MANAGEMENT
Goals of Treatment
Management of Neuropathic Pain

The earlier a diagnosis is made, the more opportunities there are to improve patient outcomes

Improved sleep quality

Improved overall quality of life

Reduced pain

Improved physical functioning

Improved psychological state

Diagnosis

Treatment of underlying conditions

Pharmacological and non-pharmacological treatment of neuropathic pain

Treatment of comorbidities

Improved quality of life

Goals in the Treatment of Neuropathic Pain

1° goal: >50% pain relief* … but be realistic!

2° goals

- Restoration or improvement in:
  - Sleep
  - Mood
  - Function
  - Quality of life

*Note: pain reduction of 30–50% can be expected with maximal doses in most patients
# Planning the Management of Painful Diabetic Peripheral Neuropathy: Treatment Goals

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &gt;50% pain relief, but be realistic!</td>
<td>• Restoration or improvement in functional measures, quality of life, sleep and mood</td>
</tr>
<tr>
<td>• Do not let &quot;realistic&quot; lead to a less aggressive pursuit of maximum relief</td>
<td>• Treatment should be modifying pain and hopefully improved function will follow</td>
</tr>
<tr>
<td></td>
<td>• If improved function does not follow, take measures to help patients optimize function in the presence of residual pain</td>
</tr>
</tbody>
</table>

Non-pharmacological Treatment
Multimodal Treatment of Neuropathic Pain

- Pharmacotherapy
- Interventional procedures
- Biofeedback
- Education
- Complementary therapies
- Physical or occupational therapy
- Sleep hygiene
- Stress management
- Lifestyle management
Various Non-pharmacological Treatments Are Available for Neuropathic Pain

1-6

Physiotherapy

Psychotherapy/CBT

Patient education

Alternative therapies and spiritual healing

Multimodal pain management programs

Various non-pharmacological treatment modalities are mentioned in guidelines, but no modality is universally recommended

CBT = cognitive behavioral therapy

Evidence for Non-pharmacological Therapies in Neuropathic Pain

- Studied therapies include:
  - Acupuncture
  - Electrostimulation
  - Herbal medicine
  - Magnets
  - Dietary supplements
  - Imagery
  - Spiritual healing

- Limited evidence for most modalities

The effectiveness of B vitamins in reducing chronic neuropathic pain has not been established

- Cannabis extract
- Carnitine
- Electrostimulation
- Magnets

AAN Guidelines: Non-pharmacologic Treatment of Diabetic Peripheral Neuropathy

**Recommended**
- Percutaneous electrical nerve stimulation (level B)

**Not recommended**
- Electromagnetic field treatment (level B)
- Low-intensity laser treatment (level B)
- Reiki therapy (level B)

**Insufficient evidence**
- Amitriptyline + electrotherapy (level U)

AAN = American Academy of Neurology
AAN Guidelines: Non-pharmacologic Treatment of Postherpetic Neuralgia

**Recommended**
- None

**Not recommended**
- Acupuncture (level B)
- Vitamin E (level B)

**Insufficient evidence**
- He:Ne laser irradiation
- Cryocautery
- Extract of *Ganoderma lucidum* (lingzhi mushroom)

AAN = American Academy of Neurology
Latin American Expert Consensus: Non-pharmacological Treatment of Neuropathic Pain

Complementary therapies*

- Acupuncture – provided it is performed by qualified practitioners and with the agreement of the patient
- Thiocytic acid and cytidine/uridine monophosphate

Insufficient evidence

- Herbal therapy**

*Although widely used in practice, little scientific evidence supports its use and the patient must be informed about this. Use or recommendation for use mandates prudence and ethical conduct.

**These types of treatment are left up to the doctor, who should consider sociocultural aspects of the patient.

South African Guidelines: Non-pharmacologic Treatment of Neuropathic Pain

**Recommended**
- Psychotherapy, particularly cognitive behavioral therapy
- Transcutaneous electrical nerve stimulation
- Physiotherapy
- Spinal cord stimulation*

**Not recommended**
- Dorsal root entry zone lesioning (DREZotomy)

*In cases of pain that cannot be managed by pharmacological and companion treatments

EFNS Guidelines: Non-pharmacologic Treatment of Neuropathic Pain

**Recommended**
- Electro-acupuncture (level B)
- High-frequency transcutaneous electrical nerve stimulation (level C)
- Repetitive transcranial magnetic stimulation* (level B)

**Not recommended**
- Peripheral electrical neurostimulation

**Insufficient evidence**
- Implanted peripheral stimulation

*Transient efficacy; EFNS = European Federation of Neurological Societies

Note: only electrical neurostimulation modalities were reviewed, other non-pharmacological methods were not considered.
IASP NeuPSIG Recommendations: Intervventional Management of Neuropathic Pain

Weakly Recommended
- Epidural or paravertebral nerve block(s) for herpes zoster
- Epidural steroid injection(s) for radiculopathy
- Spinal cord stimulation for failed back surgery syndrome with radiculopathy and complex regional pain syndrome 1

Not recommended
- Sympathetic nerve blocks for postherpetic neuralgia
- Radiofrequency lesioning for lumbar radiculopathy

IASP = International Association for the Study of Pain; NeuPSIG = Neuropathic Pain Special Interest Group
Summary of Non-pharmacologic Treatment Recommendations for Neuropathic Pain

• Transcutaneous electrical nerve stimulation is the only non-pharmacologic treatment modality recommended by the majority of guidelines

Pharmacological Treatment
Mechanism-Based Pharmacological Treatment of Neuropathic Pain

- **Medications affecting peripheral sensitization:**
  - Capsaicin
  - Local anesthetics
  - TCAs

- **Medications affecting descending modulation:**
  - SNRIs
  - TCAs
  - Tramadol, opioids

- **Medications affecting central sensitization:**
  - $\alpha_2\delta$ ligands
  - TCAs
  - Tramadol, opioids

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Therapeutic Targets of Neuropathic Pain


NMDA = N-methyl-D-aspartate; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant
Role of $\alpha_2\delta$-Linked Calcium Channels in Neuropathic Pain

Injury stimulates production of calcium channels.

Increased numbers of calcium channels
Increased calcium influx
Increased neuronal excitability

Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands
α₂δ Ligands Bind to α₂δ Subunit of Voltage-Gated Calcium Channels

Note: gabapentin and pregabalin are α₂δ ligands
Arikath J, Campbell KP. Curr Opin Neurobio 2003; 13(3):298-307;
α2δ Ligands Reduce Calcium Influx in Depolarized Human Neocortex Synaptosomes

Fink K et al. Neuropharmacology 2002; 42(2):229-36.
\( \alpha_2 \delta \) Ligands Modulate Calcium Channel Trafficking

- \( \alpha_2 \delta \) ligands reduce trafficking of voltage-gated calcium channel complexes to cell surface in vitro
- \( \alpha_2 \delta \) ligands prevent nerve-injury induced up-regulation of \( \alpha_2 \delta \) in the dorsal horn

BCH = 2-\((−)\)-endoamino-bicycloheptene-2-carboxylic acid; ER = endoplasmic reticulum; GBP = gabapentin

## Adverse Effects of $\alpha_2\delta$ Ligands

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive system</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>CNS</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Other</td>
<td>Asthenia, headache, peripheral edema, weight gain</td>
</tr>
</tbody>
</table>

$\alpha_2\delta$ ligands include gabapentin and pregabalin

CNS = central nervous system

How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation.
# Suggested Mechanisms of Analgesic Action of Antidepressants

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Site of Action</th>
<th>TCA</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reuptake inhibition</td>
<td>Serotonin, Noradrenaline</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reuptake inhibition</td>
<td>Serotonin, Noradrenaline</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reuptake inhibition</td>
<td>α-adrenergic, NMDA</td>
<td>+</td>
<td>- (+ milnepirant)</td>
</tr>
<tr>
<td>Blocking or activation of ion channels</td>
<td>Sodium channel blocker</td>
<td>+</td>
<td>(+ venlafaxine/duloxetine</td>
</tr>
<tr>
<td>Blocking or activation of ion channels</td>
<td>Calcium channel blocker</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Blocking or activation of ion channels</td>
<td>Potassium channel activator</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Increasing receptor function</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; receptor</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Opioid receptor binding/opioid-mediated effect</td>
<td>Mu- and delta-opioid receptor</td>
<td>(+)</td>
<td>(+) venlafaxine</td>
</tr>
<tr>
<td>Decreasing inflammation</td>
<td>Decrease of PGE2 production, decrease of TNFα production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GABA = γ-aminobutyric acid; NDMA = N-methyl-D-aspartate; PGE = prostaglandin E; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TNF = tumor necrosis factor

Verdu B *et al.* *Drugs* 2008; 68(18):2611-32.
# Adverse Effects of Antidepressants

<table>
<thead>
<tr>
<th>System</th>
<th>TCAs</th>
<th>SNRIss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive system</td>
<td>Constipation, dry mouth, urinary retention</td>
<td>Constipation, diarrhea, dry mouth, nausea, reduced appetite</td>
</tr>
<tr>
<td>CNS</td>
<td>Cognitive disorders, dizziness, drowsiness, sedation</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Orthostatic hypotension, palpitations</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Other</td>
<td>Blurred vision, falls, gait disturbance, sweating</td>
<td>Elevated liver enzymes, elevated plasma glucose, sweating</td>
</tr>
</tbody>
</table>

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor
Pharmacological Management of Neuropathic Pain

**STEP 1**
Initiate treatment with one or more **first-line** treatments:
- $\alpha_2\delta$ ligands (gabapentin, pregabalin)
- SNRIs (duloxetine, venlafaxine)
- TCAs* (nortriptyline, desipramine)
- Topical lidocaine (for localized peripheral pain)

**STEP 2**
- If there is partial pain relief, add another first-line medication
- If there is no or inadequate pain relief, switch to another first-line medication

**STEP 3**
If first-line medications alone and in combination fail, consider **second-line** medications (opioids, tramadol) or **third-line** medications (bupropion, citalopram, paroxetine, carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid, topical capsaicin, dextromethorphan, memantine, mexiletine) or referral to pain specialist

*Use tertiary amine TCAs such as amitriptyline only if secondary amine TCAs are unavailable
Note: there is insufficient support for the use of nsNSAIDs in neuropathic pain
nsNSAID = non-specific non-steroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
CPS Recommendations for the Pharmacological Management of Neuropathic Pain

Stepwise Pharmacological Management of Neuropathic Pain

1\textsuperscript{st} line

Pregabalin or gabapentin $\leftrightarrow$ TCAs

2\textsuperscript{nd} line

SNRIs $\leftrightarrow$ Topical lidocaine 5\% gel or cream*

3\textsuperscript{rd} line

Tramadol or controlled-release opioid analgesics

4\textsuperscript{th} line

Cannabinoids, methadone, lamotrigine, topiramate, valproic acid

Add additional agents sequentially if partial but inadequate pain relief\textsuperscript{†}

\textsuperscript{*}Useful for focal neuropathy such as post-herpetic neuralgia; \textsuperscript{†}Do NOT add SNRIs to TCAs.

CPS = Canadian Pain Society; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

AAN Guidelines: Pharmacological Treatment of Painful Diabetic Peripheral Neuropathy

1st line (level A)
- Pregabalin

2nd line (level B)
- Gabapentin
- Duloxetine
- Amitriptyline
- Opioids
- Tramadol

The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

AAN = American Academy of Neurology
AAN Guidelines: Pharmacological Treatment of Postherpetic Neurology

1st line (level A)

- TCAs (amitriptyline, * nortriptyline, ** desipramine, maprotiline)
- α₂δ ligands (gabapentin, pregabalin)
- Opioids
- Topical lidocaine patches
- Preservative-free intrathecal methylprednisolone

*Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine;

**Limited evidence (level B) to support nortriptyline over amitriptyline

AAN = American Academy of Neurology
<table>
<thead>
<tr>
<th>Line</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>• α₂δ ligands (gabapentin, pregabalin)</td>
</tr>
<tr>
<td></td>
<td>• TCAs (amitriptyline)</td>
</tr>
<tr>
<td>2nd</td>
<td>• Dual antidepressants (duloxetine)</td>
</tr>
<tr>
<td>3rd</td>
<td>• Weak opioids (tramadol)</td>
</tr>
<tr>
<td></td>
<td>• Local anesthetics (lidocaine)</td>
</tr>
<tr>
<td>4th</td>
<td>• SNRIs (fluoxetine), sodium channel blockers (carbamazepine), substance P inhibitors (capsaicin), cannabinoids, strong opioids (morphine)</td>
</tr>
</tbody>
</table>

SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
South African Guidelines: Algorithm for the Treatment of Non-localized Peripheral Neuropathic Pain

SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
South African Guidelines: Algorithm for the Treatment of Central Neuropathic Pain

CBT = cognitive behavioral therapy; TCA = tricyclic antidepressant
Treatment Recommendations for French-Speaking Maghreb: Peripheral Neuropathic Pain

1st line (level A)
- $\alpha^2\delta$ ligands (gabapentin, pregabalin)
- TCAs
- Topical lidocaine

2nd line (level B)
- SNRIs (venlafaxine XR or duloxetine)
- Tramadol

TCA = tricyclic antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor; XR = extended release
Middle East Region Expert Panel Recommendations: Treatment Algorithm for Peripheral Neuropathic Pain

**1st Line**
For peripheral neuropathic pain, treat with:
1) Pregabalin or gabapentin
2) TCA (nortriptyline or desipramine)
For focal neuropathy such as postherpetic neuralgia, treat with: topical lidocaine (patch or 5% gel or cream)

**2nd Line**
1) SNRI (duloxetine; venlafaxine XR)
2) Tramadol or other opioid analgesic (preferably controlled-release)

For patients with partial or inadequate pain relief: May add additional drugs (but do NOT combine SNRIs and TCAs)

Partial or non-response to 2nd line treatment

Refer to specialist

*In patients with focal post-herpetic neuropathy with allodynia, or any peripheral neuropathic pain associated with a small, localized area of allodynia
NMDA = N-methyl-D-aspartate; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; XR = extended release
Central Neuropathic Pain Treatment Recommendations for the Middle East Region

1st line
- $\alpha_2\delta$ ligands (gabapentin, pregabalin)

Other treatments
- Opioids*
- SNRIs*
- TCAs

*Benefit appears to be notably less than for peripheral neuropathic pain

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

### EFNS Guidelines: Pharmacological Treatment of Neuropathic Pain

<table>
<thead>
<tr>
<th>1st line</th>
<th>2nd or 3rd line</th>
<th>Postherpetic neuralgia</th>
<th>Trigeminal neuralgia</th>
<th>Central pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• $\alpha_2\delta$ ligands (gabapentin, pregabalin)</td>
<td>• Opioids</td>
<td>• $\alpha_2\delta$ ligands (gabapentin, pregabalin)</td>
<td>• Cabamazepine Oxcarbazepine</td>
<td>• $\alpha_2\delta$ ligands (gabapentin, pregabalin)</td>
</tr>
<tr>
<td>• SNRIs (duloxetine, venlafaxine ER)</td>
<td>• Tramadol*</td>
<td>• TCAs</td>
<td>• Lidocaine plasters</td>
<td>• TCAs</td>
</tr>
<tr>
<td>• TCAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>• Capsaicin</td>
<td></td>
<td>• Surgery</td>
<td></td>
</tr>
<tr>
<td>• Opioids</td>
<td>• Opioids</td>
<td></td>
<td></td>
<td>• Cannabinoids (MS)</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td></td>
<td></td>
<td>• Surgery</td>
<td>• Lamotrigine</td>
</tr>
<tr>
<td>• Opioids</td>
<td></td>
<td></td>
<td></td>
<td>• Opioids</td>
</tr>
<tr>
<td>Central pain</td>
<td></td>
<td></td>
<td></td>
<td>• Tramadol (SCI)</td>
</tr>
</tbody>
</table>

Note: recommended treatments may not all be licensed for the indication. Prescribers should also be aware of contraindications and cautions when using certain agents in certain patients (e.g., elderly).

*Tramadol may be considered first-line in patients with acute exacerbations of pain, especially for the tramadol/acetaminophen combination.

DPN = diabetic peripheral neuropathy; EFNS = European Federation of Neurological Societies; ER = extended release; MS = multiple sclerosis; SCI = spinal cord injury; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Treatment Algorithm for Painful Diabetic Peripheral Neuropathy

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

**Drug Selection According To Clinical Presentation of Neuropathic Pain**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Clinical presentation of neuropathic pain</th>
<th>Burning</th>
<th>Lancinating</th>
<th>Hyperalgesia</th>
<th>Allodynia</th>
<th>Parethesia, dysesthesia</th>
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</thead>
<tbody>
<tr>
<td>TCA</td>
<td></td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Amitriptyline</td>
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<td>+/-</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>SNRI</td>
<td></td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Venlafaxine</td>
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<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+//-</td>
</tr>
<tr>
<td>Duloxetine</td>
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<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+//-</td>
</tr>
<tr>
<td>Na⁺ channel blockers:</td>
<td></td>
<td>+/-</td>
<td>++</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Carbamazepine</td>
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<td>+/-</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>Oxcarbazepine</td>
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<td>Ca²⁺ channel α₂δ ligands:</td>
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<td>+</td>
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<td>Opioids:</td>
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<td>Morphine</td>
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<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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</tr>
</tbody>
</table>

**SNRI** = serotonin norepinephrine reuptake inhibitor; **TCA** = tricyclic antidepressant

Thai Association for the Study of Pain. *Clinical Practice Guidelines for Neuropathic Pain.*
### Drug Selection According to Conditions Causing Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug class and drug(s)</th>
<th>Type of neuropathic pain</th>
<th>Diabetic peripheral neuropathy</th>
<th>Postherpetic neuralgia</th>
<th>Trigeminal neuralgia</th>
<th>Phantom limb pain</th>
<th>Central pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amitriptyline</td>
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<td>++</td>
<td>+/-</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>SNRI</strong></td>
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<tr>
<td>Venlafaxine</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
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<td>Duloxetine</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td><strong>Na⁺ channel blocker</strong></td>
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<td>++</td>
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<td>+</td>
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<tr>
<td>Oxcarbazepine</td>
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<td>++</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td><strong>Ca²⁺ channel α₂δ ligand</strong></td>
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<td>Gabapentin</td>
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<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Pregabalin</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td><strong>Opioid</strong></td>
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<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Morphine</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Thai Association for the Study of Pain. *Clinical Practice Guidelines for Neuropathic Pain.*
Singapore Pain Management Guidelines for Painful Diabetic Peripheral Neuropathy

ER = extended release; TCA = tricyclic antidepressant
Pfizer Pte Ltd; Singapore: 2007.
# Painful Diabetic Neuropathy Treatment Recommendations: Philippines

<table>
<thead>
<tr>
<th>Agent type</th>
<th>Reason for recommendation</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>First tier</td>
<td>≥2 randomized controlled trials on painful diabetic neuropathy, functional outcomes</td>
<td>Pregabalin, gabapentin, duloxetine</td>
</tr>
<tr>
<td>Second tier</td>
<td>1 randomized controlled trial on painful diabetic neuropathy; ≥1 randomized controlled trials on other painful neuropathies</td>
<td>Venlafaxine XR, oxycodone CR, tramadol, amitriptyline</td>
</tr>
<tr>
<td>Topical</td>
<td>Mechanism of action</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Other</td>
<td>Insufficient evidence for any recommendation</td>
<td>Alpha-lipoic acid, vitamin B complex, SSRIs, capsaicin</td>
</tr>
</tbody>
</table>

CR = controlled release; SSRI = selective serotonin reuptake inhibitor; XR = extended release

Hong Kong Multidisciplinary Panel on Neuropathic Pain: Treatment Recommendations for Painful Diabetic Peripheral Neuropathy

1st line: TCAs or $\alpha_2\delta$ ligands

2nd line: tramadol

Refer to pain clinic if refractory to pharmacotherapy

Other pharmacotherapy options: systemic local anesthetics, opioids, NMDA antagonists

Physical stimulation: percutaneous or transcutaneous electrical nerve stimulation, acupuncture, spinal cord stimulation

Pain management programs, behavioral therapy

NMDA = N-methyl-D-aspartate; TCA = tricyclic antidepressants
## Prescribing Recommendations for First-Line Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting dose</th>
<th>Titration</th>
<th>Max. dosage</th>
<th>Trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α₂δ ligands</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100–300 mg at bedtime or tid</td>
<td>↑ by 100–300 mg tid every 1–7 days</td>
<td>3600 mg/day</td>
<td>3–8 weeks + 2 weeks at max. dose</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50 mg tid or 75 mg bid</td>
<td>↑ to 300 mg/day after 3–7 days, then by 150 mg/day every 3–7 days</td>
<td>600 mg/day</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30 mg qd</td>
<td>↑ to 60 mg qd after 1 week</td>
<td>60 mg bid</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg qd</td>
<td>↑ by 75 mg each week</td>
<td>225 mg/day</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td><strong>TCAs</strong> (desipramine, nortriptyline)</td>
<td>25 mg at bedtime</td>
<td>↑ by 25 mg/day every 3–7 days</td>
<td>150 mg/day</td>
<td>6–8 weeks, with ≥2 weeks at max. tolerated dosage</td>
</tr>
<tr>
<td>Topical lidocaine</td>
<td>Max. 3 5% patches/day for 12 h max.</td>
<td>None needed</td>
<td>Max. 3 patches/day for 12–18 h max.</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

But... Patients with Chronic Pain of Just One Type of Pain Pathophysiology May be Rare

- Patients may have different pathophysiologic mechanisms contributing to their pain
  - e.g., complex regional pain syndrome has multiple potential mechanisms, including nerve injury and inflammation – “mixed pain state”

- Therapies that will work better for a particular patient are likely to depend on the mechanisms contributing to the patient’s pain

- Patients with mixed pain may benefit from combination therapy

Adherence
Adherence to Neuropathic Pain Medications in Suboptimal Patients with Painful Diabetic Peripheral Neuropathy

Non-adherence to neuropathic pain medication (i.e., MPR <80%) was significantly associated with non-adherence to oral antihyperglycemic therapies.

MPR = medication possession ratio; TCA = tricyclic antidepressant

Strategies to Improve Adherence

• **S**implify regimen
• **I**mpart knowledge
• **M**odify patient beliefs and human behavior
• **P**rovide communication and trust
• **L**eave the bias
• **E**valuate adherence

Simplifying Medication Regimen

- If possible, adjust regimen to minimize:
  - Number of pills taken
  - Number of doses per day
  - Special requirements (e.g., bedtime dosing, avoiding taking medication with food, etc.)

- Recommend all medications be taken at the same time of day (if possible)
- Link taking medication to daily activities, such as brushing teeth or eating
- Encourage use of adherence aids such as medication organizers and alarms

Imparting Knowledge

• Provide clear, concise instructions (written and verbal) for each prescription
• Be sure to provide information at a level the patient can understand
• Involve family members if possible
• Provide handouts and/or reliable websites for patients to access information on their condition
• Provide concrete advice on how to cope with medication costs

## Modifying Patient Beliefs and Behaviors: Motivational Interviewing Technique

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Express empathy</td>
<td>• “It’s normal to worry about medication side effects”</td>
</tr>
<tr>
<td>• Develop discrepancy</td>
<td>• “You obviously care about your health; how do you think not taking your pills is affecting it?”</td>
</tr>
<tr>
<td>• Roll with resistance</td>
<td>• “I understand that you have a lot of other things besides taking pills to worry about”</td>
</tr>
<tr>
<td>• Support self efficacy</td>
<td>• “It sounds like you have made impressive efforts to work your new medication into your daily routine”</td>
</tr>
</tbody>
</table>

Providing Communication and Trust: Communication Tips

• Be an active listener
  – Focus on the patient
  – Nod and smile to show you understand

• Make eye contact

• Be aware of your own body language
  – Face the patient
  – Keep arms uncrossed
  – Remove hands from pockets

• Recognize and interpret non-verbal cues

McDonough RP, Bennett MS. *Am J Pharm Educ* 2006; 70(3):58;
Leaving the Bias

Learn more about how low health literacy can affect patient outcomes

Specifically ask about attitudes, beliefs and cultural norms with regards to medication

Tailor communication to patient’s beliefs and level of understanding

Acknowledge biases
Evaluating Adherence: 4-Step Strategy for Detecting Non-adherence

1. Ask an open-ended question about taking medicine

2. Normalize and universalize non-adherence to reverse the judgmental environment

3. Make the role of accurate information about adherence in medical decision-making explicit

4. Don’t ask about “forgetting” or “missed” doses until the first 3 steps have set the stage

Summary
Management: Summary

• Realistic treatment goals should be set in conjunction with the patient
• Most treatment guidelines consider TCAs and $\alpha_2\delta$ ligands as first-line therapy for most types of neuropathic pain
  – Topical lidocaine should also be considered for focal neuropathy
  – Guideline recommendations differ regarding use of SNRIs, opioids and tramadol in various types of neuropathic pain
• Non-pharmacologic treatments should be considered as complementary treatment to pharmacological therapy whenever appropriate
  – Transcutaneous electrical nerve stimulation is the only non-pharmacologic treatment modality recommended by the majority of guidelines

TCA = tricyclic antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor