Parkinson's disease: features

Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.. This results in a classic triad of features: bradykinesia, tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical

Bradykinesia

- poverty of movement also seen: mask-like facies
- difficulty in initiating movement

Tremor

- most marked at rest, 3-5 Hz
- typically 'pill-rolling'

Rigidity

- lead pipe
- cogwheel: due to superimposed tremor

Other characteristic features

- flexed posture
- short, shuffling steps
- micrographia
- drooling of saliva
- psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- impaired olfaction
- REM sleep behaviour disorder

Drug-induced parkinsonism has slightly different features to Parkinson's disease:

- motor symptoms are generally rapid onset and bilateral
- rigidity and rest tremor are uncommon

Restless legs syndrome

Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia. It is extremely common, affecting between 2-10% of the general population. Males and females are equally affected and a family history may be present

Clinical features

- uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day. Symptoms are worse at rest
- paraesthesias e.g. 'crawling' or 'throbbing' sensations
- movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

Causes and associations

- there is a positive family history in 50% of patients with idiopathic RLS
- iron deficiency anaemia
- uraemia
- diabetes mellitus
- pregnancy

The diagnosis is clinical although bloods to exclude iron deficiency anaemia may be appropriate

Management

- simple measures: walking, stretching, massaging affected limbs
- treat any iron deficiency
- dopamine agonists are first-line treatment (e.g. Pramipexole, ropinirole)
- benzodiazepines
- gabapentin

Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'

- if the cholesterol is > 3.5 mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

Thrombolysis

Thrombolysis should only be given if:

- it is administered within 3 hours** of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE

Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST*** criteria or > 50% according to NASCET**** criteria

*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this
**SIGN recommend a window of 4.5 hours
***European Carotid Surgery Trialists' Collaborative Group
****North American Symptomatic Carotid Endarterectomy Trial

Cluster headache

Cluster headaches* are more common in men (5:1) and smokers

Features

- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks

- intense pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

Management

- acute: 100% oxygen, subcutaneous sumatriptan, nasal lidocaine
- prophylaxis: verapamil, prednisolone
- consider specialist referral

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

Epilepsy: treatment

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:

- the patient has a neurological deficit
- brain imaging shows a structural abnormality
- the EEG shows unequivocal epileptic activity
- the patient or their family or carers consider the risk of having a further seizure unacceptable

Sodium valproate is considered the first line treatment for patients with generalised seizures with carbamazepine used for partial seizures

Generalised tonic-clonic seizures

- sodium valproate
- second line: lamotrigine, carbamazepine

Absence seizures* (Petit mal)

- sodium valproate or ethosuximide
- sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy

Myoclonic seizures

- sodium valproate
- second line: clonazepam, lamotrigine

Partial seizures

- carbamazepine
- second line: lamotrigine**, sodium valproate

*carbamazepine may actually exacerbate absence seizure
**the 2007 SANAD study indicated that lamotrigine may be a more suitable first-line drug for partial seizures although this has yet to work its way through to guidelines

Multiple sclerosis: features

Visual

- optic neuritis: common presenting feature
- optic atrophy
- Uhthoff's phenomenon: worsening of vision following rise in body temperature
- internuclear ophthalmoplegia

Sensory

- pins/needles
- numbness
- trigeminal neuralgia
- Lhermitte's syndrome: paraesthesiae in limbs on neck flexion

Motor

- spastic weakness

Cerebellar

- ataxia
- tremor

Others

- urinary incontinence
- sexual dysfunction
- intellectual deterioration

Neuropathic pain

Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system. It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- diabetic neuropathy
- post-herpetic neuralgia
- trigeminal neuralgia
- prolapsed intervertebral disc

NICE issued guidance in 2010 on the management of neuropathic pain:

- first-line treatment*: oral amitriptyline or pregabalin
- if satisfactory pain reduction is obtained with amitriptyline but the person cannot tolerate the adverse effects, consider oral imipramine or nortriptyline as an alternative
- second-line treatment: if first-line treatment was with amitriptyline, switch to or combine with pregabalin. If first-line treatment was with pregabalin, switch to or

combine with amitriptyline

- other options: pain management clinic, tramadol (not other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication

*please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia, duloxetine for diabetic neuropathy

Headache

Headache accounts for a large proportion of medical consultations. The table below summarises the main characteristics of common or important causes:

Migraine	Recurrent, severe, disabling headache Usually unilateral and throbbing in nature Sensitivity to light Patients often describe 'going to bed' In women may be associated with menstruation
Tension headache	Recurrent, non-disabling, bilateral headache
Cluster headache*	Pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours with clusters typically lasting 4-12 weeks Intense pain around one eye (recurrent attacks 'always' affect same side) Patient is restless during an attack Accompanied by redness, lacrimation, lid swelling More common in men and smokers
Temporal arteritis	Typically patient > 60 years old Usually rapid onset (e.g. < 1 month) of unilateral headache

	Jaw claudication (65%) Tender, palpable temporal artery Raised ESR
Medication overuse headache	Present for 15 days or more per month Developed or worsened whilst taking regular symptomatic medication Patients using opioids and triptans are at most risk May be psychiatric co-morbidity

Other causes of headache

Acute single episode

- meningitis
- encephalitis
- subarachnoid haemorrhage
- head injury
- sinusitis
- glaucoma (acute closed-angle)
- tropical illness e.g. Malaria

Chronic headache

- chronically raised ICP
- Paget's disease
- psychological

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

Triptans

Triptans are specific 5-HT1 agonists used in the acute treatment of migraine. They are generally used second line when standard analgesics such as paracetamol and ibuprofen are ineffective.

Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

- patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

Motor neuron disease: features

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

There are a number of clues which point towards a diagnosis of motor neuron disease:

- fasciculation
- absence of sensory signs/symptoms*
- lower motor neuron signs in arms and upper motor neuron signs in legs
- wasting of the small hand muscles/tibialis anterior is common

Other features

- doesn't affect external ocular muscles
- no cerebellar signs
- abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature

The diagnosis of motor neuron disease is clinical, but nerve conduction studies will show normal motor conduction and can help exclude a neuropathy. Electromyography shows a reduced number of action potentials with an increased amplitude. MRI is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy

*vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs

Myasthenia gravis

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 90% of cases*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

Investigations

- Tensilon test: IV edrophonium reduces muscle weakness temporarily
- CT thorax to exclude thymoma
- CK normal

Management

- long-acting anticholinesterase e.g. Pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

*antibodies are less commonly seen in disease limited to the ocular muscles

Migraine: diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

A At least 5 attacks fulfilling criteria B-D

B Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)

C Headache has at least two of the following characteristics:

- 1. unilateral location*
- 2. pulsating quality (i.e., varying with the heartbeat)
- 3. moderate or severe pain intensity
- 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D During headache at least one of the following:

- 1. nausea and/or vomiting*
- 2. photophobia and phonophobia

E Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not

occur for the first time in close temporal relation to the other disorder)

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (around 1 in 3 migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a
spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

Migraine: management

Migraine

- acute: 5-HT1 agonist
- prophylaxis: beta-blocker

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. SIGN released guidelines on migraine management in 2008

Acute treatment

Standard analgesia

- first-line therapy
- e.g. paracetamol, ibuprofen, aspirin
- may be poorly absorbed, often combined with anti-emetic e.g. metoclopramide* to relieve associated nausea

Triptans

- second-line therapy
- specific 5-HT1 agonists - opposes vasodilation

Ergotamine

- alpha-blocker and a partial 5-HT1 agonist
- now rarely used due to high incidence of adverse effects (e.g. nausea and vomiting)
- listed in the BNF as 'less suitable for prescribing'

Prophylaxis

Prophylaxis should be given if patients are experiencing 2 or more attacks per month. Modern treatment is effective in about 60% of patients

First-line

- beta-blockers: propranolol 80-240mg daily in divided doses

Also recommended in the SIGN guidelines

- sodium valproate
- topiramate (CKS recommend this is used under specialist supervision)
- gabapentin
- amitriptyline
- venlafaxine

The SIGN guidelines also suggest that stress management and acupuncture may be useful

5-HT2 antagonists

- pizotifen: used less commonly now due to adverse effects (weight gain and drowsiness)
- methysergide: very rarely used as associated with retroperitoneal fibrosis

*caution should be exercised with young patients as acute dystonic reactions may develop

Alzheimer's disease

Alzheimer's disease is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK

Genetics

- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apoprotein E allele E4 - encodes a cholesterol transport protein

Pathological changes

- macroscopic = widespread cerebral atrophy, particularly involving the cortex and hippocampus
- microscopic = intraneuronal neurofibrillary tangles, neuronal plaques, deficiency of neurons
- biochemical = deposition of type A-Beta-amyloid protein in cortex, deficit of Ach from damage to an ascending forebrain projection

Neurofibrillary tangles

- paired helical filaments are partly made from a protein called tau
- in AD are tau proteins are excessively phosphorylated

Management

- NICE now recommend the three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
- memantine is reserved for patients with moderate - severe Alzheimer's

Headache: red flags

Whilst headache is an extremely common symptoms there may be some features which suggest that a secondary cause needs to be excluded. The following is partly based on the British Association for the Study of Headache guidelines.

- new or unexpected headache
- thunderclap headache (severe headache with an abrupt onset)
- headache with atypical aura (duration > 1 hour, or including motor weakness)
- aura occurring for the first time in a patient during use of combined oral contraceptives
- new onset headache in a patient older than 50 years
- new onset headache in a patient younger than 10 years
- progressive headache, worsening over weeks or longer
- headache associated with postural change (e.g. Bending down) or cough
- new onset headache in a patient with a history of cancer, HIV infection

These are of course in addition to obvious worrying features such as:

- a history of recent trauma
- focal neurological signs, papilloedema
- fever, neck stiffness
- persistent vomiting

Bell's palsy

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis. The aetiology is unknown although the role of the herpes simplex virus has been investigated previously.

Features

- lower motor neuron facial nerve palsy - forehead affected*
- patients may also notice post-auricular pain (may precede paralysis), altered taste, dry eyes, hyperacusis

Management

- in the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of aciclovir and prednisolone

- following a National Institute for Health randomised controlled trial it is now recommended that prednisolone 25mg bd for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy. Adding in aciclovir gives no additional benefit
- eye care is important - prescription of artificial tears and eye lubricants should be considered

Prognosis

- if untreated around 15% of patients have permanent moderate to severe weakness

*upper motor neuron lesion 'spares' upper face

Transient ischaemic attack

NICE issued updated guidelines relating to stroke and transient ischaemic attack (TIA) in 2008. They advocated the use of the ABCD2 prognostic score for risk stratifying patients who've had a suspected TIA:

	Criteria	Points
A	**A**ge >= 60 years	1
B	**B**lood pressure >= 140/90 mmHg	1
C	**C**linical features	
	- Unilateral weakness	2
	- Speech disturbance, no weakness	1
D	**D**uration of symptoms	
	- > 60 minutes	2
	- 10-59 minutes	1
	Patient has diabetes	1

This gives a total score ranging from 0 to 7. People who have had a suspected TIA who are at a higher risk of stroke (that is, with an ABCD2 score of 4 or above) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment and investigation within 24 hours of onset of symptoms
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors

If the ABCD2 risk score is 3 or below:

- specialist assessment within 1 week of symptom onset, including decision

on brain imaging

- if vascular territory or pathology is uncertain, refer for brain imaging

People with crescendo TIAs (two or more episodes in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- aspirin plus modified-release (MR) dipyridamole is still recommended as first choice for people who have had a TIA, but now there is no recommended limit on the duration of treatment. Clopidogrel is not recommended
- MR dipyridamole monotherapy is recommended after TIA only if aspirin is contraindicated or not tolerated, again with no limit on duration of treatment.

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST* criteria or > 50% according to NASCET** criteria

*European Carotid Surgery Trialists' Collaborative Group
**North American Symptomatic Carotid Endarterectomy Trial

Peripheral neuropathy

Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss

- Guillain-Barre syndrome
- porphyria
- lead poisoning
- hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- diphtheria

Predominately sensory loss

- diabetes
- uraemia
- leprosy
- alcoholism
- vitamin B12 deficiency
- amyloidosis

Alcoholic neuropathy

- secondary to both direct toxic effects and reduced absorption of B vitamins
- sensory symptoms typically present prior to motor symptoms

Vitamin B12 deficiency

- subacute combined degeneration of spinal cord
- dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia

A high-stepping gait develops to compensate for foot drop. If found unilaterally then a common peroneal nerve lesion should be suspected. Bilateral foot drop is more likely to be due to peripheral neuropathy.

Meralgia paraesthetica

Basics

- caused by compression of lateral cutaneous nerve of thigh
- typically burning sensation over antero-lateral aspect of thigh

Seizures: acute management

Most seizures are self-limiting and stop spontaneously but prolonged seizures may be potentially life-threatening.

Basics

- check the airway and apply oxygen if appropriate
- place the patient in the recovery position
- if the seizure is prolonged give benzodiazepines

BNF recommend dose for rectal diazepam, repeated once after 10-15 minutes if necessary

Neonate	1.25 - 2.5 mg
Child 1 month - 2 years	5 mg
Child 2 years - 12 years	5 - 10 mg
Child 12 years - 18 years	10 mg
Adult	10 - 20 mg (max. 30 mg)
Elderly	10 mg (max. 15 mg)

Idiopathic intracranial hypertension

Obese, young female with headaches / blurred vision think idiopathic intracranial hypertension

The combination of a young, obese female with papilloedema but otherwise normal neurology makes idiopathic intracranial hypertension the most likely diagnosis

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign

intracranial hypertension) is a condition classically seen in young, overweight females.

Features

- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

Risk factors

- obesity
- female sex
- pregnancy
- drugs*: oral contraceptive pill, steroids, tetracycline, vitamin A

Management

- weight loss
- diuretics e.g. acetazolamide
- repeated lumbar puncture
- surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Epilepsy: pregnancy and breast feeding

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

Other points

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- sodium valproate: associated with neural tube defects
- carbamazepine: often considered the least teratogenic of the older antiepileptics

- phenytoin: associated with cleft palate
- lamotrigine: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy

Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

Medication overuse headache

Medication overuse headache is one of the most common causes of chronic daily headache. It may affect up to 1 in 50 people

Features

- present for 15 days or more per month
- developed or worsened whilst taking regular symptomatic medication
- patients using opioids and triptans are at most risk
- may be psychiatric co-morbidity

Management (from 2008 SIGN guidelines)

- simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- opioid analgesics should be gradually withdrawn

Migraine: pregnancy, contraception and other hormonal factors

SIGN produced guidelines in 2008 on the management of migraine, the following is selected highlights:

Migraine during pregnancy

- paracetamol 1g is first-line
- aspirin 300mg or ibuprofen 400mg can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

- if patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

- safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

Prescribing in patients with epilepsy

The following drugs may worsen seizure control in patients with epilepsy:

- alcohol, cocaine, amphetamines
- ciprofloxacin, levofloxacin
- aminophylline, theophylline
- buproprion
- methylphenidate (used in ADHD)

Some medications such as benzodiazipines, baclofen and hydroxyzine may provoke seizures whilst they are being withdrawn.

Other medications may worsen seizure control by interfering with the metabolism of anti-epileptic drugs (i.e. P450 inducers/inhibitors).