ORIGINAL ARTICLE

The Numbers Needed to Treat for Neurological Disorders

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ABSTRACT: ***Background:*** Numerous therapeutic interventions have been developed in the neurosciences. Clinicians need summary measures about efficacy of therapies that derive from the best available evidence, and that can be readily extrapolated to clinical practice. The number needed to treat (NNT) is intuitive and clinically applicable. We provide clinicians with a single source that summarizes important therapies in the main neurological and neurosurgical areas. ***Methods:*** Critically appraised evidence about therapies in the neurosciences was obtained from meta-analyses in all neurosciences groups in the Cochrane library, and from critically appraised topics at the University of Western Ontario. Therapies were included if they were deemed relevant and if outcomes were dichotomous. For each therapy, we obtained absolute risk differences and their 95% confidence intervals (CI), the corresponding NNTs, control and experimental event rates, and the time-frame of the outcome assessment. ***Results:*** We assembled a table of NNTs for 87 interventions in ten disease categories, deriving from meta-analyses (70%) or randomized controlled trials (30%), and assessing surgical interventions (7%), procedures (9%) or pharmacological treatments (84%). The NNTs varied widely, ranging from 1 in the use of epidural blood patch for post-dural puncture headache to 4608 for meningococcal vaccination. Preventative interventions had substantially larger NNTs. Time-frames were inappropriately short for many chronic conditions. ***Conclusions:*** Large collections of NNTs provide useful, updateable summaries of therapeutic effects in the neurosciences, an increasingly interventional clinical field.

RÉSUMÉ: Le nombre de patients devant être traités pour les maladies neurologiques. ***Contexte:*** De nombreux traitements ont été développés en neurosciences. Les cliniciens ont besoin d'une synthèse fondée sur les meilleures données sur l'efficacité de ces traitements, qui peut être facilement appliquée en pratique clinique. Nous fournissons aux cliniciens une source unique qui fait un sommaire des traitements importants dans les principaux domaines de la neurologie et de la neurochirurgie. ***Méthodes:*** Des données ayant fait l'objet d'une évaluation critique ont été tirées de méta-analyses en neurosciences dans la bibliothèque Cochrane et de sujets ayant fait l'objet d'une évaluation critique à l'Université Western Ontario. Les traitements n'ont été inclus que s'ils étaient considérés pertinents et si les résultats présentaient une dichotomie. Pour chaque traitement, nous avons présentons les différences du risque absolu ainsi que l'intervalle de confiance de 95%, le nombre de patients devant être traités (NPT), le taux d'incidents thérapeutiques dans le groupe témoin et le groupe expérimental et la durée de l'étude. ***Résultats:*** Nous fournissons une table de NPT pour 87 interventions dans 10 catégories de maladies. Ces données proviennent de méta-analyses (70%) ou d'études contrôlées randomisées (30%) et évaluent des interventions chirurgicales (7%), des techniques (9%) ou des traitements pharmacologiques (84%). Les NPT variaient considérablement, allant de 1 pour le blood-patch épidural pour traiter la céphalée suite à une brèche de la dure-mère, à 4608 pour la vaccination anti-méningococcique. Les interventions préventives comportaient des NPT considérablement plus élevés. La durée des études sur plusieurs maladies était trop courte. ***Conclusions:*** Un recueil de NPT fournit un sommaire utile, qui peut être mis à jour, sur les effets des traitements en neurosciences, un champ clinique où il y a de plus en plus d'interventions.

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Clinicians making decisions about the treatment of individual patients need summary measures about therapies that derive from the best available evidence, and that can be readily extrapolated to clinical practice. The number needed to treat (NNT) refers to the number of patients that need to receive a therapy to prevent one bad outcome, or obtain one good outcome. The NNT is one of the most intuitive and clinically applicable metrics of effectiveness. Clinicians will more readily make sense of evidence that states its effect in terms of the NNT, than that expressed as a relative risk or an odds ratio. For a more detailed discussion of the advantages, limitations and clinical applications of common measures of therapeutic effect encountered in the literature, refer to a preceding companion review article.[1]

Tapping on evidence derived from randomized controlled trials and meta-analyses, we assembled the results of a large number of therapeutic interventions in the neurosciences, expressed as NNTs. Our aim was to provide clinicians with a single source that summarized therapies in the main neurological and neurosurgical areas.

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Methods

We used two approaches to find methodologically sound therapeutic research in the neurosciences. We searched the Cochrane database of systematic reviews (http://www.thecochranelibrary.com) for meta-analyses of interventions in all Cochrane groups with neurological or neurosurgical content (Back, Dementia and cognitive improvement, Depression, Anxiety and neurosis, Developmental psychosocial and learning problems, Epilepsy, Movement disorders, Multiple sclerosis, Musculoskeletal, Neuromuscular, Pain, and Stroke). Meta-analyses were included if one of the two authors (MB, SW) deemed them relevant for the neurosciences, if outcomes assessed were dichotomous and if they contained therapeutic information important for clinicians. We also used data from individual therapeutic trials previously assessed in the Evidence Based Neurology Programme at the University of Western Ontario and resulting in Critically Appraised Topics about therapy (http://www.uwo.ca/cns/ebn/). We included reports from 1986 to 2004. Priority was given to high-quality meta-analyses; individual randomized trials were included only when a meta-analysis was not available.

We obtained NNTs and 95% confidence intervals (95%CIs) for each intervention by computing the inverse of the absolute risk difference and its corresponding 95%CI. For data derived from meta-analyses, we used the Cochrane Library's default fixed effects model for pooling absolute risk differences. For consistency, all outcomes were expressed as positive events. The NNTs expressed the effect of treatment on improving the chance of the positive event, calculated as the inverse of the experimental event rate (EER) subtracted from the control event rate (CER).

For each intervention we reported the nature of the intervention, its comparator or control group, the specific outcome assessed, the time at which outcomes were assessed, the pooled control and experimental event rates, and the pooled NNT and its 95%CI.

Results

In total, we included 87 therapeutic interventions in the following areas: Cognitive and behavorial disorders 5 (6%), Demyelinating disease 7 (8%), Epilepsy 20 (23%), Headache and pain 13 (15%), Infection 5 (6%), Movement disorders 5 (6%), Neuromuscular disorders 6 (7%), Neurooncology 2 (2%), Stroke and neurovascular disorders 20 (23%), Other disorders 4 (4%). Fifty-six (70%) interventions were derived from meta-analyses and 24 (30%) from individual randomized controlled trials. Two thirds of the interventions used a placebo control, whereas the comparator in the remaining third was an active control or comparison to usual or best medical therapy. Six (7%) were surgical interventions, 8 (9%) were procedures, and 73 (84%) were pharmacological treatments. The time of outcome assessment varied widely, ranging from 30 minutes (migraine therapy) to six years (stroke and neurovascular disorders). Twenty therapies, indicated in the Table by the presence of an asterix beside the relevant NNT, were not statistically beneficial by the NNT approach (95%CIs included infinitive or negative numbers [possibility of harm]). The NNTs also varied enormously across interventions, ranging from 1 in the use of epidural blood patch for post-dural puncture headache to 4608 for the meningococcal serogroup A vaccine.

Discussion

The large number of interventions and NNTs compiled in this article attests to the transformation of the clinical neurosciences into highly interventional fields with very effective therapies. Several additional observations can be made about this collection of NNTs for neurological disorders. Relatively short time-spans for outcome assessment were used for some chronic neurological disorders, such as Epilepsy, Alzheimer's or Parkinson's disease. Longer outcomes provide more clinically meaningful information in chronic progressive disorders. There was a paucity of surgical or interventional data derived from RCTs. Only six reports pertained to these therapies, as compared to 73 medical interventions. Hopefully, the advent of numerous interventional and "miminimally invasive" procedures will be accompanied by a corresponding increase in robust evidence about their efficacy. As expected, preventative interventions required a much larger NNT than corrective or curative interventions. In the Heart Outcomes Prevention Evaluation (HOPE) study for example,[2] 67 patients with hypertension and a previous stroke were treated to prevent a single stroke, whereas only three patients had to be treated with anticonvulsants to relieve neuropathic pain in one,[3] and seizures were controlled in one of every two patients that underwent temporal lobe surgery for epilepsy.[4]

Because NNTs and other measures of effectiveness are meaningless in the absence of the time-frame when the outcome was assessed, we provided this information for each intervention. Clinicians dealing with patients whose outcome time-frame differs, can easily adjust the NNT to the desired time-frame, assuming that the relative effect of the intervention is more or less constant within the time-frame of interest. For example, the NNT for clinical improvement of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) treated with steroids was 3.1 (95%CI 1.6, 199) at 12 weeks.[5] The NNT at 24 weeks can be calculated simply as follows: $NNT_S = NNT_T \times T / S$, where NNT_S = the NNT at the desired duration of follow-up (S) and NNT_T = the NNT for the duration of follow-up in the trial (T).[1] In the above example, therefore, $NNT_{24\ weeks} = NNT_{12\ weeks} \times 12/24 = 3.1 \times 0.5 = 1.6$ (or 2, if we round upwards). That is, a longer period of observation results in a smaller NNT, assuming that the relative risk of the outcome event, and the relative effect of the intervention is constant over time.[1]

The control event rate is also important for clinical application of the data in the Table. The baseline risk for events in our patients often differs from that in clinical trials. We can adjust the baseline risk to obtain an adjusted NNT.[1] For example, if an individual patient's risk of a poor outcome after cardiac arrest is felt to be twice that of patients enrolled in the trials assessing the effect of hypothermia,[6,7] the adjusted NNT is calculated as: $NNT_{Patient} = NNT_{Trial} / F = 6.4 / 2 = 3.2$, where F is the adjusted baseline risk of the individual patient.[1] That is, higher baseline risks result in lower NNTs. This assumes that the relative effectiveness of the intervention remains more or less constant across a range of baseline risks, an assumption that may not always be correct. Although these adjustments to NNTs make

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Table: The NNTs of therapies for common neurological disorders by category

Cognitive – Behavioral Disorders									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
Alzheimer's disease	Donepezil (8)	Placebo	Improved CBIC-Plus or CGI	6 months	0.13	0.25	0.12	8.4	(5.9, 14.5)
	Galantamine (9)	Placebo	No change or improvement in global rating of change	6 months	0.37	0.51	0.13	7.4	(5.3, 12.6)
			Increase in ADAS-Cog (>4 points)	6 months	0.16	0.34	0.18	5.5	(3.9, 8.8)
	Rivastigmine (10)	Placebo	Improved CBIC-Plus	6 months	0.20	0.27	0.07	14.3	(9.2, 32.2)
			Increase in ADAS-Cog (>4 points)	6 months	0.11	0.15	0.04	24.1	(15.5, 54.6)
Alzheimer's disease or multi-infarct dementia, mild to moderate severity (11)	Gingko biloba	Placebo	Improved CGI	6 months	0.55	0.72	0.18	5.7	(3.1, 36.7)
Hepatic encephalopathy (12)	Flumazenil infusion	Placebo	Improvement in hepatic encephalopathy	1.5 hours to 4 weeks	0.06	0.31	0.25	3.6	(2.7, 5.1)
			Survival	1.5 hours to 4 weeks	0.92	0.93	0.01	123.6*	(-19.3, 14.7)
Demyelinating Disorders									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
First demyelinating event (optic nerve, spinal cord, brain stem or cerebellar) (13, 14)	Interferon beta-1a	Placebo	Did not develop clinically definite multiple sclerosis	2 years	0.55	0.66	0.11	9.1	(4.6, 499.7)
First demyelinating event, Optic neuritis subgroup (13, 15)	Interferon beta-1a	Placebo	Did not develop clinically definite multiple sclerosis	3 years	0.63	0.72	0.09	11.5*	(-22.1, 4.6)
Optic neuritis (16, 17, 18)	Steroids	Placebo	Visual recovery	1 month	0.22	0.30	0.08	11.8	(6.7, 47.9)
				6 months	0.61	0.62	0.01	154.8*	(-15.4, 12.9)
	Intravenous Methyl-prednisolone	Placebo	Did not develop clinically definite multiple sclerosis	2 years	0.82	0.92	0.10	10.0	(5.5, 56.4)
				5 years	0.69	0.73	0.04	25.7*	(-13.9, 6.7)
Multiple sclerosis, acute exacerbation (19)	Methyl-prednisolone	Placebo	Improved	5 weeks	0.39	0.64	0.25	4.1	(2.8, 7.1)
Multiple sclerosis, relapsing-remitting	Interferon beta-1a, beta-1b or alpha-2a (20,21)	Placebo	No exacerbations	1 year	0.32	0.49	0.18	5.6	(4.0, 9.6)
				2 years	0.30	0.45	0.14	7.0	(4.9, 12.2)
			No disease progression	2 years	0.71	0.80	0.09	10.9	(6.8, 27.4)
	Glatiramer acetate (22,23)	Placebo	No exacerbations	2 years	0.27	0.34	0.07	15.1*	(-21.2, 5.6)
			No disease progression	2 years	0.68	0.82	0.13	7.5	(4.2, 36.3)

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Epilepsy/Seizures									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI) [c]**
Alcohol withdrawal (24)	Benzodiaze-pines	Placebo	No seizures	2-5 days	0.91	0.99	0.08	12.3	(8.2, 24.8)
			No delirium	2-5 days	0.94	0.98	0.04	24.0	(12.4, 391.0)
Drug-resistant partial epilepsy	Gabapentin, add-on (25)	Placebo	50% reduction seizure frequency	12-14 weeks	0.12	0.20	0.09	11.5	(7.6, 23.7)
	Lamotrigine, add-on, any dose (26)	Placebo	50% reduction seizure frequency	8-24 weeks	0.11	0.25	0.15	6.8	(5.0, 11.0)
	Levetiracetam, add-on, any dose (27)	Placebo	50% reduction seizure frequency	12-24 weeks	0.09	0.35	0.26	3.9	(3.3, 4.9)
	Oxcarbazepine, add-on, any dose (28)	Placebo	50% reduction seizure frequency	14-24 weeks	0.17	0.39	0.24	4.2	(3.4, 5.4)
	Tiagabine, add-on (29)	Placebo	50% reduction seizure frequency	12-22 weeks	0.07	0.22	0.15	6.5	(5.0, 9.2)
	Topiramate, add-on (30)	Placebo	50% reduction seizure frequency	11-19 weeks	0.13	0.45	0.31	3.2	(2.7, 3.9)
	Zonisamide, add-on, any dose (31)	Placebo	50% reduction seizure frequency	12 weeks	0.11	0.27	0.16	6.3	(4.5, 10.6)
	Vagus nerve stimulation, high level (32)	Vagus nerve stimulation, low level	50% reduction seizure frequency	12-16 weeks	0.15	0.26	0.11	9.3	(5.1, 57.7)
First unprovoked generalized seizure (33, 34)	Immediate treatment with phenytoin, phenobarbital, valproate or carbamazepine	Treatment only after seizure recurrence	Seizure free	2 years	0.49	0.75	0.26	4	(3, 6)
Pre-eclampsia	Magnesium sulfate	Placebo (35)	No eclampsia	24 hours after delivery	0.98	0.99	0.01	89.4	(65.2, 142.4)
		Phenytoin (35)	No eclampsia	24 hours after delivery	0.99	1.00	0.01	113.2	(70.0, 295.6)
Eclampsia	Magnesium sulfate	Diazepam (36)	No recurrence of convulsions	24 hours after delivery	0.77	0.90	0.13	7.5	(5.8, 10.4)
		Phenytoin (37)	No recurrence of convulsions	24 hours after delivery	0.81	0.94	0.13	7.7	(5.8, 11.4)
Head injury (38)	Prophylactic anti-epileptic drug	Placebo	Seizure free	1 week	0.85	0.95	0.10	9.8	(7.1, 16.0)
				Late seizures	0.85	0.87	0.02	62.7*	(-43.2, 18.2)
Head Injury (39)	High dose mannitol	Conventional dose mannitol	No, mild or moderate disability (GOS)	6 months	0.40	0.66	0.25	4.0	(2.8, 6.8)
Infantile spasms (40)	Vigabatrin	Placebo	Cessation of spasms	5 days	0.10	0.35	0.25	4.0	(2.0, 328.1)
	ACTH	Prednisone	Cessation of spasms	2 weeks	0.31	0.67	0.36	2.8	(1.6, 9.3)
		Vigabatrin	Cessation of spasms	20 days	0.48	0.74	0.26	3.9*	(-38.7, 1.8)
Seizure free for 2 years on antiepileptic medication (41)	Continue antiepileptic medication	Withdraw antiepileptic medication	Seizure free	2 years	0.59	0.78	0.19	5.2	(4.0, 7.4)
Temporal lobe epilepsy (4)	Surgery	Best medical therapy	Seizure free	1 year	0.03	0.38	0.35	2.9	(2.0, 5.2)
			Free of seizures impairing awareness	1 year	0.08	0.58	0.50	2.0	(1.5, 3.1)

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Headache / Pain									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI) [c]**
Diabetic neuropathic pain	Carbamazepine (3)	Placebo	Decreased pain intensity	6 weeks	0.63	0.93	0.33	3.0	(1.9, 7.4)
	Gabapentin (3, 42)	Placebo	Moderate to marked improvement in daily pain scores	8 weeks	0.33	0.59	0.27	3.8	(2.4, 8.7)
	Tricyclic antidepressants (43)	Placebo	Improvement in daily pain scores	6-12 weeks	0.46	0.79	0.33	3.0	(2.3, 4.3)
Low back pain	Benzodiaze-pines (44)	Placebo	Pain relief	8-14 days	0.30	0.52	0.22	4.6	(2.7, 16.8)
			Global efficacy (patient)	8-14 days	0.48	0.67	0.21	4.8	(2.7, 18.2)
	NSAIDs (45)	Placebo	Global Improvement	2-3 weeks	0.54	0.66	0.13	8.0	(4.8, 23.1)
Migraine	Eletriptan (46)	Placebo	Headache response	0.5 hour	0.04	0.10	0.05	19.3	(13.3, 35.0)
				4 hours	0.30	0.72	0.42	2.4	(2.1, 2.8)
			Pain-free	0.5 hours	0.00	0.01	0.01	70.1	(46.6, 140.8)
				4 hours	0.13	0.45	0.32	3.1	(2.6, 3.8)
			Sustained-relief	24 hours	0.18	0.53	0.35	2.9	(2.6, 3.2)
	Sumatriptan (47)	Placebo	Pain-free	2 hours	0.09	0.29	0.20	5.0	(4.3, 5.9)
			Headache relief	2 hours	0.29	0.60	0.29	3.4	(3.1, 3.9)
Neuropathic pain (3)	All anti-epileptic drugs	Placebo	Improvement in daily pain	6 days to 46 weeks	0.23	0.57	0.34	2.9	(2.5, 3.5)
Post-dural puncture headache (48)	Epidural blood patch	Placebo	No persistent severe postural headache	24 hours	0.00	1.00	1.00	1.00	(1.0, 1.0)
Post-herpetic neuralgia (49)	Gabapentin	Placebo	Moderate to marked improvement in daily pain scores	8 weeks	0.12	0.43	0.31	3.2	(2.4, 4.9)
	Tricyclic antidepressants (43)	Placebo	Improvement in daily pain scores	6-12 weeks	0.26	0.45	0.19	5.2	(2.9, 30.1)
Trigeminal neuralgia (3)	Carbamazepine	Placebo	Good or excellent response	6 days to 8 weeks	0.18	0.57	0.38	2.6	(2.2, 3.3)
	Lamotrigine	Placebo	Good or excellent response	2 weeks	0.57	0.77	0.20	5.1*	(-6.8, 1.8)
Infections									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI) [c]**
Bacterial meningitis (50)	Dexamethasone	Placebo	Favorable outcome (GOS 5)	8 weeks	0.75	0.85	0.10	9.7	(5.2, 72.9)
			Alive	8 weeks	0.85	0.93	0.08	13.2	(6.9, 177.1)
Cystercicosis (51)	Cysticidal therapy	Placebo	No cyst persistence	<6 months	0.36	0.39	0.11	9.1*	(-296, 4.5)
Herpes Simplex Encephalitis (52)	Acyclovir	Vidarabine	Normal function	6 months	0.14	0.38	0.24	4.2	(2.3, 25.5)
			Alive	6 months	0.49	0.81	0.33	3.1	(1.9, 8.6)
Children and high risk populations (53)	Serogroup A polysaccharide vaccine	No vaccine	No meningococcal meningitis	1-3 years	0.9998	1.0000	0.0002	4608.5	(3806.1, 5839.6)
Tuberculous meningitis (54)	Any steroid	Placebo	Alive, no disabling deficits	3-6 months	0.55	0.74	0.19	5.3	(3.0, 19.7)

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Movement Disorders									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
Neuroleptic-induced acute akathisia (55)	Clonazepam	Placebo	No akathisia symptoms	14 days	0.15	1.00	0.87	1.1	(0.9, 1.5)
Parkinson's disease, early (56)	Ropinirole	L-Dopa	Free from dyskinesias	5 years	0.05	0.36	0.31	3.2	(2.4, 4.8)
L-Dopa induced complications in Parkinson's disease	Pergolide (57)	Bromocriptine	CGI (moderate or marked improvement)	2-12 weeks	0.30	0.43	0.13	7.7	(4.2, 43.6)
	Ropinirole (58)	Placebo	CGI	26 weeks	0.31	0.59	0.27	3.6	(2.3, 8.6)
	Pramipexole (59)	Placebo	CGI (satisfactory or good improvement)	11 weeks	0.32	0.76	0.45	2.2	(1.6, 4.0)
Neuromuscular disorders									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
Amyotophic Lateral Sclerosis (60)	Riluzole	Placebo	Survival	1 year	0.56	0.66	0.10	10.1	(6.0, 31.1)
Carpal Tunnel (61)	Surgical treatment	No surgery	Improvement in symptoms	6 months	0.64	0.83	0.19	5.3	(3.2, 16.8)
Chronic inflammatory demyelinating polyneuropathy (62)	Intravenous immuno-globulin	Placebo	1 point or greater improvement on Rankin scale	6 weeks	0.12	0.31	0.19	5.1	(2.8, 29.4)
			Significant improvement on disability scale	4 weeks	0.15	0.47	0.33	3.0	(2.1, 5.3)
Chronic inflammatory demyelinating polyneuropathy (5)	Steroids	Placebo	Improved	12 weeks	0.31	0.63	0.32	3.1	(1.6, 199.1)
Guillain Barre Syndrome (63)	Plasma exchange	Placebo	Improvement in disability grade	4 weeks	0.35	0.57	0.22	4.5	(3.3, 6.9)
			No artificial ventilation	4 weeks	0.73	0.86	0.13	7.9	(5.3, 15.6)
Guillain Barre Syndrome (64)	Intravenous immuno-globulin	Plasma exchange	Functional improvement	4 weeks	0.34	0.53	0.18	5.4	(2.9, 36.9)
			No artificial ventilation	2 weeks	0.58	0.73	0.15	6.5	(3.3, 414.3)
Neurooncology									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
Single brain metastasis (65,66)	Resection + Radiotherapy	Radiotherapy	No recurrence	1 year	0.48	0.80	0.32	3.1	(1.7, 15.5)
			Survival	1 year	0.23	0.41	0.18	5.5*	(-22.4, 2.5)
Small cell lung cancer, complete remission (67)	Prophylactic brain irradiation	No radiotherapy	No brain metastases	3.5-18 years	0.51	0.73	0.21	4.7	(3.7, 6.6)
			Survival	3.5-18 years	0.88	0.84	-0.04	-22.6*	(-12.0, 303.5)
Stroke / Neurovascular disorders									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI)[c]**
Subarachnoid hemmorhage (68)	Oral nimodipine	Placebo	Good outcome	1-6 months	0.71	0.76	0.05	19.5	(11.6, 60.6)
			No clinical signs of delayed cerebral ischemia	1-6 months	0.60	0.73	0.13	7.5	(5.8, 10.7)
Ruptured intracranial aneurysm (69)	Coiling	Clipping	Alive and not dependent (mRS 1-2)	1 year	0.69	0.76	0.07	14.4	(8.9, 39.0)
			Alive	1 year	0.90	0.92	0.02	50.7*	(-117.7, 20.8)
Cardiac arrest (6,7)	Hypothermia	Normothermia	Favorable neurologic outcome	6 months	0.39	0.55	0.16	6.4	(3.6, 24.8)
			Alive	6 months	0.45	0.59	0.14	7.0	(3.9, 40.6)

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Acute stroke									
Acute stroke (70)	Intravenous rhTPA (overall)	Best medical therapy	Alive and independent	6 months	0.44	0.49	0.05	18.3	(11, 56)
	Intravenous rhTPA (0-3 hours)			6 months	0.40	0.50	0.11	9.1	(5.8, 21.6)
	Intravenous rhTPA (3-6 hours)			6 months	0.46	0.49	0.03	33.6*	(-64.3, 13.3)
Acute stroke (71)	ASA given within 48h	Placebo	Alive and independent	6 months	0.53	0.55	0.01	81.1	(45.5, 375.1)
			No recurrent stroke	6 months	0.97	0.98	0.01	145.8	(99.6, 272.0)
Acute stroke (72)	Stroke unit	General medical ward	Alive and no institutionalized care	1 year	0.55	0.60	0.05	19.3	(11.6, 57.1)
Primary Stroke Prevention									
Atrial fibrillation	Warfarin (73)	Placebo	No stroke	1 year	0.94	0.98	0.04	24.7	(17.8, 40.4)
	Aspirin (74)	Placebo	No stroke	1-2 years	0.89	0.90	0.02	56.8*	(-195.0, 24.8)
	Warfarin (74)	Aspirin	No stroke	1-2 years	0.95	0.96	0.02	56.7	(29.2, 989.1)
Asymptomatic carotid stenosis, >60% (75)	Carotid endarterectomy	Best medical therapy	No perioperative stroke or death or subsequent ipsilateral stroke	1-2 years	0.93	0.95	0.02	51.7*	(-4716.0, 25.7)
Isolated systolic hypertension (76)	Chlorthalidone and atenolol or reserpine	Placebo	No stroke	4.5 years	0.93	0.96	0.02	42.5	(27.4, 95.2)
Hypertension (2)	Ramipril	Placebo	No stroke	4 years	0.95	0.97	0.01	66.7	(43.4, 144.2)
			Alive	4 years	0.88	0.90	0.02	53.9	(31.8, 176.1)
Secondary Stroke Prevention									
Prior stroke or TIA and atrial fibrillation (77)	Warfarin	Placebo	No recurrent stroke	1 year	0.77	0.91	0.14	7.3	(5.0, 13.8)
			No vascular events	1 year	0.67	0.79	0.12	8.4	(5.1, 24.4)
Prior stroke or TIA (78)	Clopidogrel or ticlopidine	ASA	No recurrent stroke	2 years	0.94	0.94	0.01	137.5	(73.9, 991.5)
Prior stroke or TIA, high risk patients (79)	Clopidogrel + ASA	Clopidogrel	No stroke, myocardial infarction, vascular death or rehospitalization for acute ischemia	1.5 years	0.83	0.84	0.01	97.0*	(-159.8, 37.2)
			No recurrent stroke	1.5 years	0.92	0.92	0.01	193.9*	(-140.2, 57.3)
Prior stroke or TIA (80)	Dipyridamole + ASA	ASA	No recurrent stroke	2 years	0.88	0.90	0.03	33.6	(19.6, 118.5)
			Alive	2 years	0.89	0.89	0.00	571.0*	(-50.7, 43.1)
Prior stroke or TIA and hypertension (81)	Antihyperten-sive agents	Placebo	No recurrent stroke	1.8-6.8 years	0.91	0.93	0.03	39.9	(26.2, 83.6)
			Alive	1.8-6.8 years	0.92	0.93	0.01	115.3*	(-250.3, 46.9)
Prior stroke or TIA and hypertension (82)	Perindopril	Placebo	No recurrent stroke	4 years	0.86	0.90	0.04	27.1	(18.8, 48.4)
			Alive	4 years	0.90	0.90	0.004	229.4*	(-92.2, 51.1)
Prior stroke or TIA and hyperlipidemia (83)	Simvastatin	Placebo	No recurrent stroke	5 years	0.94	0.96	0.01	72.8	(50.7, 128.6)
			Alive	5 years	0.85	0.87	0.02	57.3	(37.2, 124.6)
Symptomatic carotid stenosis, NASCET 70-99% (84)†	Carotid endarterectomy	Best medical therapy	Alive and no disabling ipsilateral stroke	2-6 years	0.86	0.92	0.07	14.3	(9.6, 28.3)
Symptomatic carotid stenosis, NASCET 50-69% (84)†	Carotid endarterectomy	Best medical therapy	Alive and no disabling ipsilateral stroke	2-6 years	0.82	0.87	0.05	19.3	(10.9, 83.4)
Symptomatic carotid stenosis, NASCET <50% (84)†	Carotid endarterectomy	Best medical therapy	Alive and no disabling ipsilateral stroke	2-6 years	0.89	0.87	-0.02	-50.0*	(-23.8, 500.7)

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Other									
Neurological disorder	**Intervention**	**Control**	**Outcome[a]**	**Time[b]**	**CER**	**EER**	**ARR[c]**	**NNT[c]**	**(95% CI) [c]**
Benign Paroxysmal Peripheral Vertigo (85)	Epley Maneuvers	Placebo	Negative Dix-Hallpike	2-4 weeks	0.44	0.81	0.35	2.9	(2.0, 5.2)
			Symptom resolution	2-4 weeks	0.25	0.58	0.33	3.0	(2.0, 5.9)
Hospitalized patient (86)	Compression stockings	No prophylaxis	No deep venous thrombosis	Until discharge or fully mobile	0.71	0.85	0.15	6.7	(5.0, 10.0)
	Compression stockings plus another prophylactic measure	Prophylactic measure other than compression stockings	No deep venous thrombosis	Until discharge or fully mobile	0.86	0.97	0.11	9.0	(7.0, 12.6)
Narcolepsy / Excess Daytime Sleepiness (87)	Modafinil	Placebo	Improvement on CGI	9 weeks	0.38	0.58	0.19	5.2	(2.9, 22.7)

a = For consistency, all outcomes were expressed as positive events and NNTs as the effect of treatment on improving the chance of the positive event, calculated as the inverse of the experimental event rate (EER) subtracted from the control event rate (CER). b = The time range provided for meta-analyses was the range of the shortest and longest follow-up time of trials included in the analysis. c = Weighted pooled risk differences and NNTs from meta-analyses are provided, therefore these values may not correspond to ARRs and NNTs calculated directly from the control and experimental unweighted event rates. n = number of patients, * = not statistically significant, † = only generalizable to surgically-fit patients operated on by surgeons with complication rates <6%. Abbreviations: ACTH (adrenocorticotrophic hormone), ADAS-Cog (Alzheimer's Dementia Assessment Scale), ASA (acetylsalicylic acid), ARR (absolute risk reduction), CER (control event rate), CGI (Clinical Global Impression), CI (confidence interval), CBIC-Plus (Clinician's Interview-Based Impression of Change scale), EER (experimental event rate), GOS (Glasgow Outcome Score), NASCET (North American Symptomatic Carotid Endarterectomy Trial), NNT (number needed to treat), rhTPA (recombinant human tissue plasminogen activator), TIA (transient ischemic attack).

them more applicable to clinical practice, clinicians must be wary when making such adjustments.

Similar to other measures of therapeutic efficacy, NNTs have several limitations.[1] First, NNTs are population, disorder, treatment and outcome specific. Therefore, direct comparisons across different disease conditions should be interpreted cautiously. Second, as described in the table, one must be mindful of the differences in follow-up time and baseline risk between patients involved in the index studies and those to whom one is applying the results. Methods to adjust for these at the bedside are described in an earlier companion paper.[1] Third, NNTs generated from meta-analyses are derived by pooling data from multiple trials and therefore must be interpreted with caution since the baseline risk, clinical setting, methodology and outcomes assessed may vary among trials included in the analysis.[88] Clinical variability among studies should always be considered and may be difficult to quantify. On the other hand, an assessment of statistical variability of results among studies (eg., heterogeneity) can be helpful in this regard. The majority of NNTs from meta-analyses reported in this article were derived from the Cochrane collaboration whose standard methodology includes estimates of statistical heterogeneity (using a chi-square analysis) prior to pooling of data from different trials. Fourth, since there is no clear threshold NNT at which specific therapies become worthwhile or worthless, some authors propose measures that encompass both the benefit and harm of an intervention, such as the "threshold number needed to treat". This approach aims to determine the magnitude of an NNT below which treatment is beneficial and above which treatment may be harmful.[89,90]

In this summary, we focused only on the beneficial effects of treatments, and not on their capacity for harm, often expressed as numbers needed to treat to harm (NNH). The evidence about harm is sparsely reported and poorly organized. Also, harmful effects of new interventions are often only appreciated after many patients have been treated in open label studies, often without controls. The reporting of harmful effects is a vast topic that requires a separate analysis.

Finally, it is transparent that any attempt to compile current evidence of therapies is obsolete by the time it is assembled, not unlike textbooks or monographs. However, in contrast to some traditional compendia and reviews, we have focused on sources of evidence that have been subjected to the rigour of critical appraisal and that can be updated as new evidence accrues. We hope that this compilation of estimates of the efficacy of various neurological therapies will be a useful tool for clinicians in the neurosciences looking to incorporate evidence based care into their practices.

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