## Enhancing Clinical Translation of Analgesics for Neuropathic Pain: A Systematic Review and Meta-Analysis on the Role of Non-Evoked Pain Assessment in Preclinical Trials

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Database	
Medline	(("neuropathic pain*"[tw] OR "nerve pain*"[tw] OR "Neurodynia*"[tw] OR "neuropathy"[tw] OR "neuropathies"[tw] OR "nerve injuries"[tw] OR "nerve injury"[tw] OR "nerve damage"[tw] OR "nerve trauma"[tw] OR "nerve trauma*"[tw] OR "Nerve trauma*"[tw] OR "Neurous System/injuries"[Mesh] OR "Neuralgia"[Mesh] OR "Neuralgia*"[tw] OR Polyneuropathies[Mesh] OR Polyneuropathies [tiab] OR Polyneuropathy [tiab] OR neurodynia [tiab] OR Peripheral Nerve atrophy [tiab] OR axonopathy [tiab] OR axonopathies [tiab] OR myelinopathy [tiab] OR myelinopathies [tiab] OR neuralgic pain [tiab] OR neuralgic pains [tiab] OR "spinal nerve ligation" OR "chronic constriction injury" OR "partial sciatic nerve ligation" OR "spared nerve injury" OR "postherpetic neuralgia" OR "chemotherapy induced peripheral neuropathy" OR "diabetic peripheral neuropathy" OR "trigeminal neuralgia")
	AND
	("non-evoked pain" OR "spontaneous pain" OR "nociceptive behaviour*" OR "pain-related behaviour*" OR "pain-related behavior*" OR "pain at rest" OR "pain in the absence of stimulation" OR "painful behaviour" OR "painful behavior"))
	AND
	("animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "catacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "strepsirhini"[MeSH Terms] OR "haplorhini"[MeSH Terms] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms] OR "hominidae"[MeSH Terms] OR "hominidae"[MeSH Terms] OR "gorilla gorilla"[MeSH Terms])
Scopus	TITLE-ABS-KEY ( ( ( "neuropathic pain*" OR "nerve pain*" OR "Neurodynia*" OR "neuropathy" OR "neuropathies" OR "nerve injuries" OR "nerve injury" OR "nerve damage" OR "nerve trauma" OR "nerve trauma*" OR "Peripheral Nerve Injuries" ) AND ( "non-evoked pain" OR "spontaneous pain" OR "nociceptive behaviour*" OR "pain-related behavior*" OR "pain at rest" OR "pain in the absence of stimulation" OR "painful behavior" OR "painful behavior" ) AND (animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents ) )

Web of	AB=(( "neuropathic pain*" OR "nerve pain*" OR "Neurodynia*" OR "neuropathy"
Science	OR "neuropathies" OR "nerve injuries" OR "nerve injury" OR "nerve damage" OR
	"nerve trauma" OR "nerve trauma*" OR "Peripheral Nerve Injuries") AND ("non-
	evoked pain" OR "spontaneous pain" OR "nociceptive behaviour*" OR "pain-
	related behaviour*" OR "pain-related behavior*" OR "pain at rest" OR "pain in the
	absence of stimulation" OR "painful behaviour" OR "painful behavior") AND (
	animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR
	rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR
	hamsters OR cricetinae OR rodentia OR rodent OR rodents ))

**Supplementary Table 2**. Analgesics used in the pre-clinical studies analyzed, grouped by corresponding drug class. \*Indicates articles eligible for meta-analysis (which exclude those that evaluated only Conditioned Place Preference, CPP, the number of such articles is indicated in parentheses).

Line of use	Drug Class	Analgesic	nº articles* (CPP)
		Gabapentin	20
	Gabapentinoid	Pregabalin	15 (2)
		Mirogabalin	1
		Amitriptyline	5
	Tricyclic Andidepresants	Clomipramine	2
st	They clic Andidepresants	Desipramine	2
- St		Imipramine	1
		Duloxetine	4
		Milnacipran	1
	SNRI	Risperidone	1
		AS1069562	1
		Reboxetine	(2)
р	Mild Onicid	Tramadol	3
2nd	Mild Opioid	Buprenorphine	1
	Botulinum Toxin A	Botulinum Toxin A	2
p		Morphine	11 (2)
3 <sup>rd</sup>	Strong Opioids	Dermorphin	1
		DAMGO	(1)
	AL	Clonidine	3 (12)
	Alpha-2-agonist	Dexmedetomidine	2
		Carbamazepine	3
	Na+ channel blocker	Lidocaine	1 (7)
e <u>≤</u>		Mexiletine	1
Ins		Zonisamide	1
Inconclusive		Bupivacaine	(1)
ncc	NIMDA antoquiat	Ketamine	4
	IMDA-antagonist MK-801		(1)
		Fluoxetine	2
	SSRI-antidepresants	Citalopram	1
		Paroxetine	1
Weak against	Cannabinoid	Cannabidiol	1
		Diclofenac	2
70		Indomethacin	2
ISe(	NCAID	Lornoxicam	1
Not used	NSAID	Milnacipran	1
ž		Paracetamol	1
		GW405833	1

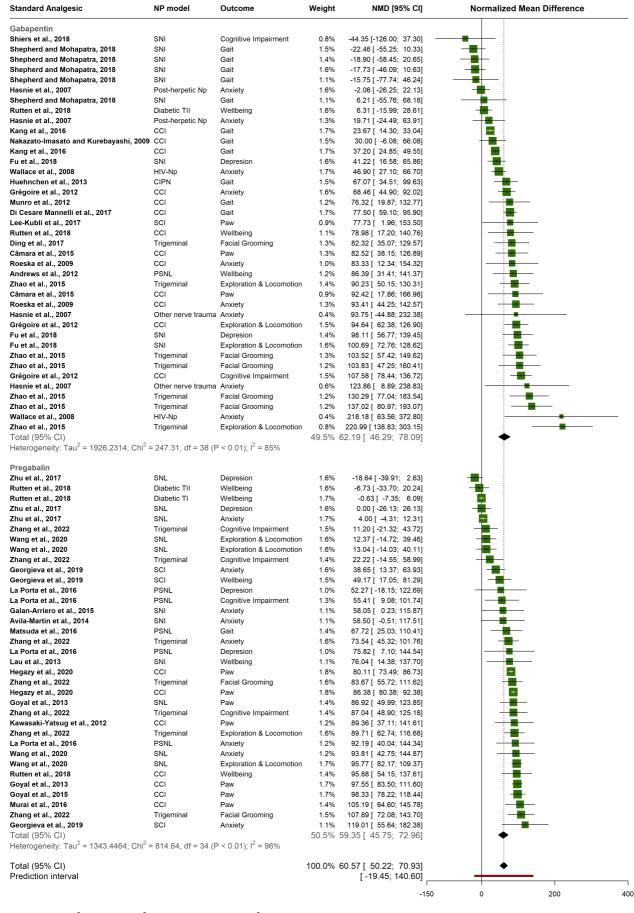
algesic Class	NP Model	Outcome		Weight 0.6%	NMD (95% CI		lean Difference
RI antibioprosants thas et al., 2017 toursea-Yaragida et al., 2007 ng et al., 2018 toursea-Yaragida et al., 2007 toursea-Yaragida et al., 2007 toursea-Yaragida et al., 2007 ng et al., 2018 ng et al., 2018 tol (60% CI) torogeneby. Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 3.81	CCI PSNL SNI PSNL Other nerve traums SNI Other nerve traums SNI	Amility Anality Anality Anality IDepresion Anality Depresion Anality	Placedite Planostine Citalopram Parcedite Flucedite Citalopram Flucedite Citalopram Citalopram Citalopram	0.8% 0.5% 0.5% 0.8% 0.8% 0.3% 0.4% 0.3% 0.3%	70.53 [ 25.27; 115.76 91.30 [ 35.83; 146.77 93.02 [ 57.35; 120.66 93.55 [ 65.19; 121.91 105.80 [ 11.06; 200.54 114.20 [ 52.88; 175.76 120.81 [ 16.48; 225.14	H M M M M M H H H H H	•
pha-2-agonist lens et al., 2018 marene-Delgado et al., 2022 rai et al., 2016 rai et al., 2016 et al., 2022 et al., 2022	SNI CCI CCI CCI SNL SNL	Cognitive impairment Plaw Plaw Plaw Anxiety Exploration & Locomotion	Cicridine Cicridine Cicridine Cicridine Dexmedetomidine Dexmedetomidine Dexmedetomidine	0.8% 0.7% 0.8% 0.4% 0.4% 0.2% 2.9% 8	6.49 (-30.71; 43.65 77.19 (-53.26; 101.16 107.85 (-80.56; 135.15 113.54 (-38.66; 187.65 128.51 (-62.26; 180.74 128.74 (-6.67; 238.64) 4.97 (-48.87; 121.06		
trongeneral, Taul = 1314, 8258, CV yellis Andridengeneralists source and Stans, 2917 source and Stans, 2917 source and Stans, 2917 source and Stans, 2917 set al., 2916 stal, 2917 stal, 2916 stal, 2916 stal, 2917 stal, 2916 stal, 2917 stal, 2916 stal, 2917 stal, 2917 stal, 2918 stal, 29	of = 22.52, of = 5 (P - C) CG Trigeninal CGCI SNL SNL SNL SNL SNL CCI SNI Trigeninal CCI SNI SSNL SNL SNL SNL SNL SNL SNL SNL SNL SN	Depresion Assisty Depresion Assisty Depresion Assisty Depresion Assisty Depresion Assisty Depresion Depres	Desipramine Clornipramine Clornipramine Desipramine Armitrojstes Armitrojstes Armitrojstes Armitrojstes Armitrojstes Carmitrojstes Desipramine Armitrojstes Clornipramine Clornipramine Clornipramine Desipramine Desipramine Desipramine Desipramine Armitrojstes Armitrojstes Armitrojstes Armitrojstes Armitrojstes Armitrojstes Armitrojstes Armitrojstes Desipramine Desipramine Desipramine	0.7% 0.4% 0.7% 0.4% 0.5% 0.7% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5	39.45   25.45   55.55   45.55		
lazzo et al., 2016 lazzo et al., 2016 tall (95% CI) terogeneity: Tau <sup>2</sup> = 840,6281; Chi	SNI SNI 2 = 98.8, df = 22 (P ×	Cognitive impairment Analety 0.01); I <sup>2</sup> = 78%	Aminiphyline Aminiphyline	0.5% 0.4% 12.3% I	12.14 [ 68.50; 95.78	i	
* channel blocker  = tri xt, 2013  = tri xt, 2022  sport et al., 2022  source and Hann, 2017  sport et al., 2022  yet et al., 2022  yet et al., 2022  yet et al., 2025  fourn et al., 2017  berogeneity. Tau² = 0; Ch²² = 5.51	Trigeminal Trigeminal CCI CCI df = 8 (P = 0.48); f <sup>2</sup> =	Wellbeirg Analety Vocalization Facial Grooming Analety Paw Paw 0%	Carbamazepine Lidocelne* Carbamazepine Carbamazepine Carbamazepine Zonisarride Mediatine*	0.2% 0.4% 0.5% 0.5% 0.5% 0.5% 0.7% 0.2% 3.1%	2,94 [-92,73; 98,61 51,36] -22,97; 125,16 99,92 [-14,44; 106,80 98,90] 18,96; 117,12 91,192 [-70,92; 111,46 100,99 [-6,75; 185,02 79,48 [-63,83; 95,13		•
100 et al., 2050 mg et al., 2050 mg et al., 2050 mg et al., 2050 mg et al., 2052 mg et al., 2012 mg et al., 2013 mg et al., 2014 mg et al., 2014 mg et al., 2025 mg et al., 2014 mg et al., 2025 mg et al., 20	SNL SNL SNL CCI CCI CCI CCI CCI SNL SNL CCI SNL PSNL CCI	Carl Cognitive Impairment Carl Exploration & Locornotion Carl Paw Paw Analety Cognitive Impairment Paw Cognitive Impairment Analety Analety Analety Cognitive Impairment Octobritive Impairment Carl Cognitive Impairment C	Minacipnan Risperticiona Minacipnan Nullinacipnan Dulloostine Dultoostine Dultoostine Dultoostine Minacipnan Risperticione AS1099962 Risperticione Minacipnan Minacipnan Dultoostine	0.3% 0.5% 0.7% 0.6% 0.3% 0.5% 0.5% 0.5% 0.5% 0.6% 0.6% 0.4% 0.4% 0.4%	-10.77 [-94.36, 72.84 0.00 [-46.92, 46.92] 41.25 [-2.77, 57.74 42.17] 8.86, 87.53 76.26 [-3.92, 10.94] 12.20 85.71 [-2.90, 71.41.45 90.94] (0.61.11.14.67 90.94) (0.61.14.14.67 90.94) (0.61.14.14.14.14.14.14.14.14.14.14.14.14.14		
mabinoid et al., 2019 Gegorio et al., 2019 Gegorio et al., 2019 Gegorio et al., 2019 Gegorio et al., 2019 Gregorio et al., 2019 Gregorio et al., 2019 Gregorio et al., 2019 Gregorio et al., 2019 Isi (95% CI) serrogarate; Tau² = 2820.9492; CI	CCI SNI CCI SNI SNI SNI	Depression Analety Depression Analety Analety Exploration & Locomotion	GW405800 Cannabidiol GW405833 Cannabidiol Cannabidiol	0.6% 0.5% 0.5% 0.6% 0.2% 0.2% 0.2% 2.7% 7	-36.36 [-76.36; 5.64 74.07 [ 26.36; 121.76 75.96 [ 29.42; 121.76 88.06 [ 62.84; 123.26 107.62 [ 9.92; 225.16 166.75 [ 84.96; 252.54 2.06 [ 22.80; 121.32	H	
In Antagonists n et al., 2018 et al., 2022 ng et al., 2011 et al., 2021 net al., 2021 et al., 2021 et al., 2021 for al., 2021 fo	SNI SNL SNI SCI	Depression Analety Depression Wellbeing	Katamina Katamina Ketamina Ketamina Ketamina Ketamina 1 Kutamina 1 Kutamina	0.4% 0.5% 0.4% 0.6% 0.6% 0.4% 0.2% 0.3% 0.5%	-15.74 [-50.11; 45.62 05.09 [ 11.47; 116.71 06.07 [ 77:1: 129.45 70:73] (22.00; 119.25 30.09 [ 42.96; 117.45 30.38 [ 14.12; 147.64 64.06 [ 3.06; 151.16 94.94 [ 30.06; 151.16 30.03 [ 49.78; 58.28	□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □	
Industrational Test and A. 2019  and the control of	CCI SCI SCI SNI HIN-Npb SCI PSRI, SNI SNI SNI CIPN PSRI, CCI Trigeninal PSRI, SNI CCI	Gogital regularistic del consistenti del consi	Progodala (Galaqueria Galaqueria	2.376 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696 0.696	4-101 (1900) 2 100		
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August - March	CCI CCI Other nerve treams Other nerve treams	Depresion Depresion Wellbeing Facial Grooming Paw Exploration & Locornotion Exploration & Locornotion Wellbeing Guil Assistry Vocatication Pastel Grooming Assistry	Morphine Morphine Morphine	0.8% 0.8% 0.7% 0.2% 0.4% 0.8% 0.8% 0.8% 0.8% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9	-16:16:158:12:2644 -7:32:[-34:57] -7:32:[-34		
tulinum Toxin A. thoreska at., 2016 an et at., 2021 an et at., 2021 an et at., 2021 tal (35% CI) teropeneity. Tau <sup>2</sup> = 483,8058; Ch	CCI Trigorninal Trigorninal Trigorninal	Anxiety Anxiety Anxiety Anxiety	Botulinum Toxin A Botulinum Toxin A Botulinum Toxin A Botulinum Toxin A	0.3% 0.5% 0.5% 0.4%	-27.83 [-107.38; 52.12 17.07 [-42.30; 78.44 69.05 [ 15.74; 122.86 91.04 [ 16.29; 165.78 40.83 [ 1.75; 79.92		•
AGO and sail, 2017 attained sail, 2017 attained sail, 2018 attail, 2018 attail, 2018 and sail, 2018 and sail, 2019 and sail, 2019 and sail, 2019 and sail, 2017 and sail, 2	SNI SNI SNI SNI Trigereinal CCI SNI, SNI CCI SNI SNI SNI SNI SNI SNI SNI SNI SNI SN	Veilbeing Anxiety Exploration & Locomotion Anxiety Facial Grooming Plaw Depression Cognitive Impointment Guit Exploration & Locomotion Plaw Cognitive Impointment Assistive Impointment Assistive Impointment Assistive Impo	Persolitanol Parsolitanol Parsolitanol Parsolitanol Parsolitanol Parsolitanol Dictrinue Lumesicom Lumesicom Lumesicom Dictrinue Lumesicom Parsolitanol Parsolitanol Parsolitanol Parsolitanol Parsolitanol Parsolitanol	0.0% 0.2% 0.7% 0.8% 0.7% 0.4% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5%	-53.00[-471.40; 200.44; 40.71[-187.91; 70.48; 11.50] 45.00; 2.00 982 (-289.35; 14.50) 15.55; 10.00 [-2.00; 14.50] 15.55; 11.40[-19.55; 42.22] 11.40[-19.55; 42.22] 11.40[-19.55; 42.22] 11.40[-19.55; 42.22] 12.40[-2.20; 12.76] 12.50[-2.20] 12.76[-2.20] 1		#
id Opinioid ephenoman, 2018 men et al., 2018 men et al., 2018 opinioid and Michapotra, 2018 opinioid and 2018 opin	SNI Diabetic TII SNI SNI SNI SNI SNI CCI Trigeminal CCI Trigeminal CCI 17 = 57.32, df = 8 (P -	Gait Wellbeing Gait Cait Cait Cait Cait Facial Grooming Depresion  1.0.01; 1 <sup>2</sup> = 86%	Buprenorphine Trarradol Buprenorphine Buprenorphine Buprenorphine Buprenorphine Trarradol Trarradol Trarradol		-37.60   -72.41   -2.75 -28.24   -46.69   10.21 -25.00   -48.95   18.95 -4.00   -10.90   -4.74 -0.00   -10.76   10.76 -0.00   -14.45   14.45   -57.36   -0.22   16.24 -69.41   44.95   90.92 -75.95   34.49   17.23 -0.79   -14.79   36.36 -0.70   -3.52   66.50		
ediction interval					30.01 [ 53.52; 66.50 [-17.12; 137.13	400 -200	50 200

Line of Use in Clinics

1st 2nd 3rd Inconclusive Not Used Weak against

**Supplementary Figure 1**. Forest plot shows the effect size of the analgesic efficacy stratified by analgesic class. For each study, the neuropathic model (NP model), behavioral outcome and the analgesic used is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapy induced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation. \*Lidocaine was locally applied. ^ considered as "strong against" in the clinical setting

**Supplementary Figure 2.** Forest plot shows the effect size of the analgesic efficacy of gabapentinoids. For each study, the neuropathic model (NP model) and the behavioral outcome is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapy-induced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation

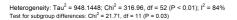


Heterogeneity:  $Tau^2 = 1583.7540$ ;  $Chi^2 = 1072.45$ , df = 73 (P < 0.01);  $I^2 = 93\%$  Test for subgroup differences:  $Chi^2 = 0.07$ , df = 1 (P = 0.79)



Standard NP mode Weight NMD [95% CI] Normalized Mean Difference Analgesic Type Alpha-2-agonist Liu et al., 2022 SNL Dexmedetomidine 1.6% 126.51 [ 62.28; 190.74] Tricyclic Andidepresants Alba-Delgado et al., 2018 Matsuzawa-Yanagida et al., 2007 PSNL Imipramine 2.3% 65.55 [ 21.69; 109.41] Alba-Delgado et al., 2018 CCI 2.2% 91.82 [ 45.19: 138.45] Palazzo et al., 2016 Amitriptyline 123.08 [ 104.56; 141.60] mipramine Alba-Delgado et al., 2018 Palazzo et al., 2016 SNI Amitriptyline 1.7% 164.71 [ 102.62; 226.80] Total (95% CI) 14.8% 105.20 [ 80.05; 130.35 Heterogeneity:  $Tau^2 = 573.3972$ ;  $Chi^2 = 16.11$ , df = 6 (P = 0.01);  $I^2 = 16.11$ Matsuzawa-Yanagida et al., 2007 PSNL 89.69 [ 35.28; 144.10] 104.92 [ 59.41; 150.43] 105.88 [ 28.81; 182.95] 116.15 [ 53.20; 179.10] Matsuzawa-Yanagida et al., 2007 PSNL Grégoire et al., 2012 CCI 7.1% 103.19 [ 74.81; 131.57] Total (95% CI) Heterogeneity:  $Tau^2 = 0$ ;  $Chi^2 = 0.41$ , df = 3 (P = 0.94);  $I^2 = 0\%$ Morphine Roeska et al., 2009 Morphine 1.7% 1.1% 90.40 [ 26.98; 153.82] Morphine 122 68 [ 34 23: 211 13] 0.7% 5.6% 94.75 [ 61.40; 128.09] Heterogeneity:  $Tau^2 = < 0.0001$ ;  $Chi^2 = 3.32$ , df = 3 (P = 0.34);  $I^2 = 10\%$ Cannabinoid De Gregorio et al., 2019 De Gregorio et al., 2019 2.1% 74.07 [ 26.38; 121.76] 88.06 [ 52.84; 123.28] De Gregorio et al., 2019 SNI Cannabidio 0.7% 107.62 [ -9.92; 225.16] 84.47 [ 56.93; 112.01] leterogeneity:  $Tau^2 = 0$ ;  $Chi^2 = 0.37$ , df = 2 (P = 0.83);  $I^2 = 0\%$ Barthas et al., 2017 Fluoxetine 2.8% 67.91 [ 38.88; 96.94] 2.2% 1.9% 2.6% 1.0% Matsuzawa-Yanagida et al., 2007 PSNL 70.53 [ 25.27; 115.79] Sang et al., 2018 Matsuzawa-Yanagida et al., 2007 91.30 [ 35.83; 146.77] 93.02 [ 57.35; 128.69] 105.80 [ 11.06; 200.54] Sang et al., 2018 Citalopram SNI Citalopram 0.9% 120.81 [ 16.48; 225.14] 80.52 [ 62.23; 98.81] Heterogeneity:  $Tau^2 = 0$ ;  $Chi^2 = 2.38$ , df = 5 (P = 0.80);  $I^2 = 0\%$ NMDA antagonists Liu et al., 2022 SNL Ketamine 1.9% 65.09 [ 11.47: 118.71] Araya et al., 2022 Trigeminal Carbamazepine 2.0% 68.87 [ 16.03; 121.71] 3.4% 62.92 [ 19.93; 105.90] Heterogeneity:  $Tau^2 = 0$ ;  $Chi^2 = 0.14$ , df = 1 (P = 0.70);  $I^2 = 0$ % Gabapentinoid Hasnie et al., 2007 Post-herpetic Np -2.06 [ -26.25: 22.13] 3.4% 2.3% 3.0% 4.00 [ -4.31; 12.31] 19.71 [ -24.49; 63.91] 38.65 [ 13.37; 63.93] 46.90 [ 27.10; 66.70] Zhu et al., 2017 Pregabalin Wallace et al., 2008 HIV-Np Gabapentin 3.1% Galan-Arriero et al., 2015 SNI Pregabalin 58 05 [ 0.23: 115 87] 58.05 [ 0.23; 115.87] 58.50 [ -0.51; 117.51] 68.46 [ 44.90; 92.02] 73.54 [ 45.32; 101.76] 83.33 [ 12.34; 154.32] 92.19 [ 40.04; 144.34] 93.41 [ 44.25; 144.87] 93.75 [ -44.88; 232.38] 93.81 [ 42.75; 144.87] Avila-Martin et al., 2014 Grégoire et al., 2012 Zhang et al., 2022 Pregabalin Gabapentir Pregabalin SNI 3.0% Trigeminal Roeska et al., 2009 CCI Gabapentin 1.5% Pregabalin Gabapentir Gabapentir La Porta et al., 2016 PSNL 2.0% Roeska et al., 2009 Hasnie et al., 2007 2.1% 2.0% Wang et al., 2020 SNL Pregabalin Georgieva et al., 2019 SCI Pregabatin 1.7% 119.01 [ 55.64: 182.38] 123.86 [ 8.89: 238.83] 218.18 [ 63.56; 372.80] 58.94 [ 39.86; 78.03] Gabapentin 35.3% Total (95% CI) Heterogeneity:  $Tau^2 = 965.5543$ ;  $Chi^2 = 103.73$ , df = 16 (P < 0.01);  $I^2 = 85\%$ Mild Opioid Caspani et al., 2014 Botulinum Toxin A Zvchowska al., 2016 CCI Botulinum Toxin A 1.3% -27.63 [-107.38: 52.12] Chen et al., 2021 Chen et al., 2021 Trigeminal Trigeminal 1.8% Chen et al., 2021 Trigeminal Botulinum Toxin A 91.04 [ 16.29; 165.79] Total (95% CI) 6.4% 40.83 [ 1.75; 79.92]  $Tau^2 = 483.8056$ ;  $Chi^2 = 6.25$ , df = 3 (P = 0.10);  $I^2 = 52\%$ 

Supplementary Figure 3. (A) Forest plot shows the effect size of the analgesic efficacy in the anxiety outcome stratified by different analgesic types. For each study, the neuropathic pain model is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapyinduced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation.(B) Comparison of the analgesic effect size between all outomes (All) and Anxiety (Axn). Only drugs that were tested at least in three studies are compared. Significant differences were only seen for the group of strong opiod (t-test).



Line of Use in Clinics

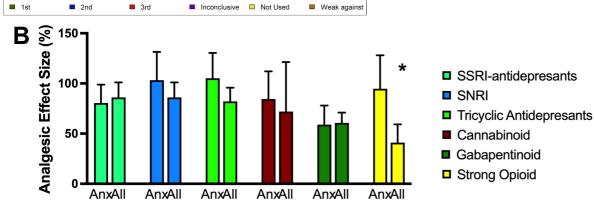
SNI

SNI

Heterogeneity: Tau<sup>2</sup> = 1734.8187; Chi<sup>2</sup> = 8.74, df = 2 (P = 0.01); l<sup>2</sup> = 77%

Chen et al., 2017

Total (95% CI)



0.6%

2.5%

1.9%

Paracetamol

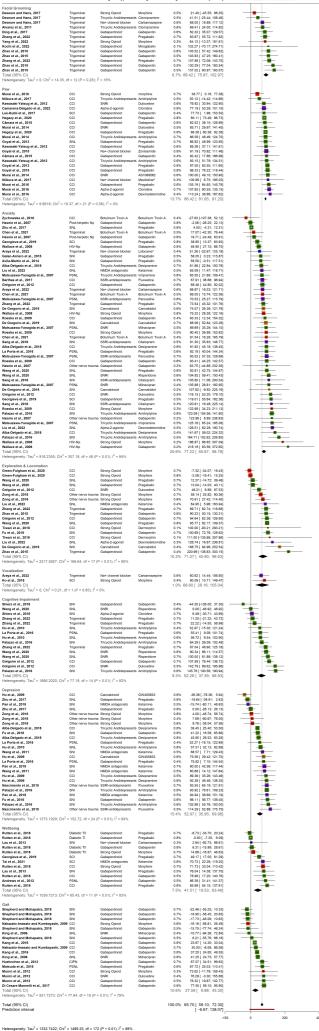
-58.71 [-187.91; 70.49]

9.62 [ -29.30; 48.54]

99.34 [ 43.50; 155.18]

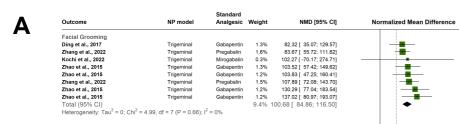
-150

100.0% 74.83 [ 63.57; 86.09] [ 11.95; 137.72]



Heterogeneity:  $Tau^2 = 1332.7422$ ;  $Chi^2 = 1489.25$ , df = 172 (P < 0.01);  $I^2 = 88\%$ Test for subgroup differences:  $Chi^2 = 68.70$ , df = 8 (P < 0.01)

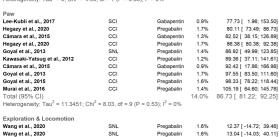
**Supplementary Figure 4.** Forest plot shows the effect size of the analgesic efficacy stratified by Outcome. For each study, the neuropathic model (NP model), analgesic class and the analgesic used is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapy induced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation.



Pregabalin Mirogabalin Gabapentin Gabapentin Pregabalin Gabapentin Gabapentin

1.3% 1.6% 0.3% 1.3% 1.2% 1.5% 1.2% 1.2% 9.4%

Supplementary Figure 5. (A) Forest plot shows the effect size of the analgesic efficacy of the gabapentinoids stratified by non-evoked pain related outcome. For each study, the neuropathic pain model is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapy-induced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation.(B) Comparison of the analgesic effect size between all drugs (A) and gabapentinoid only (GP). Note the lack of statistical significance.



Trigemina Trigeminal Trigeminal Trigeminal Trigeminal Trigeminal

Exploration & Locomotion

Wang et al., 2020 SNL
Wang et al., 2020 SNL
Zhang et al., 2022 Trigeminal
Grégoire et al., 2015 CCI
Wang et al., 2020 SNL
Fu et al., 2018 SNL
Fu et al., 2018 SNL
Fu et al., 2018 SNL
Fu et al., 2015 SN Pregabalin Pregabalin Pregabalin Gabapentin Gabapentin Pregabalin Gabapentin Gabapentin 1.6% 1.6% 1.4% 1.5% 1.7% 1.6% 0.8%

Heterogeneity: Tau<sup>2</sup> = 2105.3795; Chi<sup>2</sup> = 67.49, df =

Anxiety

Anxiety

Hasnie et al., 2007

Post-herpet

SNL

Hasnie et al., 2017

Hasnie et al., 2019

SCI

Wallace et al., 2019

Galan-Artiero et al., 2015

Avita-Martin et al., 2014

SNI

Avita-Martin et al., 2014

SNI

Cregorier et al., 2012

CCI

Zhang et al., 2022

Trigeminal

Roeska et al., 2009

CCI

La Porta et al., 2016

PSNL

Roeska et al., 2009

CCI

Hasnie et al., 2007

CDI

Hasnie et al., 2007

Wang et al., 2020

Hasnie et al., 2007

Other nerve

Wang et al., 2020

Hasnie et al., 2007

Other nerve

Wang et al., 2020

Hasnie et al., 2007

Other nerve

Wang et al., 2020

Hasnie et al., 2007

Other nerve

HIV-Np

Total (95% CI)

Heterogeneity: Tau<sup>2</sup> = 965.5543; Chi<sup>2</sup> = 103.73, df =

Coantitye Impairment -2.06 [-26.25; 22.13] 4.00 [-4.31; 12.31] 19.71 [-24.46; 63.91] 38.65 [13.37; 63.83] 38.65 [13.37; 63.83] 46.90 [27.10; 66.70] 58.05 [-0.23; 113.87] 58.50 [-0.51; 17.51] 68.46 [44.90; 92.02] 29.19 [4.00; 144.34] 93.41 [42.5; 142.57] 93.75 [-44.86; 22.38] 93.81 [42.75; 144.87] 119.01 [55.64; 182.38] 218.18 [63.56; 372.80] 58.94 [39.86; 78.03] 1.6% 1.7% 1.3% 1.6% 1.7% 1.1% 1.6% 1.6% 1.2% 1.3% 0.4% 1.2% 1.1% 0.6% 0.4% Gabapentin Pregabalin Gabapentin Pregabalin Gabapentin Pregabalin Gabapentin Pregabalin Gabapentin Pregabalin Gabapentin

Cognitive Impairment
Shiers et al., 2018
Shiers et al., 2018
Zhang et al., 2022
Trigeminal
La Porta et al., 2020
Trigeminal
Trigeminal
Trigeminal
Crahang et al., 2022
Trigeminal
Orégoire et al., 2021
Crigeminal
Trigeminal
Orégoire et al., 2012
COI
Total (95% Cu)
Heterogeneity: Tau<sup>2</sup> = 1581.5225; Chi<sup>2</sup> = 30.91, df = 5 (P -44.35 [-126.00; 37.30] 11.20 [-21.32; 43.72] 22.22 [-14.55; 58.99] 55.41 [-9.08; 101.74] 87.04 [-48.90; 125.18] 107.58 [-78.44; 136.72] 46.47 [-10.18; 82.75] Gabapentin Pregabalin Pregabalin Pregabalin Pregabalin Gabapentin 0.8% 1.5% 1.4% 1.3% 1.4% 1.5% 8.0%

 
 Wellbeing
 Diabetic TII

 Rutten et al., 2018
 Diabetic TII

 Rutten et al., 2018
 Diabetic TII

 Rutten et al., 2018
 Diabetic TII

 Georgieva et al., 2019
 SCI

 Lau et al., 2013
 SNI

 Rutten et al., 2018
 CCI

 Andrews et al., 2018
 CCI

 Total (95% CI)
 CI

 Heterogeneity: Tau² = 1277.2892; Ch² = 47.88, df = 7 (P
 -6.73 [-33.70; 20.24] -0.63 [-7.35; 6.09] 6.31 [-15.99; 28.61] 49.17 [ 17.05; 81.29] 76.04 [14.38; 137.70] 78.96 [ 17.20; 140.76] 86.39 [ 31.41; 141.37] 95.88 [ 54.15; 137.61] 41.35 [ 12.94; 69.76] Pregabalin Pregabalin Gabapentin Pregabalin Pregabalin Gabapentin Gabapentin 1.6% 1.7% 1.6% 1.5% 1.1% 1.1% 1.2% 1.4% 11.1%

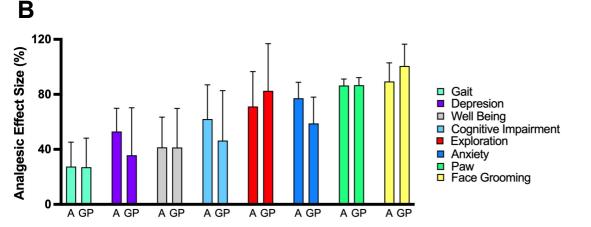
-18.64 [-39.91; 2.63] 0.00 [-26.13; 26.13] 41.22 [ 16.58; 65.86] 52.27 [-18.15; 122.69] 75.82 [ 7.10; 144.54] 98.11 [ 56.77; 139.45] 35.80 [ 1.33; 70.27] Pregabalin Pregabalin Gabapentin Pregabalin Pregabalin Gabapentin 1.6% 1.6% 1.6% 1.0% 1.0% 1.4% 8.1%

Heterogeneity: Tau<sup>2</sup> = 1397.5285; Chi<sup>2</sup> = 34.69, df = 5 (F 0.01); I<sup>2</sup> = 8

-22.46 [-55.25; 10.33] -18.90 [-58.45; 20.65] -17.73 [-46.09; 10.63] -15.75 [-77.74; 46.24] -6.21 [-55.76; 68.18] -23.67 [14.30; 33.04] -30.00 [-6.06; 66.08] -37.20 [24.65; 49.55] -67.07 [34.51; 98.63] -67.27 [25.03; 110.41] -76.32 [19.87; 132.77] -77.50 [59.10; 95.90] -27.09 [-6.01; 48.18] 1.5% 1.4% 1.6% 1.1% 1.1% 1.7% 1.4% 1.5% 1.4% 1.2% 1.7%

Total (95% CI) Prediction interval

Heterogeneity:  $Tau^2 = 1579.6542$ ;  $Chi^2 = 1072.79$ , df = 74 (P < 0.01);  $I^2 = 93\%$  Test for subgroup differences:  $Chi^2 = 57.84$ , df = 7 (P < 0.01)



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NP Model	Outcome	Analgesic Type	Standard Analgesic	Weight	NMD [95% CI]	Normalized Mean Difference
PSNL La Porta et al., 2016 La Porta et al., 2016	Depresion Cognitive Impairment	Gabapentinoid Gabapentinoid	Pregabalin Pregabalin	0.5%	52.27 [ -18.15; 122.69] 55.41 [ 9.08; 101.74]	
Matsuzawa-Yanagida et al., 2007 Matsuda et al., 2016 Matsuzawa-Yanagida et al., 2007	Anxiety Gait Anxiety	Tricyclic Andidepresants Gabapentinoid SSRI-antidepresants	Pregabalin Paroxetine	0.7% 0.7% 0.7%	65.55 [ 21.69; 109.41] 67.72 [ 25.03; 110.41] 70.53 [ 25.27; 115.79]	1
La Porta et al., 2016 Andrews et al., 2012 Matsuzawa-Yanagida et al., 2007	Depresion Wellbeing Anxiety	Gabapentinoid Gabapentinoid SNRI	Pregabatin Gabapentin Milnacipran	0.5% 0.6% 0.6%	75.82 [ 7.10; 144.54] 86.39 [ 31.41; 141.37] 89.69 [ 35.28; 144.10]	
La Porta et al., 2016 Matsuzawa-Yanagida et al., 2007 Matsuzawa-Yanagida et al., 2007	Anxiety Anxiety Anxiety	Gabapentinoid SSRI-antidepresants SNRI	Pregabalin Paroxetine Milnacipran	0.6% 0.8% 0.4%	92.19 [ 40.04; 144.34] 93.02 [ 57.35; 128.69] 105.88 [ 28.81; 182.95]	
Matsuzawa-Yanagida et al., 2007 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 6.11, d	Anxiety f = 11 (P = 0.87); l <sup>2</sup> = 0%	Tricyclic Andidepresants	Imipramine	0.6% 7.3% 8	125.16 [ 65.24; 185.08] 80.05 [ 65.47; 94.63]	•
Trigeminal Zhang et al., 2022 Chen et al., 2021	Cognitive Impairment Anxiety	Gabapentinoid Botulinum Toxin A	Pregabalin Botulinum Toxin A	0.8%	11.20 [-21.32; 43.72] 17.07 [-42.30; 76.44]	<b></b>
Deseure and Hans, 2017 Zhang et al., 2022 Deseure and Hans, 2017	Facial Grooming Cognitive Impairment Facial Grooming	Strong Opioid Gabapentinoid Tricyclic Andidepresants	Morphine Pregabatin Clomipramine	0.5% 0.8% 0.5%	21.40 [-45.55; 88.35] 22.22 [-14.55; 58.99] 41.51 [-25.44; 108.46]	
Araya et al., 2022 Araya et al., 2022 Deseure and Hans, 2017	Anxiety Vocalization Facial Grooming	Na+ channel blocker Na+ channel blocker Na+ channel blocker	Lidocaine* Carbamazepine Carbamazepine	0.5% 0.7% 0.6%	51.26 [-22.67; 125.19] 60.62 [ 14.44; 106.80] 68.00 [ 18.88; 117.12]	
Araya et al., 2022 Chen et al., 2021 Alvarez et al., 2011	Anxiety Anxiety Facial Grooming	Na+ channel blocker Botulinum Toxin A Tricyclic Andidepresants	Carbamazepine Carbamazepine Botulinum Toxin A Clomipramine	0.6% 0.6% 0.7%	68.87 [ 18.03; 121.71] 69.05 [ 15.74; 122.36] 69.41 [ 24.00; 114.82]	
Zhang et al., 2022 Ding et al., 2017 Zhang et al., 2022	Anxiety Facial Grooming Facial Grooming	Gabapentinoid Gabapentinoid Gabapentinoid	Pregabalin Gabapentin Pregabalin	0.8% 0.7% 0.8%	73.54 [ 45.32; 101.76] 82.32 [ 35.07; 129.57] 83.67 [ 55.72; 111.62]	1
Yang et al., 2022 Zhang et al., 2022 Zhang et al., 2022	Facial Grooming Cognitive Impairment Exploration & Locomotion	Strong Opioid Gabapentinoid Gabapentinoid	Morphine Pregabalin Pregabalin	0.3% 0.7% 0.8%	84.12 [-13.37; 181.61] 87.04 [ 48.90; 125.18] 89.71 [ 62.74; 116.68]	
Zhao et al., 2015 Chen et al., 2021 Kochi et al., 2022	Exploration & Locomotion Anxiety Facial Grooming		Gabapentin Botulinum Toxin A Mirogabalin	0.7% 0.4% 0.1%	90.23 [ 50.15; 130.31] 91.04 [ 16.29; 165.79] 102.27 [ -70.17; 274.71]	
Zhao et al., 2015 Zhao et al., 2015 Zhang et al., 2022	Facial Grooming Facial Grooming Facial Grooming	Gabapentinoid Gabapentinoid Gabapentinoid	Gabapentin Gabapentin Pregabalin	0.7% 0.6% 0.8%	103.52 [ 57.42; 149.62] 103.83 [ 47.25; 160.41] 107.89 [ 72.08; 143.70]	
Zhao et al., 2015 Zhao et al., 2015 Zhao et al., 2015	Facial Grooming Facial Grooming Exploration & Locomotion	Gabapentinoid Gabapentinoid Gabapentinoid	Gabapentin Gabapentin Gabapentin	0.6% 0.6% 0.4%	130.29 [ 77.04; 183.54] 137.02 [ 80.97; 193.07] 220.99 [ 138.83; 303.15]	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 703.5766; Chi <sup>2</sup> =				15.9% 7	7.21 [ 62.94; 91.49]	<b>*</b>
CCI Hu et al., 2009 Zychowska al., 2016	Depresion Anxiety	Cannabinoid Botulinum Toxin A	GW405833 Botulinum Toxin A	0.7%	-36.36 [ -78.36; 5.64] -27.63 [-107.38; 52.12]	
Nakazato-Imasato and Kurebayashi, 200 Green-Fulgham et al., 2020 Green-Fulgham et al., 2020	9 Gait Exploration & Locomotion Exploration & Locomotion	Strong Opioid Strong Opioid Strong Opioid	Morphine Morphine Morphine	0.7% 0.8% 0.9%	-16.16 [-58.81; 26.49] -7.32 [-34.07; 19.43] -2.08 [-19.41; 15.25]	- <del></del>
Kang et al., 2016 Nakazato-Imasato and Kurebayashi, 200 Kang et al., 2016	Gait	Gabapentinoid Gabapentinoid Gabapentinoid	Gabapentin Gabapentin Gabapentin	0.9% 0.8% 0.9%	23.67 [ 14.30; 33.04] 30.00 [ -8.08; 86.08] 37.20 [ 24.85; 49.55]	
Murai et al., 2016 Alba-Delgado et al., 2018 Alba-Delgado et al., 2018	Paw Depresion Depresion	Strong Opioid Tricyclic Andidepresants Tricyclic Andidepresants	Desipramine	0.7% 0.9% 0.9%	38.77 [ 0.16; 77.38] 39.45 [ 25.40; 53.50] 45.90 [ 28.52; 63.28]	-
Grégoire et al., 2012 Niikura et al., 2017 Alba-Delgado et al., 2018	Exploration & Locomotion Paw Anxiety	SNRI Tricyclic Andidepresents Tricyclic Andidepresents	Duloxetine Amitriptyline Desipramine	0.7% 0.5% 0.7%	48.21 [ 8.89; 87.53] 50.12 [-14.42; 114.66] 61.86 [ 22.94; 100.78]	-
Barthas et al., 2017 Grégoire et al., 2012 Rutten et al., 2018	Anxiety Anxiety Wellbeing	SSRI-antidepresants Gabapentinoid Strong Opioid	Fluoxetine Gabapentin Morphine	0.8% 0.9% 0.7%	67.91 [ 38.88; 96.94] 68.48 [ 44.90; 92.02] 71.73 [ 33.04; 110.42]	-
Munro et al., 2012 Hu et al., 2009 Munro et al., 2012	Gait Depresion Gait	Strong Opioid Cannabinoid SNRI	Morphine GW405833 Duloxetine	0.4% 0.7% 0.4%	73.82 [ -11.79; 159.43] 75.56 [ 29.42; 121.70] 76.29 [ -3.30; 155.88]	
Munro et al., 2012 Kawasaki-Yatsug et al., 2012 Camarena-Delgado et al., 2022 Di Cesare Mannelli et al., 2017	Gait Paw Paw Gait	Gabapentinoid SNRI Alpha-2-agonist Gabapentinoid	Gabapentin Duloxetine Clonidine Gabapentin	0.6% 0.7% 0.9% 0.9%	76.32 [ 19.87; 132.77] 76.92 [ 30.94; 122.90] 77.19 [ 53.28; 101.10] 77.50 [ 59.10; 95.90]	-
Rutten et al., 2018 Hegazy et al., 2020	Wellbeing Paw	Gabapentinoid Gabapentinoid	Gabapentin Pregabalin	0.5% 1.0%	78.98 [ 17.20; 140.76] 80.11 [ 73.49; 86.73]	
Câmara et al., 2015 Roeska et al., 2009 Murai et al., 2014	Paw Anxiety Paw	Gabapentinoid Gabapentinoid SNRI	Gabapentin Gabapentin Duloxetine	0.7% 0.5% 0.6%	82.52 [ 38.15; 126.89] 83.33 [ 12.34; 154.32] 85.71 [ 29.97; 141.45]	
Hegazy et al., 2020 Murai et al., 2014 Hu et al., 2009	Paw Paw Depresion Paw	Gabapentinoid Tricyclic Andidepresants Tricyclic Andidepresants	Desipramine	1.0% 0.7% 0.6%	86.38 [ 80.38; 92.38] 86.58 [ 48.46; 124.70] 89.36 [ 35.26; 143.46] 89.36 [ 37.11; 141.61]	
Kawasaki-Yatsug et al., 2012 Roeska et al., 2009 Goyal et al., 2015	Anxiety Paw Anxiety	Gabapentinoid Strong Opioid Na+ channel blocker	Pregabalin Morphine Zonisamide	0.6% 0.5% 0.9%	89.36 [ 37.11; 141.61] 90.40 [ 26.98; 153.82] 91.19 [ 70.92; 111.46] 91.82 [ 45.19; 138.45]	
Alba-Delgado et al., 2018 Hu et al., 2009 Câmara et al., 2015 Kawasaki-Yatsug et al., 2012	Depresion Paw Paw	Tricyclic Andidepresents Tricyclic Andidepresents Gabapentinoid Tricyclic Andidepresents	Designamine Gabapentin Amitriptyline	0.7% 0.7% 0.4% 0.7%	92.38 [ 46.46; 138.30] 92.42 [ 17.86; 166.98] 93.15 [ 51.79; 134.51]	
Roeska et al., 2009 Grégoire et al., 2012 Rutten et al., 2018	Anxiety Exploration & Locomotion Wellbeing	Gabapentinoid	Gabapentin Gabapentin Pregabalin	0.6% 0.8% 0.7%	93.15 [ 51.78; 134.51] 93.41 [ 44.25; 142.57] 94.64 [ 62.38; 126.90] 95.88 [ 54.15; 137.61]	
Goyal et al., 2013 Goyal et al., 2015 Murai et al., 2014	Paw Paw Paw	Gabapentinoid Gabapentinoid SNRI	Pregabalin Pregabalin AS1069562	0.9% 0.9% 0.6%	97.55 [ 83.50; 111.60] 98.33 [ 78.22; 118.44] 100.00 [ 49.10; 150.90]	
Murai et al., 2018 Niikura et al., 2017 Murai et al., 2016	Exploration & Locomotion Paw Paw		Dermorphin Mexiletine* Pregabalin	0.1% 0.3% 0.7%	100.00 [ 49.10; 190.90] 100.00 [ -93.21; 293.21] 100.89 [ 6.75; 195.03] 105.19 [ 64.60; 145.78]	
Grégoire et al., 2012 Murai et al., 2016 Tiwari et al., 2018	Cognitive Impairment Paw Exploration & Locomotion	Gabapentinoid Alpha-2-agonist	Gabapentin Clonidine Dermorphin	0.8% 0.8% 0.1%	107.58 [ 78.44; 136.72] 107.85 [ 80.55; 135.15] 111.00 [-135.66; 357.66]	
Murai et al., 2016 Grégoire et al., 2012 Roeska et al., 2009	Paw Anxiety Anxiety	Alpha-2-agonist SNRI Strong Opioid	Dexmedetomidine Duloxetine Morphine	0.4% 0.5% 0.4%	113.24 [ 38.86; 187.62] 116.15 [ 53.20; 179.10] 122.68 [ 34.23; 211.13]	
Alba-Delgado et al., 2018 Grégoire et al., 2012 Total (95% CI)	Anxiety Cognitive Impairment	Tricyclic Andidepresents SNRI	Desipramine Duloxetine	0.4%	141.67 [ 59.02; 224.32] 142.79 [ 89.62; 195.96] '0.88 [ 60.74; 81.02]	
Heterogeneity: Tau <sup>2</sup> = 978,0934; Chi <sup>2</sup> = SNI	408.46, df = 55 (P < 0.0	1); I <sup>2</sup> = 87%				
Shiers et al., 2018 Shepherd and Mohapatra, 2018 Shepherd and Mohapatra, 2018	Cognitive Impairment Gait Gait	Gabapentinoid Gabapentinoid Gabapentinoid	Gabapentin Gabapentin Gabapentin	0.4% 0.8% 0.7%	-44.35 [-126.00; 37.30] -22.46 [-55.25; 10.33] -18.90 [-58.45; 20.65]	
Shepherd and Mohapatra, 2018 Shepherd and Mohapatra, 2018 Pan et al., 2018	Galt Galt Depresion	Gabapentinoid Gabapentinoid NMDA antagonists	Gabapentin Gabapentin Ketamine	0.8% 0.5% 0.5%	-17.73 [ -46.09; 10.63] -15.75 [ -77.74; 46.24] -15.74 [ -80.11; 48.63]	-
Lau et al., 2013 Shepherd and Mohapatra, 2018 Shiers et al., 2018	Wellbeing Gait Cognitive Impairment	Na+ channel blocker Gabapentinoid Alpha-2-agonist	Carbamazepine Gabapentin Clonidine	0.3% 0.5% 0.7%	2.94 [-92.73; 98.61] 6.21 [-55.76; 68.18] 6.49 [-30.71; 43.69]	
Fu et al., 2018 Galan-Arriero et al., 2015 Avila-Martin et al., 2014 Palazzo et al., 2016	Depresion Anxiety Anxiety	Gabapentinoid Gabapentinoid Gabapentinoid	Gabapentin Pregabalin Pregabalin	0.9% 0.6% 0.6% 0.7%	41.22 [ 16.58; 65.86] 58.05 [ 0.23; 115.87] 58.50 [ -0.51; 117.51]	
Wang et al., 2016 Wang et al., 2011 De Gregorio et al., 2019 Lau et al., 2013	Cognitive Impairment Depresion Anxiety Wellbeing	Tricyclic Andidepresents NMDA antagonists Cannabinoid Gabapentinoid	Amitriptyline Ketamine Cannabidiol Pregabalin	0.7% 0.5% 0.7% 0.5%	64.29 [ 26.09; 102.49] 68.57 [ 7.71; 129.43] 74.07 [ 26.38; 121.76] 76.04 [ 14.38; 137.70]	
Pan et al., 2018 Wang et al., 2011 De Gregorio et al., 2019	Depresion Depresion Anxiety	NMDA antagonists NMDA antagonists Cannabinoid	Ketamine Ketamine Cannabidiol	0.7% 0.5% 0.8%	80.00 [ 42.56; 117.44] 80.88 [ 14.12; 147.64] 88.06 [ 52.84; 123.28]	<u> </u>
Sang et al., 2018 Palazzo et al., 2016 Pan et al., 2018	Anxiety Depresion Depresion	SSRI-antidepresants Tricyclic Andidepresants NMDA antagonists	Citalopram	0.6% 0.9% 0.6%	91.30 [ 35.83; 146.77] 93.92 [ 78.61; 109.23] 94.94 [ 38.69; 151.19]	
Fu et al., 2018 Fu et al., 2018 Palazzo et al., 2016	Depresion Exploration & Locomotion Depresion	Gabapentinoid	Gabapentin Gabapentin	0.7% 0.8% 0.7%	98.11 [ 56.77; 139.45] 100.69 [ 72.76; 128.62] 102.88 [ 55.76; 150.00]	-
Sang et al., 2018 De Gregorio et al., 2019 Sang et al., 2018	Anxiety Anxiety Anxiety	SSRI-antidepresants Cannabinoid SSRI-antidepresants	Citalopram Cannabidiol Citalopram	0.3% 0.3% 0.3%	105.80 [ 11.06; 200.54] 107.62 [ -9.92; 225.16] 120.81 [ 16.48; 225.14]	
Palazzo et al., 2016 Palazzo et al., 2016 Palazzo et al., 2016	Anxiety Cognitive Impairment Anxiety	Tricyclic Andidepresants Tricyclic Andidepresants Tricyclic Andidepresants	Amitriptyline Amitriptyline Amitriptyline	0.9% 0.7% 0.5%	123.08 [ 104.56; 141.60] 145.76 [ 100.58; 190.94] 164.71 [ 102.62; 226.80]	
De Gregorio et al., 2019 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 2294.0083; Chi <sup>2</sup>	Exploration & Locomotion	Cannabinoid	Cannabidiol	0.4%	168.75 [ 84.96; 252.54] 34.12 [ 44.90; 83.34]	<b>+</b>
Other nerve trauma Zong et al., 2018	Depresion	Strong Opioid	Morphine	0.6%	4.00 [-48.74; 56.74]	
Zong et al., 2018 Zong et al., 2018 Zong et al., 2018	Depresion Depresion Exploration & Locomotion	Strong Opioid Strong Opioid Strong Opioid	Morphine Morphine Morphine	0.5% 0.7% 0.8%	7.69 [-60.67; 76.05] 9.76 [-38.04; 57.56] 58.14 [ 25.92; 90.36]	<b>—</b>
Zong et al., 2018 Nascimento et al., 2015 Hasnie et al., 2007	Exploration & Locomotion Depresion Anxiety	SSRI-antidepresants Gabapentinoid	Morphine Fluoxetine Gabapentin	0.7% 0.8% 0.2%	70.91 [ 27.42; 114.40] 93.55 [ 65.19; 121.91] 93.75 [ -44.88; 232.38]	
Nascimento et al., 2015 Hasnie et al., 2007 Total (95% CI)	Depresion Anxiety	SSRI-antidepresents Gabapentinoid	Fluoxetine Gabapentin	0.5% 0.3% 5.1% 5	114.29 [ 52.88; 175.70] 123.86 [ 8.89; 238.83] 58.65 [ 31.91; 85.39]	+
Heterogeneity: Tau <sup>2</sup> = 842.2082; Chi <sup>2</sup> = SNL			Dragon - 1-	0.9%	-18.64 [-39.91; 2.63]	
Zhu et al., 2017 King et al., 2006 Wang et al., 2020 Zhu et al., 2017	Depresion Gait Cognitive Impairment Depresion	Gabapentinoid SNRI SNRI Gabapentinoid	Pregabalin Milnacipran Risperidone Precabalin	0.9% 0.4% 0.7% 0.8%	-18.64 [-39.91; 2.63] -10.77 [-94.38; 72.84] 0.00 [-46.92; 46.92] 0.00 [-26.13; 26.13]	
Zhu et al., 2017 Wang et al., 2020	Anxiety Exploration & Locomotion	Gabapentinoid Gabapentinoid	Pregabalin Pregabalin Pregabalin Pregabalin	0.8% 0.8% 0.8%	0.00 [ -28.13; 28.13] 4.00 [ -4.31; 12.31] 12.37 [ -14.72; 39.46] 13.04 [ -14.03; 40.11]	
Wang et al., 2020 King et al., 2006 Hu et al., 2010 Hu et al., 2010	Exploration & Locomotion Gait Cognitive Impairment Cognitive Impairment	SNRI Tricyclic Andidepresants	Milnacipran Amitriptyline	0.8% 0.9% 0.5% 0.7%	41.25 [ 24.73; 57.77] 52.97 [-15.30; 121.24]	
Hu et al., 2010 Hu et al., 2010 Liu et al., 2022 Liu et al., 2022	Cognitive Impairment Depresion Anxiety Evolutation & Locamation	Tricyclic Andidepresants Tricyclic Andidepresants NMDA antagonists	Amitriptyline Amitriptyline Ketamine Ketamine	0.7% 0.8% 0.6% 0.4%	56.72 [ 9.54; 103.90] 57.51 [ 32.13; 82.89] 65.09 [ 11.47; 118.71] 84.95 [ 5.96; 163.94]	
Goyal et al., 2013 Wang et al., 2020	Exploration & Locomotion Paw Cognitive Impairment	NMDA antagonists Gabapentinoid SNRI Gabapentinoid	Ketamine Pregabalin Risperidone Pregabalin	0.4% 0.8% 0.9% 0.6%	84.95 [ 5.96; 163.94] 86.92 [ 49.99; 123.85] 90.34 [ 66.11; 114.57] 93.81 [ 42.75; 144.87]	
Wang et al., 2020 Wang et al., 2020 Wang et al., 2020 Wang et al., 2020	Anxiety Exploration & Locomotion Cognitive Impairment Anxiety	Gabapentinoid Gabapentinoid SNRI SNRI	Pregabatin Pregabatin Risperidone Risperidone	0.8% 0.9% 0.7% 0.7%	93.81 [ 42.75; 144.87] 95.77 [ 82.17; 109.37] 100.00 [ 61.88; 138.12] 104.92 [ 59.41; 150.43]	
Wang et al., 2020 Liu et al., 2022 Liu et al., 2022 Total (95% CI)	Anxiety Anxiety Exploration & Locomotion	Alpha-2-agonist	Dexmedetomidine Dexmedetomidine	0.5%	104.92 [ 59.41; 150.43] 126.51 [ 62.28; 190.74] 128.74 [ 16.67; 236.81] 52.47 [ 33.33; 71.60]	
Heterogeneity: Tau <sup>2</sup> = 1512.5644; Chi <sup>2</sup> Total (95% CI)	= 240.76, df = 20 (P < 0.	01); I <sup>2</sup> = 92%			88.11 [ 61.28; 74.95]	
Prediction interval					[ -2.51; 138.74] 150	0 200 40
Heterogeneity: Tau <sup>2</sup> = 1265.9062; Chi <sup>2</sup> Test for subgroup differences: Chi <sup>2</sup> = 7.09,	= 1094.45, df = 155 (P < df = 5 (P = 0.21)	0.01); I <sup>2</sup> = 86%				

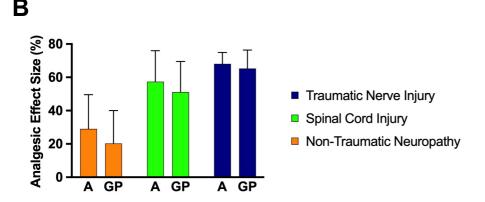
Line of Use in Clinics

I st 2nd 3rd Inconclusive Not Used Weak against

**Supplementary Figure 6.** Forest plot shows the effect size of the analgesic efficacy stratified by neuropathic pain model (comprising the traumatic nerve injury group only). For each study, the outcome, the analgesic class and the analgesic used is also noted. Abbreviations: CCI, chronic constriction injury; CINP, chemotherapy-induced neuropathic pain; PSNL, partial sciatic nerve ligation; SNI, spared nerve injury; SNL, spinal nerve ligation.

Standard NP Model Generic Outcome Analgesic Weight NMD [95% CI] Normalized Mean Difference Traumatic Nerve Injury Shepherd and Mohapatra, 2018 1.5% -22.46 [ -55.25; 10.33] Gait Gabapentin Shepherd and Mohapatra, 2018 Gait . Gabapentin 1.4% -18.90 [ -58.45; 20.65] 1.6% -18.64 [ -39.91; 2.63] Depresion Pregabalin Shepherd and Mohapatra, 2018 Gait Gabapentin 1.6% -17.73 [ -46.09; 10.63] Gait . Gabapentin 1.1% 1.6% -15.75 [ -77.74; 46.24] 0.00 [ -26.13; 26.13] Zhu et al., 2017 Depresion Pregabalin 1.7% 1.1%  $\pm$ Zhu et al., 2017 Anxiety Pregabalin 4.00 [ -4.31; 12.31] Shepherd and Mo Gait 6.21 [ -55.76; 68.18] Gabapentir Zhang et al., 2022 Cognitive Impairment Pregabalin 1.5% 11.20 [ -21.32; 43.72] Pregabalin Exploration & Locomotion 12.37 [ -14.72; 39.46] 13.04 [ -14.03; 40.11] Wang et al., 2020 Exploration & Locomotion Pregabalin 1.6% Pregabalin Gabapentin 1.4% Zhang et al., 2022 Cognitive Impairment 22.22 [ -14.55; 58.99] 23.67 [ 14.30; 33.04] Kang et al., 2016 Nakazato-Imasato and Kurebayashi, 2009 Gait Gabapentin 1.4% 30.00 [ -6.08; 66.08] . Gabapentin 37.20 [ 24.85; 49.55] 41.22 [ 16.58; 65.86] 1.6% Fu et al., 2018 Depresion Gabapentin 1.0% La Porta et al., 2016 Depresion Pregabalin 52.27 [ -18.15; 122.69] 55.41 [ 9.08; 101.74] La Porta et al., 2016 Cognitive Impairment Pregabalin Galan-Arriero et al., 2015 Anxiety Pregabalin 1.1% 58.05 [ 0.23; 115.87] Avila-Martin et al., 2014 Anxiety Pregabalin 58.50 [ -0.51; 117.51] 67.72 [ 25.03; 110.41] 1.4% Matsuda et al., 2016 Gait Pregabalin Grégoire et al., 2012 Gabapentir 1.6% 1.6% 68.46 [ 44.90; 92.02] 73.54 [ 45.32; 101.76] Anxiety Zhang et al., 2022 Anxiety Pregabalin La Porta et al., 2016 Depresion Pregabalin 1.0% 75.82 [ 7.10: 144.54] Pregabalin Munro et al., 2012 Gait Gabapentin 1.2% 76.32 [ 19.87; 132.77] 1.7% Di Cesare Mannelli et al., 2017 Gait Gabapentin 77.50 [ 59.10; 95.90] 78.98 [ 17.20; 140.76] Rutten et al., 2018 Wellbeing Gabapentin Hegazy et al., 2020 Paw Pregabalin 1.7% 80.11 [ 73.49: 86.73] + Ding et al., 2017 Gabapentin 82.32 [ 35.07; 129.57] Câmara et al., 2015 1.3% 82.52 [ 38.15; 126.89] Paw Gabapentin Gabapentin 1.0% Roeska et al., 2009 Anxiety 83.33 [ 12.34; 154.32] Zhang et al., 2022 Facial Grooming Pregabalin 83.67 [ 55.72; 111.62] Hegazy et al., 2020 Paw Pregabalin 1.7% 86.38 [ 80.38: 92.38] Wellbeing 86.39 [ 31.41; 141.37] Goyal et al., 2013 Paw Pregabalin 1.4% 86.92 [ 49.99; 123.85] 1.4% 1.2% Zhang et al., 2022 Cognitive Impairment Pregabalin 87.04 [ 48.90: 125.18] 89.36 [ 37.11; 141.61] Kawasaki-Yatsug et al., 2012 Pregabalin Zhang et al., 2022 Exploration & Locomotion Pregabalin 1.6% 89.71 [ 62.74: 116.68] 90.23 [ 50.15; 130.31] La Porta et al., 2016 Anxiety Pregabalin 1.2% 92.19 [ 40.04; 144.34] Paw Anxiety 0.9% 1.3% Câmara et al 2015 92.42 [ 17.86: 166.98] 93.41 [ 44.25; 142.57] Hasnie et al., 2007 Anxiety Gabapentin 0.4% 93.75 [ -44.88: 232.38] 93.81 [ 42.75; 144.87] Grégoire et al., 2012 Exploration & Locomotion Gabapentin 1.5% 94.64 [ 62.38; 126.90] Wang et al., 2020 Rutten et al., 2018 1.7% 1.4% 95.77 [ 82.17; 109.37] 95.88 [ 54.15; 137.61] Exploration & Locomotion Pregabalin Pregabalin Wellbeing Goyal et al., 2013 Paw Pregabalin 1.7% 97.55 [ 83.50: 111.60] 98.11 [ 56.77; 139.45] Goyal et al., 2015 Paw Pregabalin 1.6% 98.33 [ 78.22; 118.44] Fu et al., 2018 Kochi et al., 2022 1.6% 0.3% Exploration & Locomotion 100.69 [ 72.76: 128.62] 102.27 [ -70.17; 274.71] Facial Grooming Mirogabalin Zhao et al., 2015 Facial Grooming Gabapentin 1.3% 103.52 [ 57.42: 149.62] Gabapentin Facial Grooming 103.83 [ 47.25; 160.41] Murai et al., 2016 Paw Pregabalin 1.4% 105.19 [ 64.60; 145.78] Cognitive Impairment Facial Grooming 1.5% 1.5% Grégoire et al., 2012 Gabapentin 107.58 [ 78.44: 136.72] Zhang et al., 2022 Pregabalin 107.89 [ 72.08; 143.70] Hasnie et al., 2007 Anxiety Gabapentin 0.6% 123.86 [ 8.89; 238.83] 130.29 [ 77.04; 183.54] 137.02 [ 80.97; 193.07] Gabapentin Zhao et al., 2015 Facial Grooming Gabapentin 1.2% Zhao et al., 2015 0.8% 220.99 [ 138.83; 303.15] 83.6% 65.28 [ 54.17; 76.39] Exploration & Locomotion Gabapentin Total (95% CI) Heterogeneity:  $Tau^2 = 1514.3681$ ;  $Chi^2 = 725.56$ , df = 62 (P < 0.01);  $I^2 = 91\%$ Spinal Cord Injury Anxiety Georgieva et al., 2019 Georgieva et al., 2019 Pregabalin 1.6% 38.65 [ 13.37; 63.93] Pregabalin 1.5% 49.17 [ 17.05; 81.29] Wellbeing Lee-Kubli et al., 2017 Paw Gabapentin 0.9% 77.73 [ 1.96; 153.50] Anxiety Total (95% CI) 5.1% 51.17 [ 32.78; 69.56] Heterogeneity:  $Tau^2 = < 0.0001$ ;  $Chi^2 = 5.83$ , df = 3 (P = 0.12);  $I^2 = 49\%$ Non-Traumatic Neuropathy Pregabalin Hasnie et al., 2007 Anxiety Gabapentin 1.6% -2.06 [ -26.25; 22.13] 1.7% -0.63 [ -7.35; 6.09] 6.31 [ -15.99; 28.61] Rutten et al., 2018 Wellbeing Pregabalin Rutten et al., 2018 Wellbeing Gabapentin Hasnie et al., 2007 Anxiety Gabapentin 1.3% 19.71 [ -24.49; 63.91] Anxiety . Gabapentin Huehnchen et al., 2013 Gait Gabapentin 1.5% 67.07 [ 34.51; 99.63] 218.18 [ 63.56; 372.80] 20.29 [ 0.54; 40.05] Wallace et al., 2008 Anxiety Heterogeneity:  $Tau^2 = 551.8229$ ;  $Chi^2 = 42.54$ , df = 7 (P < 0.01);  $I^2 = 84\%$ Total (95% CI) 100.0% 60.69 [ 50.36: 71.02] Prediction interval [-19.21; 140.60]

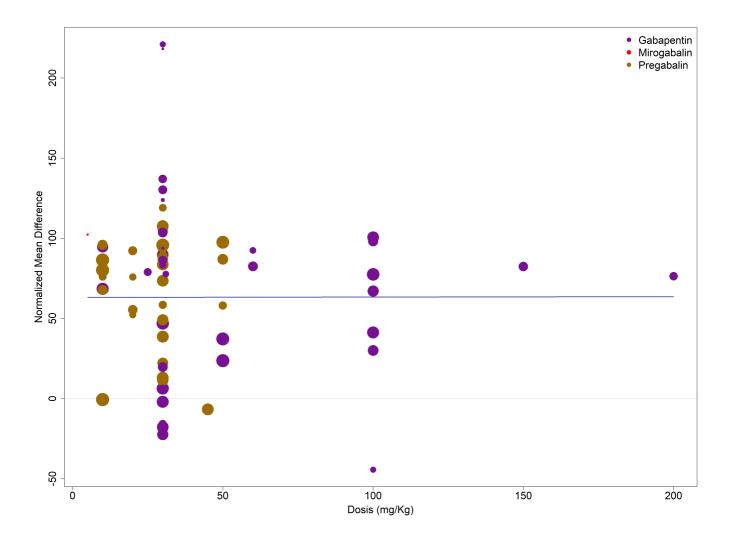
Heterogeneity:  ${\rm Tau}^2$  = 1579.6542;  ${\rm Chi}^2$  = 1072.79, df = 74 (P < 0.01);  ${\rm I}^2$  = 93% Test for subgroup differences:  ${\rm Chi}^2$  = 15.23, df = 2 (P < 0.01)

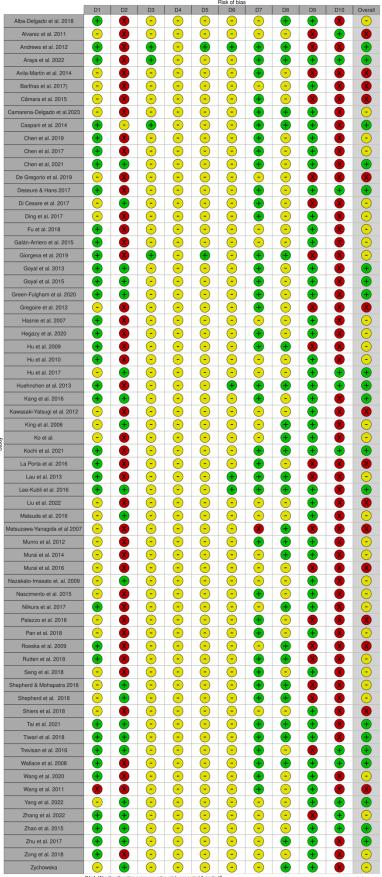


## Supplementary Figure 7. (A)

Forest plot shows the effect size of the analgesic efficacy of the gabapentinoids stratified by generic neuropathic pain model. For each study, the outcome is also noted. (B) Comparison of the analgesic effect size between all drugs (A) and gapabentinoids (GB). Note the lack of statistical significance.

**Supplementary Figure 8.** Meta-regression analysis evaluating the relationship between gabapentinoid dosage and analgesic efficacy. Gabapentinoid dosage (x-axis) and analgesic efficacy (y-axis). Each point represents an individual study, with bubble sizes reflecting the study's weight in the analysis. The solid line indicates the fitted regression line, and the shaded area represents the 95% confidence interval. The analysis was conducted using a mixed-effects model (k = 71 studies).





**Supplementary Figure 9**. Evaluatiom of the risk of bias using SYRCLE's tool. Green circle: low risk of bias; yellow, unclear risk of bias/not applicable to the study design; red circle: high risk of bias

D1: 1 Was the allocation sequence adequately generated & applied?

D2: 2 Were the groups similar at baseline or were they D3: 3 Was the allocation adequately concealed?

<sup>04: 4</sup> Were the animals randomly housed during the experiment?

D5: 5 Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?

<sup>17: 7</sup> Was the outcome assessor blinded?
18: 8 Were incomplete outcome data adequatel

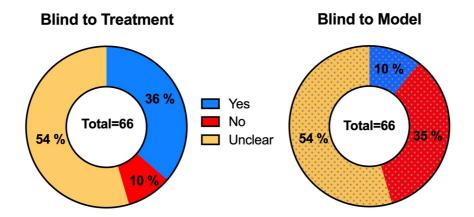
D9: 9 Are reports of the study free of selective outcome reporting?
D10: 10 Was the study apparently free of other problems that could result in high risk of bias

## **Supplementary Table 3.** Blinding conditions in the studies included in the meta-analysis according to the treatment and neuropathy

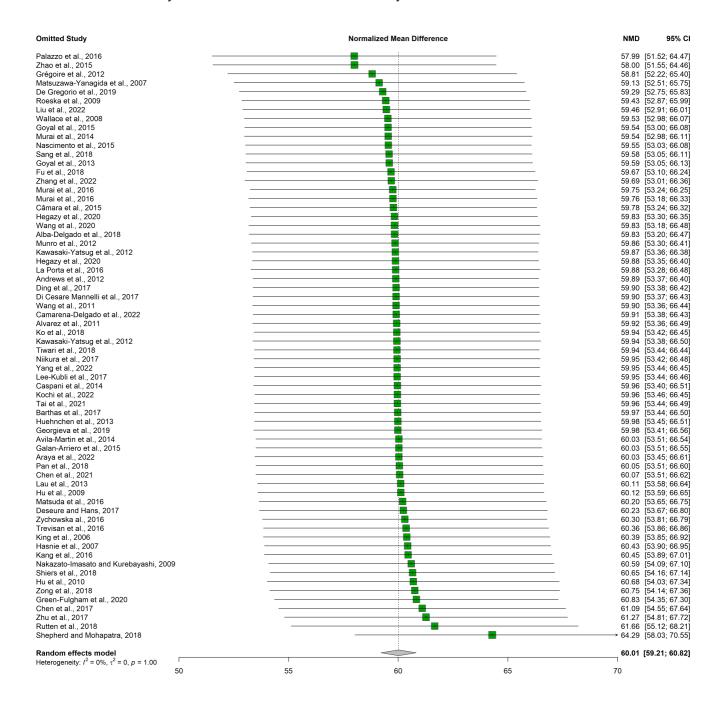
Study	Blind to Treatment	Blind to Neuropathy
Alba-Delgado et al. 2018	Unclear	Unclear
Alvarez et al. 2011	Unclear	Unclear
Andrews et al. 2012	No	Yes
Araya et al. 2022	Yes	No
Avila-Martin et al. 2014	Unclear	Unclear
Barthas et al. 2017	Unclear	Unclear
Câmara et al. 2015	Unclear	Unclear
Camarena-Delgado et al.2023	No	Yes
Caspani et al. 2014	Yes	Yes
Chen et al. 2019	Unclear	Unclear
Chen et al. 2018	Unclear	Unclear
Chen et al, 2021	Unclear	Unclear
De Gregorio et al. 2019	Unclear	Unclear
Deseure & Hans 2017	Unclear	Unclear
Di Cesare et al. 2017	Yes	No
Ding et al. 2017	Yes	No
Fu et al. 2018	Unclear	Unclear
Galán-Arriero et al. 2015	Unclear	Unclear
Giorgeva et al. 2019	Yes	No
Goyal et al. 2013	Unclear	Unclear
Goyal et al. 2015	Yes	No
Green-Fulgham et al. 2020	Unclear	Unclear
Gregoire et al. 2012	Yes	No
Hasnie et al. 2007	Yes	No
Hegazy et al. 2020	Unclear	Unclear
Hu et al. 2009	Yes	No
Hu et al. 2010	Unclear	Unclear
Hu et al. 2017	Unclear	Unclear
Huehnchen et al. 2013	Unclear	Unclear
Kang et al. 2016	Yes	No
Kawasaki-Yatsugi et al. 2012	Unclear	Unclear
King et al. 2006	Unclear	Unclear
Ko et al.	Unclear	Unclear
Kochi et al. 2021	Yes	No
La Porta et al. 2016	Unclear	Unclear
Lau et al. 2013	Yes	No
Lee-Kubli et al. 2016	Yes	No
Liu et al. 2022	Unclear	Unclear
Matsuda et al. 2016	Unclear	Unclear

Matsuzawa-Yanagida et al 2007	No	No
Munro et al. 2012	Yes	No
Murai et al. 2014	Unclear	Unclear
Murai et al. 2016	Unclear	Unclear
Nazakato-Imasato et. al. 2009	Unclear	Unclear
Nascimento et al. 2015	Unclear	Unclear
Niikura et al. 2017	Unclear	Unclear
Palazzo et al. 2016	Yes	No
Pan et al. 2018	Yes	No
Roeska et al. 2009	Yes	Yes
Rutten et al. 2018	No	Yes
Sang et al. 2018	No	Yes
Shepherd & Mohapatra 2018	No	Yes
Shepherd et al. 2018	Yes	No
Shiers et al. 2018	Unclear	Unclear
Tai et al. 2021	Unclear	Unclear
Tiwari et al. 2018	Yes	No
Trevisan et al. 2016	Yes	No
Wallace et al. 2008	Yes	No
Wang et al. 2020	Yes	No
Wang et al. 2011	Yes	No
Yang et al. 2022	Unclear	Unclear
Zhang et al. 2022	Yes	No
Zhao et al. 2015	Unclear	Unclear
Zhu et al. 2017	Unclear	Unclear
Zong et al. 2018	Unclear	Unclear
Zychowska et al., 2016	Unclear	Unclear

**Supplementary Figure 10**. Blinding conditions in the studies included in the meta-analysis according to the treatment and neuropathic condition of the animal.



## **Supplementary Figure 11.** Forest plot shows the Sensitivity Analysis performed by the leave one-out method of the analyzed studies included in the Meta-Analysis



**Supplementary Figure 12**. Assessment of publication bias using funnel plots before and after adjustment with the trim-and-fill method. Studies positioned to the right of the pyramid indicate a larger effect size of the intervention, while those on the left show a smaller effect size. The upper panel (A) shows the original funnel plot where each individual study is represented as a blue circle. The lower panel (B) presents the funnel plot adjusted using the trim-and-fill method, which imputes a total of 59 additional studies (red triangles) to correct the asymmetry and estimate the true effect.

