Question 67

A 60 year old woman has been on continuous combined hormone replacement therapy since menopause. She complains of mental slowing, weight gain, insomnia and headaches in the last 6 months. Her general practitioner has commenced her on nortriptyline one month ago with no improvement in her symptoms.

The following results are obtained:

- Serum PRL: 1900mIU/L (30-450)
- Serum LH: 0.3 mIU/L (premenopausal 0.4 – 9.0)
- Serum FSH: 0.5 mIU/L (premenopausal 1.0-9.0)
- Serum TSH: 2.1 mIU/L (0.4 -4.0)
- Free T4: 8pmol/L (10-23)

The best explanation for these results is:

A. Nortryptiline therapy  
B. Depression  
C. Prolactin secreting microadenoma  
D. Non-functioning pituitary macroadenoma  
E. Hormone replacement therapy

Answer:

I thought it was between C and D

In support of D

- Headache suggests intra-cerebral mass from sellar expansion
- PRL regulation is unique as hypothalamic control is inhibitory via dopamine. Thus a non-functioning pituitary macroadenoma can press against the stalk, interrupting dopamine transport
- Mental slowing, weight gain and insomnia could be from GH deficiency Either: lack of dopamine which stimulates GH release Or: pituitary macroadenoma compressing on somatotrophs
- Serum LH and FSH is appropriate for post-menopausal woman on HRT (if no HRT, FSH and LH would be high due to low oestrogen levels)
- Subclinical hypothyroidism is a potential cause of high PRL levels – thyroid hormones are a weak inhibitor of PRL secretion

A. Nortriptyline

- **Tricycle antidepressant** (mechanism of action unclear: blocks diverse agents eg 5HT, histamine, acetylcholamine and catecholamines)
- Side effects include weight gain, insomnia and also hyperprolactinaemia (but symptoms pre-dated medication)
- Endocrine side effects (uncommon): gynaecomastia, breast enlargement and galactorrhoea in females, libido effects, impotence, SIADH
- Predominant side effects are **anticholinergic**: dry mouth, urinary retention, constipation, blurred vision, mydriasis (dilated pupils)

- Contraindicated with MAOi, allergy and 1/12 post AMI
- If overdose, main worry is cardiac arrhythmias (QT prolongation indicates significant toxicity), hypotension and decreased GCS/ coma – supportive measures **+ bicarbonate** +/- phenytoin (for seizures and arrhythmias)
B. Eliminate immediately – depression shouldn’t cause a massive rise in PRL

E. HRT

- Menopause: permanent cessation of menstruation due to loss of ovarian follicular function
- No more oestriol produced by ovaries, small amounts in adipose tissue
- Small amounts of oestrone (weaker oestrogen) produced by adrenals and interstitial ovarian cells -> some converted into oestriol
- HRT: either combined oestrogen-progestin (progesterone to counteract oestrogen action on endometrium) or oestrogen only (if had previous hysterectomy)
- The described symptoms are NOT characteristic of any HRT side effects

- HRT \(\uparrow\) risks of:
  - Coronary heart disease (no \(\uparrow\) risk if oestrogen only)
  - Venous thrombo-embolic events (DVT and PE risk \(\uparrow\) for combined therapy; only DVT risk \(\uparrow\) for oestrogen only)
  - Stroke
  - Breast cancer (\(\uparrow\) risk in combined therapy only, very small protective effect in oestrogen-only arm)
  - Endometrial hyperplasia and carcinoma (if no progesterone and no hysterectomy)
  - Ovarian cancer (both incident and fatal in current users, risk for past users the same as lifetime non-users)
  - Gall bladder disease (\(\uparrow\) risk cholecystitis/ need for cholecystectomy)
  - \(\uparrow\) risk dementia

- HRT good for:
  - Menopausal symptoms (hot flushes, genitourinary symptoms)
  - Treatment of osteoporosis and \(\downarrow\) # rates (hip, vertebral and radius for combined, no effect on wrist for oestrogen only)
  - \(\downarrow\) risk colorectal cancer (for combined therapy only, but more likely for cancer to be advanced at diagnosis)

- In summary:
  - Combined and oestrogen only have similar \(\uparrow\) risks of thrombotic events, stroke and benefits for osteoporosis and fracture-protection
  - No \(\uparrow\) risk coronary disease and breast cancer in oestrogen only
  - No protective effect of oestrogen only for colorectal cancer
  - Overall, risks = benefits of oestrogen only therapy in post-menopausal women with hysterectomies

- Limitations of WHI study:
  - Older (mean age 63) with \(\uparrow\)er BMI (30% with > 30) with 50% current or ex-smokers - so more likely to have pre-existent/ more advanced heart disease
  - Younger post-menopausal women might derive cardiac benefit from early oestrogen only therapy (epidemiological studies)
  - Relative risks compared to placebo appear high but absolute risk of adverse event (mainly cardiac or breast cancer) is very low – 19 additional events in 10,000 women per year compared to placebo
  - This risk is even lower in a younger post-menopausal woman