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Nocturnal Asthma Uncontrolled by Inhaled Corticosteroids

Theophylline or Long-Acting β_2 Agonists?

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Abstract

Asthma is an inflammatory disease of the airways that is frequently characterised by marked circadian rhythm. Nocturnal and early morning symptoms are quite common among patients with asthma. Increased mortality and decreased quality of life are associated with nocturnal asthma. Although numerous mechanisms contribute to the pathophysiology of nocturnal asthma, increasing evidence suggests the most important mechanisms relate to airway inflammation. According to international guidelines, patients with persistent asthma should receive long term daily anti-inflammatory therapy. A therapeutic trial with anti-inflammatory therapy alone (without a long-acting bronchodilator) should be assessed to determine if this therapy will eliminate nocturnal and early morning symptoms. If environmental control and low to moderate doses of inhaled corticosteroids do not eliminate nocturnal symptoms, the addition of a long-acting bronchodilator is warranted.

Long-acting inhaled β_2 agonists (e.g. salmeterol, formoterol) are effective in managing nocturnal asthma that is inadequately controlled by anti-inflammatory agents. In addition, sustained release theophylline and controlled release oral β_2 agonists are effective. In patients with nocturnal symptoms despite low to high doses of inhaled corticosteroids, the addition of salmeterol has been demonstrated to be superior to doubling the inhaled corticosteroid dose. In trials comparing salmeterol with theophylline, 3 studies revealed salmeterol was superior to theophylline (as measured by e.g. morning peak expiratory flow, percent decrease in awakenings, and need for rescue salbutamol), whereas 2 studies found the therapies of equal efficacy. Studies comparing salmeterol to oral long-acting β_2 agonists reveal salmeterol to be superior to terbutaline and equivalent in efficacy to other oral agents. Microarousals unrelated to asthma are consistently increased when theophylline is compared to salmeterol in laboratory sleep studies.

In addition to efficacy data, clinicians must weigh benefits and risks in choosing therapy for nocturnal asthma. Long-acting inhaled β_2 agonists are generally well tolerated. If theophylline therapy is to be used safely, clinicians must be quite familiar with numerous factors that alter clearance of this drug, and they must be prepared to use appropriate doses and monitor serum concentrations. Comparative studies using validated, disease specific quality of life instruments (e.g. Asthma Quality of Life Questionnaire) have shown long-acting inhaled β_2 agonists are preferred to other long-acting bronchodilators. Examination of costs for these therapeutic options reveals that evening only doses of long-acting oral bronchodilators are less expensive than multiple inhaled doses. However, costs of monitoring serum concentrations, risks, quality of life and other outcome measures must also be considered.

Long-acting inhaled β_2 agonists are the agents of choice for managing nocturnal asthma in patients who are symptomatic despite anti-inflammatory agents and other standard management (e.g. environmental control). These agents offer a high degree of efficacy along with a good margin of safety and improved quality of life.

Asthma is an inflammatory disease of the airways that is typically characterised by marked circadian rhythm. Nocturnal and early morning symptoms are very common among patients with asthma. Because of the importance of night-time symptoms, determination of symptom frequency is an integral component in classifying asthma severity, using national[1] and international[2-4] guidelines (table I).[1] The scope of this problem is enormous considering an estimated 100 million people worldwide have asthma.[3] After a brief summary of nocturnal asthma and the approach to its initial management, this review will focus on a comparison of theophylline versus long-acting inhaled β_2 agonists in managing night-time symptoms.

1. Nocturnal Asthma

In healthy individuals, as well as patients with asthma, there is detectable circadian rhythm with pulmonary function tests. Peak expiratory flow (PEF) is highest at 4pm and lowest at 4am.[5] Whereas circadian rhythm is clinically unimportant in healthy individuals (<10% decrease at 4am), these changes are highly significant in patients with nocturnal asthma (see fig. 1).[6] Several potential mechanisms summarised in this section account for this decrease in airway calibre. Nocturnal asthma is associated with increased mortality[7] and decreased quality of life.[8]

1.1 Frequency

In a survey of 7729 patients with asthma, Turner-Warwick[9] found that 74% awakened at night at least once weekly and 64% awakened at least 3 times each week with symptoms. Another noteworthy finding of this study was that of over 3000 patients who perceived their asthma as 'mild', 26% reported awakening every night. Many patients will not tell clinicians about early morning chest tightness or mild wheezing because they do not

Table I. Stepwise approach for managing asthma in adults and children older than 5 years of age.[1]

Goals of Asthma Treatment:

- Prevent chronic and troublesome symptoms (e.g. coughing or breathlessness in the night, in the early morning or after exertion)
- Maintain (near) 'normal' pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimise the need for emergency department visits or hospitalisations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care.

Classify severity of asthma	Clinical features before treatment[a]		
	symptoms[b]	night-time symptoms	lung function
Step 4. Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV_1 or PEF ≤60% predicted PEF variability >30%
Step 3. Moderate persistent	Daily symptoms Daily use of inhaled short-acting β_2 agonist Exacerbations affect activity Exacerbations ≥2 times a week; may last days	>1 time a week	FEV_1 or PEF >60-<80% predicted PEF variability >30%
Step 2. Mild persistent	Symptoms >2 times a week but <1 time a day Exacerbations may affect activity	>2 times a month	FEV_1 or PEF ≥80% predicted PEF variability 20-30%
Step 1. Mild intermittent	Symptoms ≤2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations brief (from a few hours to a few days); intensity may vary	≤2 times a month	FEV_1 or PEF ≥80% predicted PEF variability <20%

a The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this table are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

b Patients at any level of severity can have mild, moderate or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and not symptoms.

FEV_1 = forces expiratory volume in 1 second; **PEF** = peak expiratory flow.

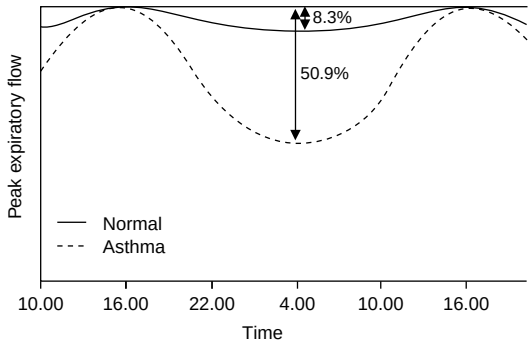

Fig. 1. Diurnal variation in peak expiratory flow is exaggerated in patients with asthma. The difference between maximal airflow at 4pm and minimal airflow at 4am normally averages 8.3%; in patients with asthma, however, the average variation may be as high as 50.9%.[6]

understand its significance and think that they simply have to tolerate it. Consequently, clinicians should carefully probe not only for night-time awakenings as a result of wheezing, but also chest tightness upon awakening in the early morning. Based on National Institutes of Health Guidelines,[1] nocturnal or early morning symptoms greater than twice monthly indicate a level of airway inflammation sufficient to warrant daily anti-inflammatory medication (table I).

1.2 Mechanisms

Although several mechanisms are likely to contribute to the pathophysiology of nocturnal asthma, an increasing body of evidence suggests mechanisms related to airway inflammation are of major importance. Martin et al.[10] studied broncheoalveolar lavage (BAL) fluid for inflammatory cells in patients with asthma with and without nocturnal symptoms. At 4am, the group with nocturnal symptoms had significantly higher eosinophil, lymphocyte, neutrophil, total leucocyte and epithelial cell counts. The overnight decrease in PEF correlated with change in BAL eosinophil and neutrophil counts. Jarjour and Busse[11] also studied BAL in patients with nocturnal asthma and found that the cytokine interleukin (IL)-1β was significantly greater at 4am. IL-1β activates alveolar macrophages, which contribute to airway inflammation. Kraft et al.[12] examined bronchial and transbronchial (sampling of alveolar tissue) biopsies of patients with nocturnal asthma. Alveolar tissue contained increased eosinophils and macrophages, compared with patients without nocturnal symptoms, and inflammation was worse at 4am. Consistent with this direct evidence of inflammatory cells is the marked reduction in nocturnal symptoms many patients have when anti-inflammatory therapy is added or optimised (see section 2.2).

In addition to airway inflammatory cells and the effect of circadian rhythm on airflow, several other mechanisms contribute to nocturnal asthma. Barnes and associates[13] have described circadian rhythm with adrenaline (epinephrine), histamine and cortisol. Adrenaline has trough serum levels in the early morning hours, and serum cortisol levels are lowest between 10pm and midnight. Serum histamine levels peak near the time (4am) of greatest reduction in airway calibre. Each of these findings has obvious implications for nocturnal asthma. Glucocorticoid receptor binding affinity may be reduced in nocturnal asthma.[14] Decreased density of β receptors on circulating leucocytes of patients with nocturnal asthma versus healthy individuals and patients with non-nocturnal asthma has been found.[15] Genetic polymorphisms of the β_2 receptor may also play a role in nocturnal asthma.[16]

Increased activity of the parasympathetic nervous system is another factor that contributes to nocturnal asthma. Cholinergic tone is highest late at night and in the early morning, and stimulation of the vagus nerve causes bronchoconstriction.[17] A further mechanism that can worsen nocturnal symptoms is gastro-oesophageal reflux disease (GORD).[18] Although treatment of GORD has been shown to improve symptoms, a concomitant increase in morning PEF has not been clearly shown.[18] Poor control of allergic rhinitis can worsen asthma as can sinusitis.[1,2] Appropriate management of these conditions improves overall asthma control, including nocturnal symptoms. Finally, if a patient with asthma has sleep apnoea, nocturnal asthma symptoms may be

reduced by use of nasal continuous positive airway pressure (CPAP).[19]

2. Initial Management Options

Application of basic principles for overall management of asthma are obviously of great importance in reducing nocturnal symptoms. Optimal use of the 4 cornerstones of management [environmental control, objective assessment and monitoring, drug therapy, (emphasising anti-inflammatories) and patient education as a partnership][1-4] will provide marked improvement in nocturnal asthma.

2.1 Objective Assessment and Monitoring

In addition to determining patient complaints of night-time and early morning symptoms, objective assessment with PEF is important. Before appropriate treatment, the classic 'morning dip' in PEF will usually be observed (fig. 1). The goal is to have less than 20% variability between evening and early morning PEF.[1] Ideally, of course, with optimal management the patient will stay in the 'green zone' (80 to 100% of personal best) even in the early morning hours and not 'dip' into the yellow (50 to 79% of personal best) or red zone (<50% of personal best).

2.2 Environmental Control

Control of the home and work/school environments is a vital component of optimal asthma management.[1-4] Special attention should always be given to the bedroom environment, specifically because nocturnal asthma is so common. Standard measures such as occlusive covers for mattresses and pillows to reduce exposure to house dust mites, elimination of cockroaches and molds, and not allowing household pets in the bedroom can be helpful in reducing nocturnal symptoms. Some busy clinicians may pay close attention to drug therapy but not ascertain lack of patient action to improve the bedroom environment (e.g. sleeping with 2 cats and no mattress/pillow covers).

2.3 Anti-Inflammatory Agents

Patients with persistent asthma should receive long term daily anti-inflammatory therapy. A therapeutic trial should first be given with anti-inflammatory therapy alone (without a long-acting bronchodilator) to assess if this therapy will eliminate nocturnal and early morning symptoms. Specifically, if low dose inhaled corticosteroids, leukotriene receptor antagonist, sodium cromoglycate or nedocromil eliminate nocturnal symptoms, then the regimen is simplified and costs are reduced. This approach is consistent with current guidelines.[1]

Several groups of investigators have found that inhaled corticosteroids are effective in increasing morning PEF and reducing nocturnal asthma.[20-28] If low to moderate doses of inhaled corticosteroids do not eliminate nocturnal symptoms, the addition of a long-acting bronchodilator is warranted (see section 3).

2.4 Patient Education

Patient eduction as a partnership is an integral part of optimal asthma management.[1-4]

Regarding nocturnal asthma, patients need consistent sharing of information about asthma as an inflammatory airway disease, the purpose of each medication (stressing prevention) and environmental control, especially in the bedroom. Teaching proper use of inhalers and peak flow meters with demonstrations and observation of patient use is essential. Nocturnal symptoms will be eliminated or markedly reduced only if adequate patient education is given.

3. Long-Acting Bronchodilators

For patients whose nocturnal asthma is not eliminated by environmental control, treatment of concomitant conditions (e.g. GORD, rhinitis), and low to moderate dose inhaled corticosteroid therapy (or other anti-inflammatories), long-acting bronchodilators are quite helpful adjunctive agents. This section reviews clinical trials for nocturnal asthma using the sustained release theophyl-

line preparations, the sustained release β_2 agonists terbutaline and salbutamol (albuterol), the oral long-acting terbutaline prodrug bambuterol and the inhalation formulations of salmeterol and formoterol. Both the placebo and short acting β_2 agonist controls are briefly reviewed. Most of the focus is on direct comparisons between the long-acting bronchodilators.

3.1 Versus Placebo or Short-Acting β_2 Agonists

Sustained release formulations of theophylline, terbutaline, and salbutamol, an oral pro-drug of terbutaline (bambuterol), salmeterol by inhalation, and formoterol by inhalation have been compared with placebo or short-acting β_2 agonists for their effects on nocturnal asthma symptoms, morning FEV1 or PEF.

3.1.1 Theophylline

Both a twice daily theophylline preparation[29] and once daily theophylline[30,31] decreased nocturnal symptoms in childhood asthma compared with placebo (table II). Both administration regimens, with their specific theophylline formulations, improved nighttime symptoms, night awakenings, early morning PEF and use of rescue bronchodilators.

Extended release theophylline has been compared to placebo or short-acting β-2 agonists for nocturnal asthma symptoms in adults both specifically with[32,33,38] and without[34-37,39] a requirement for concurrent oral or inhaled corticosteroids (table II).

Kraft et al.[34] evaluated forced expiratory volume in 1 second (FEV_1) and BAL fluid in 8 patients with asthma. The FEV_1 decreased from 26.6% on placebo to 10.4% on theophylline. There was a greater than 10% decrease in the neutrophil infiltrate in the 4am BAL cell count. Crescioli et al.[35] reported FEV_1 and responsiveness to methacholine inhalation tests in patients who had previously reported recurrent nocturnal asthma. On each control and study day, at 6am, 2pm and 10pm routine spirometry, methacholine challenge and serum theophylline concentrations (STCs) were performed. In this 5-day crossover study with a 10-day washout, patients had a greater FEV_1 at all time points on theophylline days compared with placebo. The provocative concentration of nebulised methacholine required to cause a 20% reduction in FEV_1 compared with baseline was higher (improvement) at 6am on theophylline treatment days compared with placebo days. Freeman et al.[36] found no difference in night-time symptoms but clinic FEV_1 post-inhaled bronchodilator and patient measured morning PEF were improved with theophylline. FEV1 and PEF measured in the clinic before inhaled bronchodilator were no different. Once daily theophylline formulations administered in the evening improved the early morning PEF.[37,39] However, in their short term evaluation, Richardt and Driver[37] found that theophylline increased nocturnal wakefulness (not asthma related) and decreased sleep efficiency compared with the same patients when receiving placebo.

Benefits of adding controlled-release theophylline in patients who are already taking oral or inhaled corticosteroids are also consistent. Two published trials[32,38] and one abstract[33] evaluated early morning PEF and FEV_1 in patients already taking inhaled corticosteroid therapy. Fairfax et al.[32] found that theophylline produced an improvement in symptoms of cough, wheeze, sleep disturbance and PEF in 73 completers of the original 104 patients with asthma and nocturnal symptoms enrolled. In a subgroup analysis of patients who had been taking theophylline upon entry into the study, however, the effects of theophylline on FEV_1 and forced vital capacity (FVC), compared with placebo, was less than those not taking theophylline upon entry. Busse et al.[33] reported an improvement in FEV1, FVC and PEF in a crossover study of 48 patients where theophylline was added to an inhaled corticosteroid (specific corticosteroid not reported) and β_2 agonist. Rivington and associates[38] evaluated the impact of adding a once daily theophylline preparation to patients already taking moderately high does of inhaled corticosteroids (mean dose standardised to beclomethasone 1100 μg/day, range 500 to 2000 μg/day). Morning PEF and FEV_1 along with patient rating of asthma control were higher with theophylline added.

Table II. Summary of randomised, placebo-controlled, crossover trials of extended-release theophylline (T) in patients with nocturnal asthma symptoms

No. of pts completing study (randomised)	Treatment duration	Theophylline formulation[a]	Dose	Theophylline serum concentrations after randomisation (mg/L)	Improvement in lung function versus placebo	Improvement in night-time symptoms versus placebo	Reference
10 (13) [paediatric study ages 7-14]	2wks	'Neulin SA'	idt bid	9.86 ± 2.75	am PEF $p < 0.01$ pm PEF same	Awakenings $p < 0.01$ Wheeze, cough $p < 0.01$	29
17 (23) [paediatric study]	4wks	'Uniphyllin' paediatric tablets	18 mg/kg hs	14.86 ± 2.3	am PEF $p < 0.001$	Scores $p \leq 0.001$	30
22 (25) [paediatric study]	1mo	NR	idt hs	NR	am PEF $p < 0.05$	Score $p < 0.05$	31
73 (104)	4wks	'Uniphyllin Continus'	idt hs	NR	Clinic PEF NS Patient PEF $p < 0.01$ Clinic FEV_1 $p = 0.001$	Cough $p < 0.05$) Wheeze $p < 0.001$ Waking $p < 0.05$	32
38 (48)	4wks	'Uniphyl'	idt hs	NR	Clinic FEV_1 $p < 0.001$ Clinic FVC $p = 0.004$ Clinic PEF $p = 0.05$	NR	33
8 (12)	2wks	'Uniphyl'	idt 7pm	13.0 to 21.0at 4am	4am FEV_1 $p = 0.003$	NR	34
18 (25)	5 days	'Respicur'	idt bid	8.9 to 12.8	6am FEV_1 <0.005 6am $PC_{20}FEV_1$ <0.05	NR	35
10 (15)	2wks	'Pro-Vent'	idt bid	(Mean in week 2) 10.9 ± 3.3	Clinic FEV_1 $p < 0.05$ Clinic FVC NS Clinic PEF NS Patient am PEF $p < 0.01$	NS	36
12 (15)	22 days	NR	idt hs	NR	Clinic am PEF: T > placebo	Sleep onset latency: placebo > T Within sleep wakefulness: placebo > T REM sleep: placebo = T	37

a Use of a brand name is for product identification only, and does not imply endorsement.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **hs** = once daily in the late evening or bedtime; **idt** = individualised dose titration of theophylline before randomisation so as to maintain a steady state theophylline concentration of 10-20 mg/L; **NR** = not reported; **NS** = no statistically significant difference; **$PC_{20}FEV_1$** = provocative concentration of nebulised methacholine required to cause a 20% reduction in FEV_1, compared with baseline; **PEF** = peak expiratory flow; **REM** = rapid eye movement.

3.1.2 Salmeterol

Salmeterol, a long-acting selective β_2 agonist administered via inhalation, has been studied in patients ≥12 years of age[40-53] and in one paediatric population between the ages of 4 and 11 years.[54] Where reported, morning PEF was consistently improved with salmeterol in the randomised controlled crossover studies (table III).[43,44,46-48,52,53] Night-time symptoms and rescue bronchodilator use also declined with inhaled salmeterol.

A larger parallel multicentre trial studied both clinical outcomes and quality of life in 384 of 474 patients with nocturnal symptoms enrolled.[42] Salmeterol inhalation 42μg or placebo was administered twice daily. Patients were allowed to continue theophylline, inhaled corticosteroids, and 'as needed' salbutamol. Salmeterol improved morning, evening and morning/evening differential PEF measurements at weeks 4, 8 and 12. The percentage of nights with no awakenings due to asthma increased from 28 to 77% by week 12 compared with an increase from 28 to 49% in patients treated with placebo ($p < 0.001$). Night-time supplemental salbutamol use was decreased 69% from baseline compared with only 17% for placebo. A subgroup analysis of patients also taking theophylline concurrently with the salmeterol or placebo was studied. The authors state that salmeterol improved morning PEF compared with placebo at every week throughout the study, regardless of theophylline use ($p \leq 0.013$).

A large randomised, double-blind, placebo-controlled, parallel-group study (n = 322) evaluated twice daily inhaled salmeterol compared with inhaled salbutamol 4 times daily; 25% of these patients had nocturnal asthma symptoms that interfered with their sleep at least 4 times a week.[49] The percentage of nights without symptoms increased most from baseline in the salmeterol treatment; 59 to 85% in the salmeterol group and 62 to 74% in the salbutamol group ($p < 0.001$). Britton and associates[50] compared salmeterol 50μg twice daily with salbutamol inhalations 4 times daily in 667 patients with moderate asthma in a multicentre, double-blind, parallel-group study. Over the 12-month study there was a lower incidence of asthma and related events in the salmeterol treatment group. Lai et al.[52] and Norhaya et al.[53] added inhaled salmeterol to the treatment regimen of patients who were all taking inhaled corticosteroids (nonstandardised) and found that lung function improved but night-time symptom scores were equal.

Weinstein et al.[54] reported the efficacy and safety of salmeterol powder inhalation in children ages 4 to 11 years in the US. In this parallel designed multicentre study, 207 children received either salmeterol powder or placebo twice daily for 12 weeks. The addition of salmeterol had a greater bronchodilatory effect than placebo in both users and non-users of inhaled corticosteroids. Supplemental salbutamol use in the study declined from baseline in both the placebo and salmeterol treatment groups but the decline was greater in the salmeterol group ($p = 0.004$). The percentage of nights with no awakenings increased 9.1% for salmeterol patients and 4.1% in the placebo group but this was not statistically significant ($p = 0.321$). Salmeterol was tolerated as well as placebo.

3.1.3 Formoterol

Formoterol is a long-acting β_2 agonist available in a single-dose breath-actuated device for asthma treatment in some countries. Both clinical lung function and night-time symptoms improved more with twice daily formoterol than 4 times daily salbutamol inhalations[55-59] and terbutaline aerosols[60-62] or placebo.[63] A dose of 12μg by inhalation administered twice daily is the better studied[55,56,60,63] but even low-dose formoterol 6μg twice daily was more effective than oral terbutaline (0.5mg 4 times daily) in improving morning PEF and night-time asthma symptoms.[62]

In 1998, Clauzel et al.[64] also evaluated the efficacy and ease of use of formoterol dry powder for 3 months in a non-blind study of 1380 patients with asthma who were using inhaled corticosteroids. Mean pre-dose PEF and daytime/nocturnal symptoms scores improved during the study. Rescue short-acting β agonist use was reduced by more than 3 times. By the end of the study, 71.5% of patients were receiving formoterol 12μg and 28.5% were receiving 24μg, both administered twice daily.

Table III. Summary of randomised, crossover trials of inhaled salmeterol (Sm) versus placebo (Pl) or salbutamol (Sb; albuterol) in patients with nocturnal asthma symptoms

No. patients evaluated (randomised)	Treatment duration	Dose regimen (μg)	Lung function measured in clinic	Lung function as measured at home	Night-time symptoms	Rescue bronchodilator use	Other outcome measures	Reference
10 (10)	6wks	Sm 100 bid	4am FEV_1 at 6 weeks Sm = Pl 4am FVC at 6 weeks Sm = Pl 4am $PC_{20}FEV_1$ at 6 weeks Sm = Pl	PEF stated in methods but not reported	% decreases in nights with awakening Sm>Pl	% 24h days with supplemental bronchodilator use Sm > Pl		43
38 (41)	3wks	Sm 50 bid Sm 100 hs	FEV_1 Sm 50 bid = Pl Sm 50 bid = Sm 100 hs Sm 100 hs > Pl	am PEF Sm 50 bid > Pl Sm 100 hs > Pl Sm 100 hs > Sm 50 bid	% nights no symptoms Sm 50 bid > Pl Sm 100 hs > Pl Sm 50 bid + Sm 100 hs			44
17 (20)	2wks	Sm 50 bid Sm 100 bid		PEF Sm 50 > Pl Sm 100 > Pl Sm 50 = Sm 100	Median number of asthma related night awakenings Sm 50 > Pl Sm 100 > Pl Sm 50 = Sm 100	Number of inhalations of Sb per 24h Sm 100 > Pl Sm 50 > Pl Sm 50 = Sm 100	Subjective sleep quality scores p = 0.09 Stage 0-1 wakefulness Sm 50 > Pl Stage 4 sleep Sm 50 > Pl Sleep stage 2, 3, REM Sm 50 = Sm 100 = Pl	46, 47
301 (367)	4wk	Sm 50 bid Sb 200 qid	PEF: Sm > Sb; Sm > Pl FEV_1: Sm > Sb; Sm > Pl FVC: Sm > Sb;Sm > Pl	Morning PEF Sm > Sb; Sm > Pl % diurnal variation PEF Sm > Sb; Sm > Pl	% nights with no disturbances Sm > Sb; Sm > Pl	% rescue free days Sm > Sb; Sm > Pl		48
20 (25)	2wks	Sm 50 bid + IC Sb 400 qid +IC	NR	Morning PEF Sm + 1C > Sb + 1C % diurnal variation PEF Sm + IC = Sb + IC	Night-time symptom Sm + 1C > Sb + 1C	Rescue doses Sm + 1C > Sb + 1C	Patient efficacy rating Sm + 1C > Sb + 1C	52
20 (25)	4wks	Sm 50 bid + IC Pl bid +IC	FEV_1 Sm + IC > Pl +IC	Morning PEF Sm + IC > Pl + IC	Symptom score Sm + IC = Pl + IC	Night-time doses Sm + IC = Pl + IC		53

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **hs** = dose administered at night or late evening; **IC** = inhaled corticosteroid (non-standardised); **PC20FEV1** = provocative concentration of nebulised methacholine required to cause a 20% reduction in FEV_1, compared with baseline; **PEF** = peak expiratory flow; **PEFR** = peak expiratory flow rate; **qid** = four times daily.

3.1.4 Bambuterol

Bambuterol, a prodrug of terbutaline administered at a dose of 20mg orally once daily in the evening, has been found more effective than placebo in improving lung function[65,66] and in controlling cough, wheeze and dyspneoa at night in patients with nocturnal asthma.[66] These randomised, double-blind, crossover studies had 29[65] and 28[66] patients.

3.1.5 Oral Terbutaline and Salbutamol

Both sustained release terbutaline[67-71] and controlled release salbutamol[72-74] have shown benefits in nocturnal asthma when compared with placebo. Controlled release terbutaline is compared to theophylline (section 3.2.2) and the newer controlled release salbutamol is compared with the newer β_2 agonists (section 3.2.3).

3.1.6 Corticosteroid Sparing Effects

Additive benefits of extended release theophylline[75,76] or inhaled twice daily salmeterol[77-84] to controlled doses of inhaled corticosteroids have been evaluated in placebo controlled studies (table IV). Youngchaiyud et al.[75] did not find any additional improvement in efficacy by adding sustained release theophylline 200mg twice daily to inhaled budesonide 200μg twice daily. However, no STCs were reported in the 61 patients. Ukena and associates[76] compared low dose beclomethasone with added theophylline to high dose beclomethasone alone. The clinical lung function, nocturnal symptoms and use of β_2 agonists use at night improved similarly with both groups demonstrating the corticosteroid sparing benefits of adding theophylline instead of doubling the dose of inhaled corticosteroids.

Baraniuk et al.[77] and Condemi et al.[78] both found the addition of salmeterol to low dose inhaled fluticasone propionate to improve both lung function and night-time symptoms more than high dose fluticasone alone. Weersink[82] reported salmeterol alone to be as effective as the combination of salmeterol and inhaled high dose fluticasone except for the improvement in bronchial hyperresponsiveness. Three reports[79,80,84] all concluded that adding inhaled salmeterol to inhaled beclomethasone provided better improvement in lung function than doubling the beclomethasone dose alone. In a more practice-focused study design, Wilding et al.[83] added salmeterol or placebo to inhaled corticosteroids for 6 months. In 45 patients initially taking 600μg or less of beclomethasone or budesonide, the inhaled corticosteroid dose was 19% less with salmeterol than when patients were inhaling placebo (329μg *vs* 404μg). In the 42 patients taking more than 600μg of inhaled corticosteroid, the difference was 14% (998μg with salmeterol *vs* 1162μg with placebo). Lung function tests, night-time symptoms and use of rescue bronchodilators were all best with the salmeterol addition. The authors also emphasise that the corticosteroid sparing dose of salmeterol would have been greater had the restrictions on how much inhaled corticosteroid reduction was allowed.

In children, the benefits of adding salmeterol to corticosteroids were not found.[81] Children with moderate asthma, aged 6 to 16 years, were given salmeterol 50μg with a moderate dose of beclomethasone 200μg, beclomethasone 200μg alone, or a doubling of the beclomethasone to 400μg. All drugs were administered twice daily. Night-time symptoms diminished similarly in all 3 groups. Airway responsiveness and PEF both improved similarly in all 3 groups, although treatment changes were larger with the salmeterol combination in the earlier treatment months. During the course of this one-year study most patients reported some type of adverse effect; 98%, 93% and 87%, for the salmeterol combination, the moderate dose of beclomethasone alone and the double dose beclomethasone alone, respectively. The authors conclude that neither adding salmeterol or doubling the beclomethasone provided any additional benefit over beclomethasone 200μg twice daily in this particular group of children with moderate asthma who had excellent adherence to medication. The authors feel their results may be different than findings from adult studies[79,80,84] partially because of inclusion criteria. These authors included the children based upon airway caliber and airway responsiveness, whereas adult studies, included patients based upon symptom scores in the run-in phase.

Table IV. Summary of controlled studies where either long-acting theophylline (T) or salmeterol (Sm) are given to patients who are taking inhaled corticosteroids (IC; nonstandardised) [steroid sparing effects]

No. patients completing study (randomised)	Study design	Treatment duration (wks)	Dosage regimen	Lung function measured at home	Lung function measured in clinic	Improvement in night-time symptoms	Improvement in rescue bronchodilator use	Other outcome measures	Reference
Theophylline									
61 (70)	R, DB, DD, CO 3 x 3 latin square 3 treatments	3	Bd 200µg bid T 200mg bid Bd 200µg bid and T 200mg bid	Morning PEF Bd > T; Bd + T > T Bd = Bd + T	NR	Night-time asthma symptom score Bd > T; Bd + T > T; Bd + T = Bd Number of nights sleep disturbed Bd > T; Bd + T > T; Bd = Bd + T	Number of night-time inhalations Bd > T; Bd + T > T; Bd = Bd + T		75
134 (190)	R, DB, MC, P	6	B 200µg bid + T 250mg bid B 400µg bid	Morning PEF B 200 + T > B 400 PEF variability improvement B 200 + T > B 400	NR	Symptoms B 200 + T = B 400	Number of night-time inhalations B 200 + T = B 400		76
Salmeterol									
664 (680)	R, DB, TD, MC, P	12	FP 200µg bid TA 600µg bid FP 88µg + Sm 42µ bid	Morning FEV_1 FP + SM > FP, $p \leq 0.033$ FP > TA, $p \leq 0.035$	NR	Night-time awakenings FP + Sm > TA, $p \leq 0.004$ FP > TA, p < = 0.035	Night-time salbutamol FP + Sm > TA, p + 0.004	Physician global assessment FP + Sm > TA, p < 0.001 FP + Sm > FP, p = 0.001 FP > TA, p = 0.016	77
388 (437)	R, DB, DD, MC, P	24	FP 110µg bid FP 88µg + Sm 42µg bid	Morning PEF Sm + FP > FP, p < 0.001 FEV_1 Sm + FP > FP, p = 0.13	Change in pre-dose FEV Sm + FP > FP, p < 0.038	% nights with no awakenings Sm + FP > FP, p = 0.008 No night-time awakenings Sm + FP > FP, p < 0.001	nr		78

Table IV. Contd

No. patients completing study (randomised)	Study design	Treatment duration (wks)	Dosage regimen	Lung function measured at home	Lung function measured in clinic	Improvement in night-time symptoms	Improvement in rescue bronchodilator use	Other outcome measures	Reference
290 (429)	R, DB, DD, MC, P, ITT	24	B 500μg bid B 200μg + Sm 50μg bid	Mean morning PEF change Sm + B = B	NR	Use of rescue inhaler Sm + B > B Reduction in disturbed nights Sm + B = B	Night-time inhaler use Sm + B = B		79
386 (483)	R, DB, DD, MC, P, ITT	24	B 168μg +Sm 42μg bid B 336μg bid	Morning change in PEF B 168 + Sm > B 336	FEV_1 mean change B 168 + Sm > B 336	Night-time awakenings B 158 + Sm > B 336 % nights with no awakenings B 168 + Sm > B 336	% nights with no use B 168 + Sm > B 336		80
162 (177) [aged 6-16 years]	R, DB, MC, P	54	B 200μg + Sm 50μg bid B 400μg bid B 200μg bid	Morning PEF 3 groups equal at 1 year	FEV_1 change from baseline 3 groups equal	Nocturnal symptoms 3 groups equal	3 groups equal at 1 year	Morning PEF during early months only B 200 + Sm > B 200 B 200 + SM = B 400	81
46 (50)	R, DB, DD, P	6	Sm 50μg bid FP 250μg bid Sm 50μg + FP 250μg bid	Morning FEV_1 Sm = FP = SM + FP PEF variability Sm = FP = SM + FP	PC20MCh Sm = FP = Sm + FP				82
87 (101)	R, DB, ICDA, CO	24	Sm 50μg bid + ICDA Pl bid + ICDA	FEV_1 Sm + IC > Pl + IC, p < 0.001 Morning PEF Sm + IC > Pl + IC, p < 0.001	PC20FEV1 Sm + IC > Pl + IC, p = 0.008	Night-time symptoms Sm + IC > Pl + IC, p < 0.001	Bronchodilator free days Sm + IC > Pl + IC, p < 0.001	Reduction in inhaled corticosteroid Sm > Pl	83
649 (738)	R, DB, MC, P	24	B 500μg bid + Sm 50μg bid B 500μg bid + Sm 100μg bid B 100μg bid alone	Morning PEF B 500 + Sm 50 = B 500 + Sm 100 B 500 + Sm 50 or Sm 100 > B 1000 Diurnal variation in PEF B 500 = Sm 50 or Sm 100 > B 1000	FEV_1 change from baseline B 500 + Sm 50 or Sm 100 > B 1000 B 500 + Sm 50 = B 500 + Sm 100	Nocturnal symptoms B 500 + Sm 50 or Sm 100 > B 1000 B 500 + Sm 50 = B 500 + Sm 100	nr	nr	84

B = beclomethasone by inhalation; **Bd** = budesonide inhalation; **bid** = twice daily; **CO** = crossover; **DA** = dose adjustment of theophylline allowed by physician; **DB** = double-blind; **DD** = double-dummy; **FEV_1** = forced expiratory volume in 1 second; **FP** = fluticasone propionate inhalation; **ICDA** = inhaled corticosteroid dose adjusted by physician based on symptoms; **ITT** = intention to treat analysis; **MC** = multicentre; **NR** = not reported; **$PC_{20}FEV_1$** = provocative concentration of nebulised methacholine required to cause a 20% reduction in FEV_1, compared with baseline; **P** = parallel-group; **PEF** = peak expiratory flow; **Pl** = placebo; **qid** = four times daily; **R** = randomised; **TA** = triamcinolone inhalation.

The adult studies, as a result, may include patients who are more highly symptomatic.

3.2 Comparative Trials

3.2.1 Theophylline versus Long-Acting Inhaled β_2 Agonists

Controlled-release oral theophylline has been compared with salmeterol administered by metered dose inhaler (MDI) in patients who both met the official definition of asthma and had nocturnal symptoms.[85-90]

Pollard et al.[85] reported the combined results of 2 identically designed multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group studies which compared salmeterol aerosol 42μg with extended-release theophylline capsules (Slo-BID®).[1] Both treatments were administered twice daily for 12 weeks. Of 638 adult and adolescent patients who originally entered the pre-baseline theophylline titration period, 484 patients remained for the intent-to-treat population analysis. Theophylline-related adverse effects accounted for 71 of 154 patients who withdrew before randomisation. In the 2-week non-blind theophylline titration period, the dose of theophylline was increased until a steady state serum theophylline concentration was between 10 to 20 mg/L as measured 5 to 9 hours after administration. Other bronchodilators (oral or inhaled) were not allowed, but patients who were already receiving inhaled corticosteroids, sodium cromoglycate or nedocromil were enrolled and allowed to continue using the medications, provided that the dose remained constant throughout the study. After randomisation, patients who had asthma exacerbations could stay in the study if the exacerbation could be successfully managed using only one or more of the following drugs: an additional inhaled β-agonist via nebulizer for no more than 5 days, or a prednisone burst (≤400mg total dose) for no longer than 10 days in duration. Any patient requiring more than one prednisone burst within a 28-day period was discontinued from the study.

Baseline characteristics of the patients entering each of the 3 treatment groups were comparable. Mean theophylline concentrations measured approximately 12 hours post-dose at weeks 4, 8 and 12 were 7.9 mg/L, 7.7 mg/L and 7.6 mg/L, respectively. At each week of the 12 weeks, salmeterol improved morning PEF more than theophylline or placebo ($p < 0.02$). Over the 12 weeks, morning PEF increased over baseline values by an average of 10.3 L/min in the salmeterol group, whereas in the theophylline and placebo groups, morning PEF decreased by an average of 4.5 and 4.8 L/min, respectively. Analysis of morning PEF patients who received inhaled corticosteroids versus those who did not were 10 L/min and 11 L/min, respectively, for salmeterol-treated patients, –9 L/min and l L/min, respectively, for theophylline-treated patients and –19 L/min and –8 L/min, respectively, for placebo-treated patients. Between treatment comparisons over the 12-week study favoured salmeterol over both the placebo and theophylline treatments for morning PEF ($p \leq 0.031$) in both subgroups of patients; those with or without concurrent inhaled corticosteroids. The theophylline treatment was better than placebo ($p = 0.032$) only in the group that was receiving inhaled corticosteroids. Improvement in FEV_1 was greater with salmeterol than placebo throughout the 12 weeks ($p < 0.001$) but there were no significant differences between theophylline and placebo or salmeterol and theophylline.

Salmeterol produced the greatest reduction from baseline in night-time awakenings per week, asthma score and salbutamol use compared with theophylline or placebo ($p < 0.02$). There was no change in the theophylline- or placebo-treated groups when compared from baseline. Regarding adverse effects or safety of the drugs after randomisation started, 10% of the theophylline group reported a gastrointestinal (GI) adverse effect compared with 2% in the salmeterol group and 3% in the placebo group ($p < 0.001$). At both weeks 4 and 12 patients taking salmeterol rated their medication higher than did patients in either the theophylline or placebo group ($p < 0.05$).

1 Use of a trade name is for product identification only, and does not imply endorsement

Several randomised, placebo-controlled, crossover studies[86-90] have compared extended-release theophylline with inhaled salmeterol (table V). Sleep studies were performed in the clinic sleep laboratory in 3 of these studies.[87-89] After acclimatisation to the clinic sleep laboratory, sleep studies were performed for either 1 night[89] or 2 nights[87,88] at the end of each treatment period, in conjunction with measuring changes in patient lung function.

Wiegand et al.[87] evaluated nocturnal spirometry, nocturnal polysomnography, findings from sleep questionnaires, and daily measurements of lung function and symptoms in 19 patients. On days 14 and 15 in the sleep study, fewer patients in the salmeterol treatment group experienced nocturnal awakenings and required salbutamol compared with placebo ($p = 0.019$ and $p = 0.038$, respectively). In the polysomnography measurements taken on day 14, the only difference in sleep architecture indexes found was that less stage 2 sleep was seen after treatment with theophylline than after treatment with placebo ($p = 0.034$). Sleep structure, as described by sleep efficiency, sleep latency, sleep-stage representation and the number of arousals and awakenings from sleep, was not different between treatment groups. There were no differences in mean nocturnal heart rate, oxyhaemoglobin saturation or apnoea-hypopnoea index values between the treatments. Baseline FEV_1 values measured on day 15 in the sleep laboratory were measured just before lights out between 9pm and 10.45pm; hourly FEV_1 were recorded the following 8 hours. The overall mean nocturnal FEV_1 fell from baseline overnight after treatment with placebo (-0.16L; $p = 0.031$) and theophylline (-0.22L; $p = 0.002$), but it did not change after treatment with salmeterol (-0.04L; $p > 0.05$). The difference in the overall mean change in the nocturnal FEV_1 from baseline between the salmeterol and theophylline treatment groups was significant ($p = 0.013$). The difference between salmeterol and placebo approached significance ($p = 0.055$), but the difference between theophylline and placebo was not significant. The authors do not provide a good explanation of their findings on the nocturnal FEV_1 with theophylline.

No baseline differences in the patient diary card information were found in this study.[87] The morning PEF improved more with the salmeterol group than either placebo or theophylline during the second week of treatment and was superior to placebo during the entire 15-day treatment period. Salmeterol increased ($p \leq 0.05$) the percentage of nights with no salbutamol use compared with both theophylline and placebo over the 15 days of treatment. On a 5-point scale from 0 (no symptoms) to 4 (severe symptoms, no sleep), patients recorded their perceptions of nocturnal chest tightness, shortness of breath, wheezing and cough. Baseline values for each treatment were obtained by averaging individual measurements over the 5 days before the respective treatment period. These patient-rated night-time asthma symptoms, the percentage of symptom-free nights and the number of self-reported awakenings were similar for all the treatment regimens. After randomisation, 6 patients (33%) experienced what the investigators thought were drug-related adverse events with theophylline. The adverse events included headache, tremor, dizziness, anxiety, agitation, and nausea and vomiting. No drug-related adverse events were reported for either salmeterol or placebo.

Deegan and McNicholas[89] evaluated sleep quality and oxygenation between inhaled salmeterol and oral theophylline. There was no difference in sleep stage distribution between the 2 nights (1 night with theophylline treatment and the second 3 weeks later with salmeterol treatment). Sleep efficiency was almost identical on the 2 agents, with the lower frequency of transient movement arousals on salmeterol being the only significant difference between the 2 agents ($p = 0.03$). Mean heart rates and respiratory rates were the same. Patients recorded and the authors reported PEF, rescue inhaler use and nights disturbed by asthma but the study was far too underpowered with 9 patients to draw any conclusions.

Selby et al.[88] designed an extensive set of outcome measurements to compare inhaled salmeterol with oral theophylline in patients with nocturnal asthma. The investigators compared sleep quality,

Table V. Summary of randomised, placebo-controlled, crossover trials comparing extended-release theophylline (T) with inhaled salmeterol (Sm) in patients with nocturnal asthma

No. patients completing study (randomised)	Treatment duration	Drug (formulation)[a]	Dose	Theophylline serum concentrations after randomisation (mg/L)	Lung function at clinic	Lung function at home	Night-time symptoms	Rescue bronchodilator use	Other outcome measures	Reference
98 (141)	2wks	T ('Theodur') Sm (MDI)	T idt Sm 50 bid	45% > 10μg 92% > 5μg 2% > 20μg	FEV_1 NS	Morning PEF Sm > T	% decrease in awakening nights Sm > T	Fewest Sb nights Sm > T		86
18 (19)	15 days	T (NR) Sm (NR)	T idt Sm 42μg bid	Mean 12.2 (0.7 SEM) on day 14	FEV_1 change from baseline Sm > T T = Pl	Mean morning PEF Sm > T (days 8-15) Sm > Pl (days 1-15) T > Pl (days 1-7)	Reducing nocturnal awakenings Sm > Pl	Fewest patients requiring Sb Sm > Pl Sm > T	PSQI Global Scores Sm and Pl improved; T did not Polysomnography sleep studies Sm = T + Pl except less Stage 2 with T *vs* Pl	87
15 (15)	2wks	T ('Theodur') Sm ('Diskhaler')	T idt and da Sm 50μg	> 8 mg/L except in 1 patient	FEV_1 night 14 Sm = T FVC night 14 Sm = T	Mean PEFR Sm = T	Nights without asthma awakenings Sm = T (p = 0.10)	nr	Sleep architecture Sm = T except fewer microarousals per hour of sleep with Sm Psychometric testing Sm = T	88
9 (11)	3wks	T ('Uniphyllin Continus') Sm (MDI)	T da to 15-20 mg/L Sm 50μg bid	NR	NR	PEFR No difference	Nights with asthma symptoms Sm = T	Puffs/day Sm = T	Sleep architecture was main outcome measure Sm = T except Sm had fewer movement arousals per hour	89
72 (96)	28 days	T (NR) Sm (MDI)	T 300mg bid plus ketotifen 1mg bid Sm 50μg bid	NR	FEV_1 end of first treatment period Sm > TK	am PEFR and FVC Sm = TK	Totally free of nocturnal symptoms Sm > TK % of symptom-free nights Sm > TK	Least Sb intake during night Sm > TK		90

a Use of a trade name is for product identification purposes only, and does not imply endorsement.

bid = twice daily; **da** = dose of theophylline adjusted as needed during study based on serum theophylline concentrations; **FCV** = forced vital capacity; **FEV_1** = forced expiratory volume in 1 second; **idt** = individualised dose titration of theophylline prior to randomisation so as to maintain theophylline concentration 10-20 mg/L; **MDI** = metered dose inhaler; **NR** = not reported; **NS** = not significant; **PEF** = peak expiratory flow; **PEFR** = peak expiratory flow rate; **PSQI** = Pittsburgh Sleep Quality Index, a self-administered questionnaire with 4 point scale; **Sb** = salbuterol (albuterol); **TK** = combination of extended-release theophylline and ketotifen.

6 measures of psychometric performance, and then nocturnal asthma control. One unique feature of the study design, in addition to the demanding measures for such a small number of patients, was that theophylline dosages were increased based on the theophylline value on day 3 by a physician independent of the study. Placebo dosages were adjusted with similar frequency to maintain blinding with the investigators. Regarding the psychometric performance outcome measures, fewer errors were made in the continuous attention test of visual vigilance during salmeterol therapy ($p < 0.05$). All other measures were similar between the 2 treatment groups. On nights 13 and 14 after the psychometric tests, all patients spent the night in a sleep laboratory with standardised lights out and lights on times. Patients receiving salmeterol had fewer microarousals than those receiving theophylline ($p < 0.05$) but no differences were detected in any other objective sleep quantity or quality measure.

Patients recorded at least thrice daily PEF and daily subjective sleep quality scores on a 5-point scale. The presence of possible adverse effects were sought by predetermined, standardised open questions during and at the end of each study. On day 14 of each study arm, patients and investigating physician made a subjective assessment retrospectively of asthma control on a 4-point scale. Patients also completed a 100mm visual analogue scale on quality of life and on quality of asthma control. On day 14 of the second arm, the patients were asked to express a preference between the 2 study arms. Neither the physicians' nor the patients' retrospective subjective assessment of asthma control differed between the salmeterol or theophylline treatment arms. Subjective sleep quality while receiving salmeterol was not different than while receiving theophylline, although it tended ($p = 0.07$) to be better with salmeterol. GI adverse effects of nausea and dyspepsia were similar with both salmeterol and theophylline. Quality of life score was more favourable with salmeterol than theophylline ($p = 0.05$) but the quality of asthma control was the same between salmeterol and theophylline. The blinded treatment preference was no different between treatments.

During nights 8 to 14 there was no difference between early morning PEF values in the 2 treatment groups. The number of nights without awakenings due to any reason during the nights spent at home, however, was higher with salmeterol than theophylline ($p < 0.01$). The authors conclude that in patients with nocturnal asthma, there was no major clinical advantage, but a small benefit in sleep quality, quality of life and daytime cognitive function with salmeterol. The outcome measures in these 15 patients are numerous, but used alone they cannot be interpreted. Only 15 patients were able to complete this study and no power analysis either pre-study or post-study was provided.

Fjellbirkeland et al.[86] compared inhaled salmeterol and individually dose-titrated, sustained-release theophylline in a large double-blind, multicentre, crossover study of 141 patients. The morning PEF was higher in the salmeterol-treated patients than those who received theophylline ($p < 0.001$) with a mean difference of 161 min^{-1} [95% confidence interval (CI) 8, 241 min^{-1}]. The increase in morning PEF with salmeterol was highest in a subgroup of patients whose pre-study asthma medication had not included theophylline with a mean difference of 271 min^{-1} (95% CI 15, 391 min^{-1}; $p < 0.001$). The percentage of nights where the patient awoke because of asthma fell to a median of zero in both salmeterol treatment groups that included patients whe were new to theophylline and was better ($p < 0.001$) than the theophylline treatments. When compared with baseline values, patients who received salmeterol had fewer nights where additional salbutamol was required compared with those patients who received theophylline ($p = 0.013$). Of note is the decrease in STCs during randomisation compared with the pre-randomisation individualised dose titration period of 2 weeks. Before randomisation, all patients had to achieve a mean STC of 10 to 20 mg/L using a theophylline assay kit as assessed at each of the 15 centres by an independent physician. After randomisation theophylline serum samples were available throughout

the study for 90 of the 141 patients. In these 90 patients, 92% achieved a mean STC of ≥5 mg/L but only 45% of patients had concentrations ≥10 mg/L. Both the salmeterol and theophylline treatments were well tolerated, however, the incidence of adverse events was higher in patients receiving theophylline (88 reports) compared with 57 reports in the salmeterol group. Of the 43 patients who withdrew after randomisation, 29 withdrew because of an adverse event. Eleven patients were taking salmeterol, 15 theophylline and 3 withdrew during the washout period. Only 4 of the adverse event reports during the salmeterol treatment and 9 during theophylline treatment were considered drug related.

Muir et al.[90] compared salmeterol with a combination of slow-release theophylline and ketotifen. Patient withdrawals were similar in both treatment groups. The number of patients totally free of nocturnal symptoms during the last week of each treatment period was 46 and 15% for the first period and to 39 and 26% for the second period for salmeterol and slow-release theophylline plus ketotifen, respectively ($p < 0.01$). The percentage of symptom-free nights was greater with salmeterol 67 versus 43% ($p < 0.025$). Rescue salbutamol inhalations were increased in the theophylline/ketotifen group ($p < 0.025$). At the end of the first 28-day treatment period, the mean FEV_1 was higher ($p < 0.05$) in the salmeterol group than in the slow-release theophylline/ketotifen group. At the end of the first period, the difference between treatment groups was not significant for morning PEF, FVC and FEV_{25-75}. Although no major drug-related adverse drug events were reported, 26 minor adverse drug events were reported; 4 in 3 salmeterol-treated patients and 22 (mainly GI disorders) in 15 slow-release theophylline/ketotifen treated patients ($p = 0.004$).

3.2.2 Theophylline versus Long-Acting Oral β_2 Agonists

Sustained-release theophylline has been compared with 2 oral controlled-release β_2 agonists, salbutamol[91] and terbutaline.[92,93]

Vikka et al.[92] compared terbutaline 7.5mg twice daily with a once daily evening dose of theophylline, which had been previously individually titrated to each patient. Morning PEF was higher with theophylline than terbutaline ($p < 0.01$) and mean value of symptom scores for morning dyspnea was lower ($p < 0.01$). There was no difference between treatments in the degree of dyspnoea during the night and the day, cough, sputum or number of puffs needed of short-acting β_2 agonist inhalations. In a double-blind, randomised crossover trial of 11 patients, Heins et al.[93] also found controlled-release theophylline to be more effective than controlled-release terbutaline 15mg twice daily. Supplemental β_2 agonist use decreased ($p < 0.05$), nocturnal wheezing decreased ($p < 0.05$), and more patients preferred the theophylline. There was no clinical difference in PEF between the 2 treatments.

A newer controlled-release salbutamol formulation has shown comparable benefits to a sustained release form of theophylline anhydrous capsules in a 12-week randomised, double-blind, parallel-group study in 124 patients.[91] This particular form of controlled release salbutamol is formulated as an elementary osmotic pump and is different from earlier formulations.[91] The study was not designed to answer questions specifically about nocturnal asthma signs or symptoms but changes in lung function were reported. There were no differences between the 2 treatments (salbutamol 8mg every 12 hours and individualised theophylline) in changes from baseline for FEV_1, PEF_{25-75} or FVC between treatments in weeks 1, 6 or 12.

3.2.3 Salmeterol versus Other Long-Acting β_2 Agonists

Since 1994, inhaled salmeterol has been compared with oral terbutaline,[94] the new controlled-release salbutamol,[95] bambuterol[96,97] and a single dose study with inhaled formoterol[98] (table VI).

Brambilla et al.[94] found the number of awakening-free nights was higher with salmeterol (5.3 ± 2.4) than sustained release terbutaline (4.6 ± 2.3; $p = 0.006$). The number of patients no longer awakened at night over the last week of treatment increased with salmeterol inhalations ($p = 0.003$ versus terbutaline). There was no difference between

Table VI. Summary of randomised, controlled trials comparing inhaled salmeterol (Sm) with other long-acting bronchodilators in patients with nocturnal asthma symptoms

Study design	No. patients completing study (randomised)	Treatment duration (wks)	Comparison drug	Drug dose	Lung function at home	Night-time symptoms	Rescue bronchodilator use	Other outcome measures	Reference
R, Pl, DB, DD, MC, P	151 (159)	2	TSR oral tablets	Sm 50μg bid TSR 5mg bid	Morning PEF Sm > TSR Reduction of PEF daily variations Sm > TSR	No. awakening-free nights Sm > TSR % patients with no awakenings Sm > TSR	Night use Sm = TSR		94
R, Pl, DB, DD, MC, CO WO = 7.9 days	44 (56)	3	CSR tablets	Sm 50μg bid CRS 4mg am, 8mg hs	am PEFR: Sm = CRS am FEV_1: Sm = CRS % overnight change PEF: Sm = CRS % overnight change FEV_1: Sm = CRS	Adjusted means for symptoms Sm > CRS % nights without awakening Sm > CRS % patients with no awakenings Sm = CRS	Fewest puffs/day Sm > CRS	Non-blind patient preference Sm > CRS 18 *vs* 12	95
R, Pl, DB, DD, IC, P	87 (117)	6	B, oral	Sm 50μg bid CRS 20mg hs	Morning PEF change from baseline Sm = B % overnight fall in PEF Sm = B	Awakenings in night Sm = B % nights with awakening Sm = B	No. puffs at night Sm = B		96
R, Pl, DB, DD, MC, P, ED, IC	118 (135)	6	B, oral	Sm 50μg bid CRS 20mg hs	Morning PEF change from baseline Sm = B % overnight fall in PEF Sm = B	Awakenings in night Sm = B % nights with awakening Sm = B Asthma symptoms Sm = B	No. puffs at night Sm = B		97

B = bambuterol; **bid** = twice daily; **CRS** = controlled release salbutamol; **DB** = double-blind; **DD** = double dummy; **ED** = electronic diaries used by patients; **FEV_1** = forced expiratory volume in 1 second; **hs** = dose administered at night or late evening; **IC** = inhaled corticosteroid use by all patients; **MC** = multicentre; **MDI** = metered dose inhaler; **NR** = not reported; **P** = parallel group; **PEF** = peak expiratory flow; **Pl** = placebo controlled; **R** = randomised; **SR** = sustained release; **TSR** = terbutaline SR; **WO** = washout period.

treatment groups in rescue bronchodilator use at night. Mean morning PEFs were higher ($p = 0.04$) and the PEF daily variations were reduced ($p = 0.01$) with salmeterol over sustained release terbutaline.

Martin et al.[95] compared the controlled release formulation of salbutamol with inhaled salmeterol in 46 patients with nocturnal asthma. PEF and FEV_1 improved similarly with both treatments. The trial favoured salmeterol, however, since the number of puffs of rescue short-acting salbutamol use was less ($p = 0.001$) and the percentage of patients with no night-time awakenings increased with salmeterol ($p = 0.021$).

Bambuterol, an oral terbutaline prodrug with a prolonged duration of bronchodilator action, which is administered once daily in the evening was compared with inhaled salmeterol in 2 studies.[96,97] All lung function tests and night-time symptoms were similar with both treatments in both studies.

In a single dose randomised study, inhaled salmeterol 50μg was compared with inhaled formoterol 20μg in 30 patients for changes in FEV_1 and airway conductance.[98] All patients were considered to have moderately severe asthma. Formoterol and salmeterol were similar except that formoterol had a more rapid onset of action and a greater mean change in FEV_1 in the first 10 minutes. No study comparing inhaled salmeterol with formoterol for the prolonged treatment of patients with asthma was identified.

A 6-month manufacturer-supported, randomised, non-blind, parallel group study compared the clinical efficacy of formoterol dry powder capsule 12μg twice daily and salmeterol dry powder 50μg twice daily in the treatment of patients with reversible obstructive airways disease.[99] Of the 482 patients randomised (equal numbers in the 2 treatment groups), 428 completed the study. All patients were using regular inhaled corticosteroids for at least 1 month before study enrollment. For the primary efficacy end-point, mean morning dose PEF during the last 7 days of treatment for each month, the drugs were similar. For mean evening pre-dose PEF, the estimated treatment contrasts showed a trend towards superiority of formoterol over salmeterol, which was statistically significant at 2, 3 and 4 months ($p < 0.05$, estimated contrasts 7.27, 10.45 and 10.51 L/min, respectively).

The use of rescue inhalers decreased to less than half that at baseline with both drugs. Mean symptom scores improved similarly for both drugs for both night- and daytime symptoms, as recorded during the last week of each study month. Both drugs were equally well tolerated as reported by both the number and type of adverse events. When considering only adverse events that were assessed by the investigator as more likely to be attributed to the study drugs, events were reported in 32 (13%) of patients who received formoterol and 21 (9%) patients who received salmeterol. These adverse effects included headache (7 in the formoterol group and 11 in the salmeterol group), tremor (5 with formoterol and 2 with salmeterol), asthma exacerbation (4 in each group) and palpitations (all 4 in the formoterol group).[99]

3.2.4 Non-Salmeterol Long-Acting β_2 Agonists

In a non-blind, randomised, crossover study, Gunn et al.[100] compared the efficacy, tolerance and patient acceptance of bambuterol with the new formulation of controlled release salbutamol. Patients received 3 weeks each of bambuterol 20mg once daily every night to salbutamol 8mg twice daily. Both drugs equally improved the nocturnal asthma symptoms but patients preferred once daily bambuterol. Patients felt they had less shakiness and other fewer adverse events with bambuterol compared with the controlled-release salbutamol.

4. Assessing Risks and Benefits

4.1 Theophylline

Theophylline, although an effective therapy for certain patients with nocturnal asthma, can be difficult to use safely. It has a narrow therapeutic index with a desired serum concentration range of 5 to 15 mg/L (28 μmol/L to 83 μmol/L).[1] Toxicities can occur even at STCs just above the therapeutic range. As a result, STCs should be regularly monitored to ensure patient safety. Theophylline clear-

ance and consequently STC can be affected by many factors. Heart failure, liver disease and concomitant drugs (e.g. erythromycin, ciprofloxacin, cimetidine) can decrease clearance (and increase STC), cigarette smoking and several medications (e.g. phenytoin, rifampin) increase theophylline clearance.[101,102] Despite these well documented clearance factors, toxicity is still a problem. Examples of adverse drug reactions associated with theophylline are listed in table VII.

In an evaluation of 5537 consecutive STCs obtained over a 2-year period from the emergency departments of 2 hospitals, 10% of STCs were found to be greater than 20 mg/L and 2.8% greater than 30 mg/L.[103] The most common causes of elevated STCs were self-motivated ingestion of excessive dosages (usually patient error or taking extra doses for symptom relief), prescription errors, and the presence of factors affecting theophylline clearance. Of the 116 patients with STCs above 30 mg/L, 7% experienced severe (seizure, sustained ventricular tachycardia, shock) or life-threatening (status epilepticus, ventricular fibrillation, cardiac arrest) toxicity. While only 6% of the patients in this study experienced seizure, it is important to remember that seizures can occur suddenly without warning and may occur at the lower toxic STCs (i.e. 25 mg/L). The most common cardiovascular manifestations of theophylline toxicity, which occurred in 74% of patients, were paroxysmal supraventricular tachycardia, atrial fibrillation or flutter, and multifocal atrial tachycardia.

Bittar and Friedman[104] examined the STCs in 100 patients and found that there was a progressive increase in heart rate as the STC increased (researchers used the formerly accepted therapeutic STC range of 10 to 20 mg/L). Arrhythmias occurred more often in patients where STCs were greater than 10 mg/L and multifocal atrial tachycardia occurred in patients with STCs between 14 and 38 mg/L.

As a follow-up to a study of theophylline toxicity in 1993,[105] Shannon[106] conducted a longitudinal cohort study in 356 patients with STCs greater than 30 mg/L (167 μmol/L) for 125 months.

Table VII. Theophylline adverse drug reactions related to serum theophylline concentrations (STC)

STC	Adverse effect
5-15 mg/L	Nausea, vomiting, headache, diarrhoea, insomnia, irritability (generally rare and self limiting)
>20 mg/L	Nausea, vomiting, diarrhoea, headache, insomnia, irritability palpitations, tachycardia, arrhythmias, seizures[a]
>35 mg/L[b]	Hyperglycaemia, hypokalaemia, hypotension, life-threatening arrhythmias, seizures (including status epilepticus), shock, cardiopulmonary arrest

a Seizures are possible, yet rare, at serum theophylline concentrations <30 mg/L.

b Especially with long term overmedication in the elderly.

Minor toxic effects, including sinus tachycardia (mean pulse of 128 beats/minute), did not correlate with peak theophylline concentrations. Seizures occurred in 8.1% and were usually brief. Status epilepticus, however, did occur in 7 patients. A broad range of cardiac arrhythmias occurred in almost 21% of patients. 144 patients were chronically overmedicated; these patients tended to be older (mean = 51.5 years) with a mean STC of 48 mg/L. Most cases of long term overmedication were as a result of an administration error (either by physician or patient). It should also be noted that new onset or change in cardiac and hepatic disease, as well as prescribing of an interacting drug, were also common causes of long term overmedication. Schiff et al.[107] reported similar findings in 1991, in addition to finding errors in the management of toxicity.

In the early 1990s, Johnston and Jenkinson[108] investigated the knowledge, practices and attitudes of general practitioners towards the use and monitoring of theophylline. They mailed questionnaires to all general practitioners in Nottinghamshire, England, of which 236 valid forms were returned. Alarmingly, 76% of responders did not check STCs upon therapy initiation and 48% never checked a STC. When physicians were asked to identify factors affecting theophylline concentrations, only

5% could do so correctly and 51% identified less than half.

There is also concern that theophylline causes behavioural and cognitive changes in children. Milgrom and Bender[109] undertook an extensive review of the available research in this area and found the data conflicting. It appears that while parents and some teachers report problematic behaviour, objective evidence does not support this.

4.2 Long-Acting β_2 Agonists

Long-acting inhaled β_2-agonists are generally well tolerated and examples of common adverse effects are found in table VIII. In the early 1990s, Clark et al.[110] published 3 case reports of young patients with asthma who developed respiratory arrest while using salmeterol. In another letter, a physician wrote that 2 of his elderly patients experienced fatal respiratory arrests and were found with their inhalers in their hands.[111] It is possible that these 2 patients were using their salmeterol as a 'quick reliever'. These anecdotal reports led some to question the safety of long-acting β_2 agonists in the treatment of some patients with asthma.

Castle et al.[112] conducted a nationwide surveillance study of salmeterol in the UK. They followed 16 787 patients taking salmeterol and 8393 taking salbutamol for 16 weeks. There were 12 deaths from asthma in the salmeterol group (0.07%) and 2 in the salbutamol group (0.02%). The 3-fold difference in mortality rates was not statistically different ($p = 0.105$).

A prescription-event monitoring study observed 15 407 patients on salmeterol for 1 year.[113] 73 deaths occurred that were attributable to asthma, but only 39 of these patients were taking salmeterol in the last month before their death. It was considered possible that salmeterol was related to death in 4 of the 39 patients. Even though there was a temporal relationship between salmeterol use and death in these 4 patients, there was no evidence to support salmeterol as a cause of death.

Devoy et al.[114] examined asthma mortality in England and Wales after salmeterol became available. After 2 years of product availability, patient exposure totaled 57 000 patient-years. No increase in asthma mortality was found.

Table VIII. Long-acting β_2 agonists adverse drug effects

Organ system	Adverse effects
Cardiovascular	Palpitations,[a] tachycardia[a]
Central nervous system	Tremor, dizziness, vertigo, shakiness,[a] nervousness,[a] headache
Gastrointestinal	Nausea[a], vomiting
Respiratory	Cough,[a] wheeze,[a] throat dryness[a] or irritation[a]

a Incidence reported between 1 and 3%.

A randomised, double-blind study comparing formoterol and salbutamol found that patients did not experience a worsening of asthma control over the 3-month study.[56] In a 12-month study comparing salmeterol with salbutamol, Britton et al.[50] reported that the proportion of patients who experienced an exacerbation did not increase with prolonged therapy. Another double-blind, crossover study in 91 children aged 6 to 15 years found that exacerbation rates did not differ between patients given twice daily salmeterol 50μg and placebo.[115]

There are some reports of acute bronchospasm developing after salmeterol use.[116,117] Six cases of acute bronchospasm occurred after patients inhaled salmeterol with an MDI, but no cases were seen when these patients used the dry powder formulation.[116] This suggests that other components of the formulation cause the bronchoconstriction. A study of 11 850 patients found that compared with placebo MDIs containing chlorofluorocarbons and either oleic acid or lecitin dispersants, salmeterol MDI with the same chloroflurocarbons and lecithin, had significantly less ($p = 0.02$) bronchoconstriction. The authors suggest the chlorofluorocarbons combined with oleic acid (such as found in commercial salbuterol) are more likely to produce bronchoconstriction.[117] However, the data do not appear to support this conclusion.

Concern that long-acting β_2 agonists may cause patients to develop tachyphylaxis and therefore not respond to supplemental doses of short-acting formulations has been examined.[118-121] One study followed 66 patients receiving formoterol for 5 years and found no tolerance indicated as evi-

denced by no required dose increases.[118] Several other studies have also shown no tolerance to the effects of supplemental salbutamol in patients receiving a long-acting β_2 agonists when patients were followed for a 1 year.[119-121]

Although no tolerance to the bronchodilator efficacy of long-acting β_2 agonist has been shown, some studies have shown loss of bronchoprotection (i.e. with methacholine challenge).[122] The clinical significance of this finding is yet to be determined.

5. Cost Considerations

The economic assessment of asthma therapy is difficult as both direct and indirect costs must be considered and few studies have done so. The cost of asthma drugs is a major component in the direct cost of asthma management.[123,124] This is important, as patients who are without insurance must bear the cost of therapy alone. A 1-month supply of 100 generic, slow-release theophylline 100mg can cost as little as $US10 per month. Brand name theophylline products are more expensive, ranging from US$30 to 40 per month. The cost of salmeterol inhalers include $US37 for the Diskus dry powder 50 μg/dose (28 doses) and approximately US$70 for a 13g canister aerosol inhaler.[125] More important than direct costs of drug acquisition, are indirect costs associated with physician office visits, emergency department visits and hospitalisations. Costs of monitoring STC must also be considered.

The cost of theophylline toxicity has been evaluated and a wide range of estimates has been proposed. A Veterans Administration Medical Center study proposed that the costs associated with theophylline toxicity was $US6432.11 per patient; however, this was for 2 patients who had a hospital stay of 2 weeks.[126] As a substantial number of patients with theophylline toxicity can be managed in the emergency department, the authors adjusted this figure to a cost of $US3255.62. Derby et al.[127] attempted to determine the risk of theophylline toxicity using the database for a large health maintenance organisation. The researchers found 30 hospitalisations from theophylline toxicity among 35 909 theophylline users over a 9-year period. Based on Derby's numbers, and previous cost estimates, Hamilton[128] calculated a figure of $US2.72 per patient receiving theophylline may be attributed to theophylline toxicity.

6. Quality of Life

6.1 Instruments for Measuring Asthma Quality of Life

Two common disease specific quality of life instruments for asthma often used are the Living with Asthma Questionnaire (LWAQ) and the Asthma Quality of Life Questionnaire (AQLQ). The LWAQ contains 11 domains; social/leisure, sport, holidays, sleep, work/other activities, colds, mobility, effects on others, medication usage, sex, and dysphoric states and attitudes.[129] It also examines patient knowledge of the functional limitation imposed by the illness and how much distress these limitations cause. The AQLQ was developed by Juniper et al.[130] and covers 4 domains; activity limitation, symptoms, emotional function and environmental stimuli. At each follow-up visit, patients are shown their previous responses and then asked to re-evaluate based on the last 2 weeks.

In a double-blind, parallel group study, 120 patients with asthma received either salmeterol 50μg twice daily or salbutamol 400μg twice daily.[131] In addition to respiratory end-points, the researchers evaluated the measurement properties of 4 quality of life questionnaires. Two of the instruments, LWAQ and the AQLQ, were disease specific and the other 2, the Sickness Impact Profile and rating scales, were generic. The AQLQ, LWAQ and the rating scales were responsive to within-patient improvements in the salmeterol group and showed some within-patient improvement in the salbutamol group. Statistically significant improvement with salmeterol was seen only with the AQLQ and rating scales ($p = 0.022$ and 0.045, respectively). The researchers determined that the AQLQ was more responsive and more valid than the LWAQ.

6.2 Salmeterol versus Theophylline

The results of 2 randomised, double-blind, double-dummy, placebo-controlled parallel-group studies comparing salmeterol, individually dose-titrated theophylline and placebo were combined and examined.[85] Patient satisfaction with previous asthma medications and study medications was assessed. At baseline, patients rated previous therapies and then rated their study medications at weeks 4 and 12. Patient satisfaction was higher with salmeterol compared with either theophylline or placebo ($p < 0.002$); theophylline was rated higher than placebo only at week 12 ($p = 0.01$).

Di Lorenzo et al.[132] also compared quality of life with salmeterol 50μg twice daily and sustained release theophylline twice daily. Patients filled out the Short Form (SF-36) Health Survey at the end of the run-in period and at 3, 6, 9 and 12 months. Quality of life measures improved with both drugs from baseline. Salmeterol measures were higher than theophylline in 3 domains; physical functioning after 3 months ($p = 0.02$), change in health perception at 9 months ($p = 0.03$) and social functioning at 12 months ($p = 0.04$).

Yancey et al.[133] reported patient satisfaction in patients with asthma who received either twice daily salmeterol 42μg or individually, dose-titrated theophylline added to a regimen of inhaled corticosteroids. This was a 12-week retrospective, randomised, double-blind, double-dummy, parallel-group study of patients ≥12 years of age, which compared addition of salmeterol or theophylline with therapy with or without inhaled corticosteroids. In both subgroups of patients, patients receiving salmeterol reported a higher degree of satisfaction than those receiving theophylline ($p \leq 0.04$).

6.3 Salmeterol versus Salbutamol

A 12-week multicentre, randomised, double-blind, placebo-controlled crossover trial assessed the quality of life in patients with asthma taking salmeterol 50μg twice daily, salbutamol 400μg 4 times daily or placebo.[134] Using the AQLQ, the investigators demonstrated that salmeterol was superior to placebo ($p < 0.001$) and salbutamol ($p < 0.0001$) on overall quality of life. Differences between salbutamol and placebo were not clinically significant. Another trial compared the same drug regimen and also showed an improvement in quality of life using the LWAQ after both treatments.[135] This imporvement was more sustained over the 12 months with salmeterol. Two other studies that compared salmeterol 42μg twice daily and salbutamol 180μg 4 times daily on asthma quality of life using the AQLQ also found a greater benefit in patients using salmeterol.[136,137]

6.4 Salmeterol versus Placebo

474 patients took part in a randomised, double-blind, placebo-controlled, parallel-group study conducted to evaluate the effect of salmeterol on quality of life.[42] The AQLQ was given to patients at baseline, day 1 and weeks 4, 8 and 12 of the study. At baseline, there was no difference between groups, but at weeks 4, 8 and 12 both treatment arms showed significant improvement in scores ($p \leq 0.001$). At weeks 4, 8 and 12, the salmeterol group had greater improvement than the group using only supplemental salbutamol ($p \leq 0.005$).

A retrospective analysis of 8 clinical trials compared the quality of life in patients receiving salmeterol versus other therapies (in 6 trials, other therapy was placebo).[138] The AQLQ was administered at baseline and weeks 4, 8 and 12. Salmeterol resulted in greater improvement in quality of life than the other therapies combined ($p < 0.001$). Even though the patients taking other therapies showed improvement from baseline, the salmeterol treatment was consistent for at least moderate change (increase from baseline ≥1) in the global score as well as all domains.

6.5 Salmeterol versus Formoterol

482 patients received either formoterol 12μg dry powder capsules inhaled via Aerolizer® or salmeterol 50μg powder via the Diskhaler®, both twice daily, in a non-blind, multinational study over 6 months.[139] The St George's Respiratory

Questionnaire was used as the assessment tool and patients completed it at baseline and after 3 and 6 months. Baseline scores were similar between the 2 groups. Quality of life at 3 and 6 months improved from baseline equally in both the formoterol and salmeterol treatment groups ($p < 0.0001$).

7. Conclusion

Long-acting inhaled β_2 agonists and long-acting oral bronchodilators are effective in managing nocturnal asthma that is inadequately controlled by anti-inflammatory agents.

In patients with nocturnal symptoms despite low to high doses of inhaled corticosteroids, the addition of salmeterol has been demonstrated to be superior to doubling the inhaled corticosteroid dose.

Three of 5 studies comparing salmeterol with theophylline reveal salmeterol to be superior to theophylline (e.g. morning PEF, percent decrease in awakenings, and need for rescue salbutamol) while 2 studies found the therapies of equal efficacy. Investigations comparing salmeterol with oral long-acting β_2 agonists reveal salmeterol to be either superior or at least equivalent in efficacy to other oral agents.

Long-acting inhaled β_2 agonists are generally well tolerated. If theophylline therapy is to be used safely, clinicians must be familiar with numerous factors that alter its clearance, and they must be prepared to use appropriate doses and monitor serum concentrations. Regarding quality of life considerations, long-acting inhaled β_2 agonists have been shown to be preferred to other long-acting bronchodilators. Examination of costs for these therapeutic options reveals that evening only doses of long-acting oral bronchodilators are less expensive for cost of the medication compared with inhaled bronchodilators. Costs of monitoring serum concentrations, risks, quality of life and other outcome measures must be weighed versus cost of the medication.

Long-acting inhaled β_2 agonists (salmeterol and formoterol) are the agents of choice for managing nocturnal asthma in patients who are symptomatic despite anti-inflammatory agents and other standard management (e.g. environmental control). Consistent with guidelines to use inhaled corticosteroids for persistent asthma, manufacturers will soon be marketing the combinations of formoterol with budesonide and salmeterol with fluticasone. Bambuterol may provide a once daily oral alternative to inhaled β_2 agonists in some patients in the countries it is available. More comparative studies between the long-acting inhaled β_2 agonists and bambuterol are needed before it can routinely be recommended. The long-acting inhaled β_2 agonists are effective, well-tolerated and are associated with improved quality of life.

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