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Treatment-refractory hypothyroidism. Studies report that approximately one third of patients taking thyroid hormone replacement have levels of thyroid stimulating hormone (TSH) above the reference range (0.4 to 4.5 mU/L), suggesting inadequate thyroid hormone replacement ***(BMJ 2019;364:l579)***. According to expert consensus, in a patient with persistent symptoms of hypothyroidism or raised levels of TSH despite optimum thyroid hormone replacement (up to 2.0 microgram/kg body weight), conditions that may decrease the absorption or increase the demand for thyroxine should be identified and addressed before increasing the daily dose of levothyroxine to >1.9 microgram/kg body weight. **Factors that may decrease the absorption of thyroxine include:** 1) non-adherence to treatment, 2) substances that interfere with intestinal absorption (e.g. proton pump inhibitors, coffee, food, iron, calcium, aluminium hydroxide, cholestyramine, grapefruit juice, raloxifene, multivitamins) and 3) intestinal malabsorption (e.g. short bowel syndrome, lactose intolerance, gluten enteropathy, inflammatory bowel disease, infiltrative enteropathy, infection with *Giardia* or *Helicobacter pylori)*. **Factors that may increase the demand for thyroxine include:** 1) weight gain, 2) pregnancy and 3) increased metabolism of levothyroxine due to concomitant medications (e.g. phenobarbital, phenytoin, carbamazepine, rifampicin and tyrosine kinase inhibitors). Patients should be advised of the importance of taking levothyroxine and using reminders (e.g. dosette boxes or reminders on phones) in order to improve adherence; they should be informed that the absorption of levothyroxine may be affected by other substances taken at the same time. Methods to optimise the absorption of levothyroxine include taking it on an empty stomach with water at least an hour before breakfast or any other tablets. Assessment, in addition to TSH and free thyroxine levels in the blood, should include screening tests for malabsorption (e.g. full blood count, serum levels of vitamin B12, folate, ferritin, calcium, albumin and coeliac antibody test). TSH should be rechecked after 6 weeks to see the effect of any changes. Dose increments of 25 to 50 micrograms may be appropriate for patients taking other medications that decrease the bioavailability of levothyroxine and in pregnant women (in pregnancy serum TSH should be monitored every 6 to 8 weeks). Referral to an endocrinologist should be considered if TSH levels remain elevated 6 weeks following the above advice and after excluding malabsorption, and in patients where symptoms and tests suggest true malabsorption (e.g. deficiencies of vitamin B12, folate, ferritin, or calcium and positive coeliac antibody test).

Treatment of Neisseria gonorrhoeae. There has been a recent change in the national guidance for the management of infection with *Neisseria gonorrhoeae* (NG) in patients without cephalosporin allergy ***(Epi-Insight February 2019;Vol 20, Issue 2)***. Updated guidance recommends that **patients with uncomplicated anogenital and pharyngeal gonorrhoea without cephalosporin allergy should receive 1g IM ceftriaxone monotherapy** (dual therapy with ceftriaxone and azithromycin is no longer recommended). The change in guidance occurred due to national and international concerns regarding emerging resistance in *NG* to 3rd generation cephalosporins. Clinicians are reminded to 1) send both nucleic acid amplification tests (NAAT) and charcoal swabs before treatment and 2) perform a test of cure two weeks after treatment to ensure clearance of the infection.

[**Editor's note**: further information on the management of *NG* is available on the HSE antibiotic prescribing website (https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/genital/gonorrhoea/gonorrhoea.html) and the National Guidelines for the Prevention and Control of Gonorrhoea which will be updated to reflect the change in guidance available on www.hpsc.ie]

Clozapine – monitoring for adverse events. Clozapine is an antipsychotic used for patients with treatment-resistant schizophrenia or those who have schizophrenia with severe, untreatable neurological adverse reactions to other antipsychotic agents. **The use of clozapine is restricted to patients who are registered with a clozapine monitoring service** and is usually initiated by mental health in-patient teams. A recent article discussed the **need for all healthcare professionals (HCPs) involved in the care of patients taking clozapine to be aware of the adverse effects (AEs) associated with clozapine use and the requirements for monitoring *(DTB 2019;57(3):42-47*).

AEs associated with clozapine use include **agranulocytosis** (risk highest in the first 18 weeks of treatment however may occur at any time), **hypotension** (usually in the first 4 weeks of treatment), **hypertension** (associated with long-term treatment), **tachycardia** (occurs in first 4 weeks, usually transient), **myocarditis** (most frequently occurs in first 6 to 8 weeks of treatment; potentially fatal), **cardiomyopathy** (median of 9 months), **venous thromboembolism** (rare; occurs at any time), **gastrointestinal effects** (e.g. constipation that is dose-related; associated with high mortality – ***early and aggressive treatment of constipation is essential***), **weight gain** (typically occurs in the first year), **dyslipidaemia, hyperglycaemia, sedation, enuresis, fever, seizures** (risk significantly increased when plasma clozapine level >500 microgram/L) and **hypersalivation**.

The clinical responsibilities for clozapine monitoring should be communicated between primary and secondary care. Prior to initiating clozapine, baseline investigations undertaken include blood pressure (BP), pulse, temperature, full blood count (FBC), urea and electrolytes (U&Es), ECG, fasting blood glucose, lipid and liver profiles. The patient's concomitant medications and smoking status (cigarettes can reduce clozapine levels) should be assessed. **Clinically significant interactions that may occur between clozapine and drugs/substances** include monoamine oxidase inhibitors, CNS depressants, anti-hypertensive agents, benzodiazepines, carbamazepine, lithium, phenytoin, warfarin, digoxin, CYP1A2-inducing substances (e.g. omeprazole) and CYP1A2-inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin, hormonal contraceptives). Initiation of clozapine therapy is restricted to patients with a white blood cell count (WBC) of ≥3.5 x 10^9/L and absolute neutrophil count (ANC) of ≥2.0 x 10^9/L. Many AEs are related to the speed of titration and are dose dependent; the initial dose of clozapine is given at night on day 1 and the dose is gradually increased over 2 to 3 weeks to minimise AEs such as postural hypotension. The following monitoring is recommended: **1) FBC** - while the patient is on clozapine (at least weekly for the first 18 weeks, fortnightly from week 18 to 52 and if stable after 1 year every 4 weeks), **2) clozapine plasma levels -** as required e.g. annually, change in smoking status, onset of AEs or start of interacting drug, **3) blood lipids** - every 3 months for the first year and then annually (more frequently if cardiovascular risk factors present), **4) weight -** frequently for 3 months, at 6 months and annually, **5) bowel movement status** - at each visit to primary care, **6) blood glucose** – 6 monthly, then annually, **7) BP and pulse** – 4 times a day for the first 15 days, frequently for up to 4 weeks, and at each primary care visit, **8) U&Es** – annually, **9) ECG** – before discharge to primary care and at least annually (or dose change), **10) electroencephalogram** if seizures occur or are suspected.

Patients should be assessed for signs of infection at each HCP appointment as clozapine-associated blood dyscrasias increase the risk of patients developing fatal infections. If an infection is suspected the primary care team should advise the patient to attend for a FBC immediately and to inform their mental health team. Immediate discontinuation of clozapine is required if either the WBC count is < 3.0x10^9/L or the ANC is < 1.5x10^9/L at any time during clozapine treatment. If a patient develops agranulocytosis, treatment should be stopped immediately and the patient admitted to an acute hospital. **All patients should be advised of the risks associated with clozapine and of the requirements for careful monitoring.** All patients should receive lifestyle advice; of note smoking decreases clozapine levels, therefore if a patient suddenly stops smoking clozapine levels may increase. Treatment interruptions of <48 hours can be restarted at the previous dose, however if >48 hours have elapsed, re-titration is required and the clozapine monitoring service informed. FBC monitoring should continue for at least 4 weeks after a patient stops clozapine.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. **This newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept of Therapeutics Trinity College, Trinity Centre, SJH.** Tel: Direct Line (01) 473 0589 or 1850 727 727 Email: nmic@stjames.ie @NationalNmic