Guidance Pack of Treatment Options for Type 2 Diabetes Patients

Contents:

- Flow chart of treatment options for blood glucose control
- Supporting information of medication options
- Self-Monitoring of Blood Glucose Guidance
- Treatment Options for Blood Lipids: See Surrey Prescribing Advisory Database (PAD)
- Guidance for the Treatment of Diabetic Neuropathy.

Perminder Oberai, Primary Care Pharmacist, North West Surrey Clinical Commissioning Group.
Produced November 2012
Updated September 2013
Review November 2014
**Treatment options for patients with type 2 diabetes**

Institute lifestyle interventions and agree HbA1c target with patient (usually < 59mmol/mol).
Agreed HbA1c target should be appropriate for the individual.

**First line therapy options**

- **Initiate metformin** if eGFR >45ml/min (ser creat <130micromol/l)
  - Titrate slowly to reduce incidence of side effects
  - If metformin not tolerated try metformin SR
  - If metformin not tolerated or contraindicated or if rapid response required then use a sulphonylurea (SU).
  - Offer Self Monitoring of Blood Glucose (SMBG) to patients using a SU.

**AT EVERY STEP:**
- EDUCATE: reinforce importance of lifestyle interventions
- Check adherence
- Assess hypoglycaemia risk
- Optimise BP and cholesterol management
- Refer to patient structured education if available
- Consider referral to Medicines Use Review (MUR) or New Medicines Service (NMS) at a pharmacy
- Patients to self monitor blood glucose (SMBG) if appropriate

If HbA1c is significantly high or targets have not been met:

- Teach SMBG to all patients before insulin initiation unless inappropriate
- Use human insulin first line for basal or mixed insulin in appropriate patients
- Move onto analogue insulin in patients who have problems of hypoglycaemia
- Offer insulin passport + information booklet

**Choose ONE of these options for as add-on second line therapy (order not to denote any preference)**

- **Sulphonylurea**
  - Advantages: Generally recommended as second-line
  - Disadvantages: Low cost (Consider cost of SMBG)

- **Gliptin**
  - Advantages: Low hypoglycaemic risk
  - Disadvantages: Weight neutral

- **GLP-1 mimetic**
  - Advantages: Low hypoglycaemic risk
  - Disadvantages: A second-line therapy for those whom weight loss is a therapeutic priority

- **Glitazone**
  - Advantages: Consider in people with very significant features of metabolic syndrome
  - Disadvantages: Low hypo risk

- **SGLT-inhibitor** (eg dapagliflozin)
  - Advantages: Low hypoglycaemic risk
  - Disadvantages: Weight loss

If patient is symptomatic with HbA1c>75 mmol/L and has unintentional weight loss consider early insulin or refer to secondary care.

**Choose ONE of these options for add-on third line therapy (Order not to denote any preference)**

- **Sulphonylurea**
- **Gliptin**
- **GLP-1 mimetic**
- **Glitazone**

**DO NOT use GLP-1 mimetic with a Gliptin**

**SGLT-inhibitor**
- Only for use with insulin +/- other oral hypoglycaemic agents BUT NOT as a third-line option before insulin.
- Do not use with pioglitazone due to potential increased bladder cancer risk

**Insulin**
- When targets have not been met or HbA1c is significantly high
- Teach SMBG to all patients before insulin initiation unless inappropriate
- Use human insulin first line for basal or mixed insulin in appropriate patients
- Move onto analogue insulin in patients who have problems of hypoglycaemia
- Offer insulin passport + information booklet

**PLEASE CHECK CURRENT LICENSED INDICATIONS and MONITORING REQUIREMENTS FOR MEDICATIONS:**
# Treatment Options for Patients with Type 2 Diabetes - Prescribing Information

Prices taken from September 2013 Drug Tariff

Please check full specific product characteristics for more detailed and current information: [http://www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)

## Contraindications

- Ketoacidosis
- General anaesthetics (suspend treatment)
- Iodine-containing x-ray contrast media (suspend treatment)

## Cautions and Monitoring Requirements

### Metformin

- Caution in renal impairment – determine renal function before initiation and monitor annually (or more frequently if high risk)
- Stop if eGFR <30
- Use with caution if eGFR <45
- Stop in severe acute illness e.g. pneumonia, sepsis, heart attack. Can be re-started once acute illness resolved.

### Sulphonylureas

#### Long acting:
- Glibenclamide
- Porphyria.
- Ketoacidosis.
- Severe renal impairment (avoid where possible)
- Avoid glibenclamide in the elderly, use a shorter acting alternative

#### Shorter acting:
- Glimepiride
- Gliclazide
- Tolbutamide
- Glipizide
- Can cause hypoglycaemia and usually indicates excessive dosage
- Caution in mild to moderate renal impairment – use tolbutamide or gliclazide and monitor blood glucose carefully

## Advantages

- Evidence base strong for reduction in patient-orientated outcomes (POOs – morbidity and mortality)
- No hypoglycaemia
- No weight gain
- Cost (except liquid formulation which is very expensive)

## Disadvantages

- Gastro-intestinal side effects. Titrate dose gradually to maximum tolerated. Try modified-release if standard not tolerated.
- MR preparations cannot be crushed or broken
- Use metformin sachets when patient has swallowing difficulties

### Monthly Cost

- **Metformin**
  - Standard tablets: £2.00
  - Modified-release tablets: £5.32 for 56 tabs 500mg
  - Metformin 1g sachets: £13.16 for 60 sachets
  - Metformin liquid 500mg/5ml: >£120

- **Sulphonylureas**
  - Glibenclamide: £15.00
  - Glimepiride: £6.00
  - Gliclazide: £4.00
  - Tolbutamide: £75.00
  - Glipizide: £5.00

### Contraindications

- Porphyria.
- Ketoacidosis.
- Pregancy
- G6PD deficiency

### Advantages

- Evidence that patient-oriented outcomes (POOs) are positively influenced
- Similar HbA1c reductions to metformin
- Cost
- Relatively well tolerated

### Disadvantages

- Weight gain
- Safety concerns include hypoglycaemia – more likely with longer acting agents (such as glibenclamide), at high doses, in the elderly or in the presence of renal failure
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<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td><strong>Gliptins</strong></td>
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<tr>
<td>(DPP-4 Inhibitors)</td>
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<tr>
<td>Saxagliptin</td>
<td>£31.60</td>
<td>Ketoacidosis. Pregnancy and breastfeeding</td>
<td>In combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia</td>
<td>• Similar HbA1c reductions to glitazones</td>
<td>• No POO data</td>
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<tr>
<td>Kombolyze®</td>
<td>£31.60</td>
<td></td>
<td></td>
<td></td>
<td>• No long term safety data</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>£33.26</td>
<td></td>
<td></td>
<td></td>
<td>• Cost</td>
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<tr>
<td>Janumet®</td>
<td>£33.26</td>
<td></td>
<td></td>
<td></td>
<td>• Avoid in pregnancy and whilst breastfeeding</td>
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<tr>
<td>Vildagliptin</td>
<td>£31.76</td>
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<td></td>
<td></td>
<td>• Safety concerns include skin disorders, pancreatitis, hypersensitivity reactions and liver dysfunction with vildagliptin▼</td>
</tr>
<tr>
<td>Eucreas®</td>
<td>£31.76</td>
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<tr>
<td>Linagliptin▼</td>
<td>£33.26</td>
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<tr>
<td>Jentadueto▼</td>
<td>£33.26</td>
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<td><strong>Please note:</strong> combination drugs are not routinely supported but should be considered in patients with poor compliance / high pill burden</td>
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<tr>
<td><strong>Sitagliptin</strong></td>
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<td>- has mono, dual and triple therapy license</td>
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<td>- license with insulin</td>
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<td><strong>Vildagliptin</strong></td>
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<tr>
<td>- dual therapy license with metformin or sulphonylurea or glitazones</td>
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<tr>
<td>- license with insulin</td>
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</tbody>
</table>

**Contraindications:**
- Ketoacidosis.
- Pregnancy and breastfeeding

**Cautions and monitoring requirements:**
- In combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia
- Caution in >75yrs

**Advantages:**
- Similar HbA1c reductions to glitazones
- No weight gain
- Low risk of hypoglycaemia

**Disadvantages:**
- No POO data
- No long term safety data
- Cost
- Avoid in pregnancy and whilst breastfeeding
- Safety concerns include skin disorders, pancreatitis, hypersensitivity reactions and liver dysfunction with vildagliptin▼
## Treatment Options for Patients with Type 2 Diabetes

### Prescribing Information

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<tr>
<td><strong>Saxagliptin:</strong></td>
<td></td>
<td>- dual therapy – with metformin or a sulphonylurea or a glitazone</td>
<td>- is cautioned in moderate hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- triple therapy – with metformin + sulphonylurea (not licensed for triple with a glitazone)</td>
<td>- CYP3A4 inducers like phenytoin and rifampicin may reduce the glycaemic lowering effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- as combination therapy with insulin (with or without metformin)</td>
<td><strong>Komboglyze®:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Linegliptin</strong></td>
<td>- do not use in hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- monotherapy when metformin not appropriate / tolerated - dual therapy with metformin only</td>
<td>- do not use in moderate to severe renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- triple therapy with metformin + sulphonylurea only</td>
<td><strong>Jentadueto</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>license with insulin (+/- metformin) but not the combination product</td>
<td>- do not use in moderate or severe renal impairment (CrCl &lt; 60 ml/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Jentadueto®</strong>:</td>
<td>- do not use in hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Linegliptin</strong>:</td>
<td><strong>Saxagliptin</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- reduce dose to 2.5mg in moderate or severe renal impairment. Do not use in end stage renal disease.</td>
<td>- is cautioned in moderate hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- do not use in severe hepatic impairment</td>
<td>- CYP3A4 inducers like phenytoin and rifampicin may reduce the glycaemic lowering effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- avoid in heart failure</td>
<td><strong>DPP-4 Inhibitors should be continued only if the patient shows a reduction of at least 0.5% in HbA1c in 6 months. This should be explained to the patient at initiation</strong></td>
</tr>
</tbody>
</table>

**Advantages**

**Disadvantages**
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<tr>
<td><strong>GLP-1s</strong></td>
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<tr>
<td>Exenatide(Byetta®)</td>
<td>£68.24</td>
<td>Pregnancy and breastfeeding</td>
<td>Check renal (and hepatic function with liraglutide) prior to initiation</td>
<td>• Similar HbA1c reductions to insulin and some other comparators</td>
<td>• Parenteral</td>
</tr>
<tr>
<td>Exenatide once-weekly: Bydureon®</td>
<td>£73.36</td>
<td>Ketoacosis.</td>
<td>In patients taking Byetta® and CrCl: 30-50 ml/min, dose escalation should proceed conservatively</td>
<td>• Weight loss</td>
<td>• No POO data from RCTs</td>
</tr>
<tr>
<td>Liraglutide(1.2mg)</td>
<td>£78.48</td>
<td>Acute pancreatitis.</td>
<td>History of pancreatitis. Patients should be told how to recognise signs and symptoms of pancreatitis</td>
<td>• Low risk of hypoglycaemia</td>
<td>• No long term safety data</td>
</tr>
<tr>
<td>Liraglutide(1.8mg but not recommended for use)</td>
<td>£117.72</td>
<td>Severe gastro-intestinal disease (exenatide▼)</td>
<td>Heart failure - limited experience with liraglutide in New York Heart Association (NYHA) class I-III and no experience in heart failure NYHA class III-IV</td>
<td></td>
<td>• Cost</td>
</tr>
<tr>
<td>Lixisenatide▼</td>
<td>£54.14 (20mcg) £27.07 (10mcg)</td>
<td>Do not use liraglutide or lixisenatide in inflammatory bowel disease, gastroparesis</td>
<td>Caution in patients &gt;70yrs</td>
<td></td>
<td>• Potentially severe pancreatitis and renal failure with exenatide▼</td>
</tr>
<tr>
<td><strong>Liraglutide</strong>: only licensed for use with the basal insulin detemir</td>
<td></td>
<td>In hepatic impairment do not use liraglutide</td>
<td>Reduction of dose of concomitant sulphonylurea or insulin may be needed to avoid hypoglycaemia. Caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio</td>
<td>• Similar HbA1c reductions to insulin and some other comparators</td>
<td>• Very common GI side-effects</td>
</tr>
<tr>
<td>Exenatide▼ and Lixisenatide▼ licensed for use with any basal insulin</td>
<td></td>
<td><strong>Renal impairment:</strong> -do not use exenatide▼ if creatinine clearance &lt;30ml/min, Bydureon▼ and Lixisenatide▼ if CrCl &lt;50ml/min, or liraglutide if &lt;60ml/min.</td>
<td>Dual Therapy: Continue therapy if 1% HbA1c reduction at 6 months. (<a href="#">Please explain to the patient at initiation</a>)</td>
<td></td>
<td>Use in patients with: --A body mass index (BMI) ≥ 35 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, OR --A BMI &lt; 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.</td>
</tr>
<tr>
<td>NHS Surrey has produced amber shared care guidance for patients who are taking large doses of insulin and may benefit the addition of a GLP-1 mimetic. NHS Surrey Guidance</td>
<td></td>
<td><strong>Advantages</strong>:</td>
<td><strong>Disadvantages</strong>:</td>
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</tbody>
</table>

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**Please note:**

- Parenteral
- No POO data from RCTs
- No long term safety data
- Cost
- Potentially severe pancreatitis and renal failure with exenatide▼
- Very common GI side-effects

**Use in patients with:**

- A body mass index (BMI) ≥ 35 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, OR
- A BMI < 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
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<tbody>
<tr>
<td><strong>Glitazones</strong></td>
<td></td>
<td><strong>Pioglitazone</strong></td>
<td></td>
<td>• Similar HbA1c reductions to metformin or sulfonylurea</td>
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<tr>
<td></td>
<td>£4.00 for generic tablets</td>
<td>Current or history of bladder cancer</td>
<td>• No convincing evidence that POOs (patient orientated outcomes) are positively influenced</td>
<td></td>
</tr>
<tr>
<td></td>
<td>£35.89 for combination product Pioglitazone15mg/metformin 850mg (Competact®)</td>
<td>Patients with uninvestigated macroscopic haematuria</td>
<td>• Safety concerns include heart failure (particularly in combination with insulin), fractures, new-onset or worsening diabetic macular oedema, possible association with bladder cancer with pioglitazone</td>
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<tr>
<td></td>
<td></td>
<td>Diabetic ketoacidosis</td>
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<td>• Low risk of hypoglycaemia</td>
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<td>Cardiac failure or history of heart failure (NYHA stages I to IV)</td>
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<td>• Cost</td>
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<td>Hepatic impairment</td>
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<td></td>
<td></td>
<td>Pregnancy and breastfeeding</td>
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<td></td>
<td></td>
<td>Risk factors for bladder cancer and heart failure should be assessed before initiating</td>
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<td>Liver enzymes should be checked prior initiation in all patients. Do not initiate in patients with increased baseline liver enzyme levels (ALT &gt; 2.5 X upper limit of normal) or with any other evidence of liver disease. Periodic monitoring of liver enzymes is also required</td>
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<td>Weight increase may be a symptom of cardiac failure; therefore weight should be closely monitored</td>
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<td>Fracture risk should be considered</td>
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<td>Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors</td>
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<td></td>
<td></td>
<td><strong>Pioglitazone and should be continued only if the patient shows a reduction of at least 0.5% in HbA1c in 6 months. This should be explained to the patient at initiation</strong></td>
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</table>
| SGLT inhibitors        | **£36.59**   | Patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m²)  
Patients receiving loop diuretics  
Patients > 75 years  
Patients concomitantly treated with pioglitazone  
Pregnancy  
Breast-feeding | Patients who are volume depleted, e.g. due to acute illness (such as GI illness) or have intercurrent conditions that may lead to volume depletion. Monitoring of volume status (e.g. physical examination, BP measurements,) and electrolytes is recommended. Temporary interruption of dapagliflozin is recommended for patients who develop volume depletion until depletion is corrected  
Dapagliflozin may increase diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations  
Experience in heart failure, NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV  
Could cause increase in haematocrit.  
Dapagliflozin has not been studied in combination with glucagon-like peptide 1 (GLP-1) analogues  
A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin | - Low risk of hypoglycaemia  
- No weight gain | - No POO data  
- No long term safety data  
- Cost  
- Potential increase in urinary tract and genital infections |
Self-monitoring of Blood Glucose Guidelines (SMBG)

**Diet and Exercise**
- Metformin, pioglitazone, Gliptins, GLP-1 mimetics, SGLT2 inhibitors as monotherapy or in combination

**Sulphonylureas nataglinide, replaginide**, as monotherapy or in combination with other diabetes drugs

**INSULIN** as monotherapy or with or without other diabetes drugs

- Low risk of hypoglycaemia
- Patients do not routinely need to test unless there is an agreed purpose to test.

- Increased risk of hypoglycaemia
- Test two to three times a week.
- Drivers will need to test before driving (see DVLA guidance or Diabetes UK)

- High risk of hypoglycaemia
- Drivers may need to test before driving (see DVLA guidance or Diabetes UK)
- If on ONCE DAILY insulin with oral agents then depending on patient circumstances, one or more blood tests a day, at different times of the day.
- If on TWICE DAILY insulin regimen then 1-2 blood tests a day often before meals when insulin is due.
- If on a basal bolus regimen and carbohydrate counting may need at least 4 blood tests a day.
- If on an insulin pump then 4-6 blood tests a day.

**Blood glucose levels should be taken at various times in the day:**
- Before meals
- 2 hours post meal
- At bedtime

**Key questions to think about before continuing SMBG:**
1. Is SMBG appropriate for this patient?
2. Is the patient’s blood glucose well controlled?
3. What value does self-monitoring add to the patient’s care?

Consider stepping down or stopping SMBG in the following:
- When patient’s therapy is changed and does not cause hypoglycaemia.
- If patients control is quite stable.
- After pregnancy (if not breastfeeding)
- Once recovered from intercurrent illness (Including on discharge from hospital)
- If SMBG has a negative effect on wellbeing.
- If no action is being taken on results

Consider stepping up SMBG in the following:
- Initiation or escalation of treatment
- Deteriorating control eg. Increased frequency of hypoglycaemia
- Planning or during pregnancy
- Breastfeeding
- Intercurrent illness (refer to local sick day rules if available)
- Ensure safety during activity e.g. exercise or driving

Testing times and targets should be agreed with patients regularly
- Consider using just HbA1c testing, in those who will not benefit from SMBG testing
- Structured education should always be offered when initiating and continuing SMBG
Treatment of Diabetic Neuropathy

- In patients with diabetes, poor glycaemic control is a key risk factor for peripheral diabetic neuropathy.
- A Canadian Health Technology Assessment concludes that in patients with neuropathic pain there is no statistically significant difference in clinical response rates between tricyclic antidepressants, anticonvulsants and serotonin-norepinephrine reuptake inhibitors (SNRIs).

**Step 1**

Can be combined with step 2 OR step 3 to maximise treatment

**Tricyclic antidepressant** (TCA) (a)- unless contra-indicated. NB: TCAs are not licensed for use as painkillers although they have proven efficacy

*Amitriptyline* - titrate slowly to reduce side effects.

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
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</thead>
<tbody>
<tr>
<td>10mg</td>
<td>20mg</td>
<td>30mg</td>
<td>40mg</td>
<td>50mg</td>
</tr>
</tbody>
</table>

- Take at night to reduce ‘hangover effect’ and promote sleep.
- Usual maximum dose is 50mg daily but 75mg may be used if patient deriving benefit with limited side effects.
- Titrate down slowly if stopping therapy.

Consider use of **nortriptyline** if side effects of amitriptyline are not tolerated or in patients with cardiac disease. Patients should be encouraged to persist with treatment as some tolerance to side-effects seems to develop.

**Step 2**

1st choice if TCA contraindicated or lancinating pain (electric shock-like piercing or stabbing sensation)

**Gabapentin**

- Continue increasing as above to maximum 1200mg TDS - determined by efficacy and side effects.
- Anticonvulsants should be weaned down but not stopped suddenly (or inadvertently run out of). Advice should be given to patient and carer(s) of possible drowsiness and effect on driving.

**Step 3**

**Duloxetine 60mg** once daily. In trials a total daily dose of 120mg (60mg twice daily) was not found to be superior to 60mg per day (7). Response is seen within one week and is unlikely if not seen by eight weeks. Patient to be reviewed on a regular basis every 3 months.

Contraindicated in (for full details see SPC):
- Liver disease resulting in hepatic impairment
- Severe renal impairment (creatinine clearance <30 ml/min)

Abrupt discontinuation of duloxetine should be avoided. When stopping treatment with duloxetine the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions.

**Step 4**

Refer to secondary care specialist diabetes or pain clinic if:

- Patient’s symptoms are unresponsive to treatment and an acceptable reduction in pain is not achieved.
- The patient is responding but suffering unacceptable side-effects and all options above have been considered.
- The patient does not want drug therapy.
- Need further advice or diagnosis on the particular clinical symptom set.
- Bio-psychosocial needs and difficulty in managing/coping.

This Treatment of Diabetic Neuropathic pain guidance produced by Mandeep Allingham, Prescribing Advisor, NHS North West Surrey CCG Dec 2013
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