Brain Health Maintenance:

Discovery of New Drugs affordably – Re-purposing Principles

This is used here to Discover Novel Drugs that can treat a neuro-inflammatory disease

(Multiple sclerosis or thinning of white matter)

Initial screening of candidate drugs

Eligibility criteria for publications

Inclusion criteria

- Reporting of primary data from clinical trial(s).
- Qualitative or quantitative data on either safety or efficacy.

Exclusion criteria

- Studies reporting secondary analyses of previously published data.
- Reports of protocols for potential clinical trials.
- Studies in patients with relapsing-remitting MS.
- Use of interventions already licensed for clinical application in MS.
- Studies reporting interventions not administered orally.
- Studies reporting combination interventions.
- Studies reporting only non-pharamacological interventions (e.g. acupuncture, aromatherapy, physiotherapy, exercise).
- Studies reporting use of levodopa treatment for Parkinson's disease.

Systematic evaluation: Candidate drugs

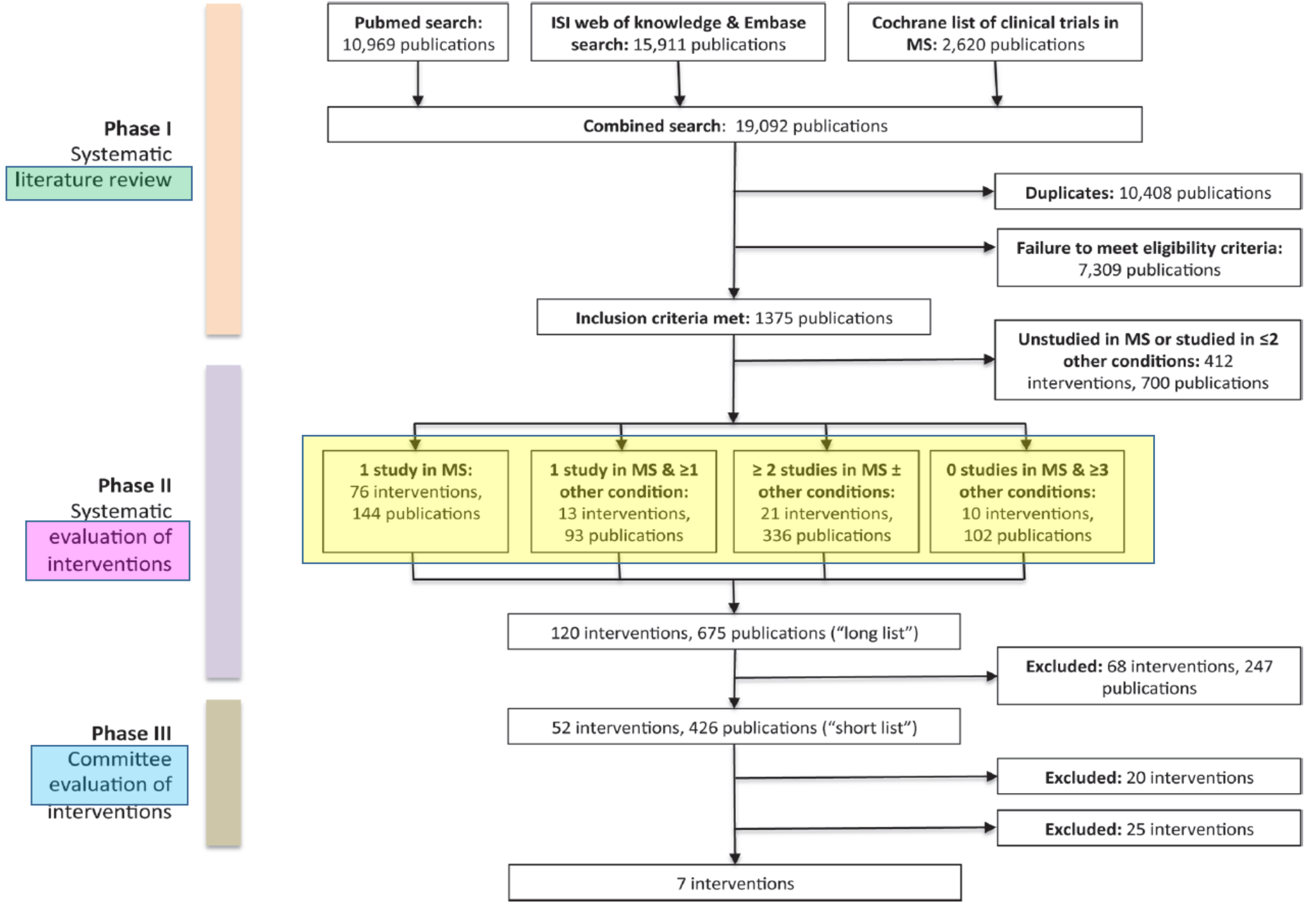
Meta-Analysis

	CAMARADES	Delphi	GRADE
Binary response items:			
Yes (1 point); No (0 points)			
Peer reviewed publication	X		
Statement of potential conflicts of interest	X		
Sample size calculation	X	X	
Random allocation to group	X	X	X
Ternary response items:			
Yes (1 point); No (0 points); Not Clear (0.5 points)			
Were the groups similar at baseline regarding the most important prognostic indicators?		X	
Were the eligibility criteria specified?		X	
Were point estimates and measures of variability presented for the primary outcome measures?		X	
Was there an intention to treat analysis?		X	
Quinary response items:			
N/A; Definitely yes (1 point); Probably yes (0.75 points); Probably no (0.25 points); Definitely no (0 points)			
Was selection of treatment and control groups drawn from the same population?			X
Can we be confident that patients received the allocation treatment?			X

Overall Score of each Meta-analysis : Product of 4 scores of - Safety ● Efficacy ● Quality ● Study Efficiency

Selection process:

Publications & Interventions



Phase-1:

Systematic Survey of Literature

Candidate drugs excluded during short-listing, with reason of Rejection

[MOA = mechanism of action]

Drug	Reason for exclusion
15+- Dexoxyspergualin	Immunosuppressive MOA
4 Ammonium Phosphate	Limited biological plausibility
Adrenocorticotropic Hormone	Immunosuppressive MOA
Adrenocorticotropic Hormone 1–17	Immunosuppressive MOA
Amantidine/Isoprinosine	Symptomatic benefit
Anastal	Combination therapy
Antithymocyte Globulin	Immunosuppressive MOA
Arachidonic Acid	Limited biological plausibility
Azathioprine	Immunosuppressive MOA
Azathioprine & Prednisolone	Immunosuppressive MOA
Azathioprine/6-mercaptopurine	Immunosuppressive MOA
Baclofen	Symptomatic benefit

Short-listed drugs ranked by overall drug scores

	Number of publications	Efficacy Score	Safety Score	Quality Score	Patient Sample Size Score	Overall Drug Score
Dextromethorphan + Quinidine	3	3·3	2·3	4	3	56·2
Amantadine	57	3·1	2·4	2·2	1·9	55·2
Memantine	34	2·7	2	2·6	2·4	51·6
Gabapentin	8	2·7	2·5	2·9	2·5	46·7
4-Aminopyridine	10	2·7	2·5	3	2·1	44·4
Modafinil	8	2·9	2·4	3·1	2·1	44·4
Creatine	12	2·1	2·3	2·7	2·4	35·9
Selegiline	11	2·7	1·9	2·7	2·3	34·2
L-amphetamine sulfate	1	3	3	4	3	32·5
Minocycline	11	2·3	2·6	2·3	2·2	31·9
Vitamin E	9	2·1	2	3	2·4	31·1
Coenzyme Q_{10}	9	2·2	1·9	3·2	2·3	30·6

(1)

Phase-2:

Evaluation of Interventions

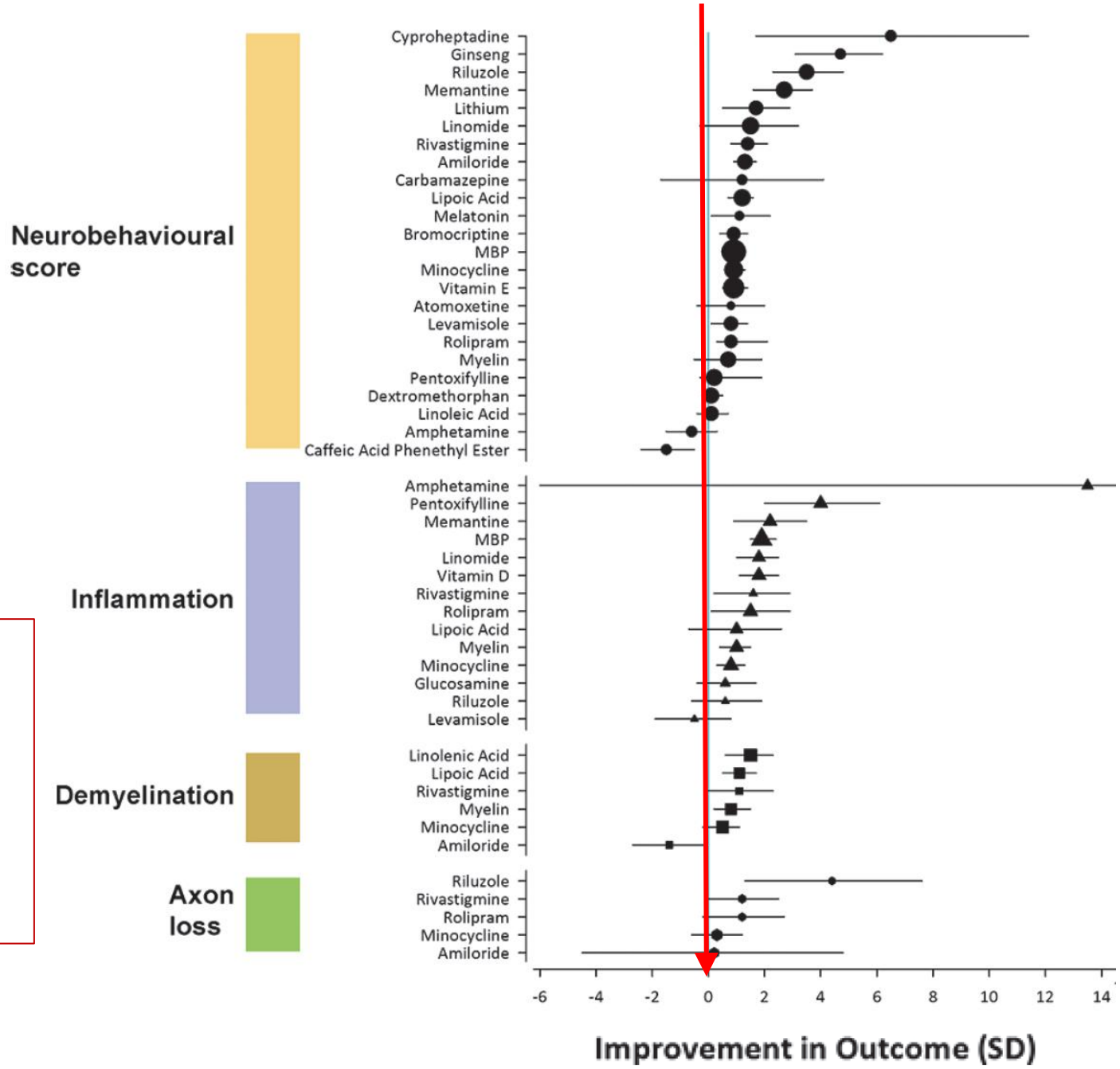
Neurobehavioral & Pathological efficacy outcomes

Expanded in Next Slide

Symbol estimates of efficiency of drugs.

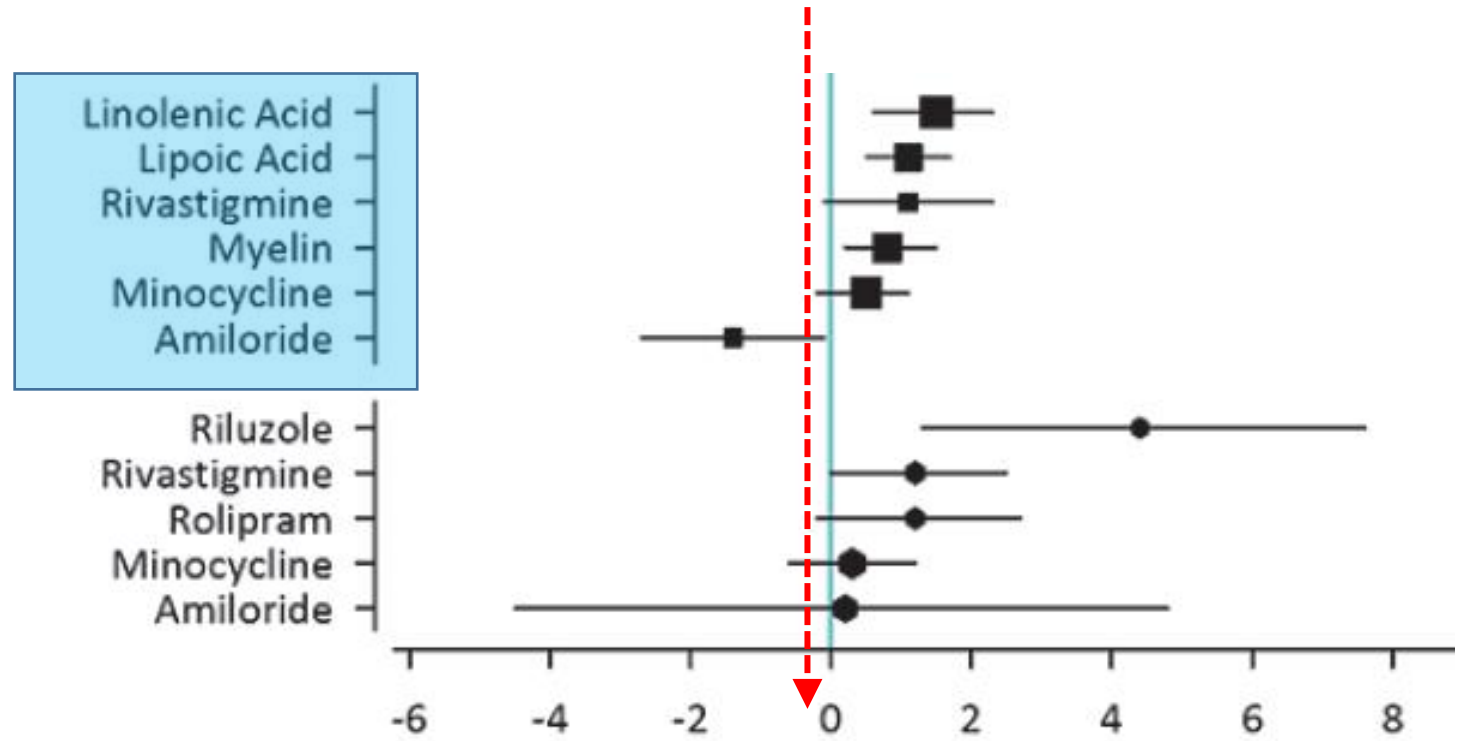
Symbol's diameter denote:
$\log_{10}$ (No. of animals in that study

Vertical line represents: Effect = nil or zero



Demyelination

Axon loss



Phase-3:

Assessment by Domain Knowledge Committee

Drugs Rejected

Committee review phase

[EAE = experimental allergic encephalomyelitis, i.e. Experimental Multiple sclerosis disease in animals]

	Drug	Reason for exclusion
Excluded after round 1	4-Aminopyridine	Risk of seizures, limited efficacy data
	Atomoxetine	Safety profile, no efficacy data in MS
	Clofibrate	Safety profile, neutral efficacy data
	Bromocriptine	Safety profile
	Dextromethorphan	Requires co-administration with quinidine
	Diazepam	Safety profile, limited evidence for efficacy
	Ginseng	Limited clarity around MOA, no efficacy data in MS
	Imipramine	Limited evidence for efficacy
	Isoniazid	Likely symptomatic benefit only, no efficacy data in MS
	Levamisole	Safety profile
	Linomide	Safety profile
Excluded after round 2	Amantadine	Limited evidence for neuroprotective MOA
	Aspirin	No evidence in EAE, insufficient basis to trial as neuroprotective agent in SPMS
	Carbamazepine	Better safety and efficacy data for same-class alternative (oxcarbazepine)
	Coenzyme Q_{10}	Limited efficacy data in MS
	Creatine	Safety profile, limited efficacy data

Final recommendations as candidate drugs for Multiple Sclerosis (MS)

Intervention	Current main clinical application and mechanism of action
Ibudilast	***Anti-inflammatory use in asthma*:** non-selective phosphodiesterase (PDE 3,4,10,11) inhibitor and macrophage Migration Inhibitor Factor (MIF) inhibitor.
Riluzole	***MND/ALS*:** glutamate release inhibitor/inactivation of voltage-dependent sodium channels.
Amiloride	***Diuretic*:** acid sensing ion channel blocker.
Pirfenidone	***Pulmonary fibrosis*:**antagonises synthesis of TGF-beta & TNF-alpha; antifibrotic/anti-inflammatory activity.
Fluoxetine	***Antidepressant*:** selective serotonin reuptake inhibitor.
Oxcarbazepine	***Anticonvulsant*:** voltage sensitive sodium channel blocker.
PUFA class (Linoleic Acid, Lipoic acid; Omega-3 fatty acid, Max EPA oil)	***None / dietary supplements*:** mechanism of action unclear.

[PUFA = polyunsaturated fatty acids. MND/ALS = motor neurone disease / amyotrophic lateral sclerosis]

Limitations of this Approach

- Possibility of incomplete ascertainment of relevant publications, and publication bias favouring studies with positive findings.
- Does not overcome problems that were inherent in the design and execution of the primary studies.
- Exclusion of drugs based on their mode of action will have overlooked drugs with more than one relevant mode of action.