Novel Pharmacologic Approaches in Neuropathic Pain Therapy

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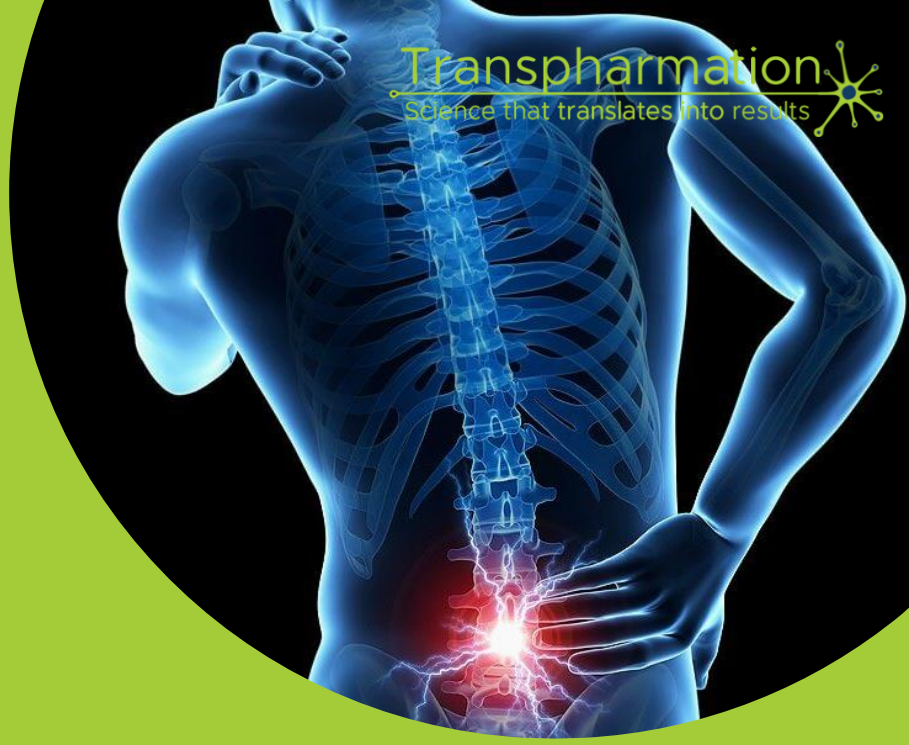




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Neuropathic Pain



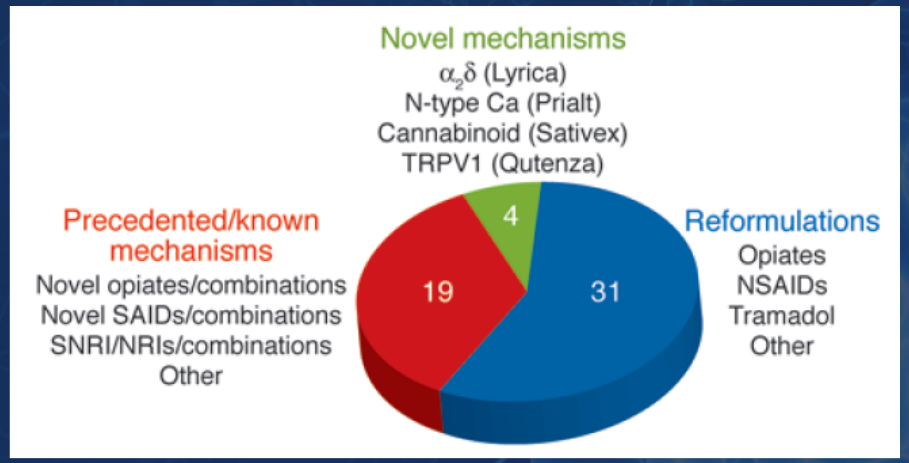


Occurs after a primary lesion or disease of the somatosensory nervous system

- Metabolic disorders (peripheral diabetic neuropathy)
- Associated with viral infections (post-herpetic neuropathy)
- Autoimmune disorders (MS, Guillain-Barre)
- Chemotherapy (CIPN)
- Trauma (peripheric or central – SCI)

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“New modalities”- Then and now



Burgess & Williams, 2010

Table 1. Pharmacotherapy for neuropathic pain.

		Drugs	Dose range	Adverse effect
First-line therapy	Gabapentinoids	Gabapentin	150–600 mg/day	Lethargy, vertigo, peripheral swelling, blurred vision
		Pregabalin	300–3600 mg/day	Lethargy, vertigo, peripheral swelling, increased body weight
	Tricyclic antidepressants (TCAs)	Amitriptyline	10–150 mg/day	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention
	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20–120 mg/day	Nausea, lethargy, constipation, ataxia, dry mouth
		Venlafaxine	150–225 mg/day	Nausea, vertigo, lethargy, hyperhidrosis, hypertension
Second-line therapy	Opioids	Tramadol	25–400 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
		Tapentadol	50–600 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
	Topical treatment	Lidocaine	5% patches or gel	Local erythema, itching and rash
		Capsaicin	8% patches	Pain, erythema, itching; rare cases of high blood pressure
Third-line therapy	Strong opioids	Morphine	10–120 mg/day	Nausea, vomiting, constipation, dizziness and lethargy
		Oxycodone	10–120 mg/day	Nausea/vomiting, constipation, lethargy, respiratory control
	Neurotoxin	Botulinum toxin	25–300 U BTX-A 0.9% saline	Pain at injection site

Table 1 reports the dose range and the side effects in accordance with Electronic Medicines Compendium (eMC).[6]

Cavalli et al, 2019

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Novel Modalities

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- Toxins and Venoms
- Psychedelics
- RNA interference
- Gene editing therapies

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Toxins and Venoms

Transpharmation
Science that translates into results

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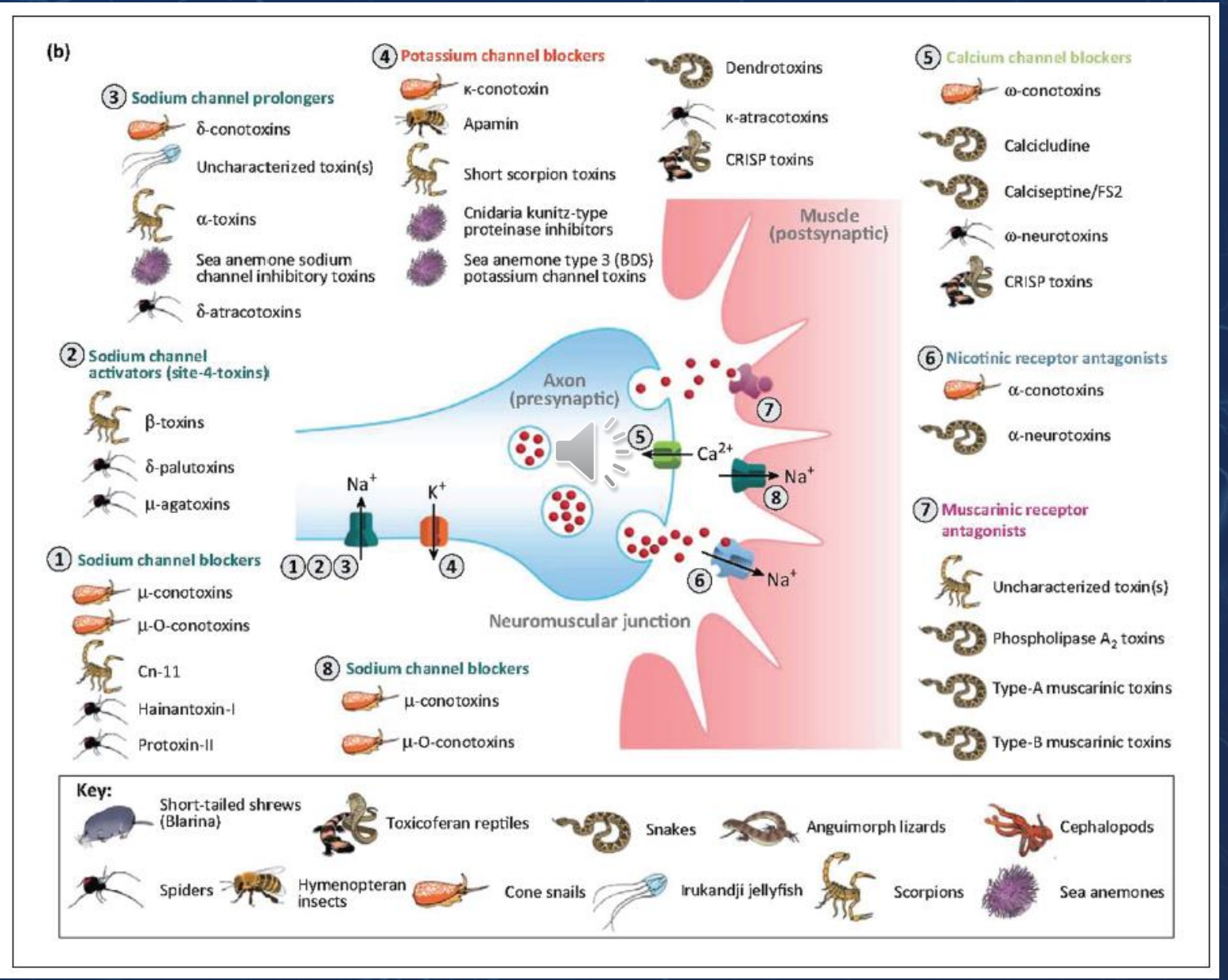
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Cavalli et al, 2019

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Toxins and Venoms



Trim & Trim, 2013
(Casewell et al, 2012)

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Psychedelics

Transpharmation
Science that translates into results

- Cannabis
- Ketamine



- **Psylocibin**

Cavalli et al, 2019

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Psychedelics

Table 2. Phase III Clinical Trials.

NCT number	Study title	Drug	Results
NCT01536314	Prophylaxis of neuropathic pain by memantine	*Memantine EBIXA®* *Placebo: lactose*	*Memantine prevented post-mastectomy pain and diminished chemotherapy-induced pain symptoms*
NCT00313378	Effects of perioperative systemic ketamine on development of long-term neuropathic pain after thoracotomy	*Ketamine*	*Ketamine did not prevent chronic pain after thoracotomy*
NCT00224588	KETOR: Effects of peri-operative administration of ketamine on long-term post thoracotomy pain	*Ketamine*	*Data not available*
NCT00872144	Sativex for the treatment of chemotherapy-induced neuropathic pain	*Sativex®*	*Sativex reduced chemotherapy-induced neuropathic pain in five participants that trended toward statistical significance*
NCT01604265	A study of Sativex in the treatment of central neuropathic pain due to multiple sclerosis	*Sativex®*	*Sativex reduced pain and sleep disturbance in patients with multiple sclerosis*
NCT01606202	A study of cannabis-based medicine extracts and placebo in patients with pain due to spinal cord injury	*GW-1000-02* *Placebo*	*GW-1000-02 improved pain score*
NCT00713817	A study to determine the maintenance of effect after long-term treatment of Sativex® in subjects with neuropathic pain	*Sativex®* *Placebo*	*Sativex showed no effect*
NCT00713323	A study to compare the safety and tolerability of Sativex® in patients with neuropathic pain	*Sativex®* *Placebo*	*Sativex improved pain score*
NCT00711880	A study of Sativex® for relief of peripheral neuropathic pain associated with allodynia	*Sativex®* *Placebo*	*Sativex reduced global neuropathic pain score, sleep disturbance, dynamic and punctate allodynia*
NCT00710554	A study of Sativex® for pain relief of peripheral neuropathic pain, associated with allodynia	*Sativex®* *Placebo*	*Sativex reduced the peripheral neuropathic pain NRS scores and the sleep quality score*
NCT00391079	Sativex versus placebo when added to existing treatment for central neuropathic pain in MS	*Sativex®* *Placebo*	*Sativex reduced neuropathic pain and improved sleep and quality of life*
NCT00710424	A study of Sativex® for pain relief due to diabetic neuropathy	*Sativex®* *Placebo*	*Sativex improved diabetic neuropathy pain*
NCT00959218	Efficacy and safety of the pain relieving effect of dronabinol in central neuropathic pain related to multiple sclerosis	*Dronabinol®* *Placebo*	*Dronabinol reduced pain intensity and adverse events over time*
NCT01555983	Vaporized cannabis and spinal cord injury pain	*Vaporization of cannabis*	*Vaporized cannabis decreased pain associated with injury or disease of the spinal cord*

Cavalli et al, 2019

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Psychedelics

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Psylocibin

- Primary outcomes of the action at 5-HT2a receptors
- Downstream effects of psychedelics (reduction of TNFa)
- Changes in brain connectivity (functional and anatomic)

Cavalli et al, 2019

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Psychedelics

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Psylocibin

Original Articles

Relief from intractable phantom pain by combining psilocybin and mirror visual-feedback (MVF)

Vilayanur Ramachandran, Chaipat Chunharas, Zeve Marcus, Timothy Furnish & Albert Lin

Pages 105-110 | Received 06 Jul 2017, Accepted 16 Apr 2018, Published online: 15 May 2018

Cavalli et al, 2019

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RNAi and Gene Editing Therapies

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- ASO
- SiRNA
- CRISPR-Cas9

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RNAi and Gene Editing Therapies

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- ASO (anti-sense oligonucleotides)
- SiRNA (small interfering RNA)

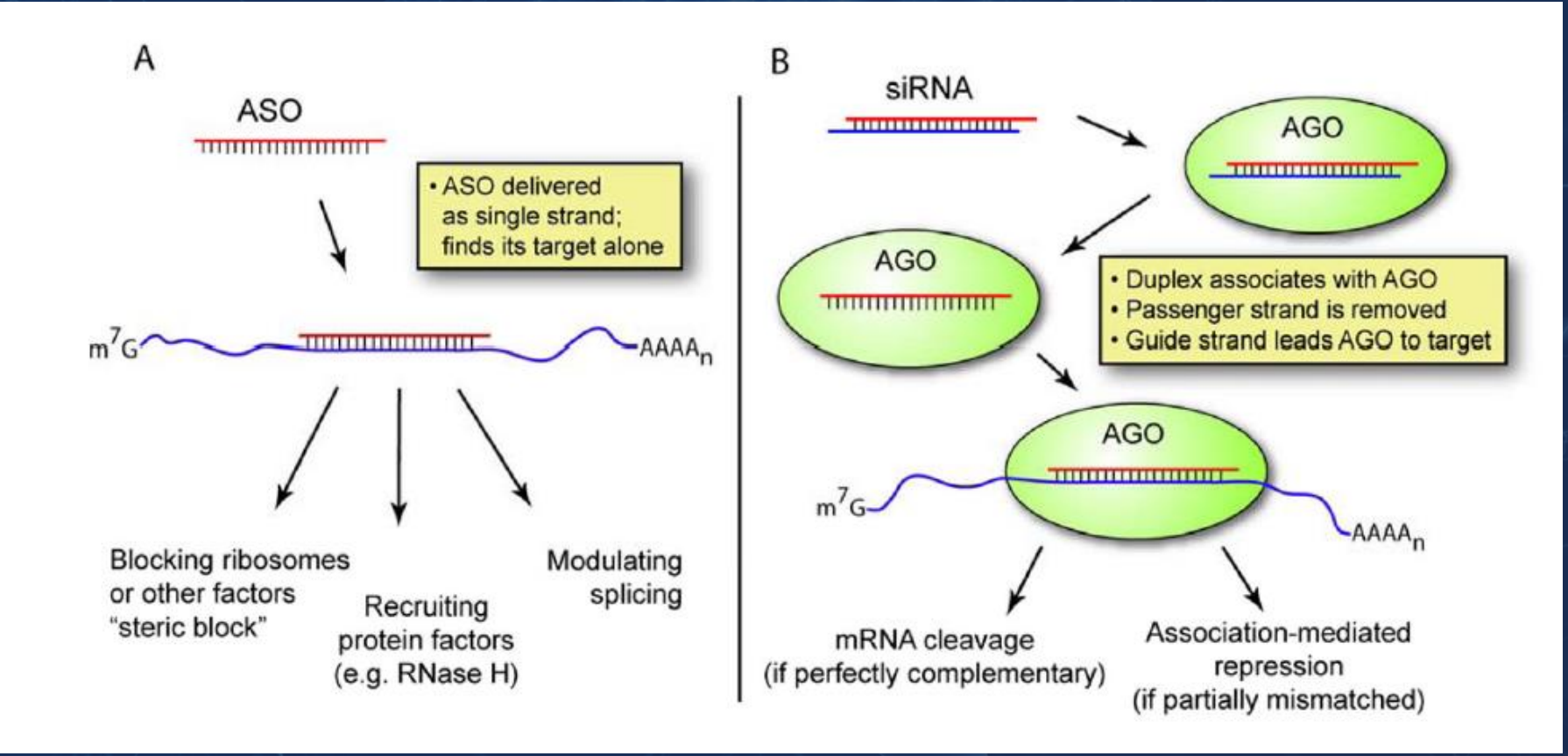
} Post-transcriptional

- CRISPR/ Cas9

— Pre-transcriptional

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RNAi



Watts & Corey, 2014

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RNAi

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- ASOS and siRNA can inhibit the translation of specific sequences of mRNA
- The most obvious targets are voltage gated ion channels from the somatosensorial neuronal afferences. (e.g. SCN9A and SCN10A)
- Indirect ways to inhibit expression of those channels have also been demonstrated (TNFa and Nav 1.7)

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Gene editing therapies – CRISPR/Cas9

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- CRISPR/Cas 9 technology allows for cheap and reliable editing of the genome
- Strong therapeutic potential
- Technology can be readily adapted for different targets

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Gene editing therapies

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Long-lasting analgesia via targeted in situ repression of $Na_V1.7$ in mice

Ana M. Moreno[1,*], Fernando Alemán[1,*], Glaucilene F. Catroli[2], Matthew Hunt[2], Michael Hu[1], Amir Dailamy...
+ See all authors and affiliations

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Gene editing therapies – CRISPR/Cas9

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- CRISPR/Cas 9 technology allows for cheap and reliable editing of the genome
- Strong therapeutic potential
- Technology can be readily adapted for different targets
- Development of safe and efficient delivery technologies is needed

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Conclusions (Pre-clinical)

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- Clinical trials repurposing known drugs could lead to pre-clinical research in order to refine molecules, vehicles, and to research mechanisms.
- New drugs relying on central effects could require development of new pre-clinical endpoints (affective component of pain) .
- With RNAi and CRISPR/Cas 9 technologies, pre-clinical research uses “less usual” routes of administration.

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