Autonomic Neuropathy in Diabetes

**Aim(s) and objective(s)**

Autonomic Neuropathy can be a disabling complication of diabetes. It is difficult to recognise, diagnose and manage. Treatment options are limited but include improving glycaemic control and symptomatic measures.

This guideline serves to increase awareness of these possible complications in Diabetes and assist in their management.

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**User group**

Primary Care Clinicians
Secondary Care Clinicians
Diabetes Specialist Staff

This guideline is not intended to serve as a protocol or standard of care. That is best based on all clinical data available for an individual case and may be subject to change as scientific knowledge and technology advances and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same result. Ultimately a judgement must be made by the appropriate healthcare professional(s) responsible for a particular clinical procedure or treatment plan following discussion with the patient, covering the diagnostic and treatment options available. It is advised that any significant departure from the guideline should be documented in the patient’s medical record at the time the decision is taken.

**Guideline**

**BACKGROUND**

Autonomic neuropathy affects the autonomic neurons of either or both of the parasympathetic and sympathetic nervous systems. It is usually accompanied by somatic (peripheral) neuropathy but can occur in isolation. There are a wide variety of clinical features and presentations ranging from subclinical to significant disability. It is important to recognise and correctly diagnose autonomic neuropathy as management and treatment can be offered to control symptoms and reduce the risk of progression. Referral to the Diabetes Specialist Team should be considered for further advice on managing these complications.

Patients with clinically overt autonomic dysfunction have been found to have a relatively high mortality rate, mainly due to its association with renal failure, sudden cardiac death (arrhythmia) and blood pressure fluctuation increasing the risk of cerebral and cardiac ischaemia. Improvements in glycaemic control have little beneficial effect on symptomatic autonomic neuropathy since the advanced histological changes within the nerves (axonal loss, demyelination, obliteration of vasa nervorum) are only partially, if at all, reversible. Improvement in glycaemic control can, however reduce the risk of progression by up to 62%.

**Risk Factors**

- Poor glycaemic control
- Hypertension
- Dyslipidaemia
- More common in women
- Type 1 and Type 2 Diabetes
Common Presentations
- Genitourinary – Impotence, retrograde ejaculation, urinary hesitancy, overflow incontinence
- Gastrointestinal – nausea and vomiting, abdominal distension, dysphagia, diarrhoea
- Sweating and temperature regulation
- Cardiovascular – postural hypotension, arrhythmias, supine hypertension, loss of diurnal variation in blood pressure

Erectile Dysfunction
Sexual dysfunction is an important and common problem in diabetic men (estimated to affect around 25-30%), but other causes need to be considered and treated, if appropriate. The aim is to restore or compensate for sexual dysfunction in accordance with the patient’s wishes.

History
The history should be elicited tactfully, aiming to define the dysfunction and to identify any possible contributory factors. If there is a partner, his/her presence is helpful. Relevant areas to question are:
- Nature of the dysfunction – is it a lack of tumescence or early collapse of erection or both? How long has it been going on? Did it start suddenly or gradually? Do spontaneous or early morning erections ever occur? Is libido normal and sexual stimulation present? Is there a problem with orgasm and ejaculation, and what is considered normal? Details of the current relationship, the partner’s attitude and couple’s expectations. What remedies have been tried already?
- Relevant current medical history (apart from diabetes), looking for endocrine abnormalities (hair loss, gynaecomastia, weight gain, change in heat tolerance), vascular disease (exercise related chest or leg pain, if not already sought) and neurological disorder (problems with sensation, co-ordination and motor function)
- Relevant past medical history, particularly about pelvic surgery, radiotherapy or trauma, psychiatric or psychological problems
- Medication – many drugs can cause erectile dysfunction, including thiazide diuretics, β blockers, antidepressants, tranquilisers, anxiolytics and H2 antagonists
- Lifestyle – smoking and alcohol, major life changes, the use of recreational or body building drugs

Sudden onset, the presence of some erections, ejaculatory problems and major life events and/or psychological problems suggests a psychogenic cause, whereas gradual onset, no tumescence, the presence of risk factors, past history of pelvic disease or treatment, certain medication or illicit drug use and heavy alcohol consumption suggest an organic cause.

Examination
Examination can be limited to the genitalia – abnormalities in testicular size, fibrosis in the penile shaft, retractability of the foreskin. Examination for the presence of secondary sexual characteristics (breasts, beard growth) may be suggested by the history.

Investigation
Further investigations are indicated by the findings of the history and examination. A free serum testosterone is the preferred screening investigation for suspected hypogonadism. Extensive endocrine investigations are usually unnecessary.
Intervention
Patients may not always be enthusiastic about medical intervention. Clear unbiased information about treatment options can be offered in general practice.

- Treatable underlying causes, such as medication, should be corrected.
- Glycaemic control needs to be optimised
- Discourage smoking
- Psychosexual or general counselling
- Referral should be considered to urology if the patient has never had an erection and/or if there is severe vascular problems and/or if the patient opts for an intervention beyond the practitioners competence
- Referral should be considered to Endocrinology if a hormone abnormality is found, although treatment may not restore potency

Therapeutic options

**Phosphodiesterase 5 Inhibitors**

First Choice - Sildenafil (Viagra®):
This selectively inhibits Phosphodiesterase 5, an enzyme that breaks down cyclic guanosine monophosphate (GMP), an intracellular second messenger that produces smooth muscle relaxation and maintains penile blood flow. Sildenafil has no effect on libido and does not produce an erection in the absence of sexual stimulation. It is contraindicated in severe hepatic impairment, hypotension (BP <90/50mmHg), recent CVA or MI, hereditary degenerative retinal disorders and concurrent treatment with nitrates, nicorandil and ritonavir. Cardiovascular disease and multiple regimens for blood pressure control are not contraindications to treatment provided the person can undertake activities of daily living without cardiac symptoms. It should be prescribed with caution in penile deformity, conditions predisposing to priapism and in concurrent treatment with cimetidine, erythromycin, ketoconazole, itraconazole. Its side effects include headache, flushing, dyspepsia through relaxation of the oesophageal sphincter and transient visual disturbances, which consist of a bluish tinge to white colours and lasts less than 20mins. It is formulated in doses of 25, 50 and 100mg. The maximum quantity that can be prescribed on the NHS is 1 tablet per week. The initial recommended dose is 50mg, reduced to 25mg in the elderly or those with moderate hepatic or severe renal impairment. The dose may be increased to 100mg if necessary and if tolerated. It should be taken 1 hour before sexual activity on an empty stomach and not repeated within 24 hours.

Second Choice – Tadalafil (Cialis®) This is available as tablets - 10mg or 20mg. It should be taken approximately 30 minutes to 12 hours before sexual activity. Subsequent doses should be adjusted according to response to a maximum of 20mg as a single dose. It should not be repeated within 24 hours. It may be a suitable alternative for those who develop visual disturbances with sildenafil or for whom a longer duration of action is required.

**Apomorphine**
Apomorphine is a dopamine agonist that activates specific neural events in the paraventricular nucleus of the hypothalamus. Oxytocinergic pathways then relax smooth muscle in the corpus cavernosum, which leads to an erection within 20mins of use. The dose is 1 sublingual tablet of 2 or 3mg, not to be repeated within 8 hours and its use on the NHS is restricted as for sildenafil.

**Others**
Other treatments should be considered if either of the above is contraindicated, unsuitable or ineffective. These include intracavernosal prostaglandin (alprostadil) injections, transurethral alprostadil (MUSE), vacuum devices and penile prosthesis. Referral to a specialist clinic is usually warranted for these treatments.
Orthostatic (Postural) Hypotension
This is defined as an otherwise unexplained fall in systolic blood pressure of 25-30mmHg on standing for 2 minutes. In fact, the blood pressure may continue to drop for 15 minutes. This is a rare complication and can be difficult to manage. It is often associated or exacerbated by eating, exercise and raised temperature. Symptoms include nausea, palpitations, light-headedness, tinnitus and shortness of breath. Syncope can occur (especially with micturition or defecation). Antihypertensive agents and tricyclics may aggravate orthostatic hypotension and should be avoided. Support stockings may help prevent venous pooling. Referral to a specialist is advised. Try tilting the head of the bed up at night, stand up slowly and increase fluid intake. Consider salt supplementation and compression stockings. It may respond to fludrocortisone.

Gastroparesis and Diabetic Diarrhoea
This rarely affects patients with Type 2 Diabetes. It is a diagnosis of exclusion and managed symptomatically (e.g. prokinetic agents - metoclopramide, domperidone, erythromycin, codeine phosphate, loperamide). Try eating small meals and often, lower the fat content of the diet to ease digestion.

Bladder Pareses
Again rare but may cause hesitancy, retention and predispose to urinary infection. Prostatic disease should be excluded. Try timed voiding schedules and bladder contraction increased by the Valsalva manoeuvre. Self catheterisation may be required in a few patients.

Gustatory Sweating
Drenching sweats of the head and upper torso whilst eating. It is unrelated to hypoglycaemia. It is difficult to manage. Topical or oral anticholinergic agents may be helpful

Anhidrosis/ Hypohidrosis
No or reduced sweating. Most apparent in the palms, soles of the feet and axillae. Hyperhidrosis (excessive sweating) can occur as a compensatory mechanism.

Temperature Regulation
Hypothermia and hyperpyrexia can result from disruption of the various temperature regulatory mechanisms. Sweating, shivering and vasoactive reflexes can be affected

References

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