Psychopharmacological Neuroprotection in Neurodegenerative Diseases, Part III: Criteria-Based Assessment: A Report of the ANPA Committee on Research

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Neuroprotective therapies for neurodegenerative diseases (NDDs) have proven elusive. The established psychotropic agents commonly used to treat the neuropsychiatric manifestations of NDDs are potential neuroprotective therapies, and neuropsychiatrists and others may benefit from a knowledge of the neuroprotective properties of these medications. This report identifies FDA-approved, first-line psychotropic drugs affecting intracellular mechanisms and meriting disease-modifying clinical trials in NDDs. The authors evaluated evidence for neuroprotection according to 1) preclinical; and 2) clinical criteria. Despite low-to-moderate preclinical evidence scores and scant clinical evidence, the most promising investigative priorities are 1) lithium and paroxetine in Alzheimer's disease (AD); 2) lithium in tauopathies (frontotemporal lobar degeneration [FTLD], FTDP-17); 3) lithium-plus-valproate in AD and amyotrophic lateral sclerosis; 4) pramipexole and valproate in Parkinson's disease; 5) amantadine and buspirone in multiple system atrophy; and 6) antidepressants in Huntington's disease. Preliminary clinical results signal caution regarding olanzapine use in AD and poor tolerability of lithium in progressive supranuclear palsy and corticobasal degeneration. These preliminary findings can lead to further clinical drug trials on the use of these well-known medications, not only for their psychotropic effects, but also for neuroprotection in NDDs.

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Neurodegenerative diseases (NDDs) are common and impose substantial morbidities and costs on patients, caregivers, and society.[1] The two most common, Alzheimer's disease (AD) and Parkinson's disease (PD), affect more than 5 million people in the United States and are exponentially increasing with population demographic trends;[2] and they result in considerable morbidities and costs.[3] Neuropsychiatric disturbances are prominent among these morbidities and can contribute significantly to quality of life in NDDs.[1] Clinicians prescribe psychotropic drugs to treat the neuro-

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psychiatric disturbances in NDDs[3] without regard to their potential neuroprotective effects. Psychotropics affect the intracellular mechanisms that are common to the pathobiology of a variety of NDDs (i.e., pathological proteins, proteasome, mitochondria, apoptosis), suggesting the possibility that psychotropics may function neuroprotectively across a number of these diseases.[1,3] The potential to modify the course of a disease through these effects has substantial implications for both patients and society.[1,4] The neuroprotective effects of established psychotropic medications are worth investigating, given the unsatisfying results from clinical trials of newer neuroprotective agents. Also, there is considerable advantage to re-purposing established psychotropic drugs because much is already known about their absorption, metabolism, excretion, toxicity, safety, blood–brain barrier penetration.

For these reasons, we previously reviewed the preclinical neuroprotective literature of psychotropic drugs pertaining to basic common neurodegenerative intracellular mechanisms.[1] In that work, we identified particular drugs as especially promising in view of consistent findings supporting putative neuroprotective properties. Subsequently, we considered a wider array of neuroprotective actions of psychotropics by pharmacological class and pharmacodynamic mechanism.[3] We further proposed provisional criteria[1,3] (Table 1) to assess neuroprotective evidence with a view toward identifying candidate agents most likely to succeed in clinical neuroprotective trials using delayed-start or randomized-withdrawal designs.[5]

This report updates the literature of FDA-approved first-line psychotropics to June 10, 2010. Over the intervening 33 months, there has been an exponential increase in relevant publications. We evaluated these data according to the previously-published provisional criteria,[1,3] shown in Table 1. This report focuses on common neurodegenerative intracellular effects in mature neural tissues. Neurons and glia may behave differently from non-neural cells, and immature and mature neurons can behave differently,[6] and even, sometimes, oppositely[7] with respect to apoptosis. For example, neurons and SK-N-SH neuroblastoma cells are differentially sensitive to antipsychotic-induced apoptosis.[6] Since NDDs generally involve mature neurons and glia, we therefore confined the present literature review to these mature cells and excluded studies done in cell-lines related to neuroblastomas (e.g., SK-N-SH, Neuro-2a, N1E-115, etc.), pheochromocytomas (e.g., PC12, KNA, KAT45, etc.), other malignancies, and other im-

TABLE 1. Criteria For Selecting Candidate Agents For Clinical Disease-Modifying Trials

Pre-Clinical Criteria
- Experimental evidence of a neuroprotective action using an established neuroprotective model at physiological drug doses (1-1,000 μM concentration in *ex vivo* normalized preparations of cultured cells or drug doses of 1-1,000 mM in *in vivo* live animals)
- Independent replication of the neuroprotective action in the same model and at the same dose
- Replication of the neuroprotective action in at least one other model at a physiological dose
- Replication of the neuroprotective action in neural tissue, preferably mature neurons or glia, at a physiological dose
- Independent replication of the neuroprotective action in the specified neural tissue at the same site and in the same animal at the same dose (e.g., replication of a rat striatal neuron finding in a rat striatal neuron model, rather than in rat cerebellar granule cells)
- Evidence in an accepted animal model for a specific disease (e.g., transgenic mice, MPTP primate model, etc., their limitations notwithstanding)
- Evidence of multiple neuroprotective actions that have been demonstrated as above
- A greater overall neuroprotective-positive "valence" (the number of neuroprotective actions minus the number of neurodegenerative actions demonstrated for the agent of interest (e.g., an agent with three distinct neuroprotective actions (e.g., inhibition of Aβ production, tau hyperphosphorylation, and mitochondrial permeability transition pore formation) and one neurodegenerative action (e.g., proteasome inhibition) might be assigned a positive valence of 3-1=2 (recognizing at the present time that these different actions may someday be demonstrated to have differentially weighted correlation coefficients with neurodegenerative progression)

Clinical Criteria
- Clinical evidence indicative of delayed progression (e.g., lack of deterioration in MMSE: after several years in a patient rigorously diagnosed with AD, 6 years or more in a given Hoehn-and-Yahr stage in a patient rigorously diagnosed with PD, failure of temporal lobe atrophy to progress on MRI serial medial temporal lobe quantitations in rigorously diagnosed AD, failure of flouro-DOPA binding to decline over a suitable time-frame in rigorously-diagnosed PD, etc.)
- Evidence of more benign disease course than expected for patients in a case series or clinical trial (particularly if symptomatic effects of the drug can be controlled for)

Provisional Preclinical and Clinical Criteria: for predicting which psychotropics should be studied clinically for effective translational neuroprotection.[1,3]

AD: Alzheimer's disease; DOPA: dihydroxyphenylacetic acid; μM: micromolar; mM: millimolar; MMSE: Mini-Mental State Exam; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI: magnetic resonance imaging; PD: Parkinson's disease.

mature cell-lines. For this reason, assessment by Table 1 preclinical criteria is limited to findings in mature neural tissues.

This report particularly emphasizes the extent of replication of these findings (Table 1: Preclinical Criteria 2–5). Also, we consider findings in disease-specific animal models (Table 1: Preclinical Criterion 6). In some cases (e.g., antidepressants), the disease-specific animal model literature also evaluates psychotropic effects on neuronal stem cells and glial progenitors in the mature brain (e.g., hippocampal neural stem cells in AD models, subventricular zone neurogenesis in Huntington's disease [HD] models), which are intrinsic to a drug's overall neuroprotective properties (via neuro-restoration), and so we selectively consider these findings in these models, provided they derive from or pertain to a disease-related brain structure of interest in mature adult animals. Multiple neuroprotective actions (Table 1: Preclinical Criterion 7) constituting neuroprotective valences (Table 1: Preclinical Criterion 8) are considered for each drug. Finally, this report reviews and assesses the clinical-trial literature (Table 1: Clinical Criteria).

Pending criteria predictive validity, the findings below represent an advance and refinement in selecting currently-prescribed psychotropics as candidates for disease-modifying clinical trials in NDDs.

METHOD

Preclinical findings in mature neural tissue and clinical findings in NDDs treated with psychotropics were evaluated by Table 1 criteria. Relevant studies were identified through a literature search (PubMed search terms, February 1, 2010: (alpha-synuclein OR beta-amyloid OR tau OR TDP-43 OR ubiquitin OR proteasome OR mitochondrial viability OR mitochondria OR mitochondrial transition pore OR cytochrome c release OR endosome OR lysosome OR autophagy OR endoplasmic reticulum OR leukocyte viability OR apoptosis) AND (pramipexole OR ropinirole OR amantadine OR haloperidol OR fluphenazine OR trifluoperazine OR thiothixene OR chlorpromazine OR thioridazine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR aripiprazole OR clozapine OR paliperidone OR iloperidone OR asenapine OR tetrabenazine OR pimavanserin OR lithium OR carbamazepine OR oxcarbazepine OR valproate OR amitriptyline OR imipramine OR nortriptyline OR desipramine OR clomipramine OR trimipramine OR doxepin OR protriptyline OR maprotiline OR bupropion OR fluoxetine OR sertraline OR fluvoxamine OR paroxetine OR citalopram OR s-citalopram OR trazodone OR nefazodone OR venlafaxine OR duloxetine OR mirtazapine OR buspirone OR diazepam OR chlordiazepoxide OR flurazepam OR temazepam OR chlorazepate OR clonazepam OR lorazepam OR oxazepam OR alprazolam OR zaleplon OR zolpidem OR zopiclone OR s-zopiclone OR cyproheptadine OR hydroxyzine OR benztropine OR trihexyphenidyl OR modafinil OR melatonin OR ramelteon) AND (neuron OR neuronal OR neurons OR glia OR glial OR neuroglia)).

Citations were reviewed to exclude findings in non-neural tissue and immature or malignancy-related cell lines. The review was limited to mature neural tissues (except in disease-specific animal models, where stem cells in mature brain were also considered) for reasons detailed above. We considered studies of any methodology but excluded models distinct from NDD (e.g., stroke, tardive dyskinesia, etc.). Cell culture conditions not typical of NDD (e.g., hyperosmotic stress, oxygen deprivation, etc.) were also excluded. The sole exception involved mature cerebellar granule cells (CGNs) that require hyperkalemic conditions for survival and reliably undergo apoptosis after withdrawal of serum or potassium.[8]

We focused on intracellular processes common across NDDs specified in the search terms (proteins, ubiquitin–proteasomal system, mitochondria, and apoptosis), and did not consider studies of intracellular calcium influx or other disease mechanisms unless those studies also considered the intracellular processes of interest. DNA fragmentation and condensation was required to ascertain apoptosis, whereas other indices (apoptotic mediator concentration, cell viability) were considered insufficient. The single exception to this involved CGN studies (as noted, CGNs are well documented to undergo apoptosis with serum/potassium deprivation). A single reviewer evaluated each abstract to determine whether it might potentially provide information on relevant intracellular processes after meeting the above methodological inclusions, even if not clearly stated, in which case the article itself was then reviewed.

In assessing Preclinical Criterion 6 (disease-specific animal models), outcomes consistent with putative neuroprotection were considered even if the study did not specifically address the intracellular targets required for cell and tissue studies, provided that outcomes were

relevant to disease-specific clinical outcomes. In interpreting the results and applying the findings in specific NDDs, findings from mature neural tissues in a disease-specific animal model were considered to be relevant to only that disease, whereas data pertaining to neural stem-cells in mature animals were considered to be potentially applicable to any disease, regardless of model.

Two studies considered combined treatment of lithium with valproate. The results of this combined treatment were considered separately and not included in the neuroprotective scores for either drug unless findings pertain to either drug given by itself.

Clinical findings evaluated by Table 1 Clinical Criteria were identified through a literature search (PubMed search terms, June 10, 2010: (pramipexole OR ropinirole OR amantadine OR haloperidol OR fluphenazine OR trifluoperazine OR thiothixene OR chlorpromazine OR thioridazine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR aripiprazole OR clozapine OR paliperidone OR iloperidone OR asenapine OR tetrabenazine OR pimavanserin OR lithium OR carbamazepine OR oxcarbazepine OR valproate OR amitriptyline OR imipramine OR nortriptyline OR desipramine OR clomipramine OR trimipramine OR doxepin OR protriptyline OR maprotiline OR bupropion OR fluoxetine OR sertraline OR fluvoxamine OR paroxetine OR citalopram OR s-citalopram OR trazodone OR nefazodone OR venlafaxine OR duloxetine OR mirtazapine OR buspirone OR diazepam OR chlordiazepoxide OR flurazepam OR temazepam OR chlorazepate OR clonazepam OR lorazepam OR oxazepam OR alprazolam OR zaleplon OR zolpidem OR zopiclone OR s-zopiclone OR cyproheptadine OR hydroxyzine OR benztropine OR trihexyphenidyl OR modafinil OR ramelteon) AND (clinical trial OR randomized controlled trial) AND (neuroprotection OR neuroprotective OR disease-modifying OR disease modifying OR disease modification OR progression OR disease progression OR biomarker OR beta-amyloid OR tau protein OR alpha-synuclein OR huntingtin OR TAR DNA binding protein 43 OR TAR DNA-binding protein 43 OR TDP-43 OR TDP 43 cerebrospinal fluid OR imaging OR magnetic resonance imaging OR single photon emission computed tomography OR positron emission tomography) AND (neurodegenerative disease OR Alzheimer's disease OR Parkinson's disease OR Huntington's disease OR frontotemporal lobar degeneration OR FTLD OR FTD OR frontotemporal dementia OR ALS OR amyotrophic lateral sclerosis OR progressive supranuclear palsy OR corticobasal degeneration OR Pick's disease OR MSA OR multiple system atrophy)). Methods specific to the quantitative evaluation of Table 1 criteria are described in respective Results sections.

RESULTS

The preclinical search returned 623 citations. Review of abstracts resulted in 103 potentially relevant articles that, after review, yielded 96 studies with potentially contributory results. The findings are presented and summarized for each Table 1 preclinical criterion, quantitatively for the composite preclinical criteria, and by disease for the clinical criteria.

Pre-Clinical Criterion 1 The search was limited to neurons and glia. The review was limited to established preclinical models using physiological doses in *mature* neurons and glia.

Pre-Clinical Criteria 2–5 Replicated neuroprotection was classified as replication within a given model, *independent* replication within the model, replication in at least one other model, and *independent* replication in at least one other model. The degree to which replication was achieved for findings is indicated in Table 2 (unreplicated findings are not included in this table). As seen in Table 2, findings that have been the best established in terms of independent replications within and across different models include apoptosis of cortical neurons induced by haloperidol, reduced tau phosphorylation (Thr181, Tau1, AT8, Thr231) and apoptosis by lithium, and neuroprotective increases in alpha-synuclein (αSyn) by valproate. Table 3 displays the replication of findings across various antidepressants, irrespective of the specific antidepressant with which the finding was associated (Table 3 findings were not included in the quantitative analysis).

Within animal models, multiple benefits in the amyotrophic lateral sclerosis (ALS) G93A transgenic mouse (Table 2) of lithium, hippocampal neurogenesis in rodents with antidepressants (Table 3), and improved motor performance in the R6/2 HD transgenic mice with nortriptyline and sertraline (Table 3) have each been independently replicated. Across models, Complex I inhibition by haloperidol and other neuroleptics, decreased Aβ42, tau phosphory-

TABLE 2. Criterion 2: Replication of Findings

	RWIM	IRWIM	ROM	IROM
Neuroleptics				
Neuroleptics inhibit frontal cortical Complex I[9,10]	√		√	√
Haloperidol inhibits frontal cortical Complex I[9,10]	√		√	√
Haloperidol inhibits Complex II[11]	√			
Haloperidol induces striatal AIF translocation[12]			√	
Haloperidol induces cortical apoptosis[13-15]	√	√	√	√
Atypical Antipsychotics	RWIM	IRWIM	ROM	IROM
Risperidone and clozapine inhibit frontal cortical Complex I[9]	√			
Clozapine increases Complex IV[10]	√			
Lithium	RWIM	IRWIM	ROM	IROM
Decreased Aβ1-42 in transgenic AD mouse models[16,17]			√	√
Decreases tau[18]	√			
Decreases fibrillar tau in transgenic FTDP-17 mouse models[19,20]			√	
Decreases tau phosphorylation at:				
Thr181[21-24]	√	√	√	√
Tau1 (Ser195/199/198/202/Thr205)[19,21,25-30]	√	√	√	√
Ser199[23,29,31]			√	√
Ser202[32,33]			√	√
AT8 (Ser199/Ser202/Thr205)[17,20,21,24,28,29]	√	√	√	√
Thr231[21,24,32,34]	√	√	√	√
8D8 (Ser396)[21,23,29,32]			√	√
Ser404[29,32,35]			√	√
PHF1 (Ser396/Ser404)[20,25,26,33]			√	√
Decreased cytochrome c release[36, 37]			√	√
Decreases apoptosis in CGNs[30,35,38,39]	√	√	√	√
Decreases disease progression in G93A SOD1 transgenic ALS mice				
Preserves motoneurones[40,41]	√	√		
Delayed disease onset[40,41,42]	√	√		
Improved motor function[40-42]	√	√		
Improved grip strength[40,41]	√	√		
Prolonged survival[40,41]	√	√		
Carbamazepine	RWIM	IRWIM	ROM	IROM
Induced apoptosis[8,43,44]	√		√	√
Valproic Acid	RWIM	IRWIM	ROM	IROM
Increased αSyn[45-47]	√	√	√	√
Increased αSyn in CGNs after toxic exposures (6-OHDA, glutamate)[45,46]			√	√
Decreased mono-ubiquitylated αSyn[46,47]			√	
Prevents αSyn nuclear translocation[46,47]			√	
Decreased Aβ and neuritic plaques in amyloidopathic transgenic AD mice[48]			√	
Decreased tau phosphorylation at Thr205 and Ser400[49]			√	
Inhibited free radical damage[50]			√	
Inhibited apoptosis[45,47,49,51]			√	√
Imipramine	RWIM	IRWIM	ROM	IROM
Increased hippocampal neurogenesis[52,53]	√		√	√
Desipramine	RWIM	IRWIM	ROM	IROM
Decreased neuron apoptosis[54,55]			√	√
Nortriptyline	RWIM	IRWIM	ROM	IROM
Decreased neuron apoptosis[54,56]			√	√
Fluoxetine	RWIM	IRWIM	ROM	IROM
Decreased rat hippocampal neural stem cell apoptosis[57,58]			√	
Stimulated rat hippocampal neural stem cell[52,57,58]			√	√
Sertraline	RWIM	IRWIM	ROM	IROM
Increased hippocampal, cortical, and striatal BDNF[59]	√			
Increased hippocampal neurogenesis[59]	√			
Increased striatal neurogenesis[59]	√			
Paroxetine	RWIM	IRWIM	ROM	IROM
Decreased hippocampal and cortical Aβ1-17[60]			√	
Decreased hippocampal and amygdalal HT7 tau[60]			√	

TABLE 2. Criterion 2: Replication of Findings (Continued)

	RWIM	IRWIM	ROM	IROM
Benzodiazepines	RWIM	IRWIM	ROM	IROM
Diazepam reduced t-butyl-hydroxy-peroxide neuronal cytochrome c release[61]			√	
Clonazepam did not induce free radicals in rat cortical neurons or glia[62]			√	

Each finding is classified according to its replication status, including whether it has been replicated within a given mature neural model (RWIM), independently replicated within that model (IRWIM), replicated outside that model (ROM) in a different mature neural model, or independently replicated outside that model (IROM) in a different mature neural model. Checks indicate replication, whereas blanks indicate a lack of replication for that category. Complexes I, II, and IV pertain to the complexes of the mitochondrial respiratory chain.

Aβ, A-beta, or beta-amyloid protein; AD: Alzheimer's disease; AIF: apoptotic-inducing factor; ALS: amyotrophic lateral sclerosis; αSyn: alpha-synuclein; BDNF: brain-derived neurotrophic factor; CGN: cerebellar granule cell; FTDP-17: frontotemporal dementia with parkinsonism linked to mutations on Chromosome 17; G93A SOD1: gene mutation in superoxide dismutase 1; 6-OHDA: 6-hydroxydopamine; Ser: serine; Thr: threonine. Other terms regard specific antibodies for tau protein epitopes and species (AT8, 8D8, HT7, PHF1, Tau1).

lation (Ser199, Ser202, Ser396, Ser404, PHF1), and cytochrome c release with lithium, apoptosis with carbamazepine, and decreased apoptosis with valproate have each been independently replicated (Table 2). Independently replicated findings for antidepressants across models include hippocampal neurogenesis with imipramine, decreased neuronal apoptosis with desipramine and nortriptyline, hippocampal neural stem-cell stimulation with fluoxetine (Table 2), and upregulated hippocampal neural stem-cell brain-derived neurotrophic factor (BDNF) in rats with imipramine and mice with sertraline (Table 3). Other findings have not been independently replicated.

Findings for Criteria 1–5 (Table 2 and Table 3) suggest the potential danger of haloperidol, especially in cortical dementias, and the potential benefit of lithium, especially in AD and tauopathies, and valproate in PD and synucleinopathies. Less well-replicated findings suggest the potential danger of haloperidol, neuroleptics, and carbamazepine in NDDs (especially PD with neuroleptics) and the potential benefit of lithium in ALS, AD, and tauopathies, valproate in various NDDs, and various antidepressants in AD, hippocampal sclerosis, and HD.

Pre-Clinical Criterion 6 Evidence in accepted disease-specific animal models is presented in Table 4. Findings for each drug in specific animal models are presented with corresponding neuroprotective action scores (NPASs). NPASs indicate the number of times neuroprotective (+), absence of a significant difference (±), and pro-degenerative (–) findings were obtained over the total number of experiments detailed in the papers assessing the property. For example, an NPAS of 13+/7±/4– indicates that of a total of 24 experiments detailed in articles addressing the prop-

TABLE 3. Replicated Antidepressant Findings Across Drugs

Antidepressants	RWIM	IRWIM	ROM	IROM
Decreased IL-1β, IL-6, and TNFα[57,63]	√			
Increased BDNF in hippocampal neural stem cells[59,64]			√	√
Increased hippocampal neurogenesis in mice[52,59]	√	√		
Increased hippocampal neurogenesis in rats[53,58,63,64]	√	√		
Decreased hippocampal neural stem cell LPS-induced apoptosis[57,63,64]	√			
Decreased MPTP mouse survival[65]	√			
Decreased caudate medium spiny neuron glutamate-induced apoptosis in YAC128 transgenic HD mouse model[54]	√			
Improved motor performance in R6/2 transgenic HD mouse model[56,59]	√	√		

Replicated findings collectively across antidepressants (not considering specific drugs or antidepressant classes). Each finding is classified according to its replication status, including whether it has been replicated within a given mature neural model (RWIM), independently replicated within that model (IRWIM), replicated outside that model (ROM) in a different mature neural model, or independently replicated outside that model (IROM) in a different mature neural model. Checks indicate replication, whereas blanks indicate a lack of replication for that category.

BDNF: brain-derived neurotrophic factor; HD: Huntington's disease; IL: interleukin; LPS: lipopolysaccharide; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; R6/2 HD: R6/2 HD mouse model; TNF: tumor necrotic factor; YAC128: HD yeast artificial chromosome 128 HD mouse model.

TABLE 4. Findings in Disease-Specific Animal Models

	NPAS
Dopamine Agonists	
Pramipexole decreased αSyn in rotenone PD mouse[66]	1+/0±/0−
Pramipexole inhibited ROS in MPTP rat model of PD[67]	4+/0±/0−
Pramipexole decreased DA neuron death in rotenone mouse[66]	2+/0±/0−
Pramipexole decreased motor deficits in rotenone PD mouse[66]	1+/0±/0−
Neuroleptics	
Trifluoperazine decreased glutamate-induced apoptosis in CN MSN in HD YAC128 Tg mouse[54]	1+/1±/0−
Atypical Antipsychotics	
Quetiapine decreased β-secretase activity in APP/PS1 AD Tg mice)[68]	5+/3±/0−
Quetiapine decreased Aβ42 and Aβ40 in APP/PS1 AD Tg mice[68]	6+/2±/0−
Quetiapine decreased Aβ Plaques in APP/PS1 AD Tg mice[68]	8+/0±/0−
Quetiapine decreased RNS in APP/PS1 AD Tg mice[68]	2+/0±/0−
Quetiapine improved memory in APP/PS1 AD Tg mice[68]	13+/7±/0−
Low-dose clozapine delayed death in G93A ALS Tg mice[69]	1+/0±/1-
Standard dose clozapine accelerated paralysis (G93A)[69]	0+/0±/1-
Standard dose clozapine accelerated mortality (G93A)[69]	0+/0±/1-
VMAT-2 Inhibitors	
Tetrabenazine improved motor performance in YAC128 Tg mouse model of HD[70]	11+/4±/0−
Tetrabenazine decreased MSN loss in YAC128 Tg HD mouse model[70]	2+/0±/0−
Mood Stabilizers: Lithium	
Decreased αSyn aggregation (male ALS G93Amice)[41]	3+/1±/0−
Decreased UBQ aggregation (male ALS G93Amice)[41]	3+/0±/0−
Decreased SOD1 aggregation (male G93A mice)[41]	4+/0±/0−
Decreased APP in AD APPV171I/APPsw(KM670/671NL) mice[17]	2+/0±/0−
Decreased β CTF in AD APPV171I/APPsw mice[17]	2+/0±/0−
Decreased Aβ40 in female AD APPsw/PS1 mice[16]	2+/0±/0−
Decreased Aβ42 in female AD APPsw/PS1 mice[16]	2+/0±/0−
Decreased Aβ42 in AD APPV171I/APPsw mice[17]	2+/0±/0−
Decreased Aβ42 plaques in APPV171I/APPsw mice[17]	2+/0±/0−
Decreased Thr181 phos in SAMP8 senescent mice[23]	1+/0±/0−
Decreased Thr181 phos in late PS1/APPsw/tauP301L mice[24]	2+/0±/0−
Decreased Tau1 dephos in FTDP-17 VLW mice[19]	1+/0±/0−
Decreased Ser199 phos in SAMP8 mice (0.5mM)[23]	1+/0±/0−
Decreased Ser202 phos in Tauopathic htau23 overexpressing mice[32]	2+/0±/0−
Decreased Ser202 phos in FTDP17 P301L/4R0N mice[33]	2+/2±/0−
Decreased AT8 phos in AD APPV717I/APPsw mice[17]	4+/0±/0−
Decreased AT8 phos in *late* AD PS1M146V/APPsw/tauP301L mice[24]	2+/0±/0−
Decreased AT8 phos in FTDP-17 GSK-3β/tauG272V/tauP301L/tauR406W mice[20]	3+/0±/0−
Decreased Thr212 phos in SAMP8 mice (0.5mM)[23]	1+/0±/0−
Decreased Thr217 phos in SAMP8 mice (0.5mM)[23]	1+/0±/0−
Decreased AT100 phos in *late* PS1M146V/APPsw/tauP301L AD mice[24]	2+/0±/0−
Decreased Thr231 phos in *late* PS1M146V/APPsw/tauP301L AD mice[24]	2+/0±/0−
Decreased Thr231 phos in Tauopathic htau23 overexpressing mice[32]	2+/0±/0−
Decreased Ser396 phos in SAMP8 mice (0.5mM)[23]	2+/0±/0−
Decreased Ser 396 phos in Tauopathic htau23 overexpressing mice[32]	2+/0±/0−
Decreased tau phos at Ser 404 in Tauopathic htau23 overexpressing mice[32]	2+/0±/0−
Lithium 0.2mM decreased tau phos at PHF1 in FTDP-17 P301L/4R0N mice[33]	2+/2±/0−
Lithium 0.6mM prevented phos at PHF1 in FTDP-17 GSK-3β/tauG272V/tauP301L/tauR406W mice[20]	2+/0±/0−
Lithium 0.8mM reversed phos at PHF1 in FTDP-17 GSK-3β/tau/tau/tau VLW mice[20]	1+/1±/0−
Lithium 0.8mM decreased fibrillar tau phos in FTDP-17 GSK-3β/VLW mice[20]	5+/0±/0−
Decreased fibrillar tau aggregation in VLW mice[19]	1+/0±/0−
Decreased filamentous tau aggregation in VLW[19]	1+/0±/0−
Activated autophagy and LC3-positive autophagic vacuoles in male ALS G93A mice (assumes that autophagy of diseased Mt is neuroprotective)[41]	3+/0±/0−
Increased mitochondrial number in motor neurons in male ALS G93A mice[41]	2+/0±/0−
Inhibited quinolinate apoptosis in HD rat STR[71]	2+/0±/0−
Inhibited apoptosis in SAMP8 mouse CGNs[23]	38+/3±/0−
In AD APPV717I/APPsw mice, lithium preserved:	
FL CTX dendrite structure[17]	1+/0±/0−
HC CTX dendrite structure[17]	1+/0±/0−
In PD MPTP mice, lithium prevented nigrostriatal DA neuron loss[72]	6+/0±/0−
In HD quinolinic acid rat, lithium 1mEq/L:	
Decreased loss of striatal neurons[71]	1+/0±/0−
D1-bearing medium spiny striatal neurons[71]	5+/0±/0−
Induced striatal neuronal and astroglial progenitor proliferation[71]	2+/0±/1−

TABLE 4. Findings in Disease-Specific Animal Models (Continued)

	NPAS
Increased motor neuron survival in G93A ALS mice	
Li_2CO_3 0.2% p.o. beginning age 8 weeks[40]	20+/0±/0−
Li_2CO_3 1mq/kg beginning age 75 days (males only)[41]	13+/3±/0−
Decreased corticospinal neuron pathology in G93A[41]	1+/0±/0−
Decreased astrocytosis in G93A[41]	3+/0±/0−
Increased Lamina VII neurons (interneurons)inG93A[41]	7+/0±/0−
Improved spatial learning in APPV717I/APPsw[17]	1+/0±/0−
Delayed disease onset in ALS G93A mice	
Li_2CO_3 1mq/kg beginning age 75 days (males only)[41]	3+/0±/0−
Li_2CO_3 0.2% p.o. beginning age 8 weeks[40]	1+/0±/0−
LiCl 60mg/kg i.p. bid beginning age 30 days[42]	1+/0±/0−
Improved motor function in ALS G93A mice[40,41,42]	
Li_2CO_3 1mq/kg beginning age 75 days (males only)[41]	3+/0±/0−
Li_2CO_3 0.2% p.o. beginning age 8 weeks[40]	1+/0±/0−
LiCl 60mg/kg i.p. bid beginning age 30 days[42]	3+/0±/0−
Improved grip strength in ALS G93A mice[40,41]	
Li_2CO_3 1mq/kg beginning age 75 days (males only)[41]	3+/0±/0−
Li_2CO_3 0.2% p.o. beginning age 8 weeks[40]	1+/0±/0−
Improved stride length in ALS G93A mice[41]	3+/0±/0−
Improved extension reflex in ALS G93A mice[40]	0+/1±/0−
Improved survival in ALS G93A mice[40,41]	
Li_2CO_3 1mq/kg beginning age 75 days (males only)[41]	1+/0±/0−
Li_2CO_3 0.2% p.o. beginning age 8 weeks[40]	1+/0±/0−
Mood Stabilizers: Valproic Acid	
Increased α-secretase processing in AD APP23(sw) mouse[48]	1+/0±/0−
Increased β-secretase processing in AD APP23(sw) mouse[48]	1+/0±/0−
Decreased γ-secretase processing in AD APP23(sw) mouse[48]	1+/0±/0−
Decreased Aβ in AD APP23(sw) mouse[48]	1+/0±/0−
Decreased Aβ1-40 in AD APP23/PS45(PS1 G384A) mouse[48]	1+/0±/0−
Decreased Aβ1-42 in AD APP23/PS45(PS1 G384A) mouse[48]	1+/0±/0−
Decreased Aβ neuritic plaques in AD APP23(sw) mouse[48]	10+/0±/0−
Decreased Aβ neuritic plaques in AD APP23/PS45(PS1 G384A) mouse[48]	3+/0±/0−
Improved spatial memory deficits in 7-month-old APP23 AD mice[48]	3+/0±/0−
Increased αSyn in the PD rotenone rat SN[47]	3+/0±/0−
Increased αSyn in the PD rotenone rat STR[47]	2+/0±/0−
Decreased mono-ubiquitylated αSyn in PD rotenone rat STR[47]	2+/0±/0−
Decreased mono-ubiquitylated αSyn in PD rotenone rat SN[47]	3+/0±/0−
Prevented αSyn nuclear translocation in PD rotenone rat SN[47]	1+/0±/0−
Prevented nigrostriatal neuronal loss in the rotenone PD mice[47]	5+/0±/0−
Prevented SN apoptosis in the rotenone PD mouse model[47]	1+/0±/0−
Valproate 300 mg/kg improved neurological function in ALS G93A mice[42]	3+/0±/0−
Valproate 300 mg/kg improved survival time (lifespan) by 13 days in ALS G93A mice[42]	1+/0±/0−
Increased spinal cord SMN protein concentrations in SMA mice[73]	4+/0±/0−
Decreased lumbar spinal motor neuron degeneration in SMA mice[73]	4+/3±/0−
Improved neuromuscular junction innervation in SMA mice[73]	2+/0±/0−
Increased lumbar spinal cord astrocyte proliferation in SMA mice[73]	1+/0±/0−
Increased lumbar spinal cord neurogenesis in SMA mice[73]	1+/0±/0−
Improved muscle atrophy in SMA mice[73]	1+/0±/0−
Increased motor evoked potentials in SMA mice[73]	1+/0±/0−
Improved motor function in SMA mice[73]	4+/0±/0−
Mood Stabilizers: Lithium	
Li60mg/kg+VPR300 mg/kg delayed disease onset by 15 days in G93A[42]	1+/0±/0−
Li60mg/kg+VPR300 mg/kg improved neurological function at day 120 in ALS G93A[42]	3+/0±/0−
Li60mg/kg+VPR300 mg/kg improved survival time (lifespan) by 18 days in ALS G93A[42]	1+/0±/0−
Antidepressants	
Paroxetine decreased Aβ1-17 in 3XTgAD PS1-M146V/APPswe/P301L AD mouse HCNs[60]	3+/0±/0−
Paroxetine decreased Aβ1-17 in 3XTgAD cerebral cortex[60]	1+/0±/0−
Paroxetine decreased Aβ1-40 in 3XTgAD HCNs[60]	2+/0±/0−
Paroxetine decreased HT7 human tau in HC CA1 in male>female 3XTgAD l[60]	3+/1±/0−
Paroxetine decreased HT7 human tau in amygdala in male>female 3XTgAD[60]	3+/1±/0−
Paroxetine improved spatial navigation (implies memory acquisition but not retention) in 3xTgAD[60]	5+/2±/0−

TABLE 4. Findings in Disease-Specific Animal Models (Continued)

Antidepressants	NPAS
Reduced MPTP mouse survival	
Desipramine[65]	0+/0±/1-
Fluoxetine[65]	0+/0±/1-
Decreased glutamate-induced apoptosis in CN medium spiny neurons in YAC128 Tg HD mouse[54]	
Desipramine[54]	2+/0±/0−
Nortriptyline[54]	2+/0±/0−
Maprotiline[54]	2+/0±/0−
Improved motor performance in R6/2 HD mouse	
Nortriptyline[56]	3+/5±/0−
Sertraline[59]	3+/0±/0−
Nortriptyline delayed disease-onset in R6/2 HD mouse[56]	1+/0±/0−
Sertraline reduced striatal atrophy in HD R6/2 mice[59]	2+/0±/0−
Sertraline increased HC neurogenesis in HD R6/2[59]	2+/0±/0−
Sertraline increased striatal neurogenesis in HD R6/2[59]	2+/0±/0−
Sertraline increased HC, CTX, and STR BDNF in R6/2 HD mouse[59]	3+/0±/0−
Sertraline prolonged survival in R6/2 HD mouse[59]	2+/0±/0−
Nortriptyline decreased spinal cord cytochrome c release in G93A ALS mice[56]	4+/0±/0−
Nortriptyline delayed disease-onset in G93A SOD1 ALS mouse[56]	2+/1±/0−
Nortriptyline decreased motor-neuron death in G93A SOD1 ALS mouse[56]	2+/0±/0−
Nortriptyline decreased ventral horn atrophy in G93A SOD1 ALS mouse[56]	1+/0±/0−
Nortriptyline improved motor performance in G93A SOD1 ALS mouse[56]	17+/19±/0−
Nortriptyline reduced disease duration at higher doses in G93A SOD1 mouse[56]	2+/1±/0−
Nortriptyline prolonged survival in G93A SOD1 ALS mouse[56]	2+/1±/0−

Specific findings in animal models with their neuroprotective action scores, including the number of times neuroprotective (+), absence of significant difference (±), and pro-degenerative (–) findings have been obtained in all experiments documented in the reviewed literature. The more positive scores reflect a greater number of neuroprotective findings in animal models, whereas the more negative scores signal more pro-degenerative findings in animal models.

Aβ: A-beta or beta-amyloid protein; AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; APP: amyloid precursor protein; αSyn: alpha-synuclein; AT8: AT8 tau epitope; AT100: AT100 tau epitope; βCTF: beta C-terminal fragment of amyloid; BDNF: brain-derived neurotrophic factor; CA1: CA1 sector of the hippocampus; CGN: cerebellar granule neuron; CN: caudate nucleus; CTX: cortex; D1: dopamine 1 receptor; DA: dopamine; dephos: dephosphorylation; FTDP-17: frontotemporal dementia with parkinsonism associated with mutations of the tau gene on Chromosome 17; G93A: G93A mutation in SOD1 mouse model of ALS; GSK: glycogen synthase kinase; HC: hippocampus; HCN: hippocampal neuron; HD: Huntington's disease; HT7: HT7 tau epitope; htau: human tau; Li: lithium; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN: medium spiny neuron; Mt: mitochondrion or mitochondrial; PD: Parkinson's disease; PHF1: PHF1 tau epitope; phos: phosphorylation; PS: presenilin; R6/2: huntingtin exon-1 with expanded polyglutamine repeat transgenic mouse model of HD; RNS: reactive nitrogen species; ROS: reactive oxygen species; Ser: serine; SMA: spinal muscular atrophy; SMN: SMN protein in spinal muscular atrophy mouse model; SN: substantia nigra; SOD1: superoxide dismutase 1 enzyme; STR: striatum; Tau1: Tau1 epitope; Tg: transgenic; Thr: threonine; UBQ: ubiquitin; VPR: valproic acid; YAC: yeast artificial chromosome.

erty, 13 found neuroprotection, 7 found no effect (neither neuroprotective nor neurodegenerative), and 4 found a prodegenerative effect.

In Table 4, drugs showing benefit in AD animal models include quetiapine, lithium, valproate, and paroxetine. In tauopathic diseases, including FTDP-17, lithium has potential. In PD models, pramipexole, lithium, and valproate have had positive results. In HD, trifluoperazine, tetrabenazine, lithium, desipramine, nortriptyline, maprotiline, and sertraline are all promising. ALS models suggest low-dose clozapine, lithium, valproate, lithium-plus-valproate, and nortriptyline as possible treatments. For spinal muscular atrophy (SMA), valproate has had benefit. Deterioration occurred with desipramine and fluoxetine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD, but this might be unique to the MPTP model. Deterioration in the ALS mouse was noted with standard doses of clozapine, whereas a lower dose, similar to the dose used in PD patients, actually extended survival.

Pre-Clinical Criterion 7 Evidence of *multiple* neuroprotective actions was derived from assessment of NPASs. NPASs were transformed into *neuroprotective valences*. The neuroprotective *valence* for a drug is the net sum of its neuroprotective and neurodegenerative pre-valence scores. If the sum of the three components (i.e., +, ±, and – scores) of an NPAS for an individual action was a positive value, the resulting pre-valence score for the action was 1+. Likewise, if the NPAS sum was a negative value, then the pre-valence score for that action was 1–, indicating an overall prodegenerative finding across studies for the action. To obtain the valence for the drug, the positive and negative pre-valence for the individual actions were summed. Valences for a drug >1+ indi-

cate multiple neuroprotective actions. Higher valences indicate a greater number of documented neuroprotective actions. All findings, including those in animal models, are included in these scores. Drug valence scores correct for countervailing pro-degenerative actions by their subtraction from the total score. Consequently, the higher the positive valence score, the greater the number of neuroprotective actions outweighing any coexisting pro-degenerative actions that the drug might have. (Similarly, the greater the negative valence score, the more likely a drug is to promote or accelerate NDD.) Valences are presented in Table 5 and are also stated in terms of findings in specific disease models. (It is worth mentioning that although a single substantive *clinically-proven* pro-degenerative action would likely be sufficient to preclude further drug development, the *clinical* relative risks of *preclinical* pro-degenerative actions relative to *preclinical* neuroprotective actions are not yet clear. For example, it is not currently clear whether anti-mitochondrial effects will outweigh salutary pathogenic protein effects or direct antiapoptotic effects. Thus, the existence of preclinical deleterious actions should not necessarily exclude clinical

TABLE 5. Individual Drug Neuroprotective Valence Scores by Pharmacological Class

Drug	Valence	AD	PD	Tau	HD	ALS	SMA
Dopamine agonists							
Pramipexole	4+		4+				
Neuroleptics							
Haloperidol	5−						
Fluphenazine	0						
Trifluoperazine	3+				1+		
Thiothixene	0				0		
Chlorpromazine	1−						
Atypical antipsychotics							
Risperidone	2−						
Olanzapine	1−						
Quetiapine	5+	5+					
Aripiprazole	1+						
Low-dose clozapine	1+					1+	
Standard-dose clozapine	2−					2–	
VMAT-2 inhibitor							
Tetrabenazine	2+		0		2+		
Mood stabilizers							
Lithium	36+	13+	1+	4+		8+	0
Carbamazepine	0						
Oxcarbazepine	1−						
Valproic acid	27+	6+	3+			2+	8+
Lithium+valproate	5+					3+	
Antidepressants							
Tricyclics							
Imipramine	11+						
Desipramine	8+		1−		1+		
Nortriptyline	13+				6+	7+	
Tetracyclics							
Maprotiline	1+				1+		
SSRIs							
Fluoxetine	8+		1−				
Sertraline	9+				6+		
Paroxetine	4+	4+					
Benzodiazepines							
1-5 μM diazepam	1+						
25-50 μM diazepam	2−						
Clonazepam	0						

These studies were done in models *directly* relevant to the disease of interest.

Neuroprotective valences of drugs by pharmacological class. A neuroprotective valence is determined by the sum of its valence score for neuroprotective actions minus its valence score for neurodegenerative actions, as described in the text. The higher the positive valence, the greater the neuroprotective potential, as determined from the sum of its neuroprotective and pro-degenerative actions.

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; Lithium+valproate: combined treatment with lithium and valproate administered together; μM: micromolar; PD: Parkinson's disease; SMA: spinal muscular atrophy; SSRIs: selective serotonin-reuptake inhibitor; Tau: tauopathies (i.e., tauopathic diseases); VMAT-2: vesicular monoamine transporter 2.

consideration of a drug if noteworthy preclinical beneficial actions are apparent.)

Pre-Clinical Criterion 8 Neuroprotective valence was determined as for Criterion 7, and, in Table 6, drugs are listed in rank order according to their valences. Although Criterion 8 seems redundant with the preceding one for the drugs at hand, it is actually distinct because it is possible to have a large number of neuroprotective actions yet still have a low or even negative valence because of an even greater number of pro-degenerative actions. Fortunately, the drugs considered here had minimal countervailing effects, so valences parallel NPAS and pre-valence scores.

On the basis of these valences, the glycogen synthase kinase 3-β (GSK-3β)-inhibitor lithium is the most promising neuroprotective agent, followed by the GSK-3β and histone deacetylase (HDAC) inhibitor valproate, the tricyclic antidepressants nortriptyline and imipramine, and the atypical antipsychotic quetiapine. Less-robust agents are the antidepressants sertraline, desipramine, and fluoxetine. Drugs warranting caution in NDDs include oxcarbazepine, diazepam, and the antipsychotics, particularly haloperidol, clozapine, and olanzapine. Valences can covary with the intensity with which a drug has been studied, and some effective agents may have low scores due to minimal investigation. Furthermore, there is a difference in how various drugs have been studied. For example, investigations of neuroleptics have focused primarily upon their mitochondrial respiratory chain effects, fostering more negative valences. Also, whereas lithium, valproate, and quetiapine have exerted *neuroprotective* actions, antidepressant valences primarily reflect *neuro-restorative* effects on neural stem-cell proliferation in animal models because of the orientation of the investigations. Thus, caution is warranted in applying valence findings because drugs have been studied unevenly, with important domains not investigated for some of them.

TABLE 6. Rank Ordering of Drugs by Neuroprotective Valence

Drug	Valence	AD	PD	Tau	HD	ALS	SMA
Lithium	36+	13+	1+	4+		8+	0
Valproic acid	27+	6+	3+			2+	8+
Nortriptyline	13+				6+	7+	
Imipramine	11+						
Sertraline	9+				6+		
Desipramine	8+		1−		1+		
Fluoxetine	8+		1−				
Quetiapine	5+	5+					
Lithium+valproate	5+					3+	
Pramipexole	4+		4+				
Paroxetine	4+	4+					
Trifluoperazine	3+				1+		
Tetrabenazine	2+		0		2+		
Aripiprazole	1+						
Low-dose clozapine	1+					1+	
Maprotiline	1+				1+		
1-5μM diazepam	1+						
Fluphenazine	0						
Thiothixene	0				0		
Carbamazepine	0						
Clonazepam	0						
Chlorpromazine	1−						
Olanzapine	1−						
Oxcarbazepine	1−						
Risperidone	2−						
Standard-dose clozapine	2−					2−	
25-50 μM diazepam	2−						
Haloperidol	5−						

These studies were done in models *directly* relevant to the disease of interest. Rank ordering of drugs by their neuroprotective valences. The higher the positive valence, the greater the neuroprotective potential; the greater the negative valence, the greater its pro-degenerative potential. Caution is warranted because drugs have been studied unevenly, with important actions not investigated for some of them.

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; Lithium+valproate: combined treatment with lithium and valproate administered together; μM: micromolar; PD: Parkinson's disease; SMA: spinal muscular atrophy; Tau: tauopathies (i.e., tauopathic diseases).

Quantitative Evaluation Of Psychotropics According To The Provisional Pre-Clinical Criteria

Drugs were quantitatively assigned a *neuroprotective index score* for the degree to which they met the Table 1 provisional preclinical neuroprotective criteria. To provide a measure of the quality and strength of the available preclinical evidence regarding a given drug's effect on neurodegenerative processes, we devised an equation to consider three factors represented in the provisional preclinical criteria, resulting in a neuroprotective index score for each drug. The neuroprotective index score is the multiplied product of three factors, specifically: 1) replication; 2) NPAS; and 3) valence scores, reflecting degree of replication, experimental weight, and multiplicity of actions, respectively. Thus, the neuroprotective index score can be affected by how often a finding has been replicated across various models, how consistently it has been observed in animal models, and the number of different beneficial actions relative to detrimental actions for the drug associated with the finding. Criterion 1 was not scored, since all drugs considered in this report met that criterion. Criteria 2–5, replication, was quantitated by crediting 1 point for each of the four categories of replication in Table 2, with scores ranging from 1 to 4. Criterion 6, animal-model findings, was quantitated by transforming Table 4 NPASs. NPAS scores of 1–5 were scored as 1; 6–10 as 2; 11–15 as 3; and >15 as 4. Criteria 7 and 8 were factored in together, using the valence score, transformed by applying the same cut-offs to the valence score as to the NPASs. The relative likelihood of the finding translating to clinical neuroprotection is theoretically predicted by its neuroprotective index score (Table 7). The neuroprotective index score was computed by multiplying the replication score for the finding by the transformed animal-model NPAS for the same finding, and multiplying this product by the transformed valence score. The most robust findings (neuroprotective index score ≥16) suggest the usefulness of lithium in AD, tauopathies, and ALS, and valproate in PD.

Provisional Clinical Criteria

The clinical criteria search returned 193 citations, with 54 initially appearing to be of possible relevance. The data that can potentially address neuroprotection, however, were quite limited.

In AD, a randomized, placebo-controlled, 26-week trial of the atypical antipsychotic olanzapine 2.5–7.5 mg/day in non-psychotic and non-agitated patients with moderate AD demonstrated more dramatic cognitive deterioration on the ADAS–Cog at 12 and 26 weeks with active drug, especially in those with greater cognitive impairment at baseline.[74] Although a retrospective study of bipolar disorder indicated reduced dementia incidence after 10 years of lithium treatment,[75] a 10-week, randomized, single-blind, placebo-controlled trial of lithium (0.5–0.8 mM/liter) revealed no clinical benefit or change in total tau, phospho-tau, GSK, or Aβ,[76] although a subgroup with increased serum BDNF showed ADAS–Cog improvement.[77] Studies of sertraline in AD[78] and citalopram in dementia[79] were not designed to assess neuroprotection.

In PD, although no ropinirole studies met our preclinical criteria, a 5-year, multicenter, double-blind study of 288 patients with early PD randomized to either ropinirole or *L*-dopa found less dyskinesia (20% versus 45%) with ropinirole, but no difference in clinical markers of PD progression.[80] In the REAL-PET ropinirole trial in 186 patients with PD randomized to ropinirole or *L*-dopa, fluorine-18-DOPA positron-emission tomography (PET) scans at 2 years revealed the rate of putamenal ^{18}F-DOPA signal decline to be one-third slower in the ropinirole group.[81,82] A smaller, double-blind study of 45 patients failed to show any difference at 2 years.[83] It has been argued, however, that lack of a placebo in the REAL-PET study may indicate that PET differences instead reflect greater *L*-dopa toxicity[84] and that the study was underpowered and excluded too many normal baseline scans,[85] making the results inconclusive. In the CALM–PD study, a multicenter, double-blind, 24 month trial in 301 patients with PD randomized to either pramipexole-plus-placebo, *L*-dopa, or *L*-dopa-plus-placebo, pramipexole demonstrated fewer dopaminergic motor complications with pramipexole but greater UPDRS Parkinson Scale improvement with *L*-dopa,[86] suggesting either a lack of dose-equivalence or intrinsic pharmacological differences between the treatments, rather than neuroprotection. Dopamine transporter imaging (β-CIT) in 82 subjects showed reduced decrement with pramipexole at 2 years;[87] however, this may instead indicate greater *L*-dopa toxicity,[84] or may not even reflect disease progression,[84] but, rather, biased subject-selection[88] or greater transporter down-regulation by pramipexole.[89] Open-label extension studies of ropinirole[90] and pramipexole[91] are further confounded by lack of blinding and the addition of other medications. Thus, neu-

roprotective findings for dopamine agonists in PD remain inconclusive.

In multiple system atrophy (MSA), an open-label, 3-month trial of amantadine in olivopontocerebellar atrophy (OPCA; N=12) and Friedreich's ataxia (N=17) revealed improvements in movement-time in both groups,[92] but the finding could be purely of symptomatic origin. A double-blind, placebo-controlled, crossover study of amantadine in MSA (N=8) was only 3 weeks in duration.[93] Eighteen patients with OPCA were randomized to open-label buspirone 15 mg/day (N=9) or buspirone 15 mg/day-plus-estrogen 0.625 mg/day (N=9) for 12 months, revealing symptomatic motor improvement with buspirone alone at 1 month but not at 12 months;[94] however, there was substantial rating variability in the buspirone group over time. Thus, neither amantadine nor buspirone can be concluded or excluded as neuroprotective in MSA.

ALS

A 9-month futility study of r-pramipexole (30–60 mg/day) found no difference in slopes of deterioration for revised ALS Functional Rating Scale scores or functional vital capacity.[95] Although an initial 15-month, rater-blind, parallel group investigation with randomization to either lithium 150 mg po bid–tid (lithium levels 0.4–0.8 mEq/liter)-plus-riluzole 100 mg po qd (N=16) or riluzole 100 mg po qd alone (N=28), indi-

TABLE 7. Neuroprotective Index Scores (Replication × Animal Model × Drug Valence)

Lithium	
Decreased Aβ1-42 in AD APPsw/PS1 mice and APPV171I/APPsw mice	2 × 1 × 4= 8
Decreased Thr181 phos in SAMP8 senescent mice and PS1/APPsw/tP301L mice	4 × 1 × 4=16
Decreased Tau1 dephos in FTDP-17 VLW mice	4 × 1 × 4=16
Decreased Ser199 phos in SAMP8 mice (0.5 mM)	2 × 1 × 4= 8
Decreased Ser202 phos in Tauopathic htau23 overexpressing and FTDP17 P301L/4R0N mice	2 × 1 × 4= 8
Decreased AT8 phos in AD APPV717I/APPsw mice, PS1M146V/APPsw/tauP301L mice, and GSK-3β/tauG272V/tauP301L/tauR406W mice	4 × 2 × 4=32
Decreased Thr231 phos in *late* PS1M146V/APPsw/tauP301L AD mice and tauopathic htau23 overexpressing mice	4 × 1 × 4=16
Decreased Ser396 phos in SAMP8 mice and tauopathic htau23 overexpressing mice	2 × 1 × 4= 8
Decreased tau phos at Ser 404 in Tauopathic htau23 overexpressing mice	2 × 1 × 4= 8
Decreased tau phos at PHF1 in FTDP-17 P301L/4R0N and GSK-3β/tG272V/tP301L/tR406W mice	2 × 1 × 4= 8
Decreased fibrillar tau phos in FTDP-17 VLW and GSK-3β/VLW mice	1 × 2 × 4= 8
Delayed disease-onset in ALS G93A mice	2 × 1 × 4= 8
Increased motor-neuron survival in G93A ALS mice	2 × 4 × 4=32
Improved motor function in ALS G93A mice	2 × 2 × 4=16
Improved grip strength in ALS G93A mice	2 × 1 × 4= 8
Prolonged survival in ALS G93A mice	2 × 1 × 4= 8
Valproic acid	
Decreased Aβ in AD APP23(sw) mice and APP23/PS45(PS1 G384A) mouse	1 × 1 × 4= 4
Decreased Aβ neuritic plaques in AD APP23(sw) and APP23/PS45(PS1 G384A)	1 × 3 × 4=12
Increased αSyn in the PD rotenone rat	4 × 1 × 4=16
Decreased mono-ubiquitylated αSyn in PD rotenone rat	1 × 1 × 4= 4
Prevented αSyn nuclear translocation in PD rotenone rat	1 × 1 × 4= 4
Nortriptyline	
Decreased glutamate-induced apoptosis in CN MSNs in YAC128 HD mouse	2 × 1 × 3= 6
Sertraline	
Increased hippocampal and striatal neurogenesis in HD R6/2 mouse	1 × 1 × 2= 2
Increased HC, CTX, and STR BDNF in HD R6/2 mouse	1 × 1 × 2= 2
Desipramine	
Decreased glutamate-induced apoptosis in CN MSNs in YAC128 HD mouse	2 × 1 × 2= 4
Paroxetine	
Decreased hippocampal neurons Aβ1-17 in 3xTgAD PS1-M146V/APPswe/P301L AD mouse	1 × 1 × 1= 1
Decreased Aβ1-17 in 3xTgAD cerebral cortex	1 × 1 × 1= 1
Paroxetine decreased HT7 human tau in HC CA1 in 3XTgAD	1 × 2 × 1= 2

Neuroprotective Index Scores reflecting the product of replication score, transformed animal model score, and neuroprotective valence score for drugs with a positive valence. The greater the neuroprotective index score, the better the finding has been established and the more likely it is to predict translational clinical neuroprotection. References for these findings can be found in Table 2 and Table 4.

Aβ: A-beta or beta-amyloid protein; AD: Alzheimer's disease; APP: amyloid precursor protein; αSyn: alpha-synuclein; AT8: AT8 tau epitope; BDNF: brain-derived neurotrophic factor; CA1: CA1 sector of the hippocampus; CN: caudate nucleus; CTX: cortex; DMI: desipramine; FTDP-17: frontotemporal dementia with parkinsonism associated with mutations of the tau gene on Chromosome 17; G93A: G93A mutation in superoxide dismutase-1 mouse model of amyotrophic lateral sclerosis; GSK: glycogen synthase kinase; HC: hippocampus; HD: Huntington's disease; HT7: HT7 tau epitope; htau: human tau; Li: lithium; MSN: medium spiny neuron; NTP: nortriptyline; PD: Parkinson's disease; PHF1: PHF1 tau epitope; PS: presenilin; Ser: serine; Thr: threonine; VPR: valproic acid; YAC: yeast artificial chromosome.

cated strikingly less death, progression, and disability in the lithium arm,[41] a more recent, placebo-controlled futility study (lithium 150 mg/day, 0.4mEq/liter; with riluzole dose unclear) failed to find any differences in endpoint achievement at 5.4 months.[96] Patients were younger, with higher lithium doses, and standardized riluzole doses for a longer duration (albeit without placebo administration) in the positive study; however, a recent multicenter, single-blind, randomized, dose-finding study of lithium 0.2–0.4 mEq/liter (N=84) versus 0.4–0.8 mEq/liter (N=87) found lithium to be poorly tolerated and showed no difference in death rate between the two doses.[97] In a randomized trial of valproate 1,500 mg/day versus placebo in ALS (N=163), neither survival nor functional status were different at either 12 or 16 months.[98] Thus, r-pramipexole, lithium, and valproate do not appear to be neuroprotective in ALS.

The results of clinical trials do not permit firm clinical conclusions except that there are preliminary data suggesting that olanzapine may promote neurodegeneration in AD, and lithium is likely futile as a neuroprotectant in most ALS patients. (Several forthcoming studies in AD, progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD] are discussed in the next-to-last Discussion paragraph.)

DISCUSSION

This report applies a rigorous inclusion requirement and a presumptively valid quantitative method to produce a broad comprehensive review of commonly-prescribed psychotropic agents that could double as neuroprotective therapies. The findings indicate a potential neuroprotective role for lithium, paroxetine, or lithium-plus-valproate in AD, lithium in frontotemporal lobar degeneration (FTLD) and in combination with valproate in ALS, pramipexole and valproate in PD, amantadine and buspirone in MSA, and antidepressants in HD. This report, limited to psychotropic medicines, should prove of special relevance to neuropsychiatrists and others who use these drugs in NDD with neuropsychiatric symptoms.

The best-documented, most robust, and promising preclinical findings are shown in Table 7 and are considered to have the highest probability of translating to clinical neuroprotection in human patients. The neuroprotective index scores of this table reflect replicated findings in drugs with proven benefit in disease-specific animal models and a net positive neuroprotective valence. Dopamine agonist, neuroleptic, atypical antipsychotic, and the VMAT-2 inhibitor tetrabenazine findings did not fulfill the Table 7 composite criteria. Lithium showed potential neuroprotection in reducing Aβ1–42, tau phosphorylation, and fibrillar tau in aging, amyloidopathic, and tauopathic mouse models (Table 7). In particular, tau phosphorylation was reduced at epitopes relevant to AD (Thr181, Ser199, AT8, Thr231, Ser396) and tauopathies including PSP, FTLD, and FTDP-17 (Tau1, Ser202, AT8, Thr231, Ser396, Ser404), and MSA (Tau1).

In the G93A SOD1 transgenic mouse model of ALS, lithium showed both neuronal and overall neuroprotective properties in most studies. Valproate reduced Aβ and neuritic plaques in amyloidopathic transgenic mouse models of AD and increased αSyn while decreasing nuclear translocation in the rotenone rat model of PD. The antidepressant paroxetine reduced cortical and hippocampal Aβ processing and hippocampal HT7 human tau in a transgenic model of AD. In HD mouse models, nortriptyline and desipramine preserved caudate medium spiny neurons against glutamate apoptosis, and sertraline increased both BDNF and hippocampal and striatal neurogenesis. Thus, the most robust preclinical findings detailed in Table 7 suggest neuroprotective potential for lithium, valproate, and paroxetine in AD, lithium in tauopathies and ALS, valproate in PD and perhaps other synucleinopathies, and several antidepressants in HD.

Although a number of psychotropics have been studied in AD, PD, MSA, and ALS, the only conclusions that can be drawn from these clinical trials are that olanzapine may deteriorate cognition in AD, and lithium is probably not a useful neuroprotectant in most ALS cases, at least when given with riluzole. Initial findings needing replication include lithium neuroprotection in AD with increased BDNF levels and in *early* ALS, and the futility of r-pramipexole and valproate in ALS. Neuroprotective paradigms are needed to resolve the neuroprotective efficacy of ropinirole and pramipexole in PD, and amantadine and buspirone (using more sensitive measures) in MSA. Clinical studies have relied on a difference in slope-deterioration between treatments to measure progression rather than delayed-start or randomized-withdrawal designs.[5] At present, no disease-modifying neuroprotective agents have been conclusively demonstrated in clinical trials.

Additional studies in the literature require more detailed discussion. Moderate neuroprotective index scores for motor-neuron survival and motor function with lithium in the ALS G93A SOD1 mutation mouse model (Table 7; scores of 32 and 16, respectively, and an average of 14.4 across ALS findings, out of possible scores of 1 to 64) contrast somewhat with negative clinical findings, although it has been argued that this mutation model is not representative of human disease, and the mutation is present only in a small minority of ALS patients.

Moderate scores in AD models with tau mutations suggest therapeutic potential for lithium in tauopathic diseases, although poor tolerability resulted in premature discontinuation in 13 of 14 patients with progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) during a 28-week, open-label, safety and tolerability trial (recently published as an abstract).[105] For valproate, a low-to-moderate neuroprotective index score was achieved for Aβ neuritic plaque reduction in AD amyloid- and presenilin-mutant mice. Forthcoming results of a 26-month, randomized, placebo-controlled trial in 313 patients with AD with clinical rating, biomarker, and brain-volume outcomes[106] (manuscript in review process) indicate no difference in slopes of deterioration on clinical ratings (Tariot PN, personal communication; January 2011). The valproate group showed greater loss in hippocampal and whole-brain volume, accompanied by greater ventricular expansion. It is unclear whether these changes may be due to direct drug effects such as osmotic shifts or metabolic toxicity or influences on AD pathology, and it is unknown whether these effects are reversible or clinically relevant. Although valproate levels averaged 40–50 μg/ml, the levels may not have been sufficient to engage molecular targets (Tariot PN, personal communication). Alternatively, these negative results may reflect a translational predictive failure of Aβ neuritic plaque or amyloid transgenic mouse models. After all, the neuroprotective valence and neuroprotective index score are only as good as the models that they are based upon, and model and tolerability confounds prevent a current assessment of their predictive capability. It is also possible that higher and more robust neuroprotective index scores are needed to predict clinical neuroprotection, since even moderate scores were not consistently obtained across the findings and models of Table 7. Toward this, simultaneous administration of lithium-plus-valproate might potentially produce quantitatively greater and more robust neuroprotective index scores and result in clinical therapeutic effects.

There are several caveats in interpreting how well the present findings generalize and can predict clinical translation. First, we focused on findings in mature neural tissues because of substantial differences in how mature and immature tissues behave with respect to the common intracellular processes considered here, yet it remains possible that some potentially relevant preclinical findings might be excluded by this requirement. Second, the concepts of neuroprotective valence and the composite neuroprotective index score remain to be validated. Although it makes sense that drugs with a multiplicity of different neuroprotective actions and minimal prodegenerative effects (i.e., higher positive valence) will more likely be neuroprotective in human clinical trials, this concept remains to be validated, especially in light of disappointing results for lithium, a drug with a high valence, in ALS. Forthcoming data will also indicate whether the neuroprotective index score is a predictor of clinical neuroprotection in humans.

There are the limitations inherent to a review of the literature. Although the best strategy available, the literature search may have missed some data because of indexing inconsistencies. Several studies were not identified by the preclinical[42,69,95,99] and clinical[78,80] search strategies, but rather by bibliographic extension. Furthermore, the search strategy targeted the proteins, organelles, and processes specified, and although this produced a number of citations pertaining to additional neurodegenerative processes, the review cannot be considered to be fully comprehensive with respect to processes such as "oxidation." Obviously, this review also does not consider additional neuroprotective mechanisms, for example, "inflammation." There are also reporting biases in the literature. Drug actions have been investigated unevenly and unsystematically across and within neuroprotective actions, and animal models vary in their translational predictive power.

There are several perspective-related issues that can make the interpretation of some of the results difficult at this point. For example, an increase in αSyn can lead to proteasomal inhibition, apoptosis, and inclusion formations including Lewy bodies, pathological tau, and Aβ and yet a rise in αSyn can also effect a neuroprotective response. Proteasomal inhibition would seem to be pro-apoptotic, and yet the administration of subtoxic proteasome inhibitors has been associated with neuro-

protection.[100] In the case of αSyn, mono-ubiquitylation and nuclear translocation predict apoptosis, in contrast to a non-ubiquitylated rise in αSyn concentration.[47] Nevertheless, seemingly similar responses can, at times, signal *either* neuroprotection or neurodegeneration, and whether a particular response is neuroprotective or pro-apoptotic may also depend on both its extent and whether it is occurring early or late in the disease process.

There are several drug-related issues that can affect generalizability and translational prediction. Drug dose can make a difference in effects. Low doses of lithium, for example, activate autophagy in extraneuronal models,[101] whereas these same doses may be ineffective in activating other neuroprotective functions. On the other hand, in preclinical models of neuroprotection, a bell-shaped rather than open-ended sigmoid-shaped dose-response curve is often encountered. Thus, too high a dose may exceed the therapeutic window of neuroprotection for some mechanisms. This could help explain the diverging effects of low versus standard doses of clozapine[69] and diazepam.[61,102] Results may also vary with the type of apoptogen, neurotoxin, and locus of action. For example, valproate prevented nigral loss in the rotenone,[47] but not the MPTP[103] mouse model of PD. Some neuroprotective actions of psychotropics may relate to their pharmacodynamic mechanisms.[3] For example, $5HT_{1a}$ receptor agonists may inhibit apoptosis through nerve growth factor signaling.[104] Duration of treatment can affect neuroprotection as well. For example, hippocampal Bcl-2 expression is upregulated by chronic but not acute treatment with antidepressants.[58,64] Taken together, a given psychotropic can have plural neuroprotective mechanisms and, simultaneously, have pro-degenerative effects, with the capacity to act as both friend and foe, depending on dosing and context.

In conclusion, despite limitations and other issues in interpreting the literature, several established psychotropic medications have sufficient promise to warrant further study as neuroprotective agents. We need clinical trials using designs adequate to assess disease-modification[5,107] as follow-up to these preclinical and clinical data. Priorities include the agents identified by the provisional preclinical neuroprotective criteria and resolution of initial findings in the clinical trials, including dopamine agonists (PD, ALS), amantadine (MSA), lithium (AD with elevated BDNF, tauopathies, early ALS), valproate (AD, PD, synucleinopathies, ALS), lithium-plus-valproate (AD, ALS), nortriptyline (HD), desipramine (HD), sertraline (HD), paroxetine (AD), and buspirone (MSA-C). Secondary priorities include study of the other agents identified by each of the provisional preclinical neuroprotective criteria in isolation. It will be of interest to identify which provisional criteria prove to be most predictive of clinical translational benefit. Equivocal results in clinical neuroprotective trials will signal the need to develop better preclinical models with improved abilities to predict translational treatments in human disease.

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