Impact of Different Pharmacological Treatments on Outcomes in Adult Rats after Traumatic Brain Injury: A Systematic Review and Meta-analysis

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Abstract

Many pharmacological interventions have been developed to treat Traumatic brain injury and its alterations. Many interventions have been investigated pre clinically to evaluate their effects on motor, cognition and behavioural functioning following Traumatic Brain injury. But, most of these studies have not been able to provide sufficient conclusions regarding the efficacy of these drugs mostly due to their small sample sizes. So, a systematic review and meta-analysis (1990-2020) was conducted to examine the effects of pharmacological interventions in rodents after traumatic brain injury on functional outcomes. The PubMed database searches were conducted using 56 key terms. Weighted mean effect sizes, percent overlap, fail-safe (Nfs) and confidence intervals were calculated for the interventions. Total, 125 interventions were evaluated in 285 preclinical studies using 51 activities. Interventions investigated by multiple studies and with great treatment benefits were majorly focused. Out of all the interventions, 42 improved the cognitive outcomes, 44 improves motor and 6 improved the behavioural functioning. The treatment benefits were majorly affected by drug dosage and treatment intervals used in the studies.

Key Words: Traumatic brain injury, Traumatic brain injury models, Weight drop model, Pharmacological interventions, Neurotrauma.

INTRODUCTION

Traumatic brain injury (TBI) refers to a blunt, penetrating or acceleration/deceleration force-derived craniocerebral injury. It is an insult to the brain generally caused by external mechanical forces e.g. blow or jolt to the head, head injury due to accidental mishaps, sports, blasts or penetration of objects etc. As per World Health Organization, the major cause of TBI is motor vehicle injuries and by 2030, TBI would be a leading cause of mortality as well as disability. TBI is a complex neurotrauma which may cause temporary or permanent damage to the brain thereby resulting in memory deficits, neurological or neuropsychological abnormalities and even death.[1] TBI is a leading cause of death among young adults and the number of TBI related deaths is increasing worldwide. Furthermore, it is a major cause of disabilities also as survivors of TBI often suffer from impairment of cognitive, physical and psycho-social functions which compromises their quality of life. These patients require long term care and incur economic cost to health systems. It is often regarded as a silent epidemic due to lack of awareness regarding its impact and magnitude. Due to a large number of deaths and long term neuropsychological impairments, TBI is considered as a global public health concern which requires urgent attention. Currently surgery, neurocritical care, neurorehabilitation and various pharmacological interventions based on TBI associated impairments are the main treatment options.[2]

Despite recent advancements, there is a lack of pharmacological alternatives due to heterogeneous and complex nature of TBI. So, a variety of pharmacological interventions like anti-inflammatory drugs, catecholamines, cholinergic agents, serotonergic drugs, vasodilators etc. have been investigated for potential improvement in cognitive and behavioural outcomes. In order to assess the pharmacotherapeutic potential of all these interventions, consolidation of the results obtained from preclinical studies is required. Wheaton *et al.*, 2011(3) reported a critical evidence regarding the impact of pharmacological treatments on outcome in adult rodents following TBI. Since then to our knowledge, no other systematic review or meta-analysis has been reported. Therefore, the present meta-analysis assessed the effect of pharmacological interventions on outcome following experimental TBI in rodents.

RESEARCH QUESTION

What are the effects of different pharmacological interventions on cognitive, behavioural and motor problems in impact mediated animal models of TBI?

METHODS

An extensive literature search was carried out for preclinical TBI studies through electronic database PubMed ranging from year 1990 to 2020.

Search strategy

Search terms (n=56) used for literature survey are provided in Table 1. Firstly, different broad terms were searched alone and then combinations of these terms were searched. In addition to this, the reference lists of all the included studies were also screened.

Inclusion/Exclusion criteria

This meta-analysis included controlled studies which evaluated the effect of pharmacological interventions in rodent models of TBI as per the inclusion criteria. The details of the inclusion/exclusion criteria are provided in Table 2. Only published studies available in English language were included in the study.

Table 1: Key terms searches in Database

Traumatic brain injury	Pharmacology	
Post-TBI	Drug treatment	Herbals
Pharmacological treatments	Dexamethasone	Methylprednisolone
Corticosteroids	Calcium	Anti-oxidants
Apocynin	biotherapeutics	Anxiety
Estrogen	Progesterone	NMDA
Cholinergics	Adrenergics	Nootropics
Glutamate	Sodium	NLRP3
PARP	Inflammation	GABA receptor
NADPH oxidase	Statins	Hormones
TBI models	Magnesium	Acetylcholine
TBI treatment	Vitamins	Herbal treatment
Bradykinin antagonists	NADPH oxidase	Mania
Cyclo-oxygenase	Anti-convulsants	Oxidative stress
5-HT antagonists	Nitric oxide	Haloperidol
Post injury treatment	Inosine	Antibodies
Pharmacological intervention	5-HT agonists	Neuro protectives
L-name	Immunomodulators	Beta-blockers
Amphetamine	Cannabinoids	

Table2: Selection criteria

Inclusion criteria	Exclusion criteria
i. Studies included between 1990- 2020.	i. Studies other than 1990-2020.
ii. Involved only published studies in English.	ii. Non-published or published in other languages than English.
iii. Studies involving experiments on rodents only.	iii. Studies involving experiments on mammals.
iv. Studies involving biochemical, histological, and functional battery tests.	iv. Studies involving premature or young animals.
v. Studies involving adult male and female animals.	v. Studies involving pregnant or cycling female animals.
vi. Studies involving either non-transgenic or transgenic animals.	vi. Studies involving surgical treatment to the animals.
vii. Post injury treatment to the animals.	vii. Studies involving hyperbaric oxygen treatment to the animals.
viii. Non- surgical interventions to the animals.	viii. Pre- injury treatment to the animals.
ix. Studies involving pharmacological interventions including bio-therapeutic treatment to the animals.	ix. Surgically altered animals.
x. Controlled groups for the comparisons where necessary.	x. Studies without controlled group where it was necessary to keep.
	xi. Combinational therapies
	xii. Environmental enrichment treatments

Types of outcome measures

Effectiveness of the different pharmacological interventions was analyzed against TBI as per following outcome in animal models of TBI:

1. Improvement in cognitive parameters
2. Improvement in behavioral parameters
3. Improvement in motor problems

Data collection

The initial literature search with broad key terms identified 6553 articles (Fig. 1). After preliminary screening on the basis of inclusion criteria, 234 articles were shortlisted for further closer study. After closer examination of the full version of papers, 82 articles were excluded due to poor fulfilment of inclusion criteria requirements, thereby reducing the number of articles to 152 only. Seventy one articles had reported multiple studies with respect to the treatments, dosage, different injury to treatment times etc. Thus these were considered as separate studies and 71 articles provided 204 studies. Hence, in total, the data was collected and compiled from 285 studies that examined the effect of 125 pharmacological interventions on the outcomes of post traumatic brain injury in rodent models of TBI.

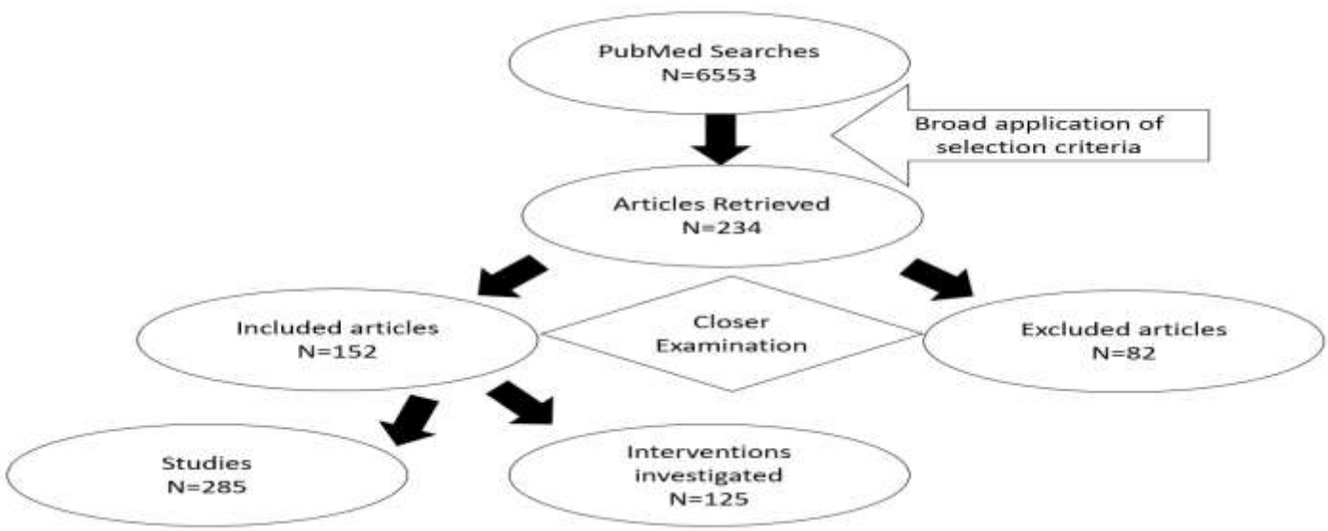

Figure1: Scheme of study-selection.

Data Analysis

Each pharmacological intervention was classified as per chemical group or primary mechanism of action. To determine the effect sizes of the drug treatments, Cohen's d effect size was calculated using mean of two groups and pooled standard deviation. Effect sizes were determined in such a way that positive value indicates improvement. The values of the effect sizes were described 0.2 as small, 0.5 as moderate and 0.8 as large. The mean and standard deviations values were collected from the included studies. However, if studies reported standard error mean, then standard deviations were calculated using Revman software. The values were used further to calculate the effect size of each measure of individual studies. The studies examined a particular intervention for same measure were averaged to evaluate the treatment effects. However, it was noted that studies used different sample size which can affect the end results hence there was a need of weight effect sizes before proceeding them to average. Thus, mean weighted effect sizes (M_{dw}) from independent studies were calculated using inverse variance and then they were averaged. In addition to this weighted standard deviation (SD_{dw}), Confidence Interval (95%) and Nfs were calculated for cognitive, behavioural and motor test outcomes following treatment with different pharmacological interventions[96,148]. Confidence interval not equal to zero predicts the considerable difference between the groups. Percentage overlap was calculated to evaluate the overlapping of test scores from two groups. Nfs was calculated to test any biasness with significant result. However, to build the confidence for the study, more focus was given to collect high quality studies than low quality. Hence, the studies were categorized on the basis of their quality according to the set quality criteria. A set of 20 questions was set up to grade the studies with the quality. The scoring was done on the basis of fulfilment of requirements provided in the quality criteria. The scoring was done between 0(none of the requirement fulfilled)-20 (all the requirements fulfilled). This was further used to rank studies in the five groups (5=Highest, 4=High, 3= Moderate, 2= Low, 1= Lowest). The findings were sought based on the interventions. Cognition, motor and behavioural findings were then described for the drugs examined in multiple and single studies. The treatment effects have been reported along with the Confidence intervals (95%), Nfs and Overlap percentage (Table 3).

RESULTS

Out of 285 studies in the meta-analysis, 215 studies examined rats, the majority of which utilized (169) Sprague Dawley rats, and (70) examined mice, majority were (22)C57BL/6 mice and (19) C57BL/6J mice. Data were analyzed for a total of 6124 rodents. Out of 160 studies specified injury severity, 129 studies reported moderate injury, 29 reported severe injury and 2 reported mild injury. Majority of the studies employed CCI model (N=115), with the rest using FPI (N=98), weight drop model(N=54), while others utilized PBBI (14) and SCI (4). Most of the studies were of high-highest quality.

In most of the studies, the animals were treated with the drugs within 1h post injury and undergone testing within 30days. A total of 51 activities associated measures were utilized to determine the drug's effects including measures of cognition (e.g., Morris water maze, Object recognition task), behavior (e.g., Y-maze test, open field test, locomotor and exploratory activity), motor function (e.g. Grip test, hanging wire test, rota rod test).

Treatment effects

Statins- HMG-CoA reductase inhibitors

Statins have shown their significant role in lowering the cholesterol levels. Statins have also shown their effect in treating the traumatic brain injury in some of the studies. Studies investigating Statins such as Simvastatin, Atorvastatin have been used to study their effects on the Behavioural, motor and cognitive. Twelve high/highest quality studies were used meeting the requirements of the quality criteria. The interventions were given at 30-1440mins (24h) post injury. Only two studies investigating Simvastatin and five investigating Atorvastatin showed large treatments effects on motor function (NSS). In addition to this, one study determining Atorvastatin showed high treatment effects in Cognition function(Morris water maze) and behavioural function (Corner turn test) (Table 3).

Hormonal Drugs

The hormonal drugs such as Progesterone, estrogen and allopregnanolone were investigated in the ten high-highest quality studies using CCI model for TBI induction. The different dosages along with different time to treatment were noted for the study. The effects of the interventions were collected and observed on cognition and motor functioning. The interventions were given 60mins post injury. Only three studies investigating Progesterone showed medium treatment effects in cognition whereas Allopregnanolone in three studies were found to show the high treatments effects in cognition function (MWM). Moreover, two studies for Progesterone showed large effects in motor function (BSN) (Table 3).

Table 3: Drugs with their beneficial treatment effects														
Drug and Measure	**Construct**	**Nstudies**	**Nanimals**	**Injury to treatment**	**Injury model**	**Injury severity**	**Mdw**	**SDdw**	**95% CI**		**Nfs**	**OL %**	**Study Quality**	**References**
STATINS														
Simvastatin									lower limit	upper limit				
Neurological severity score	Motor	2	16	180-1440mins	CCI	NS/Moderate/Severe	2.05	1.4	1.92	2.17	19	19	High/Highest	87,132
Atorvastatin														
Morris water maze	Cognitive	1	32	60mins-1440mins	CCI	Severe/moderate	0.9		-7.01	8.81	4	49	Highest	132
Neurological severity score*	Motor	5	17	60mins-1440mins	CCI	Severe/moderate	1.82	4.31	1.8	1.83	41	23	Highest	91,132,138,
HORMONAL DRUGS														
Progesterone														
BSN	motor	2	14	60mins	CCI	NS	0.95	0.013	-7.5	9.4	8	45	High	118
Raloxifene														
MWM-working memory, swim latency	Cognitive	1	16	15mins	CCI	NS	1.08		-13.12	15.28	4	45	High	82
Alpha-beta hydrolase domain 6 modulators														
WWL70														
Rota rod test*	Motor	2	23	30mins	CCI	NS	1.82	3.58	-2.52	6.16	16	23	High	130
Beam walk test*	Motor	2	23	30mins	CCI	NS	0.9	1	-0.33	2.13	7	49	High	130
MISCELLANEOUS														
Fingolimod														
NSS*	Motor	1	12	Immediate	CCI	NS	0.89		0.24	1.53	4	49	High	53
Morris water maze*	Cognitive	1	12	Immediate	CCI	NS	1.06		-7.83	7.75	4	41	High	53
A20														
Morris water maze	Cognitive	1	20	30mins	FPI	Moderate	1.98		-1.95	2.18	9	19	Highest	14
Bromocriptine														
Morris water maze	Cognitive	1	20	1440mins	CCI	moderate	1.01		-9.89	11.9	4	45	Highest	77
Chloroquine														
Morris water maze	Cognitive	1	10	immediate	weight drop model	NS	2.73		-4.22	9.68	13	10	Highest	32
C1-INH														
Morris water maze*	Cognitive	2	24	10-60mins	CCI	NS	1.12	0.11	-2.06	4.3	9	41	Highest	89

NBP														
adhesive dot removal*	motor	1	14	5mins	CCI	NS	0.83		-0.94	2.6	3	53	High	154
cylinder test*	motor	1	14	5mins	CCI	NS	1.02		-3.36	5.4	4	45	High	154
General Anaesthetic														
Sevoflurane														
NSS	Motor	1	12	60mins	weight drop model	NS	1.84		0.99	2.68	8	23	High	58
Etomidate														
Morris water maze	Cognitive	1	24	5mins	CCI	NS	0.826		-12.4	14.05	3	53	High	40
Nootropics														
Lidocaine														
beam walk test	Motor	1	22	30mins	FPI	moderate	2.11		1.74	2.47	10	17	High/moderate	56
Citicoline														
NSS	Motor	1	28	30mins	weight drop model	Severe	1.81		1.08	2.53	8	23	Highest	108
CDP-choline														
Morris water maze	Cognitive	1	20	1140mins	CCI	NS	1.51		-1.92	4.94	7	29	High	41
NADPH oxidase inhibitor														
Apocynin														
NSS	Motor	1	5	30mins	FPI/CCI	Moderate/NS	2.82		2.55	3.08	13	9	Highest	47
Beam latency test	Motor	1	10	30mins	FPI	Moderate/NS	1.33		-0.06	2.72	6	35	Highest	47
Anxiolytic drugs														
Etifoxine														
Bilateral adhesive removal test	Motor	1	18	30mins	CCI	NS	2.84		0.95	4.72	13	8.8	High	124
Limb-use asymmetry	Motor	1	18	30mins	CCI	NS	1.86		1.82	2.24	8	21	High	124
Anti-oxidants														
OPC-14117														
Exploratory activity	Behaviour	1	38	immediate	CCI	Moderate	2.6		1.34	3.85	12	11	High	6
Stilbazulenyl nitrone														
Neuroscore	Motor	1	16	5mins	FPI	NS	1.26		-2.15	2.97	5	35	High	9
Pegorgotein														
Beam walk test	Motor	1	16	30mins	FPI	Moderate	2.07		0.34	3.79	9	17	High	56
Herbal and Dietary supplements														
Resveratrol														

Beam walk	Motor	2	20	5mins	CCI	NS	2.4	5.07	1.44	3.35	22	13	Highest	125
Morris water maze	Cognitive	2	20	5mins	CCI	NS	1.22	0.054	-5.35	7.79	10	38	Highest	125
XFZY														
NSS	Motor	2	16	1440mins	CCI	NS	1.99	2.001	1.27	2.7	18	19	Highest	136
Morris water maze	Cognitive	2	16	1440mins	CCI	NS	1.86	0.11	-2.32	6.04	17	21	Highest	136
Non-immunosuppressants														
NIM811														
Morris water maze*	Cognitive	1	10	15mins	CCI	Severe	0.89		-6.36	8.14	4	48	High	97
NLRP3 inflammasome inhibitor														
Oridonin														
mNSS*	Motor	1	30	30mins	CCI	NS	2.41		1.97	2.84	11	13	Highest	141
MCC950														
NSS*	Motor	2	24	60mins/immediate	CCI	moderate	0.9	5.3	0.32	1.47	7	48	Highest	69,139
Morris water maze*	Cognitive	1	24	immediate	CCI	moderate	0.9		-11.09	12.89	4	48	Highest	69
CD-K inhibitor														
CR8														
Morris water maze	Cognitive	2	21	180mins	CCI/FPI	moderate	1.34	0.18	-2.39	5.07	11	35	Highest	75
Roscovitine														
Morris water maze	Cognitive	2	20	30-180mins	CCI/FPI	moderate	1.35	0.08	-2.4	5.1	12	32	Highest	73,62
Footfaults	Motor	1	24	30-180mins	CCI/FPI	moderate	1.21		-3.21	5.63	5	38	Highest	73
Cholinergics														
Scopolamine														
Morris water maze	Cognitive	1	16	15mins	FPI	NS	1.65		-4.65	7.95	7	24	moderate	55
Galantamine														
novel object recognition-Familiar*	Cognitive	1	20	30mins	CCI	moderate	1.97		-4.47	8.41	9	19	High	153
Morris water maze*	Cognitive	1	20	30mins	CCI	moderate	0.99		-2.22	4.2	4	45	High	153
BIBN99														
Morris water maze	Cognitive	4	18	1440-15840mins	FPI	moderate	1.1	0.91	-2.02	4.22	18	41	High	107
Rivastigmine														
Morris water maze*	Cognitive	2	30	5mins	Weight drop model	severe	2.97	0.2	-1.42	7.36	28	7	Highest	24
Corticosteroids														
Hydrocortisone														
NSS	Motor	1	60	immediate	FPI	severe	1.46		0.95	1.96	6	29	High	22

COX-2 inhibitor														
Nimesulide														
Barnez maze test	cognitive	1	20	30mins	weight drop model	moderate	3.36		1.34	5.37	16	5	Highest	18
rota rod test	Motor	1	20	30mins	weight drop model	moderate	-1.22		-3.44	0.99	5	38	Highest	18
Meloxicam														
NSS	Motor	1	24	30mins	weight drop model	mild	1.35		0.07	2.62	6	32	Highest	54
Anti-manic drugs														
Lithium														
beam walk test*	Motor	3	13	15mins	CCI	NS	2.18	0.08	-0.55	4.91	30	16	High/Highest	145,147
Morris water maze*	Cognitive	1	34	15mins	CCI	NS	1.63		-4.93	8.19	7	27	Highest	147

Note: * Findings are mouse models of TBI while others are rat models

GABA receptor Modulators

There were four studies of high quality for evaluating the impact of one drug Suritozole on Cognitive and spatial learning by Morris water maze. The studies used FPI model for inducing moderate injury in the animals. The treatments provided to the animal were at 24h post injury or 60mins prior activity tests. All the studies showed small treatment effects in cognition function (Morris water maze) (Table 3).

Alpha-Beta hydrolase Domain 6

Two studies investigated one drug to determine the outcomes of drug on the cognition and motor functions by MWM and Rota rod test respectively. The studies used CCI model but unspecified injury severity. The drugs were administered 30mins post brain injury. Both studies showed large treatment effects in motor function tested by rota rod test and beam walk test. And one study showed small effect in cognition (Morris water maze) (Table 3).

Nootropics

There were three studies investigating two treatments and their effects. The cognitive and motor functions were evaluated by the neurological functional tests and MWM. The studies used FPI and weight drop models with either moderate or severe injury in the experimental animals. The drugs were administered immediately or 30-1440mins(24h) post injury. One study investigating Lidocaine showed large treatment effect in motor functioning (Beam walk test) and the other one study showed the large effect in NSS (motor function). Third study investigating CDP-C showed large treatment effects in cognition tested by Morris water maze (table 3).

Antibiotics

This group involves a two high-quality study evaluating the effect of drug on cognitive function. These studies utilized the weight drop model with unspecified injury severity. The treatment was given immediately or 30mins after TBI induction. Only one study investigating rapamycin showed medium effects in motor function (NSS).

NADPH oxidase Inhibitors

To evaluate the efficacy of the drugs on improvement on the functioning, four highest quality studies were evaluated. The studies utilized FPI and CCI models. Out of four studies, three studies induced moderate injuries but the other did not describe the severity of the injury. The animals were provided with the treatment immediately or 30mins after TBI. Afterwards, motor and cognitive functions were determined. The large treatment effects were shown by two studies investigating Apocynin in motor function tested by Beam walk test and NSS. Three studies showed medium treatment effects in locomotor and exploratory activity(rearing) whereas small effects showed small effects in locomotor and exploratory activity(crossing) (table 3).

Anxiolytic drugs

This group includes a single high-quality study that evaluated the motor functioning. The study used CCI model for inducing the brain injury. However, the study did not specify the injury severity. The treatment was given 30mins after the injury. Afterwards, the tests were performed whose results were evaluated. The study showed the large effects in motor function tested by bilateral adhesive removal and limb asymmetry test. And showed little effect in beam walk test (Table 3).

Immunosuppressants and Non-Immunosuppressants

There were 15 high-highest studies involved in this group evaluating the motor and cognitive functions. The studies utilized CCI, PBBI and FPI models for induction. In addition to this, four studies described the injury severity as moderate, one as severe and the rest of the studies did not describe the injury severity. The treatments were given at 15-30mins post head injury. All studies investigating the cyclosporin A showed no improvement in the motor and cognition functions. The functions were determined by Beam balance, Morris water maze, Rota rod tests and composite neuroscore.

There were two high-highest quality studies in the non-immunosuppressants evaluating motor and cognitive functions. The models utilized was CCI model with severe injury. The treatments were given 15mins after the injury induction. Only one study showed the large treatment effects in Morris water maze tested cognition functioning, while the other showed no improvement in motor functions determined by composite neuroscore (Table 3).

Table 4: Drugs with their beneficial treatment effects

Drug and Measure	Construct	Nstudies	Nanimals	Injury to treatment	Injury model	Injury severity	Mdw	SDdw	95% CI		Nfs	OL%	Study Quality	References
									Lower limit	Upper limit				
Anticonvulsant drugs														
Aniracetam														
Morris water maze	Cognitive	4	18	1440-15840mins	FPI	moderate	2.41	0.074	-0.43	5.25	44	13	High	7
pyruvate														
Morris water maze	Cognitive	1	20	15mins	CCI	NS	0.97		-263	4.57	4	45	Highest	119
PARP inhibitors														
L-2286														
beam balance test	motor coordination	1	17	30mins	Weight drop model	Severe	3.1		3.04	3.15	15	7	Highest	83
open field test	Behaviour	1	17	30mins	Weight drop model	Severe	-1.39		-10.5	7.74	6	32	Highest	83
elevated plus maze test	Behaviour	1	17	30mins	Weight drop model	Severe	2.07		-0.14	4.28	9	17	Highest	83
INO-1001														
Morris water maze*	Cognitive	1	22	immediate	CCI	NS	0.9		-13.7	15.5	4	48	High	30
PJ34														
NSS**	Motor	2	16	5mins	CCI	moderate	16.26	12.61	16.12	16.39	161	2	Highest	128,129
beam walk test	Motor	2	22	180-1440mins	CCI	moderate	1.85	0.006	-2.35	6.05	16	21	High	127
20-HETE inhibitors														
HET0016														
contralateral hindlimb foot-faults	Motor	1	38	5mins	CCI	NS	6.14		6.1	6.17	30	2	Highest	122
NSS*	Motor	1	18	5mins	CCI	NS	1.99		1.24	2.73	9	19	Highest	33
Corner turn test*	Motor	1	18	5mins	CCI	NS	1.7		-3.06	6.46	8	25	Highest	33
rota rod test*	Motor	1	18	5mins	CCI	NS	-1.76		-6.47	2.95	8	23	Highest	33
Benzothiazoles														
Riluzole														
memory score	Cognitive	2	26	15mins	FPI	moderate	-0.81	0.003	-9.17	7.55	6	53	Highest	99
Calcium Channel blockers														
SNX-185														
beam cross test	motor	3	16	5mins	FPI	NS	0.929	0.17	-1.2	3.04	11	48	High	85

S-emapamil														
Morris water maze	Cognitive	2	12	15mins	FPI	moderate	0.82	0.004	-5.55	7.199	6	53	Highest	101
CNS stimulants														
Methylphenidate														
Morris water maze	Cognitive	1	16	1440mins	CCI	moderate	1.28		-11.69	14.25	5	35	Highest	78
Glutamate antagonist														
AIDA														
Beam walk performance	motor coordination	1	20	5mins	FPI	moderate	1.23		-6.84	9.3	5	38	High	94
MAO-B inhibitor														
L-Deprenyl														
Morris water maze	Cognitive	1	20	1440mins	FPI	moderate	1.35		-12.15	14.85	6	32	Highest	18
Rasagiline-														
motor function-disability score*	motor	2	20	5mins	weight drop model	severe	2.29	10.01	2.11	2.28	21	14	High	68
Morris water maze*	cognitive	2	20	5mins	weight drop model	severe	1.65	0.11	-1.73	5.03	15	25	High	68
BRADYKININ RECEPTOR ANTAGONIST														
HOE-140														
novel object recognition*	Cognitive	2	14	30mins	FPI	moderate	-1.86	0.05	-8.16	4.44	17	21	High	48
NMDA antagonist														
Indole-2carboxylic acid														
Morris water maze	Cognitive	2	29	15mins	FPI	moderate	2.06	0.52	0.01	4.1	19	17	Highest	126
Kynurenate														
Morris water maze	Cognitive	1	28	15mins	FPI	moderate	1.8		-4.39	7.99	8	23	Highest	126
memory score	Motor	1	28	15mins	FPI	moderate	-1.76		-11.83	8.31	8	23	Highest	126
MK-801														
Morris water maze	Cognitive	4	16	15mins/immediate	FPI/weight drop model	NS	2.04	0.13	-0.02	4.1	37	19	High	55,57
CP-98113														
Morris water maze	Cognitive	1	25	15mins	FPI	moderate	1.6		-4.55	7.75	7	27	Highest	103
TRH analogue														
2-ARA-53a														
beam walking test	Motor	1	16	30mins	CCI	moderate	1.53		-5.42	8.48	7	29	High	44
Morris water maze	Cognitive	1	16	30mins	CCI	moderate	1.53		-4.36	7.42	7	29	High	43
YM-14673														

righting reflex	Motor	2	12	30mins	FPI	moderate	4.26	0.04	2.28	6.23	41	2	High	43,44
1-ARA-35b														
Morris water maze*	Cognitive	7	22	30-1440mins	FPI	Moderate	1.48	0.1	-1.33	4.29	45	29	Highest/High	43
Foot-faults*	Motor	8	22	30-1440mins	FPI	moderate	1.39	0.103	-0.51	3.29	48	32	High	43
Biotherapeutics														
Vitamin B3														
bilateral tactile adhesive removal test	Motor	1	18	15mins	CCI	NS	2.38		0.63	4.12	11	13	High	63
Morris water maze-RM	Cognitive	1	18	15mins	CCI	NS	1.29		-0.63	3.21	6	35	High	63
Vitamin B2														
bilateral tactile adhesive removal test	Motor	1	15	15mins	CCI	NS	2.03		-6.31	10.37	9	19	High	67
Morris water maze-RM	Cognitive	1	15	15mins	CCI	NS	1.18		-12.99	15.35	5	38	High	67
COG1410														
Morris water maze-WM	Cognitive	1	14	30mins	CCI/weight drop model	NS	0.83		-3.13	4.79	3	53	High	64
Rota rod test*	motor	2	24	3h	weight drop model	NS	-1.2	0.004	-13.12	10.72	10	38	High	84
Cerebrolysin														
adhesive removal	Motor	1	60	60-1440mins	weight drop model	NS	2.74		1.7	3.77	13	10	Highest	150
Morris water maze	Cognitive	2	41	60mins	weight drop model	NS	4.01	1.86	3.33	4.68	38	2	Highest	150,151
Foot-faults	Motor	1	60	60mins	CCI	NS	5.21		2.17	8.24	25	2	Highest	150
rota rod test	Motor	2	10	60-120mins	CCI	NS	-3.6	0.21	-7.72	0.52	34	4	High	116
grid walk test	Motor	2	10	60-120mins	CCI	NS	-1.07	0.05	-5.49	3.35	9	4	High	116
placement errors	Motor	2	10	60-120mins	CCI	NS	1.19	0.03	-2.17	4.55	10	38	High	116
inclined plane	Motor	2	10	60-120mins	CCI	NS	-0.86	0.035	-6.05	4.33	7	48	High	116
Erythropoietin														
Hindlimb foot-faults	Motor	2	13	1440mins	CCI	NS	1.45	1.16	1.13	1.76	13	29	Highest	137
rhEpo														
NSS	Motor	1	36	60mins	Weight drop model	NS	1.65		1.17	2.12	7	25	High	142
TSG-6														
Morris water maze-RM*	Cognitive	1	20	360mins	CCI	NS	0.91		-22.88	24.7	4	48	High	133
Morris water maze-WM*	Cognitive	1	20	360mins	CCI	NS	1.28		-13.89	16.45	5	35	High	133
antibody APP														
Morris water maze	Cognitive	1	20	immediate	CCI	NS	2.5		-1.63	6.63	12	12	High	70
alpha-MSH														
neuroscore	Motor	1	12	30mins	CCI	NS	0.8		-0.02	1.62	3	53	Highest	114

Apo-E														
rota rod test	Motor	2	6	30mins	FPI	NS	-1.62	0.002	-17.16	13.92	14	27	Highest	95
Morris water maze	Cognitive	2	6	30mins	FPI	NS	2.89	0.123	-2.17	7.95	13	8	Highest	95
rh SDF-1alpha														
NSS	Motor	1	12	30mins	CCI	NS	1.33		0.72	1.93	6	35	Highest	88
Morris water maze	Cognitive	1	12	30mins	CCI	NS	1.83		-6.01	9.67	8	23	Highest	88
Albumin														
Neurological score	Motor	1	17	15mins	FPI	NS	0.94		-0.9	2.78	4	48	High	113
anti-ICAM1														
Neuroscore-pulsion	motor	1	20	60mins	FPI	Moderate	-1.29		-1.45	-1.21	6	35	High	8
Neuroscore-flexion	motor	1	20	60mins	FPI	Moderate	-5.36		-5.55	-5.16	26	2	High	8
Neuroscore-inclined plane	motor	1	20	60mins	FPI	Moderate	-0.96		-1.5	-0.41	4	45	High	8
IgG														
Neuroscore-flexion	motor	1	20	60mins	FPI	Moderate	-4.25		-4.4	-4.01	2	2	High	81
Neuroscore-inclined plane	motor	1	20	60mins	FPI	Moderate	-2.81		-3.34	-2.27	13	9	High	81
Magnesium supplements														
MgSO4														
rota rod test	Motor	6	26	15-1440mins	weight drop model	moderate/severe	-2.93	0.163	-5.95	0.098	82	8	Highest/High	59,60,61
MgCl2														
Rota rod test	motor	1	16	30mins	weight drop model	severe	-0.85		-17.26	15.51	3	48	Highest	60
Magnesium														
Open field test	Behaviour	1	16	30mins	weight drop model	severe	-1.26		-42.88	40.36	5	35	High	51
Serotonergic														
8-OH-DPAT														
elevated wooden beam	Motor	1	20	15mins	CCI	moderate	2.68	2.24	1.48	3.87	37	10	Highest	79
Morris water maze	Cognitive	7	23	15-1440mins	CCI	moderate/NS	1.86	0.18	-0.58	4.3	58	21	High/Highest	27,28,143
6n														
marble burying behaviour	behaviour	2	12	11thday	weight drop model	NS	3.2	1.46	2.12	4.27	15	6	High	13
open field test	behaviour	2	12	11thday	weight drop model	NS	2.17	0.002	-19.06	23.4	10	16	High	13
elevated plus maze	behaviour	2	12	11thday	weight drop model	NS	2.32	0.22	-1.1	5.71	11	14	High	13
Repinotan HCI														
Morris water maze	Cognition	1	19	5mins	CCI	Moderate	0.91		-7.47	9.29	4	48	High	80
iNOS inhibitors														

DETA														
Corner test	Motor	1	32	1440mins	CCI	severe	4.2		3.86	4.53	20	2	High	93
Anti-psychotics														
Haloperidol														
beam balance	Motor	3	25	1440mins	CCI	moderate/NS	-15.59	13.39	-16.82	-14.35	231	2	High	50,67
elevated narrow beam	Behaviour	3	25	1440mins	CCI	moderate/NS	-0.69	0.59	-1.9	0.52	7	57	High	50,67

Note: * Findings are mouse models of TBI while others are rat models

Anti-Oxidants

This category involves the three high quality studies involving three drugs. The studies used CCI and FPI models to induce moderate injuries in two studies. However, one study did not describe the injury severity. The treatments were given immediate or 5-30mins post injury induction in the animals. Motor and cognitive activities were determined after the interventions. Two studies investigating OPC-14117 and Pegorgotein showed medium treatment effects in cognition (Morris water maze). And two studies investigating Pegorgotein and Stilbazulenyl nitrone showed large effect in motor function determined by beam walk test and neuroscore respectively. Moreover, OPC-14117 showed large treatment effect in behavioural aspect tested by exploratory activity while Pegorgotein showed little effect in motor functioning tested by beam balance test (table 3).

Herbal and Dietary Supplements

There were 9 high-highest studies involving the three treatments with unspecified the injury severity. However, the model used for inducing the TBI in animals was CCI. The interventions were administered 5mins-1440mins(24h) post injury. The cognitive and motor activity evaluation was done. Two studies investigating resveratrol showed large treatment effects in motor and cognitive functions tested by beam walk and Morris water maze but little effect in beam balance test(motor function). In addition, Sulforaphane investigated by three studies showed medium effects in Morris water maze tested cognition function. Moreover, Ginseng showed large and medium treatment effects in motor function tests (rota rod and beam balance tests respectively) determined by two studies. And, XFZY showed the large treatment effects in motor and cognition tested by NSS and Morris water maze tests (table 3).

NLRP3 Inflammasome Inhibitors

There were three highest studies involved in this group involving CCI models. Out of these studies, two studies specified the severity of the injury as moderate and the other did not specify the severity. The treatments were given immediately or 30-60mins post injury. The motor and cognitive activities were evaluated after the treatment. One study investigating Oridonin showed large effects in motor determined by NSS but negligible effects in rota rod and Hanging wire tests determining motor function. Whereas, MCC950 investigated by two studies for motor (NSS) function showed large treatment effects and one showed large treatment effects in cognition (MWM) and in motor (rota rod test) (table 3).

CD-K inhibitors

The group involves the four highest studies investigating two different treatments. The models used in the studies were FPI and CCI inducing moderate injuries in all the studies. The interventions were administered between 30mins-180mins post injury. The cognitive, behavioural and motor functions were evaluated in the studies. Two studies investigating CR8 showed large treatment effects in Morris water maze test(cognition) and motor score whereas negative effect size in object recognition test(cognitive). The other two studies determined the treatment effect of Roscovitine which showed large effect in cognition (MWM) whereas one showed large effect in foot-faults showing improvement in motor coordination. The neuroscore investigated by one study focusing Roscovitine showed negligible effects (table 3).

Cholinergics

There were 18 high/highest quality studies involving six drugs. The models used in the studies were CCI, FPI and weight drop models. Moreover, out of 18 studies, 2 studies specified the injuries as severe, 14 as moderate one as mild and the other did not specify the injury severity. In the studies, the treatments were given immediately or between 5mins to 15,840mins(11days) post injury. Five studies determining Donepezil showed medium effects in motor (elevated narrow beam) whereas negligible effects in cognition (MMW) tested in six studies and motor (elevated wooden beam) in five studies. And, Galantamine showed large treatment effects in cognition (object recognition-familiar objects and Morris water maze). The other four studies showed large effects in Morris water maze tested cognition. While two studies showed large treatments effects of Rivastigmine in cognition (MWM). In

addition to this, ENA713 effects determined by four studies showed negligible effects in motor (NSS) function. And, one study investigated scopolamine showed large effects in cognition (MWM) (table 3).

Corticosteroids

This group involves the 8 high quality studies with FPI models and injury severity as moderate and severe in each two studies. However, the other studies did not specify the injury severity. In addition to this, it was noted that the interventions were administered immediately after TBI induction. Out of all the studies, only one study investigating Hydrocortisone showed large treatment effect in motor functioning (NSS). Whereas, other studies investigating Methylprednisolone and Dexamethasone showed very little or negligible effects in motor (mNSS and NSS) and cognition (Morris water maze) (table 3).

COX-2 Inhibitors

There were two highest studies evaluating behavioural, motor and cognitive functioning. These studies utilized the weight drop model with mild and moderate injuries, the interventions were given 30mins after head injury. Two studies investigating Nimesulide and Meloxicam showed large effects in behaviour (Barnez maze test) and motor (NSS) respectively. In addition to this, Nimesulide also showed beneficial effects in rota rod test (motor function) (table 3).

ACTH Analogue

This group included the single highest study of one drug for evaluation of behavioural functioning with the induction of TBI by CCI model. The induced injury was severe. In addition to this, the treatment was given 3h/180mins post brain injury. The study investigating Cosyntropin showed medium effect in cognition tested by MWM and negligible effect in behavioural and cognitive functioning (Open field test and Novel object recognition).

Anti-Convulsant

This group involved the 13 high/highest quality studies evaluating the motor, behavioural and cognitive functioning. The interventions were given 15-15840mins(11days) post injury. The models utilized in the studies were PBBI, FPI and CCI models. Out of these studies, severity of the injury was described as moderate in four studies, severe in six studies. However, the other three studies did not specify the severity. Four studies for Levetiracetam showed little effect in cognition and little effect in motor (beam walk test) investigated by one study. While, four studies investigating Aniracetam showed large treatment effects in cognition (MWM). In addition to this, Ethyl pyruvate showed large effects in MWM tested Cognition (table 4).

Anti-manic drugs

There were four high-highest quality studies utilizing the CCI model. The severity of the injury was not specified in any of the study. The drugs were administered at 15mins post injury. Out of four studies investigating Lithium, three showed largely improved motor function (Beam walk test) and in cognition (MWM). However, the other showed medium treatment effects in motor (rota rod test)(table 3).

PARP inhibitors

There were ten studies investigating the four drugs. The models used for TBI induction were FPI, weight drop and CCI. Out of 8 studies, 6 studies specified the moderate and one specified the severe injury but the other one did not specify the injury severity. Cognitive, behavioural and motor functions were evaluated in these studies. The drugs were administered immediately or 5-1440mins(24h) post injury. L-2286 is found to show large benefits in motor coordination (beam balance) and behaviour (elevated plus maze). Moreover, another intervention INO-1001 also has beneficial effects in cognition tested by Morris water maze test. Whereas, PJ34 showed large treatment effects in motor function (NSS and beam walk) but small in cognition (MWM) (table 4).

20-HETE inhibitors

There were two highest quality studies evaluating the motor and cognitive functions after interventions. The studies utilized the CCI model. However, the severity of the injury was not specified in any of the study. The animals were provided with the treatments at 5-120mins post injury. Two studies investigating HET0016 showed large treatment effects in motor tested by contralateral hindlimb foot-faults, NSS and Corner turn test (table 4).

Benzothiazole

This group included the four highest quality studies utilizing the models such as FPI. The studies have described the injuries as moderate. Moreover, the interventions were given 15mins post injuries. Cognitive and motor activities were evaluated after the treatment. All studies showed negligible effects in motor coordination teste by Neurologic motor function, global NSS and Contra flexion and cognitive tested by memory score (table 4).

Calcium Channel Modulators

The Calcium channel regulators were studied using eight studies with high or highest quality scale. The effects of the drugs were studied and evaluated for cognitive and motor functions. The studies used FPI model for inducing moderate injuries in four studies. The other three studies did not specify the injury severity. The interventions were given 5-15mins post injury induction. Three studies investigating SNX-185 showed negligible effects in motor (MWM) function and large effects in behavioural function (Beam cross latency). While Ziconotide showed little effect in behavioural function (Beam walk test). In addition to this, S-emapamil showed large treatment effects in two studies (Morris water maze-cognition). Whereas, LOE-908 showed negligible effects in motor and cognitive (NSS and Memory score respectively) (table 4).

CNS stimulants

This group involves a single highest quality study evaluating the cognition. The study used the CCI model for TBI induction with moderate severity in the animals. The intervention was provided 24h post injury to the animals. Methylphenidate investigated showed large effect in cognition (Morris water maze) and very little effect in motor coordination (Righting reflex).

Glutamate Antagonist and Anti-Diabetics

The glutamate antagonist group involves a single high-quality study evaluating behaviour, motor and cognition. The study used the FPI model for induction with moderate severity. The treatment was given 5mins after the injury. AIDA showed large effects in motor and cognition (Beam walk performance and Morris water maze) (table 4).

The anti-diabetics include single high-quality study evaluating cognition. The study employed CCI model for injury induction. However, the severity of the injury was not specified. The intervention was given 10mins after injury. Glibenclamide showed negligible effect in Cognition (MWM) (table 4).

MAO-B inhibitors

This involves the three highest quality study. The study focused on the cognitive functions improved by the drug using FPI and weight drop model as induction model. The moderate to severe scale injury was induced in the studies. The drugs were administered 5-1440mins(24h) post injury. Out of three studies, one study investigated L-Deprenyl which showed large treatment effect in cognition tested by MWM. And the other two studies investigated Rasagiline showed large treatment effects in motor and cognition (motor function test and MWM tests respectively)(table 4).

Bradykinin receptor Modulators

There were six high quality studies investigating two different drugs focusing on motor and cognitive functions. The models involved in the studies for TBI induction were weight drop model and FPI model. However, the injury severity was not specified in four studies and moderate in two studies. The drugs were administered 30-480mins post injury. Four studies investigated LF16-068Ms showed negligible treatment effects on motor (NSS) whereas two studies investigating HOE-140 showed very little effect in locomotor and exploratory activity(crossing)(table 4).

NMDA receptor Antagonist

There were 14 high or highest quality studies evaluating the effects of seven drugs on motor and cognitive deficits. The models used in the studies were FPI and weight drop models. Out of these studies, 6 did not specify the injury severity and 8 specified the moderate severity of the injury. The drugs were given immediately or 15-1440mins(24h) post TBI. Two studies including Indole-2 carboxylic acid showed large effect in cognition (MWM) where kyrunate showed large treatment effect in cognition determined by one study. In addition to this, MK801 enlarged the treatment effects in cognitive functioning (MWM). Furthermore, CP98113 showed large treatment effects in cognition (MWM). Where the treatments effects in cognition (Memory score) were found to be negligible by CP98113, CP101581, CP101606 and in Morris water maze by NPS1506. Whereas, HU211 showed medium treatment effects in cognition (MWM). Moreover, D-cycloserine showed negligible effects in motor (NSS delta) and Cognitive (Novel object recognition) (table 4).

Biotherapeutics

There were 33 high- highest quality studies which investigated the effects of drugs on behavioural, cognitive and motor functioning. The models utilized in the studies were CCI, FPI and weight drop model. The injury severity was described as moderate in six studies and the rest of studies did not specify the severity of the injury. The treatments were given immediately or at 15-1440mins post TBI. From the two studies investigating Astaxanthine, large treatment effects were seen in motor (NSS). Whereas COG1410 showed medium effects (motor, cognitive) in beam walk, limb use asymmetry, MWM (reference memory) and Bilateral tactile removal tests. While, large effects in working memory (MWM). Other biotherapeutics also were found to show the treatment effects given in table(4).

Magnesium Supplements

There were ten high and highest quality studies investigated the effects of Magnesium on cognitive and motor functioning using FPI and Weight drop model. The induced injuries were moderate to severe or non-specified. The cognitive and spatial learning were evaluated by MWM and Motor functioning evaluated by Rota rod test, Angleboard scoring. The drugs were administered 15-1440mins(24h) post injury. All the studies investigating $MgSO_4$, $MgCl_2$ and Mg showed negligible treatment effects (table 4).

Serotonergics

The serotonergic groups were investigated using 15 High-Highest quality studies. The studies focused on the effects of the treatments on cognitive and motor functioning using the CCI models or weight drop model with moderate or non-specified injuries. The interventions were given 15-1440mins(24h) post injury. Out of the studies, seven studies showed the large treatment effects in cognition (MWM) and three studies showed large treatment effects in motor (elevated wooden beam test). In addition to this, two studies showed medium effects in motor (elevated narrow beam). The other studies investigating Buspirone, and 6n showed treatments effects shown in table (4).

Adrenergics

There were two Adrenergics (Nor-epinephrine, Atomoxetine) investigate by 8 studies high quality studies. The studies were based on the effects on motor and cognitive functioning using moderate or not specified TBI- models such as Sensorimotor cortex injury and fluid percussion injury model. The interventions were administered 24-11days post injury. Five studies investigating Atomoxetine showed medium effects in cognition (MWM) whereas negligible effects in motor (righting reflex). In addition to this, Nor-epinephrine showed negligible effects in motor (beam walk test) (table 4).

TRH analogues

There were 18 high/highest quality studies evaluating the outcomes of five drugs on motor and cognitive functions. The studies used CCI and FPI models inducing moderate injuries to the animals. The drugs were administered 30-1440mins(24h) after TBI induction. The studies investigating 1-ARA-35b showed large effects in cognition (MWM), motor (Foot-faults) whereas YM14673 showed large treatment effects in motor (righting reflex) and medium effect in motor (composite neuroscore). Moreover, 2-ARA-53a showed large effects in beam walk(motor) and Morris water maze (cognition)test (table 4).

Potassium Channel Modulators

There were two high quality studies utilizing FPI model for TBI induction. The induced injury was of moderate severity. The drug was administered at 10mins post injury.BMS-204532 showed negligible treatment effects in memory function (memory score).

General Anaesthetics

There were two high quality studies included in this group. The study utilized the CCI and weight drop model. However, the severity of the injury was specified. The interventions were administered at 5-60mins post injury. The drugs such as etomidate and sevoflurane. The former one showed the large treatment effects in Morris water maze and medium in beam walk test. Whereas, Sevoflurane improved the motor performance (NSS) (table 3).

INOS modulator

There were four high quality studies involved in this group. The models used for injury induction were FPI and CCI models with severe injury in one study and unspecified in rest of the studies. The drugs were administered at 6h-24h post injury. The motor functions were evaluated in the studies. The nitric oxide donor DETA improved motor coordination tested by Corner turn test. Whereas, other interventions such as AG, L-NIL and 1400W showed no improvement in motor functions (NSS) (table4)

Anti-Psychotics

There were four high quality studies involving the utilization of CCI model. The injury severity was moderate in two studies and rest of the studies did not specify the severity. The drugs were administered 24h post injury. The activities were performed to evaluate the cognition, motor functions. The drugs such as Haloperidol, Risperidone showed no improvement in any of the motor, behaviour and cognitive performances (table 4).

Miscellaneous

There were 19 studies involving the different drugs with different mechanism of actions. The effects were evaluated using different tests for cognitive and motor functions. The models utilized in different studies of this group were FPI, weight drop and CCI models. The severity of the injuries was described as moderate in 3 studies, severe in one and unspecified in rest of the studies. The interventions were administered immediately or at 1-1440mins(24h) after the injury. The treatment effects shown by different studies in table (3). The effects were shown in cognition, motor and behaviour determined by Morris water maze, Beam balance, Vibressae evoking forelimb test, NSS and so on. The drugs such as Fingolimod, A20, Necrostatin, Bromocriptine, Chloroquine, NBP and C1-INH showed large treatment benefits.

DISCUSSION

This study evaluated the data for rodents from 285 studies that determined behavioural, cognition and motor function effects of 125 interventions. For ongoing situation, a treatment was observed to be efficacious in reducing cognitive, behavioural and motor dysfunctions in rodents post injury if there was large and considerable improvement in measure(d>/=0.8, 95% CL not to be zero) based on multiple studies. While, taking account this criterion to publish the studies with considerable findings (Nfs>3), it was observed that there were 42 treatments improves the cognition function(d>/=0.8) and 44 treatments improved the motor function. While 6 interventions improved behavioural outcomes.

Cognition Function

The cognition functions in rodents after TBI were estimated using various tests such as Morris water maze, Novel object recognition. The cognition performance was improved by the Statins (atorvastatin with d=0.9), Cholinergics (Scopolamine[55]; d=1.65, Galantamine[154]; d=1.97, BIB99[107]; d=1.1, Rivastigmine[24]; d=2.97) shown in table (3). The cholinergics work by increasing the level of Acetylcholine that gets reduced by TBI induction. The Cox-2 inhibitor Nimesulide act as anti-inflammatory showed the treatment benefit in cognition improvement with d=3.36 tested by Barnez maze test. The effect is said to be associated with the selective inhibition of COX-2 enzyme[18]. Antimanic drugs such as Lithium has shown its effects in Morris water maze (d=1.63) indicating improvement in cognition performance.

Treatment with Anti-convulsants has come into the picture to reduce the seizure occurrence after TBI. Their benefit in cognition tested by MWM was foreseen with the use of Aniracetam(d=2.41) and Ethyl pyruvate(d=0.97) along with neuroprotection by reducing BBB disruption, neuroinflammation[7,119]. The PARP inhibitors such as INO-1001 improvised the effect in Morris water maze(d=0.9) along with the prevention of NAD+ destruction and deactivating the inflammatory cascade[30,35]. Calcium channel blocker S-emapamil has also shown improvement in Morris water maze(d=0.82) but not in other memory function. This can be due to involvement of number of factors in progression of TBI. However, it can prevent the entry of Calcium thereby reducing the edema[111]. In addition to this, MAO- B inhibitors such as Rasagiline and L-Deprenyl has shown improvement in cognition with d=1.65 and d=1.35 respectively. The binding capacity with the receptors vary with drugs due to which the effect sizes also vary[68,155]. Finally, Serotonergic drugs have also shown their treatment benefits on cognitive aspects in which OH-DPAT (5HT-2 antagonist) showed the improvement in Morris water maze test(d=1.86), Repinotan HCI (5-HT1A antagonist) (d=0.91). Since, the action of the drugs is on different receptor so as their efficacy[27,28,79,143]. In concern with the hormonal drugs, Allopregnanolone[42] showed improvement in cognition(d=0.75), Raloxifene[82] shown improvement in the working memory (d=1.08) than reference memory(d=0.14) along with the neuroprotective properties.

Motor Function

Calcium channel modulators such as SNX-185, a N-type voltage gated Calcium channel blocker have shown improvement in beam cross test. The doses of SNX-185 used were 50,100 and 200pmol. Out of these doses, most improvement was found with the 100pmol(d=1.32), more improvement with 200pmol(d=0.83), medium with 50pmol (d=0.47). After treatment with the SNX-185, a long-term cellular neuroprotection was seen in the rodents with the improvement of beam walk performance associated with brain regions including sensory and motor cortices. The beam walk test was typically associated with the sensory motor function which was seen to be improved. However, the motor performance tested by MWM test was not enhanced with the treatment altogether with three studies. However, the dose of 200pmol showed the improvement (d=0.98)[85]. In concern with the statins (HMG-CoA reductase inhibitor), Simvastatin(d=2.05) and Atorvastatin(d=1.82) showed improved motor performance tested by NSS, whereas atorvastatin also improved cognition (MWM). In addition to this, the statins also attenuated the inflammatory factors with maintenance of cerebral blood flow[132]. The hormonal drugs such as Progesterone has shown improvement in motor activity (MWM)(d=0.59) and Bilateral tactile removal test(d=0.95). progesterone was provided for different period of times. The treatment for 5days(d=1.1) was more effective than 3 days(d=0.24) (MWM). In other studies, the motor performances were improved by alpha-beta hydrolase domain 6 modulator WWL70(Rota rod) and beam walk test). As alpha-beta hydrolase inhibition upregulates the cannabinoid receptor showing the desirable effects[130].The cholinergics such as Donepezil improved the motor activity (elevated narrow beam) with most effective doses 2mg/kg(d=1.88), 3mg/kg(d=1.35)[52,117]. In concern with the corticosteroids, Hydrocortisone has shown improvement in motor coordination(d=1.46) along with reduction in tight junctions of vascular epithelial cells and neural

death[22]. Additionally, Biotherapeutics such as Vitamin B3 and B2 have shown improvement in motor functioning with treatment benefits (d=2.38, d=2.03) respectively. In addition, B3 was found to reduce lesion size and cell death at the site of injury[63]. The mechanism of B2 is associated with the scavenging of free radicals but shows no effects on cerebral edema[66]. And, COG1410 have shown treatment benefits in tests such as (tapered beam walk(d=0.4), limb use asymmetry(d=0.6), bilateral tactile removal test(d=0.56). The other biotherapeutics also showed the treatment benefits in motor coordination such as N-acetyl-seryl-aspartyl-lysyl-proline in NSS(d=5.3), Cerebrolysin in adhesive removal(d=2.74), foot-faults(d=5.21), placement errors(d=1.19), Erythropoietin in hindlimb foot-faults(d=1.45), rEPo in NSS(d=1.65), alpha-MSH in neuroscore(d=0.8), rh SDF-alpha in NSS(d=1.33), rhIL-1a in composite neuroscore(d=0.74), Albumin in neurological score(d=0.94).

The Serotonergic OH-DPAT which 5-HT2 antagonist improved the motor performance in elevated wooden beam(d=2.68), with most effective dose of 0.1mg/kg(d=3.28)[27,28,79,143]. Finally, TRH analogues such as 2-ARA-53a has shown improvement in motor coordination in beam walk test(d=1.53), YM-14673 improved the righting reflex(d=4.26) and 1-ARA-35b improved in the foot-faults(d=1.39). it has been seen that YM-14673 has improved the alertness and motor coordination after treatment. TRH analogues has shown the neuroprotective effects along with the motor and cognition improvement after injury[45,98].

Behavioural Function

The behavioural functions were determined by the activities such as Corner Turn test, Locomotor and exploratory activity, Barnez maze test, Open field test, elevated plus maze test, Beam cross test, Radial arm maze performance, staircase test, Y-maze test, marble burying behaviour, elevated narrow beam. Apocynin has shown in the improvement with medium effect size(d=0.6) in locomotory and exploratory activity(rearing), however improved effect was shown with the dose of 0.5mg/kg (d=1.53) than 0.05mg/kg (-0.47) and 5mg/kg(d=0.85). PARP inhibitors such as L-2286 at the dose of 100ug showed greater improvement in lowering anxiety (elevated plus maze test (d=2.07)) and motor performance (beam balance d=3.1) in rats. The benefits of L-2286 were seen when treated 30mins after injury[83]. Moreover,5- HT3 antagonist such as 6n has shown in behavioural activity determined by open field, marble burying and elevate plus maze tests. Two doses of 6n were used which were 1mg/kg and 2mg/kg. From the studies, It was found that the effects are dose dependent. The improvement in behaviour was more with 2mg/kg (d=2.46(open field), d=2.38(elevated plus maze), d=3.63(marble burying behaviour) than with 1mg/kg (d=1.67, d=1.8 and d=2.53 respectively). It was found that 6n improves the stress related behaviour dysfunction associated with the dose treatment[13].

Other Beneficial Treatment effects

There are some drug treatments that have shown large treatment effects on selected aspects but were studied by only one study. These include the drugs such (edema inhibitor)Albumin[8], (Anti-oxidants) OPC-14117[6] , Stilbazulenyl nitrone[9], and Pegorgotein[56], (Antibiotics)Rapamycin[38], (General anaesthetic) Etomidate[40],(Cox inhibitors) Nimesulide[18], Meloxicam[54], (Corticosteroids) Hydrocortisone[22], (Vitamin B family)[63,66] Vitamin B3 and B2, NLRP3 inflammasome inhibitor)MCC950[69] and Oridonin[141], (Anti-inflammatory, neuroprotective) Anti-APP[70], (CNS stimulant)Methylphenidate[78],Serotonergic(Repinotan HCl)[80], (PARP inhibitors) L-2286[83], 3-aminobenzamide[86], (Biotherapeutics) , rh-SDF-alpha[88] and Alpha-MSH[114] (C1 esterase inhibitor) C1-INH[89], (NMDA antagonist) , (Nitric oxide donor) DETA[93], (Glutamate antagonist) AIDA[94], (NMDA blocker) CP-98113[102,103] (Phosphatidylcholine synthesis enhancer)Citicoline[108],HU-211[120], (ACTH analogue) Cosyntropin[123], (Anxiolytic)Etifoxine[124] , (anti-inflammatory)TSG-6[133], (Inhibitor of growth factor-β1)N-acetyl-seryl-aspartyl-lysyl-proline[152], (Cholinergics) Galantamine[153], (Neuroprotective)NBP[154] , (MAO-B inhibitor) L-Deprenyl[155]. Their further investigation is required to verify the treatment effects in preclinical studies.

Conclusion

A wide range of studies were included according to the selection criteria. The studies evaluated the cognition, behavioural and motor functions improved by the 125 treatments. Out of 125, 42 treatments improved cognition, 44 improved motor and 6 treatments improved behavioural outcomes after TBI induction. The studies mostly utilized CCI, weight drop models to induce focal TBI in rodents after which the treatments were provided within 24-48hrs after induction. The treatments such as Atorvastatin, C1-INH, and Vitamin B3 and B2 showed large treatment benefits with other treatments discussed above in terms of the cognition, behavioural and motor function. In most of the studies, the rodents were treated with interventions within 1 hour post injury. However, in case

of humans it has been seen that the treatment was provided after 1 hour post injury. Hence these factors may have an effect in improvement of the condition of the patients. Therefore, models should be focused for early as well as late treatments before investigating them in clinical trials. Moreover, the drug concentrations were not reported into the studies. Thus, the drug concentrations are considered to be sufficient to show any effect. This consideration is not applicable for negative results.

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