

## LETTERS

Correspondence in relation to critical appraisal by Chapman *et al*

We write to raise some of a number of serious concerns about the recent paper 'Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal'.<sup>1</sup> We believe that it is written in a misleading fashion and contains important errors of fact, presentation and inference.

Tabulated data for symptoms, reliever use and exacerbations are presented only for patients randomly assigned to SMART. The lead author had access to the analysis by Bateman *et al*<sup>2</sup> that included full comparative data, as he wrote an accompanying editorial<sup>3</sup> and cited it in the present paper. It is unscientific, knowing that symptoms and reliever use outcomes are remarkably similar for fixed-dose and SMART, to not present all the data. It is worse then to imply that fixed-dose, even at the highest approved and marketed doses, achieved target levels of control in the populations studied.

The Cochrane review by Cates and Lasserson,<sup>4</sup> limited to comparisons of SMART compared with inhaled corticosteroid monotherapy, is wrongly invoked to support the contention that SMART does not reduce exacerbations compared with current best practice. Furthermore, the Cochrane authors' conclusions are selectively edited, removing their definition of current best practice and the qualifying phrase 'although results of five large trials are awaiting full publication'. Chapman and his co-authors are clearly aware of these data. Another Cochrane review that did examine SMART compared with fixed-dose combination therapy, concluding that SMART reduces severe exacerbations requiring oral corticosteroids but not hospitalisation, is not mentioned.<sup>5</sup>

Suggesting that SMART is proved to be associated with concerning airway inflammation is similarly disingenuous and is inconsistent with key messages constructed by the authors.<sup>6</sup> It is misleading to omit to say that eosinophil counts were in the range of control, that there was no difference in the number of patients who would have been eligible, per protocol, for a maintenance dose increase or decrease, and that fixed-dose combination treatment did not achieve greater improvement in any other asthma endpoint despite more than double the inhaled corticosteroid dose.

This paper purports to be a critical analysis and is published under 'Review' in the table of contents. The authors could have presented a balanced description of peer-reviewed evidence, robustly discussing the pros and cons of different medication regimens in clinical practice, but did not. Misrepresentation of scientific evidence is of grave concern. The appropriate response is for the paper to be retracted.

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## Single maintenance and reliever therapy (SMART) of asthma

We write to raise concerns about the recent paper by Chapman *et al* on single maintenance and reliever therapy (SMART) of asthma,<sup>1</sup> on the basis that it misrepresents published scientific evidence. The errors include:

1. Reporting outcome measures for one treatment arm from several double-blind studies (table 1 and accompanying text), but omitting the published data<sup>2</sup> for comparator arms from the same studies which would have been highly relevant to the authors' conclusions.
2. Selective omission of data from a peer-reviewed study<sup>3</sup> that would have avoided the authors' doubts about the validity of double-blind double-dummy methodology.

3. Selective citing of text from one Cochrane review,<sup>4</sup> with juxtaposition of text to imply that its conclusions were relevant to the studies described immediately before, and failure to cite a more relevant Cochrane review.<sup>5</sup>
4. Criticism of peer-reviewed publications on the basis of the use of outcome measures which were standard for other randomised controlled trials in asthma at the time (eg, criteria for exacerbations), or on the basis of omission of outcome measures which were either not available (eg, the adherence device used in a 1994 publication) or which have already been reported in a peer-reviewed publication (eg, a composite measure of asthma control<sup>2</sup>).

Misrepresentation of scientific evidence, whether in a data paper or a review, damages the scientific credibility of a journal. It is difficult to understand how the above errors could have passed through the usually rigorous *Thorax* peer review system, and this should be a matter of concern to the Editorial Board. The errors in the article, given their number and nature, cannot be addressed by simply publishing an erratum. We call on *Thorax* to respond appropriately.

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## Single maintenance and reliever therapy

The paper by Chapman *et al*<sup>1</sup> reviewing single maintenance and reliever therapy (SMART) in asthma is important in highlighting some of the inadequacies of existing research evaluating this treatment method.

The authors also claim that SMART fails to achieve adequate asthma control as measured by GINA criteria and provide a table detailing seven studies and associated control indices.

While these outcomes are far from ideal, the authors fail to point out that they were no worse than the comparator arm, which varied across the studies from conventional inhaled steroid therapy to fixed dose combination inhaled steroid/long-acting beta-agonist inhalers in high dose (ie, 'optimal therapy'). This inadequate control therefore reflects the severity of disease in the trial subject group rather than being a specific deficiency of SMART therapy.

It is disingenuous to claim that SMART fails to achieve adequate asthma control without pointing out that in this patient group standard, 'optimal', therapy does no better.

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## Authors' response

We thank our colleagues who have forwarded questions and comments to the editors of *Thorax*, thereby engaging in

a discussion of asthma strategy we believe to be long overdue. We must leave the editors of *Thorax* to respond to comments directed to their principles and policies, but suspect that our review was regarded by the editors and reviewers as a summary of single maintenance and reliever therapy (SMART) outcomes from a traditional yet unexplored perspective that might spark discussion in an important area. In doing so, we believe that the journal has behaved responsibly by encouraging scientific debate. The tenets of single maintenance and reliever therapy of asthma have represented a marked departure from contemporary asthma management perspectives. These include the following: (1) that a reactive and bronchodilator-driven strategy of asthma care is superior to the prevention of asthma symptoms and disability as long as a small aliquot of inhaled corticosteroid is inhaled at times of acute wheezing and breathlessness; (2) that comprehensive asthma control is no longer needed to evaluate asthma treatment and it is sufficient to measure the time between severe exacerbations; and (3) that rising sputum and biopsy markers of inflammation are of no concern in the choice of maintenance strategies. Until the present correspondence, the absence of discussion and debate concerning these proposals has puzzled us.

Dr Peters and Professor Jenkins have entitled their letter 'Critical appraisal of Symbicort maintenance and reliever treatment misrepresents clinical evidence'.<sup>1</sup> We had used the acronym SMART to represent 'single maintenance and reliever therapy' to engage in a broad discussion of asthma management principles and not a review of a specific pharmacotherapy; that will be the intended meaning of the acronym in this letter.<sup>2</sup> Peters and Jenkins state that we have implied that fixed dose treatments 'achieved target levels of control' in reference to the review of control outcomes by Bateman and colleagues.<sup>3</sup> We can find no mention of fixed dose treatment outcomes in this paragraph of our publication. Elsewhere in the review we have noted that the primary outcome for inhaled corticosteroids/long-acting  $\beta$  agonists (ICS/LABA) given in SMART fashion was superior to lower doses of ICS/LABA given in fixed dose fashion and also superior to fixed dose ICS monotherapy.

We thank Drs Peters, Yan, Reddel and Professor Jenkins<sup>1–4</sup> for highlighting the second relevant Cochrane review.<sup>5</sup> A thorough reading will reveal that, in the studies examined by Cates and Lasserson, the dosage of maintenance ICS was reduced during the run-in so that, under these conditions, exacerbations requiring oral steroids (but not hospitalisations) occurred less frequently when patients inhaled ICS/LABA rather than short-acting bronchodilator alone. This finding is consistent with our hypothesis that SMART may allow patients to self-treat exacerbations at home without seeking

medical care, and begs the question whether it is better to prevent symptoms and exacerbations entirely by adequate amounts of maintenance anti-inflammatory therapy or to rescue patients once symptoms have occurred.

All correspondents appear concerned that, in the table, we displayed only the SMART control outcomes and not outcomes for the comparator limbs. We believe that this was appropriate as our aim was to examine the clinical usefulness of SMART in terms of the control parameters used widely to monitor asthma in the clinical setting. It was not our goal to analyse further the well-known superiority of ICS/LABA to ICS monotherapy or the superiority of higher doses of ICS/LABA to lower doses of ICS/LABA. Bowler and Serisier suggest that the poor control outcomes seen in these trials 'reflects the severity of disease' of participants.<sup>6</sup> We respond that the failure of SMART therapy to control severe disease would hardly recommend its use in moderate or mild disease. Indeed, Cates and Lasserson's Cochrane review noted that no superiority was demonstrable with SMART in mild disease.<sup>5</sup> We must add that it is probably more accurate to describe study participants as having severely uncontrolled disease at recruitment and not necessarily as having severe disease, given that optimal education, compliance and treatment may have controlled their disease.

Reddel and Yan<sup>4</sup> suggest that our review of SMART results has been selective, a challenge that is difficult to address as we attempted to distil a large body of research literature, analysis and commentary into a review of acceptable length. In our review we acknowledged the well-known and often-emphasised primary outcome of SMART trials, but also attempted to discuss the much less frequently mentioned (and often concealed) effect of SMART therapy on asthma control. We have been chastised for highlighting this outcome and commenting on the dearth of discussion around control, but must note that Bateman and colleagues' manuscript estimating control (on a week-by-week rather than long-term basis) has only recently been published and was available to add to our review only at the galley proof stage of manuscript production.<sup>3</sup> We did not wish to criticise the use of exacerbations as an end point in asthma trials but wished to point out that, by limiting the choice of primary end point to 'time to severe exacerbation' in all but one SMART trial (which used peak flow),<sup>7</sup> the body of research has concealed the generally poor asthma control outcomes seen with this strategy. Although we referenced in our review the paper by Kuna and colleagues using double-dummy methodology,<sup>8</sup> we suspect we are not alone in believing that blinding remains difficult and sometimes impossible when inquisitive and observant asthma patients are given