Neuropatic Pain Drugs

Pharmacodynamic & Pharmacokinetic

Nyeri neuropatik

- Merupakan akibat dari fungsi abnormal sistem saraf perifer, sentral, maupun simpatis.
- Kasus nyeri neuropatik (tanpa memandang kausa) menunjukkan mekanisme patofisiologi & gambaran klinis yang hampir serupa.
- **Nyeri neuropatik** merupakan sindroma nyeri kronik yang sangat mempengaruhi segala aspek dari kehidupan pasien.
- Pada kondisi nyeri neuropatik, etiologi biasanya sudah berlalu, tetapi nyeri tetap mengganggu.
- Berdasarkan 2 fakta tersebut di atas, maka pengobatan terhadap fenomenologi dan mekanisme lebih penting daripada pengobatan etiologi (Meliala, 2004).

Penatalaksanaan nyeri neuropati

- Hampir sebagian besar nyeri neuropatik tidak berespon terhadap NSAID dan analgesik opioid
- Terapi utamanya :
    1. tricyclic antidepressants (TCA's)
    2. anticonvulsants
    3. systemic local anesthetics
- Agen farmakologi yang lain : corticosteroid, terapi topikal dengan substance P depletors, obat-obat otonom and NMDA receptor antagonists
- Contoh obat baru : pregabalin (Lyrica) dari Pfizer → untuk nyeri neuropati

NMDA: N-methyl-D-aspartate

Mulai terapi kausatif (jika memungkinkan)
Mulai terapi simtomatik, dengan 1 / lebih terapi berikut:

- TCA sekunder (nortriptilin, desipramin) atau SSNRI /selektif serotonin norandrenaline reuptake inhibitor (duloksetin)
- Ca++ channel α2δ ligand (Gabapentin, Pregabalin)
- lidokain topikal, dengan/tanpa terapi lini pertama lainnya untuk nyeri neuropatik perifer lokal
- opioid atau tramadol, dengan/tanpa terapi lini pertama lain pada nyeri neuropatik akut, kanker, eksaserbasi episodik nyeri berat

Evaluasi kemungkinan terapi non-farmakologis

PENATALAKSANAAN

Obat yang banyak digunakan sebagai terapi nyeri neuropati :

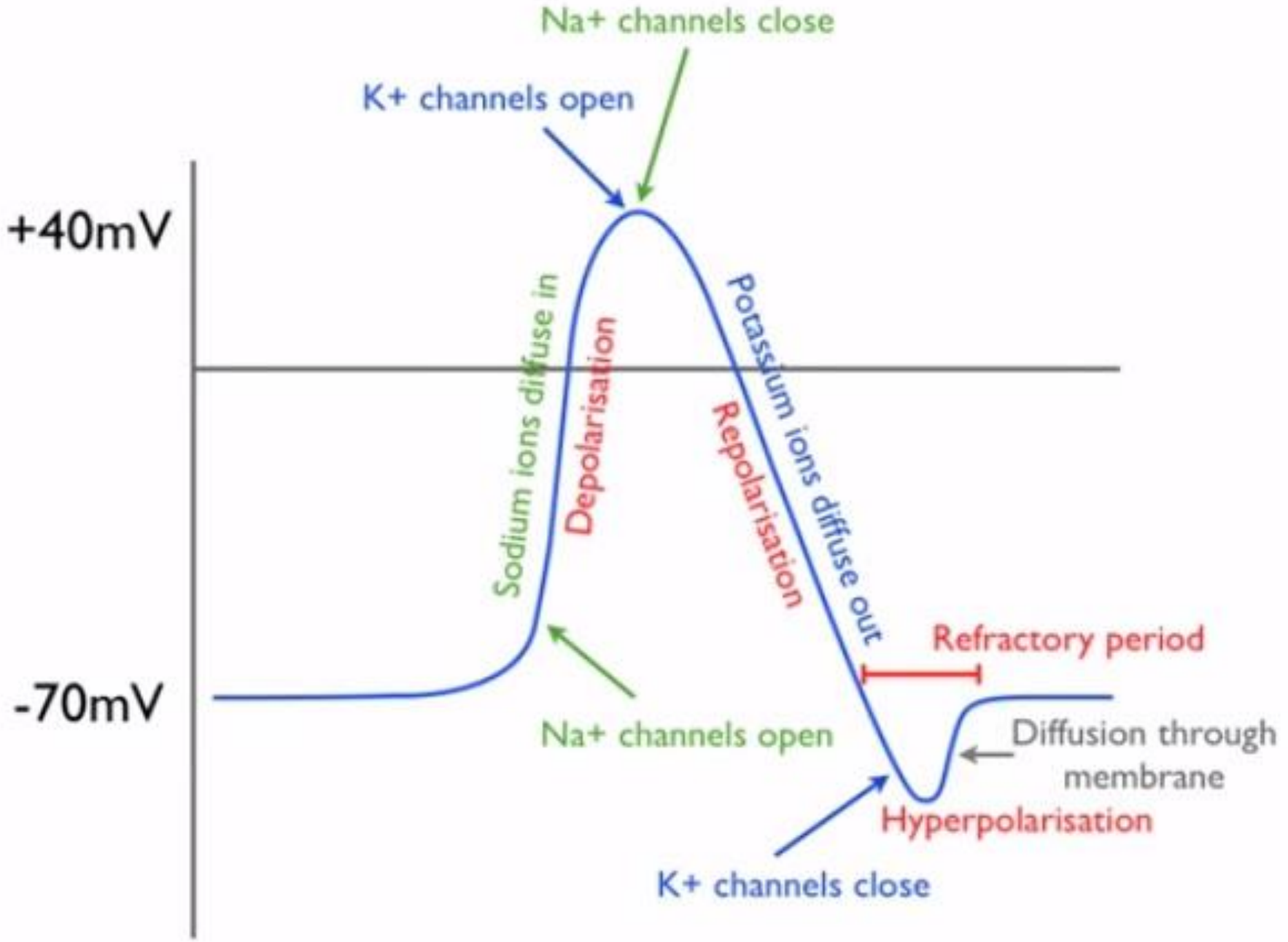
- anti depresan trisiklik (TCA) dan
- anti konvulsan karbamasepin.

1. Anti depresan

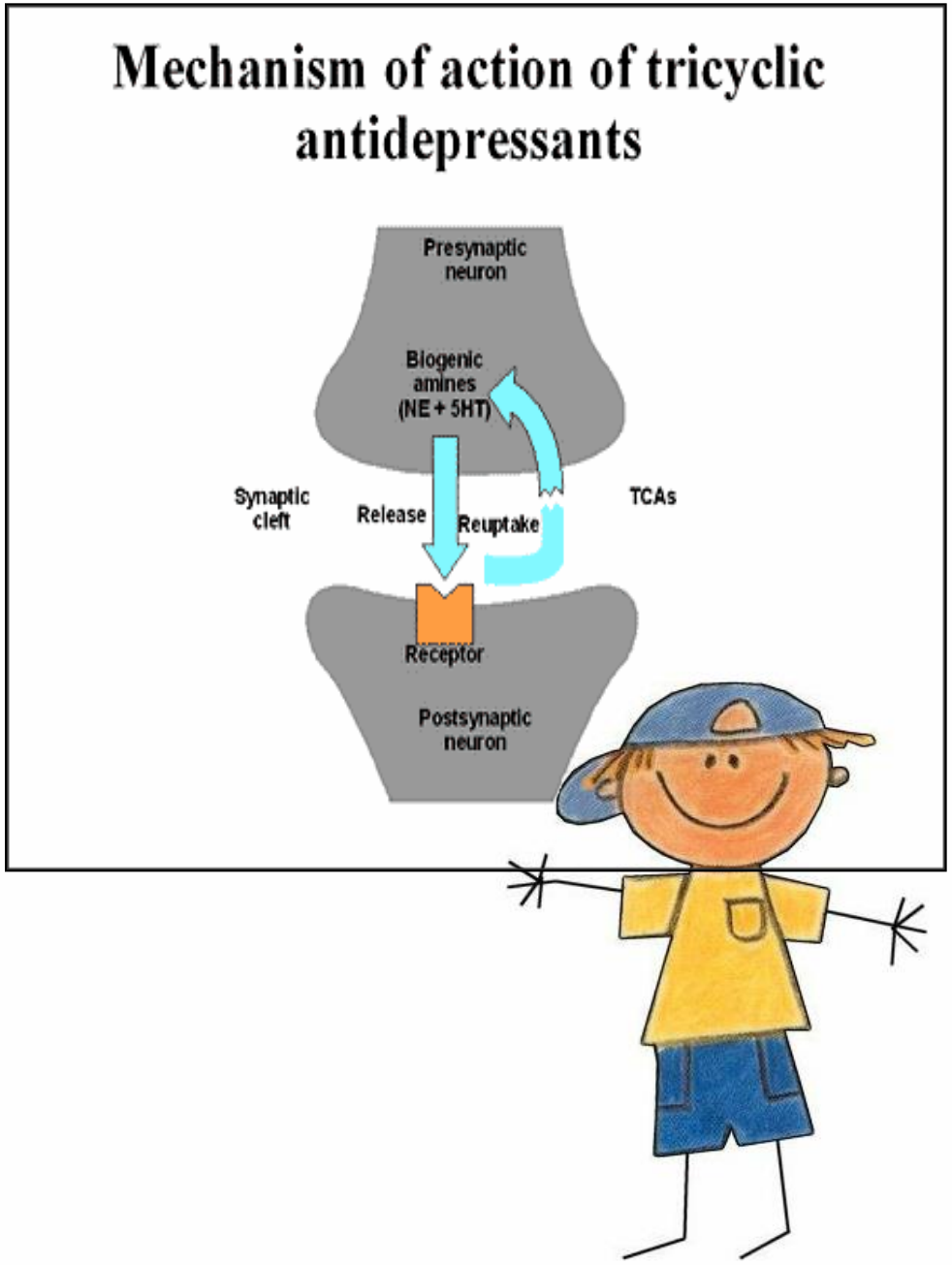
Yang paling sering digunakan adalah golongan antidepresan trisiklik (TCA) : amitriptilin, imipramin, maprotilin, desipramin.

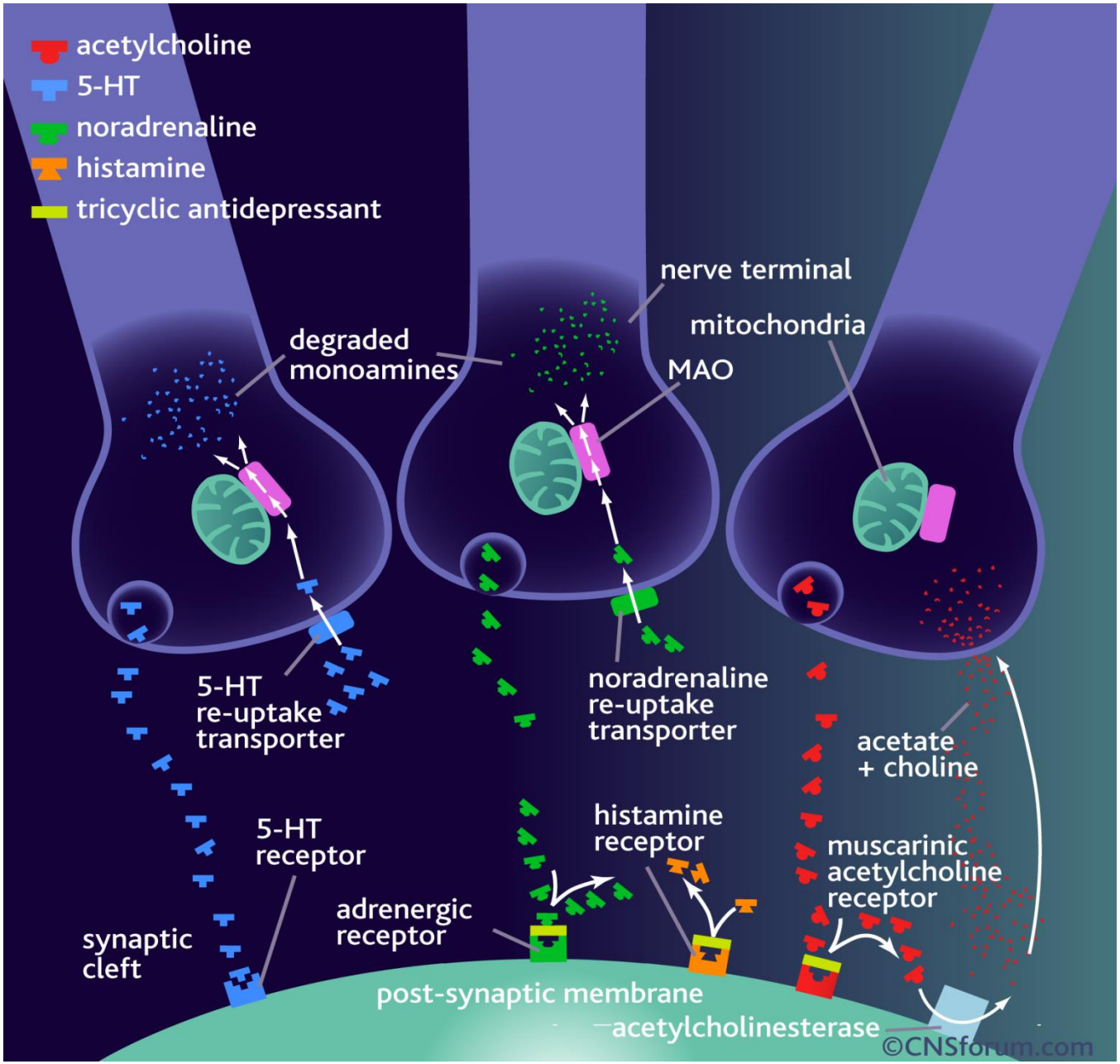
Mekanisme kerja TCA :
terutama memodulasi transmisi serotonin (5-HT) dan norepinefrin (NE). Anti depresan trisiklik menghambat reuptake serotonin dan noradrenalin oleh reseptor presineptik. Disamping itu, anti depresan trisiklik juga menurunkan jumlah reseptor 5-HT (autoreseptor), sehingga secara keseluruhan mampu meningkatkan konsentrasi 5-HT dicelah sinaptik. Hambatan reuptake NE juga meningkatkan konsentrasi NE dicelah sinaptik →menyebabkan penurunan jumlah reseptor β-adrenalin yang akan mengurangi aktivitas adenilsiklasi →sehingga mengurangi siklik AMP dan mengurangi pembukaan Na-channel →berarti **depolarisasi menurun dan nyeri berkurang**.

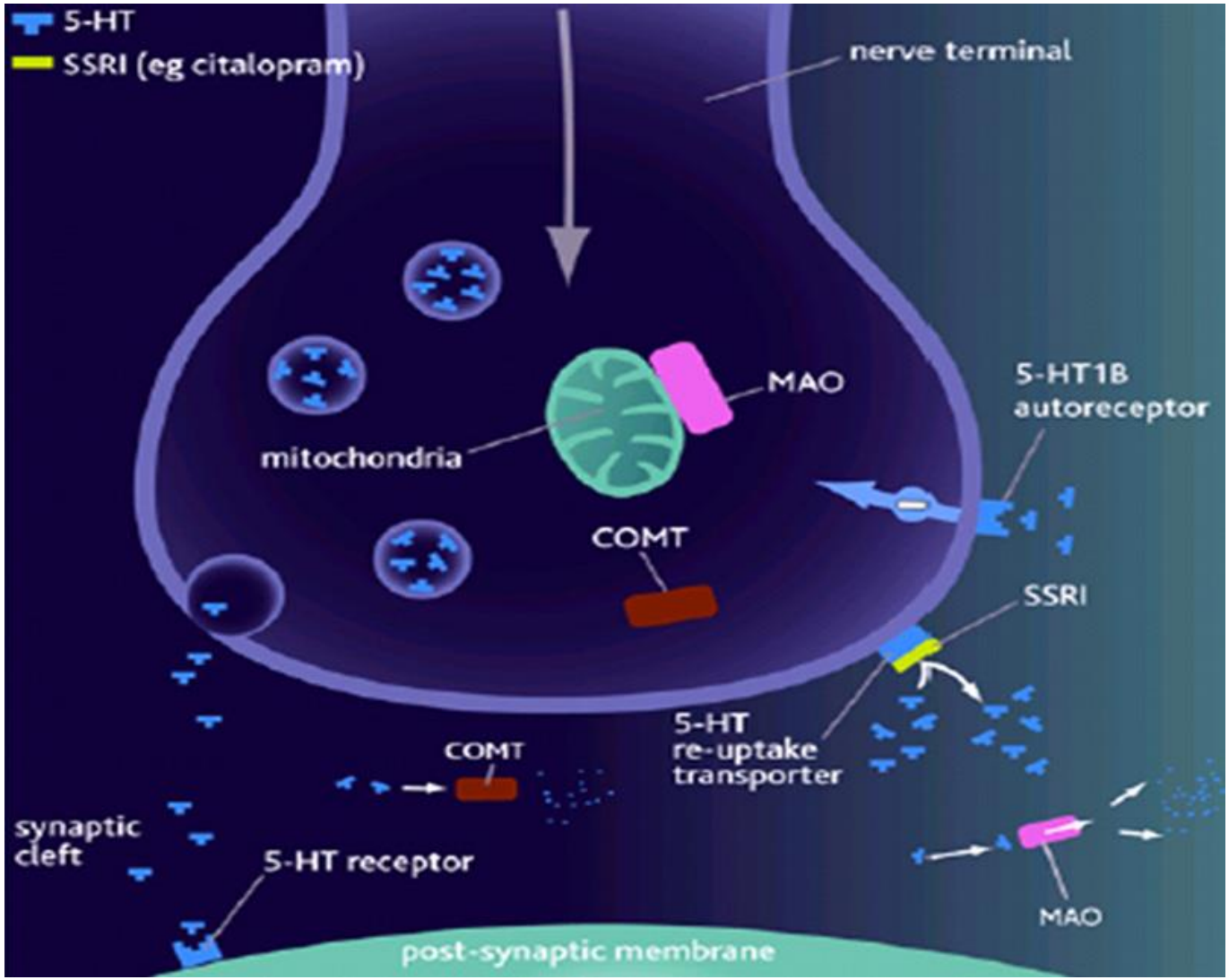
Serotonin or **5-hydroxytryptamine** (**5-HT**) is a monoamine neurotransmitter



The [putative antineuralgic] mechanism of action of the tricyclic antidepressants (TCAs) is that they inhibit the reuptake of the biogenic amines, mostly norepinephrine (NE), as well as serotonin (5HT). I talked about the 2 important descending inhibitory pathways originating from the brainstem to the spinal cord with 5HTand NE being their major neurotransmitters. So, basically the tricyclic works by enhancing inhibition from the brainstem to the spinal cord. The tertiary amines **inhibit the reuptake of NE as well as 5HT**, whereas the secondary amines are relatively selective NE reuptake inhibitors.

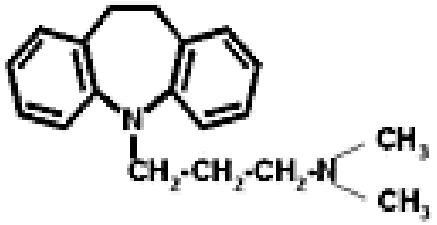




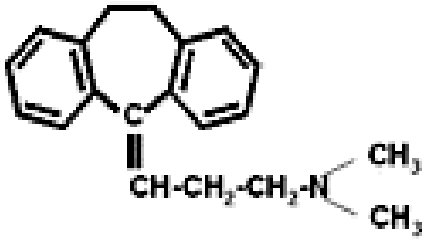


Chemical structures of tricyclic antidepressants

Tertiary amines



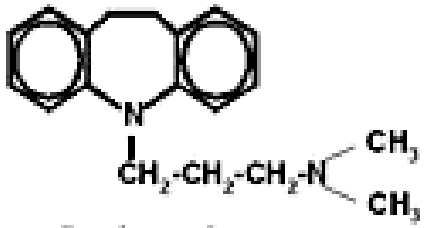
Imipramine



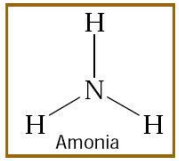
Amitriptyline

Secondary amines

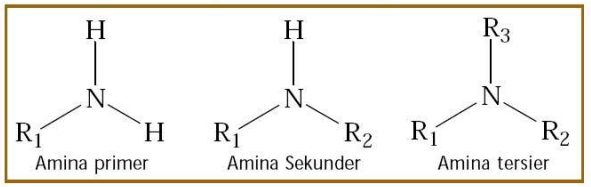
Nortriptyline



Desipramine



Amonia



Antidepressants and painful diabetic neuropathy

- Double-blind, placebo-controlled, cross-over trial of amitriptyline, desipramine (selective NE blocker), and fluoxetine (SSRI)
- Mean doses: amitriptyline 105 mg, desipramine 111mg, fluoxetine 40 mg
- Moderate or significant pain relief in 74% of amitriptyline, 61% of desipramine, 48% of fluoxetine, and 41% of placebo-treated patients

Efficacy of TCAs in post-herpetic neuralgia

Study	n	Response	
		Amitriptyline	Placebo
Watson et al. (1982)	24	67%	5%
Max et al. (1988)	24	47%	8%
		Desipramine	Placebo
Kishore-Kumar et al. (1990)	19	63%	11%
		Amitriptyline	Maprotilene
Watson et al. (1992)	32	44%	18%
		Amitriptyline	Zimelidine
Watson and Evans (1985)	15	60%	7%

Max MB. *Ann Neurol.* 1994;35(suppl):S50–S53.

Common side effects associated with tricyclic antidepressants

	Sedation	Anti-cholinergic effects	Hypo-tension	Cardiac effects	Seizures	Weight gain
Amitriptyline	+++	+++	+++	+++	++	++
Clomipramine	++	+++	++	+++	+++	+
Desipramine	0/+	+	+	++	+	+
Nortriptyline	+	+	+	++	+	+

0/+=minimal; +=mild; ++=moderate; +++=moderately severe.
From Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, 9th edition.

TCAs in neuropathic pain

- TCAs have significantly better efficacy than the SSRIs for the relief of pain in patients with painful peripheral neuropathies
- The tertiary amines seem to be slightly more effective than the secondary amines, but with worse adverse events profile

Table I. Suggested mechanisms of action of antidepressants in relation with persistent pain signalling

Mechanism of action	Site of action	TCA	SNRI	SRI
Reuptake inhibition of	Serotonin	+	+	+
monoamine	Noradrenaline	+	+	–
Receptor antagonism	α-Adrenergic	+	–	–
	NMDA	+	(+) milnacipran	–
Blocker or activator of ion channels	Sodium channel blocker	+	(+) venlafaxine – duloxetine	(+) only fluoxetine
	Calcium channel blocker	+	?	(+) citalopram fluoxetine
	Potassium channel activator	+	?	–
$GABA_B$ receptor	Increase of receptor function	+ amitriptyline desipramine	?	+ fluoxetine
Opioid receptor binding/ opioid-mediated effect	μ- and δ-Opioid receptor	(+)	(+) venlafaxine	(+) paroxetine
Inflammation	Decrease of PGE_2 production	+	?	+ fluoxetine
	Decrease of TNFα production	+	?	?

PGE_2 = prostaglandin E_2; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **TNF**α = tumour necrosis factor-α; + indicates mechanism of action documented *in vitro* and/or *in vivo*; (+) indicates mechanism of action documented *in vitro* and/or *in vivo* at high concentration; – indicates no known mechanism of action; ? indicates not investigated/not known.

1. Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain. The primary mode of action is an interaction with pathways running through the spinal cord from serotoninergic and noradrenergic structures in the brain stem and midbrain. Tricyclic antidepressants (TCA) including amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine) are often the first drugs selected to alleviate neuropathic pain. The mechanism of action is predominantly by blocking the reuptake of norepinephrine and serotonin (dual-acting) together with a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca^{2+} or Na^{+}), and interaction with adenosine and NMDA receptor.

Selective serotonin reuptake inhibitors (sertraline, paroxetine, fluoxetine, and citalopram) selectively inhibit the reuptake of serotonin. These antidepressants have a more favourable side-effect profile compared with TCA but their effectiveness in managing neuropathic pain is disputed due to conflicting reports in the available literature (second-line pharmacological treatment). SSRI may be, at this time, more appropriate for the management of psychological dysfunction associated with severe neuropathic pain [44, 45].

2. Anti konvulsan

Golongan obat yang mempunyai kemampuan untuk menekan kepekaan abnormal dari neuron-neuron di sistem saraf sentral.

Nyeri neuropati timbul karena adanya aktifitas abnormal dari sistem saraf, dipicu oleh hipereksitabilitas sistem saraf sentral yang dapat menyebabkan nyeri spontan dan paroksismal.

Reseptor NMDA dalam influks Ca2+ sangat berperan dalam proses kejadian wind-up pada nyeri neuropati. Prinsip pengobatan nyeri neuropati adalah penghentian proses hiperaktivitas terutama dengan blok Na-channel atau pencegahan sensitisasi sentral dan peningkatan inhibisi.

wind up, yaitu meningkatnya eksitabilitas dan sensitivitas neuron medula spinalis.

NMDA: N-methyl-D-aspartate

2. Anticonvulsant Medication

The rationale for the use of antiepileptic drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain. Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca^{2+} or Na^{+}), effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release), and/or neuromodulation systems (blocking the NMDA receptor) [46-49]. Initially, carbamazepine and phenytoine were used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, side effects and complicated pharmacokinetic profile limit their use in treating neuropathic pain. Despite the introduction of these newer anticonvulsants with a more favourable side-effect profile, carbamazepine remains the drug of choice in treatment of trigeminus neuralgia. However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with similar mechanism of action to that of carbamazepine but with a better side-effect profile may replace carbamazepine for treating trigeminus neuralgia [50].

1

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a. Karbamazepin dan Okskarbasepin

Mekanisme kerja utama adalah memblok voltage-sensitive sodium channels (VSSC).
Efek ini mampu mengurangi cetusan dengan frekuensi tinggi dari neuron.

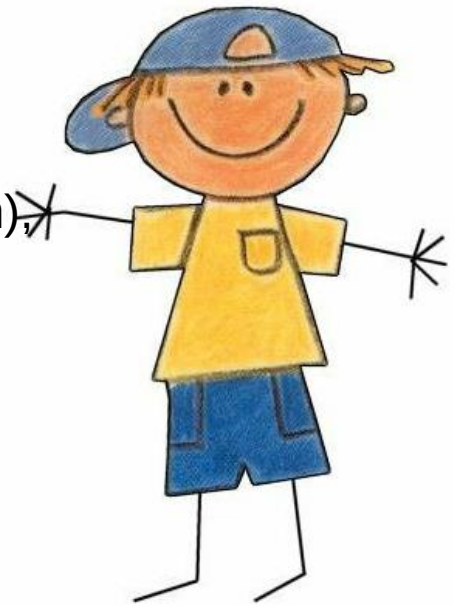
Okskarbasepin →efek pada berbagai jenis nyeri neuropati menunjukkan hasil yang memuaskan, ≥ Karbamazepin dan mempunyai efek samping minimal.

b. Lamotrigin

Merupakan anti konvulsan baru untuk stabilisasi membran melalui VSCC, merubah atau mengurangi pelepasan glutamat maupun aspartat dari neuron presinaptik, meningkatkan konsentrasi GABA di otak.

Khusus untuk nyeri neuropati penderita HIV, digunakan lamotrigin sampai dosis 300 mg perhari →hasilnya, efektivitas lamotrigin lebih baik dari plasebo, tetapi 11 dari 20 penderita dilakukan penghentian obat karena efek samping.

Efek samping utama lamotrigin adalah ruam kulit (skin rush), terutama bila dosis ditingkatkan dengan cepat.



c. Gabapentin

Akhir-akhir ini, penggunaan gabapentin untuk nyeri neuropati cukup populer mengingat efek yang cukup baik dengan efek samping minimal.

Gabapentin populer sebagai obat nyeri neuropati diabetika, neuralgia pasca herpes, sklerosis multipel, nyeri neuropati terkait infeksi HIV, nyeri neuropati terkait kanker dan nyeri neuropati deafferentasi.

Mekanisme : gabapentin mampu masuk ke dalam sel untuk berinteraksi dengan reseptor α2β yang merupakan subunit dari Ca^{2+}-channel.

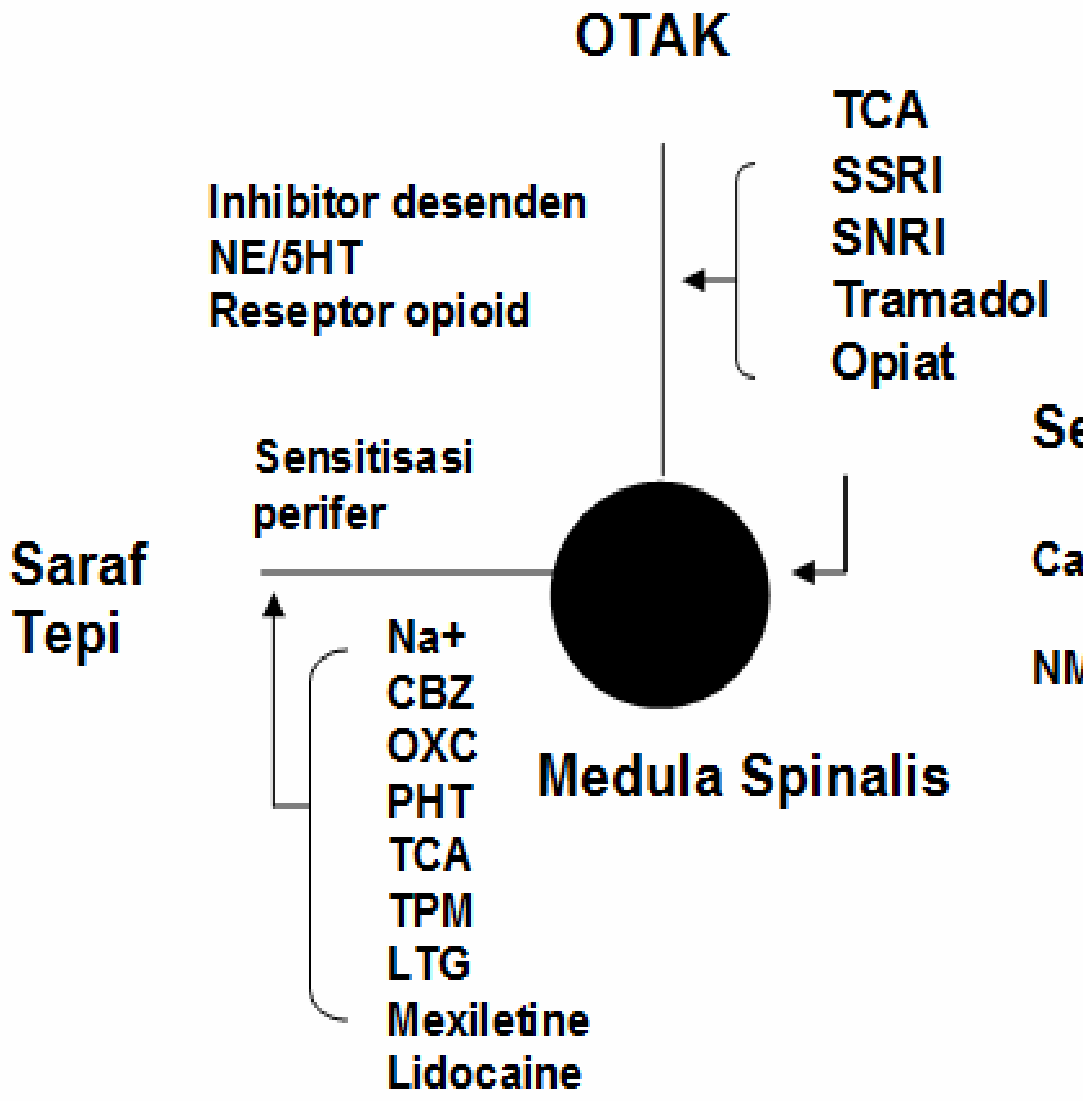
Gabapentin and pregabalin are emerging as first-line treatment for neuropathic pain (reducing elements of central sensitization), especially in post zoster neuralgia and diabetic polyneurpathy. More recently, the combination of gabapentin with opioids seem to display synergistic effects in relieving neuropathic pain [52, 53]. Although gabapentin was expected to act as a GABA agonist, the mechanism of action is likely to be mediated via binding to the α2δ-subunit of voltage-gated calcium channels and inhibition of glutamate release presynaptically and postsynaptically in the central nervous system. Gabapentin has a favourable safety profile with minimal concern for drug interactions and no interference with hepatic enzymes. Renal failure, however, results in higher gabapentin concentrations and longer elimination half life making dose adjustments necessary [54, 55]. Pregabalin (3-isobutyl GABA) is a structural analogue of gabapentin, but showed greater analgesic activity in rodent models of neuropathic pain than gabapentin. Recent studies confirm the effectiveness of pregabalin in peripheral (including postherpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain [56-59].

Langkah-langkah Terapi Farmakologis pada Nyeri Neuropatik

Kelas Terapi	Obat dan Dosis	Indeks Terapeutik	Efek Samping Utama	Peringatan	Keuntungan lain
Lini I *Ca++ channel α2δ ligand*	Gabapentin *100-300 mg malam* *Atau 3 x 100-300 mg/hari*	++	Sedasi, *dizziness*, udem perifer	Insufisiensi renal	Perbaikan gangguan tidur, interaksi obat signifikan (-)
	Pregabalin *50 mg 3 x sehari atau 75 mg 2 x sehari*	++	Sedasi, *dizziness*, udem perifer	Insufisiensi renal	Perbaikan gangguan tidur, ansietas, interaksi signifikan(-)
	Duloksetin *30 mg sekali sehari*	++	Nausea	Disfungsi hepatik, insufisiensi renal, alkoholism, terapi bersama tramadol	Perbaikan depresi
SSNRI	Venlafaksin *37,5 mg 1 atau 2 x sehari*	+	Nausea	Terapi bersama tramadol, penyakit jantung	Perbaikan depresi
TCA Sekunder	*Nortriptilin, 25 mg saat hendak tidur malam*	+	Sedasi, mulut kering, pandangan kabur, berat badan >>, retensi urin	Penyakit jantung, glaukoma, risiko *suicide*, kejang, terapi bersama tramadol	Perbaikan depresi dan insomnia
Lini II Golongan Opioid	Morfin, oksikodon, metadon, levorpanol *Morfin 10 mg/4 jam atau sesuai kebutuhan*	+	Nausea/ vomit, konstipasi, *drowsiness, dizziness*	Riwayat *drug abuse*, risiko bunuh diri	Analgesik onset cepat
	Tramadol *50 mg 1 atau 2x sehari*	+	Nausea/vomit, konstipasi, *drowsiness, dizziness*, kejang	Riwayat *drug abuse*, risiko bunuh diri, terapi bersama SSRI, SSNRI, TCA	Analgesik onset cepat

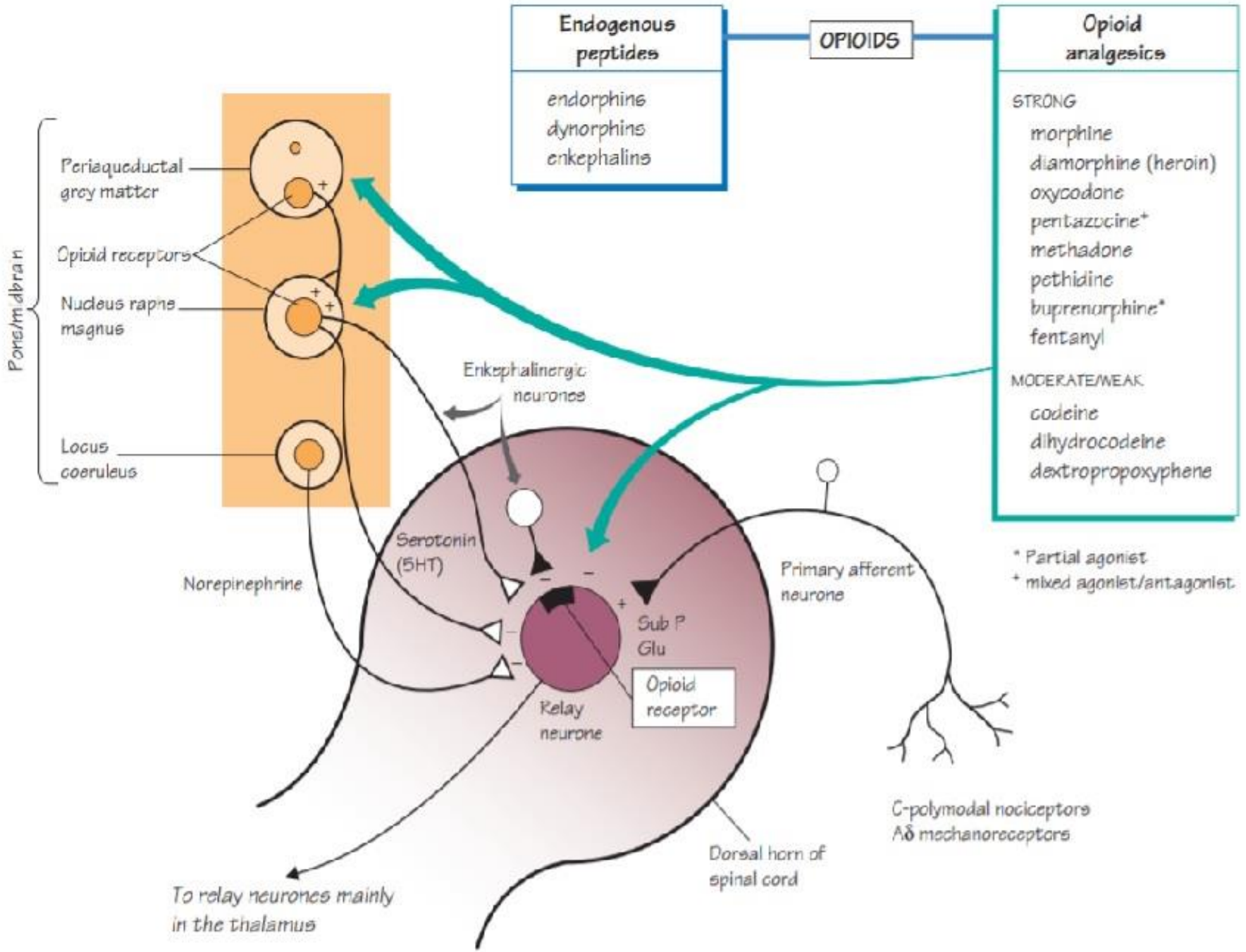
Prinsip terapi nyeri neuropatik berdasarkan mekanisme

SSRI : selective serotonin reuptake inhibitor
SNRI : Serotonin-norepinephrine reuptake inhibitors
TCA: tricyclic antidepressant
GBP: gabapentin; LTG: lamotrigine; LVT: levetiracetam;
NMDA: N-methyl-D-aspartate
NMDAR: NMDA receptor : glutamate receptor and ion channel protein found in nerve cells. It is activated when glutamate and glycine (or D-serine) bind to it, and when activated it allows positively charged ions to flow through the cell membrane.

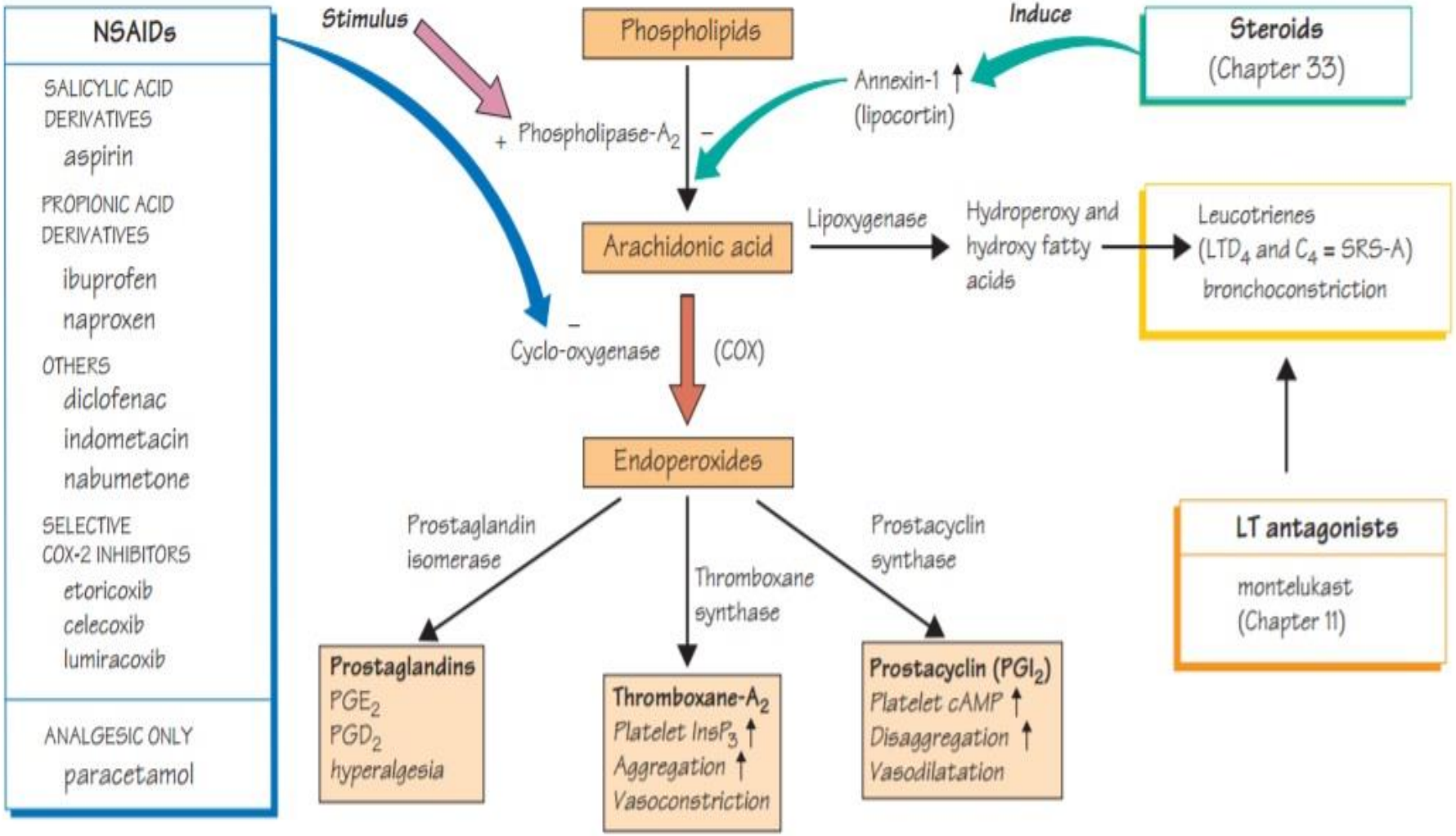


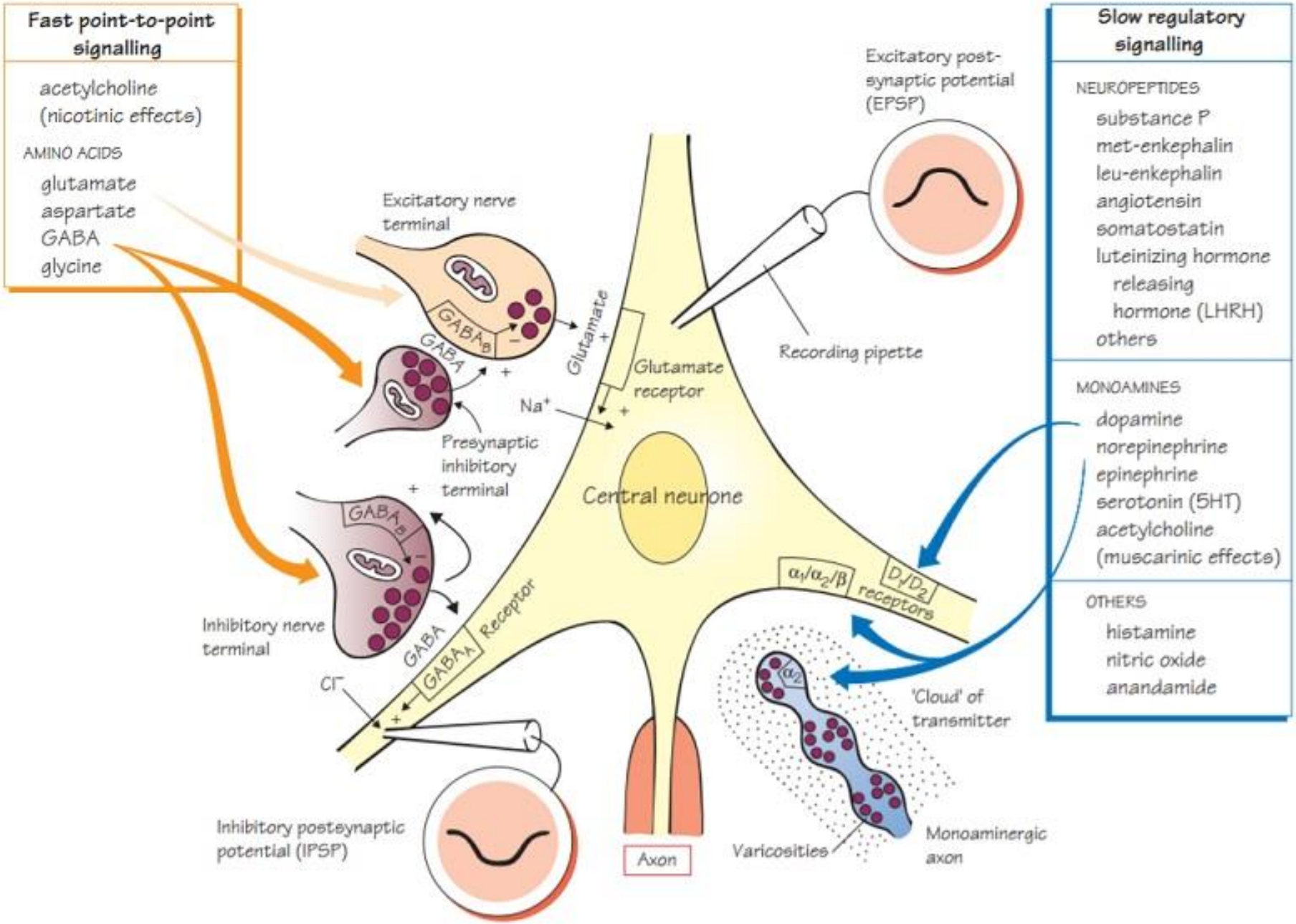
Sensitisasi Sentral

Ca++ : Pregabalin, GBP,OXC,LTG,LVT
NMDA : Ketamin, TPM Dextromethorphan Methadone
Lainnya:
Capsaicin
NSAIDs
COX inhibitor
Levodopa



32 Non-steroidal anti-inflammatory drugs (NSAIDs)





Glutamate is the main central excitatory transmitter. It depolarizes neurones by triggering an increase in membrane Na+ conductance.

γ-Aminobutyric acid (GABA) is the main inhibitory transmitter, perhaps being released at one-third of all central synapses. It hyperpolarizes neurones by increasing their membrane Cl^- conductance and stabilizes the resting membrane potential near the Cl^- equilibrium potential.

γ-Aminobutyric acid is present in all areas of the central nervous system, mainly in local inhibitory interneurones. It rapidly inhibits central neurones, the response being mediated by postsynaptic GABAA receptors

Many GABAB receptors are located on presynaptic nerve terminals and their activation results in a reduction in transmitter release (e.g. of glutamate and GABA itself).

CONTOH OBAT GOLONGAN OPIAT

MORFIN

- Digunakan sebagai standar analgesik opiat lain
- Umumnya diberikan secara s.c., i.m, iv.
- Dosis oral 2 x dosis injeksi.
- Efek samping: depresi respirasi, mual-muntah, nggliyeng, konstipasi, dll
- Metabolisme di hepar → hati-hati pada pasien dg penyakit liver

KODEIN

- Waktu paruh 3 jam, efikasi 1/10 morfin, ketergantungan lebih rendah
- Digunakan untuk nyeri ringan dan sedang
- Dosis oral 30 mg setara dg aspirin 325-600 mg

PETIDIN

- Waktu paruh 5 jam, efektivitas > kodein, tapi < morfin, durasi analgesianya 3-5 jam, efek puncak tercapai dlm 1 jam (injeksi) atau 2 jam (oral)
- Diberikan secara oral atau im
- Efek sampingnya setara dengan morfin
- Dosis 75-100 mg petidin setara dg 10 mg morfin

TRAMADOL

- Waktu paruh 6 jam, efikasi 10-20% morfin, sebanding dg petidin
- Sifat adiktif minimal, efek samping lebih ringan drpd morfin

FENTANIL

- Waktu paruh 3 jam, digunakan pasca operasi, tapi biasanya untuk anaestesi
- Efikasinya 80 x morfin, efeknya berakhir dlm 30-60 menit (dosis tunggal)
- Bisa diberikan dalam bentuk plester yang akan melepaskan obatnya 25 mg/jam untuk 72 jam →untuk pasien kanker kronis

Efek samping utama obat golongan opiat

Efek	Manifestasi
Perubahan mood	Disforia, euforia
Kesadaran	Lemah, mengantuk, apatis, tidak bisa konsentrasi
Stimulasi CTZ	Mual, muntah
Depresi pernafasan	Kecepatan respirasi turun
Menurunkan motilitas GI	Konstipasi
Meningkatkan tonus spinkter	Biliary spasm, retensi urin
Pelepasan histamin	Urikaria, pruritus, asma
Toleransi	Perlu dosis lebih besar untuk mencapai efek yang sama
Dependensi	Terjadi gejala putus obat jika dihentikan secara tiba-tiba