

3476 patients were treated. Incidence of any adverse events (AEs), serious AEs and investigator-defined drug-related AEs was similar across treatment groups within each trial. AEs reported by  $\geq 5\%$  of patients were similar across all treatment groups within each trial (Table). The number of cardiovascular AEs was small in all five studies and comparable between tiotropium Respimat® and placebo. No deaths occurred in any trial. Conclusion: Once-daily tiotropium Respimat® is well tolerated and comparable with placebo in adult patients with symptomatic asthma receiving at least low- to high-dose ICS.

**P232 TREATMENT OF ALLERGIC RHINITIS WITH THEOPHYLLINE : A DOUBLE-BLIND, RANDOMISED, Crossover STUDY**

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**Background** Allergic rhinitis and Asthma are considered as 'one airway disease'. Theophylline has been used as a bronchodilator in asthma for decades but more recently its anti-inflammatory properties have been identified. We hypothesise that treatment with low dose theophylline in patients with persistent allergic rhinitis is likely to improve the total nasal symptom scores and there by demonstrate a clinically meaningful difference.

**Methods** This was a single centre double- blind, randomised, placebo-controlled cross-over study of the effects of theophylline (one capsule of Theophylline 200 mgs as Uniphyllin continus twice a day for 4 weeks) in 21 patients with persistent allergic rhinitis in Norwich, U. K. Reference: NCT0113278. Primary outcome was Total Nasal Symptom Score (TNSS) after each intervention period. Secondary endpoint measures were differences in the domiciliary average total nasal symptom score, differences in nasal peak inspiratory flow (PNIF), differences in domiciliary nasal peak inspiratory flow and difference in Sino-Nasal Outcome Test (SNOT)-22.

**Results** Primary Endpoint

There was no significant ( $p = 0.276$ ) difference in Total Nasal Symptoms scores during Theophylline treatment period and placebo period, mean (SD) (Table). The intention-to-treat analysis results were in keeping with the per protocol analysis.

**Secondary End points**

PNIF in the Theophylline period was  $112.38(\pm 43.49)$  compared to the placebo period  $122.86(\pm 53.77)$ ,  $p = 0.171$  (Table). There was no change in SNOT-22 ( $p = 0.867$ ) between treatment periods but there was a non-significant improvement with Theophylline ( $39.00 \pm 19.78$ ) compared to placebo ( $38.00 \pm 19.63$ ) treatment period. There was a non-significant improvement in the domiciliary total nasal symptom scores (TNSS) between Theophylline ( $3.53 \pm 2.35$ ) and placebo ( $2.81 \pm 2.46$ ). Nasal scrape samples were stained with HDAC2 antibodies and the signals were very weak.

**Abstract P232 Table 1** Changes after intervention between treatments: Per Protocol Results

Outcome Variable	Placebo	Theophylline	p Value	95% CI
	Mean (SD)	Mean (SD)		
TNSS	4.90 (3.08)	4.14 (2.33)	0.276	-0.76 (-2.13,0.61)
PNIF	122.86 (53.77)	112.38 (43.49)	0.171	-10.48 (-25.49,4.54)
SNOT-22	38.00 (19.63)	39.00 (19.78)	0.867	0.63 (-6.67,7.92)

**Conclusion** This is the first study evaluating Theophylline in persistent rhinitis. Low-dose Theophylline had no significant effects on Total nasal Symptom scores; Rhinosinusitis symptoms and nasal patency assessed using peak nasal inspiratory flow. There was a non-significant improvement in the total nasal symptom scores and sino-nasal outcome test and domiciliary nasal scores.

**P233 LONG-TERM IMPACT OF INHALED CORTICOSTEROIDS ON BONE MINERAL DENSITY AND FRACTURE RISK IN PATIENTS WITH ASTHMA: SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Background** A recent meta-analysis of 16 randomised controlled trials (RCTs) and 7 observational studies demonstrated a modest but statistically significant increase in fracture risk with inhaled corticosteroid (ICS) use in chronic obstructive pulmonary disease. However, it is not clear whether ICS use has similar skeletal adverse effects in patients with asthma. We aimed to evaluate the association between ICS and fractures and changes in bone mineral density when used for  $>12$  months in asthma.

**Methods** We initially searched MEDLINE and EMBASE in July 2013, and performed an updated PubMed search in June 2014. We used a combination of search terms involving drug name and adverse effects of interest, and we also hand-searched reference lists of existing systematic reviews and trial reports. We selected RCTs and controlled observational studies of any ICS vs non-ICS control treatment for asthma (at least 52 weeks duration). Meta-analysis of odds ratios was conducted using RevMan 5.3 with the primary outcome measure being fracture events. We also analysed mean differences in bone mineral density (gram per cm squared) using inverse variance method. Heterogeneity was assessed using the I<sup>2</sup> statistic.

**Results** We selected nine RCTs and 11 observational studies for the meta-analysis. There was no significant association between ICS and fractures in children in one RCT, or in a pooled analysis of two observational studies, (OR 1.02, 95% CI 0.94–1.10). No significant fracture risk in adults was reported in 4 observational studies (pooled OR 1.09, 95% CI 0.45–2.62). Meta-analysis of bone mineral density at the lumbar spine did not show significant reductions with ICS use in children (three RCTs and three observational studies), or in adults (three RCTs and four observational studies). Similarly, meta-analysis of bone mineral density at the neck of femur in adults did not demonstrate significant reductions compared to control (three RCTs and four observational studies).

**Conclusion** In our systematic review of 20 studies, use of ICS for  $>12$  months in patients with asthma was not associated with statistically significant adverse effects on bone mineral density or fractures.

**P234 IMPACT OF INHALED CORTICOSTEROIDS ON GROWTH IN CHILDREN WITH ASTHMA: SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Background** There are major concerns and uncertainty regarding a possible reduction in growth velocity and final height of children with asthma who are long-term users of inhaled corticosteroids (ICS). We aimed to evaluate the association between ICS use of >12 months and growth.

**Methods** We initially searched MEDLINE and EMBASE in July 2013, followed by a PubMed search updated to June 2014. We used a combination of search terms involving drug names and adverse effects of interest (such as growth or height), and we also hand-searched reference lists of existing systematic reviews and trial reports. We selected RCTs and controlled observational studies of any ICS vs non-ICS control treatment in patients with asthma (treatment duration of at least 52 weeks). Meta-analysis of continuous outcomes (growth velocity in cm/year or final height in cm) was conducted using RevMan 5.3. We analysed mean differences using inverse variance method, random effects model. Heterogeneity was assessed using the I<sup>2</sup> statistic.

**Results** We found 21 relevant studies (seventeen RCTs and four observational studies) after screening 1876 hits from the search. Meta-analysis of 16 RCTs showed a significant association between ICS use and reduction in growth velocity compared to controls (pooled Mean Difference -0.35cm/year, 95% CI -0.54 to -0.18). No significant reduction in growth velocity with ICS was reported in two observational studies of lower quality (pooled Mean Difference 0.03cm/year, 95% CI -0.61 to 0.67). Analysis of final adult height showed a mean reduction of -1.20 cm (95% CI -1.90 cm to -0.50 cm) with budesonide versus placebo in a high quality RCT. Meta-analysis of two lower quality observational studies found a non-statistically significant pooled mean reduction in final adult height of -0.85 cm (95% CI -3.35 to 1.65).

**Conclusion** Use of ICS for 12 months or more in children with asthma has a limited impact on annual growth velocity, with a slight reduction in final adult height. When interpreted in the context of the typical final adult height in the UK, ICS users may experience less than 0.7% reduction in height compared to non-ICS users.

#### P235 PREDNISOLONE/CORTISOL SPOT TEST OF NON-ADHERENCE IN CORTICOSTEROID-DEPENDENT ASTHMA

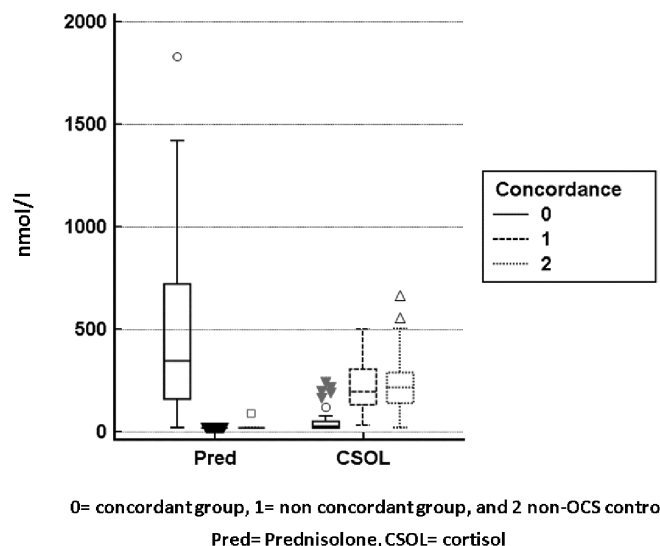
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**Background** About 40% of severe asthmatics require maintenance oral corticosteroids (OCS) for disease control. However, significant proportion of these patients continues to have poor disease control due to OCS unresponsiveness or non-adherence (Gamble 2009).

**Methods** Using a validated in-house developed liquid chromatography/mass tandem spectrometry (LQ/MSMS), we conducted spot measurement of serum prednisolone, prednisone and cortisol in 111 patients attending our severe asthma clinic over a 12 months period. Patients not on maintenance OCS comprised the control group. Suppressed cortisol (20nmol/l, were considered as compatible with adherence to OCS, whilst unsuppressed cortisol and undetectable prednisolone were considered as non-adherent. For validation purposes the test was repeated multiple times in few cases.

**Results** The prednisolone/cortisol spot test was conducted on 111 patients (79% females) with 44 (40%) were not on regular OCS (control group) and 67 (60%) on maintenance OCS. The



Abstract P235 Figure 1

spot test revealed non-adherence in 27/67 (40%) of patients and adherence in 40/67 (60%) of patients. The prednisolone/prednisone/cortisol assays were similar in non-adherent group and non-OCS group (figure). The mean daily prednisolone dose was 16.3, 20.1, and 0.0 mgs in the adherent, non-adherent and non-OCS groups respectively. Non-adherent patients had lower BMI, and higher exacerbations frequency, blood eosinophil count, and fraction exhaled nitric oxide than OCS adherent group. The non-adherent group resembled more the non-OCS group with regard to aforementioned parameters.

We conclude that this prednisolone/cortisol spot test is reproducible and diagnostic of non-adherence to OCS in 40% of patients on maintenance OCS, and should be routinely measured in severe asthma clinics to improve patients management.

#### P236 RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND BONE TURNOVER MARKERS IN SEVERE ASTHMA PATIENTS ON SYSTEMIC CORTICOSTEROIDS

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**Objectives** Measure bone turnover markers (BTM) CTx, P1NP and bone-specific alkaline phosphatase (BsALP) in a severe asthma population using systemic corticosteroids (SCS). Assess bone mineral density (BMD) change in regional severe asthma clinics.

**Background** Severe asthma often requires regular SCS use. SCS cause several adverse effects including reduced bone metabolism; resorption is increased and formation is decreased resulting in osteoporosis. DXA scans monitor BMD in the hip and spine every 3–5 years. BMD decrease is treated with bone sparing medication (BSM), but treatment is retrospective and response takes years to assess. BTM represent markers of systemic bone metabolism and may offer a more efficient alternative. CTx is a resorption marker, P1NP and BsALP are formation markers.

**Method** Patients attending Manchester or Belfast severe asthma clinic with two or more DXA scans were identified from case files. We measured BTM in Manchester severe asthma patients