patient education,[6] and patient self management plans.[7] Structured antismoking advice and nicotine replacement therapy have both been shown to be effective in reducing smoking. Allergen avoidance is ineffective and is not recommended. What we know about the effect of giving patients information about asthma is limited to patients attending accident and emergency departments, but there it has been shown to reduce subsequent reattendance. Written self management plans, based either on symptoms or peak flow readings, are effective in reducing morbidity in primary care settings.

One of the strengths of guidelines such as those produced by the North of England evidence based guideline development project is that they start with precisely formulated questions rather than being driven by the available evidence. One side effect of this is that they expose limitations in the available evidence.

Randomised controlled trials are combined in systematic reviews, and the strength of the evidence is objectively graded. In a guideline the strength of the recommendation is then explicitly linked to the strength of evidence and its relevance to the question. This process needs to be a continuous one, with reviews and guidelines updated as new trial data emerge. The Cochrane Collaboration has been pivotal in both establishing and maintaining up to date systematic reviews on the Cochrane library.[1]

The production of national guidelines, as well as evidence based summaries such as *Clinical Evidence*, plays an important part in digesting and presenting Cochrane reviews. A cycle can be created whereby relevant questions and high quality evidence synthesis drive evidence based practice and pull research towards the most relevant unanswered questions for day to day patient care. The funding of this work by healthcare agencies world wide is vital in supporting this health service focus, because the other major funder of research—the pharmaceutical industry—concentrates on developing and testing new products, rather than establishing the effectiveness of off patent or non-drug interventions.

The British Thoracic Society guidelines on asthma are probably the most widely known and comprehensive guidelines on asthma available in Britain **(OK??)**, but there is a striking gap in evidence to support many of the practical steps recommended by the British Thoracic Society guidelines.[8] These include the stepwise sequencing of asthma therapies, the point at which to initiate inhaled corticosteroids, the role of doubling the dose of inhaled corticosteroids in avoiding acute exacerbations, and the role of leukotriene antagonists. This last is a good example of poor research planning. Existing comparisons of leukotriene antagonists with placebo are of little help in deciding how this new treatment compares with existing practice. The NHS spent £465m on drugs and appliances for asthma in 1997, and there are large differences in cost between different devices. There are no reliable data on either the cost effectiveness of different sequencing strategies or different devices. The North of England guidelines adopt the British Thoracic Society consensus that the cheapest device that can be used by a patient should be prescribed. However, there is a need for pragmatic, cost effectiveness trials in this area.

Ten years after the first use of the term evidence based medicine[9] it is clear that the process by which research influences practice needs to be as rigorous as primary research. Similarly, passive dissemination of guidelines, however evidence based, does not influence practice significantly. Guidelines need to be operationalised using multifaceted interventions such as academic detailing, prompts and reminders, templates, and managed care systems.[10] Primary care organisations need to develop processes whereby updated evidence based guidelines are translated into educational activity, clinical governance, and local computer templates and protocols. But the first step is to do the updating—and that the North of England group have done.

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Hormone replacement therapy and the breast

We should worry about the increase in the risk of breast cancer

Increasing numbers of women in their 50s and 60s are using hormone replacement therapy to alleviate menopausal symptoms. The effect of long term use of these agents in women aged over 50 on the breast is only now becoming apparent. Hormone replacement therapy given to perimenopausal women increases breast pain and nodularity, increases the frequency of benign cysts and fibroadenomas in the breast, and results in the growth of some already established benign lesions.[1]

Breast density increases in 17% to 73% of women who use hormone replacement therapy depending on

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how breast density is assessed. No clear relation exists between duration of therapy and change in density on mammography. Combinations of oestrogen and progestogen increase breast density more than oestrogen alone. Continuous use of combined preparations of oestrogen and progestogen increase density more than their sequential use.[2] Hormone replacement therapy affects both the sensitivity and specificity of breast screening. This is because the efficacy of breast screening depends on the decreasing breast density seen with age.

In a recent study of 103 770 women from Australia the sensitivity of two year mammographic screening in women aged 50-69 was 64.3% (95% confidence interval 57 to 72) in those given hormone replacement therapy compared with 79.8% (76 to 84) in non-users.[3] There were also more interval cancers, false negatives (odds ratio 1.60 (1.04 to 2.21), and false positives (1.12 (1.04 to 1.19) and a significant reduction in specificity in women taking hormone replacement therapy. In countries where hormone replacement therapy is widely used this reduction in the sensitivity of mammography could undermine the capacity of population based mammographic screening programmes to reduce mortality due to breast cancer.[3]

The combined analysis of studies of early hormone replacement therapy reported an increased risk of breast cancer of 1.023 for each year of use, the risk being 1.35 (1.21 to1.49) for women who took hormone replacement therapy for five or more years.[4] There were too few data to correlate type of hormone replacement therapy and risk. More recent studies have reported significantly higher levels of risk of breast cancer in women taking combined oestrogen and progestogen preparations compared with women taking oestrogen alone.[5–9] The annual increased risk varied from 4% to 9% for combined preparations compared with 1% to 3.3% for oestrogen alone. Excess risk at five years was higher, ranging from 25% to 40% for oestrogen and progestogen combined compared with a range of 1% to 17% for oestrogen alone. The relative risk of developing breast cancer after 10 or more years' use of oestrogen and progestogen together was 2.43 (1.79 to 3.30) in one study.[8]

Continuous combined preparations containing a testosterone derived progestogen also appear to be associated with a significantly greater risk than the use of sequential oestrogen and progestogen.[8] Such is the concern surrounding the use of combined oestrogen and progestogen preparations that it was recently stated that "the burden of proof should no longer be on epidemiologists and other investigators to demonstrate that such agents increase the risk of breast cancer; rather it should shift to the proponents of their use to demonstrate that they do not."[10]

Most studies have found that breast cancers that develop in women on hormone replacement therapy are smaller, less clinically advanced, have a lower rate of node positivity, are better differentiated and are of more favourable histological type than cancers that develop in women who do not use hormone replacement therapy. Consistent with these findings, most studies have shown either a reduction or no significant effect of hormone replacement therapy on mortality due to breast cancer. Studies published so far have been based on preparations many of which are no longer in common use, and in most follow up has been less than 10 years. One large study of 1 121 700 nurses recruited in 1976 reported after 18 years of follow up that there was excess mortality due to breast cancer in women who had taken hormone replacement therapy for five years or longer (relative risk 1.45, 1.01 to 2.09).[11]

It may be time to reassess the value of hormone replacement therapy. Some doubt that its benefits in reducing the risk of bone loss exceed its risk,[12] and evidence suggests that there is an increased risk in the rate of coronary events with short term hormone replacement therapy and a decreased risk with only long term use.[13] The current evidence suggests that the effects of hormone replacement therapy on the breast, particularly the effects of combinations of oestrogen and progestogen on breast density and risk of breast cancer, also need to be considered. The use of progestogens and their mode of delivery need particular attention. One option is delivering progestogen directly to the uterus and combining this with systemic oestrogen—this should alleviate menopausal symptoms while limiting the risk of breast cancer. Alternative agents to control menopausal symptoms, such as tibolone, a synthetic steroid with weak oestrogen, androgenic, and progestogenic activity but with few apparent ill effects on the breast, need to be considered for women with no residual cyclical hormonal production. The evidence that hormone replacement therapy reduces the effectiveness of breast screening and causes breast cancer in women over the age of 50 is clear; the challenge for clinicians is to control menopausal symptoms while limiting these unwanted effects.

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