In Part I of this report, the authors reviewed preclinical and clinical evidence of neuroprotection by psychotropics and proposed criteria to predict translational neuroprotection. Here, the authors review a broad array of neuroprotective mechanisms and, based on evidence reviewed in Part I, consider agents with pharmacodynamic mechanisms of action that may be associated with neuroprotection. The neuroprotective potential of the pharmacodynamic mechanisms discussed here are held in common with drugs that evidenced neuroprotective potential in Part I. The agents examined here have symptomatic utility in neurodegenerative disease neuropsychiatric disorders and combine the most promising pharmacodynamic mechanisms yet have received insufficient research to date. Modafinil, duloxetine, ziprasidone, s-zopiclone, and ramelteon are evaluated in terms of their putative neuropsychiatric symptomatic and heuristic neuroprotective disease-modifying potentials. The authors review these agents in terms of their potential for clinical neuroprotection and suggest a criterion-based research agenda for future studies of their neuroprotective potential. Further research is needed with regard to the 10 translational neuroprotective candidate criteria, neuroprotective clinical trials, the correlation of psychotropic pharmacodynamic mechanisms with neuroprotective actions, and the translational predictive utility of the proposed candidate criteria.


Dr. Lauterbach is affiliated with the Mercer University Center for Translational Studies in Alzheimer’s, Parkinson’s, and Neurodegenerative Diseases and the Departments of Psychiatry and Behavioral Sciences and Internal Medicine (Neurology Section) at Mercer University School of Medicine in Macon, Georgia; Drs. Shillcutt and Coburn are affiliated with the Department of Psychiatry and Behavioral Sciences at Mercer University School of Medicine in Macon; Dr. Victoroff is affiliated with the Department of Clinical Neurology and Psychiatry at the University of Southern California Keck School of Medicine and with the Department of Neurology at Rancho Los Amigos National Rehabilitation Center in Downey, California; Dr. Mendez is affiliated with the Neuropsychiatric Program at the Greater Los Angeles VA and with the Departments of Neurology and Psychiatry at David Geffen School of Medicine at UCLA in Los Angeles. Address correspondence to Edward C. Lauterbach, M.D., Founding Director, Mercer University Center for Translational Studies in Alzheimer’s, Parkinson’s, and Neurodegenerative Diseases and Professor Emeritus of Psychiatry and Neurology, 331-4D College Street, Macon, GA 31201; eclbgnp@earthlink.net (e-mail).

Neurodegenerative diseases are assuming increasing importance over time and have been classified into families, for example tauopathies characterized by aberrant tau protein (e.g., Alzheimer’s disease, Pick’s disease, progressive supranuclear palsy, corticobasal degeneration), synucleinopathies (e.g., Parkinson’s disease, dementia with Lewy bodies, multiple system atrophies), amyloidopathies (e.g., Alzheimer’s disease, Down’s syndrome), etc.

Neuropsychiatric conditions abound in these neurodegenerative diseases, and psychotropic drugs are routinely applied in treating them. Aggression, agitation, anxiety, apathy, depression, disinhibition, and psychosis are among the many behavioral complications in neurodegenerative diseases, are highly prevalent, and add tremendously to patient distress and caregiver burden.¹–²⁹ Psychotropics are often prescribed to control neuropsychiatric behavioral disturbances in these diseases.²,³,⁸,⁹,¹¹–¹⁶,¹⁸,¹⁹,²³,²⁹–³⁸ Thus, it is fortuitous that drugs that provide clinical benefit in neurodegenerative diseases may also afford the neuroprotective capacity to deter the progression of underlying pathobiologies.

In Part I of this report, we reviewed preclinical effects of psychotropics on selected pathophysiological processes operant in neurodegenerative disease. Here, we review the broader diversity of neuroprotective actions and the potential effects of selected psychotropics representing pharmacological classes of drugs with promising neuroprotective potential. These psychotropics are selected to represent pharmacodynamic drug classes with multiple neuroprotective actions. We will overview these neuroprotective actions and provide some examples of the complexity of their interactions.

A Diversity of Neuroprotective Actions

A wide array of mechanisms provide potential opportunities for neuroprotective treatment in the neurodegenerative diseases. Briefly, the enzyme glycogen synthase kinase-3 (GSK-3) promotes alpha-synuclein (αSyn) expression,³⁹ beta-amyloid (Aβ) production,⁴⁰ and tau phosphorylation.³⁹,⁴¹ The neurodegenerative diseases are linked to pathological protein accumulation, for example, αSyn, particularly in Parkinson’s disease,⁴² Parkinson’s disease dementia,⁴³ and dementia with Lewy bodies,⁴³ and Aβ and hyperphosphorylated tau, especially in Alzheimer’s disease.⁴²,⁴⁴,⁴⁵ The newly emergent transactive response RNA/DNA binding protein TDP-43 affects RNA splicing⁴⁶ and is the dominant component of ubiquinated inclusions present in the TDP-43 proteinopathies, including frontotemporal lobar degeneration with ubiquitin immunoreactive inclusions (FTLD-U) and amyotrophic lateral sclerosis,⁴⁷ although psychotropic effects on TDP-43 remain to be discovered. It is these pathogenic protein inclusions that form the pathological stigmata of the neurodegenerative diseases, namely, Lewy bodies (αSyn) in Parkinson’s disease and amyloid plaques (Aβ) and neurofibrillary tangles (hyperphosphorylated tau) in Alzheimer’s disease.

Interestingly, treatments lowering plasma Aβ are thought to reduce the risk of developing Alzheimer’s disease,⁴⁸–⁵⁰ and it is likely that modulation of plasma αSyn, Aβ, and tau concentrations can similarly lower the risk of developing other neurodegenerative diseases. Consistent with this concept, plasma αSyn oligomers are increased in Parkinson’s disease⁵¹,⁵² and in multiple system atrophy.⁵² Just as the plasma Aβ 42/40 ratios fall at the onset of Alzheimer’s disease,⁵³,⁵⁴ plasma αSyn concentrations also appear to fall with the advent of Parkinson’s disease,⁵⁵ presumably attributable to deposition within the CNS. Consequently, reductions in plasma pathogenic proteins may, in the future, translate to reduced brain neuropathology in a number of neurodegenerative diseases.

Pathogenic proteins can lead to proteasomal⁵⁶–⁵⁸ and mitochondrial dysfunction,⁵⁹,⁶⁰ increase intracellular calcium⁶¹ and free radicals,⁶² and compromise axonal transport and cytoskeletal integrity,⁶³ leading to apoptosis.

The proteasome degrades damaged, toxic, excessive, and unwanted proteins from cells.⁶⁵ Undesirable proteins are tagged with a poly-ubiquitin chain by the E1-E3 ubiquitin conjugase-ligase system.⁵⁶ Poly-ubiquitylated proteins then enter the proteasome for degradation. The 26S proteasome consists of a 20S proteolytic core capped by 19S caps.⁵⁶ Unwanted proteins enter the caps, ubiquitin chains are cleaved, and the protein is unfolded and fed into the proteolytic core for cleavage into peptide fragments. It is interesting to note that the ubiquitinopathic frontotemporal dementia FTDU-17 is associated with tau-negative, ubiquitin-positive inclusions, and that mutant PARK 2 autosomal recessive juvenile Parkinson’s disease parkin has E3 ubiquitin ligase activity (part of the E1-E3 ubiquitin conjugase-ligase system). Oxidative stress impairs both ubiquitylation and proteasomal function, and proteasomal dysfunction engenders additional oxidative stress and free radical formation.⁶⁴ Proteasomal failure further leads to impaired degradation of pathogenic proteins, apoptotic mediators (e.g., caspases and bcl-2 pro-
While the release of reactive oxygen species and consequent mitochondrial dysfunction advances the course of neurodegenerative disease,67 mitochondrial respiratory dysfunction, including complex I68 and complex II69,70 deficiencies and the complex I inhibitors rotenone71 and tumor necrotic factor,72 each leads to apoptosis. Additionally, free radicals including reactive oxygen species and reactive nitrogen species result in lipid peroxidation that advances the course of neurodegenerative disease.73,74 In Parkinson’s disease, free radicals are linked to dopaminergic neuronal loss.75 Reactive species include peroxide radicals, especially linked to dopamine oxidation and superoxide dismutase, and nitric oxide, especially related to inducible nitric oxide synthase, constituting major mechanisms of interest in neurodegenerative diseases.73,76 Nitric oxide promotes the generation of free radicals,77 which in turn advance the progression of neurodegenerative diseases.78

There are several apoptotic pathways that play key roles in neurodegenerative diseases, including mitochondrial-, death receptor-, and p53-mediated apoptotic pathways.79,80 The mitochondrial pathway involves cytochrome c-related activation of caspase-9, which activates caspase-381 and the apoptotic cascade.82 This mitochondrial apoptotic pathway plays a principal role in neurodegenerative diseases.83 The death receptor, or Fas pathway, involves FADD and caspase-8 activation, whereas the p53 pathway involves glyceraldehyde-3-phosphate dehydrogenase and Bax, with caspase-8 and Bax initiating the apoptotic cascade.79,80

In addition, glutamate excitotoxicity is a leading theory of neurodegeneration in Alzheimer’s disease,84 Parkinson’s disease,85,86 Huntington’s disease,87,88 and amyotrophic lateral sclerosis,89,90 and is a basis for the potential neuroprotective effects of memantine84,91 and riluzole.92 Glutamate mediates apoptosis through mechanisms that include glutamatergic N-methyl-D-aspartate (NMDA) receptors,93,94 calcium influx95 and free radicals.93,95,96 Inhibition of GSK-3β protects against glutamate-induced, caspase-3-mediated apoptosis.97

Inflammatory processes are also evident in the neurodegenerative diseases. Aβ neuritic plaques and proinflammatory cytokines in Alzheimer’s disease lead to microglial activation and inflammation.98 Activated microglia, reactive astrogliosis, and lymphocytic infiltration are also apparent in the substantia nigra in Parkinson’s disease as a later concomitant of neurodegeneration,99,100 possibly related to αSyn and oxidative stress.64,100 Activated microglia then produce cytokines, reactive oxygen and nitrogen species, and eicosanoids that propagate further neurodegeneration.101 It is interesting to note that sleep loss may promote inflammation.102 Sleep loss is often present in neurodegenerative diseases, especially related to fragmentary daytime napping, depression, psychosis, or insomnia.

These neurodegenerative mechanisms occur in the absence of neurodegenerative diseases and are balanced by neuroregenerative processes, including neurotogenesis and the influence of neurotrophic factors. Cytoskeletal derangements occur in neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease related to changes in tau and tubulin, and there is evidence that certain drugs and hormones can affect this and stimulate neurotogenesis.103 Neuritogenesis is key to neuronal and synaptic recovery and regeneration after injury and is a treatment target in neurodegenerative diseases.104 Neurotrophic factors include brain-derived neurotrophic factors (BDNF) and glial-derived neurotrophic factors (GDNF). BDNF105,106 and GDNF105–110 constitute important treatment targets in Alzheimer’s disease,106 Parkinson’s disease,106,108–110 Huntington’s disease,105 amyotrophic lateral sclerosis,107 spinal muscular atrophy,107 with GDNF showing more potential than BDNF in most models.105,107,109 Persephin and other GDNFs have promoted neuronal survival and neuritogenesis in a midbrain dopamine neuron model of Parkinson’s disease.111

Complex Interactions Between Neurodegenerative Mechanisms

The number of neuroprotective mechanisms is complex. The interaction of various mechanisms with each other is also complex. For example, proteasomal inhibition increases the accumulation of pathogenic proteins, impairs mitochondrial function, and triggers apoptosis. Further complexity of interaction is apparent in considering specific mechanisms, for example, pathogenic proteins.

It has been found that Aβ and tau each facilitate αSyn
aggregation in Parkinson’s disease\textsuperscript{112–114} and that αSyn is linked to Alzheimer’s disease\textsuperscript{115} and facilitates tau aggregation in Alzheimer’s disease.\textsuperscript{112} αSyn and tau each independently initiate amyloid formation.\textsuperscript{116} Moreover, GSK-3 promotes Aβ formation by phosphorylating amyloid precursor protein\textsuperscript{40} and also promotes tau hyperphosphorylation to pathogenic tau\textsuperscript{41} in Alzheimer’s disease. In Parkinson’s disease, GSK-3 alleles are associated with Parkinson’s disease risk.\textsuperscript{113,114} Furthermore, GSK-3β inhibitors may reduce αSyn\textsuperscript{39} and αSyn upregulates GSK-3β,\textsuperscript{117} suggesting that GSK-3β and αSyn mutually upregulate each other in Parkinson’s disease models. These pathological proteins interact at various levels in the pathological chain of events that involves protein processing at the proteasome, mitochondrial destabilization, free radical generation, apoptotic pathway activation, cell death, and neuroinflammation.

GSK-3, αSyn, tau, and Aβ each inhibit the proteasome,\textsuperscript{56} impair mitochondrial function,\textsuperscript{59,60} generate free radicals,\textsuperscript{62} and result in apoptosis.\textsuperscript{42,118} These processes are compounded by their induction of microglial activation\textsuperscript{98–100} and neuroinflammation.\textsuperscript{101} Mutual upregulation of αSyn and GSK-3β in Parkinson’s disease can lead to apoptosis by GSK-3β-induced bcl-2 downregulation,\textsuperscript{117} and by synphilin-1 phosphorylation\textsuperscript{119} that induces endoplasmic stress and proteasomal dysfunction\textsuperscript{119} in Parkinson’s disease. Also, in Parkinson’s disease models, GSK-3 further provides pathways through which rotenone,\textsuperscript{120} 6-hydroxydopamine,\textsuperscript{121} 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),\textsuperscript{120,122} and L-dopa\textsuperscript{123,124} mediate apoptosis. Finally, apoptosis is also indirectly triggered by tau and Aβ\textsuperscript{118} in both Alzheimer’s disease and Parkinson’s disease\textsuperscript{42} by inhibiting proteasomal\textsuperscript{56} and mitochondrial\textsuperscript{60} function and inducing free radical damage,\textsuperscript{62} microglial activation,\textsuperscript{98–100} and inflammation.\textsuperscript{101}

These relationships of pathogenic proteins to specific neurodegenerative mechanisms are just one example of the complexity of interaction between various components of the neurodegenerative process. Thus, neuroprotective strategies that address individual neurodegenerative mechanisms can potentially enhance their neuroprotective effects through these complex interactions.

Neuroprotection Targets

It is apparent from the above discussion that a number of independent mechanisms produce neurodegenerative processes through which rotenone, 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and L-dopa mediate apoptosis. Finally, apoptosis is also indirectly triggered by tau and Aβ in both Alzheimer’s disease and Parkinson’s disease by inhibiting proteasomal and mitochondrial function and inducing free radical damage, microglial activation, and inflammation. These relationships of pathogenic proteins to specific neurodegenerative mechanisms are just one example of the complexity of interaction between various components of the neurodegenerative process. Thus, neuroprotective strategies that address individual neurodegenerative mechanisms can potentially enhance their neuroprotective effects through these complex interactions.

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Preclinical Criteria

- Experimental evidence of a neuroprotective action using an established neuroprotective model at physiological drug doses (1–1000 μM concentration in ex vivo normalized preparations of cultured cells or drug doses of 1–1000 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 3 distinct neuroprotective actions (e.g., inhibition of Aβ production, tau hyperphosphorylation, and PTP formation) and 1 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 for 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 fluoroDOPA 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)

These are putative criteria for assessing the probability that an agent will demonstrate a translational neuroprotective effect in a clinical trial. Since the predictive utility of these factors remains to be demonstrated, an equal weighting is assigned to each criterion. It is suggested that the more criteria an agent meets, the greater the likelihood that it will yield significant results in a clinical neuroprotective trial.

R

The drugs considered here appear to have been neglected and subjected to little research thus far, as is evident in Part I of this report. They are selected based on evidence in Part I of this report supporting the neuroprotective potential of psychotropic drugs possessing their mechanisms of action. We consider representative drugs of pharmacological classes that have symptomatic utility in neurodegenerative diseases and should now be subjected to preclinical investigations according to the criteria in Table 1. Based on these criteria, research using delayed-start (staggered start) and randomized-withdrawal designs125 can be undertaken to determine their disease-modifying neuroprotective utility. Examples of wakefulness promoting, anxiolytic, antidepressant, antipsychotic, and hypnotic agents are provided.

**METHODS**

The method is specified in Part I of this report but, briefly, it relied on the Part I search strategy extended by bibliographic review and other sources including literature searches of peer reviewed published articles for the drugs specified and for neuroprotective actions ranging beyond those focused on in Part I.

Modafinil Modafinil is a drug with symptomatic potential in neurodegenerative diseases that binds to the dopamine transporter,126–128 and increases synaptic DA.127 It may act as a direct dopamine D2 receptor agonist129 and may secondarily stimulate noradrenergic activity.130–132 Dopaminergic and noradrenergic deficits occur in Alzheimer’s disease and Parkinson’s disease, and these modafinil actions could improve daytime somnolence, sundowning, cognition, and neuropsychiatric disorders in dementia. Modafinil has effectively treated excessive daytime sleepiness in Parkinson’s disease133 and atypical lateral sclerosis.134 Performance on the clock drawing task, which integrates executive, visuospatial, and other cognitive functions that are impaired in dementia and is commonly used to screen for dementia, improved in healthy middle-aged subjects given modafinil.135 Modafinil has also been demonstrated to increase hippocampal glutamate release.136 Glutamate is critical for proper memory
function through the process of long-term potentiation. Increasing glutamate release may lead to improved memory function in disorders where the hippocampus is degenerating. In various disorders, modafinil has improved executive function, verbal fluency, attention, verbal memory, apathy, fatigue, depression, and response inhibition. Improvements in cognition and response inhibition may further improve impulsivity, disinhibition, and aggression. Moreover, modafinil has been suggested to potentially improve Parkinson’s disease symptoms related to enhanced glutamatergic striatal stimulation and reduced striatopallidal GABA release.

Modafinil appears to simultaneously enhance glutamatergic symptomatic function while blocking its neurotoxic effects, consistent with a neuroprotective action potentially applicable in a number of neurodegenerative diseases, including Alzheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis. Modafinil also dose-dependently blocks MPTP neurotoxicity in the marmoset monkey Parkinson’s disease model through antioxidant effects and the modulation of nigrostriatal monoamines. This same effect has been observed in nigral neuronal and glial cells in black mice. Thus, modafinil neuroprotective properties against glutamate toxicity and nigral degeneration may translate to clinical neuroprotection in patients with neurodegenerative diseases. The potential neuroprotective actions of modafinil are summarized in Table 2.

**Duloxetine** The antidepressant duloxetine is a dual serotonin and norepinephrine reuptake inhibitor (SNRI). Duloxetine has improved several measures of depression and cognition in a double-blind, placebo-controlled trial in geriatric patients. Experience with selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibiting antidepressants, together with neurotransmitter correlate findings for certain neuropsychiatric disorders, suggests that duloxetine has the potential to improve depression, anxiety, delusions, sleep, agitation, aggression, disinhibition, excitement, wandering, overall cognition, attention, executive functioning, and memory across neurodegenerative diseases. Apathy and urinary incontinence may also respond to duloxetine. Apathy and other dopamine-related symptoms can respond to duloxetine because norepinephrine reuptake inhibitors block frontal dopamine reuptake. Indeed, apathy responds to agents that increase frontal dopamine. Similarly, in Parkinson’s disease, neurotransmitter correlates and agents that affect neurotransmitters further evidence the potential for improvements in Parkinson’s disease visuospatial processing as well as bradyphrenia, akinesia, postural instability, freezing, dyskinesia, and Parkinson’s disease symptoms related to enhanced glutamatergic striatal stimulation and reduced striatopallidal GABA release.

| TABLE 2. Potential Neuroprotective Actions of Psychotropics Supported by Preclinical Studies |
|-----------------------------------------------|-------------|
| Neuronal Preservation                        | DLX ZPR ZPC RMT |
| Protects hippocampal neurons                 | MDF         |
| Protects dopamine neurons                    | MDF         |
| Neuroinflammation                            | DLX ZPR ZPC RMT |
| Protects against glutamate toxicity          | MDF         |
| Protects against Aβ toxicity                 | ZPR         |
| Protects against MPP+ toxicity               | ZPR         |
| Pathogenic Protein Inhibition                | DLX ZPR ZPC RMT |
| Inhibits CSK-3                               | ZPR         |
| Inhibits Aβ formation                        | ZPR         |
| Inhibits Aβ aggregation                      | ZPR         |
| Inhibits Aβ-induced pathology                | ZPR         |
| Inhibits pathogenic tau formation            | ZPR         |
| Inhibits tau-induced pathology               | ZPR         |
| Inhibits deSyn aggregation                   | ZPC         |
| Maintains proteasome                         | ZPC         |
| Free Radical Protection                      | DLX ZPR ZPC RMT |
| Induces antioxidant enzymes                  | ZPR         |
| Inhibits nitric oxide synthase                | ZPR         |
| Protects against free radicals               | ZPC         |
| Prevents dopamine auto-oxidation             | ZPC         |
| Mitochondrial Protection                     | DLX ZPR ZPC RMT |
| Maintains mitochondria                       | ZPC         |
| Protects complex I                            | ZPC         |
| Protects complex IV                          | ZPC         |
| Promotes ATP production                      | ZPC         |
| Anti-Apoptotic Properties                    | DLX ZPR ZPC RMT |
| Inhibits apoptotic processes                 | ZPR         |
| Inhibits glutamate apoptosis                  | ZPR         |
| Inhibits Aβ apoptosis                         | ZPR         |
| Inhibits MPP+ apoptosis                       | ZPC         |
| Reduces neuroinflammation                    | ZPC         |
| Neurogenesis Activation                      | DLX ZPR ZPC RMT |
| Stimulates BDNF                               | ZPR         |
| Stimulates GDNF                               | ZPC         |
| Stimulates neuritogenesis                     | ZPC         |

This table depicts documented neuroprotective actions of the drugs considered here, or of other members of their mechanistic classes. DLX=duloxetine, MDF=modafinil, RMT=ramelteon, ZPC=zopiclone, ZPR=ziprasidone.

kinson’s disease stage. Urinary incontinence in dementia usually results from either sphincteric or detrusor muscle dysfunctions. Duloxetine is thought to work centrally at Onuf’s nucleus in the sacral spinal cord to improve sphincter tone mediated through 5HT2 and alpha-1 receptor effects during urine storage but not during voiding, thereby significantly improving stress urinary incontinence.

In addition, a recent placebo-controlled study in women with overactive bladders due to documented detrusor instability revealed improved detrusor stability with reduced episodes of incontinence and voiding. This presumably is related to raising the sensory threshold for triggering micturition mediated by the 5HT1a receptor at the primary afferent neurons in the superficial dorsal horn of the sacral spinal cord.

Duloxetine and agents with related modes of action together have demonstrated neuroprotective properties in neurodegenerative models relevant to neurodegenerative diseases, such as reducing pathogenic tau and Aβ, proteins that also facilitate and synergize α5n pathogenic oligomeric fibrillation and promote proinflammatory inclusions in Alzheimer’s disease and Parkinson’s disease. Other properties include inhibition of GSK-3β (thereby reducing α5, tau, and Aβ formation) and reductions in free radical production, nitric oxide synthase activity, mitochondrial permeability transition pore development, apoptosis (especially 6-hydroxydopamine- and glutamate-induced apoptosis in Parkinson’s disease and Alzheimer’s disease models), microglial activation, and inflammation. These drugs also upregulate BDNF and GDNF. We will sequentially summarize the evidence for SSRIs, selective norepinephrine reuptake inhibitors (NERIs), and SNRIs.

SSRIs reduce Aβ and tau concentrations and inhibit GSK-3β and apoptosis, including in the hippocampal formation. The SSRI paroxetine preserved cognitive performance and reduced hippocampal Aβ and tau levels in transgenic mice. Additionally, antidepressants have effects on GSK-3, affecting neuronal pathological protein concentrations. The SSRI fluoxetine and the SNRI imipramine have each inhibited GSK-3. SSRI-induced GSK-3β inhibition appears to be mediated by 5HT1a receptor stimulation, which inhibits GSK-3β through serine 9 phosphorylation. SSRIs improve cell proliferation in several models and inhibit several types of apoptosis in a variety of cell lines. Fluoxetine improved contextual memory and cell proliferation in Aβ transgenic mice. Fluoxetine, clomipramine, and citalopram have inhibited apoptosis in neoplastic models. Of particular relevance in Alzheimer’s disease, fluoxetine enhanced cell proliferation and prevented dentate gyrus apoptosis in a rat model.

Selective NERIs block free radical generation including intramitochondrial radicals, mitochondrial permeability transition pore development, and several types of apoptosis in various cell lines. The selective NERI desipramine has inhibited HDAC inhibitor/perifosine-induced and tumor necrotic factor α-induced reactive oxygen species production, glutamate-induced mitochondrial permeability transition pore opening in Huntington’s disease transgenic mice, and apoptosis in a wide variety of models. These apoptotic models include glutamate in transgenic Huntington’s disease mice and 6-OHDA in neuronal PC12 cells relevant to Parkinson’s disease.

SNRIs like duloxetine inhibit GSK-3β, nitric oxide synthase, mitochondrial permeability transition pore opening, and several types of apoptosis in various cell lines. Duloxetine inhibits nitric oxide synthase and, hence, free radical generation. The SNRI nortriptyline blocked glutamate-induced mitochondrial permeability transition pore opening and apoptosis in a transgenic mouse Huntington’s disease model. As noted above, glutamate is also key to Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. Imipramine inhibited tumor necrotic factor α-induced apoptosis and cisplatin-induced clustering of CD95 apoptotic death receptors.

All three types of antidepressants reduce microglial activation and the expression of interleukin-6 and nitric oxide, and several antidepressants including duloxetine upregulate the neurotrophic factors BDNF and GDNF to produce ex vivo and in vivo neuroprotection. BDNF is reduced in the frontal and temporal cortex and hippocampus in Alzheimer’s disease. Chronic administration of duloxetine upregulates BDNF mRNA in frontal cortical synaptosomes, providing the potential to maintain or improve frontal cognition. In Parkinson’s disease, BDNF is colocalized with dopamine neurons in the substantia nigra where it can function neuroprotectively, and it may have a beneficial neuromodulatory action as well. Plasma BDNF levels were significantly lower in depressed patients than in healthy control subjects and normalized after 1 month of antidepressant treatment. The same phenomenon has been demonstrated for serum
GDNF,246 a target in most neurodegenerative diseases. Antidepressant-induced increases in GDNF have been shown to be neuroprotective in both ex vivo247 and in vivo248 models and are mediated through a monoamine-independent mechanism.110,249 Each of these effects is particularly relevant to Parkinson’s disease pathogenesis64 and has the potential to protect against neurodegeneration in Parkinson’s disease and other neurodegenerative diseases. In principle, duloxetine offers the potential to combine the symptomatic and neuroprotective properties of the different antidepressants into an effective neurodegenerative disease treatment. The potential neuroprotective actions of duloxetine are summarized in Table 2.

Ziprasidone Ziprasidone is an atypical antipsychotic with D2 antagonist, 5HT2 inverse agonist, and 5HT1a agonist properties, as well as SNRI activity.250,251 Ziprasidone modes of action thereby confer antipsychotic, antidepressant, and anxiolytic properties translating to a broad therapeutic potential in neurodegenerative diseases.

Aside from antipsychotic effects on hallucinations and delusions,252 other ziprasidone benefits include effects on agitated behavior,253–256 anxiety,257 depression,250,251,258,259 sleep,260 and cognition.251,261 Although results from controlled studies in dementia are lacking, in three frail elderly patients with dementia, ziprasidone was effective in improving psychosis, agitation, depression, and cognition in each case.262 Additionally, improvement in negative symptoms263,264 and cognition266–268 in schizophrenia trials suggests that apathy and cognition (particularly executive function, working memory, episodic memory, attention/vigilance, and psychomotor speed) may improve in patients with dementia. Moreover, MMSE scores269 and working memory270 are sensitive to serotonin availability. Furthermore, as referenced in the duloxetine section, the dual SNRI action of ziprasidone suggests specific additional nonantipsychotic-mediated therapeutic effects on a wide variety of symptoms. These include hallucinations, delusions, depression, anxiety, apathy, sleep, agitation, aggression, irritability, disinhibition, excitement, wandering, incontinence, overall cognition, attention, executive function, memory, and visuospatial function. In Parkinson’s disease, at doses low enough to invoke ziprasidone actions other than D2 blockade, it is possible that beneficial effects may be seen on bradyphrenia, motor symptoms including akinesia, postural instability, freezing, stage, disability, dyskinesia, and on/off syndrome. In contrast to most other atypical antipsychotics, early clinical evidence suggests minimal motor impairment in Parkinson’s disease with ziprasidone.255,271

Ziprasidone and agents with related modes of action together demonstrate neuroprotective properties in neurodegenerative models, including inhibition of GSK-3β, pathogenic protein formation, and GSK-3β and Aβ pathogenic effects. These drugs have also improved mitochondrial energy production and energy preservation after injury and protected against mitochondrial depolarization, transition pore development, and cytochrome c release. Additionally, these agents have reduced free radical production and lipid peroxidation, particularly free radicals induced by Aβ, and inhibited apoptosis, especially that induced by glutamate, Aβ, MPP+, and the proteasome inhibitor MG132 (relevant to Huntington’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, Parkinson’s disease, and other neurodegenerative diseases). Finally, SNRI properties of ziprasidone further suggest the capacity to reduce GSK-3β, pathogenic protein concentrations, nitric oxide synthesis, other free radicals, mitochondrial depolarization, apoptosis, microglial activation, and neuroinflammation while upregulating BDNF and GDNF.

In considering the putative neuroprotective effects of ziprasidone, we will sequentially consider the neuroprotective effects associated with D2 antagonists, drugs with 5HT2 antagonist properties, and 5HT1a agonists (SNRI properties are described in the duloxetine section).

D2 antagonists inhibit Aβ formation,272 Aβ-induced calcium imbalances,273 and apoptosis induced by glutamate in Huntington’s disease transgenic mice,274 MPP+ in a Parkinson’s disease model,274,275 and MG132 proteasome inhibition in PC12 cells.276 These actions are mediated through antipsychotic effects on D2 receptors,273 sigma receptors,272,273 respiratory chain complex I and II inhibition,276 and mitochondrial transition pore development.274,275

Ziprasidone and other D2-5HT2 antagonist antipsychotics have inhibited GSK-3,212 leading to reductions in Aβ, tau, αSyn, and mitochondrial dysfunction (see introduction). 5HT2 receptor stimulation regulates GSK-3β activity by reducing serine 9 phosphorylation,214 indicating that 5HT2 antagonism can promote GSK-3β inhibition. D2-5HT2 antagonists have increased
energy charge and redox reaction velocity, increased ATP production, and prevented ATP reductions after injury. They also have reduced superoxide radicals, protected against Aβ-induced reactive oxygen species, and inhibited mitochondrial depolarization, mitochondrial permeability transition pore development, and cytochrome c release. Ziprasidone has been shown to reduce lipid peroxidation. Finally, D2-5HT2 antagonists exhibit antiapoptotic properties including calmodulin antagonism and endonuclease inhibition and have inhibited apoptotic events in a variety of models, including Aβ-induced and MPP+-induced apoptosis in neuronal PC12 cells.

In light of its SNRI properties, ziprasidone may have the additional antiapoptotic property of monoamine oxidase B inhibition. 5HT1a agonists have also demonstrated antiapoptotic effects. Moreover, 5HT1a receptor stimulation also inhibits GSK-3β through serine 9 phosphorylation.

The combined D2 and 5HT2 antagonist, 5HT1a agonist, and SNRI properties of ziprasidone suggest a wealth of potential neuroprotective actions for this agent. The potential neuroprotective actions of ziprasidone are summarized in Table 2.

S-Zopiclone S-zopiclone is a short half-life nonbenzodiazepine cyclopyrrolone GABA-A receptor subunit agonist with preference for omega-1 receptors. Short half-life benzodiazepine receptor site-specific agonists such as s-zopiclone are considered first-line treatments for sleep disturbances in Alzheimer’s disease and Parkinson’s disease. Short half-life hypnotics have been found to be safe and effective without notable side effects in the elderly and zopiclone is particularly well tolerated and effective.

S-zopiclone and zopiclone have each been demonstrated to improve anxiety, depression, and cognitive impairment in patients with insomnia. S-zopiclone REM suppression may also improve REM behavior disorder in synucleinopathic neurodegenerative diseases. Moreover, “sleep benefit” has been observed for Parkinson’s disease motor symptoms. Similarly, sleep appears to replenish neurotransmitter availability in dementia, especially acetylcholine, the depletion of which has been linked to behavioral and cognitive disturbances. Consistent with this concept, sleep disturbances are correlated with reduced function in Alzheimer’s disease and in nondemented elderly.

A number of neuropsychiatric features are sensitive to sleep, including cognitive and noncognitive conditions. Noncognitive neuropsychiatric conditions that are sensitive to sleep include depression, anxiety, perceptual distortions and hallucinations, aggressive behavior, and apathy. Sleep-sensitive cognitive conditions include delirium, cognitive impairment, psychomotor impairment, attention and vigilance, working memory, learning, short-term recognition memory encoding, semantic memory retrieval, hippocampus-dependent declarative memory, visual memory, visual processing, long-term memory, frontal executive performance, response inhibition, and other higher cognitive functions.

Zopiclone and similar agents have improved insomnia and nocturnal wandering, anxiety, agitation arising within the context of dementia. These drugs have also been reported to improve aggression in brain disease, psychosis, depression, and apathy in schizophrenia. Thus, zopiclone has the potential to improve a wide range of neuropsychiatric, cognitive, and motor disturbances in patients with neurodegenerative diseases.

Although the effects of s-zopiclone on neurodegenerative disease pathophysiology are in the early stages of investigation, s-zopiclone and other drugs sharing properties of s-zopiclone seem to exhibit neuroprotective properties that include protection against pathogenic proteins, free radical-induced lipid peroxidation, mitochondrial transition pore development, cytochrome c release, and apoptosis. There is also evidence of neurorestorative effects on GSK-3β over-activity, proteasomal processing, hippocampal neuronal ATP production, neuroinflammation, and BDNF expression.

GABA-A agonists have been shown to protect against Aβ-induced neurotoxicity, glutamate-induced free radical formation, free radical-induced lipid peroxidation, calcium-induced mitochondrial permeability transition pore development, and ischemia-induced mitochondrial cytochrome c release. They also promote ATP recovery in ischemic hippocampal slices and may protect against apoptosis induced by Aβ and by glutamate in hippocampal neurons. These antiapoptotic properties are in contrast to GABA-A agonists that bind to peripheral benzodiazepine (TSPO) receptors (e.g., diazepam) and promote apoptosis. Finally, sleep deprivation, often present in neurodegenerative diseases, has been associated with GSK-3β activation.
altered proteasomal processing, oxidative damage, impaired mitochondrial integrity and function, neurodegenerative inflammation, and decreased BDNF expression. (While sleep deprivation increases BDNF in developing rats, developing tissue and organisms are different from mature tissues and organisms.) Correction of the insomnia with treatment can potentially reverse these impairments. S-zopiclone and related drugs may therefore provide polyclonal neuroprotection in these diseases. The potential neuroprotective actions of s-zopiclone are summarized in Table 2.

Ramelteon Ramelteon is a melatonin (MT) MT1 and MT2 receptor agonist with demonstrated efficacy in elderly subjects with insomnia. Ramelteon is more potent and has greater affinity at melatonin receptors than does melatonin itself. As mentioned above (see s-zopiclone section, third paragraph), a large number of neuropsychiatric features are sensitive to sleep. Additionally, reduced melatonin excretion has been observed in beta-blocker hallucinosis, a condition that resembles the hallucinations and delirial features of Parkinson’s disease and dementia with Lewy bodies. Consistent with these symptoms induced by beta-blockers, noradrenergic locus coeruleus degeneration is observed in Parkinson’s disease and dementia with Lewy bodies, suggesting a potential link between these symptoms and melatonin receptor activity.

Melatonin administration itself has improved sleep and has demonstrated efficacy in neuropsychiatric disturbances in general including anxiety, delirium, disturbances of attention, some aspects of memory, daytime sleepiness and “sun-downing behavior” in dementia, and REM behavior disorder that is commonly seen in dementia with Lewy bodies and Parkinson’s disease dementia. Melatonin has also been suggested as a treatment for fluctuations in cognition and alertness in Parkinson’s disease. The greater potency and affinity of ramelteon at melatonin receptors may lead to outcomes superior to those obtained with melatonin.

Melatonin has many neuroprotective actions in preclinical models, as exemplified in Parkinson’s disease and Alzheimer’s disease. As mentioned in the s-Zopiclone section, sleep deprivation promotes neurodegenerative disease through effects on GSK-3β, the proteasome, oxidative damage, mitochondrial impairment, and neuroinflammation. Besides improvement in these functions ascribable to alleviating insomnia in neurodegenerative disease, results of melatonin treatment studies suggest ramelteon may exert neuroprotective effects by preserving dopaminergic striatal, and hippocampal neurons. Other potential neuroprotective actions include inhibiting αSyn aggregation and Aβ fiber formation, aggregation, and deposition and preventing tau and Aβ-induced αSyn oligomerization. Moreover, ramelteon has the potential to inhibit nitric oxide synthase, scavenge free radicals, induce antioxidant enzymes, prevent dopamine auto-oxidation, maintain mitochondrial integrity, and protect against losses of complex I in Parkinson’s disease and complex IV. Furthermore, ramelteon may be able to prevent apoptotic cascades, particularly those induced by glutamate, Aβ, and MPP+ and neurogenesis. Each of these effects is particularly relevant to neurodegenerative disease pathogenesis (see introduction), and ramelteon may prove to clinically protect against neurodegeneration.

The evidence is far too extensive to review here (see Part I of this report, and Table 3 of the online data supplement to Part I of this report), but by way of examples in Parkinson’s disease, melatonin prevented αSyn aggregation after maneb and rotenone exposure in Parkinson’s disease models and has preserved dopaminergic tyrosine hydroxylase-positive nigral neurons bearing MT1 and MT2 receptors after 6-hydroxy-dopamine lesions in rats. Melatonin has prevented nigrostriatal free radical damage in mice and rats treated with MPTF and has led to essentially full nigrostriatal recovery in rats treated with MPTF and those treated with 6-hydroxydopamine. Melatonin reduced auto-oxidative semiquinone formation and increased l-dopa bioavailability in rats treated with intrastriatal l-dopa. A rat striatal 6-hydroxydopamine study indicated neuroprotection by melatonin manifest in reduced nigral neurodegeneration as evidenced by apomorphine-induced turning behavior. Melatonin reduced nigrostriatal neuronal apoptosis in an MPTF mouse model. BDNF is colocalized with dopamine neurons in the substantia nigra, where it may exert...
neuromodulatory and neuroprotective effects. BDNF and GDNF correlate with MT1 receptor activity, and melatonin increases both GDNF and BDNF and promotes the viability of MT1 and MT2 receptor-bearing neural stem cells derived from rat ventral midbrain. It also significantly increases tyrosine hydroxylase and its mRNA, indicative of enhanced nigral dopaminergic neurotrophism that is highly relevant to Parkinson’s disease. Melatonin and dopamine exhibit similar gene expression and protein profiles. Recently, ramelteon has been demonstrated to increase neuronal BDNF concentrations in cultured mouse cerebellar granule cells bearing MT1 and others bearing MT2 receptors.

Neither melatonin nor ramelteon has undergone clinical trials for its clinical and disease-modifying neuroprotective properties in neurodegenerative disease, and melatonin preclinical and ramelteon clinical findings remain to be confirmed in neurodegenerative disease patients. An important caveat regards the need to determine which of the above neuroprotective properties of melatonin are mediated through melatonin receptors and other mechanisms common to both melatonin and ramelteon. The potential neuroprotective actions of ramelteon are summarized in Table 2.

**Directions for Future Research**

The potential neuroprotective actions for each agent have been specified above. In Table 1 (also discussed in Part I of this report), we have indicated candidate criteria for potential prediction of translational neuroprotection in clinical patients.

1. We therefore suggest that each of these promising agents be evaluated in terms of the specific enumerated neuroprotective actions in accord with the criteria of Table 1. Such inquiries can clarify the mechanisms of these drugs and may determine the likelihood of positive outcomes in randomized, double-blind, placebo-controlled delayed-start or randomized-withdrawal neuroprotective clinical trials. Although ethical issues regarding withholding treatment have been raised in such trials, it cannot be known whether a given drug has neuroprotective efficacy until such trials are conducted. In evaluating antidepressants in patients with depression, these procedures might be modified by using an antidepressant with less robust neuroprotective properties to supplant the placebo, avoiding an ethical dilemma by providing equally efficacious treatment for the depression.

2. Furthermore, given that these agents are widely used to treat clinical neuropsychiatric conditions that arise in the context of neurodegenerative disease, and given that their safety and tolerability are known, neuroprotective clinical trials need not necessarily await the fulfillment of the Table 1 criteria. Nevertheless, caution is advised in light of adverse events recently identified for psychotropic drugs (e.g., increased death and stroke risks with antipsychotics) in elderly populations, the population most at risk for the most common neurodegenerative diseases.

3. Research should be continued into the correlation of psychotropic pharmacodynamic mechanisms with neuroprotective actions.

4. Finally, research to determine the clinical neuroprotective predictive utility of each of the Table 1 criteria can greatly assist the efforts of propelling agents of interest from preclinical studies to the clinical trial stage.

**CONCLUSION**

The above examples suggest that psychotropics may have neuroprotective potential. These neuroprotective properties based on preclinical studies are summarized in Table 2.

It should be remembered that the properties of the drugs discussed above do not necessarily emanate from research data on the drugs themselves, but from agents representative of their class with similar pharmacodynamic properties. Whether the pharmacodynamic properties that are relevant to their psychotropic effects pertain to their neuroprotective actions is a subject of ongoing research, but there is preliminary evidence justifying this assumption for at least some of the effects of each drug mentioned.

These agents act at multiple levels of pathophysiological processes operant across the spectrum of neurodegenerative diseases. Although it is possible that strategic combinations of these agents may afford neuroprotective benefit superior to monotherapy in clinical trials, at the present time, selection of agents should be determined by their clinical symptomatic effects because they have not yet been comprehensively and systematically investigated in neurodegenerative disease models. Moreover, some of the drugs have been subjected to less comprehensive preclinical investigations than others, with neuroprotective features of some drugs being investigated only recently.
The preliminary status of this neuroprotective research notwithstanding, a future strategy that may be useful is to use several drugs that each target the primary neurodegenerative processes in a selected disease of interest. Ziprasidone is a single drug that represents such an approach, combining the actions of D2-5HT2 antagonists, SNRIs, and 5HT1a agonists. Still, it seems more plausible that effective disease management will require identifying several drugs with complementary benefits. Consistent with this combination strategy, the combination of memantine with a cholinesterase inhibitor, cognitive enhancers with neuroprotective effects in preclinical models, yields progressively greater improvement in potential neuroprotective outcomes when coadministered than when a cholinesterase inhibitor is administered individually. On the other hand, some combination therapies have actually abolished efficacy while multiplying toxicity, and animal trials should first be conducted to evaluate this. In any event, it is important that these psychotropic drugs now be studied systematically in neurodegenerative drugs preclinical models and that they be investigated for clinical neuroprotective efficacy in patients with those diseases.

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