On-line Supplemental Materials:

http://www.adelaide.edu.au/psychology/research/Wheaton_et_al/Journal_of_Psychopharmacology_2011_supplemental_materials

Tables A-D

Figure A

Appendix A

Table A: Key search terms used in database searches

Traumatic brain injury	Pharmacology	
traumatic brain injury	pharmacology	drug therapy
TBI	pharmacological treatment	pharmacotherapy
head injury	drug treatment	drug
head injuries	magnesium or Mg	substance P
brain injury	cyclosporin A or CyA	progesterone
brain injuries	oestrogen	dexanabinol
head trauma	dexamethasone	dynorphin
concussion	methylphenidate	amitriptyline
post-concussion	phenelzine	opiate
post concussion	glutamate	calcium
post-concussion syndrome	free radical scavenger	NMDA
post concussion syndrome	treatment	

Table B : Demographic data, treatment and cognitive or behavioural tests used for each study included in the review.

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
SEROTONERGIC TREATMENTS											
POST-ACUTE											
68	*Open-label (no blinding, not randomised)* Repeated measures	20	29.10	-	84 (8 – 144)	severe	Citalopram (Ciprimil) Selective Serotonin Reuptake Inhibitor & Carbamazepine (Tegretol) Sodium Channel Blocker	10mg – 20mg/day 100mg/day	3 months (90 days)	6.7	Brief Psychiatric Rating Scale; Clinical Global Impression Scale
67	*Open-label (no blinding, not randomised)* Repeated measures	13	30 (7)	-	36 (mid) (24 – 48)	mild	Amitriptyline (Tryptanol) Tricyclic antidepressant	100mg – 250mg/day	6 weeks (42 days)	6.9	Hamilton Rating Scale for Depression
57	*Open-label (no blinding, not randomised)* Repeated measures	10	42	-	30 (mid) (16 – 44)	mild	Amitriptyline (Tryptanol) Tricyclic antidepressant Phenelzine (Nardil) Monoamine oxidase inhibitor	100mg – 300mg/day (max) 45mg/day	4 weeks (28 days)	7.2	Hamilton Rating Scale for Depression Hamilton Rating Scale for Depression
55	*RCT* *(double-blinded)* Independent groups repeated measures	3	36 (8)	30 (9)	60 (mid) (24 – 96)	severe	Desipramine (Norpramin) Tricyclic antidepressant	150mg – 300mg/day	4 weeks	8.0	Affect/Mood Scale
MIXED											
77	*Open-label (no blinding, not randomised)* Repeated measures	10	-	-	22 (3 – 73)	mild/moderate	Milnacipran (Ixel) Serotonin Noradrenaline Reuptake Inhibitor	30mg – 150mg/day	6 weeks (42 days)	7.8	Mini-mental State Exam; Hamilton Rating Scale for Depression
12 (Study 2)	*RCT (double-blinded)* Independent groups repeated measures	10	33.6 (12.3)	35.5 (7.2)	4 (>2 < 52)	mild/moderate	Sertraline (Zoloft) Selective Serotonin Reuptake Inhibitor	25mg – 100mg/day	4 weeks (28 days)	9.5	Beck Depression Inventory; Hamilton Rating Scale for Depression, Rivermead Post-concussion Symptoms Questionnaire; SmithKline Beecham Quality of Life Scale; Critical Flicker Fusion Threshold; Choice Reaction Time; Compensatory Tracking Task (tracking and peripheral); Mental Arithmetic Test; Sternberg Memory Scanning Task, Digit Symbol Substitution Test; Mini-mental State Exam

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Table B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
DOPAMINERGIC TREATMENTS											
POST-ACUTE											
70	*RCT (double-blinded)* Independent groups repeated measures	9	30.10 (11.5)	38.3 (9.8)	142 (> 24)	-	Methylphenidate (Ritalin) Stimulant	20mg/day	Single dose (1 day)	7.0	Modified Posner Paradigm; Working Memory Task
69	*RCT (single-blinded)* Independent groups repeated measures	19	-	-	108 (mid) (> 24)	severe	Methylphenidate (Ritalin) Stimulant	30mg/day	6 weeks (42 days)	8.3	State & Trait Anger; Profile of Mood States; Katz Adjustment Scale (belligerence, psychopathology); Organic Signs & Symptoms Inventory
33	*RCT (double-blinded)* Cross-over	12	27.58	-	208 (56 – 432)	moderate/ severe	Methylphenidate (Ritalin) Stimulant	.30mg/kg	1 week (7 days)	8.5	WAIS Digit Symbol; Stroop Interference; Choice reaction time; Sternberg Memory Scanning Task; Selective Reminding Test; Serial Digit Learning; Gordon Diagnostic System; Digit Span
22	*RCT (double-blinded)* Cross-over	19	30.8	-	74 (5 – 464)	mild/moderate/ severe	Methylphenidate (Ritalin) Stimulant	.50mg/kg/ day	6 days (non-consecutive – drug given 90 minutes before task)	9.0	Distraction Task; Phasic Arousal Task; Choice reaction time; Behavioural Inattention Task; Visual go/no-go Task
71	*Open-label (no blinding, not randomised)* Repeated measures	22	36 (11.8)	-	270 (24 – 960)	mild/moderate/ severe	Amantadine (Symmetrel) Stimulates dopamine release	100mg – 400mg/day	3 months (90 days)	8.3	Trails A & B; Controlled Oral Word Association Test; Digit Span; Californian Verbal Learning Test; Rey Osterreith Complex Figure (immediate and delayed)
73	*Open-label (no blinding, not randomised)* Repeated measures	7	48.9 (2.4)	-	99 (> 12)	mild/moderate/ severe	Quetiapine (Seroquel) Dopamine antagonist	25mg – 300mg/day	6 weeks (42 days)	6.1	Clinical Global Impression Scale; The Overt Aggression Scale-Modified; Neurobehavioral Functioning Inventory (Aggression); Repeatable Battery for the Assessment of Neuropsychological Status
74	*Retrospective Open-label (no blinding, not randomised)* Repeated measures	5	27 (10)	-	8 (5 – 10)	severe	Ziprasidone (Geodon) Dopamine antagonist	20mg – 80mg/day	2 weeks	8.9	Agitated Behaviour Scale
71	*Open-label (no blinding, not randomised)* Repeated measures	8	23 (4)	-	10 (6 – 15)	severe	Apomorphine (Apokyn) Dopamine agonist	2mg – 8mg/hour	84 – 180 days	8.0	Coma Near-Coma Scale, Disability Rating Scale

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Table B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
MIXED											
12 (Study 1)	*RCT (double-blinded)* Independent groups repeated measures	10	35.3 (8)	35.5 (7.2)	5 (> 2 < 52)	mild/moderate	Methylphenidate (Ritalin) Stimulant	5mg – 20mg/day	4 weeks (28 days)	9.5	Beck Depression Inventory; Hamilton Rating Scale for Depression, Rivermead Post-concussion Symptoms Questionnaire; SmithKline Beecham Quality of Life Scale; Critical Flicker Fusion Threshold; Choice Reaction Time; Compensatory Tracking Task (tracking and peripheral); Mental Arithmetic Test; Sternberg Memory Scanning Task; Digit Symbol Substitution Test; Mini-mental State Exam.
56	*RCT (double blinded)* Cross-over	40	26.3 (9)	-	34 (mid) (<2 – 66)	moderate/severe	Methylphenidate (Ritalin) Stimulant	15mg – 30mg/ twice daily	2 weeks (14 days)	9.5	Ruff 2 and 7 Selective Attention Test; Selective Attention Task; 4 Choice Reaction Time Task; Sustained Attention to Response Task; Symbol Digit Modalities Test; Letter Number Sequencing; Rating Scale for Attentional Behaviour
23	*RCT (double-blinded)* Independent groups repeated measures	15	-	-	4 (mid) (< 1 – 6)	moderate/severe	Amantadine (Symmetrel) Stimulates dopamine release	200mg/day	6 weeks (42 days)	7.0	Mini-mental State Exam; Disability Rating Scale; Glasgow Outcome Scale; Functional Independence Measure
CHOLINERGIC TREATMENTS											
POST-ACUTE											
30	*Open-label (no blinding, not randomised)* Repeated measures	10	41	-	63 (48 – 240)	mild/moderate/ severe	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	8 weeks (56 days)	6.4	Memory Assessment Scale
32	*Open-label (no blinding, not randomised)* Repeated measures	10	43 (8)	-	180 (> 24)	moderate/severe	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	3 months (90 days)	8.9	Dysexecutive Questionnaire; Hospital Anxiety & Depression Scale; Divided attention (reaction time – dual task); Visual & Verbal Span; Revy Auditory Verbal Memory Test (recall & learning); Trail Making Test A & B; Stroop (errors, interference, reading, naming); Figural, Phonological & Categorical Fluency
17	*Open-label (no blinding, not randomised)* Repeated measures	4	29.5	-	162 (mid) (140 – 184)	severe	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	3 months (90 days)	7.8	Rey Auditory Verbal Learning Test (learning and recall); Complex Figure Test; Rivermead Behavioural Memory Test

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Table B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
31	*RCT (double-blinded)* Independent groups repeated measures	9	33 (6)	31 (6)	18 (8 –44)	mild/moderate/ severe	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	10 weeks (70 days)	10.0	Weschler Memory Scale (logical memory – immediate recall; visual reproduction – immediate recall); PASAT (2.4; 2.0; 1.6; 1.2s)
75	*RCT (blinding not reported)* Independent groups repeated measures	13	42 (4)	40 (3)	21 (4 – 36)	not specified	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	6 weeks (42 days)	6.5	Mini Mental State Exam, Wechsler Memory Scale, Boston Naming Test, Colored Progressive Matrices.
29	*RCT (double-blinded)* Independent groups repeated measures,	8	26.5 (5.8)	25.2 (5.8)	20 (6 – 49)	moderate/severe	Physostigmine (Eserine Sulphate) Acetylcholinesterase inhibitor & Lecithin Cholinesterase precursor	3mg – 4.5mg/day	1 week (7 days)	9.5	Continuous Performance Test; Digit Span; Digit Cancellation; Visual Recognition Memory; Selective Reminding Test (consistent long term recall)
MIXED											
78	*Retrospective Open-label (matched, non-treated controls) (no blinding, not randomised)* Independent groups	10	32.6	31.8	5 (2)injury to rehab (treatment administered between 3 – 84 days after rehab admission)	moderate/severe	Donepezil (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	1 month (mean) (28 days)	7.0	Functional Independence Measure (total score, change scores, efficiency scores)
SODIUM CHANNEL BLOCKERS											
POST-ACUTE											
18	*Open-label (no blinding, not randomised)* Repeated measures	10	33.7 (14.8)	-	58 (11 – 88)	severe	Carbamazepine (Tegretol) Sodium Channel Blocker	400-800mg/day	8 weeks (56 days)	8.1	Shortened Neurobehavioural Rating Scale; Agitated Behaviour Scale; Mini Mental State Exam; Global Neurobehavioural Rating Scale
37	*Open-label (no blinding, not randomised)* Repeated measures	26	33.5 (1.2)	-	256 (28 – 700)	severe	Lysine Vasopressin Antidiuretic peptide	8units/day (2 squirts of nasal spray/day)	4 weeks (28 days)	7.2	WMS Logical Memory (immediate and delayed recall); Queen Square Battery (verbal and non-verbal recognition); Rey Auditory Verbal Learning Test
39	*Open-label (no blinding, not randomised)* Repeated measures	5	-	-	264 (mid) (144 –384)	severe	Desmopressin – (DDAVP) Antidiuretic peptide	160Ug/day (4 daily intranasal dosages)	7 days	7.2	Progressive Matrices; Digit Span (forward & backward); Benton Visual Retention Test; Forced Choice Word Recognition; Cued Word Recall

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Table B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
PEPTIDE TREATMENTS											
POST-ACUTE											
76	*Open-label (no blinding, not randomised)* Repeated measures	20	31.6 (2.24)	-	92	mild/moderate/ severe	Cerebrolysin Neurotrophic peptide	30ml/day	5 days per week for 4 weeks (20 days)	8.3	Syndrome Kurztest
MIXED											
38	*Open-label (no blinding, not randomised)* Repeated measures	20	30.1 (2)	-	81 (mid) (3 – 158)	mild/moderate/ severe	Cerebrolysin Neurotrophic peptide	30ml/day	5 days per week for 4 weeks (20 days)	6.7	Glasgow Outcome Scale; Syndrome Kurztest
PHOSPHOLIPID INTERMEDIATES											
POST-ACUTE											
34	*RCT (blinding not reported)* Independent groups repeated measures	5	-	-	180 (min) (> 24)	severe	Citicholine (CDP choline) Superoxide radical scavenger	1g/day (via oral)	3 months (90 days)	4.8	Trail Making Test B; Sevillas Computerized Neuropsychological Test Battery; Verbal Fluency Task; Benton Visual Retention Test; Lurias Memory Words

Note: RCT = randomised controlled trial.

Table C: Chemical group, pharmacological category and method of action of drugs.

Chemical Group	Pharmacological Category	Method of Action	Drug (Brand Name)
Serotonergic	Antidepressant	Selective Serotonin Reuptake Inhibitor	Sertraline (Zoloft) Citalopram (Ciprimil)
		Tricyclic	Amitriptyline (Tryptanol) Desipramine (Norpramin)
		Serotonin Noradrenaline Reuptake Inhibitor	Milnacipran (Ixel)
		Monoamine Oxidase Inhibitor (Serotonin, Dopamine, Norepinephrine Agonist)	Phenelzine (Nardil)
Dopaminergic	Central Nervous System Stimulant	Dopamine & Noradrenaline Release	Methylphenidate (Ritalin)
		Dopamine Release	Amantadine (Symmetrel)
	Anti-Parkinsonian	Dopamine Agonist	Apomorphine (Apokyn)
	Antipsychotic	Dopamine Antagonist	Quetiapine (Seroquel) Ziprasidone (Geodon)
Cholinergic	Anti-dementia	Acetylcholinesterase inhibitor	Donepezil (Aricept) Physostigmine (Eserine)
		Acetycholine precursor	Lecithin
Sodium Channel Blocker	Antipsychotic/Antiepileptic	Modulator of ion homeostasis	Carbamazepine (Tegretol)
Peptide	Anti-diuretic	Peptide	Lysine Vasopressin (LVP) Desmopressin (DDAVP/Stimate)
	Neurotrophic	Peptide	Cerebrolysin
Phospholipid Intermediate	Antioxidant	Inhibitor of free radical production	CDP-Choline (Citicholine)

Table D : Weighted effect sizes for cognitive and behavioural measures for serotonergic, dopaminergic, and cholinergic treatments, sodium channel blockers, peptides and phospholipid intermediates.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
SEROTONERGIC									
POST-ACUTE (> 4 weeks post-injury)									
DESIPRAMINE (Norpramin)									
Independent Groups Repeated Measures									
Affect/Mood Scale	Depression	1	10	24 - 120	severe	.36	1	73	55[a]
AMITRIPTYLINE (Tryptanol)									
Repeated Measures									
HAM-D	Depression	2	23	32 – 39	mild	1.00*	9	45	57,67[b]
CITALOPRAM (Ciprimil) & CARBAMAZEPINE (Tegretol)									
Repeated Measures									
Clinical Impression Scale	Psychosocial	1	20	84	severe	.91	4	48	68
Brief Psychiatric Scale	Psychosocial	1	20	84	severe	.60	2	62	68
PHENELZINE (Nardil)									
Repeated Measures									
HAM-D	Depression	1	10	32	mild	.55	2	62	57
MIXED (< 4 weeks - > 4 weeks post-injury)									
SERTRALINE (Zoloft)									
Independent Groups Repeated Measures									
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	-.86	3	48	12 (Study 2)
Motor Speed – CRT	Psychomotor Speed	1	20	4	mild/moderate	-.81	3	53	12 (Study 2)
Mental Arithmetic Test	General Cognition	1	20	4	mild/moderate	-.69	3	57	12 (Study 2)
Choice Reaction Time	Cognitive Speed	1	20	4	mild/moderate	-.66	2	57	12 (Study 2)
WAIS Digit Symbol	Attention	1	20	4	mild/moderate	.65	2	57	12 (Study 2)

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
HAM-D	Depression	1	20	4	mild/moderate	.50	2	67	12 (Study 2)
Memory Scanning Task	Memory	1	20	4	mild/moderate	-.50	2	67	12 (Study 2)
Flicker Fusion Threshold	Arousal	1	20	4	mild/moderate	-.41	1	73	12 (St.udy 2)
BDI	Depression	1	20	4	mild/moderate	-.30	1	79	12 (Study 2)
Mini-Mental State Exam	General Cognition	1	20	4	mild/moderate	-.03	1	100	12 (Study 2)
Quality of Life Scales	Psychosocial	1	20	4	mild/moderate	.07	1	92	12 (Study 2)
Compensatory Tracking	Attention	1	20	4	mild/moderate	.10	1	92	12 (Study 2)
MILNACIPRAN (Ixel)									
Repeated Measures									
HAM-D	Depression	1	10	22	mild/moderate	1.85	7	21	77
Mini-Mental State Exam	General Cognition	1	10	22	mild/moderate	1.20	5	38	77
DOPAMINERGIC									
POST-ACUTE (> 4 weeks post-injury)									
METHYLPHENIDATE (Ritalin)									
Independent Groups Repeated Measures									
KAS – General Psychopathology	Psychosocial	1	38	116	severe	1.02	4	45	69
State Trait Anger Scale	Anger/Aggression	1	38	116	severe	.83	3	53	69
KAS - Belligerence	Anger/Aggression	1	38	116	severe	.82	3	53	69
Profile of Mood States	Anger/Aggression	1	38	116	severe	.75	3	53	69
Organic Signs & Symptoms	Psychosocial	1	38	116	severe	.75	3	53	69
Working Memory Task	Memory	1	18	142	not specified	.51	2	67	70
Modified Posner Paradigm	Attention	1	18	142	not specified	.12	0	92	70
Cross-Over									
Distraction Task	Attention	1	19	74	mild/moderate/severe	.56	2	62	22[1c]
Behavioural Inattention	Attention	1	19	74	mild/moderate/severe	.17	0	85	22[1c]
Serial Digit Learning	Memory	1	12	208	moderate/severe	.14	0	92	33

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
GDS – Distractability	Attention	1	12	208	moderate/severe	.14	0	92	33
Choice Reaction Time	Cognitive Speed	2	31	74 – 208	mild/moderate/severe	.11*	0	92	33,22[1c]
Phasic Arousal Task	Attention	1	19	74	mild/moderate/severe	.09	1	92	22[1c]
Stroop Interference	Attention	1	12	208	moderate/severe	-.07	1	92	33
WAIS-R Digit Symbol	Attention	1	12	208	moderate/severe	.05	1	92	33
Memory Scanning Task	Memory	1	12	208	moderate/severe	-.05	1	92	33
WAIS-R Digit Span	Attention	1	12	208	moderate/severe	.04	1	100	33
Selective Reminding Test	Memory	1	12	208	moderate/severe	.02	1	100	33
GDS – Vigilance	Attention	1	12	208	moderate/severe	.02	1	100	33
Visual Go/No-Go Task	Attention	1	19	74	mild/moderate/severe	.02	1	100	22[1c]
APOMORPHINE (Apokyn)									
Repeated Measures									
Disability Rating Scale	Global outcome	1	7	10	severe	5.67	27	2	71[d]
Coma Near-Coma Scale	Arousal	1	7	10	severe	4.44	21	2	71[d]
AMANTADINE (Symmetrel)									
Repeated Measures									
COWAT	Verbal/Language	1	22	270	mild/moderate/severe	.31	1	79	72
Complex Figure Test	Memory	1	22	270	mild/moderate/severe	.21	0	85	72
Trail Making Test B	Attention	1	22	270	mild/moderate/severe	.17	0	85	72
Trail Making Test A	Attention	1	22	270	mild/moderate/severe	.14	0	92	72
CVLT	Memory	1	22	270	mild/moderate/severe	.14	0	92	72
WAIS-R Digit Span	Attention	1	22	270	mild/moderate/severe	-.04	1	100	72
QUETIAPINE (Seroquel)									
Repeated Measures									
Overt Aggression Scale-M	Anger/Aggression	1	7	99	mild/moderate/severe	4.25	20	4	73
Clinical Impression Scale	Psychosocial	1	7	99	mild/moderate/severe	4.25	20	4	73

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
NFI-Aggression	Anger/Aggression	1	7	99	mild/moderate/severe	2.00	9	19	73
RBANS	Memory/Attention	1	7	99	mild/moderate/severe	2.00	9	19	73
ZIPRASIDONE (Geodon)									
Repeated Measures									
Agitated Behaviour Scale	Anger/Aggression	1	5	8	severe	3.07	14	7	74
MIXED (< 4 weeks - > 4 weeks post-injury)									
METHYLPHENIDATE (Ritalin)									
Independent Groups Repeated Measures									
HAM-D	Depression	1	20	4	mild/moderate	1.59	7	27	12 (Study 1)
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	.67	2	57	12 (Study 1)
Quality of Life Scales	Psychosocial	1	20	4	mild/moderate	.61	2	62	12 (Study 1)
BDI	Depression	1	20	4	mild/moderate	-.51	2	67	12 (Study 1)
WAIS Digit Symbol	Attention	1	20	4	mild/moderate	.46	1	67	12 (Study 1)
Mini-Mental State Exam	General Cognition	1	20	4	mild/moderate	.26	0	79	12 (Study 1)
Compensatory Tracking	Attention	1	20	4	mild/moderate	.23	0	85	12 (Study 1)
Memory Scanning Task	Memory	1	20	4	mild/moderate	.08	1	92	12 (Study 1)
Motor Speed – CRT	Psychomotor Speed	1	20	4	mild/moderate	-.07	1	92	12 (Study 1)
Flicker Fusion Threshold	Arousal	1	20	4	mild/moderate	-.05	1	92	12 (Study 1)
Mental Arithmetic Test	General Cognition	1	20	4	mild/moderate	.04	1	100	12 (Study 1)
Choice Reaction Time	Cognitive Speed	1	20	4	mild/moderate	.04	1	100	12 (Study 1)
Cross-Over									
SustainedAttention to Response	Attention	1	40	8	moderate/severe	.10	1	92	56
Attentional Behaviour	Attention	1	40	8	moderate/severe	.10	1	92	56
Four Choice Reaction Time	Attention	1	40	8	moderate/severe	.05	1	92	56
Symbol Digit Modalities	Attention	1	40	8	moderate/severe	-.03	1	100	56
Ruff 2 & 7 Test	Attention	1	40	8	moderate/severe	-.02	1	100	56
Letter Number Sequencing	Attention	1	40	8	moderate/severe	.01	1	100	56

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
Selective Attention Task	Attention	1	40	8	moderate/severe	-.01	1	100	56
AMANTADINE (Symmetrel)									
Independent Groups Repeated Measures									
Disability Rating Scale	Global Outcome	1	35	4	moderate/severe	.83	3	53	23
GOS (6 weeks)	Global Outcome	1	35	4	moderate/severe	.80	3	53	23
Mini-Mental State Exam	General Cognition	1	35	4	moderate/severe	.31	1	79	23
Functional Independence	Psychosocial	1	35	4	moderate/severe	-.30	1	79	23
CHOLINERGIC									
POST-ACUTE (> 4 weeks post-injury)									
DONEPEZIL (Aricept)									
Independent groups repeated measures									
Paced Auditory Serial Addition Test	Attention	1	18	18	mild/moderate/severe	2.93	14	7	31
Weschler Memory Scale-(original/III)	Memory	2	44	18 - 21	mild/moderate/severe	1.56*	15	27	31,75
Boston Naming Test	Memory	1	26	21	not specified	1.56	7	27	75
Mini Mental State Exam	General Cognition	1	26	21	not specified	1.27	5	35	75
Coloured Progressive Matrices	General Cognition	1	26	21	not specified	.31	1	79	75
Repeated measures									
Rey Auditory Verbal Learning Test	Memory	1	4	174	severe	1.59	7	27	17
Complex Figure Test	Memory/Perception	1	4	174	severe	.85	3	48	17
Rivermead Memory Test	Memory	1	4	174	severe	.61	2	62	17
Memory Assessment Scale	Memory	1	10	63	mild/moderate/severe	-.56	2	62	30
Rey Auditory Verbal Memory Test	Memory	1	10	180	moderate/severe	.53	2	67	32
Reaction Time – Dual Task	Attention	1	10	180	moderate/severe	.50	2	67	32
Dysexecutive Questionnaire	Psychosocial	1	10	180	moderate/severe	.47	1	67	32
Stroop Colour	Attention	1	10	180	moderate/severe	.34	1	79	32
Non-verbal Fluency (figural/categorical)	Executive	1	10	180	moderate/severe	.26	0	79	32

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
Visual Span	Attention	1	10	180	moderate/severe	.25	0	79	32
Trail Making Test B	Attention	1	10	180	moderate/severe	.25	0	79	32
Hospital Anxiety & Depression Scale	Depression	1	10	180	moderate/severe	.23	0	85	32
Stroop Interference	Attention	1	10	180	moderate/severe	.22	0	85	32
Verbal span	Attention	1	10	180	moderate/severe	.20	0	85	32
Trail Making Test A	Attention	1	10	180	moderate/severe	.17	0	85	32
Verbal Fluency	Verbal /Language	1	10	180	moderate/severe	.09	1	92	32
Stroop Word	Attention	1	10	180	moderate/severe	.09	1	92	32
PHYSOSTIGMINE (Eserine) + LECITHIN									
Independent groups repeated measures									
Continuous Performance Test	Attention	1	16	20	moderate/severe	.30	1	79	29
Digit Cancellation	Attention/Perception	1	16	20	moderate/severe	-.29	1	79	29
Selective Reminding Test	Memory	1	16	20	moderate/severe	-.16	0	85	29
Visual Recognition Memory	Memory	1	16	20	moderate/severe	-.05	1	92	29
Digit Span	Attention	1	16	20	moderate/severe	.01	1	100	29
MIXED (< 4 weeks - > 4 weeks post-injury)									
DONEPEZIL (Aricept)									
Independent groups									
Functional Independence Measure	Psychosocial	1	28	5	moderate/severe	.18	0	85	78
SODIUM CHANNEL BLOCKERS									
POST-ACUTE (> 4 weeks post-injury)									
CARBAMAZEPINE (Tegretol)									
Repeated Measures									
Shortened Neurobehavioural	Psychosocial	1	10	58	severe	2.20	10	16	18[e]
Global Neurobehavioural	Psychosocial	1	10	58	severe	1.90	9	21	18[e]
Agitated Behaviour Scale	Anger/Aggression	1	10	58	severe	1.01	4	45	18[e]

Cont'd

Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
Mini-Mental State Exam	General Cognition	1	10	58	severe	.12	0	92	18[e]
PEPTIDES									
POST-ACUTE (> 4 weeks post-injury)									
LYSINE VASOPRESSIN (LVP)									
Repeated measures									
Weschler Memory Scale	Memory	1	26	256	severe	.62	2	62	37
Rey Auditory Verbal Learning Test	Memory	1	26	256	severe	.43	1	73	37
Queen Square Battery	Memory	1	26	256	severe	.33	1	79	37
CEREBROLYSIN									
Repeated measures									
Syndrome Kurztest	Memory/Attention	1	20	92	mild/moderate/severe	.41	1	73	76
DESMOPRESSIN (DDAVP)									
Repeated measures									
Word Recognition	Memory	1	5	391	severe	-.39	1	73	39
Word Recall	Memory	1	5	391	severe	-.38	1	73	39
Benton Visual Retention Test	Memory	1	5	391	severe	.29	1	79	39
Digit Span	Attention	1	5	391	severe	-.16	0	85	39
Progressive Matrices	General Cognition	1	5	391	severe	.07	1	92	39
MIXED (< 4 weeks - > 4 weeks post-injury)									
CEREBROLYSIN									
Repeated measures									
Syndrome Kurztest	Memory/Attention	1	20	81	mild/moderate/severe	1.54	7	29	38[g]
GOS (1 month)	Global Outcome	1	20	81	mild/moderate/severe	.83	3	53	38[g]

Cont'd

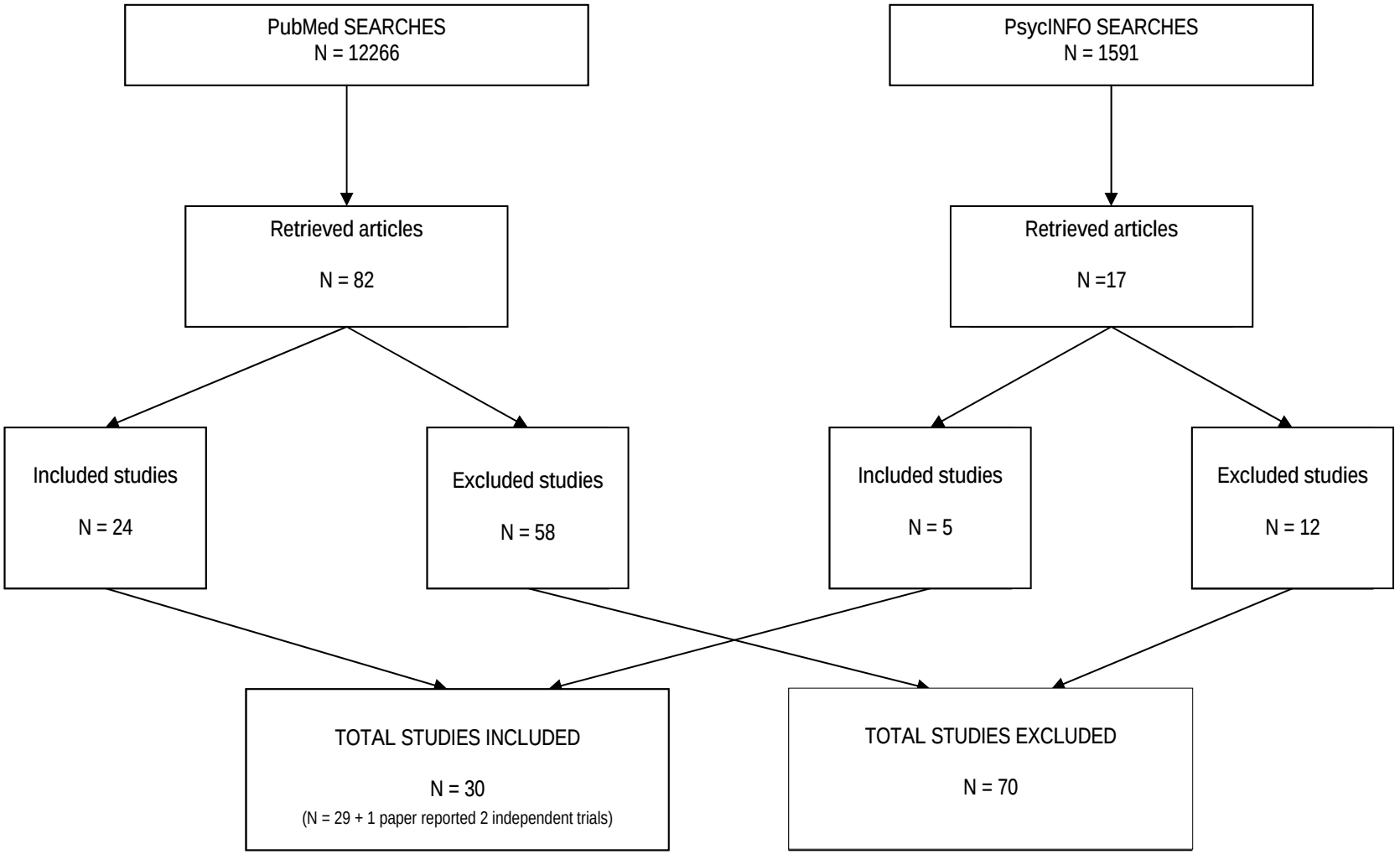
Table D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Ref
PHOSPHOLIPID INTERMEDIATES									
POST-ACUTE (> 4 weeks post-injury)									
CDP-CHOLINE (Citicholine)									
Independent Groups Repeated Measures									
Visual Retention Test	Memory	1	10	180	severe	.62	2	62	34
Lurias Memory Words	Memory	1	10	180	severe	.51	2	67	34
Neuropsychological Battery	Attention	1	10	180	severe	-.45	1	67	34
Verbal Fluency	Verbal/Language	1	10	180	severe	.36	1	73	34
Trail Making Test B	Attention	1	10	180	severe	-.09	1	92	34

Note. $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; CRT = Choice Reaction Time; GDS = Gordon Diagnostic System; GOS = Glasgow Outcome Scale; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; NFI = Neurobehavioural Functioning Inventory; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

[1] Single group repeated cross-over design
* HAM-D : SD = .04, Min = .97, Max = 1.03.
* Choice Reaction Time : SD = .06, Min = .06, Max = .15
*WMS : SD = 1.53, Min = .67, Max = 2.84
Participants concurrently taking:
[a] psychoactive medications
[b] temazepam for night sedation
[c] carbemazepine
[d] anti-epileptic and anti-spasticity drugs
[e] neuroleptics
[f] citicholine and piracetam
[g] Participants concurrently taking anticonvulsants

Figure A: Details of electronic database searches



Appendix A: Criteria for a study inclusion in meta-analysis

a was published in a journal;

b was in English;

c was not a case study;

d had treatment and control group data for participants who had sustained non-penetrating TBIs (Note: in a single sample repeated measures design, participants act as their own control);

e participants were aged 16 years or older. Where age ranges were not reported, a study was deemed eligible for inclusion if the mean age +/- one standard deviation met these criteria;

f no participant was known to have: sustained a previous TBI; had physical, visual or language impairments that could independently affect test performance; a pre-existing psychiatric or neurological disorder (e.g. schizophrenia, dementia); or a past or present history of substance abuse;

g participants were administered the one or more measures of cognition and /or behaviour;

h a pharmacological agent was administered to the treatment group in the post-acute ($\geq$ 4 weeks post-injury) stage following TBI. Given the subjective nature of this cut-off, if some participants were treated prior to this period (mixed treatment interval), these studies were included but analysed separately; and

i the format of the reported results enabled the calculation of an effect size (i.e. means, standard deviations, *t* tests, one-way *F* statistics, exact *p* values) or this information was provided by authors in response to a written request. Where raw data were reported, these were converted to means and standard deviations. It was not possible to additionally screen studies for the use of other pharmacological agents (e.g. antipsychotics, neuroleptics) because these data were not consistently reported. However, those studies that did report this information are identified in the Results section and in the relevant tables.

Appendix B : Methodological quality rating system

Question		Score
1	Demographically matched control group or condition provided	1
2	The control group is matched to the treatment group on initial performance	1
3	Patients were randomly allocated to groups	1
4	The method of randomization was provided	1
5	The cognitive or behavioural test is clearly described (or a reference provided)	1
6	The scores for each measure are specified (i.e. error, accuracy, speed)	1
7	The age of the participants is specified (M/SD/Range)	1
8	The severity of injury is specified	1
9	The measure/s of injury severity are provided (i.e. GCS, PTA, LOC)	1
10	The gender of participants is specified	1
11	Relevant premorbid demographic statistics are reported (e.g. education, IQ)	1
12	The initial sample size for each group is specified	1
13	The time from injury to treatment is specified	1
14	The drug dosage is specified	1
15	Significant test statistics are provided that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
16	The N for each group on each testing occasion is reported	1
17	Non-significant test statistics are reported that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
18	Group allocation is blinded to the assessor	1
19	Group allocation is blinded to the patient	1
20	N lost to follow-up is reported	1
	TOTAL SCORE / 20	

Note: M = Mean score; SD = Standard deviation of score; GCS = Glasgow Coma Scale; PTA = duration of post-traumatic amnesia; LOC = duration of loss of consciousness; N = number of participants; IQ = intelligence quotient.