Appendix

Table S1: Search terms used

Search term	Individual terms used
At least one therapy	
ICS monotherapy	"inhaled corticosteroid?" or "ICS" or "beclomethasone" or "Clenil" or "Becotide" or "Becloforte" or "budesonide" or "Pulmicort" or "ciclesonide" or "Alvesco" or "flunisolide" or "Aerospan" or "fluticasone" or "Flovent" or "Flixotide" or "Arnuity" or "mometasone" or "Asmanex"
LTRA monotherapy	"leukotriene receptor antagonist?" or "LTRA" or "antileukotriene?" or "Montelukast" or "Singulair" or "Kipres" or "Zafirlukast" or "Accolate" or "Vanticon" or "Pranlukast" or "Onon" or "Ultair" or "Azlaire"
SABA monotherapy	"short-acting beta? agonist?" or "short-acting beta?-agonist?" or "SABA" or "Salbutamol" or "albuterol" or "Ventolin" or "Proventil" or "ProAir" or "Salamol" or "Pulvinal" or "Terbutaline" or "Bricanyl" or "Levosalbutamol" or "levalbuterol" or "Xopenx" or" "Pirbuterol" or "Maxair"
Methylxanthine monotherapy	"Methylxanthine?" or "Theophylline" or "An Fei Li" or "Antong" or "Asmalon" or "Bi Chuan" or "Etipramid" or "Protheo" or "Quelesu" or "Shi Er Ping" or "Asmapax" or "Asmaphylline" or "Bronchophylin" or "Euphyllin" or "Nuelin" or "Unicontin" or "Theodur" or "Teofilina" or "doxofylline" or "doxofilina" or "Lang Ming" or "Jian Fang Neng" or "Asmadox" or "Amril" or "Bestofyline" or "Dofasma" or "Doxobid" or "Yili"
ICS + SABA combination therapy	One individual term for ICS monotherapy PLUS one individual term for SABA monotherapy
ICS + LABA combination therapy	One individual term for ICS monotherapy PLUS "long-acting beta? agonist?" or "long-acting beta?-agonist?" or "LABA" or "formoterol" or "salmeterol" or "formoterol" or "vilanterol" or "formoterol" OR "Symbicort" or "Bufomix" or "Duoresp" or "Vannair" or "Advair" or "Seretide" or "AirFluSal" or "Sirdupla" or "Rolenium" or "Adoair" or "Viani" or "Dulera" or "Zenhale" or "Foster" or "Fostair" or "Breo" or "Relvar"
LTRA + SABA combination therapy	One individual term for LTRA monotherapy PLUS one individual term for SABA monotherapy
At least one outcome/keyword	
Epidemiology	"Epidemiolog*" or "prevalence?" or "incidence?"
Clinical and humanistic burden outcome	"death?" or "mortalit*" or "morbidit*" or "symptom?" or "event?" or "awakening?" or "control?" or "symptom-free day?" or "asthma control day?" or "attack?" or "exacerbation?" or "worsening" or "breathlessness" or "airflow limitation?" or "dyspn?ea" or "use of medication?" or "nebuli?ation?" or "acute severe asthma?" or "course of oral steroid?" or "OCS" or "lung function?" or "FEV1" or "quality of life" or "QoL" or "HRQoL" or "disabilities" or "patient satisfaction?" or "wellbeing" or "patient reported outcomes" or "caregiver burden?" or "disease burden?" or "burden of illness" or "SF36" or "EQ5D" or "anxiety and depression QoL scales" or "asthma QoL scales" or "Asthma Control Questionnaire" or "ACQ" or "St. George* Respiratory Questionnaire" or "SGRQ" or "time out? from school" or "time out? from work"
Economic burden outcome	"cost? of illness" or "indirect healthcare cost?" or "direct healthcare cost?" or "hospitali?ation" or "economic burden?" or "resource use?" or "productivity loss*" or "absenteeism?" or "presenteeism?" or "sick benefit?" or "societal cost?" or "unscheduled visit? to emergency department" or "unscheduled visit? to ED" or "primary care practitioner?" or "GP" or "HCP"

Note: question mark symbol (?) is a 'wild card' character that permits the search to detect the use of UK vs US spelling (in this case, hospitalisation and hospitalization). This is a widely used approach to simplify database search strings.

ACQ: Asthma Control Questionnaire; ED: emergency department; EQ5D: EuroQOL five dimensions questionnaire; FEV_1: forced expiratory volume in 1 second; GP: general practitioner; HCP: healthcare professional; HRQoL: health-related quality of life; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; QoL: quality of life; SABA: short-acting β_2-agonist; SF-36: Short-Form Health Survey 36; SGRQ: St. George's Respiratory Questionnaire.

Table S2: Categorisation of studies by mild asthma definition,† for RCTs and other/observational studies

Mild asthma category	Study, year	Definition
RCTs		
#1 Treatment level	Bateman et al (2018)[27]	Patients requiring GINA 2012 Step 2 treatment.
	Camargos et al (2018)[32]	Asthma symptoms present in patients naïve to controller treatment in prior 2 years, asthma controlled in previous 8 weeks with ICS (250–500 μg of beclomethasone, or equivalent, daily).
	O'Byrne et al (2018)[39]	Patients requiring GINA 2012 Step 2 treatment.
#2 Symptom frequency	Martinez et al (2011)[37]	Symptoms >2 days/week, SABA use > 2 days/week, >2 night time awakenings/month if not using controller medication or using daily controller treatment.
	Pauwels et al (2003)[42]	Symptoms: wheeze, cough, dyspnoea, or chest tightening at least once per week, but not as often as daily.
	Wongtim et al (1995)[81]	Mild asthma defined per NIH 1991 guidelines (i.e. lung function [reversibility; minimal/no evidence of airway obstruction] and symptoms [<1–2 times/wk]).
#3 FEV_1 ≥80% and symptoms < daily	Basyigit et al (2004)[82]	Minimum lung function (FEV_1 >80% predicted) and use of low-dose ICS before study.
	Bousquet et al (2005)[30]	Baseline FEV_1 80% predicted, daytime symptoms, SABA use ≥2 days/ week (but not every day) of the first week of run-in, not taking controller therapy, and at enrolment receiving only β-agonists. Study also required confirmation of asthma diagnosis either by β-agonist reversibility ≥12% or positive exercise challenge in prior month.
	Chrousos et al (2005)[83]	Pre-bronchodilator FEV_1≥ 80% of predicted. Study also required confirmation of asthma diagnosis by β–agonist reversibility ≥12% (FEV_1), diurnal variation of 20% in PEF or positive methacholine challenge test result.
	Chuang et al (2007)[84]	Symptoms >once/week, PEF > 80%. Study also required confirmation of asthma diagnosis by PEF variability 20–30% as defined by NAEPP 1997.
	Chuchalin et al (2005)[34]	ATS criteria, pre-bronchodilator FEV_1 ≥ 80% of predicted.
	Chuchalin et al (2008)[33]	Pre-bronchodilator PEF ≥80% predicted, and daytime asthma score ≥1 on 3-6 days of the previous 7 consecutive days. Study also required confirmation of asthma diagnosis by PEF reversibility ≥15%
	Currie et al (2003)[85]	FEV_1≥80% predicted current treatment with SABA alone or ICS dose <800 μg/day. Study also required confirmation of asthma diagnosis with reversibility.
	Garcia Garcia et al (2005)[36]	Pre-bronchodilator FEV_1 ≥80% of predicted twice during run-in, FEV_1 or PEF ≥70% at visit 3 during run-in, symptoms requiring β-receptor agonist use on ≥2 and ≤4 days in run-in.
	Karaman et al (2004)[86]	Clinically stable with FEV_1 >80% of predicted.
	Maiti et al (2011)[87]	Pre-bronchodilator FEV1 ≥80% of predicted. Study also required confirmation of asthma diagnosis with reversibility.
	Ng et al (2007)[38]	Pre-bronchodilator FEV_1 ≥80% of predicted, or if symptoms ≥1 /week but <1/day, or if night time symptoms >2/month. Study also required confirmation of asthma diagnosis by improvement in FEV1 by ≥15% after inhaled β-agonist.
	Reddel et al (2008)[43]	Pre-bronchodilator FEV_1 >80% of predicted and SABA use≤2 times/week (criteria to be satisfied at

		both screening and randomisation visit).
	Renzi et al (2010)[44]	FEV_1 >80% of predicted, symptom score of ≥2 on 3 of last 7 days, only SABA treatment allowed (used on ≥4 of last 7 days).
	Riccioni et al (2002)[88]	PEF ≥80% of predicted.
	Shimoda et al (2005)[89]	Per GINA 2002, i.e. FEV_1 ≥80% of predicted and symptoms (>1 /week but <1/day).
	Tamaoki et al (2008)[90]	Per GINA 2006 Step 1, i.e. FEV_1 or PEF ≥80% of predicted, symptoms <1/week .and which respond to bronchodilators
	Vatrella et al (2002)[91]	Per GINA 1995, i.e. FEV_1 ≥80% of predicted, symptoms ≥1/week but <1/day, treatment with controller ± long-acting bronchodilator.
	Zeiger et al (2005)[92]	Per NAEPP 2002 and GINA 2002: FEV_1 during run-in FEV_1 ≥80% of predicted, day time symptoms, and SABA use on an average of ≥2 days but ≤6 days/week during the last 2 weeks of run-in.
	Zietkowski et al (2006)[93]	Pre-bronchodilator PEF or FEV_1 ≥80% of predicted, symptoms >1/week but <1/day.
#4 FEV_1 >60–80% and symptoms <daily	Berger et al (2009)[49]	*Pre bronchodilator FEV_1 60–85% of predicted, uncontrolled asthma during last 7 days of screening (symptom daytime score >1, SABA use for ≥3 days and PEF <90% on ≥3 days).
	Boulet et al (2000)[94]	Per NHLBI 1992, i.e. Pre-bronchodilator FEV_1 70–90% of predicted and treatment either did not include ICS or only low-dose ICS.
	Drazen et al (1996)[35]	Pre-bronchodilator FEV_1 ≥70% of predicted, use of SABA only.
	Herjavecz et al (1999)[56]	Pre-bronchodilator PEF ≥70% of predicted, asthma symptoms and SABA use occurring on ≥3 days of the last 6 days of run-in period.
	O'Byrne et al (2001)[40]	Either post-bronchodilator FEV_1 ≥80% and not taking ICS, or post-bronchodilator FEV_1 ≥70% and using low-dose ICS. Rescue medication use: ≥2 inhalations/week in last 2 weeks of run-in.
	O'Sullivan et al (2003)[95]	Pre-bronchodilator FEV_1 ≥60%, with SABA as-needed.
	Papi et al (2007)[41]	Per NAEPP 1997, i.e. pre-bronchodilator FEV_1 ≥75% predicted.
	Peters et al (2007)[57]	After 4–6 weeks' run-in receiving fluticasone: pre-bronchodilator FEV_1 80≥% of predicted, ACQ score <1.5 and <16 inhalations of rescue β–agonist per week in final 2 weeks of run-in.
	Stone et al (2001)[96]	FEV_1 50–90% of predicted, treatment with SABA only (and SABA use ≥4 actuations for symptoms during 4 of the last 7 days), and receiving either low-dose ICS or no ICS.
	Tattersfield et al (2001)[46]	FEV_1 ≥65% predicted, SABA only in previous 3 months but required to have ≥4 SABA inhalations in last 7 days of run-in.
	Tomlinson et al (2005)[47]	Per ATS 1987, i.e. FEV_1 >50%, ACQ score >6 (max 36).
	van Grunsven et al (1996)[48]	*FEV_1 >50% of predicted.
	Verberne et al (1996)[59]	FEV_1 and FVC ≥70% of predicted; prior treatment with rescue β-agonist with or without maintenance disodium cromoglymate.
	Vermetten et al (1999)[97]	PEF >60% of predicted, patients receiving inhaled budesonide or beclomethasone for ≥6 weeks, and rescue SABA.
	Woodcock et al (2002)[60]	FEV_1 ≥70% of predicted, with 'satisfactory' SABA use.
#5 Miscellaneous definitions[§]	Arets et al (2002)[24]	Per BTS 1993, i.e. doctor-diagnosed asthma, treatment to be minimal use of LABA and no recent ICS use (i.e. excluded if used >100 μg per day of budesonide or beclomethasone in prior 4 weeks, or used

		>1600 μg salbutamol during >30% days of year prior to study entry).
	Bailey et al (2008)[25]	**FEV_1 60–90% of predicted, symptomatic, on low-dose ICS.
	Barnes et al (2007)[99]	FEV_1 >80% predicted and treated with low-dose ICS.
	Bateman et al (2012)[26]	**Pre-bronchodilator FEV_1 40–90% of predicted, presence of symptoms or SABA use on >50% of the run-in days, and no recent ICS use.
	Boushey et al (2005)[29]	Pre-bronchodilator FEV_1 ≥70% of predicted, and either: symptoms or SABA (>2 days/week) or PEF variability of 20–30%.
	Busse et al (2001)[31]	**Pre-bronchodilator FEV_1 50–80% of predicted, asthma symptom score of ≥2 on ≥4 of 7 days prior to randomisation, SABA use on ≥6 of 7 days prior to randomisation, no ICS use within 2 month of screening.
	Busse et al (2001)[54]	**Pre-bronchodilator FEV_1 50–80% of predicted, use of SABA for >6 weeks prior to study, no ICS use within 1 month of screening.
	van der Molen et al (1998)[100]	** Pre-bronchodilator FEV_1 >50% of predicted, weekly need for ≥3 doses SABA.
	Villaran et al (1999)[98]	Described as 'mild'. Study also required confirmation of diagnosis of asthma from airway responsiveness (FEV_1 improvement of ≥12% after β-agonist or airway hyper- responsiveness).
#6 Included patients aged <5 years	Bisgaard et al (2005)[28]	No symptoms or β–agonist use in a typical week in the prior 3 months.
	Robertson et al (2007)[22]	**Doctor-diagnosed intermittent asthma, asymptomatic between episodes and no asthma medication between.
	Shah et al (2014)[101]	Per revised CDC guidelines mentioned in Nelson textbook of Pediatrics, i.e. FEV_1 ≥80% of predicted, symptoms >2 days/week but not daily, SABA treatment >2days/week but not more than once on any day.
	Skoner et al (2005)[58]	**At screening patients had symptom (PAQ) scores of 6.3–7.3 (scale 0–27) and 1.5–1.7 days/week with uncontrolled asthma.
	Szefler et al (2007)[45]	Per NAEPP 2002 guidelines, i.e. PEF or FEV_1 ≥80% of predicted and symptoms >2 times/week but <1 per day, β_2-agonist use on ≥3 of 7 consecutive days during run-in.
Observational/other		
#1 Treatment level	Ding and Small (2017)[50]	Per GINA 2015 Step 1 and Step 2 treatment.
	Friedman et al (2010)[51]	Not treated with mometasone or fluticasone propionate in previous 7 days, and with fewer than 3 SABA canister claims in prior 6 months.
	Friedman et al (2010)[52]	Not treated with mometasone or beclometasone dipropionate in previous 7 days, and with ≤2 SABA canister claims in prior 12 months.
	McIvor et al (2009)[23]	Physician-diagnosed mild asthma, recurrent but not daily symptoms, patients receiving low-dose ICS, experiencing sleep disturbance from exacerbations.
	Navaratnam et al (2009)[53]	Not treated with mometasone or fluticasone propionate-salmeterol in previous 7 days, and with ≤2 SABA canister claims in 365-day pre-index period.
#3 FEV_1 ≥80% and symptoms < daily	Giraud et al (2006)[55]	*Mild-to-moderate per GINA 2002 criteria; patients were to be corticosteroid naïve or not taking ICS or systemic corticosteroids in the previous 4 weeks.
	Lai et al (2003)[62]	*Population sample: based on symptom frequency, severity and pattern, asthma severity on the basis of GINA 1995.
#4 FEV1 >60–80% and symptoms <daily	Soyer et al (2009)[61]	**Physician-diagnosed severity, based on symptoms.

#6 Included patients aged <5 years	König et al 1996[63]	Treatment with bronchodilators, symptoms ≤3 days/week.
	Robertson et al (1992)[64]	*Treatment type and symptom frequency.

†This table does not focus on how asthma *per se* was diagnosed, but rather on how the severity of 'mild' was defined/described. The use of exacerbation criteria in the definition of mild asthma was excluded from this table since these data are captured in Table 2.

§Miscellaneous definitions not captured by the other five categories, e.g. 'doctor-diagnosed mild asthma', or 'mild asthma based on airway hyper-responsiveness' alone, or, studies that did not state that patients had 'mild asthma' but included patients with disease characteristics similar to those in the other five categories

*Study included patients with different severities of asthma but was included if data reported separately for mild asthma.

**Asthma severity not explicitly described by study authors as 'mild'.

ATS: American Thoracic Society; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroid, NAEPP: National Asthma Education and Prevention Program; NIH: National Institute of Health; PEF: peak expiratory flow; SABA: short-acting β_2-agonist

Table S3: Treatment regimen details for active treatment arm(s) of studies included in this review

Study, year	Active treatment(s)	No· of pts
RCTs		
Category 1: RCTs that primarily defined mild asthma by treatment level		
Bateman et al (2018)[27]	P bid + BUD/FORM 200 µg/6µg as-needed	2089
	BUD 200 bid + TERB 0.5mg as-needed	2087
Camargos et al (2018)[32]	BDP 250 µg/qid + ALB 4 hrly for 7 days on worsening ('intermittent')	94
	BDP 250 µg bid ('continuous')	94
O'Byrne et al (2018)[39]	P bid + BUD/FORM 200 µg/6µg as-needed	1277
	P bid + TERB 0.5 mg as-needed	1277
	BUD 200 µg bid + TERB 0.5mg as-needed	1282
Category 2: RCTs that primarily defined mild asthma by symptom frequency		
Martinez et al (2011)[37]	BDP 40 µg bid + BDP/ALB rescue	71
	BDP 40 µg bid + P/ALB rescue	72
	Placebo bid + BDP/ALB rescue	71
Pauwels et al (2003)[42]	BUD od (200 µg <11 yrs or 400 µg ≥11 yrs) + usual asthma medication	3597
Wongtim et al (1995)[81]	BUD 400 µg bid	10
Category 3: RCTs that primarily defined mild asthma with a composite definition of FEV_1 ≥80% and symptoms < daily		
Basyigit et al (2004)[82]	Z 20 mg bid	10
	BUD 200 µg bid	10
	T 200 mg bid	10
Bousquet et al (2005)[30]	MON 10 mg od	325
	FP 100 µg bid	320
Chrousos et al (2005)[83]	MF DPI 400 µg od	18
	HFA-BDP MDI 200 µg bid	18
	CFC-BDP MDI 800 µg bid	17
Chuang et al (2007)[84]	Ketotifen 1 mg[§]	12
	MON 5 mg[§]	13
Chuchalin et al (2005)[34]	As needed FORM 4.5 µg	561
	As needed TERB 0.5 µg	569
Chuchalin et al (2008)[33]	FSC 100/50 µg od	973
	FP 100 µg bid	970
Currie et al (2003)[85]	FSC 125/25 µg bid; FP 250 µg bid (crossover study)	14
Garcia Garcia et al (2005)[36]	MON 5 mg od (10 mg od if pt had turned 15)	495
	Fluticasone 100 µg bid	499
Karaman et al (2004)[86]	MON 5 mg od	20
	BUD 400 µg bid	22
	MON 5 mg od + BUD 400 µg bid	21
Maiti et al (2011)[87]	SAL 100 µg bid	30
	Levosalbutamol 50 µg bid	30
Ng et al (2007)[38]	MON 5 mg od	13†
	BUD 200 µg bid (crossover study)	15†

Reddel et al (2008)[43]	FP 125 µg bid	23
Renzi et al (2010)[44]	FSC 100/50 µg bid	253
	FP 100 µg bid	263
Riccioni et al (2002)[88]	BUD 400 µg bid	15
	MON 10 mg od	15
	BUD 400 µg bid + MON 10 mg od	15
Shimoda et al (2005)[89]	BUD 400 µg od	15
	MON 10 mg od	12
Tamaoki et al (2008)[90]	BDP 100 µg bid	38
	Pranlukast 225 mg bid	36
Vatrella et al (2002)[91]	FP 100 µg bid	8
	NS 4 mg bid	8
	FP 100 µg bid for 8 wks followed by NS 4 mg bid for 8 wks	8
	NS 4 mg bid for 8 wks followed by FP 100 µg bid for 8 wks (partial crossover study)	8
Zeiger et al (2005)[92]	MON 10 mg od	189
	FP 88 µg bid	191
Zietkowski et al (2006)[93]	CIC 80 µg od	12
	CIC 160 µg od	12
	FP 100 µg bid	11
Category 4: RCTs that primarily defined mild asthma with a composite definition of FEV_1 approximately >60–80% and symptoms < daily		
Berger et al (2009)[49]	CIC 80 µg bid	170
	CIC 160 µg od	173
	CIC 80 µg bid/CIC 160 µg od	171
Boulet et al (2000)[94]	FP 200 µg od	230
	FP 100 µg bid	231
Drazen et al (1996)[35]	Regular ALB (two inh qid) + ALB as needed[¶]	126
Herjavecz et al (1999)[56]	DB period: BUD 400 µg od	90
	BUD 200 µg bid	91
	OL period (all pts): 8 wks BUD 200 µg od, then 8 wks BUD 100 µg od	
O'Byrne et al (2001)[40]	Group A (corticosteroid-free patients):	
	BUD 100 µg bid	228
	BUD 100 µg bid + FORM 6 µg bid	231
	Group B (patients taking ≤400 µg BUD or equiv for ≥3 months):	
	BUD 100 µg bid	322
	BUD 100 µg bid + FORM 6 µg bid	323
	BUD 200 µg bid	312
	BUD 200 µg bid + FORM 6 µg bid	315
O'Sullivan et al (2003)[95]	FP 100 µg bid; FP 100 µg bid + MON 10 mg od (crossover study)	28
Papi et al (2007)[41]	BDP 250 µg bid + ALB 100 µg as needed	106
	BDP 250 µg/ALB 100 µg bid + ALB 100 µg as needed	109
	P bid + BDP 250 µg/ALB 100 µg as needed	122
Peters et al (2007)[57]	MON 5 mg od (6–14 yrs) or 10 mg od (≥15 yrs)	166
	FSC 100/50 µg od	165
	FP 100 µg bid	169

Stone et al (2001)[96]	FP 100 µg bid pMDI propelled by HFA 134a	178
	FP 100 µg bid CFC pMDI	173
Tattersfield et al (2001)[46]	BUD 200 µg bid	87
	BDP 250 µg bid	74
	Alternative non-corticosteroid treatment	78
Tomlinson et al (2005)[47]	BDP 200 bid	47
	BDP 1000 µg bid	48
van Grunsven et al (1996)[48]	Continuous ICS during previous year, then received SABA	19
	No ICS during previous year, then SABA	70
Verberne et al (1996)[59]	SM 50 mg bid	15
	SAL 200 µg bid	15
Vermetten et al (1999)[97]	BDP 400 µg bid	120
	BDP 200 µg bid + SM 50 µg bid	113
Woodcock et al (2002)[60]	BDP 200 µg bid MDI using HFA-134a propellant	86
	BDP 200 µg bid MDI using CFC propellant	86
Category 5: RCTs that defined mild asthma by other/miscellaneous criteria		
Arets et al (2002)[24]	FP 250 µg bid	35
Boushey et al (2005)[29]	BUD 200 µg bid	73
	Z 20 mg bid	76
	Oral + inhaled P with intermittent courses of rescue BUD 800 µg bid 10-day course or PRED 0.5 mg/kg 5-day course ('intermittent therapy')	76
	All patients were treated at the end of the run-in period with 10 days' of high intensity treatment (prednisone, LTRA and high-dose ICS)	
Villaran et al (1999)[98]	MON 10 mg od	102
	SM 50 µg bid	95
Category 5: RCTs that did not describe their patients as having 'mild asthma' but included patients with disease characteristics similar to the categories described above		
Bailey et al (2008)[25]	FSC 100/50 µg bid	239
	FP 100 µg bid	236
Barnes et al (2007)[99]	FSC 100/50 µg bid	561
	FP 100 µg bid	538
Bateman et al (2012)[26]	FF 25, 50, 100 or 200 µg od	97, 100, 110, 95
	FP 100 µg bid	102
Busse et al (2001)[31]	FP 88 µg bid	271
	MON 10 mg od	262
Busse et al (2001)[54]	FP 88 µg bid	113
	Z 20 mg bid	111
van der Molen et al (1998)[100]	BUD 400 µg bid 4 wks + BUD 200 µg od 8 wks	44
	BUD 100 µg bid 4 wks + BUD 200 µg od 8 wks	40
Category 6: RCTs that included patients <5 years old		
Bisgaard et al (2005)[28]	MON 4 mg od (5 mg od if pt ≥6 yrs)	278
Shah et al (2014)[101]	MON od (4 mg od 2–5 yrs or 5 mg od >5 yrs)	30
	BUD 200 µg bid	30
Szefler et al (2007)[45]	BIS 0.5 mg od	197

	MON 4 or 5 mg od	198
Category 6: RCTs that included patients <5 years old that did not describe their patients as having 'mild asthma' but included patients with disease characteristics similar to mild asthma		
Robertson et al (2007)[22]	MON od (4 mg 2–5 yrs or 5 mg 6–14 yrs) for 7+ days	107
Skoner et al (2005)[58]	Levalbuterol 0.31 mg	58
	Levalbuterol 0.63 mg	51
	Racemic ALB (1.25 mg <33lb; 2.5 mg ≥33 lb)	52
OBSERVATIONAL/OTHER		
Category 1: Observational/other studies that primarily defined mild asthma by treatment level		
Ding and Small (2017)[50]	GINA 2015 Step 1 treatment: SABA or SAMA, NOS	524
	GINA 2015 Step 2 treatment:	
	low-dose ICS	377
	LTRA	181
	xanthine	33
Friedman et al (2010)[51]	Claims data:	
	MF[¶]	692
	FP[¶]	692
Friedman et al (2010)[52]	Claims data:	
	MF[¶]	1273
	BDP[¶]	1273
McIvor et al (2009)[23]	ICS discontinued at enrolment visit in all patients	
	Interventions: MON od (5 mg 6–14 yrs; 10 mg ≥15 yrs)	534
Navaratnam et al (2009)[53]	Claims data:	
	MF[¶]	4094
	FSC[¶]	4094
Category 3: Observational/other studies that primarily defined mild asthma with a composite definition of FEV_1 ≥80% and symptoms < daily		
Giraud et al (2006)[55]	ICS monotherapy (prescribed ICS dosage in beclomethasone equivalent: 479±62 µg/day [mean±SD])	94
Lai et al (2003)[62]	Quick-relief bronchodilator (SABA [inhaled/oral], FORM [inhaled], anticholinergic)	1257
	ICS	285
	Other preventative treatments (leukotriene modifiers, sodium cromoglycate, nedocromil)	16
	T	255
	Unknown treatment/P	530
Category 4: Observational/other studies that primarily defined mild asthma with a composite definition of FEV_1 approximately >60–80% and symptoms < daily		
Soyer et al (2009)[61]	ICS: ≈23%[¶]	522
	LTRA: ≈6%[¶]	
	ICS+ LTRA: ≈4%[¶]	
	ICS + LABA: ≈14%[¶]	
	ICS+ LABA + LTRA: ≈3%[¶]	
	No treatment: ≈50%[¶]	
Category 6: Observational/other studies that included patients <5 years old		
König et al 1996[63]	Bronchodilators as needed	84

Robertson et al (1992)[64]	β_2-agonist or no treatment (of 17 children with mild asthma)	14

[§]No dose frequency given;.†A total of 19 patients were enrolled in this cross-over study; this is the number of patients used to determine the overall number of patients included in this review (see Results) [¶]No dosage information given

ALB: albuterol; BDP: beclomethasone dipropionate; bid: twice daily; BIS: budesonide inhalation suspension; BUD: budesonide; CFC: chlorofluorocarbon; CIC: ciclesonide; DB: double-blind; DPI: dry powder inhaler; FEV_1: forced expiratory volume in 1 second; FORM: formoterol; FP: fluticasone propionate; FSC: fluticasone propionate/salmeterol combination; GINA: Global Initiative for Asthma; HFA: hydrofluoroalkane; hr: hour; ICS: inhaled corticosteroid; inh: inhalation; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; MDI: metered-dose inhaler; MF: mometasone furoate; MON: montelukast; no·: number; NOS: not otherwise specified; NS: nedocromil sodium; od: once daily; OL: open-label; qid: four times daily; P: placebo; pMDI: pressurised metered-dose inhaler; PRED: prednisone; pt: patient, qid, four times daily; RCT: randomised controlled trial; SABA: short-acting β_2-agonist; SAL: salbutamol; SAMA: short-acting muscarinic antagonist; SD: standard deviation; SM: salmeterol; T: theophylline; TERB: terbutaline; wks: weeks; yr: year; Z: zafirkulast.

Table S4: Definition of an exacerbation or SARE

Exacerbation severity	Study (year)	Definition
Prospective RCTs		
Mild	**PEF**	
	Chuchalin et al (2008)*,[33] Papi et al (2007),[41] Reddel et al (2008)†[43]	Morning PEF >20%/≥20% below baseline
	Investigator opinion	
	Reddel et al (2008)[43]	According to investigator opinion
	Symptoms/worsening asthma/other	
	Chuchalin et al (2008)§,[33] Papi et al (2007)[41]	Night-time awakenings caused by asthma symptoms
	Reddel et al (2008)[43]	Nocturnal asthma and/or early waking requiring salbutamol on ≥2 consecutive days
	Chuchalin et al (2008)[33]	Additional reliever compared with baseline on >3 occasions per 24-h period for ≥2 consecutive days
	Reddel et al (2008)[43]	Increase in 24-h salbutamol use by >2 occasions over baseline on 2 consecutive days
	Papi et al (2007)[41]	>3 additional puffs/day rescue medication (albuterol or beclomethasone and albuterol) vs. last 1 week of run-in for ≥2 consecutive days
Moderate	**Oral corticosteroid use**	
	Chuchalin et al (2008)¶[33]	Deterioration in asthma requiring OCS
	ICS use	
	O'Byrne et al (2018)[39]	Deterioration in asthma requiring initiation of prescribed ICS
	PEF	
	Chuchalin et al (2008)[33]	Morning PEF >30% below baseline on ≥2 consecutive days
	Investigator opinion	
	Chuchalin et al (2008)[33]	According to investigator opinion
Severe	**Systemic corticosteroid use**	
	Bateman et al (2018),[27] O'Byrne et al (2001),[40] Papi et al (2007),[41] Reddel et al (2008)[43]	Event/period/symptoms requiring oral/systemic corticosteroid
	Hospitalisation/ED visit/unscheduled care	
	Chuchalin et al (2008),[33] O'Byrne et al (2001)[40] Renzi et al (2010)[44]	Event/period/symptoms requiring hospitalisation
	O'Byrne et al (2001)[40]	Event/period/symptoms requiring unscheduled ED visit
	PEF	
	O'Byrne et al (2001)[40]	Morning PEF >25% below baseline on 2 consecutive days
	Papi et al (2007)[41]	Morning PEF >30% below baseline on 2 consecutive days
	Investigator opinion	
	O'Byrne et al (2001),[40] Papi et al (2007)[41]	According to investigator opinion
	Symptoms/worsening asthma/other	

	Papi et al (2007)[41]	>8 puffs/day of rescue medication for 3 consecutive days
SARE	**Hospitalisation/ED treatment**	
	Pauwels et al (2003)[42]	Hospitalisation/emergency treatment (treatment of acute airway obstruction with systemic corticosteroids and nebulised/parenteral bronchodilators in a healthcare setting) because of worsening asthma, or death from asthma
Undefined severity	**Corticosteroid use**	
	Bailey et al (2008)[25]	Asthma worsening requiring OCS
	Bisgaard et al (2005)[28]	Rescue use of OCS/ICS for ≥1 day
	Boushey et al (2005)[29]	Exacerbation warranting initiation of prednisone
	Busse et al (2001)[54]	Required OCS
	Ng et al (2007)[38]	Systemic corticosteroid due to worsening in asthma
	Hospitalisation/ED visit/unscheduled care	
	Bailey et al (2008)[25]	Hospitalisation for treatment of asthma; unscheduled visit for acute asthma
	Bisgaard et al (2005)[28]	Event/period/attack/symptoms requiring hospitalisation/hospital treatment
	Martinez et al (2011)[37]	Event/period/attack/symptoms requiring unscheduled ED visit
	Ng et al (2007)[38]	Unscheduled visit to general practitioner, A&E/ED department or out-patient clinic due to asthma symptoms
	Robertson et al (2007)[22]	Unscheduled visits to GP, specialist, ED or hospital admission
	PEF	
	Martinez et al (2011)[37]	PEF <70% reference value before each albuterol use or a PEF <50% reference value despite relief treatment
	Symptoms/worsening asthma/other	
	Bailey et al (2008)[25]	≥30% decrease in FEV_1 or ≥30% decrease PEF for 2 days
	Bateman et al (2012)[26]	Worsening asthma requiring any treatment other than study medication or rescue salbutamol alone
	Berger et al (2009)[49]	Decrease in FEV_1 of ≥20% vs· baseline, night-time awakening with albuterol use on ≥3 of any 7 consecutive days, use of ≥8 puffs of albuterol on ≥4 of any 7 consecutive days, decrease in a.m. PEF to <80% of baseline on ≥4 days
	Bisgaard et al (2005)[28]	Any 3 consecutive days with daytime symptoms and ≥2 β-agonist treatments per day; Rescue use of ICS for ≥1 day
	Drazen et al (1996)[35]	Worsening symptoms plus increase in β-agonist use of ≥8 puffs/24 hrs for 48 hrs or fall in PEF ≥35% from best 3-day average from run-in
	Martinez et al (2011)[37]	>12 puffs albuterol in 24 hrs (excluding use before exercise); Excessive ICS use because of controller plus rescue corticosteroids or rescue corticosteroid use alone prompted a prednisone course, which counted as an exacerbation; Symptoms that led to inability to sleep or do daily activities for ≥2 consecutive days
Database/survey studies		
Undefined severity	**Oral corticosteroid use**	
	Friedman et al (2010)[51] Friedman et al (2010)[52]	An outpatient visit in which patients received a prescription for OCS

	Navaratnam et al (2009)[53]	
	Nebulised medication	
	Friedman et al (2010)[51] Friedman et al (2010)[52] Navaratnam et al (2009)[53]	An outpatient visit in which patients received nebulised medication
	Hospitalisation/ED visit/outpatient visit	
	Friedman et al (2010)[51] Friedman et al (2010)[52] Navaratnam et al (2009)[53] Ding, Small (2017)[50]	An asthma episode that required hospitalisation
	Friedman et al (2010)[51] Friedman et al (2010)[52] Navaratnam et al (2009)[53] Ding, Small (2017)[50]	An asthma episode that required treatment in an ED
	Friedman et al (2010)[51] Friedman et al (2010)[52] Navaratnam et al (2009)[53]	An outpatient visit in which patients received nebulised medication or a prescription for OCS
	Symptoms/worsening asthma/other	
	Ding, Small (2017)[50]	Physician-confirmed worsening of symptoms beyond normal day-to-day variation and treatment(s) prescribed for exacerbations use of rescue inhalers.
Moderate-to-severe	**Hospitalisation/ED visit**	
	Ding, Small (2017)[50]	An exacerbation requiring OCS, antibiotics, treatment in ED or hospital admission.

[*] ≥2 consecutive days. [†] ≥2 of 3 consecutive days. [§] ≥2 consecutive nights. [††] In the Chuchalin study, exacerbations requiring OCS were described by the authors as moderate whereas in other studies included in this table, such exacerbations were described as severe.

A&E: accident and emergency; ED: emergency department; FEV_1: forced expiratory volume in 1 second; GP: general practitioner; hr: hour; ICS: inhaled corticosteroid; OCS: oral corticosteroids; PEF: peak expiratory flow; RCT: randomised controlled trial; vs·: versus

Table S5: ATS/ERS Task Force definition of a mild, moderate and severe exacerbation[11]

Severity	Definition
Mild	No definition provided as not justifiable with present methods of analysis
Moderate	One or more of the following: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use These features should last for 2 days or more, but not be severe enough to warrant systemic steroid use and/or hospitalisation ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, may be classified as moderate exacerbations
Severe	At least one of the following: a) Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations b) A hospitalisation or ER visit because of asthma, requiring systemic corticosteroids

ATS: American Thoracic Society; ER: emergency room; ERS: European Respiratory Society.

Table S6: Alignment in mild asthma RCTs of study definition of a severe exacerbation or SARE with the ATS/ERS Task Force definition[11]

Task Force Definition[11] Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids		
	Study (year)	**Study definition (reason for broad alignment only, if applicable)**
Aligned	Bateman et al (2018)[27]	Worsening asthma leading to the use of systemic corticosteroids for ≥3 days Inpatient hospitalisation, or an ED visit leading to the use of systemic corticosteroids
	O'Byrne et al (2018)[39]	Use of systemic corticosteroids for ≥3 days Inpatient hospitalisation, or an ED visit leading to the use of systemic corticosteroids
	Reddel et al (2008)[43]	Use of oral corticosteroids (oral prednisolone 50 mg/day was given for 7–10 days if PEF fell by ≥30% baseline for ≥2 of 3 consecutive days, or at investigator discretion)
Broadly aligned	Chuchalin et al (2008)[33]	Deterioration in asthma requiring hospital admission *(systemic corticosteroid use not specified)*
	O'Byrne et al (2001)[40]	Need for treatment with oral corticosteroids, as judged by the investigator Hospital admission or emergency treatment for worsening asthma *(duration of corticosteroid use not specified)*
	Papi et al (2007)[41]	Need for treatment with oral corticosteroids, as judged by the investigator *(duration of corticosteroid use not specified)*
	Pauwels et al (2003)[42]	A SARE which required admission or emergency treatment for worsening asthma or death due to asthma. Emergency treatment was defined as treatment of acute airway obstruction with systemic corticosteroids and nebulised or parenteral bronchodilators administered in a healthcare setting *(duration of corticosteroid use not specified; exacerbations defined only by use of oral corticosteroids were not included)*

ATS, American Thoracic Society; ED: emergency department; ERS: European Respiratory Society; PEF: peak expiratory flow; RCT: randomised controlled trial; SARE: severe asthma-related event.

Table S7: History of systemic corticosteroid use recorded at baseline in prospective trials

Study (year)	Age range, years	Study groups, n	Parameter(s)	Data for specified parameter for each study group
Bisgaard et al (2005)[28]	2–5	278,271	Patients using oral corticosteroid in last 1 year	33%
			Patients using ≤2 oral corticosteroid courses for worsening asthma in last 1 year relative to first visit	89%, 95%
			Patients using ≥3 oral corticosteroid courses for worsening asthma in last 1 year relative to first visit	11%, 5%
Martinez et al (2011)[37]	5–18	71, 72, 71,74	Patients using ≥1 prednisone course in last 1 year	27%, 26%, 34%, 28%
Pauwels et al (2003)[42]	5–66	3597,3568	Patients using oral/systemic corticosteroid in 6 weeks prior to randomisation§	4.0%, 4.5%
Peters et al (2007)[57]	≥6	166, 169, 165	Patients using ≥1 oral corticosteroid course in last 1 year	28.3%, 28.4%, 31.5%
Verberne et al (1996)[59]	7–16	15, 15	Mean no. prednisolone courses per patient in last 1 year	0.13, 0.20

§ Patients excluded if >30 days of inhaled or oral corticosteroid treatment per year in previous 2 years

Table S8: Administrative or medical record data on exacerbations occurring over periods of ≥24 weeks from observational/other studies in mild asthma

	Study (year)	Age range, years	Study description, pts with mild asthma (n)	Follow-up duration	Asthma medication, where reported (% pts)	Outcome	Data*
Studies not excluding pts with an exacerbation history	König et al (1996)[63]	≤17	Retrospective chart review (84)	Not reported	Bronchodilators (100%)	Mean (±SD) no of hospitalisations/year	0.6±1.2
						Mean (±SD) no of ED visits/year	1.2±0.5
						Mean (±SD) no of unscheduled doctors' visits/year	1.9±0.8
	Robertson et al (1992)[64]	≤20	Retrospective review of asthma-related deaths in State of Victoria, Australia between May 1986-April 1989 (17 considered to have previously had mild asthma)	12 months prior to death	β_2-agonist or no treatment: 82.4% of the 17 children considered to have had mild asthma	Proportion of pts with ≥1 hospital admission in 12 months prior to death	17.6%
Studies that excluded pts with an exacerbation history§	Friedman et al (2010)[51]	12–25	Retrospective claims analysis (1384)	365 days post-index	MF-DPI (50%) FP (50%)	Mean no·of post-index exacerbations	MF-DPI: 0.12 FP: 0.14
	Friedman et al (2010)[52]	12–65	Retrospective claims analysis (2546)	1 year post-index	MF (50%) BDP (50%)	Mean no of post-index exacerbations per patient	MF: 0.12 BDP: 0.19
	Navaratnam et al (2009)[53]	12–65	Retrospective administrative claims database study (8188)	365 days post-index	MF 50% FSC 50%	Mean no of exacerbations	MF: 0.14 FSC: 0.16

*Data reported only for patients with mild asthma. §Studies excluded patients with a history of exacerbations in the 1-year pre-index period.(index date was defined as the date of the first filled asthma medication prescription[51-53])

BDP: beclomethasone dipropionate; DPI: dry powder inhaler; ED: emergency department; FP: fluticasone propionate; FSC: fluticasone propionate/salmeterol combination; MF: mometasone furoate; no·: number; pts: patients; SD: standard deviation

Table S9: Guidelines or reports used to help define mild asthma

Guideline	RCT N (study publ. date)	Observational/other N (study publ. date)
ATS standards for the diagnosis and care of patients with COPD and asthma		
1987	7 (1996–2002)[31,47,48,54,56,59,88]	0
No date	1 (2005)[34]	0
GINA guidelines		
1995	2 (2002)[60,91]	1 (2003)[62]
1998	2 (2005)[30,36]	0
2002	3 (2005–2006)[89,92,93]	1 (2006)[55]
2006	1 (2008)[90]	0
2012	2 (2018)[27,39]	
2015		1 (2017)[50]
NAEPP guideline for the diagnosis and management of asthma		
1991	1 (1995)[89]	0
1997	3 (2007–11)[37,41,84]	0
2002	2 (2005–07)[45,92]	0
NHLBI/NIH		
1992 International consensus report on the diagnosis and treatment of asthma	1 (2000)[94]	0

ATS: American Thoracic Society; COPD: chronic obstructive pulmonary disease; GINA: Global Initiative for Asthma; NAEPP: National Asthma Education and Prevention Program: NHLBI: National Heart, Lung, and Blood Institute; NIH: National Institutes of Health; publ: publication; RCT: randomised controlled trial.

References

1. GINA. Global strategy for asthma management and prevention: Global Initiative for Asthma, 2018.
2. Jackson DJ, Sykes A, Mallia P, et al. Asthma exacerbations: origin, effect, and prevention. J Allergy Clin Immunol 2011; 128: 1165-1174.
3. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12: 204.
4. Chapman KR. Impact of 'mild' asthma on health outcomes: findings of a systematic search of the literature. Respir Med 2005; 99: 1350-1362.
5. Ding B, DiBonaventura M, Karlsson N, et al. A cross-sectional assessment of the prevalence and burden of mild asthma in urban China using the 2010, 2012, and 2013 China National Health and Wellness Surveys. J Asthma 2017; 54: 632-643.
6. Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007; 62: 591-604.
7. Hekking PP, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015; 135: 896-902.
8. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract 2017; 3: 1.
9. Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008; 32: 545-554.
10. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007; 120: S94-138.
11. Reddel HK, Taylor DR, Bateman ED, et al. American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing

endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180: 59-99.

12. Global Initiative for Asthma. 2019 GINA Report, Global Strategy for Asthma Management and Prevention. 2019. https://ginasthma.org/gina-reports/ (accessed July 09 2019).
13. Brozek GM, Farnik M, Lawson J, et al. Underdiagnosis of childhood asthma: A comparison of survey estimates to clinical evaluation. Int J Occup Med Environ Nealth 2013; 26: 900-909.
14. Nolte H, Nepper-Christensen S, Backer V. Unawareness and undertreatment of asthma and allergic rhinitis in a general population. Respir Med 2006; 100: 354-362.
15. Tirimanna PR, van Schayck CP, den Otter JJ, et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract 1996; 46: 277-281.
16. van Schayck CP, van Der Heijden FM, van Den Boom G, et al. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. Thorax 2000; 55: 562-565.
17. Aaron SD, Vandemheen KL, FitzGerald JM, et al and the Canadian Respiratory Research Network. Reevaluation of diagnosis in adults with physician-diagnosed asthma. JAMA 2017; 317: 269-279.
18. Aaron SD, Boulet LP, Reddel HK, et al. Underdiagnosis and overdiagnosis of asthma. Am J Respir Crit Care Med 2018; 198: 1012-1020.
19. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. Can Respir J 2010; 17: 74-80.
20. Bloom CI, Nissen F, Douglas IJ, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. Thorax 2018; 73: 313-320.
21. James AL, Elliot JG, Abramson MJ, et al. Time to death, airway wall inflammation and remodelling in fatal asthma. Eur Respir J 2005; 26: 429-34.
22. Robertson CF, Price D, Henry R, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. Am J Respir Crit Care Med 2007; 175: 323-329.

23. McIvor RA, Kaplan A, Koch C, et al. Montelukast as an alternative to low-dose inhaled corticosteroids in the management of mild asthma (the SIMPLE trial): an open-label effectiveness trial. Can Respir J 2009; 16 Suppl A: 11A-21A.
24. Arets HGM, Kamps AWA, Brackel HJL, et al. Children with mild asthma: do they benefit from inhaled corticosteroids? Eur Respir J 2002; 20: 1470-1475.
25. Bailey W, Castro M, Matz J, et al. Asthma exacerbations in African Americans treated for 1 year with combination fluticasone propionate and salmeterol or fluticasone propionate alone. Curr Med Res Opin 2008; 24: 1669-1682.
26. Bateman ED, Bleecker ER, Lotvall J, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: A randomized trial. Respir Med 2012; 106: 642-650.
27. Bateman ED, Reddel HK, O'Byrne P, et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018; 378: 1877-1887.
28. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005; 171: 315-322.
29. Boushey H, Sorkness C, King TS, et al and the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. N Eng J Med 2005; 352: 1519-1528.
30. Bousquet J, Menten J, Tozzi CA, et al. Oral montelukast sodium versus inhaled fluticasone propionate in adults with mild persistent asthma. J Applied Res 2005; 5: 402-414.
31. Busse W, Raphael GD, Galant S, et al and the Fluticasone Propionate Clinical Research Study Group. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: A randomized clinical trial. J Allergy Clin Immunol 2001; 107: 461-468.
32. Camargos P, Affonso A, Calazans G, et al. On-demand intermittent beclomethasone is effective for mild asthma in Brazil. Clin Transl Allergy 2018; 8:7.

33. Chuchalin A, Jacques L, Frith L. Salmeterol/fluticasone propionate via Diskus™ once daily versus fluticasone propionate twice daily in patients with mild asthma not previously receiving maintenance corticosteroids. Clin Drug Investig 2008; 28: 169-181.
34. Chuchalin A, Kasl M, Bengtsson T, et al. Formoterol used as needed in patients with intermittent or mild persistent asthma. Respir Med 2005; 99: 461-470.
35. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. N Eng J Med 1996; 335: 841-847.
36. Garcia-Garcia ML, Wahn U, Gilles L, et al. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics 2005; 116: 360-369.
37. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377: 650-657.
38. Ng DKK, Chan CH, Chow PY, et al. Oral montelukast versus inhaled budesonide in children with mild persistent asthma: a pilot study. HK J Paediatr 2007; 12: 3-10.
39. O'Byrne P, FitzGerald J, Bateman E, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. N Engl J Med 2018; 378: 1865-1876.
40. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001; 164: 1392-1397.
41. Papi A, Canonica GW, Maestrelli P, et al and the BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007; 356: 2040-2052.
42. Pauwels RA, Pedersen S, Busse WW, et al and the START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003; 361: 1071-1076.

43. Reddel HK, Belousova EG, Marks GB, et al. Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomised controlled trial. Prim Care Respir J 2008; 17: 39-45.
44. Renzi PM, Howard LA, Ortega HG, et al. Low-dose fluticasone propionate with and without salmeterol in steroid-naive patients with mild, uncontrolled asthma. Respir Med 2010; 104: 510-517.
45. Szefler SJ, Baker JW, Uryniak T, et al. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007; 120: 1043-1050.
46. Tattersfield A, Town GI, Johnell O, et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 2001; 56: 272-278.
47. Tomlinson JEM, McMahon AD, Chaudhuri R, et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 2005; 60: 282-287.
48. van Grunsven PM, Dompeling E, van Schayck CP, et al. Treatment of mild asthma with inhaled corticosteroids: is discontinuation of therapy possible? Fam Med 1996; 28: 46-51.
49. Berger WE, Kerwin E, Bernstein DI, et al. Efficacy and safety evaluation of ciclesonide in subjects with mild-to-moderate asthma not currently using inhaled corticosteroids. Allergy Asthma Proc 2009; 30: 304-314.
50. Ding B, Small M. Disease burden of mild asthma: Findings from a cross-sectional real-world survey. Adv Ther 2017; 34: 1109-1127.
51. Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. J Asthma 2010; 47: 994-1000.
52. Friedman HS, Urdaneta E, McLaughlin JM, et al. Mometasone furoate versus beclomethasone dipropionate: effectiveness in patients with mild asthma. Am J Manag Care 2010; 16: e151-156.

53. Navaratnam P, Friedman HS, Urdaneta E. Mometasone furoate vs fluticasone propionate with salmeterol: multivariate analysis of resource use and asthma-related charges. Curr Med Res Opin 2009; 25: 2895-2901.
54. Busse W, Wolfe J, Storms W, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. J Fam Pract 2001; 50: 595-602.
55. Giraud V, Rogeaux Y, Dusser D. Asthma control following initial inhaled corticosteroid monotherapy in mild to moderate asthma: a 4- to 8-week observational study. Respiration 2006; 73: 617-622.
56. Herjavecz I, Blomqvist P, Serrano A. Efficacy of once- and twice-daily administration of budesonide via Turbuhaler as initial therapy in patients with mild persistent asthma. Respir Med 1999; 93: 230-235.
57. Peters SP, Anthonisen N, Castro M,et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 2007; 356: 2027-2039.
58. Skoner DP, Greos LS, Kim KT, et al. Evaluation of the safety and efficacy of levalbuterol in 2-5-year-old patients with asthma. Pediatr Pulmonol 2005; 40: 477-486.
59. Verberne AA, Hop WC, Creyghton FB, et al. Airway responsiveness after a single dose of salmeterol and during four months of treatment in children with asthma. J Allergy Clin Immunol 1996; 97: 938-946.
60. Woodcock A, Williams A, Batty L, et al. Effects on lung function, symptoms, and bronchial hyperreactivity of low-dose inhaled beclomethasone dipropionate given with HFA-134a or CFC propellant. J Aerosol Med 2002; 15: 407-414.
61. Soyer OU, Beyhun NE, Demir E, et al. A multicenter survey of childhood asthma in Turkey. II: Utilization of asthma drugs, control levels and their determinants. Pediatr Allergy Immunol 2009; 20: 172-179.

62. Lai CK, De Guia TS, Kim YY, et al; and the Asthma Insights and Reality in Asia-Pacific Steering Committee. Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. J Allergy Clin Immunol 2003; 111: 263-268.
63. Konig P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. J Allergy Clin Immunol 1996; 98: 1103-1111.
64. Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. Pediatr Pulmonol 1992; 13: 95-100.
65. RCP. Why asthma still kills: The National Review of Asthma Deaths (NRAD). London, 2014.
66. Campbell DA, McLennan G, Coates JR, et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. Eur Respir J 1994; 7: 490-497.
67. Robertson CF, Rubinfeld AR, Bowes G. Deaths from asthma in Victoria: a 12-month survey. Med J Aust 1990; 152: 511-517.
68. NAEPP. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program : Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007.
69. Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract 2016; 66: e152-157.
70. NICE. Asthma: diagnosis, monitoring and chronic asthma management, 2017.
71. Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet 2017; 389: 157-166.
72. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017; 50: 1701103.
73. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care 2015; 60: 455-468.
74. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. Thorax 2006; 61: 722-728.

75. Thien F, Beggs PJ, Csutoros D, et al. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. Lancet Planet Health 2018; 2: e255-e263.
76. Beasley R, Holliday M, Reddel HK, and the Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019; 380: 2020-2030.
77. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019; 394: 919-928.
78. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019; 53: 1901046.
79. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 2017; 357: j1415.
80. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy 2018; 11: 193-204.
81. Wongtim S, Mogmued S, Chareonlap P, et al. Effect of inhaled corticosteroids on bronchial hyperresponsiveness in patients with mild asthma. Asian Pac J Allergy Immunol 1995; 13: 81-85.
82. Basyigit I, Yildiz F, Kacar Ozkara S, et al. Effects of different anti-asthmatic agents on induced sputum and eosinophil cationic protein in mild asthmatics. Respirology 2004; 9: 514-520.
83. Chrousos GP, Ghaly L, Shedden A, et al. Effects of mometasone furoate dry powder inhaler and beclomethasone dipropionate hydrofluoroalkane and chlorofluorocarbon on the hypothalamic-pituitary-adrenal axis in asthmatic subjects. Chest 2005; 128: 70-77.
84. Chuang SS, Hung CH, Hua YM, et al. Suppression of plasma matrix metalloproteinase-9 following montelukast treatment in childhood asthma. Pediatr Int 2007; 49: 918-922.

85. Currie GP, Stenback S, Lipworth BJ. Effects of fluticasone vs. fluticasone/salmeterol on airway calibre and airway hyperresponsiveness in mild persistent asthma. Br J Clin Pharmacol 2003; 56: 11-17.
86. Karaman O, Sunneli L, Uzuner N,et al. Evaluation of montelukast in 8 to 14 year old children with mild persistent asthma and compared with inhaled corticosteroids. Allergol Immunopathol (Madr) 2004; 32: 21-27.
87. Maiti R, Prasad CN, Jaida J, et al. Racemic salbutamol and levosalbutamol in mild persistent asthma: A comparative study of efficacy and safety. Indian J Pharmacol 2011; 43: 638-643.
88. Riccioni G, Ballone E, D'Orazio N, et al. Effectiveness of montelukast versus budesonide on quality of life and bronchial reactivity in subjects with mild-persistent asthma. Int J Immunopathol Pharmacol 2002; 15: 149-155.
89. Shimoda T, Obase Y, Matsuse H, et al. A study of the usefulness of anti-inflammatory treatment for mild intermitteny asthma (Step 1): budesonide vs. montelukast. Allergol Int 2005; 54: 123-130.
90. Tamaoki J, Isono K, Taira M, et al . Role of regular treatment with inhaled corticosteroid or leukotriene receptor antagonist in mild intermittent asthma. Allergy Asthma Proc 2008; 29: 189-196.
91. Vatrella A, Pelaia G, Parrella R, et al. A single-blind, partial crossover clinical trial of the effects of inhaled fluticasone propionate and nedocromil sodium on airway hyperresposivenes to methacholine. Curr Ther Res 2002; 63: 316-327.
92. Zeiger RS, Bird SR, Kaplan MS, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. Am J Med 2005; 118: 649-657.
93. Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, et al. Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma. Respir Med 2006; 100: 1651-1656.
94. Boulet LP, Cowie RL, Negro RD, et al. Comparison of once- with twice-daily dosing of fluticasone propionate in mild and moderate asthma. Can Respir J 2000; 7: 239-247.

95. O'Sullivan S, Akveld M, Burke CM, et al. Effect of the addition of montelukast to inhaled fluticasone propionate on airway inflammation. Am J Respir Crit Care Med 2003; 167: 745-750.
96. Stone DWG, Mairs ML, Willits L, et al. A comparison of fluticasone propionate, 100μg twice daily, administered via a CFC and non-CFC propellant, HFA 134a, in adult patients with asthma. Clin Drug Investig 2001; 21: 695-703.
97. Vermetten FA, Boermans AJ, Luiten WD,et al. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. J Asthma 1999; 36: 97-106.
98. Villaran C, O'Neill SJ, Helbling A, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast/Salmeterol Exercise Study Group. J Allergy Clin Immunol 1999; 104: 547-553.
99. Barnes NC, Jacques L, Goldfrad C, et al. Initiation of maintenance treatment with salmeterol/fluticasone propionate 50/100 microg bd versus fluticasone propionate 100 microg bd alone in patients with persistent asthma: integrated analysis of four randomised trials. Respir Med 2007; 101: 2358-2365.
100. van der Molen T, Meyboom-de Jong B, Mulder HH, et al. Starting with a higher dose of inhaled corticosteroids in primary care asthma treatment. Am J Respir Crit Care Med 1998; 158: 121-125.
101. Shah MB, Gohil J, Khapekar S, et al. Montelukast versus budesonide as a first line preventive therapy in mild persistent asthma in 2 to 18 y. Indian J Pediatr 2014; 81: 655-659.