Supplementary table 1a. Correlation matrix.

Correlations

			Publication year	RD	RD_Harm	Study size	Study duration	Placebo response	Active drug response	Quality score	ITT analysis	Parallel design	Outcome 50% or 30% pain reduction	Active placebo	Add-on treatment	Dropout during placebo	Dropout during active
Spearman's rho	Publication year	Correlation Coefficient	1.000	-.506**	-.263**	.282**	.275**	.195*	-.371**	.254**	.629**	.302**	.420**	-.137	.006	.066	-.142
		Sig. (2-tailed)	.	.000	.005	.004	.002	.046	.000	.005	.000	.001	.000	.129	.950	.493	.131
		N	128	105	112	105	128	105	105	119	106	128	105	125	111	112	114
	RD	Correlation Coefficient	-.506**	1.000	.229*	-.491**	-.433**	-.463**	.568**	-.341**	-.384**	-.301**	-.259**	.017	-.115	-.028	.174
		Sig. (2-tailed)	.000	.	.025	.000	.000	.000	.000	.001	.000	.002	.008	.863	.280	.789	.089
		N	105	105	95	105	105	105	105	97	93	105	105	104	90	95	96
	RD_Harm	Correlation Coefficient	-.263**	.229*	1.000	-.094	-.079	.067	.216*	-.161	-.161	-.008	.040	-.176	-.160	.099	.781**
		Sig. (2-tailed)	.005	.025	.	.367	.410	.518	.036	.104	.123	.934	.698	.066	.113	.298	.000
		N	112	95	112	95	112	95	95	103	93	112	95	110	99	112	112
	Study size	Correlation Coefficient	.282**	-.491**	-.094	1.000	.570**	.372**	-.262**	.172	.583**	.587**	.423**	.024	.006	.062	-.065
		Sig. (2-tailed)	.004	.000	.367	.	.000	.000	.007	.092	.000	.000	.000	.805	.952	.550	.532
		N	105	105	95	105	105	105	105	97	93	105	105	104	90	95	96
	Study duration	Correlation Coefficient	.275**	-.433**	-.079	.570**	1.000	.385**	-.161	.271**	.481**	.532**	.347**	.057	.039	.190*	.037
		Sig. (2-tailed)	.002	.000	.410	.000	.	.000	.100	.003	.000	.000	.000	.531	.684	.045	.697
		N	128	105	112	105	128	105	105	119	106	128	105	125	111	112	114
	Placebo response	Correlation Coefficient	.195*	-.463**	.067	.372**	.385**	1.000	.369**	.231*	.175	.311**	.102	.034	-.034	-.217*	-.085
		Sig. (2-tailed)	.046	.000	.518	.000	.000	.	.000	.023	.093	.001	.299	.729	.753	.034	.409
		N	105	105	95	105	105	105	105	97	93	105	105	104	90	95	96
	Active drug response	Correlation Coefficient	-.371**	.568**	.216*	-.262**	-.161	.369**	1.000	-.206*	-.262*	-.121	-.262**	.104	-.142	-.281**	-.007
		Sig. (2-tailed)	.000	.000	.036	.007	.100	.000	.	.043	.011	.218	.007	.295	.182	.006	.950
		N	105	105	95	105	105	105	105	97	93	105	105	104	90	95	96
	Quality score	Correlation Coefficient	.254**	-.341**	-.161	.172	.271**	.231*	-.206*	1.000	.244*	.127	.153	.035	.147	.108	-.009
		Sig. (2-tailed)	.005	.001	.104	.092	.003	.023	.043	.	.013	.170	.135	.709	.128	.279	.929
		N	119	97	103	97	119	97	97	119	103	119	97	116	109	103	105
	ITT analysis	Correlation Coefficient	.629**	-.384**	-.161	.583**	.481**	.175	-.262*	.244*	1.000	.670**	.531**	-.118	.140	.207*	-.011
		Sig. (2-tailed)	.000	.000	.123	.000	.000	.093	.011	.013	.	.000	.000	.234	.177	.046	.914
		N	106	93	93	93	106	93	93	103	106	106	93	104	95	93	93
	Parallel design	Correlation Coefficient	.302**	-.301**	-.008	.587**	.532**	.311**	-.121	.127	.670**	1.000	.537**	-.022	.032	.062	.025
		Sig. (2-tailed)	.001	.002	.934	.000	.000	.001	.218	.170	.000	.	.000	.807	.738	.518	.796
		N	128	105	112	105	128	105	105	119	106	128	105	125	111	112	114
	Outcome 50% or 30% pain reduction	Correlation Coefficient	.420**	-.259**	.040	.423**	.347**	.102	-.262**	.153	.531**	.537**	1.000	-.135	-.153	.061	.105
		Sig. (2-tailed)	.000	.008	.698	.000	.000	.299	.007	.135	.000	.000	.	.173	.151	.557	.308
		N	105	105	95	105	105	105	105	97	93	105	105	104	90	95	96
	Active placebo	Correlation Coefficient	-.137	.017	-.176	.024	.057	.034	.104	.035	-.118	-.022	-.135	1.000	.219*	-.277**	-.235*
		Sig. (2-tailed)	.129	.863	.066	.805	.531	.729	.295	.709	.234	.807	.173	.	.022	.003	.013
		N	125	104	110	104	125	104	104	116	104	125	104	125	109	110	112
	Add-on treatment	Correlation Coefficient	.006	-.115	-.160	.006	.039	-.034	-.142	.147	.140	.032	-.153	.219*	1.000	-.195	-.151
		Sig. (2-tailed)	.950	.280	.113	.952	.684	.753	.182	.128	.177	.738	.151	.022	.	.053	.136
		N	111	90	99	90	111	90	90	109	95	111	90	109	111	99	99
	Dropout during placebo	Correlation Coefficient	.066	-.028	.099	.062	.190*	-.217*	-.281**	.108	.207*	.062	.061	-.277**	-.195	1.000	.636**
		Sig. (2-tailed)	.493	.789	.298	.550	.045	.034	.006	.279	.046	.518	.557	.003	.053	.	.000
		N	112	95	112	95	112	95	95	103	93	112	95	110	99	112	112
	Dropout during active	Correlation Coefficient	-.142	.174	.781**	-.065	.037	-.085	-.007	-.009	-.011	.025	.105	-.235*	-.151	.636**	1.000
		Sig. (2-tailed)	.131	.089	.000	.532	.697	.409	.950	.929	.914	.796	.308	.013	.136	.000	.
		N	114	96	112	96	114	96	96	105	93	114	96	112	99	112	114

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

RD=Risk difference = 1/NNT (numbers needed to treat), RC_Harm = 1/NNH (numbers needed to harm).

Supplementary table 1b. Correlation matrix. Parallel group design studies

Correlations

			Publication year	RD	RD_Harm	Study size	Study duration	Placebo response	Active drug response	Quality score	ITT analysis	Outcome 50% or 30% pain reduction	Active placebo	Add-on treatment	Dropout during placebo	Dropout during active
Spearman's rho	Publication year	Correlation Coefficient	1.000	-.366**	-.245*	-.013	.206	.060	-.252*	.055	.327**	.269*	-.050	.081	-.135	-.275*
		Sig. (2-tailed)	.	.002	.025	.918	.058	.621	.035	.636	.007	.024	.651	.497	.223	.011
		N	85	70	83	70	85	70	70	76	67	70	84	72	83	84
	RD	Correlation Coefficient	-.366**	1.000	.237*	-.287*	-.355**	-.474**	.403**	-.299*	-.172	.038	-.192	-.237	.092	.251*
		Sig. (2-tailed)	.002	.	.050	.016	.003	.000	.001	.018	.190	.756	.111	.073	.453	.037
		N	70	70	69	70	70	70	70	62	60	70	70	58	69	69
	RD_Harm	Correlation Coefficient	-.245*	.237*	1.000	-.100	-.145	.077	.250*	-.234*	-.060	-.030	-.263*	-.200	.129	.805**
		Sig. (2-tailed)	.025	.050	.	.416	.192	.531	.038	.045	.631	.810	.017	.095	.244	.000
		N	83	69	83	69	83	69	69	74	66	69	82	71	83	83
	Study size	Correlation Coefficient	-.013	-.287*	-.100	1.000	.389**	.231	-.053	.014	.206	-.032	.265*	-.017	.015	-.086
		Sig. (2-tailed)	.918	.016	.416	.	.001	.054	.664	.912	.114	.791	.026	.900	.903	.483
		N	70	70	69	70	70	70	70	62	60	70	70	58	69	69
	Study duration	Correlation Coefficient	.206	-.355**	-.145	.389**	1.000	.213	-.146	.210	.263*	.051	.039	.126	.205	-.012
		Sig. (2-tailed)	.058	.003	.192	.001	.	.076	.229	.068	.032	.676	.727	.290	.063	.913
		N	85	70	83	70	85	70	70	76	67	70	84	72	83	84
	Placebo response	Correlation Coefficient	.060	-.474**	.077	.231	.213	1.000	.535**	.159	-.080	-.167	.078	-.308*	-.315**	-.145
		Sig. (2-tailed)	.621	.000	.531	.054	.076	.	.000	.216	.541	.168	.519	.018	.008	.234
		N	70	70	69	70	70	70	70	62	60	70	70	58	69	69
	Active drug response	Correlation Coefficient	-.252*	.403**	.250*	-.053	-.146	.535**	1.000	-.154	-.166	-.153	-.081	-.460**	-.291*	.020
		Sig. (2-tailed)	.035	.001	.038	.664	.229	.000	.	.231	.204	.205	.506	.000	.015	.870
		N	70	70	69	70	70	70	70	62	60	70	70	58	69	69
	Quality score	Correlation Coefficient	.055	-.299*	-.234*	.014	.210	.159	-.154	1.000	.180	-.094	.137	.367**	.017	-.131
		Sig. (2-tailed)	.636	.018	.045	.912	.068	.216	.231	.	.154	.469	.242	.002	.884	.261
		N	76	62	74	62	76	62	62	76	64	62	75	70	74	75
	ITT analysis	Correlation Coefficient	.327**	-.172	-.060	.206	.263*	-.080	-.166	.180	1.000	-.043	.089	.232	.114	-.009
		Sig. (2-tailed)	.007	.190	.631	.114	.032	.541	.204	.154	.	.747	.474	.077	.361	.943
		N	67	60	66	60	67	60	60	64	67	60	67	59	66	66
	Outcome 50% or 30% pain reduction	Correlation Coefficient	.269*	.038	-.030	-.032	.051	-.167	-.153	-.094	-.043	1.000	.110	-.082	-.053	-.052
		Sig. (2-tailed)	.024	.756	.810	.791	.676	.168	.205	.469	.747	.	.365	.543	.663	.670
		N	70	70	69	70	70	70	70	62	60	70	70	58	69	69
	Active placebo	Correlation Coefficient	-.050	-.192	-.263*	.265*	.039	.078	-.081	.137	.089	.110	1.000	.288*	-.430**	-.376**
		Sig. (2-tailed)	.651	.111	.017	.026	.727	.519	.506	.242	.474	.365	.	.015	.000	.000
		N	84	70	82	70	84	70	70	75	67	70	84	71	82	83
	Add-on treatment	Correlation Coefficient	.081	-.237	-.200	-.017	.126	-.308*	-.460**	.367**	.232	-.082	.288*	1.000	-.061	-.088
		Sig. (2-tailed)	.497	.073	.095	.900	.290	.018	.000	.002	.077	.543	.015	.	.615	.466
		N	72	58	71	58	72	58	58	70	59	58	71	72	71	71
	Dropout during placebo	Correlation Coefficient	-.135	.092	.129	.015	.205	-.315**	-.291*	.017	.114	-.053	-.430**	-.061	1.000	.635**
		Sig. (2-tailed)	.223	.453	.244	.903	.063	.008	.015	.884	.361	.663	.000	.615	.	.000
		N	83	69	83	69	83	69	69	74	66	69	82	71	83	83
	Dropout during active	Correlation Coefficient	-.275*	.251*	.805**	-.086	-.012	-.145	.020	-.131	-.009	-.052	-.376**	-.088	.635**	1.000
		Sig. (2-tailed)	.011	.037	.000	.483	.913	.234	.870	.261	.943	.670	.000	.466	.000	.
		N	84	69	83	69	84	69	69	75	66	69	83	71	83	84

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

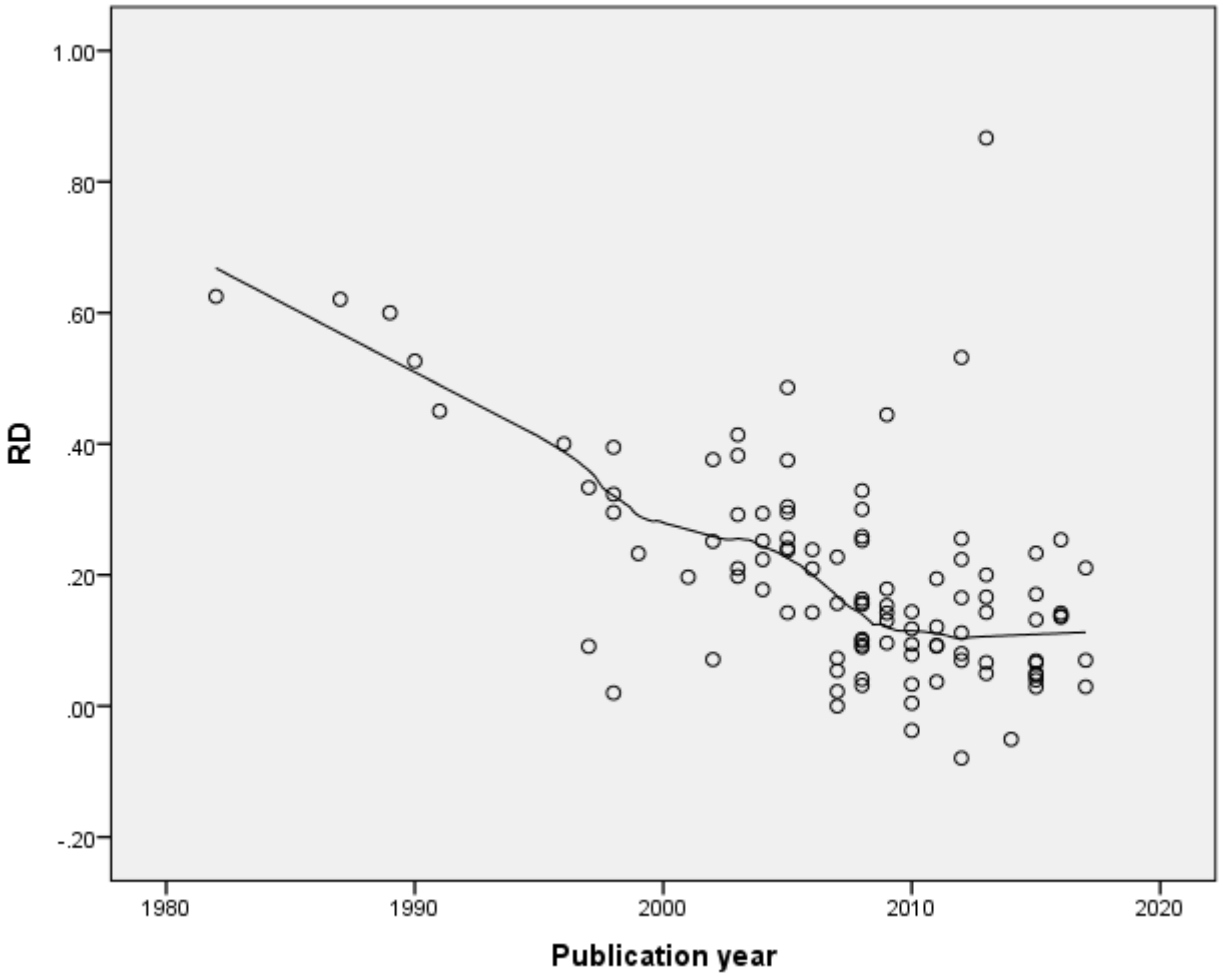
RD=Risk difference = 1/NNT (numbers needed to treat), RC_Harm = 1/NNH (numbers needed to harm).

Supplementary table 2. NNT for 50% or 30% pain reduction and Patient Global Impression of Change (PGIC).

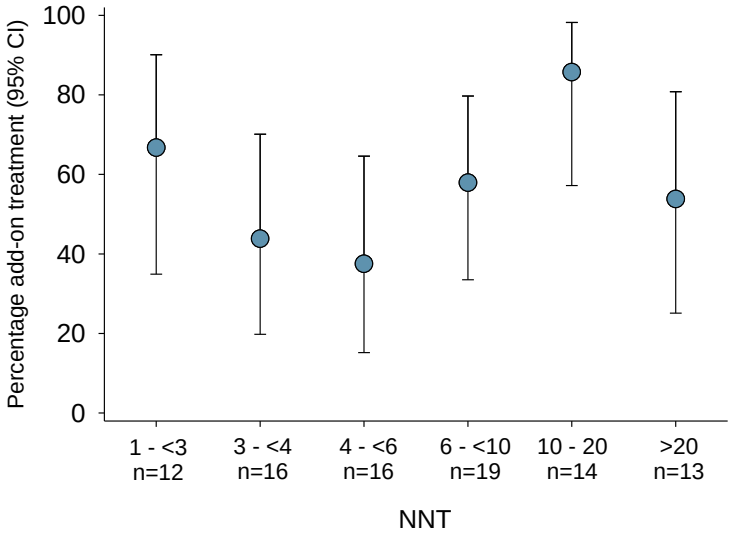
	NNT (50% or 30% pain reduction)	NNT (PGIC)
Pregabalin	7.0 (5.9-8.7)	5.4 (4.7-5.4)
Capsaicin 8% patch	12.0 (8.3-21.4)	8.3 (6.3-12.2)

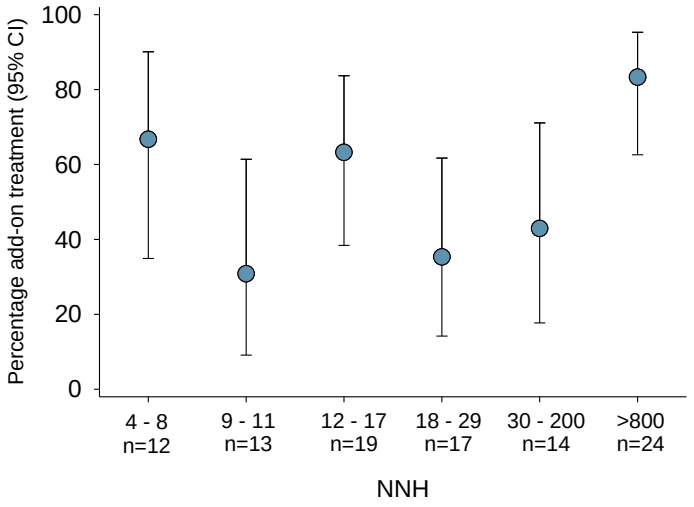
While not part of our planned analysis, the fact that studies where the NNT was based on 30% or 50% pain reduction had higher NNT compared to those that used pain relief encouraged further analysis. Pain relief scales were mainly used in early studies and very few studies reported both pain relief and 30% or 50% pain reduction, but for two drug classes several studies (pregabalin (n=17) and capsaicin 8% patches (n=7)) reported both 50% or 30% pain reduction and at least much (or alternatively at least some) improvement on the PGIC. Although PGIC is a combined outcome including also adverse effects, we compared NNT for pregabalin and capsaicin 8% trials and NNT was generally lower when based on PGIC (calculated based on the ITT population) than the NNT based on 50% or 30% pain reduction.

Supplementary figure 1.
The relation between the risk difference (RD) (the inverse of NNT(numbers needed to treat) in individual studies and publication year.
Line indicate a Loess fit line (50% of points of fit, Epanechnikov kernel).

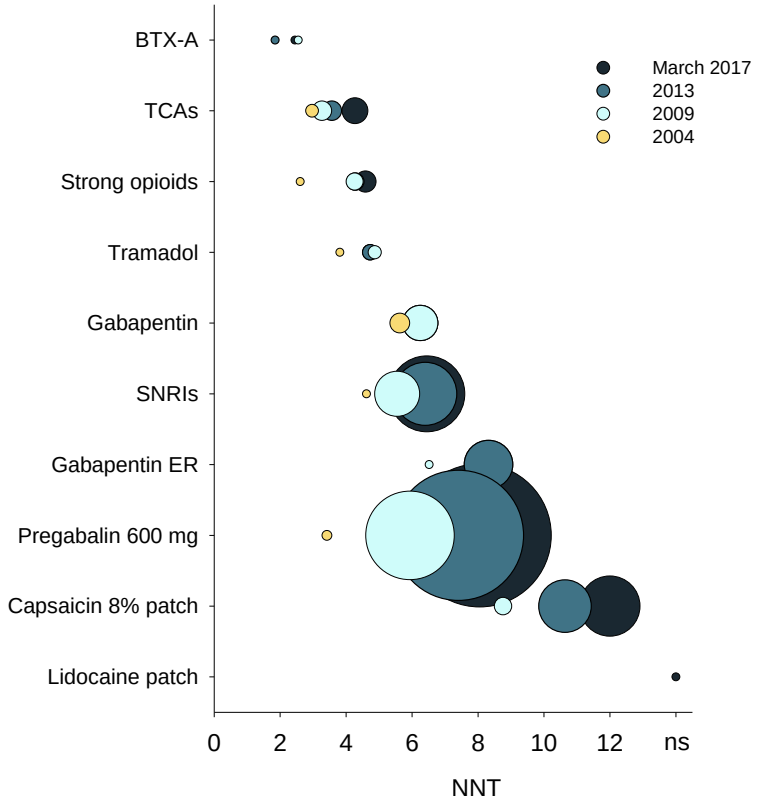


Supplementary figure 2.
No relation between numbers needed to treat (NNT) and numbers needed to harm (NNH) and percentage of studies with add-on treatment.

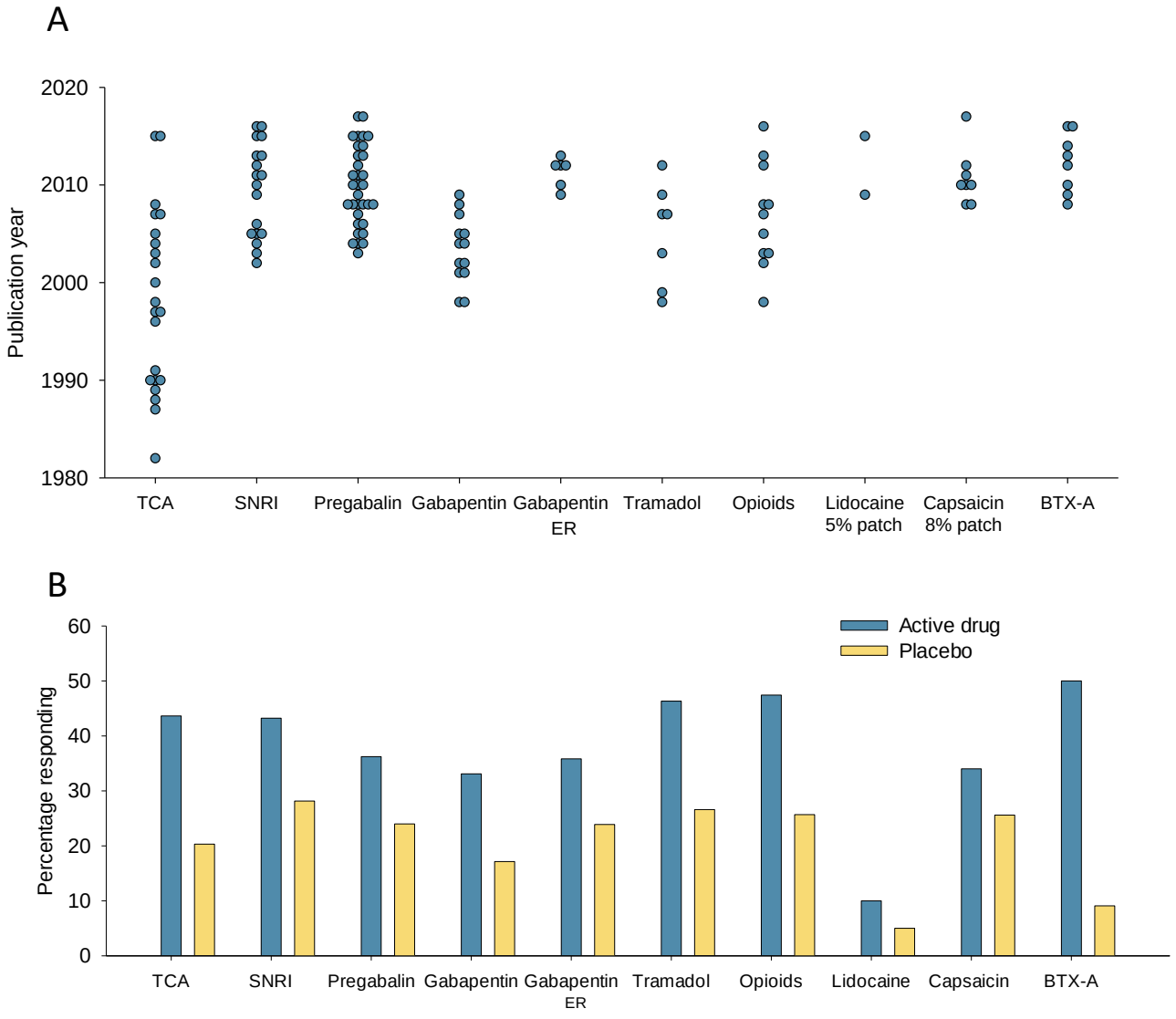




Supplementary figure 3.
Combined NNT values (fixed-effects Mantel-Haenszel method) for various drug classes in all central and peripheral neuropathic pain conditions for drug classes recommended for the treatment of neuropathic pain. For pregabalin, only trials in doses up to 600 mg were included.
The circle sizes indicate the relative number of patients who received active treatment drugs in studies for which dichotomous data were available.
NNT: Numbers needed to treat. BTX-A: botulinum toxin type A; TCAs: tricyclic antidepressants; SNRIs: serotonin-noradrenaline reuptake inhibitors; Gabapentin ER: Gabapentin extended release or gabapentin enacarbil.
Publication year for unpublished studies was arbitrarily set to one year after the results were posted.



Supplementary figure 4. Publication year for each study (A) and combined percentage responding to active drug and placebo (B) based on drug class.

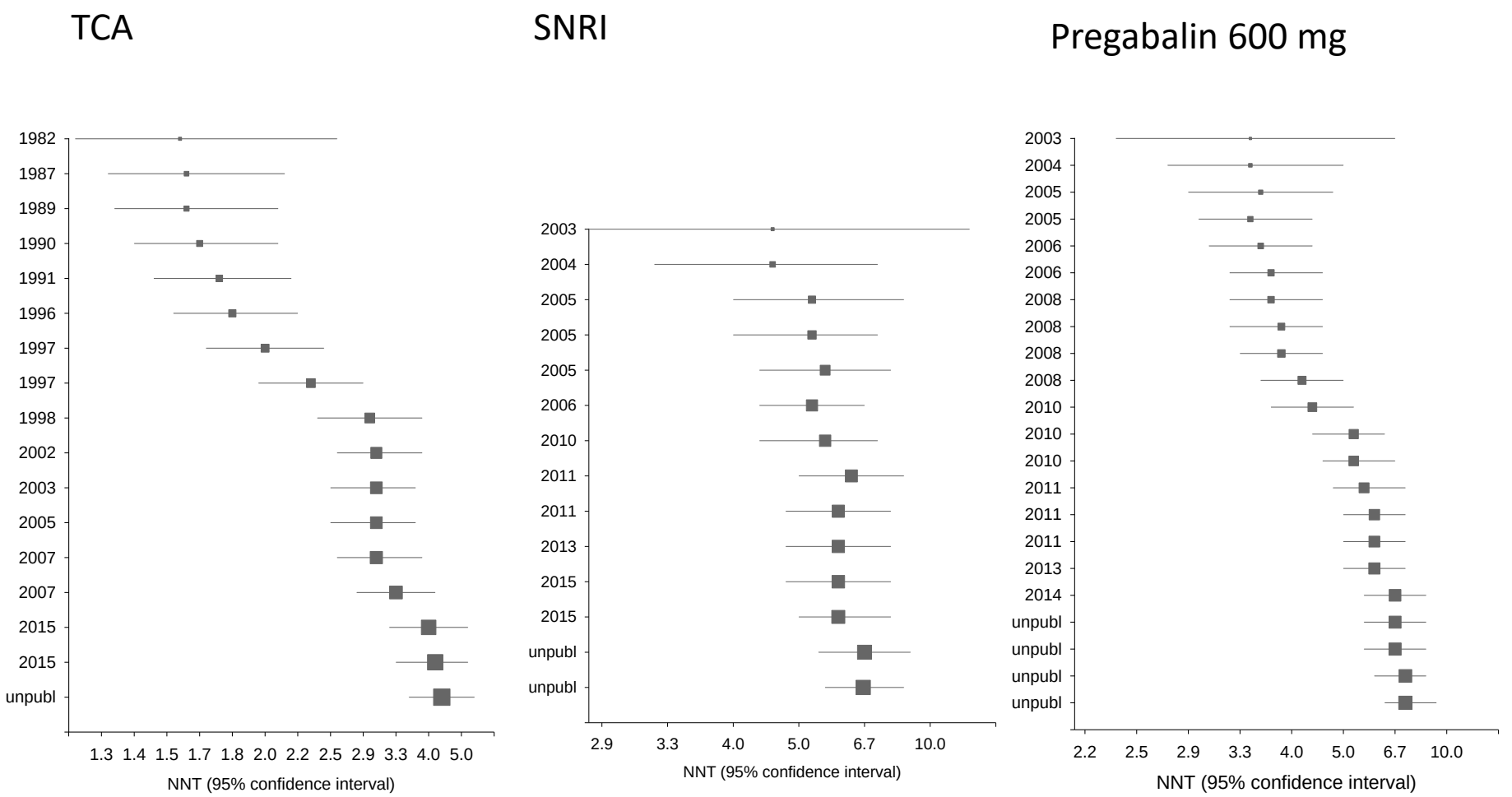


TCA=Tricyclic antidepressants, SNRIs=serotonin-noradrenaline reuptake inhibitors, BTX-A: botulinum toxin type A, Gabapentin ER: Gabapentin extended release or enacarbil

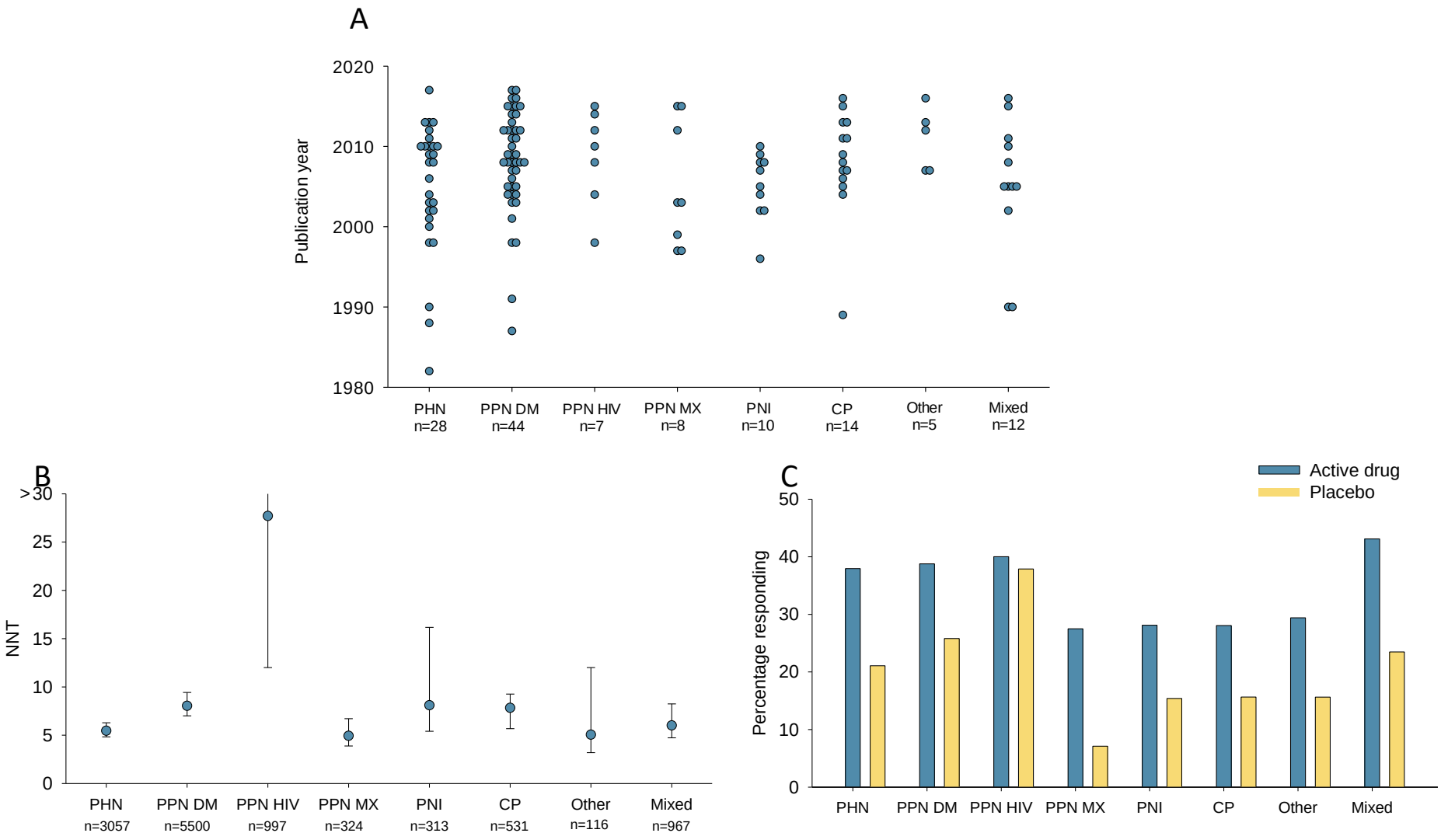
In figure A, each circle indicates one study (drug comparison to placebo).

In figure B, the y-axis indicates the combined percentage of patients responding to active drug or placebo within each drug class.

Supplementary figure 5. Cumulative NNT (random effect) of trials with tricyclic antidepressants (TCA), serotonin-noradrenaline reuptake inhibitors (SNRI), and pregabalin up to 600 mg daily.

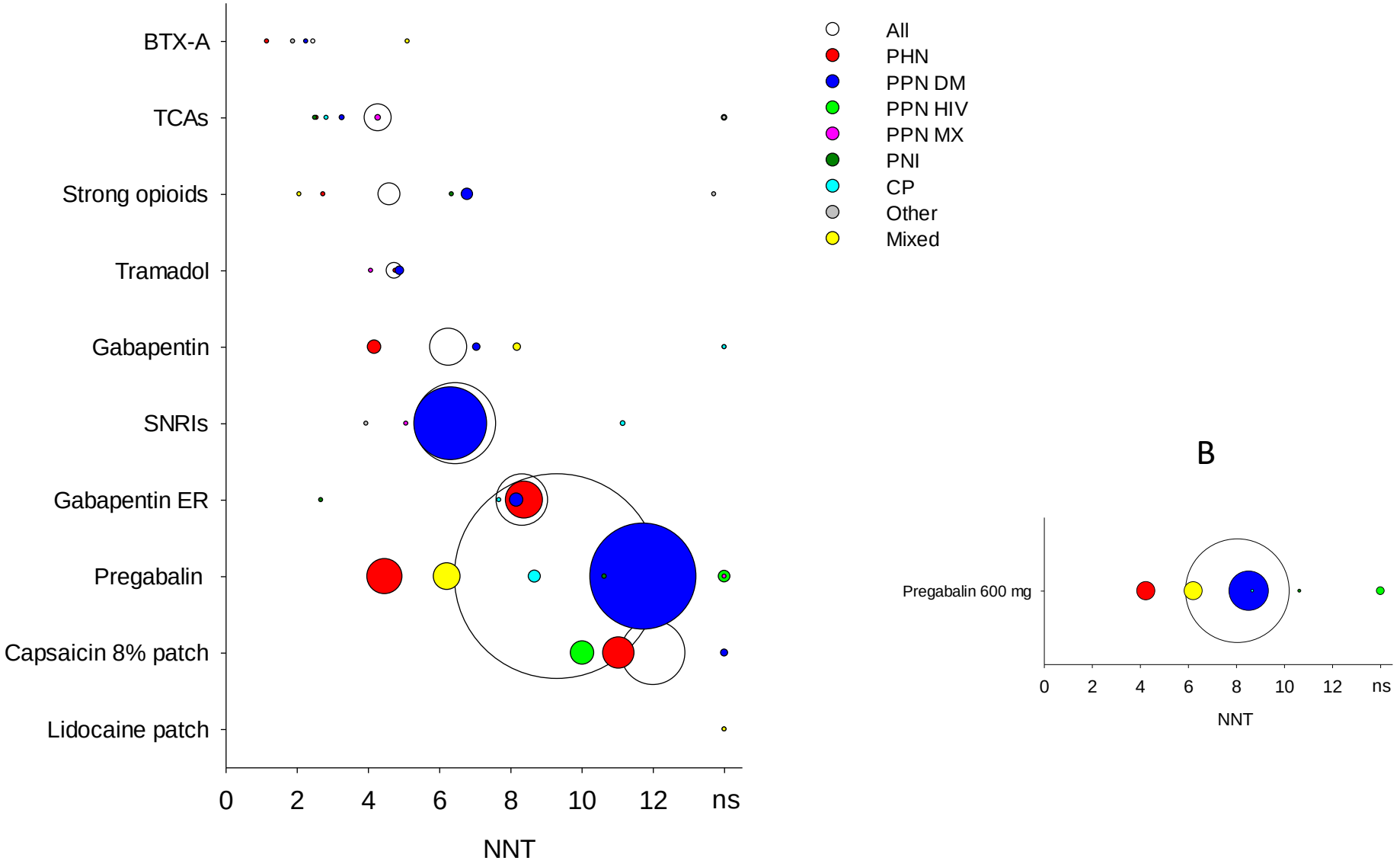


Supplementary figure 6. Publication year for each study (A), Combined NNT (B), and combined percentage responding to active drug and placebo (C) based on pain condition.



PHN=Postherpetic neuralgia, PPN=Painful polyneuropathy, DM=Diabetes mellitus, MX=Mixed, PNI=Peripheral nerve injury, CP=Central pain
In figure A, each circle indicates one study (drug comparison to placebo).
In figure B, the y-axis indicates the combined NNT=Numbers needed to treat (fixed-effects Mantel-Haenszel method) within each pain condition.
In figure C, the y-axis indicates the combined percentage of patients responding to active drug or placebo within each pain condition.

Supplementary figure 7. Combined NNT values (fixed-effects Mantel-Haenszel method) for various drug classes in different pain conditions. The circle sizes indicate the relative number of patients who received active treatment drugs in studies for which dichotomous data were available. In B, only studies with pregabalin up to 600 mg per day are included.



NNT: Numbers needed to treat. BTX-A: botulinum toxin type A; TCAs: tricyclic antidepressants; SNRIs: serotonin-noradrenaline reuptake inhibitors; Gabapentin ER: Gabapentin extended release or gabapentin enacarbil. PHN=Postherpetic neuralgia, PPN=Painful polyneuropathy, DM=Diabetes mellitus, MX=Mixed, PNI=Peripheral nerve injury, CP=Central pain

References for additional 20 comparisons

1. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016;15:555-65.
2. Brown TR, Slee A. A randomized placebo-controlled trial of duloxetine for central pain in multiple sclerosis. Int J MS Care 2015;17:83-9.
3. Chappell AS, Iyengar S, Lobo ED, Prucka WR. Results from clinical trials of a selective ionotropic glutamate receptor 5 (iGluR5) antagonist, LY5454694 tosylate, in 2 chronic pain conditions. Pain 2014;155:1140-9.
4. Demant DT, Lund K, Finnerup NB, Vollert J, Maier C, Segerdahl MS, et al. Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. Pain 2015;156:2234-44.
5. Dinat N, Marinda E, Moch S, Rice AS, Kamerman PR. Randomized, Double-Blind, Crossover Trial of Amitriptyline for Analgesia in Painful HIV-Associated Sensory Neuropathy. PLoS One 2015;10:e0126297.
6. Gao Y, Guo X, Han P, Li Q, Yang G, Qu S, et al. Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract 2015;69:957-66.
7. Ghasemi M, Ansari M, Basiri K, Shaigannejad V. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci 2014;19:106-11.
8. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol 2016;79:569-78.
9+10. Holbech JV, Bach FW, Finnerup NB, Brosen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain. 2015;156:958-66.
11. Huffman C, Stacey BR, Tuchman M, Burbridge C, Li C, Parsons B, et al. Efficacy and Safety of Pregabalin in the Treatment of Patients With Painful Diabetic Peripheral Neuropathy and Pain on Walking. Clin J Pain 2015;31:946-58.
12. Liu Q, Chen H, Xi L, Hong Z, He L, Fu Y, et al. A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Pregabalin for Postherpetic Neuralgia in a Population of Chinese Patients. Pain Pract 2017;17:62-9.
13. Mu Y, Liu X, Li Q, Chen K, Liu Y, Lv X, et al. Efficacy and safety of pregabalin for painful diabetic peripheral neuropathy in a population of Chinese patients: A randomized placebo-controlled trial. J Diabetes 2018;10(3):256-65 (also: Clinicaltrials.gov NCT01332149).
14. Raskin P, Huffman C, Yurkewicz L, Pauer L, Scavone JM, Yang R, et al. Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy Using an NSAID for Other Pain Conditions: A Double-Blind Crossover Study. Clin J Pain 2016;32:203-10.
15. Schukro RP, Oehmke MJ, Geroldinger A, Heinze G, Kress HG, Pramhas S. Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component: A Randomized, Double-blind, Placebo-controlled Crossover Trial. Anesthesiology 2016;124:150-8.
16. Simpson DM, Rice AS, Emir B, Landen J, Semel D, Chew ML, et al. A randomized, double-blind, placebo-controlled trial and open-label extension study to evaluate the efficacy and safety of pregabalin in the treatment of neuropathic pain associated with human immunodeficiency virus neuropathy. Pain 2014;155:1943-54.
17. Simpson RW, Wlodarczyk JH. Transdermal Buprenorphine Relieves Neuropathic Pain: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial in Diabetic Peripheral Neuropathic Pain. Diabetes Care 2016;39:1493-500.
18. Simpson DM, Robinson-Papp J, Van J, Stoker M, Jacobs H, Snijder RJ, et al. Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. J Pain 2017;18:42-53.
19. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain 2015;156:2013-20.
20. Clinicaltrials.gov NCT00603265. Safety and Efficacy Study of ADL5859 in Participants With Neuropathic Pain Associated With Diabetic Peripheral Neuropathy