Usefulness of GOLD classification of COPD severity

In 2001 the US National Heart, Lung and Blood Institute (NHLBI) and the World Health Organization announced guidelines for the diagnosis, management, and treatment of COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD). One key aspect of these guidelines is that COPD is classified by severity into five stages which constitute the basis of treatment recommendations. However, to date there has been little evidence for the usefulness of these severity stages.

We retrospectively reviewed 1000 patients with COPD diagnosed clinically in 2001; 500 patients originated from a pulmonary rehabilitation hospital. Patients’ symptoms (based on a standardised interview), findings of a standardised lung examination, lung function data, and chest radiographic findings are routinely documented in a database. The inclusion criteria were symptoms of COPD (chronic cough with chronic sputum production for more than 2 years) and radiographic findings of COPD (hyperinflation, diaphragmatic flattening). Patients with a history of asthma (variability of spirometric parameters, improvement in forced expiratory volume in 1 second (FEV1) of >20% after inhalation of β2 agonists, symptoms predominantly at night, seasonal allergies, allergic rhinitis, or eczema) were excluded from the study, as were those in whom FEV1, and forced vital capacity (FVC) differed by more than 5% according to the American Thoracic Society (ATS) guidelines1 and patients with an abnormal chest radiograph or chronic cough caused by a disease other than COPD.

FEV1 and FEV1/FVC were determined three times. The predicted values for FEV1 were taken from the European Respiratory Society (ERS) guidelines. The individual values of FEV1 and FEV1/FVC for all patients are shown in fig 1. Almost 14% of patients clinically diagnosed as having COPD could not be classified because they had an FEV1/FVC ratio of >70%, despite having a reduced FEV1, (<80% predicted). This combination is not represented in the GOLD classification. Less than 5% of all patients were classified as GOLD stage I.

The finding that the GOLD classification missed an important subgroup of patients with mild COPD challenges any proposed advantage of this classification scheme over existing guidelines from the ATS and ERS.2 Only six patients not classified as having COPD by GOLD were missed using the ATS criteria (stage I: FEV1 >80%) and ERS criteria (mild: FEV1 <70% and FEV1/FVC >88% for men and >89% for women). Obviously, any arbitrary classification of a continuous variable such as FEV1, and FEV1/FVC results in a borderline group of patients. The GOLD classification, however, provides no guidance as to the further diagnosis of the unclassified subgroup (fig 1). Our results also show that stage I disease (FEV1/FVC <70% and FEV1 >80% predicted) was very rare, constituting only 4–5% of the patients. This indicates that the distribution of the stages, especially stage I, is inhomogeneous.

Despite its retrospective design, this study was strengthened by the fact that lung function data, chest radiographic findings, and the results of a standard clinical examination were available for all patients. It therefore offers the chance to investigate the clinical impact of the GOLD classification, especially in patients with mild COPD.

Our study therefore suggests that GOLD criteria miss an important subgroup of patients with clinically diagnosed COPD, which reduces its usefulness as a clinical tool.

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References

Sahaja yoga in asthma

Since the publication of our paper on Sahaja yoga in the management of moderate to severe asthma3 we have received a large number of enquiries. One issue that has been raised about the technique used in the study warrants clarification and further acknowledgegment.

The Sahaja yoga meditation technique used in the study was not developed by the authors. The technique was taught to subjects in the intervention group by experienced Sahaja yoga practitioners free of charge. The technique itself was developed by yoga expert H H Shri Mataji Nirmala Devi and she permitted the investigators to conduct the study on the following reasonable conditions: (1) that no part of the technique be misrepresented, misappropriated or commercialised by the investigators; (2) that the founder and practitioners of the process be appropriately
acknowledged as the true source and custodians of the technique and its associated knowledge; and (3) that it be made clear that the Sahaja yoga technique is, as a matter of policy and philosophical conviction, always made available free of charge.

The authors sincerely regret any misunderstanding that may have led readers or members of the public to believe otherwise. They sincerely and gratefully acknowledge the important and crucial role played by H.H. Shri Mataji Nirmala Devi and the Sahaja yoga practitioners of Australia in the execution of this study, and sincerely regret not having made more appropriate acknowledgements in the original article.

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Reference

Homeopathy in childhood asthma

We read with interest the article by White et al. on the use of homeopathy as an adjunct in the treatment of childhood asthma. We also obtained negative findings in an open study in which we assessed the effects of homeopathy on spirometry and exhaled nitric oxide (eNO) in children with stable asthma.

Twelve asthmatic children (4 boys, median age 13.5 years, range 7–18) who satisfied the following inclusion criteria were recruited: (1) stable asthma with no clinical indication for change in treatment, on any dose of inhaled corticosteroid and any other asthma medication; (2) raised eNO level at the start of the study despite clinical stability; (3) identifiable sensitivity to house dust mite (HDM, n=3) or cat (n=2) and HDM (n=9) by history and skin prick test (SPT); (4) no hospital admission or emergency department attendance for asthma in the previous 3 months; (5) no history of consumption of oral corticosteroid in the previous 3 months. The children were randomised to homeopathic treatment within the previous 6 months, allergen desensitisation within the previous year, or HDM avoidance measures or removal of household pet to which the subject had a positive SPT in the previous 3 months.

At baseline all recruited patients underwent SPT if this had not been done within the previous 2 years, eNO measurement (NIOX, Aerocrene, Sweden), and spirometric testing (Vitalograph, Buckingham, UK) measuring forced expiratory volume in 1 second (FEV1). The mean of three best efforts was recorded and the result was expressed as percentage predicted. The homeopathic remedy was prescribed according to the child’s SPT result. This was a preparation of HDM or cat dander (or both, if appropriate) in the form of two lactose globules. The preparation was made according to the principles laid out in the British Homeopathic Pharmacopoeia. The patients were told to take the globules daily for the next 4 weeks while continuing with the same conventional asthma treatment. A diary was given to each child to encourage compliance and to document any break-through symptoms or side effects from the remedy during the study period. The subjects were told to return for eNO measurement and spirometric assessment after 4 weeks (visit 1) on the homeopathic remedy, and to return again 4 weeks later (visit 2) to assess the response after stopping the remedy. The spirometric test results of one patient from the first and second visits were missing.

No side effects were reported and all subjects were compliant with the homeopathic remedy. Using the Wilcoxon signed ranks test, there was no significant difference at baseline and at visits 1 and 2 in FEV1 (86% (interquartile range (IQR) 75.1–93.3) vs 89% (85% (IQR 80.0–95.0) vs 85% (74% (89.0), respectively) and eNO (54 ppb (IQR 36.2–99.6) vs 68 ppb (37% (80.0–97.0) vs 76 ppb (45.6–131.4), respectively). This could be because of the small sample size, or that the homeopathic remedy genuinely did not have any anti-inflammatory effect.

This study provides important baseline data for the calculation of the sample size needed to carry out a randomised, placebo controlled, double blind study. A sample size of 65 subjects per treatment arm would have 80% power to detect a difference of 10% in mean FEV1, assuming a standard deviation of difference of 28% (or more). To perform a single test with a two sided significance level of 0.05.

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References

Homeopathy deserves to be scientifically appraised by good quality studies and the results published without bias which could distort the treatment of childhood asthma: a randomised controlled trial. Thorax 2002;57:110–5.

Homeopathy by White et al. published recently in Thorax has critical flaws which seriously undermine its validity. Classification of asthma severity could be established at entry by using the results of a recent publication by White et al. which we assessed the effects of homeopathy on spirometry and exhaled nitric oxide (eNO) in children with stable asthma.

The authors sincerely regret any misunderstanding that may have led readers or members of the public to believe otherwise. They sincerely and gratefully acknowledge the important and crucial role played by H.H. Shri Mataji Nirmala Devi and the Sahaja yoga practitioners of Australia in the execution of this study, and sincerely regret not having made more appropriate acknowledgements in the original article.

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The efficacy and clinical effectiveness of homeopathy engenders considerable debate; it is therefore essential that clinical trials are accurately interpreted and reported. The recent publication by White et al. has highlighted this issue.

The study—which assessed classical homeopathy as an adjunctive treatment for childhood asthma—concluded that, based on the primary outcome (the active quality of living scale of the Childhood Asthma Score-naire), classical homeopathy was not superior to placebo. We disagree with this conclusion. The scale used to assess the primary outcome was inappropriate; it does not distinguish between asthmatics and non-asthmatics' and
is more suitable as a cross sectional measure than as a longitudinal outcome, and the ability to identify any therapeutic improvement was severely reduced due to ceiling/flooring effects in both the primary and some secondary outcome data. For example, baseline scores identified that the study population had good quality of life, and that two of the three age groups studied had mild asthma. Any therapeutic improvement would therefore be hard to identify, let alone quantify.

Other design issues were apparent—for example, no data were reported on homeopathic exacerbations (an indicator of the healing response), and the security of blind-pathic exacerbations (an indicator of the treatment effect size) was statistically highly significant (p=0.01) with 95% confidence intervals not including zero. This again was an intention to treat analysis, and while there are good reasons for performing such analyses, effect size estimates should be based on data for subjects who have actually taken the treatment and had its impact evaluated; in this case, 20% did not. In addition, there was a floor effect (see above) in one of the severity scales. A similar pattern is seen for other subscales of the CAQ, but no statistical analysis is presented.

The question most frequently posed about homeopathy is “is it all placebo effect?” Most meta-analyses have concluded that it is not. If the outcome measures which could not have improved are excluded, the results of this trial accord with those of the largest meta-analysis of homeopathy; they “are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo.” The treatment effect size was relatively small, but classical homeopathy is a complex and non-standardised intervention. The practitioners involved had no particular experience of asthma episodes in the preceding year was zero. These are all “hard” floor/ceiling effects; no improvement at all could have been expected. There is also a strong suggestion of floor/ceiling effects in other outcomes such as days lost from school, but we cannot be certain from the published data. Other secondary outcomes show relative floor/ceiling effects—for instance, the mean final value in the CAQA parent’s severity score was 5.5 on a scale of 5–19. Since this was an intention to treat analysis, 20% of the values were simply pretreatment values carried forward.

Other CAQ subscales analysed as secondary outcomes consistently favour homeopathy. For the severity subscales the improvement was statistically highly significant (p<0.01) with 95% confidence intervals not including zero. This again was an intention to treat analysis, and while there are good reasons for performing such analyses, effect size estimates should be based on data for subjects who have actually taken the treatment and had its impact evaluated; in this case, 20% did not. In addition, there was a floor effect (see above) in one of the severity scales. A similar pattern is seen for other subscales of the CAQ, but no statistical analysis is presented.

The paper by White et al. in the April issue of Thorax purports to show that adjunctive homeopathic treatment has no effect on the quality of life of asthmatic children. The primary outcome measure was the active Quality of Life (QoL) scale of the Childhood Asthma Questionnaire (CAQ). This measure was inappropriate, and no such conclusion is justified. As table 1 shows, the children enrolled had QoL scores virtually identical to those of non-asthmatic children in a large scale validation study cited in the paper by White et al. Furthermore, the CAQ QoL scale does not discriminate between non-asthmatic and mildly asthmatic children.

Similar floor and ceiling effects are seen in the secondary outcome measures for example, in the homeopathy group at entry the peak expiratory flow rate was 100.4% of expected and the median number of asthma episodes in the preceding year was zero. These are all “hard” floor/ceiling effects; no improvement at all could have been expected. There is also a strong suggestion of floor/ceiling effects in other outcomes such as days lost from school, but we cannot be certain from the published data. Other secondary outcomes show relative floor/ceiling effects—for instance, the mean final value in the CAQA parent’s severity score was 5.5 on a scale of 5–19. Since this was an intention to treat analysis, 20% of the values were simply pretreatment values carried forward.

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The question most frequently posed about homeopathy is “is it all placebo effect?” Most meta-analyses have concluded that it is not. If the outcome measures which could not have improved are excluded, the results of this trial accord with those of the largest meta-analysis of homeopathy; they “are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo.” The treatment effect size was relatively small, but classical homeopathy is a complex and non-standardised intervention. The practitioners involved had no particular experience of asthma. There is thus considerable scope for refinement.

Regrettably, the conclusions do not adequately reflect the shortcomings of the trial. The authors state that “there was no evidence of a clinically relevant change in quality of life score”, but omit to mention that none was expected since the QoL scores were normal at entry. There is no reference to the many floor/ceiling effects. Our greatest concern is that the bias in the interpretation of the results will carry through to future meta-analyses and reviews.

The study by White et al. of quality of life in children with asthma treated with homeopathy is fatally flawed. The Childhood Asthma Quality of Life instrument used was validated in a study by French et al. The children entered into the study by White et al. had scores consistent with those of children who don’t have asthma. For a statistically significant improvement to occur in this score, the treated group would have to develop scores of around 100%—that is, better than normal non-asthmatic children. This is clearly highly unlikely. In addition, a similar “ceiling effect” applies to the peak expiratory flow readings which at entry were 100.4% and 96.9% of expected for the verum and placebo groups, respectively.

This is a very poor quality trial which does absolutely nothing to further our understanding of the potential value of homeopathic treatment in children with asthma. In fact, the press release from the journal has been picked up by the media and used to support the headline “Homeopathy of no use in asthma.”

Publishing this quality of research at best does not improve our necessary evidence and, at worst, contributes to the denial of services which may indeed be of value to patients. A close analysis of the study shows that the treatment group had a trend to better outcomes than the placebo group. If this were a pilot study, it would be indicating that there is indeed a potential benefit to asthmatic children from homeopathy which should be investigated with a proper trial of good methodological quality.
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References

Author’s reply
These authors are to be thanked for their contribution to the debate about the interpretation of the results of our trial, and it is conceded that ceiling effects may exist which limit the interpretation of our results. If the children were already effectively medicated, it may not have been possible to show any benefit from homeopathic treatment in quality of life. It may not have been possible to show any differential change in conventional medication or global indicators, which were absent from the results. Because of ethical issues, it may be difficult to conduct a definitive trial in children with severe asthma.
Leckridge, Fisher et al, and Brien and Lewith suggest that we should have concentrated instead on the small changes in the severity subscales, the estimate of which is not clinically relevant. However, the severity scale measures symptoms only, and active quality of life is much more appropriate for the holistic approach of homeopathy.
The claim by Fisher et al and Dantas that the homeopaths were inadequate to the task is speculative and one we reject. Dantas would prefer us to have used more rigorous criteria for inclusion and assessment, but the study was especially designed to reflect “real life” pragmatically by rigorously applying the criteria used by the GPs, the children, and their families. We cited his paper as the only systematic and objective report on homeopathic aggravations that we were aware of, and if we gave the impression that he stated that aggravations are a hallmark of success, then we regret it.

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BOOK REVIEW

Statistics in Clinical Practice

This is a very clearly written introduction to statistics, suitable for medical students and doctors who need a quick update in order to understand the current literature. Professor Coggon moves rapidly through types of data (continuous, ordinal or univariate and multivariate) to methods of summarising data on which a fair amount of time is spent. Tabular and graphical (dot, line, bar and pie chart) presentations are discussed with numerous illustrations from everyday clinical practice. The interpretation of graphical data and its limitations—a very important part of understanding current medical research—are thoroughly discussed. The concept of probability is introduced and combining probabilities is explained. Sensitivity and specificity are defined here but could more appropriately be placed later as they are, in fact, properties of statistical tests. Hypothesis testing, confidence intervals, and the basis of sample size calculations (though not how to calculate the size of a sample) are also discussed. The author explains the two most common methods of statistical modelling—linear regression and survival analysis—and concludes with a section on meta-analyses and the importance of involving statisticians very early in the planning stage of a study.
This is an excellent introduction to practising statistics in medicine and will be extremely useful for medical students and clinicians alike. Medical researchers will, however, need to follow this text with a more advanced one.

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