: Gray TA, Alsamman K, Murray E, Sims AH, Hupp TR. Engineering a synthetic cell panel to identify signalling components reprogrammed by the cell growth regulator anterior gradient-2. Mol Biosyst. 2014 Jun;10(6):1409-25. doi: 10.1039/c4mb00113c. Epub 2014 Apr 7. PMID: 24710632.

214: Page C, Cazzola M. Bifunctional drugs for the treatment of asthma and chronic obstructive pulmonary disease. Eur Respir J. 2014 Aug;44(2):475-82. doi: 10.1183/09031936.00003814. Epub 2014 Apr 2. PMID: 24696121.

215: Duechs MJ, Tilp C, Tomsic C, Gantner F, Erb KJ. Development of a novel severe triple allergen asthma model in mice which is resistant to dexamethasone and partially resistant to TLR7 and TLR9 agonist treatment. PLoS One. 2014 Mar 11;9(3):e91223. doi: 10.1371/journal.pone.0091223. PMID: 24618687; PMCID: PMC3949744.

216: Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. J Asthma Allergy. 2014 Feb 27;7:11-21. doi: 10.2147/JAA.S38841. PMID: 24600237; PMCID: PMC3942115.

217: Rorie A, Goldner WS, Lyden E, Poole JA. Beneficial role for supplemental vitamin D3 treatment in chronic urticaria: a randomized study. Ann Allergy Asthma Immunol. 2014 Apr;112(4):376-82. doi: 10.1016/j.anai.2014.01.010. Epub 2014 Feb 5. PMID: 24507460.

218: Todorova M, Trendafilova A. Sideritis scardica Griseb., an endemic species of Balkan peninsula: traditional uses, cultivation, chemical composition, biological activity. J Ethnopharmacol. 2014 Mar 14;152(2):256-65. doi: 10.1016/j.jep.2014.01.022. Epub 2014 Jan 30. PMID: 24487281.

219: Gruba SM, Meyer AF, Manning BM, Wang Y, Thompson JW, Dalluge JJ, Haynes CL. Time- and concentration-dependent effects of exogenous serotonin and inflammatory cytokines on mast cell function. ACS Chem Biol. 2014 Feb 21;9(2):503-9. doi: 10.1021/cb400787s. Epub 2013 Dec 19. PMID: 24304209; PMCID: PMC4083829.

220: Suijkerbuijk AW, de Wit GA, Wijga AH, Heijmans M, Hoogendoorn M, Rutten-van Mölken M, Maurits EE, Hoogenveen RT, Feenstra TL. Maatschappelijke kosten van astma, COPD en respiratoire allergie [Societal costs of asthma, COPD and

Supplementary data

respiratory allergy]. Ned Tijdschr Geneeskd. 2013;157(46):A6562. Dutch. PMID: 24220178.

221: Peters SP, Bleeker ER, Kunkelman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger LC, Engle LL, Dimango EA, Israel E, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Szeefler SJ; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol*. 2013 Nov;132(5):1068-1074.e1. doi: 10.1016/j.jaci.2013.08.003. Epub 2013 Sep 29. PMID: 24084072; PMCID: PMC3826080.

222: Park GY, Lee YG, Berdyshev E, Nyenhuis S, Du J, Fu P, Gorshkova IA, Li Y, Chung S, Karpurapu M, Deng J, Ranjan R, Xiao L, Jaffe HA, Corbridge SJ, Kelly EA, Jarjour NN, Chun J, Prestwich GD, Kaffe E, Ninou I, Aidinis V, Morris AJ, Smyth SS, Ackerman SJ, Natarajan V, Christman JW. Autotoxin production of lysophosphatidic acid mediates allergic asthmatic inflammation. *Am J Respir Crit Care Med*. 2013 Oct 15;188(8):928-40. doi: 10.1164/rccm.201306-1014OC. PMID: 24050723; PMCID: PMC3826286.

223: Morphew T, Scott L, Li M, Galant SP, Wong W, Garcia Lloret MI, Jones F, Bollinger ME, Jones CA. Mobile health care operations and return on investment in predominantly underserved children with asthma: the breathmobile program. *Popul Health Manag*. 2013 Aug;16(4):261-9. doi: 10.1089/pop.2012.0060. PMID: 23941048.

224: Anderson WJ, Short PM, Williamson PA, Morrison AE, Palmer C, Tavendale R, Lipworth BJ. Proof-of-concept evaluation of trough airway hyper-responsiveness following regular racemic or levosalbutamol in genotype-stratified steroid-treated persistent asthmatic patients. *Clin Sci (Lond)*. 2014 Jan 1;126(1):75-83. doi: 10.1042/CS20130213. PMID: 23829494.

225: Riley JP, Fuchs B, Sjöberg L, Nilsson GP, Karlsson L, Dahlén SE, Rao NL, Adner M. Mast cell mediators cause early allergic bronchoconstriction in guinea-pigs *in vivo*: a model of relevance to asthma. *Clin Sci (Lond)*. 2013 Dec;125(11):533-42. doi: 10.1042/CS20130092. PMID: 23799245.

226: Guyer AC, Long AA. Long-acting anticholinergics in the treatment of asthma. *Curr Opin Allergy Clin Immunol*. 2013 Aug;13(4):392-8. doi: 10.1097/ACI.0b013e328362a775. PMID: 23756872.

227: Clarke SA, Calam R, Morawska A, Sanders M. Developing web-based Triple P 'Positive Parenting Programme' for families of children with asthma. *Child Care Health Dev*. 2014 Jul;40(4):492-7. doi: 10.1111/cch.12073. Epub 2013 May 12. Erratum in: *Child Care Health Dev*. 2015 May;41(3):503. PMID: 23662595.

228: Caffarelli C, Santamaria F, Vottero A, Bernasconi S. Progress in Pediatrics in 2012: choices in allergy, endocrinology, gastroenterology, hematology, infectious diseases, neurology, nutrition and respiratory tract illnesses. *Ital J Pediatr*. 2013 May 8;39:26. doi: 10.1186/1824-7288-39-26. PMID: 23651601; PMCID: PMC3660281.

229: Bollmeier SG, Lee SY. The emerging role of tiotropium for patients with asthma. *Ann Pharmacother*. 2013 May;47(5):704-13. doi: 10.1345/aph.1R641. Epub 2013 Apr 23. PMID: 23613100.

230: Rand TG, Robbins C, Rajaraman D, Sun M, Miller JD. Induction of Dectin-1 and asthma-associated signal transduction pathways in RAW 264.7 cells by a triple-helical (1, 3)- β -D glucan, curdlan. *Arch Toxicol*. 2013 Oct;87(10):1841-50. doi: 10.1007/s00204-013-1042-4. Epub 2013 Mar 30. PMID: 23543010.

231: Lipworth BJ. Emerging role of long acting muscarinic antagonists for asthma. *Br J Clin Pharmacol*. 2014 Jan;77(1):55-62. doi: 10.1111/bcp.12123. PMID: 23534447; PMCID: PMC3895347.

232: Amin M, Anwar F, Naz F, Mahmood T, Saari N. Anti-Helicobacter pylori and urease inhibition activities of some traditional medicinal plants. *Molecules*. 2013 Feb 7;18(2):2135-49. doi: 10.3390/molecules18022135. PMID: 23434867; PMCID: PMC6270356.

233: Sjåheim TB, Bjørntuft Ø, Drabløs PA, Kongerud J, Halstensen TS. Increased bronchial density of CD25⁺Foxp3⁺ regulatory T cells in occupational asthma: relationship to current smoking. *Scand J Immunol*. 2013 May;77(5):398-404. doi: 10.1111/sji.12035. PMID: 23421612.

Supplementary data

- 234: Newcomb DC, Boswell MG, Sherrill TP, Polosukhin VV, Boyd KL, Goleniewska K, Brody SL, Kolls JK, Adler KB, Peebles RS Jr. IL-17A induces signal transducers and activators of transcription-6-independent airway mucous cell metaplasia. *Am J Respir Cell Mol Biol.* 2013 Jun;48(6):711-6. doi: 10.1165/rcmb.2013-0017OC. PMID: 23392574; PMCID: PMC3727878.
- 235: Peters SP. Tiotropium bromide triple combination therapy improves lung function and decreases asthma exacerbations. *Evid Based Med.* 2013 Oct;18(5):179. doi: 10.1136/eb-2012-101100. Epub 2013 Jan 24. PMID: 23349214.
- 236: Zarowitz BJ, O'Shea T. Chronic obstructive pulmonary disease: prevalence, characteristics, and pharmacologic treatment in nursing home residents with cognitive impairment. *J Manag Care Pharm.* 2012 Oct;18(8):598-606. doi: 10.18553/jmcp.2012.18.8.598. PMID: 23127147.
- 237: Adi H, Young PM, Traini D. Co-deposition of a triple therapy drug formulation for the treatment of chronic obstructive pulmonary disease using solution-based pressurised metered dose inhalers. *J Pharm Pharmacol.* 2012 Sep;64(9):1245-53. doi: 10.1111/j.2042-7158.2011.01370.x. Epub 2011 Oct 27. PMID: 22881437.
- 238: Al-Sheyab NA, Gallagher R, Roydhouse JK, Crisp J, Shah S. Feasibility of a peer-led, school-based asthma education programme for adolescents in Jordan. *East Mediterr Health J.* 2012 May;18(5):468-73. doi: 10.26719/2012.18.5.468. PMID: 22764433.
- 239: Vollmer WM, Feldstein A, Smith DH, Dubanoski JP, Waterbury A, Schneider JL, Clark SA, Rand C. Use of health information technology to improve medication adherence. *Am J Manag Care.* 2011 Dec;17(12 Spec No.):SP79-87. PMID: 22216772; PMCID: PMC3641901.
- 240: MacSharry J, O'Mahony C, Shalaby KH, Sheil B, Karmouty-Quintana H, Shanahan F, Martin JG. Immunomodulatory effects of feeding with *Bifidobacterium longum* on allergen-induced lung inflammation in the mouse. *Pulm Pharmacol Ther.* 2012 Aug;25(4):325-34. doi: 10.1016/j.pupt.2012.05.011. Epub 2012 Jun 13. PMID: 22705947.
- 241: Bjerg A, Lundbäck B, Lötvall J. The future of combining inhaled drugs for COPD. *Curr Opin Pharmacol.* 2012 Jun;12(3):252-5. doi: 10.1016/j.coph.2012.03.004. Epub 2012 Mar 30. PMID: 22465638.
- 242: Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, Baloira A, Carrizo S, Esteban C, Galdiz JB, González MC, Miravitles M, Monsó E, Montemayor T, Morera J, Ortega F, Peces-Barba G, Puente I, Rodríguez JM, Sala E, Sauleda J, Soriano JB, Viejo JL. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol.* 2012 Sep;48(9):331-7. English, Spanish. doi: 10.1016/j.arbres.2011.12.009. Epub 2012 Feb 15. PMID: 22341911.
- 243: Hirsch R, Deng H, Laochachai MN. Azithromycin in periodontal treatment: more than an antibiotic. *J Periodontal Res.* 2012 Apr;47(2):137-48. doi: 10.1111/j.1600-0765.2011.01418.x. Epub 2011 Nov 4. PMID: 22050485.
- 244: Lechuga-Ballesteros D, Noga B, Vehring R, Cummings RH, Dwivedi SK. Novel cosuspension metered-dose inhalers for the combination therapy of chronic obstructive pulmonary disease and asthma. *Future Med Chem.* 2011 Oct;3(13):1703-18. doi: 10.4155/fmc.11.133. PMID: 21942257.
- 245: Banerjee ER. Triple selectin knockout (ELP^{-/-}) mice fail to develop OVA-induced acute asthma phenotype. *J Inflamm (Lond).* 2011 Aug 11;8:19. doi: 10.1186/1476-9255-8-19. PMID: 21835035; PMCID: PMC3170177.
- 246: Feng L, Zhang Y, Chen R, Hao Y. The Chinese version of the Pediatric Quality of Life Inventory™ (PedsQL™) 3.0 Asthma Module: reliability and validity. *Health Qual Life Outcomes.* 2011 Aug 7;9:64. doi: 10.1186/1477-7525-9-64. PMID: 21819618; PMCID: PMC3161836.
- 247: Short PM, Williamson PA, Elder DHJ, Lipworth SIW, Schembri S, Lipworth BJ. The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting β-agonist therapy in COPD. *Chest.* 2012 Jan;141(1):81-86. doi: 10.1378/chest.11-0038. Epub 2011 Jul 28. PMID: 21799028.
- 248: Hagan JB, Taylor RL, Kita H, Singh RJ. Analysis of fluticasone propionate in induced sputum by mass spectrometry. *Allergy Asthma Proc.* 2011 Jul-Aug;32(4):18-21. doi: 10.2500/aap.2011.32.3454. PMID: 21781401.

Supplementary data

- 249: Barnes PJ. Triple inhalers for obstructive airways disease: will they be useful? *Expert Rev Respir Med.* 2011 Jun;5(3):297-300. doi: 10.1586/ers.11.26. PMID: 21702649.
- 250: Sung CC, Chi H, Chiu NC, Huang DT, Weng LC, Wang NY, Huang FY. Viral etiology of acute lower respiratory tract infections in hospitalized young children in Northern Taiwan. *J Microbiol Immunol Infect.* 2011 Jun;44(3):184-90. doi: 10.1016/j.jmii.2011.01.025. Epub 2011 Jan 18. PMID: 21524612; PMCID: PMC7105033.
- 251: Saini B, Shah S, Kearey P, Bosnic-Anticevich S, Grootjans J, Armour C. An interprofessional learning module on asthma health promotion. *Am J Pharm Educ.* 2011 Mar 10;75(2):30. doi: 10.5688/ajpe75230. PMID: 21519420; PMCID: PMC3073104.
- 252: Cazzola M, Segreti A, Bettencelli G, Calzetta L, Cricelli C, Pasqua F, Rogliani P. Change in asthma and COPD prescribing by Italian general practitioners between 2006 and 2008. *Prim Care Respir J.* 2011 Sep;20(3):291-8. doi: 10.4104/pcrj.2011.00033. PMID: 21509419; PMCID: PMC6549849.
- 253: Jonas DE, Wines RCM, DelMonte M, Amick HR, Wilkins TM, Einerson BD, Schuler CL, Wynia BA, Shilliday BB. Drug Class Review: Controller Medications for Asthma: Final Update 1 Report [Internet]. Portland (OR): Oregon Health & Science University; 2011 Apr. PMID: 22132427.
- 254: Chen R, Hao Y, Feng L, Zhang Y, Huang Z. The Chinese version of the Pediatric Quality of Life Inventory™ (PedSQL™) Family Impact Module: cross-cultural adaptation and psychometric evaluation. *Health Qual Life Outcomes.* 2011 Mar 23;9:16. doi: 10.1186/1477-7525-9-16. PMID: 21429195; PMCID: PMC3072920.
- 255: Balreira A. Triple terapia en el tratamiento de la EPOC [Triple therapy in chronic obstructive pulmonary disease]. *Arch Bronconeumol.* 2010;46 Suppl 8:25-30. Spanish. doi: 10.1016/S0300-2896(10)70064-8. PMID: 21334553.
- 256: El-Hefnawy AS, Wadie BS. Severe stress urinary incontinence: Objective analysis of risk factors. *Maturitas.* 2011 Apr;68(4):374-7. doi: 10.1016/j.maturitas.2011.01.005. Epub 2011 Feb 2. PMID: 21292413.
- 257: Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger L, Engle LL, DiMango EA, Fahy JV, Israel E, Jarjour N, Kazani SD, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Bleeker ER; National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med.* 2010 Oct 28;363(18):1715-26. doi: 10.1056/NEJMoa1008770. Epub 2010 Sep 19. PMID: 20979471; PMCID: PMC3011177.
- 258: Malfertheiner P, Selgrad M. Helicobacter pylori infection and current clinical areas of contention. *Curr Opin Gastroenterol.* 2010 Nov;26(6):618-23. doi: 10.1097/MOG.0b013e32833efede. PMID: 20827182.
- 259: Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv.* 2010 Oct;23(5):323-8. doi: 10.1089/jamp.2009.0785. PMID: 20804428.
- 260: Farley MM. 2009 H1N1 influenza: a twenty-first century pandemic with roots in the early twentieth century. *Am J Med Sci.* 2010 Sep;340(3):202-8. doi: 10.1097/MAJ.0b013e3181e937b0. PMID: 20697263; PMCID: PMC7119454.
- 261: Barnes PJ. Inhaled corticosteroids in COPD: a controversy. *Respiration.* 2010;80(2):89-95. doi: 10.1159/000315416. Epub 2010 May 26. PMID: 20501985.
- 262: Ohar JA, Donohue JF. Mono- and combination therapy of long-acting bronchodilators and inhaled corticosteroids in advanced COPD. *Semin Respir Crit Care Med.* 2010 Jun;31(3):321-33. doi: 10.1055/s-0030-1254072. Epub 2010 May 21. PMID: 20496301.
- 263: Williamson PA, Short PM, Clearie KL, Vaidyanathan S, Fardon TC, Howaniec LJ, Lipworth BJ. Paradoxical trough effects of triple therapy with budesonide/formoterol and tiotropium bromide on pulmonary function outcomes in COPD. *Chest.* 2010 Sep;138(3):595-604. doi: 10.1378/chest.10-0247. Epub 2010 Apr 23. PMID: 20418370.
- 264: Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, Covar RA, Guilbert TW, Larsen G, Morgan WJ, Moss MH, Spahn JD, Taussig LM; Childhood Asthma Research

Supplementary data

- and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med.* 2010 Mar 18;362(11):975-85. doi: 10.1056/NEJMoa1001278. Epub 2010 Mar 2. PMID: 20197425; PMCID: PMC2989902.
- 265: Simoni-Wastila L, Blanchette CM, Qian J, Yang HW, Zhao L, Zuckerman IH, Pak GH, Silver H, Dalal AA. Burden of chronic obstructive pulmonary disease in Medicare beneficiaries residing in long-term care facilities. *Am J Geriatr Pharmacother.* 2009 Oct;7(5):262-70. doi: 10.1016/j.amjopharm.2009.11.003. PMID: 19948302.
- 266: Molfino NA. Increased vagal airway tone in fatal asthma. *Med Hypotheses.* 2010 Mar;74(3):521-3. doi: 10.1016/j.mehy.2009.10.002. Epub 2009 Nov 10. PMID: 19906493.
- 267: Gordon E, Lazarus SC. Management of chronic obstructive pulmonary disease: moving beyond the asthma algorithm. *J Allergy Clin Immunol.* 2009 Nov;124(5):873-80; quiz 881-2. doi: 10.1016/j.jaci.2009.09.040. PMID: 19895979.
- 268: Jeppsson MC, Lindh CH, Kristiansson MH, Nielsen J, Jönsson BA. Methylhexahydrophthalic anhydride adducted albumin tryptic peptides in nasal lavage fluid. *Inhal Toxicol.* 2009 Oct;21(12):1013-20. doi: 10.1080/08958370802715997. PMID: 19772480.
- 269: Zarei S, Jeddi-Tehrani M, Akhondi MM, Zeraati H, Pourheidari F, Ostadkarampour M, Tavangar B, Shokri F. Primary immunization with a triple diphtheria-tetanus-whole cell pertussis vaccine in Iranian infants: an analysis of antibody response. *Iran J Allergy Asthma Immunol.* 2009 Jun;8(2):85-93. PMID: 19671937.
- 270: Vilozni D, Livnat G, Dabbah H, Elias N, Hakim F, Bentur L. The potential use of spirometry during methacholine challenge test in young children with respiratory symptoms. *Pediatr Pulmonol.* 2009 Jul;44(7):720-7. doi: 10.1002/ppul.20978. PMID: 19499592.
- 271: Fleischel O, Giménez-Arnau E, Lepoittevin JP. Nuclear magnetic resonance studies on covalent modification of amino acids thiol and amino residues by monofunctional aryl 13C-isocyanates, models of skin and respiratory sensitizers: transformation of thiocarbamates into urea adducts. *Chem Res Toxicol.* 2009 Jun;22(6):1106-15. doi: 10.1021/tx9000539. PMID: 19405514.
- 272: Goplen N, Karim MZ, Liang Q, Gorska MM, Rozario S, Guo L, Alam R. Combined sensitization of mice to extracts of dust mite, ragweed, and Aspergillus species breaks through tolerance and establishes chronic features of asthma. *J Allergy Clin Immunol.* 2009 Apr;123(4):925-32.e11. doi: 10.1016/j.jaci.2009.02.009. PMID: 19348928; PMCID: PMC2683988.
- 273: Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. *Respir Med.* 2009 May;103(5):670-91. doi: 10.1016/j.rmed.2008.11.017. Epub 2009 Jan 19. PMID: 19155168.
- 274: Sun RS, Chen XH, Sui JF, Liu RQ, Cheng TM, Ran XZ, Yang T. Detecting anti-FcepsilonRI autoantibodies in patients with asthma by flow cytometry. *J Int Med Res.* 2008 Nov-Dec;36(6):1214-9. doi: 10.1177/147323000803600607. PMID: 19094429.
- 275: Shah S, Roydhouse JK, Sawyer SM. Medical students go back to school--the Triple A journey. *Aust Fam Physician.* 2008 Nov;37(11):952-4. PMID: 19037472.
- 276: Maffey AF, Venialgo CM, Barrero PR, Fuse VA, Márques Mde L, Saia M, Villalba A, Teper AM, Mistchenko AS. Nuevos virus respiratorios en niños de 2 meses a 3 años con sibilancias recurrentes [New respiratory viruses in children 2 months to 3 years old with recurrent wheeze]. *Arch Argent Pediatr.* 2008 Aug;106(4):302-9. Spanish. doi: 10.1590/S0325-00752008000400005. PMID: 18766276.
- 277: Tsuchida H, Takahashi S, Nosaka E, Kuraya T, Yamashita M, Morimoto K. Novel triple neurokinin receptor antagonist CS-003 inhibits respiratory disease models in guinea pigs. *Eur J Pharmacol.* 2008 Oct 31;596(1-3):153-9. doi: 10.1016/j.ejphar.2008.07.046. Epub 2008 Jul 31. PMID: 18706408.
- 278: Kumon M, Yabe Y, Kasuya Y, Suzuki M, Kusai A, Yonemochi E, Terada K. Applicability of DPI formulations for novel neurokinin receptor antagonist. *Int J Pharm.* 2008 May 22;356(1-2):102-9. doi: 10.1016/j.ijpharm.2007.12.044. Epub 2008 Jan 9. PMID: 18294787.
- 279: Rootmensen GN, van Keimpema AR, Looyens EE, van der Schaaf L, Jansen HM, de Haan RJ. Reliability in the assessment of videotaped inhalation technique. *J*

Supplementary data

Aerosol Med. 2007 Winter;20(4):429-33. doi: 10.1089/jam.2007.0623. PMID: 18158715.

280: Sharif S, Goldberg B. Detection of IgE antibodies to bacitracin using a commercially available streptavidin-linked solid phase in a patient with anaphylaxis to triple antibiotic ointment. Ann Allergy Asthma Immunol. 2007 Jun;98(6):563-6. doi: 10.1016/S1081-1206(10)60736-3. PMID: 17601270.

281: Venkatasamy R, Spina D. Protease inhibitors in respiratory disease: focus on asthma and chronic obstructive pulmonary disease. Expert Rev Clin Immunol. 2007 May;3(3):365-81. doi: 10.1586/1744666X.3.3.365. PMID: 20477680.

282: Matsumoto K, Inoue H, Tsuda M, Nakano T, Komori M, Fukuyama S, Nakanishi Y. Different profiles of IL-10+IFN-gamma-IL-4-CD4+ T cells in the peripheral blood in atopic and non-atopic asthmatics. Respiration. 2008;75(3):281-7. doi: 10.1159/000101475. Epub 2007 Mar 29. PMID: 17396024.

283: Hakim F, Vilozni D, Adler A, Livnat G, Tal A, Bentur L. The effect of montelukast on bronchial hyperreactivity in preschool children. Chest. 2007 Jan;131(1):180-6. doi: 10.1378/chest.06-1402. PMID: 17218573.

284: Bernstein DI, Wang N, Campo P, Chakraborty R, Smith A, Cartier A, Boulet LP, Malo JL, Yucesoy B, Luster M, Tarlo SM, Hershey GK. Diisocyanate asthma and gene-environment interactions with IL4RA, CD-14, and IL-13 genes. Ann Allergy Asthma Immunol. 2006 Dec;97(6):800-6. doi: 10.1016/S1081-1206(10)60972-6. PMID: 17201240.

285: Fardon T, Haggart K, Lee DK, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. Respir Med. 2007 Jun;101(6):1218-28. doi: 10.1016/j.rmed.2006.11.001. Epub 2006 Dec 18. PMID: 17178217.

286: Pahl A, Bauhofer A, Petzold U, Cnota PJ, Maus J, Brune K, Szelenyi S. Synergistic effects of the anti-cholinergic R,R-glycopyrrrolate with anti-inflammatory drugs. Biochem Pharmacol. 2006 Dec 15;72(12):1690-6. doi: 10.1016/j.bcp.2006.07.025. Epub 2006 Sep 25. PMID: 16996482.

287: Herszberg B, Ramos-Barbón D, Tamaoka M, Martin JG, Lavoie JP. Heaves, an asthma-like equine disease, involves airway smooth muscle remodeling. J Allergy Clin Immunol. 2006 Aug;118(2):382-8. doi: 10.1016/j.jaci.2006.03.044. Epub 2006 May 30. PMID: 16890762.

288: Currie GP, Lee DK, Menzies D, Lipworth BJ. Evaluating the effects of "triple therapy" with inhaled corticosteroids, long-acting beta₂-agonists, and leukotriene modifiers in asthma. Chest. 2006 Jul;130(1):301-2. doi: 10.1378/chest.130.1.301. PMID: 16840420.

289: Larsen K, Macleod D, Nihlberg K, Gürcan E, Bjerner L, Marko-Varga G, Westergren-Thorsson G. Specific haptoglobin expression in bronchoalveolar lavage during differentiation of circulating fibroblast progenitor cells in mild asthma. J Proteome Res. 2006 Jun;5(6):1479-83. doi: 10.1021/pr050462h. PMID: 16739999.

290: Abe M, Hayashi Y, Murai A, Shibata K, Sakata N, Igarashi R, Katsuragi T, Tanaka K. Effects of inducible nitric oxide synthase inhibitors on asthma depending on administration schedule. Free Radic Biol Med. 2006 Mar 15;40(6):1083-95. doi: 10.1016/j.freeradbiomed.2005.10.057. Epub 2005 Nov 21. PMID: 16540403.

291: De Swert KO, Joos GF. Extending the understanding of sensory neuropeptides. Eur J Pharmacol. 2006 Mar 8;533(1-3):171-81. doi: 10.1016/j.ejphar.2005.12.066. Epub 2006 Feb 7. PMID: 16464447.

292: Kritikos V, Saini B, Bosnic-Anticevich SZ, Krass I, Shah S, Taylor S, Armour C. Innovative asthma health promotion by rural community pharmacists: a feasibility study. Health Promot J Austr. 2005 Apr;16(1):69-73. doi: 10.1071/he05069. PMID: 16389935.

293: Schelfhout V, Louis R, Lenz W, Heyrman R, Pauwels R, Joos G. The triple neurokinin-receptor antagonist CS-003 inhibits neurokinin A-induced bronchoconstriction in patients with asthma. Pulm Pharmacol Ther. 2006;19(6):413-8. doi: 10.1016/j.pupt.2005.10.007. Epub 2005 Dec 20. PMID: 16364669.

294: Robbins RA, Thomas AR, Proctor LM, Hoyt JC, Hayden JM. Heat decreases formoterol delivery. Chest. 2005 Dec;128(6):4036-40. doi: 10.1378/chest.128.6.4036. PMID: 16354878.

Supplementary data

- 295: Rice-McDonald G, Bowler S, Staines G, Mitchell C. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. *Intern Med J.* 2005 Dec;35(12):693-8. doi: 10.1111/j.1445-5994.2005.00972.x. PMID: 16313543.
- 296: Montuschi P, Martello S, Felli M, Mondino C, Barnes PJ, Chiarotti M. Liquid chromatography/mass spectrometry analysis of exhaled leukotriene B4 in asthmatic children. *Respir Res.* 2005 Oct 19;6(1):119. doi: 10.1186/1465-9921-6-119. PMID: 16236169; PMCID: PMC1283153.
- 297: Chan HW, Smith NJ, Hannan RD, Thomas WG. Tackling the EGFR in pathological tissue remodelling. *Pulm Pharmacol Ther.* 2006;19(1):74-8. doi: 10.1016/j.pupt.2005.04.005. Epub 2005 Jun 24. PMID: 15979363.
- 298: Khanna S, Sobhia ME, Bharatam PV. Additivity of molecular fields: CoMFA study on dual activators of PPARalpha and PPARgamma. *J Med Chem.* 2005 Apr 21;48(8):3015-25. doi: 10.1021/jm049383s. PMID: 15828840.
- 299: Wei H, Zhang J, Xiao W, Feng J, Sun R, Tian Z. Involvement of human natural killer cells in asthma pathogenesis: natural killer 2 cells in type 2 cytokine predominance. *J Allergy Clin Immunol.* 2005 Apr;115(4):841-7. doi: 10.1016/j.jaci.2004.11.026. PMID: 15806008.
- 300: Benke G, Abramson M, Raven J, Thien FC, Walters EH. Asthma and vaccination history in a young adult cohort. *Aust N Z J Public Health.* 2004 Aug;28(4):336-8. doi: 10.1111/j.1467-842x.2004.tb00440.x. PMID: 15704697.
- 301: Meltzer EO, Berman GD, Corren J, Pedinoff AJ, Doyle G, Waksman JA, Butkerait P, Cooper SA, Berlin RG, Wason S. Addition of ibuprofen to pseudoephedrine and chlorpheniramine in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2004 Nov;93(5):452-9. doi: 10.1016/S1081-1206(10)61412-3. PMID: 15562884.
- 302: Murai A, Abe M, Hayashi Y, Sakata N, Katsuragi T, Tanaka K. Comparison study between the mechanisms of allergic asthma amelioration by a cysteinyl-leukotriene type 1 receptor antagonist montelukast and methylprednisolone. *J Pharmacol Exp Ther.* 2005 Feb;312(2):432-40. doi: 10.1124/jpet.104.074922. Epub 2004 Oct 6. PMID: 15470084.
- 303: Lee CG, Cho SJ, Kang MJ, Chapoval SP, Lee PJ, Noble PW, Yehualaeshet T, Lu B, Flavell RA, Milbrandt J, Homer RJ, Elias JA. Early growth response gene 1-mediated apoptosis is essential for transforming growth factor beta1-induced pulmonary fibrosis. *J Exp Med.* 2004 Aug 2;200(3):377-89. doi: 10.1084/jem.20040104. PMID: 15289506; PMCID: PMC2211975.
- 304: Hallgren J, Bäckström S, Estrada S, Thuveson M, Pejler G. Histidines are critical for heparin-dependent activation of mast cell tryptase. *J Immunol.* 2004 Aug 1;173(3):1868-75. doi: 10.4049/jimmunol.173.3.1868. PMID: 15265919.
- 305: Goleva E, Dunlap A, Leung DY. Differential control of TH1 versus TH2 cell responses by the combination of low-dose steroids with beta2-adrenergic agonists. *J Allergy Clin Immunol.* 2004 Jul;114(1):183-91. doi: 10.1016/j.jaci.2004.04.001. PMID: 15241363.
- 306: Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. *J Allergy Clin Immunol.* 2004 Jun;113(6):1117-21. doi: 10.1016/j.jaci.2004.01.756. PMID: 15208593.
- 307: Soni KK, Khare ML, Saxena RC. Spasmolytic activity of a herbal drug isolated from *Tephrosia purpurea* in guinea pigs. *Anc Sci Life.* 2004 Apr;23(4):59-65. PMID: 22557142; PMCID: PMC3330980.
- 308: Rimaniol AC, Till SJ, Garcia G, Capel F, Godot V, Balabanian K, Durand-Gasselin I, Varga EM, Simonneau G, Emilie D, Durham SR, Humbert M. The CX3C chemokine fractalkine in allergic asthma and rhinitis. *J Allergy Clin Immunol.* 2003 Dec;112(6):1139-46. doi: 10.1016/j.jaci.2003.09.041. PMID: 14657873.
- 309: Flores G, Abreu M, Chaisson CE, Sun D. Keeping children out of hospitals: parents' and physicians' perspectives on how pediatric hospitalizations for ambulatory care-sensitive conditions can be avoided. *Pediatrics.* 2003 Nov;112(5):1021-30. doi: 10.1542/peds.112.5.1021. PMID: 14595041.
- 310: Köhler D. Novolizer: the new technology for the management of asthma therapy. *Curr Opin Pulm Med.* 2003 Apr;9 Suppl 1:S11-6. PMID: 12974537.
- 311: Rizzo CA, Anthes JC, Corboz MR, Chapman RW, Shih NY, Reichard GA, Ng KJ,

Supplementary data

- Hey JA. Development and potential utility of dual and triple NK receptor antagonists. *Curr Top Med Chem.* 2003;3(12):1410-22. doi: 10.2174/1568026033451844. PMID: 12871172.
- 312: Rodrigo GJ, Rodrigo C. Triple inhaled drug protocol for the treatment of acute severe asthma. *Chest.* 2003 Jun;123(6):1908-15. doi: 10.1378/chest.123.6.1908. PMID: 12796167.
- 313: Joos GF, De Swert KO, Schelfhout V, Pauwels RA. The role of neural inflammation in asthma and chronic obstructive pulmonary disease. *Ann N Y Acad Sci.* 2003 May;992:218-30. doi: 10.1111/j.1749-6632.2003.tb03152.x. PMID: 12794061.
- 314: Cazzola M, Noschese P, Salzillo A, Piccolo A. Asthma treatment must be always tailored to the individual patient. *Monaldi Arch Chest Dis.* 2002 Jun-Aug;57(3-4):213-7. PMID: 12619388.
- 315: Bradshaw D, Schneider M, Dorrington R, Bourne DE, Laubscher R. South African cause-of-death profile in transition--1996 and future trends. *S Afr Med J.* 2002 Aug;92(8):618-23. PMID: 12244621.
- 316: Zhu Z, Lee CG, Zheng T, Chupp G, Wang J, Homer RJ, Noble PW, Hamid Q, Elias JA. Airway inflammation and remodeling in asthma. Lessons from interleukin 11 and interleukin 13 transgenic mice. *Am J Respir Crit Care Med.* 2001 Nov 15;164(10 Pt 2):S67-70. doi: 10.1164/ajrccm.164.supplement_2.2106070. PMID: 11734470.
- 317: Abe M, Shibata K, Akatsu H, Shimizu N, Sakata N, Katsuragi T, Okada H. Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats. *J Immunol.* 2001 Oct 15;167(8):4651-60. doi: 10.4049/jimmunol.167.8.4651. PMID: 11591795.
- 318: Fyrnys B, Stang N, Wolf-Heuss E. Stability and performance characteristics of a budesonide powder for inhalation with a novel dry powder inhaler device. *Curr Opin Pulm Med.* 2001 Apr;7 Suppl 1:S7-11. PMID: 11385814.
- 319: Dahl M, Nordestgaard BG, Lange P, Tybjaerg-Hansen A. Fifteen-year follow-up of pulmonary function in individuals heterozygous for the cystic fibrosis phenylalanine-508 deletion. *J Allergy Clin Immunol.* 2001 May;107(5):818-23. doi: 10.1067/mai.2001.114117. PMID: 11344348.
- 320: Dubé J, Chakir J, Dubé C, Grimard Y, Laviolette M, Boulet LP. Synergistic action of endothelin (ET)-1 on the activation of bronchial fibroblast isolated from normal and asthmatic subjects. *Int J Exp Pathol.* 2000 Dec;81(6):429-37. doi: 10.1046/j.1365-2613.2000.00173.x. PMID: 11298190; PMCID: PMC2517744.
- 321: Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, Henry RL, Gibson PG. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial. *BMJ.* 2001 Mar 10;322(7286):583-5. doi: 10.1136/bmj.322.7286.583. PMID: 11238152; PMCID: PMC26550.
- 322: Danckwerts MP. Optimization and development of a core-in-cup tablet for modulated release of theophylline in simulated gastrointestinal fluids. *Drug Dev Ind Pharm.* 2000 Jul;26(7):767-72. doi: 10.1081/ddc-100101296. PMID: 10872096.
- 323: Sacchi S, Kantarjian HM, Freireich EJ, O'Brien S, Cortes J, Rios MB, Kornblau S, Giles FJ, Koller C, Gajewski J, Talpaz M. Unexpected high incidence of severe toxicities associated with alpha interferon, low-dose cytosine arabinoside and all-trans retinoic acid in patients with chronic myelogenous leukemia. *Leuk Lymphoma.* 1999 Nov;35(5-6):483-9. doi: 10.1080/10428199909169612. PMID: 10609785.
- 324: Salmon M, Walsh DA, Koto H, Barnes PJ, Chung KF. Repeated allergen exposure of sensitized Brown-Norway rats induces airway cell DNA synthesis and remodelling. *Eur Respir J.* 1999 Sep;14(3):633-41. doi: 10.1034/j.1399-3003.1999.14c25.x. PMID: 10543287.
- 325: Baraniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, Srebro S, Rickard KA. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest.* 1999 Sep;116(3):625-32. doi: 10.1378/chest.116.3.625. PMID: 10492263.
- 326: Li JT, Goldstein MF, Gross GN, Noonan MJ, Weisberg S, Edwards L, Reed KD, Rogenes PR. Effects of fluticasone propionate, triamcinolone acetonide, prednisone, and placebo on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol.* 1999 Apr;103(4):622-9. doi: 10.1016/s0091-6749(99)70234-4. PMID: 10200011.

Supplementary data

- 327: Golish J, Curtis-McCarthy P, McCarthy K, Kavuru M, Wagner W, Beck G, Eng P. Albuterol delivered by metered-dose inhaler (MDI), MDI with spacer, and Rotahaler device--a comparison of efficacy and safety. *J Asthma*. 1998;35(4):373-9. doi: 10.3109/02770909809075671. PMID: 9669832.
- 328: Gibson PG, Shah S, Mamoon HA. Peer-led asthma education for adolescents: impact evaluation. *J Adolesc Health*. 1998 Jan;22(1):66-72. doi: 10.1016/S1054-139X(97)00203-6. PMID: 9436069.
- 329: Tibes U, Friebe WG. Phospholipase A2 inhibitors in development. *Expert Opin Investig Drugs*. 1997 Mar;6(3):279-98. doi: 10.1517/13543784.6.3.279. PMID: 15989628.
- 330: Piletta PA, Wirth S, Hommel L, Saurat JH, Hauser C. Circulating skin-homing T cells in atopic dermatitis. Selective up-regulation of HLA-DR, interleukin-2R, and CD30 and decrease after combined UV-A and UV-B phototherapy. *Arch Dermatol*. 1996 Oct;132(10):1171-6. doi: 10.1001/archderm.132.10.1171. PMID: 8859027.
- 331: Spong CY, Sherer DM, Ghidini A, Jenkins CB, Seydel FD, Eglinton GS. Second-trimester amniotic fluid or maternal serum interleukin-10 levels and small for gestational age neonates. *Obstet Gynecol*. 1996 Jul;88(1):24-8. doi: 10.1016/0029-7844(96)00110-X. PMID: 8684756.
- 332: Li YQ, Yuan W, Zhang SL. [Clinical and experimental study of xiao er ke cuan ling oral liquid in the treatment of infantile bronchopneumonia]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1992 Dec;12(12):719-21, 737, 708. Chinese. PMID: 1304839.
- 333: Vichyanond P, Chokephaibulkit K, Kerdsoonsuwan S, Visitsuntorn N, Tuchinda M. Clinical evaluation of the "Siriraj Spacer" in asthmatic Thai children. *Ann Allergy*. 1992 Nov;69(5):433-8. PMID: 1456485.
- 334: Iamandescu IB. NSAIDs-induced asthma: peculiarities related to background and association with other drug or non-drugs etiological agents. *Allergol Immunopathol (Madr)*. 1989 Nov-Dec;17(6):285-90. PMID: 2635829.
- 335: Findeisen DG. Unter Stress leiden oder Stress geniessen? Methodik und Ergebnisse einer klinisch bewährten Antistress-Dreiklang-Strategie am Beispiel der Asthmakrankheit [Suffering from stress or enjoying stress? Method and results of a clinically successful anti-stress triple strategy exemplified by asthma]. *Fortschr Med*. 1989 Mar 30;107(10):72-3. German. PMID: 2714726.
- 336: Henry DA. Side-effects of non-steroidal anti-inflammatory drugs. *Baillieres Clin Rheumatol*. 1988 Aug;2(2):425-54. doi: 10.1016/s0950-3579(88)80021-9. PMID: 3066501.
- 337: van der Vet AP, Kreukniet J, van Drost RH, Maes RA, Fokkens JK, Hamelink MJ. Combination therapy of theophylline and terbutaline as sustained-release preparations in patients with asthmatic bronchitis. *Int J Clin Pharmacol Ther Toxicol*. 1987 Oct;25(10):558-64. PMID: 2828249.
- 338: Conradson TB, Eklundh G, Olofsson B, Pahlm O, Persson G. Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. *Chest*. 1987 Jan;91(1):5-9. doi: 10.1378/chest.91.1.5. PMID: 2431838.
- 339: Tønnesen P. Intracutaneous and skin prick testing with serotonin and histamine. *Allergy*. 1986 Apr;41(3):196-202. doi: 10.1111/j.1398-9995.1986.tb00300.x. PMID: 3717531.
- 340: Kraemer R, Meister B. Fast real-time moment-ratio analysis of multibreath nitrogen washout in children. *J Appl Physiol* (1985). 1985 Oct;59(4):1137-44. doi: 10.1152/jappl.1985.59.4.1137. PMID: 4055593.
- 341: Fisher AA. The persulfates: a triple threat. *Cutis*. 1985 Jun;35(6):520, 523-5. PMID: 4017646.
- 342: Giles GG, Lickiss N, Gibson HB, Shaw K. Respiratory symptoms in Tasmanian adolescents: a follow up of the 1961 birth cohort. *Aust N Z J Med*. 1984 Oct;14(5):631-7. doi: 10.1111/j.1445-5994.1984.tb05015.x. PMID: 6597710.
- 343: Khil'ko TF. Reaktsiya trojnoego rozentroobrazovaniia--novyi metod otsenki kletochnykh mehanizmov imuniteta pri vozdeistvii faktorov proizvodstvennoi sredy [The triple rosette formation reaction--a new method for assessing the mechanisms of cellular immunity during exposure to factors in the industrial environment]. *Gig Tr Prof Zabol*. 1984 Sep;(9):20-3. Russian. PMID: 6334007.

Supplementary data

344: Rebuck AS, Gent M, Chapman KR. Anticholinergic and sympathomimetic combination therapy of asthma. *J Allergy Clin Immunol.* 1983 Mar;71(3):317-23. doi: 10.1016/0091-6749(83)90086-6. PMID: 6219156.

345: Lefcoe NM, Toogood JH, Blennerhassett G, Baskerville J, Paterson NA. The addition of an aerosol anticholinergic to an oral beta agonist plus theophylline in asthma and bronchitis. A double-blind single dose study. *Chest.* 1982 Sep;82(3):300-5. doi: 10.1378/chest.82.3.300. PMID: 6213382.

346: Grimwood K, Johnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalational powder, or nebuliser? *Br Med J (Clin Res Ed).* 1981 Jan 10;282(6258):105-6. doi: 10.1136/bmj.282.6258.105. PMID: 6779890; PMCID: PMC1503918.

347: Tripathi RM, Sen PC, Das PK. Studies on the mechanism of action of Albizzia lebbeck, an Indian indigenous drug used in the treatment of atopic allergy. *J Ethnopharmacol.* 1979 Dec;1(4):385-96. doi: 10.1016/s0378-8741(79)80003-3. PMID: 544953.

348: Muittari A, Mattila MJ. Objective and subjective assessment of ephedrine combinations in asthmatic outpatients. *Ann Clin Res.* 1979 Jun;11(3):87-9. PMID: 386912.

349: Cohen BM. Physiologic/clinical comparisons of a sustained-release decongestant combination, its components and placebo in patients with allergic rhinitis. *J Asthma Res.* 1975 Sep;13(1):7-13. doi: 10.3109/02770907509104153. PMID: 57959.

350: Abramson HA. Triple blind disaster. *J Asthma Res.* 1965 Sep;3(1):1-2. PMID: 5318624.

351: GOLDFARB AA, ROMANOFF A. Clinical evaluation of a new triple drug aerosol for asthma. *Ann Allergy.* 1962 May;20:307-14. PMID: 13899746.