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Breast cancer and hormone replacement therapy (HRT). The Women's Health Initiative (WHI) study (n=16,608) which evaluated estrogen plus progestin (combined HRT) compared to placebo in women aged 50-79 years was stopped early (after a mean of 5.3 years) when the health risks exceeded the benefits, one of which was an increased risk of breast cancer. Questions in relation to HRT remain, including the cumulative, long-term effect of combined HRT on breast cancer incidence and whether breast cancer mortality is increased by combined HRT use. Previous observational studies suggested that breast cancer associated with HRT had favourable characteristics. A follow-up of the original WHI study included 12,788 women from the original study who consented for continued follow-up of breast cancer incidence. The study assessed the effects of combined HRT on cumulative breast cancer incidence and mortality after a mean follow up of 11 years, (*JAMA Oct 2010;304:1684-1692*). The results showed that **combined HRT was associated with a significantly increased risk of invasive breast cancer compared to placebo (hazard ratio [HR] 1.25, p=0.004)**. The study also found that those on combined HRT with breast cancer were more likely to present with positive lymph nodes (HR 1.78, p=0.03), however there was no evidence of a differential effect of combined HRT on receptor-positive versus receptor negative tumours and no significant differences among HRT users and breast cancer incidence with age, body mass and Gail risk score (a model used to quantify a woman's risk of developing breast cancer). More women died from breast cancer in the combined HRT than in the placebo group (HR 1.96, p=0.049) and similarly the all-cause mortality was higher with combined HRT (HR 1.57; p=0.045). The discrepancy between these findings and the observational studies may be related to potential confounding factors in the observational analysis. The authors concluded that the use of combined HRT increases the incidence of breast cancer which is more commonly node positive and the findings suggest that breast cancer mortality may also be increased.

An accompanying editorial (*JAMA Oct 2010;304:1719-1720*) discusses the issues surrounding HRT and advises that this study addresses many of the questions in relation to HRT and breast cancer. They suggest that additional randomised trials are required to determine whether lower or shorter durations of HRT could alleviate menopausal symptoms without increasing cancer risk.



Possible risk of severe liver injury with dronedarone. Dronedarone (Multaq®), an anti-arrhythmic agent, is licensed for use in clinically stable adult patients with a history of, or current non-permanent, atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. The European Medicines Agency (EMA) has recently become aware of serious liver injury in patients taking dronedarone. Since it was first licensed in 2009 there have been **reports of liver function test (LFT) abnormalities and liver cell damage associated with its use, including 2 cases of acute liver failure requiring transplantation**. These latter cases occurred at 4.5 and 6 months after starting dronedarone treatment in patients with normal baseline LFTs. Although these two patients were also taking other medicines at the time, a causal relationship with dronedarone could not be excluded. Therefore the EMA's scientific committee (CHMP) has recommended that the **following safety measures for use of dronedarone should be implemented immediately:**

- Before starting treatment with dronedarone, all patients should have their LFTs checked and these tests should be repeated monthly for 6 months, at months 9 and 12 and periodically thereafter
- Prescribers should contact their patients currently taking dronedarone within the next month to arrange for LFTs to be carried out now and at regular intervals thereafter (as per above schedule)
- Prescribers should discontinue dronedarone in patients with elevated alanine aminotransferase (ALT > 3 X upper limit of normal). Such patients should be investigated as appropriate and monitored until the enzyme level returns to normal
- Patients should be advised to contact their doctor immediately in case of the development of any signs or symptoms of liver injury and to talk to their doctor or pharmacist if they have any questions about dronedarone

The CHMP has begun an assessment of all available data concerning the possible risks of liver injury associated with the use of Multaq® and their impact on its benefit-risk balance and will publish their findings and recommendations when the review is complete. The NMIC will keep readers updated with any new safety data arising from the review.



Preventing exacerbations in chronic obstructive pulmonary disease (COPD).

Acute exacerbations of COPD are associated with significant morbidity and mortality and are the most common cause of emergency respiratory hospital admissions, in addition to impacting on health service costs. COPD is a progressive systemic disease; **cigarette smoking is the most important causal**

factor in its development and smoking cessation reduces both the rate of decline in lung function and improves survival. The evidence on the use of drug and non-drug interventions in preventing exacerbations of COPD was recently reviewed and is summarised below (*DTB 2010;48:74-7 & BMJ 2011;342:c7207*).

The long-acting antimuscarinic drug tiotropium has been shown to reduce the likelihood of exacerbations and hospitalisations compared to placebo or ipratropium, but not the rate of decline in FEV1. Unwanted effects of antimuscarinics include visual disorders, dry mouth, constipation, micturition difficulties and arrhythmias. A systematic review found a slightly increased likelihood of cardiovascular events with ipratropium or tiotropium however a randomised controlled trial showed a lower likelihood of cardiac events with tiotropium compared to placebo.

The long-acting beta 2 agonist (LABA), salmeterol has been shown to be associated with reduced exacerbations in patients with severe COPD compared to placebo. LABAs are associated with tremor, headache, muscle cramps and palpitations. There have been concerns regarding the risk of tachyarrhythmias with LABAs however a meta-analysis found no significant increased risk of cardiovascular events in those receiving salmeterol.

Evidence suggests that inhaled corticosteroids (ICS), when used long-term (>6 months) are associated with a slight to moderate reduction in the number of exacerbations of COPD compared to placebo. Unwanted effects of ICS include oropharyngeal candidiasis, hoarseness and they are also associated with increased pneumonia in patients with COPD.

The evidence relating to the use of **combinations of drugs** is conflicting; a systematic review found that adding LABA to ICS reduced the rate of exacerbations in patients with moderate-severe COPD by 9% compared to controls while a RCT found that there was a reduction in hospitalisations with combination therapy compared to placebo but not compared with salmeterol or fluticasone alone. Another systematic review found that the combination of LABA and ICS was no better than LABA alone at preventing severe exacerbations but moderately better at preventing moderate exacerbations. There is insufficient evidence to show whether triple therapy (antimuscarinic + LABA + ICS) is superior to a combination of ICS plus a bronchodilator or a combination of a LABA plus antimuscarinic.

Other findings: Mucolytic therapy was shown to reduce the mean number of exacerbations by 0.04 per month. There is insufficient evidence to support the use of **prophylactic antibacterial therapy** to prevent exacerbations. A systematic review found that **influenza vaccination reduced the exacerbation rate relative to placebo however another systematic review found no overall benefit for anti-pneumococcal vaccines on morbidity or mortality**. **Long-term oxygen therapy** increased the survival of patients with severe hypoxaemia due to COPD but there is no proven effect of long-term oxygen therapy in preventing COPD exacerbations. There is no robust evidence to suggest that **domiciliary non-invasive positive pressure ventilation** reduces exacerbations of COPD. Evidence suggests that **pulmonary rehabilitation programmes** are associated with reduced hospitalisations and mortality from COPD however they are not universally available for patients. **Patient education programmes** appear to reduce the likelihood of hospitalisations however there is insufficient evidence on what the form and content of these should take. **Disease management programmes** also show reduced exacerbations however it is unclear which elements of the programme are the most important.

The authors conclude that smoking is the most important causal factors for the development of COPD and the **most effective intervention for patients with COPD is stopping smoking**. Drugs however can reduce the frequency of exacerbations although their effect is modest; there is insufficient evidence to show that any further benefit is obtained from triple therapy. Decisions on drug treatment should take into account the frequency of exacerbations in the particular patient and the possibility of unwanted effects.



Hormonal Contraception Bulletin Correction.

A typographical error in the last NMIC bulletin, "Frequently Asked Questions on Hormonal Contraception" NMIC 2010; Vol 16: No 5, has been brought to our attention by one of our readers. On page 2 of the bulletin it should state that **"All of the COC preparations in Ireland contain \leq 35 micrograms EE"**. The corrected version of the bulletin is now freely available on the NMIC website (www.nmic.ie). We

apologise for this error and thank the reader for bringing it to our attention.