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Tibolone: the good and the bad!!

Tibolone is authorised for the management of menopausal symptoms. It has oestrogenic, progestogenic and androgenic activities. A recent randomised controlled trial compared the effect of 1.25mg of tibolone/day vs. placebo on the risk of vertebral and clinical fractures after 3 years' treatment in 4,538 women (60-85 years) with bone mineral density (BMD) T scores of ≤ -2.5 (*NEJM 2008; 359: 697-708*). It also planned to assess the risks of breast cancer, cardiovascular disease and endometrial cancer after 5 years. All patients received calcium and vitamin D supplementation. Results showed >90% of patients received at least 80% of

their scheduled doses during a median of 34 months' treatment. **The tibolone group** showed increases in BMD in the spine and femoral neck and **had less new vertebral fractures (70 vs. 126) compared with placebo** (=absolute risk reduction of vertebral fracture of 8.6/1,000 person years). This risk reduction was greater in those who had already had a vertebral fracture at baseline (=20.8/1,000). Similar reductions in absolute risk for non-vertebral fractures were also reported. **Tibolone patients also reported fewer breast cancers (6 vs. 19 = 1.9/1,000 person years absolute risk reduction)** and fewer colon cancers (4 vs. 13 = 1.3/1,000 absolute risk reduction) during the study period. However, during the study, **a total of 28 strokes were reported in the tibolone group compared with 13 in the placebo group**, representing an increase in absolute risk of stroke of 2.3/1,000 person years. **The increased risk of stroke appeared to be greater in the first year of treatment.** The study was stopped early due to the results on fracture and risk of stroke; there was no significant difference in rates of venous thromboembolism or coronary heart disease events between the 2 groups at the time of study discontinuation. The main adverse effects with tibolone treatment related to vaginal discharge and/or bleeding or breast discomfort and 4 cases of endometrial cancer were reported in tibolone patients compared with none in the placebo group. No significant difference in the incidence of endometrial hyperplasia was reported between the groups. The authors commented that tibolone appeared to be particularly beneficial in preventing both vertebral and non-vertebral (such as wrist / hip) fractures in women who had previously had a vertebral fracture. They noted the apparent protective effect against breast cancer was at variance with the Million Women Study, but that that was an observational study. They postulated that the effect might be similar to that of raloxifene and tamoxifen. Because of the increased risk of stroke reported in the study, they stated that the potential risks and benefits of tibolone should be evaluated at an individual level when considering its use and they recommended that tibolone should not be used in older women, or those with known risk factors for stroke.



Benzodiazepine use and risk of fracture in the elderly.

Studies have reported up to a 50% increased risk of fractures in older patients taking benzodiazepines (BZDs). Long-acting BZDs (e.g. diazepam, chlordiazepoxide or flurazepam) or higher doses of shorter-acting agents (e.g. daily dose of >2mg alprazolam, >3mg lorazepam, >15mg temazepam) are specifically designated as **inappropriate for older patients** i.e. their potential for causing harm outweighs any potential benefit. A recent study (*BJCP 2008; 66: 276-82*) compared the risk of fracture in older people according to the type and dose of BZD prescribed. All cases of fracture in BZD users >65 years (n=200) over a 10-year period, were identified from a population database and compared with BZD users of the same

age with no fracture (n=2678) in the database. Results showed that there was a **significantly higher risk of fracture (1.5-1.8 fold increase)** in "high-dose" users and those with a longer duration of use (>2-fold increase noted with 14-90 days' use), irrespective of the type of BZD used. The results were not changed when adjusted for age, sex, dementia, alcohol intake, or bone mineral density. Unsurprisingly, the effect of daily dose on those with a BMI <26 was high. The authors conclude that, regarding the risk of fracture, a high daily dose and duration of use >14 days are potentially inappropriate, irrespective of whether a short- or long-acting BZD is used.



How to manage hypothyroidism Adult hypothyroidism (HT) and its management in primary care was recently reviewed (*BMJ 2008; 337: 284-289*). In the UK the annual incidence is 0.6-3.5/1,000 (men: women). The **commonest cause** is autoimmune thyroiditis; rarer causes include iatrogenic (post surgery or radioiodine therapy), iodine deficiency, drugs (e.g. amiodarone, lithium), congenital hypothyroidism and disorders of the pituitary or hypothalamus. **Symptoms** may develop over years and range from fatigue to severe impairment of consciousness.

Diagnosis of HT is confirmed by an increase in serum thyroid stimulating hormone (TSH). Those presenting with symptomatic HT often have TSH $>10\text{mU/L}$ in association with reduced thyroxine. Adults with less severe HT (*sub-clinical HT*) may have TSH between 5-10 mU/L with a normal serum thyroxine. A 30% diurnal variation occurs in TSH levels, which can give the impression of fluctuating disease. In autoimmune HT, circulating antibodies are detected in up to 90% of patients. Of note, triiodothyronine (T3) may be normal in severe HT therefore it is not a helpful investigation.

Treatment: Patients with *overt HT* and TSH $>10\text{mU/L}$ require treatment, unless the patient has drug-induced HT or is in the recovery phase of thyroiditis. **Confirmation of raised TSH is recommended on a second sample**, as treatment is likely to be for life. It is controversial whether patients with *sub-clinical HT* should be treated. Thyroid peroxidase antibody (TPA) should be checked and TSH levels repeated within 3 months to determine if the rise is persistent or transient (i.e. associated with non-thyroidal illness). In patients with symptoms of HT and persistently elevated TSH, a 3-6 month therapeutic trial with levothyroxine is suggested; up to 50% of patients will improve. In asymptomatic patients, with stable elevation of TSH and TPA present, the risk of progression to overt HT is approx 5% per year. These patients require annual monitoring of TSH. In the absence of TPA, the risk of progression to overt HT in such patients is 2% per year, and monitoring of TSH every 3 years is recommended. However **mild HT should always be treated in pregnancy or in someone trying to conceive**. These patients also require specialist referral due to the adverse obstetric outcomes associated with HT. Secondary HT (due to pituitary or hypothalamic disease) should be suspected in patients with symptoms of HT and normal TSH.

Dosage: Levothyroxine is commonly titrated upwards from a starting dose (*the current Summary of Product Characteristics and BNF recommend starting with 50-100 microgram daily*) unless the patient is >50 years or has ischaemic heart disease, where the starting dose should be lower. After starting levothyroxine, TSH and free thyroxine levels should be measured at 8-12 weeks and the dose adjusted accordingly. The aim is to achieve a TSH of 0.4-2.5mU/l with improvement of symptoms. Patients stabilised on levothyroxine should have annual measurements of TSH but more regular monitoring is recommended for a patient who is pregnant, is on oestrogen, has a large change in weight or is elderly. **Surveys suggest that up to 48% of patients taking levothyroxine are either over or under-treated**. Non-compliance should be suspected in patients with persistent elevation of TSH with normal or raised thyroxine. Persistently raised TSH can also be caused by drugs or malabsorption. Specialist referral should be considered for patients whose symptoms do not respond or worsen after levothyroxine, those with persistently elevated TSH while on full dose or with co-existing morbidity or complications.



Safety Update! Interactions with statin therapy. Recently, a fatal interaction between atorvastatin and fusidic acid (causing rhabdomyolysis and kidney damage) was brought to public attention in Ireland (www.imb.ie). Myopathy with statins typically occurs in $<1:10,000$ patients on standard doses (*Lancet 2007; 370: 1781-90*). However, the risk of myopathy with all statins seems to be particularly affected by drug

interactions and especially those related to metabolism of statins via the cytochrome P450 system. Prescribers are reminded of the need to check for potential interactions when prescribing medicines to patients on statin therapy or in those for whom statin therapy is being considered. Drug interaction information is found in section 4.6 of the Summary of Product Characteristics (SPC). **When considering concomitant therapy with a statin, you are advised to look at the SPC for each medicine to get all available information: www.medicines.ie or www.imb.ie**