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**Definition of neuropathic pain**

According to NeuPSIG (Special Interest Group on Neuropathic Pain), neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. This common type of pain is often underdiagnosed and undertreated, and it is associated with suffering, disability and impaired quality of life.

**Drugs used for neuropathic pain**

**Classification**

**Anticonvulsants** – Gabapentoids (gabapentin, pregabalin), carbamazepine
**Antidepressants** – Amitriptyline, nortriptyline, duloxetine, venlafaxine
**Opioids**– Morphine, oxycodone, tramadol, Tapentadol
**Topical agents** – Lignocaine, capsaicin cream (0.25–0.75%)/patch (8%), botulinum toxin type A (Botox)
**Others** – Cannabinoids

**Anticonvulsants**

**Gabapentoids - Gabapentin & Pregabalin**

These are the second generation of anticonvulsant. They are non-natural branched-chain amino acids – chemical analogues of gamma-aminobutyric acid (GABA), with no activity in the GABAergic neuronal system. Pregabalin can be used for central and peripheral neuropathic pain, while gabapentin is used mainly for peripheral neuropathic pain.

They exert their effect through alpha-2delta type 1 subunits of voltage-gated calcium channels. This effect results in a moderate decrease in calcium influx due to degranulation and calcium uptake inhibition, and decreases the release of excitatory neurotransmitters (glutamate, noradrenaline and substance P), leading to a subtle reduction in postsynaptic neuronal hyperexcitability.

**Carbamazepine**

Carbamazepine is a first-generation antiepileptic agent, used mainly as a first-line treatment for trigeminal neuralgia only.

It is a sodium channel blocker in the central nervous system. In addition, it antagonises the A1 adenosine receptor, increases dopaminergic transmission, potentiates voltage-gated potassium channels, and inhibits L-type voltage-gated calcium channels and presynaptic glutamate release.

**Table 1. Dosages, pharmacokinetics and side effects of anticonvulsants**

|  |  |  |  |
| --- | --- | --- | --- |
|  **Drug** | **Dosages (starting, titration and maximum)** | **Pharmacokinetics** | **Side effects** |
|  Gabapentin | 100 mg three times daily or 300 mg at bedtime. Increase by 100–300 mg every 1–7 days as tolerated. Maximum dose 3600 mg | Negligible protein binding. Slow absorption, 2–3 hours to maximal absorption. Dose dependent oral bioavailability (80%) an increase in dose at higher doses will lead to a small increase in plasma drug concentration. Not metabolised in the liver, excreted unchanged in the urine. Elimination half-life 6–8 hours | Sedation, dizziness, weight gain, peripheral oedema, blurry vision, memory disturbances, dry mouth, constipation. Follow-up of weight recommended in diabetic patients. Adverse effects are dose related and reversible |
|  Pregabalin | 50 mg three times daily or 75 mg twice daily. Increase to 300 mg daily after 3–7 days, then 150 mg/day every 3–7 days as tolerated. Maximum dose 600 mg | Negligible protein binding. Fast absorbtion,1 hour to maximal absorption. Dose-independent oral bioavailability (>90%). Not metabolised in the liver, excreted unchanged in urine. Elimination half-life 6 hours | Sedation, dizziness, weight gain, peripheral oedema, blurry vision, memory disturbances, dry mouth, constipation. Follow-up of weight recommended in diabetic patients. Adverse effects are dose related and reversible |
|  Carbamazepine | 100–200 mg daily. Increase weekly by 100–200 mg daily, maximum 1600 mg daily | 75% bound to plasma proteins. Metabolised in the liver (cytochrome P-450 [CYP]) and excreted in the urine. Has an active metabolite: carbamazepine epoxide. Elimination half-life 10–20 hours but diminishes with auto-induction (CYP3A4) up to 4–12 hours as clearance increases by up to 300% | Somnolence, dizziness, headache, ataxia, nystagmus, diplopia, blurred vision, nausea, rash, hyponatraemia, leukopenia, thrombocytopenia and hepatotoxicity. Liver enzymes, blood cells, platelets and sodium levels to be monitored, at least during the first year |

**Antidepressants**

**Tricyclic antidepressants (TCAs) – amitriptyline and nortriptyline**
These are used as a first-line drug in neuropathic pain. It acts mainly by competitive blockade of neuronal uptake of noradrenaline and serotonin; it also blocks muscarinic, histaminergic and alpha-1 and -2 adrenoceptors. Nortriptyline also blocks beta-adrenoceptors.

These are mainly used as a second-line drug in neuropathic pain. Duloxetine is used as a first-line drug in painful diabetic neuropathy; it competitively blocks neuronal uptake of noradrenaline and serotonin.

**Table 2: Dosages, pharmacokinetics and side effects of antidepressants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Dosages (starting, titration and maximum)** | **Pharmacokinetics** | **Side effects** |
| TCAs, amitriptyline,nortriptyline | Amitriptyline 10 mg at bedtime. Increase by 10 mg every 3–7 days as tolerated, up to a maximum of 70 mg. Nortriptyline 25 mg at bedtime. Increase by 25 mg every 3–7 days, up to a maximum dose of 150 mg | Highly protein bound (>90%). Readily absorbed. Substantial first-pass metabolism. Metabolised by CYP oxidative enzymes into nortriptyline. Mainly excreted through the urine as a free metabolite or as glucuronide and sulphate conjugates. Elimination half-life up to 24 hours | Sedation, confusion, conduction blocks, orthostatic hypotension, weight gain, anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision) |
| SNRIs, duloxetine | 30 mg once daily. Increase to 60 mg once daily after 1 week up to a maximum of 60 mg twice daily. | Highly protein bound (>90%). Metabolised in the liver, involving two CYP isozymes (CYP1A2 and CYP2D6) and 70% is excreted renally. The dose is reduced in renal impairment and is contraindicated in the presence of alcohol use disorders. Elimination half-life about 12 hours | Nausea, vomiting, headache, diarrhoea, constipation, insomnia, somnolence, dizziness, dry mouth, hyperhidrosis, reduced appetite, sexual dysfunction |
|  Venlafaxine |  37.5 mg once or twice daily. Increase by 75 mg each week up to a maximum dose of 225 mg |  It is a racemic mixture of the R (+) and S (–) enantiomer. It is extensively metabolised in the liver via the CYP2D6 isoenzyme to O-desmethyl-venlafaxine, which is an active metabolite with a longer half-life (10 hours) than venlafaxine (4 hours). It is mainly excreted through the kidneys. It has a greater affinity for serotonin at a low dose but noradrenaline uptake increases in a dose-dependent fashion |  Nausea, vomiting, anorexia, headache, constipation, insomnia, nervousness, diaphoresis, reduced appetite, sexual dysfunction |

*Overdose of TCAs*

Cardiovascular system: sinus tachycardia, hypotension, prolongation of the PR interval, widening of the QRS complex, flattening or inversion of T waves, pulseless electrical activity. Central nervous system: excitation, seizures, hyperthermia, mydriasis.

*Number needed to treat*(NNT)

NNT (relative to placebo): lower value suggests better efficacy.
 **Table 3: Neuropathic conditions, drugs and NNT**

|  |  |  |
| --- | --- | --- |
|  **Neuropathic conditions** | **Drugs** | **NNT**  |
|  Various neuropathic conditions | GabapentinPregabalinAmitriptylineTCASelective serotonin reuptake inhibitorSNRI | 4.3–6.43.8–4.82.5–4.21.9–3.83.9–2.73.4–14 |
|  Trigeminal neuralgia | Carbamazepine | 1.4–2.8 |
|  Post-herpetic neuralgia | GabapentinPregabalin | 4.3–7.73.9–5.3 |
|  Diabetic neuropathy | GabapentinPregabalinDuloxetine | 4.7–285–115–10 |
|  Central neuropathic pain |  Pregabalin | 3.5–14 |

**Opioids**

Opioids are used as second- or third-line analgesics in patients with chronic neuropathic pain.

They are useful during exacerbations of pain or in patients with intermittent pain in whom long-term treatment is not indicated. Opioids used in neuropathic pain can be classified as weak (e.g. tramadol and Tapentadol) and strong opioids (e.g. morphine and oxycodone).

**Mechanism of action**
Opioid receptors are widely distributed in the central and peripheral nervous systems. Opioids interact with G-protein coupled receptors (presynaptic and postsynaptic) in the dorsal horn of the spinal cord and modulate the descending inhibitory pathways.

Tramadol and Tapentadol have some additional mechanisms; tramadol inhibits serotonin and norepinephrine reuptake, whereas Tapentadol inhibits norepinephrine reuptake.

They have a narrow therapeutic index, with large interindividual variability in response and tolerance. Sustained release preparations are commonly used in neuropathic pain, while immediate-release preparations are used for breakthrough pain.

**Table 4: Dosages, pharmacokinetics and side effects of opioids**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Dosages (starting, titration and maximum)** | **Pharmacokinetics** | **Side effects** |
|  Tramadol |  50 mg up to four times daily. Dose adjusted according to response, up to maximum of 400 mg/day | High oral bioavailability (75–80%). Metabolised in the liver by cytochrome P450 isozyme into O- and N-desmethyl tramadol, which undergoes secondary conjugation with glucuronic acid and sulphuric acid before being excreted into the urine. Elimination half-life 5–7 hours. Pharmacokinetics are significantly altered in severe hepatic and renal impairment |  Nausea, vomiting, abdominal pain, constipation, dizziness, headache, somnolence, dry mouth |
| Tapentadol |  50 mg up to four times daily. Dose adjusted according to response, up to maximum of 600 mg/day | Low oral bioavailability (35–40%). Mainly undergoes conjugation with glucuronic acid to inactive metabolites. To a lesser extent, it is metabolised in the liver by cytochrome P450 isozymes to form N- desmethyl and hydroxyl Tapentadol, both of which undergo secondary conjugation before being excreted into the urine. Elimination half-life 4–6 hours |  Nausea, vomiting, dizziness, sleepiness, itchiness, dry mouth, headache, fatigue |
|  Morphine |  5 mg every 4 hours. Dose adjusted according to response, up to maximum dose 80–120 mg/day | Low oral bioavailability (35–40%). Undergoes glucuronidation in the liver into mainly inactive (morphine 3-glucuronide) metabolite and to a lesser extent active (morphine 6-glucuronide) metabolite which are excreted in the urine. Morphine 6-glucuronide is 6–10 times more potent than the parent compound. Elimination half-life 2–3 hours. Dose adjustment recommended in hepatic and renal impairment |  Nausea, vomiting, constipation, drowsiness, dizziness. Long-term side effects: cognitive impairment, endocrinological and immunological changes |
|  Oxycodone |  5 mg every 4–6 hours. Dose adjusted according to response up to maximum dose 400 mg/day | High oral bioavailability (70–85%). Metabolised in the liver by cytochrome P450 isozymes, undergoes O- and N-demethylation into active (nor oxycodone, oxymorphone) and inactive (noroxymorphone) metabolites, which are subsequently glucuronidated and excreted in the urine. Elimination half-life 3–4 hours. Dose adjustment recommended in hepatic and renal impairment |  Nausea, vomiting, constipation, loss of appetite, dizziness, drowsiness, tiredness, dry mouth |

**Caution**
Opioids are associated with a risk of abuse and addiction. Addressing high-risk factors for abuse, use of risk assessment tools and written treatment agreement are recommended before initiation of treatment.

**Cannabinoids**

These include Nabilone (tetrahydrocannabinol [THC]) and Sativex (cannabidiol [CBD]). Multiple studies have failed to find a statistically significant analgesic effect in neuropathic pain from spinal cord injury, painful diabetic neuropathy or mixed conditions.

**Mechanism of action**

Cannabinoids bind to G-protein coupled receptors – cannabinoid (CB1 and CB2) receptors. CB1 receptors are widely distributed in the brain and may be responsible for psychoactive effects, while CB2 receptors are mostly located in peripheral cells, and may play a role in immune function. These receptors are activated by endocannabinoids, phytocannabinoids and tetrahydrocannabinol. The analgesic effect may include modulation of neurone and immune cell functioning.

**Pharmacokinetics**

These agents undergo metabolism in the liver and are excreted through the kidneys. Cytochrome P450 isoenzymes (CYP2D6 and CYP3A4) are inhibited. The absorption of the drugs is slow, and peak concentrations are relatively low. The plasma half-life is 24–36 hours, and the pharmacodynamic effect is prolonged by oral administration. Sativex (sublingual and oropharyngeal spray) achieves its peak plasma concentration in 45–120 minutes.

**Dosages**

Sativex: up to a maximum of 12 sprays per day.

**Side effects**

THC has a high psychoactive effect and the potential for abuse, whereas CBD has a limited psychoactive effect.

Dizziness is the most common side effect, and sedation, dysphoria, dry mouth and muscle weakness are other side effects.

**Caution**

Heart disease, seizure disorder, psychosis or schizophrenia (should not be used).

**Topical agents**

**Table 5: Drugs, dosages, mechanism of action and side effects**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drugs** | **Dosages and uses** | **Mechanism of action** | **Side effects** |
|  Lignocaine plasters (5%) |  Up to 3–4 plasters for 12 hours. Used in post-herpetic neuralgia and localised neuropathic pain |  Sodium channel blocker |  Local erythema |
| Capsaicin cream (0.025–0.075%)Capsaicin patch 8% | Cream: Daily application, used for localised neuropathic painPatch: Single application in peripheral neuropathic pain in non-diabetics and post-herpetic neuralgia. May provide pain relief up to 3 months |  Agonist activity at the transient receptor potential of vanilloid receptor 1 (TRPV1) on A-delta and C fibres. Depletion of substance P from primary afferent nociceptors, which then become desensitised |  Burning, itching, erythema, pain and elevated blood pressure during application |
|  Botulinum toxin type A (Botox) |  100–200 IU subcutaneously or intradermal. Used in post-herpetic neuralgia, localised neuropathic pain, headache and trigeminal neuralgia |  Peripheral actions are due to reduced neurotransmitter release and reduction in TRPV1 activity. Central actions via retrograde axonal transport are likely to play a role |  Injections are painful and local effects are transient |

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**Further reading**

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