BJA Education, 18(9): 277–283 (2018)

doi: 10.1016/j.bjae.2018.06.002
Advance Access Publication Date: 30 July 2018

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix
Matrix codes: 1A02, 2E03, 3E00

Treatments for neuropathic pain: up-to-date evidence and recommendations

B.C. Fitzmaurice and A.T.A. Rayen*

Sandwell and West Birmingham NHS Trust, Birmingham, UK

*Corresponding author: arasu.rayen@nhs.net

Learning objectives

By reading this article, you should be able to:

- Recognise neuropathic pain and initiate treatment.
- Describe the National Institute for Health and Care Excellence (NICE) recommendations on pharmacotherapy for neuropathic pain.
- Recognise future development in treatment of neuropathic pain.

Key points

- Neuropathic pain is often poorly managed, and only 33–50% patients benefit from first-line analgesics.
- Treatment should be based on the updated recommendations by NICE and other expert groups.
- Combination therapies are beneficial compared with monotherapy.
- Pain phenotyping may allow for more stratified and personalised therapies.

Neuropathic pain (NeP) affects 6–10% adults worldwide. It represents an even greater burden than non-neuropathic chronic pain, significantly impacting on patients' lives and with wider socio-economic consequences.[1,2]

The International Association for the Study of Pain (IASP) defines NeP as 'pain caused by a lesion or disease of the somatosensory nervous system'. It is divided into central or peripheral NeP according to the site of the lesion.[3] NeP encompasses a range of clinical conditions: from peripheral NeP conditions such as peripheral diabetic neuropathy (PDN) to central NeP conditions, for example, central post-stroke pain. Regardless of the underlying aetiology, NeP is now regarded as a distinct clinical condition; patients present with similar hallmark characteristics: allodynia, hyperalgesia, and dysaesthesia.[4] Despite its multitude of causes, a general unified pharmacological approach is advised to manage NeP. We describe the recommended pharmacological approach to manage NeP and some novel invasive procedures that are reserved for those with refractory NeP. Generally, medical treatment is coupled with psychological input to produce the holistic approach to therapy that these patients require.

The treatment of NeP is challenging and inadequate for a variety of reasons. These include diagnostic difficulties and insufficient knowledge about available treatment options. Important and commonly prescribed drugs may be unlicensed for these indications.[3] Furthermore, available medications have limited effectiveness, adverse effects, and abuse potential.[1,4] Outside the specialist setting there remains considerable variation in the correct sequencing of therapeutic classes, initiation of treatment, and achieving therapeutic dosing. National essential medicines lists (NEMLs) are the lists of medicines deemed necessary by the WHO to meet priority health needs. Analysis of 112 NEMLs shows great deficiencies in the scope of neuropathic agents.[2] Therefore, drugs with better efficacy/safety profile and which act on novel targets are needed.[5]

Bethany Fitzmaurice FRCA *is specialty registrar in anaesthesia in West Midlands Deanery, with an interest in chronic pain management. She has published and presented on chronic pain subjects.*

Arasu Rayen DA (Ind), DA (UK), FRCA, FFPMRCA, MSc (Pain Management), PG Cert Med Ed, FHEA*, is a consultant in pain management at Sandwell and West Birmingham NHS Trust who has published and presented in national and international meetings on chronic pain subjects. He is a former editor of Pain News, the official newsletter of British Pain Society.*

Accepted: 26 June 2018

Recommendations and guidelines

Over the past decade, there have been only a few recommendations in this subject area despite new pharmacotherapies and several good quality clinical trials. Reasons for this are multifactorial including lack of consistency in methods used to assess the quality of evidence.

2017 National Institute for Health and Care Excellence guidelines for the non-specialist setting

The current National Institute for Health and Care Excellence (NICE) guidelines are based on both clinical evidence and cost-effectiveness after a meta-analysis of 115 studies (18,087 patients) (see Table 1). NICE recommends providing an individualised treatment plan with regular reviews.[3]

NICE guidance

(i) First-line for all NeP, except trigeminal neuralgia (TGN):
  (a) Choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment.
(ii) Second-line:
  (a) If initial treatment with a first-line agent is ineffective or not tolerated, offer one of the remaining three first line drugs. Trial all four first-line agents if needed.
(iii) Tramadol should only be considered if acute rescue therapy is needed.
(iv) Consider capsaicin cream for patients with localised NeP who are intolerant to or wish to avoid oral medications.
(v) Carbamazepine is the first-line drug for TGN. Early specialist referral required if it is not effective or tolerated.
(vi) Do not start the following in a non-specialist setting, unless advised by a specialist: cannabis sativa extract, capsaicin patch, lacosamide, lamotrigine, levetiracetam, morphine, oxcarbazepine, topiramate, venlafaxine, and long-term tramadol.

Revised 2015 IASP Neuropathic Pain Specialist Interest Group recommendations

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) is an internationally accepted method to provide new evidence-based recommendations (http://www.gradeworkinggroup.org.). Using GRADE, the Neuropathic Pain Specialist Interest Group (NeuPSIG) of the IASP revised its previous recommendations (Table 2). The NeuPSIG recommendations are more applicable to the chronic pain specialist setting[4] (See Table 2).

How do these recommendations differ from previous NeuPSIG recommendations?

(i) Gabapentin enacarbil (extended release) and duloxetine are now added as first-line treatments along with tricyclic antidepressants and regular gabapentin.
(ii) Lidocaine plaster is no longer first-line because the evidence is weak. It remains second-line for peripheral NeP because it has an excellent safety profile. Where there are safety concerns with first-line treatments, lidocaine plaster can still be considered as first-line.
(iii) Strong opioids are now third-line because of weak evidence (previously first or second-line).
(iv) High concentration capsaicin patches (8%) are, for the first time, considered in the recommendations for NeP.

Novel therapeutic agents

Tapentadol

Tapentadol is a single molecule agent with dual actions: mu-opioid receptor agonism and selective norepinephrine reuptake inhibition. Tapentadol has a better adverse effect profile including good gastrointestinal (GI) tolerability, improved treatment adherence, and lower tolerance and abuse potential compared with older opioids.[1,6] Metabolism is by hepatic glucuronidation, meaning a lower risk of adverse interactions with other drugs metabolised by CYP450 enzymes.[1]

In one study with patients with severe chronic neuropathic low back pain, monotherapy with tapentadol was as effective as combination therapy with pregabalin.[6] The incidence of dizziness and somnolence was clinically and statistically significantly lower in the group receiving tapentadol alone. These findings suggest a role for tapentadol as a single agent in this difficult-to-treat group of patients.

Cannabinoids

Cannabinoid receptors, CB1 and CB2, have been linked to pain modulation, with receptor activation causing inhibitory effects on pain responses. Furthermore, endocannabinoids have been shown to interact with other receptor systems including γ-aminobutyric acid, serotonergic, adrenergic and opioid receptors, many of which are involved in the analgesic mechanisms of medications commonly used for NeP.[7]

Tetrahydrocannabinol (THC) is the component in cannabis responsible for its therapeutic effects. Another component, cannabidiol (CBD), has a possible additive effect, and is thought to decrease the psychoactive effects of THC.[5] Significant adverse events are rare and include headache, confusion, agitation, and paranoid ideation. In one trial the number of patients with adverse events decreased during treatment, suggesting increased tolerance over time. Long-term safety data for use in NeP are limited. One-year follow-up reported predominantly GI adverse effects and an increased risk of chronic bronchitis with cannabis use.[7]

In the past decade, the use of cannabis and selective (synthetic) cannabinoids has gained popularity for the treatment of NeP. There has been no consensus on the role of selective cannabinoids in NeP, with contradictory recommendations from both national and international pain societies. The Canadian Pain Society has advised selective cannabinoids as third-line agents for NeP.[7,8] It recommends close monitoring with long-term treatment and quotes history of psychosis as a contraindication.[7,8] NeuPSIG has recommended against use of cannabinoids because of weak evidence.[7]

THC may not be an effective analgesic on its own, but it has a pronounced synergistic effect when combined with opioids and may play a role in weaning patients from high-dose opioids. Selective cannabinoids may therefore have a role as combined analgesic therapy for refractory NeP (GRADE: weak recommendation, moderate quality evidence).[7]

The first systematic review and meta-analysis on the analgesic efficacy of selective cannabinoids as adjuncts in relieving refractory central and peripheral NeP was published in 2017.[7] Seventeen percent of patients were unable to tolerate

Table 1 Evidence summary from meta-analysis as the basis for the updated NICE recommendations.[3]Table 1

Drug	Daily dose	Number needed to treat	95% Confidence interval	Number needed to harm	95% Confidence interval	Evidence quality	Safety profile	Number of trials in meta-analysis
Antidepressants								
Amitriptyline	25–150 mg N.B. No evidence of a dose–response effect	3.6	3.0–4.4	13.4	9.3–24.4	Moderate		18
SNRIs	Duloxetine 20–120 mg Venlafaxine 150–225 mg	6.4 (combined)	5.2–8.4	11.8 (combined)	9.5–15.2	High		14
Anticonvulsants								
Pregabalin	150–600 mg N.B. Dose–response gradient exhibited	7.7	6.5–9.4	13.9	11.6–17.4	High		25
Gabapentin	900–3600 mg N.B. No dose–response effect	6.3	5.0–8.3	25.6	15.3–78.6		Good	14
Gabapentin enacarbil (extended release)	1200–3600 mg N.B. No dose–response effect	8.3	6.2–13.0	31.9	17.1–230.0		Good	14
Topiramate				6.3	3.6–6.7		Poor	
Zonisamide				2.0	1.3–4.6		Poor	
Oxcarbazepine				5.5	4.3–7.9		Poor	
Weak opioid agonist/SNRI								
Tramadol/Tramadol extended release	Up to 400 mg	4.7	3.6–6.7	12.6	8.4–25.3	Moderate		7
Mu-opioid agonist/noradrenaline reuptake inhibitor								
Tapentadol		10.2	5.3–185.5					2
Strong opioids	Oxycodone 10–120 mg Morphine 90–240 mg N.B. Maximum effectiveness associated with 180 mg morphine or equivalent	4.3 (combined)	3.4–5.8	11.7 (combined)	8.4–19.3	Moderate		13 N.B. Type of pain = mainly peripheral neuropathic
Capsaicin	8% patch (showed sustained efficacy compared with 0.04% cream)	10.6	7.4–18.8			High		7 N.B. Type of pain = post-herpetic neuralgia and HIV-related painful polyneuropathy
Botulinum	Botulinum toxin A[a] 50–200 units (administered s.c. in the region of pain)	1.9	1.5–2.4				Good	6 N.B. Type of pain=peripheral neuropathic

NICE, National Institute for Health and Care Excellence; SNRI, selective serotonin and norepinephrine reuptake inhibitor.

[a] Potent neurotoxin, may have analgesic effects by its action on neurogenic inflammation; a mechanism that may be involved in some peripheral neuropathic pain conditions.[16].

Table 2 NeuPSIG recommendations based on the GRADE classification.[2]Table 2

Drug	Total daily dose and dose regimen	GRADE strength of recommendation	Tolerability and safety	Cost
First line				
Gabapentin	1200–3600 mg, in three divided doses	STRONG	Moderate–high	Low–moderate
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	STRONG	Moderate–high	Low–moderate
Pregabalin	300–600 mg, in two divided doses	STRONG	Moderate–high	Low–moderate
SNRIs, duloxetine, or venlafaxine[a]	Duloxetine 60–120 mg Venlafaxine extended release 150–225 mg	STRONG	Moderate	Low–moderate
TCAs[b]	25–150mg, once a day or in two divided doses	STRONG	Low–moderate	Low
Second line				
Capsacin 8% patches[c] N.B. Indication = peripheral neuropathic pain	1–4 patches to the painful area for 30–60 min every 3 months	WEAK	Moderate–high N.B. Potential safety concerns over sensation with long–term use	Moderate–high
Lidocaine plasters N.B. Indication = peripheral neuropathic pain	1–3 5% plasters to region of pain one per day for up to 12 h	WEAK	High	Moderate–high
Tramadol	200–400 mg, in three divided dose (or two for extended release)	WEAK	Low–moderate	Low
Third line				
Botulinum toxin A N.B. Specialist use, Indication = peripheral neuropathic pain, third line because the quality of evidence is weak	50–200 units to the painful area every 3 months	WEAK		
Strong opioids	Individual titration	WEAK		
Recommendations AGAINST use				
Cannabinoids N.B. Because of negative trial results, potential misuse, diversion, long-term mental health risks		WEAK		
Valproate		WEAK		
Levetiracetam N.B. Because of generally negative trials and safety concerns		STRONG		
Mexiletine N.B. Because of generally negative trials and safety concerns		STRONG		

Sustained-release oxycodone and morphine are the opioids most studied. Long-term use may be associated with abuse, cognitive impairment, and endocrine and immunological changes. Prescription requires risk assessment strict monitoring and treatment agreements. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SNRI, selective serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressants.

[a] Duloxetine is the most studied and therefore the most recommended SNRI.

[b] The tertiary amine TCAs (amitriptyline, imipramine, clomipramine) are not recommended at doses greater than 75 mg day^{-1} in >65 yr because of major anticholinergic and sedative adverse effects, and an increased risk of sudden cardiac death at doses >100 mg day^{-1}.

[c] The long-term safety of repeated application of high-concentration capsaicin patches is not clearly established. They may exacerbate progressive neuropathy by degeneration of epidermal nerve fibres.

the maximum allowed dose, therefore potentially preventing attainment of therapeutic levels.

Typical daily dosing regimens:

- Nabilone (oral, 1–4 mg)
- Dronabinol (oral, 2.5–10 mg)
- Nabiximols [oromucosal THC-CBD spray, range 1–48 sprays (mean 8.3 sprays)]
- Cannabis (smoked or vaporised medical marijuana, containing 1.875–34 mg THC).

These doses were associated with a significant reduction in mean numerical rating scale (NRS) scores, improved Quality of Life (QoL) measures, sleep, and patient satisfaction.

Sequential combination therapies

Combination of two or more analgesics have been recommended by the WHO, the American Pain Society (APS), and the American College of Rheumatology (ACR).[1] Monotherapy with current agents can have limited efficacy even when maximum doses are reached, and with dose-related adverse effects. Combination therapy with two or more different drugs may improve efficacy, as the aetiology of NeP is related to more than one biochemical pathway.[1,4] The overall incidence of adverse effects can be reduced, particularly if the combination displays synergism, thus allowing for decreased dosages.[4]

COMBO-DN study

The COMBO-DN study is a multinational trial designed to answer the common clinical question: 'Is it better to increase the dose of the current first-line recommended monotherapy or to combine with another first-line recommended drug early on in patients with insufficient pain relief?'

In the trial, the efficacy and tolerability of maximal dose monotherapy (either duloxetine 120 mg day^{-1} or pregabalin 600 mg day^{-1}) was compared to a combination regimen with lower dosages. The study group was patients with PDN who had not previously responded to the standard dose of either pregabalin or duloxetine.

The results consistently favoured combination therapy, supporting the theory that pharmacotherapies with differing mechanisms of action may complement each other and have additive effects in clinical practice.[9]

Cochrane review 2012

This review demonstrated the superior efficacy of two-drug combinations. RCTs have proved that gabapentin–morphine and nortriptyline–pregabalin yield greater efficacy when applied together; hence anticonvulsant–opioid and antidepressant–anticonvulsant combinations have been recommended for NeP. A further trial has shown that an antidepressant–opioid combination in the form of nortriptyline–morphine was superior to monotherapy.[10,11]

Ideally, combinations of drugs that have similar adverse effect profiles should be avoided, so combination therapy in clinical practice requires vigilance. One common approach to reduce the risk of toxicity is 'sequential combination therapy'. Patients are first commenced on monotherapy. If only a partial response to treatment is observed, the patient receives add-on therapy. This may be subsequently lead to differing dose ratio than might have otherwise been attained. Future research should aim to clarify the optimal ratios and therefore cost-effectiveness.[10]

Novel techniques

Pharmacotherapy delivery

Domiciliary s.c. lidocaine

Systemic intravenous lidocaine is well established in the treatment of NeP. A single infusion can provide relief for several weeks to months. Some patients experience dramatic but brief pain relief. However, it is impractical and costly to provide very frequent infusions. Subcutaneous lidocaine has shown promising results in providing continual analgesia, with no adverse events, no difficulties with self-injection, and high patient acceptability.[12] Self-administration of s.c. lidocaine may substantially reduce healthcare costs.

Topical treatments

The use of topical treatment in managing NeP is becoming increasingly popular.

Topical clonidine

$Alpha_2$ receptors in nociceptors are expressed within the epidermis and are associated with increased nociceptor excitability. Topical clonidine, an α_2 adrenergic agonist, targets these receptors. In patients with PDN with functional nociceptors in the affected areas, clonidine topical gel has been shown to significantly reduce pain levels. The dosing regimen in this study was 3.9 mg daily (0.65 g doses, applied to both feet three times per day). Plasma clonidine concentrations in subjects were generally below the lower limit of detection (10 pg ml^{-1}) compared with the typical plasma concentrations attained in the treatment of hypertension (1000 pg ml^{-1}). Therefore the action of topical clonidine is thought to be mediated peripherally.[13]

Topical ketamine–gabapentin–imipramine–bupivacaine

Topical creams with multiple anti-NeP agents have been successful in treating NeP. They act multi-modally to reduce sensation via pain nerve fibres by targeting multiple receptors simultaneously. An anti-NeP topical cream with ketamine 10%, gabapentin 10%, imipramine 3%, and bupivacaine 5% was shown to resolve NeP symptoms for several hours; it was also successful in reducing flare-ups in a patient with cervicalgia and TGN, refractory to several treatments.[10] Ketamine and gabapentin are more effective together as they mitigate glutaminergic calcium influx more effectively in combination. These agents offer effective non-invasive, non-systemic therapy, but with the limitation of the cost required for the compounding process.[14]

Interventional treatments

Erector spinae plane block

The ESP block is a novel technique in the treatment of thoracic NeP. It is an interfascial plane block. Local anaesthetic is administered deep to the erector spinae muscle in order to gain proximity to dorsal and ventral rami of the thoracic spinal nerves. It has been successful in severe cases of refractory NeP, producing an extensive multi-dermatomal sensory block, both posteriorly and anteriorly. In comparison, the pectoral and serratus plane block provide only anterior coverage. It has easily recognisable sonoanatomy and lends itself to the insertion of an indwelling catheter.[15]

Dorsal root entry zone ablation treatments

Dorsal root entry zone (DREZ) procedures are indicated in complex and resistant segmental, and more recently, diffuse NeP after complete spinal cord injury. Alternative approaches such as neuromodulation require a permanent prosthetic implant. DREZ targets nociceptive fibres in the lateral bundle of the dorsal rootlet, the deafferented neurons in the dorsal horn, and the medial portion of the Lissauer tract.[16]

Deep brain stimulation

Deep brain stimulation (DBS) has been used in refractory chronic pain for many decades. Standard DBS can be ineffective as not all patients respond to stimulation along primary sensory pathways. In 2014, the first case series of DBS of the anterior cingulate cortex (ACC) to target the affective component of pain was described. Twenty-four patients underwent bilateral ACC DBS. Inclusion criteria included failed pharmacotherapy for at least 2 yr or failed standard DBS. Six months after surgery the mean NRS pain score decreased from 8.0 to 4.27 ($P=0.004$). Patients described that pain was still present but less bothersome. Efficacy was sustained for up to 42 months. ACC DBS can improve QoL and alleviate otherwise treatment-resistant chronic NeP.[17]

Pain phenotyping

Clinical phenotyping describes the process of identifying relevant clinical criteria and classifying patients into corresponding subgroups. It is assumed that the different subgroups have varying underlying pain mechanisms, and therefore may respond differentially to treatments.[5]

Our current way of classifying NeP is generally inadequate. Regardless of aetiology, patients should be classified according to their clinical phenotype. This is now facilitated by validated NeP questionnaires and standardisation of sensory testing, such as quantitative sensory testing (QST). One example describes the presence of mechanical allodynia depicting preserved nociceptive function. This can predict response to various treatments including sodium channel blockers, clonidine gel, and botulinum.

The COMBO-DN trial demonstrated that patients with certain clinical phenotypes predicted clinical response to duloxetine or pregabalin, either alone or in combination.[9] Patients with pressing and evoked pain not responding to a standard dose of duloxetine showed improvement when a standard dose of pregabalin was added to the regimen. Conversely patients describing pain with characteristics of paraesthesia and dysaesthesia received benefit from maximising the dose of duloxetine. Patients with peripheral NeP with preserved thermal sensation responded positively to botulinum toxin A. A higher therapeutic response correlated with less severe thermal deficits. In the future, it may be possible to incorporate therapeutic algorithms such as this, which could be fundamental in predicting therapeutic responses and thus reduce the incidence of therapeutic failures.[5]

Mechanistic updates

Additional insights into antidepressants and gabapentinoids

The onset of therapeutic effects of antidepressants is delayed. Hence their action is thought to be via long-term molecular and neural plasticity, recruiting downstream mechanisms such as chromatin regulation, gene expression, recruitment of neurotrophins, and stimulating neurogenesis.

The action of antidepressant drugs on noradrenaline is a crucial component in the treatment of NeP. There are two proposed mechanisms for this: recruitment of descending noradrenergic pathways and peripheral noradrenaline recruitment from sympathetic nerves in the dorsal root ganglia. They may also act indirectly on proinflammatory cytokines.[18]

Gabapentinoids also activate this inhibitory descending noradrenergic pathway. In addition, like antidepressants, they may impact on proinflammatory cytokines. In comparison to the slow onset of antidepressants, the acute administration of gabapentinoids at high doses demonstrates efficacy against NeP.[18]

Future perspectives

Cebranopradol

This is a promising unique, centrally-acting agent. It is a single molecule but has dual agonist action at opioid and nociception/orphanin FQ peptide (NOP) receptors.[1] Compared with traditional opioids, cebranopradol is more potent against neuropathic than nociceptive pain. In preclinical testing it showed antinociceptive, antihyperalgesic, and antiallodynic actions, with significantly higher potency than morphine. The adverse effect profile of cebranopradol is favourable compared with morphine at equianalgesic doses; it also has lower incidences of opioid-induced respiratory depression and pruritus, and delayed onset of tolerance. In addition, NOP agonism reduces dopamine release from neurones involved in reward pathways. Thus the combination of NOP and MOP (μ-opioid peptide) receptor agonism may attenuate opioid reward pathways in a similar manner to buprenorphine. The results of phase III clinical trials are awaited.[1]

Angiotensin II type 2 receptor antagonists

In the past two decades, there has been a collaborative global research effort on the pathophysiology of NeP. This has revealed a multitude of 'pain targets' including receptors, enzymes, and ion channels. Despite promising results in animal models this failed to translate into humans. One exception is the AT_2 receptor antagonists, which represent a completely new analgesic class. EMA401 is a first-in-class orally active, highly selective, peripherally restricted AT_2 receptor antagonist that has been successful in a clinical proof-of-concept trial in patients with postherpetic neuralgia.[8]

Conclusion

The treatment of NeP is complex, and as such it would be impossible to suggest a specific 'neuropathic pain ladder'. In general, a multimodal approach is adopted, recognising the requirement of the biopsychosocial approach to these patients.

Recommended first-line treatments are the gabapentinoids (gabapentin, pregabalin), and antidepressants (duloxetine, amitriptyline). It is important to recognise when treatment is not successful and switch medication early, rather than uptitrating. It should be borne in mind that patients may benefit from combination therapy. This should be trialled early, with emerging evidence of efficacy and tolerability of moderate doses compared with maximal dose monotherapy. Antidepressant–gabapentinoid, antidepressant–opioid, and gabapentinoid–opioid are supported combinations. Local anaesthetic blocks and more invasive procedures tend to be reserved as an adjunct to pharmacotherapy, or in those patients refractory to it.

Tapentadol targets both nociceptive and neuropathic pathways and has been in clinical use in certain patient groups and geographical locations since 2011. It tends to be reserved for those in whom morphine has proved inadequate or not tolerated. The opioid cebranopradol is an exciting prospect in the treatment of chronic NeP, but more data are needed.

Declaration of interest

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to BJA Education.

References

1. Raffa RB, Burdge G, Gambrah J *et al*. Cebranopadol: novel dual opioid/NOP receptor agonist analgesic. *J Clin Pharmacol Ther* 2017; **42**: 8–17
2. Kamerman PR, Wadley AL, Davis K *et al*. World Health Organization (WHO) essential medicines list: where are the drugs to treat neuropathic pain? *Pain* 2015; **156**: 793–7
3. National Institute for Health and Care Excellence (NICE) (Published 2013, Updated 2017) Neuropathic pain in adults: pharmacological management in non-specialist settings: NICE Guideline [CG173]. Available from https://www.nice.org.uk/guidance/cg173 (accessed 23 May 2017).
4. Finnerup NB, Attal N, Haroutounian S *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; **14**: 162–73
5. Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? *Pain* 2015; **156**: S104–14
6. Baron R, Binder A, Attal N, Casale R, Dickenson AH, Treede R-D. Neuropathic low back pain in clinical practice. *Eur J Pain* 2016; **20**: 861–3
7. Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. *Anesth Analg* 2017; **125**: 1638–52
8. Smith MT, Anand P, Rice AS. Selective small molecule angiotensin II type 2 receptor antagonists for neuropathic pain: preclinical and clinical studies. *Pain* 2016; **157**: S33–41
9. Tesfaye S, Wilhelm S, Lledo A *et al*. Duloxetine and pregabalin: high dose monotherapy or their combination? The "COMBO-DN study" — a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013; **154**: 2616–25
10. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012; **7**. CD008943
11. Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. *Pain* 2015; **156**: 1440–8
12. Nandi P, Kruglov D, Cregg R. Domiciliary subcutaneous lidocaine for the treatment of neuropathic pain – a preliminary report. *Br J Pain* 2017; **11**: 5–96
13. Campbell CM, Kipnes MS, Stouch BC *et al*. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* 2012; **153**: 1815–23
14. Iqbal M, Monroe B, Ahmed S, Krishnan K, Hollenbach D. Topical ketamine–gabapentin–imipramine–bupivacaine for treatment of trigeminal neuralgia facial pain. *Region Anesth Pain M* 2016; **41**
15. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. *Reg Anesth Pain Med* 2016; **41**: 621–7
16. Mehta S, Orenczuk K, McIntyre A *et al*. Neuropathic pain post spinal cord injury: part 2. Systematic review of dorsal root entry zone procedure. *Spinal Cord Inj Rehabil* 2013; **19**: 78–86
17. Boccard SG, Prangnell SJ, Pycroft L *et al*. Long-term results of deep brain stimulation of the anterior cingulate cortex for neuropathic pain. *Br J Neurosurg* 2017; **31**: 122–3
18. Cremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: mechanistic insights. *Neuroscience* 2016; **338**: 183–206