Chapter 6 Additional notes

6.1 Drugs used in diabetes

6.1.1 Insulins

6.1.1.1 Short-acting insulins

- Insulins should always be prescribed by brand
- Soluble acting insulins take 30 to 60 minutes to act and can last for 6 to 8 hours and giving greater potential for hypoglycaemia
- Soluble acting insulin is used in insulin infusions (sliding scales)
- Soluble insulins should be administered 20 minutes before food
- All patients starting on insulin must inform the DVLA and also their motor vehicle insurance company
- Apidra®, Humalog® and Novorapid® advantageous in patients with very high post-prandial sugars
- People with glycaemic control problems should be properly assessed for underlying
- causes before these newer, more expensive insulins are considered (including education, understanding of the disease and its management)
- Rapid acting insulin analogues have a more rapid onset of action compared to soluble insulin, and should be injected with or just after food.
- Rapid acting insulins allow patients to adjust insulin doses according to carbohydrate intake
- All available pen devices are equally easy to use and reliable, costs are similar

6.1.1.2 Intermediate and long acting insulins

- The intermediate acting insulins are usually administered twice daily
- These insulins are first choice in type 2 diabetes when insulin is commenced in addition to oral antidiabetic medication
- Long acting insulin analogues should be administered at the same time each day and are usually once daily. Some patients may require BD dosing on specialist advice.
- Any decision to commence an insulin analogue needs to be balanced carefully against the lack of long term safety data and increased prescribing costs (see NPC document 'Key Therapeutic Topics' for full information).

6.1.2 Antidiabetic drugs

6.1.2.1 Sulfonylureas

- All patients prescribed oral antidiabetic medication who also have complications must inform the DVLA and also their motor vehicle insurance company
- Sulphonylureas should be stopped in pregnancy
- If also on insulin the dose of glimepiride should be reduced to 4mg daily
- Sulphonylureas can cause hypoglycaemia episodes
- Glibenclamide is not recommended for prescribing due to long duration of action and potential for serious hypoglycaemia in the over 70 year olds
- Sulphonylureas can lead to weight gain

Dosing information

- **Glimepiride:** Recommended start on 1mg once daily with breakfast and titrate up to the usual recommended maximum dose of 4mg. Licensed maximum dose is 6mg once daily, although there is little evidence of increased therapeutic affect at this dose.
- **Gliclazide:** Recommended: twice daily dosing; can be titrated up to a maximum dose of 160mg twice daily. Taken with breakfast and evening meal. 40mg once daily or twice daily maybe appropriate in the elderly. Dual excretion mechanism of action makes gliclazide safer in renal impairment.
- Consult the renal drug handbook for dosing advice in patients with renal impairment

6.1.2.2 Biguanides

- Glucophage® SR should only be used where the standard metformin tablets have been tried and are not tolerated due to GI problems. Any new prescription of the SR preparation should be reviewed soon after initiation (recommend checking HbA1c after 3 months and assess patient for compliance/adverse effects). Discontinue if not tolerated or ineffective.
- Metformin can be used in pregnancy under specialist supervision.
- Gastrointestinal side effects (nausea, vomiting, diarrhoea, abdominal pain) are common but are minimised by starting the medication slowly.
- Liquid formulations of metformin are available however are considerably more expensive. Prescribers should assess the need for a liquid preparation on an individual patient basis.
- **Dosing information**
- **Metformin**: Recommended: 500mg once daily with breakfast for the first week, 500mg twice a day with breakfast and evening meal for the second week.
- Can be titrated to the usual maximum dose of 1g twice a day or 850mg three times a day.
- Rarely prescribed as 1g three times a day. Evidence of added therapeutic effect at this dose is limited and doses >2500g/day significantly increase side effects.
- **Glucophage® SR**: Recommended: For those unable to tolerate standard release metformin, start at 500mg once daily and titrate to maximum dose of 2g once daily to be taken with main meal (dose can be split into twice a day dosing if once daily is not tolerated). This product has a reduced incidence of gastrointestinal side effects.

6.1.2.3 Other antidiabetic drugs

Pioglitazone

- Full effect of poiglitazone may not be seen for 3 – 6 months
- Pioglitazone is contraindicated in heart failure, patients should be monitored regularly for signs and symptoms of heart failure and treatment should be stopped if these develop
- Pioglitazone is contraindicated in patients with hepatic impairment; liver enzymes should be checked periodically based on clinical judgement. If ALT increases to three-times the upper limit of normal the patient should be reassessed as soon as possible. If ALT remains greater than three-times upper limit of normal – cease pioglitazone
- The risk of fracture should be considered in the care of patients, especially women, treated with pioglitazone. This can be assessed using FRAX: FRAX WHO Fracture Risk assessment tool

DPP-4 inhibitors (Gliptins)

MHRA Gliptins: Risk of pancreatitis Sept 2012

Acute pancreatitis associated with gliptins has been reported. Inform patients of the symptoms of acute pancreatitis. If pancreatitis is suspected, the DPP-4 inhibitor should be discontinued.

- Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months) –as per NICE CG87.
- Monotherapy:
  Saxagliptin, Sitagliptin and Linagliptin – YES – only if metformin contra-indicated or not tolerated.
- Renal impairment:
  Saxagliptin: Dose reduced to 2.5mg for use in moderate to severe renal impairment; caution in patients with severe renal impairment due to very limited experience of use in this group of patients.
  Sitagliptin: Dose is 50mg per day for use in moderate renal impairment and 25mg per day for use in severe renal impairment.
  Linagliptin: No dose adjustment required.
- Saxagliptin is currently cheaper than other gliptins.
- There are no head-to-head trial data to support the use of any gliptin over another in relation to patients who may fast during Ramadan.

GLP-1 receptor mimetics

- Patients should be warned of the common side effects before starting the treatment – nausea, vomiting.
- Patients who have had pancreatitis cannot use GLP-1 receptor mimetics.
- If the patient is prescribed antibiotics they must be taken an hour apart from the GLP-1 receptor mimetic injection.
- If patients are prescribed sulphonylureas in combination with a GLP-1 receptor mimetic the dose should be reduced initially due to the risk of hypoglycaemia.
- Exenatide is contraindicated if eGFR < 30ml/min. For patients with renal impairment (eGFR 30-50ml/min) dose escalation should be undertaken more cautiously.
- Liraglutide should be avoided if eGFR < 60ml/min except under specialist advice.
- Lixisenatide should be used in caution in patients with moderate renal impairment and avoided in patients with severe renal impairment.
- Exenatide slows gastric emptying. As a result it has several drug interactions consult www.medicines.org.uk for most up-to-date information.
- Patients prescribed warfarin should be monitored more closely as exenatide can cause an increase in INR.

Other diabetic agents (no class)

- **Repaglinide:** Recommended: initially 500 microgram dose, within 30 minutes of meal (1mg dose if transferring from another oral hypoglycaemic agent). Adjust dose at 1-2 week intervals depending on response, up to maximum of 4mg as a single dose. Maximum licensed total daily dose is 16mg daily.
- **Nateglinide**: Recommended: 60mg three times a day within 30 minutes of food. Can be adjusted up to 180mg three times a day.

6.1.5 Treatment of diabetic neuropathy

- Painful diabetic neuropathy is estimated to affect 16-26% of patients with diabetes.
- For diabetic neuropathy – discontinue treatment if inadequate response after 2 months. Treatment should be reviewed after one month to identify if the treatment is beneficial in line with UK primary care guidelines for neuropathic pain.
- Review of treatment should include assessment of:
  - Pain reduction
  - Adverse effects
  - Daily activities and participation (including ability to work and drive)
  - Mood (in particular, whether the person may have depression and/or anxiety)
  - Quality of sleep
  - Overall improvement as reported by the person
- Neuropathic pain improves with improved glycaemic control; non-pharmacological methods should also be employed and may avoid the need for pharmacological therapy.
- Neuropathic symptoms fluctuate early in the disease therefore, periodic trials of cessation of therapy should be considered
- Amitriptyline is unlicensed for diabetic neuropathy. Start at doses of 10mg daily, increasing to 75mg daily. Doses above this should be used only under Specialist supervision.
- Nortriptyline is an alternative to amitriptyline if this is not tolerated. Doses are the same as for amitriptyline.
- If duloxetine and amitriptyline are not effective (at maximum tolerated doses) the patient should be changed to gabapentin and subsequently if not tolerated, contra-indicated or ineffective to pregabalin. If the patient is still not managed on this drug alone it can be used in combination with duloxetine or amitriptyline.
- Pregabalin should be prescribed as twice daily dosing to improve patient adherence, reduce overall treatment cost and is as efficacious as thrice-daily.
- Patients should be referred to specialist clinics if the duloxetine/amitriptyline or pregabalin fail to control pain as documented above.
- Capsaicin cream 0.075% may be used in diabetic patients for severe neuropathic pain – see chapter 10 for more details.

6.2 Thyroid and antithyroid drugs

6.2.1 Thyroid hormones

- On initiation of levothyroxine: Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia. If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose
- When prescribing levothyroxine, micrograms should not be abbreviated
- There have been concerns recently of differences in bioavailability in the solution, with an increase in potency of around 10% which is particularly significant in patients on higher doses, therefore the solution is not recommended for prescribing.

6.2.2 Antithyroid hormones

- Counselling for patients is required with carbimazole/propylthiouracil due to the risk of blood dyscrasias and bone marrow suppression. Warn patient to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise or non-specific illness develops
- If the patient has signs of bone marrow suppression (neutropenia and agranulocytosis) treatment should be stopped promptly:
- A white blood cell count should be performed if there is any clinical evidence of infection
- Carbimazole/propylthiouracil should be stopped promptly if there is clinical or laboratory evidence of neutropenia
- Signs and symptoms of liver injury should be closely monitored in the first 6 months. TFTs should be under taken every 1-3 months until stable. (See references below NELM/FDA)
- Higher doses than 40mg daily should be prescribed under Specialist supervision only.
- Propylthiouracil is used where this is a known sensitivity to carbimazole or in pregnancy.
- Lugols iodine (aqueous iodine) is sometimes used prior to partial thyroidectomy, in patients prescribed antithyroid drugs, but there is little evidence of beneficial use.

6.3 Corticosteroids

6.3.1 Replacement therapy

- Fludrocortisone (mineralocorticoid) is commonly used in deficiency states in combination with hydrocortisone (cortisol).
- When prescribing fludrocortisone do not abbreviate micrograms.

6.3.2 Glucocorticoid therapy

- Steroids have many side effects (short-term and long-term) associated with their use – consult the BNF or SPC for the prescribed drug for full information.
- Where ever possible, the course of steroid treatment should be kept as short as possible.
- Warn patients about the short-term and long-term adverse effects associated with their use.
- Steroid cards should be issued to all patients who are prescribed steroids for longer than 3 weeks.
- Steroids should be given early in the day to reduce insomnia.

Equivalent anti-inflammatory doses of corticosteroids (as per BNF):

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action	
Prednisolone 5 mg	
≡	Betamethasone 750 micrograms
≡	Dexamethasone 750 micrograms
≡	Hydrocortisone 20mg
≡	Methylprednisolone 4 mg
≡	Triamcinolone 4 mg

- Different preparations of dexamethasone contain different salts. Ensure patients receive equivalent doses when transfer from injection to oral formulations.

Dose equivalence between dexamethasone formulations is:
- 1mg dexamethasone tablets =
- 1.2mg dexamethasone phosphate (injections) =
- 1.3mg dexamethasone sodium phosphate (injections and oral solutions)

- Withdrawal of corticosteroids: gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:
  - Recently received repeated courses (especially if taken for >3 weeks)
  - Taken a short course within 1 year of stopping long-term therapy
  - Other possible causes of adrenal suppression
  - Received >40mg daily prednisolone (or equivalent)
  - Been given repeat doses in the evening
  - Received more than 3 weeks treatment
- Corticosteroids that are taken for longer than 3 weeks must not be stopped abruptly.
- Hydrocortisone is first-line treatment for adrenocortical insufficiency and hypersensitivity.
- For adrenocortical insufficiency usual maintenance dose is 10mg in the morning, 5mg at midday and 5mg in the early evening. Annual testing of cortisol day curves should be performed to check adequacy of replacement
- Dexamethasone has very high glucocorticoid activity and low mineralocorticoid activity therefore is suited to treat those conditions where additional fluid retention or oedema may be a problem e.g. cerebral oedema.
- Methylprednisolone is used IV for specific conditions requiring high dose, short-term treatment.
- Triamcinolone depot injections are not recommended for use in preference to oral prednisolone for hay fever and other allergies (see ref UKMi Q&A)

6.4 Sex hormones

6.4.1 Female sex hormones

6.4.1.1 Oestrogens and HRT

The benefits of *short-term treatment* are still considered to outweigh the risks for the majority of women.

- The lowest effective dose should be used for the shortest duration
- Each decision to start HRT should be made on an individual basis with a fully informed woman.
- Treatment should be reviewed at least annually in the light of new knowledge and changes in a woman's risk factors.

Prevention of osteoporosis

- HRT should not be considered first-line therapy for the long-term prevention of osteoporosis in women >50 years old and at an increased risk of fractures.
- The use of HRT for the prevention of osteoporosis is well established, although the benefits appear to be confined to current or recent users, and it is unlikely that taking oestrogen therapy in the first decade after the menopause protects against fractures in later life. Not all preparations are licensed for osteoporosis prophylaxis. It is also useful in preventing bone loss, only for as long as it is used
- This advice does not necessitate any urgent changes but women currently receiving HRT, as long-term prophylaxis should have their treatment reviewed at the next appointment.

Women with premature menopause

- HRT may be used in younger women who have experienced a premature menopause (due to ovarian failure, surgery or other causes) for treating their menopausal symptoms and preventing osteoporosis until the age of 50 years. After this age, therapy for preventing osteoporosis should be reviewed and HRT considered a second-line choice.

Healthy women without symptoms

- The risk: benefit of HRT is generally unfavourable. Further information is available from: MHRA HRT March 2010

Definite Benefits

- Control of menopausal symptoms – such as hot flushes, night sweats and vaginal dryness.

General notes

- Oral preparations tend to be cheaper and more widely used
- Prior to prescribing patients should be made aware that Premarin®, Prempak-C® and Premique® are derived from horse urine
- Products containing 2/3 different formulations will attract multiple prescription charges. This should be discussed with the patient when prescribing
- Raloxifene is licensed for the treatment and prevention of postmenopausal osteoporosis; unlike HRT therapy, raloxifene does not reduce menopausal vasomotor symptoms
- Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women: **NICE TA160: Osteoporosis - primary prevention**
- **NICE TA161: Osteoporosis -secondary prevention** recommends raloxifene as an alternative treatment option in osteoporosis, under the certain circumstances
- Estradiol levels are rarely indicated. If it is thought necessary to perform such tests, please seek advice from the biochemistry laboratory or a specialist as to which test to use
- Tibolone should only be prescribed in post-menopausal women with predominantly androgenic symptoms e.g. decreased libido, vaginal atrophy, pre-existing low mood. See SPC for additional prescribing notes of tibolone.

6.4.1.2 Progestogens

- Progesterone pessaries are not recommended for prescribing
- Progesterones have been used for the prevention of spontaneous abortion in women with a history of recurrent miscarriage (habitual abortion) but there is no evidence of benefit and they are not recommended for this purpose.

6.4.2 Male sex hormones

- Oral testosterone is often not sufficient to provide adequate testosterone replacement, but may have a place for use in elderly patients who are unable to apply gels/inappropriate for implants/injection
- Two gel products are included to provide for patient preference, Testogel® has a runnier consistence; Tostran® is available as a multi-dose dispenser, allows more dose flexibility.
- Testosterone buccal muco-adhesive tablets have been included as an option for patients who require high doses of testosterone as this is the most cost-effective option in comparison.
- Sustanon® injection may be used for androgen deficiency.
- Implants may be used in gynaecology to improve libido (unlicensed). A 25mg implant is available, but on a named patient basis only.
- Hepatotoxicity. Direct hepatic toxicity including jaundice, hepatitis and hepatic failure has been reported (usually after several months) in patients treated with cyproterone acetate 200-300mg daily. Liver function tests should be performed before treatment and whenever symptoms suggestive of hepatotoxicity occur-if confirmed cyproterone should normally be withdrawn.
- Finasteride results in shrinkage of prostatic glandular tissue. The evidence suggests that it can reduce the risk of acute urinary retention and need for surgery, although such events are relatively uncommon. It may be useful in men whose prostates are particularly large where TURP/surgery is not indicated or desired. Improvement may take 6 months to be observed. Treatment of BPH is more fully reviewed in chapter 7.

6.5 Hypothalamic and pituitary hormones and anti-oestrogens

Growth hormone

Adults:

- Treatment is recommended in adults only if the following 3 criteria are fulfilled (as per NICE TA64):

  Severe growth hormone deficiency, defined as peak GH response of <9mU/litres (3mg/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test.

A perceived impairment of quality of life (QoL) as demonstrated by a reported score of at least 11 in disease-specific 'Quality of Life Assessment of growth hormone deficiency in adult' (QoL-AGHDA) questionnaire.
Already receiving treatment for any other pituitary hormone deficiencies as required.

- Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months. Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved.
- Treatment for adult-onset growth hormone deficiency should be stopped only when the patient's physician consider it appropriate.
- Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone disorders; maintenance treatment can be prescribed in the community under a shared care protocol.
- Somatropin (Genotropin®) can be used with the Genotropin® pen and GoQuick® pen – these are available free of charge from clinics.

Growth hormone receptor antagonists

- Treatment should be initiated by a specialist experienced in the management of acromegaly
- Rotate injection site to prevent lipohypertrophy
- Maximum dose should not exceed 30mg/day
- See SPC for full monitoring requirements

6.5.2 Posterior pituitary hormones

- MHRA: Desmopressin nasal spray: Removal of the primary nocturnal enuresis (bedwetting) indication. At the request of the MHRA, the indication for the treatment of primary nocturnal enuresis (PNE) has been removed from all desmopressin nasal spray products. Desmopressin tablets currently remain licensed for primary nocturnal enuresis and may be an option for those patients with swallowing difficulties.
- Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal). The risk of hyponatraemia convulsions can also be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs that increase secretion of vasopressin (e.g. tricyclic antidepressants).
- In nocturia and nocturnal enuresis limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards.
- In nocturia periodic blood pressure and weight checks are needed to monitor for fluid overload.

6.6 Drugs affecting bone metabolism

6.6.2 Bisphosphonates and other drugs affecting bone metabolism

- A weekly preparation should be used for osteoporosis to improve concordance and tolerability.
- Risedronate 30mg is only licensed for patients with Paget's Disease (not osteoporosis)
- Oral bisphosphonates are absorbed very poorly; therefore counselling should be given to the patient as to how and when administration is most appropriate.
- Before considering a second-line treatment, check compliance with patient.
- All oral bisphosphonates should be taken in combination with calcium & vitamin D. First-choice formulation is listed in chapter 9; the patient should be offered the product they like the best to achieve concordance.
- Alendronic acid, and possibly risedronate, can cause severe oesophageal reactions. Patients should be advised to discontinue treatment and seek medical attention if they develop symptoms of oesophageal irritation, new or worsening heartburn, pain on swallowing or retrosternal pain. Strict guidelines on administration should be followed.
- Raloxifene is a treatment option in women who are unable to tolerate or are contra-indicated to bisphosphonates or if the patient has further fragility fractures on Bisphosphonates.
- Zoledronic acid is contraindicated in patients with creatinine clearance < 35 ml/min.

- Strontium is an option for patients who are unable to take oral bisphosphonates and are unable to have injectable treatments – see NICE TA160 (primary prevention) and NICE TA161 (secondary prevention)

  Strontium is contraindicated in patients with current VTE or a history of VTE, as well as patients who are temporarily or permanently immobilised, in line with MHRA guidance.

  When treating patients > 80 years of age at risk of VTE, doctors should re-evaluate the need to continue treatment with strontium.

  Prescribers should make patients aware of the time-to-onset and likely signs and symptoms of severe skin reaction such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

  The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3-6 weeks for DRESS. Symptoms or signs of SJS or TEN include progressive skin rash, often with blisters or mucosal lesions; symptoms of DRESS include rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease).

  Patients should stop treatment immediately when symptoms of severe allergic reactions, including skin rash, occur. Treatment should not be re-started at any time in these patients.
- The MHRA have issued guidancearound the use of bisphosphonates which includes information about:

  Oesophageal irritation, oesophageal ulcers
  Oesophageal cancer (benefits considered to outweigh risks)
  Osteonecrosis of the jaw
  Atrial fibrillation
  Atypical femoral fractures
  Adverse effects on renal function
- Severe allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported in patients taking strontium ranelate (although these are rare (<1 in 10,000)). DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Cessation of the drug usually leads to subsistence of DRESS. Patients should be advised to stop taking strontium ranelate and consult their doctor immediately if skin rash develops. Treatment with strontium ranelate should not be restarted
- MHRA Drug Safety update warns of severe symptomatic hypocalcaemia in patients receiving denosumab 60 mg (Prolia©). Pre-existing hypocalcaemia must be corrected prior to initiating denosumab. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

6.7 Other endocrine drugs

- MHRA: Ergot derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses
- The ergot-derived dopamine-receptor agonists, bromocriptine, cabergoline, lisuride and pergolide have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions. Before starting treatment with these ergot derivatives, investigations such as measurement of ESR, U&Es and a chest X-ray may be appropriate. If long-term treatment is expected, then lung function tests may be helpful. Patients should be monitored for progressive fibrotic disorders. The British Endocrine Society recommends annual ECHO for patients who are prescribed bromocriptine and cabergoline.
- Excessive daytime sleepiness and sudden onset of sleep can occur with dopaminergic drugs. Patients starting treatment with these drugs should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery.
- Bromocriptine and cabergoline can be used in pregnancy however advice should be sought from the Specialist or local medicines information centre before prescribing or before the patient is planning on becoming pregnant.
- Cabergoline has an advantage of administration on a once weekly basis although it is more expensive than bromocriptine. Evidence suggests it is better tolerated.