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## APPENDIX 1. Neuroprotective Effects By Psychotropic Class

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The following findings are consistent with the preponderance of preclinical study findings that are evident by inspection of Tables 1-3. Direct acting dopamine D2 receptor agonists are useful in treating PD, apathy syndromes, and other disorders. Newer non-ergoline agonists have found increasing use over older agents. While a number of studies have been carried out using the non-ergoline pramipexole, we could find no studies of ropinirole. Nevertheless, it appears that pramipexole has clinical neuroprotective potential, with preliminary evidence of reduced  $\alpha$ Syn accumulation, A $\beta$  secretion, A $\beta$  fibril-induced free radical generation, and apoptosis.

Amantadine can be classified as a presynaptic dopamine releaser and as an NMDA antagonist, but more data are needed to guide assessment of its clinical neuroprotective potential.

Antipsychotic drugs vary in their apoptotic effects and, except for often inhibiting Complex I, a number of them exhibit mitochondrial protective properties. High potency neuroleptics (haloperidol, fluphenazine, and trifluoperazine) tend to promote apoptosis while low potency neuroleptics and atypical antipsychotics (chlorpromazine, thioridazine, risperidone, olanzapine, quetiapine, and clozapine) tend to inhibit apoptosis, although trifluoperazine may have anti-apoptotic properties in some AD and PD models. A $\beta$ -induced apoptosis has been inhibited by the atypical antipsychotics, including risperidone, olanzapine, and quetiapine. Risperidone, olanzapine, and clozapine have inhibited 1-methyl-4-phenylpyridine ion (MPP<sup>+</sup>)-induced apoptosis. Antipsychotics generally reduce Complex I activity and increase Complex IV activity, although clozapine only mildly reduces Complex I while thioridazine and olanzapine do not reduce Complex I. Fluphenazine protects mitochondrial function in some models. Clozapine generates ROS while olanzapine and quetiapine protect against A $\beta$ -induced ROS. Trifluoperazine, chlorpromazine, and quetiapine have been demonstrated to prevent mitochondrial membrane depolarization and mitochondrial PTP formation. Haloperidol, trifluoperazine, chlorpromazine, and thioridazine promote apoptosis in malignancy.

Lithium may inhibit proteasomal and mitochondrial cytochrome oxidase c activity, but it reduces A $\beta$  production, tau hyperphosphorylation, mitochondrial membrane depolarization, cytochrome c release, and apoptosis, and may enhance neuronal viability. Preclinical evidence suggests that lithium has potential utility in AD, PD, HD, and cerebrovascular disease.

Anticonvulsants seem to have mixed effects, depending upon the model, especially carbamazepine and valproate, whereas oxcarbazepine is predominantly proapoptotic. Carbamazepine has mixed effects on tau phosphorylation, oxidative stress, mitochondrial dysfunction, and apoptosis in neural tissues. Early evidence indicates that oxcarbazepine increases ROS, diminishes ATP production, depolarizes mitochondrial membranes, and induces apoptosis. Valproate promotes mitochondrial dysfunction, has mixed effects on mitochondrial PTP development and apoptosis (antiapoptotic in neural tissue and proapoptotic in microglia and malignant cell lines), and may inhibit A $\beta$  production but may not inhibit tau phosphorylation while it increases  $\alpha$ Syn levels. Valproate should not be used in patients with mitochondrial diseases.

Tricyclic antidepressants are generally proapoptotic, although the secondary amines nortriptyline and desipramine were protective in NDD models. Amitriptyline, imipramine, and nortriptyline killed neutrophils, and imipramine and clomipramine induced apoptosis in immature cells and especially in leukemia. Nortriptyline blocked glutamate-induced mitochondrial depolarization and apoptosis in a HD mouse model and reduced apoptosis in an ALS mouse model. Desipramine inhibited ROS production, mitochondrial PTP opening, and apoptosis in several models, particularly in the HD transgenic mouse model. Clomipramine inhibited Complex III, depolarized mitochondrial membranes although it did not release cytochrome c, reduced cell viability, and promoted apoptosis, particularly in malignancies and leukemias.

The tetracyclic maprotiline did not affect tau phosphorylation or microtubule assembly, and it inhibited glutamate - induced mitochondrial PTP opening and apoptosis in a transgenic mouse model.

The SSRIs exhibit some neuroprotective properties in some models but are pro-apoptotic in malignancies and some leukocytes. The SSRI fluoxetine uncouples oxidative phosphorylation and stimulates state 4 respiration, has variable effects on mitochondrial PTP but promotes its development in neoplasias, kills neutrophils, and protects neural stem cells and hippocampal neurons from apoptosis, yet it promotes apoptosis in malignancies. Similarly, paroxetine released cytochrome c and promoted apoptosis in malignancies, although preliminary data suggest this agent may reduce A $\beta$  and hyperphosphorylated tau in an AD transgenic mouse model. Citalopram induced ROS, mitochondrial depolarization, apoptosis, and reduced cell viability in leukemias. SSRIs and clomipramine prevent serotonin - induced apoptosis however.

Among anxiolytics, buspirone has inhibited apoptosis in several neuronal models. Traditional anxiolytics are generally GABA-A agonists, which have been demonstrated to protect against A $\beta$ -induced neurotoxicity. The central benzodiazepine receptor agonist clonazepam has some anti-apoptotic properties whereas the peripheral benzodiazepine receptor agonist diazepam is pro-apoptotic. On the other hand, the peripheral benzodiazepine receptor agonist diazepam uncoupled oxidative phosphorylation, promoted mitochondrial depolarization, mitochondrial PTP development, and cytochrome c release (although it promoted ATP recovery and prevented cytochrome c release in ischemic hippocampus in a single study). Diazepam has also been observed to promote several types of apoptosis in several neuronal models and in multiple malignancies. In contrast, chlordiazepoxide did not bind to mitochondrial peripheral benzodiazepine receptors, nor did it affect mitochondrial metabolism. Similarly, zolpidem, a GABA-A agonist that binds to the omega-1 central benzodiazepine receptor site, did not increase calcium-induced mitochondrial permeability transition. Clonazepam, another central benzodiazepine receptor agonist, blocked mitochondrial calcium influx in hypoxia, inhibited sodium/calcium exchange, restored ATP production in Complex I deficiency, attenuated mitochondrial depolarization, and blocked mitochondrial PTP development and calcium efflux. Yet this drug had mixed effects on apoptosis, with increased apoptosis in immature rats, particularly involving the frontal lobe, although it did not induce apoptosis in malignant cell lines.

Diphenhydramine displayed mixed effects, producing premalignant changes in rat liver mitochondria, preventing hypoxic uncoupling of oxidative phosphorylation, and promoting apoptosis in malignant cell lines.

The hormone melatonin has inhibited A $\beta$  formation and deposition in most models and tau phosphorylation at sites relevant to AD, activated tau - dephosphorylating phosphatase PP-2A, protected mitochondrial function, inhibited free radicals, prevented mitochondrial PTP development and cytochrome c release, improved cellular viability, and inhibited apoptosis. These actions, suggest beneficial potential in NDDs, especially AD and PD. Data on cell viability in malignancies remains inconclusive, but initial evidence suggests that melatonin may promote mitochondrial function and cell survival and inhibit apoptosis in some forms of neoplastic disease while impairing mitochondrial function and promoting apoptosis in others.

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## APPENDIX 2. Drugs By Neuroprotective Action

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The following findings are consistent with the preponderance of preclinical study findings that are evident by inspection of Tables 1-3.  **$\alpha$ Syn.** In the context of limited data, pramipexole and melatonin offer potential to reduce  $\alpha$ Syn pathology. Pramipexole displayed anti-aggregation properties in a single study using SH-SY5Y dopaminergic neuroblastoma cells. Valproate seems to increase  $\alpha$ Syn concentrations, but it is unknown whether this is beneficial or deleterious, particularly in PD. Melatonin has inhibited  $\alpha$ Syn aggregation, conferring a potential advantage in PD.

**A $\beta$ .** Lithium, valproate, paroxetine, and melatonin are the most promising neuroprotective agents with respect to A $\beta$  pathology. Older dopamine agonists have inhibited A $\beta$  fibril formation, although data for non-ergoline dopamine agonists were not evident. Haloperidol may acutely increase cortical amyloid precursor protein but may inhibit A $\beta$  formation and A $\beta$  - induced calcium influx, although studies are limited. Lithium, a GSK-3 $\beta$  inhibitor, inhibits A $\beta$  production and secretion in most but not all models. Valproate has inhibited A $\beta$  production in the only two models that it has been tested in. Paroxetine was found to reduce A $\beta$  in an AD transgenic mouse model. Melatonin has inhibited A $\beta$  formation and deposition in most models.

**Tau.** Lithium, paroxetine, and melatonin show the greatest neuroprotective potential in regard to tau hyperphosphorylation. It is apparent that haloperidol can increase tau phosphorylation and inhibit dephosphorylation. Trifluoperazine can also inhibit tau assembly and dephosphorylation. Chlorpromazine can inhibit tau hyperphosphorylation. Lithium inhibits tau hyperphosphorylation in a wide variety of models, including hyperphosphorylation induced by A $\beta$ , and at sites relevant to AD, including tau-1 and PHF-1 sites. Lithium also deters the aggregation of hyperphosphorylated tau while it promotes tau dephosphorylation and tau binding to microtubules, microtubule assembly, and axonal transport. Carbamazepine and valproate have not inhibited neuronal tau phosphorylation. In a single rat study, the antidepressants desipramine, maprotiline, and citalopram did not alter tau phosphorylation. Paroxetine has been found to reduce hyperphosphorylated tau in an AD transgenic mouse model. Melatonin has inhibited tau phosphorylation at sites relevant to AD in a number of studies, and activated the tau - dephosphorylating phosphatase PP-2A.

**Ubiquitin.** The effects of pharmacotherapeutic drugs upon ubiquitinopathic processes is yet emerging (Table 4), and it is too early to project therapeutic efficacy at this time.

**Proteasome.** Although data are quite limited, to date, valproate is the most promising drug with respect to neuroprotection at the level of the proteasome. Haloperidol and fluphenazine may inhibit proteasomal activity, as may lithium. Valproate may augment proteasomal function, but this remains to be empirically demonstrated. Two studies suggest that melatonin may inhibit the proteasome.

**Free Radicals And The Mitochondrion.** Drugs of greatest antioxidant and mitochondrial protective neuroprotective potential include pramipexole, trifluoperazine, quetiapine, desipramine, clonazepam, and melatonin. Several studies, including one conducted in ALS patients, indicate that pramipexole scavenges and reduces free radicals, including ROS induced by A $\beta$  fibrils, A $\beta$  oligomers, and MPP<sup>+</sup>, relevant to AD, PD, and ALS. The NMDA antagonists amantadine, memantine, and MK-801 protected nucleus basalis cholinergic neurons against mitochondrial failure in a single study, suggesting an advantage in AD. Trifluoperazine has mitochondrial protective properties in some models. Olanzapine and quetiapine have protected against A $\beta$ -induced ROS, however clozapine has generated ROS. Carbamazepine reduced mitochondrial activity in astrocytes and in CGNs but not in rat hippocampal neurons. Initial evidence indicates that oxcarbazepine is associated with increased ROS and diminished ATP production. Valproate can lead to clinical deterioration in mitochondrial disease and should be avoided in these conditions. Valproate is associated with mitochondrial structural damage, carnitine deficiency, reduced beta - oxidation, and reduced oxidative phosphorylation. Imipramine has increased ROS whereas desipramine has inhibited ROS formation. Citalopram promoted ROS generation in leukemia. Clonazepam, a central benzodiazepine receptor agonist, blocked mitochondrial calcium influx in hypoxia, inhibited sodium/calcium exchange, and restored ATP production in Complex I deficiency. The antihistamine diphenhydramine induced premalignant changes in rat liver mitochondria and prevented hypoxic histamine - induced uncoupling of oxidative phosphorylation. Melatonin protected mitochondrial function in non-malignant tissue, however there have been mixed findings in neoplasia.

**Electron Transport System Effects.** Drugs of greatest neuroprotective potential regarding the electron transport system include thioridazine, olanzapine, and melatonin. Complex I deficiencies have been observed in PD whereas Complex IV, and to a lesser extent, Complex III deficiencies have been seen in AD. Studies indicate Complex I inhibition with the neuroleptics haloperidol, fluphenazine, thiothixene, and chlorpromazine, and with the atypical antipsychotics risperidone, quetiapine, and, variably, clozapine, although clozapine is far less potent than the other drugs in this respect. Risperidone reduced Complex I activity in the hippocampal region, frontal cortex, and striatum in a single study, potentially relevant to AD, FTLN, HD, PD, and other NDDs. Thioridazine, olanzapine, and clozapine have not inhibited Complex I in some models. In fact, clozapine has restored ATP production in human Complex I deficiency, and risperidone, olanzapine, and quetiapine have protected against reduced cellular viability after exposure to rotenone, a Complex I inhibitor. Melatonin has protected against Complex I loss in 6-hydroxydopamine and MPP<sup>+</sup> PD models and has repeatedly been demonstrated to stimulate Complex I, suggesting that melatonin would be safest to use in PD, followed by thioridazine, olanzapine, and clozapine. Haloperidol has reduced Complex II and V. The tricyclic antidepressant clomipramine has inhibited Complex III in a rat study whereas melatonin has protected Complex III from oxidative damage. Haloperidol, fluphenazine, thiothixene, chlorpromazine, clozapine, and melatonin stimulate Complex IV, of note in AD. Fluoxetine uncouples oxidative phosphorylation and stimulates state 4 respiration. Diazepam uncoupled oxidative phosphorylation, although it promoted ATP recovery in a single study of ischemic hippocampal slices. In contrast, chlordiazepoxide did not affect mitochondrial metabolism.

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## APPENDIX 2. Continued

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**Mitochondrial PTP.** Drugs of greatest neuroprotective potential with respect to mitochondrial depolarization and PTP development include pramipexole, trifluoperazine, thioridazine, quetiapine, lithium, nortriptyline, clonazepam, and melatonin. Several studies indicate the effectiveness of pramipexole against PTP development induced by  $MPP^+$ ,  $H_2O_2$ , and rotenone, usually in neuroblastoma cells, including dopaminergic SH-SY5Y. Trifluoperazine is very effective in preventing mitochondrial PTP development across a wide range of models. Similarly, chlorpromazine prevents mitochondrial PTP development in normal cells, but not in neoplasia. Thioridazine also prevents mitochondrial PTP development in normal cells, but also in neoplastic cells although evidence is limited to one study of leukemia. Quetiapine protected PC 12 cells against  $A\beta$ -induced mitochondrial membrane depolarization. Lithium stabilizes mitochondrial membrane potentials and prevents PTP development and cytochrome c release in several models. In a single study, carbamazepine did not depolarize mitochondrial membranes in rat hippocampal neurons. Preliminary evidence indicates that oxcarbazepine depolarizes mitochondrial membranes. Valproate seems to induce mitochondrial PTP development without mitochondrial membrane depolarization or release of cytochrome c, except in leukemic cells. Imipramine depolarized mitochondrial membranes whereas nortriptyline antagonized glutamate-induced depolarization. Nortriptyline has inhibited PTP development and cytochrome c release in an HD yeast model and ALS mouse model, respectively. Desipramine and maprotiline inhibited glutamate-induced mitochondrial PTP opening, but potentiated morphine-induced mitochondrial PTP opening. Clomipramine depolarized mitochondrial membranes but did not release cytochrome c. Fluoxetine has variable effects on mitochondrial PTP but opens it in neoplasias, as does paroxetine. Citalopram induced mitochondrial depolarization in leukemia. Diazepam promotes mitochondrial depolarization, mitochondrial PTP development, and cytochrome c release (although not in ischemic hippocampus in a single study). Zolpidem, however, did not increase calcium-induced mitochondrial permeability transition. Clonazepam prevented mitochondrial depolarization and blocked mitochondrial PTP development and calcium efflux. Melatonin has inhibited mitochondrial PTP development and cytochrome c release in non-malignant cell lines and, specifically, in AD and PD models.

**Cell Viability.** Drugs of greatest neuroprotective potential in regard to cellular viability include olanzapine, quetiapine, lithium, nortriptyline, and maprotiline. Haloperidol has reduced cell viability in SH-SY5Y cells and rotenone-treated PC12 cells. However, olanzapine improved cell viability in both rotenone-treated and untreated PC12 cells, and blocked superoxide dismutase 1 (SOD1) decrement, suggesting olanzapine's potential to improve viability in PD and ALS, respectively. Quetiapine also improved the viability of PC12 cells exposed to rotenone, suggesting potential utility in PD. Lithium improved CGN viability. Carbamazepine has had variable effects on lymphocyte viability. Valproate enhanced rat cortical neuronal viability in a single study. Different antidepressants appear to have significantly different effects: amitriptyline, imipramine, nortriptyline, and fluoxetine have killed neutrophils. In contrast, imipramine, clomipramine, and citalopram have reduced the viability of leukemic cells, and imipramine and fluoxetine have reduced the viability of HT29 human colon carcinoma cells. Nortriptyline protected motor neurons from death in an ALS mouse model. Clonazepam did not affect cell survival in rat glioma cells. In two studies, melatonin has been found to improve cell survival in peripheral blood mononuclear and N2a neuroblastoma cells.

**Apoptosis.** Drugs of greatest anti-apoptotic neuroprotective potential include pramipexole, amantadine, risperidone, olanzapine, quetiapine, lithium, valproate, nortriptyline, desipramine, and maprotiline.

A number of studies show that pramipexole protects against apoptosis, including apoptosis induced by dopamine in dopaminergic neurons and induced by  $MPP^+$ ,  $A\beta$ , and  $H_2O_2$  in neuroblastomas. Two studies showed that amantadine protected against apoptosis induced by influenza virus in non-neural cells. Haloperidol may protect against dopamine-induced apoptosis, but it is otherwise proapoptotic in neural tissues. Fluphenazine, trifluoperazine, chlorpromazine, are proapoptotic, at least in malignant cell lines. Thioridazine did not promote apoptosis in neurons or lymphocytes, but did so in neoplastic cells. Risperidone has inhibited apoptosis in PC12 cells after exposure to  $A\beta$  and  $MPP^+$ . Olanzapine inhibits apoptosis in neural cells produced by various neurotoxins, including  $A\beta$  and  $MPP^+$ . Quetiapine protected PC 12 cells against  $A\beta$ -induced apoptotic marker increases. Clozapine has protected against  $MPP^+$ -induced apoptosis although nitrenium ion formation is associated with agranulocytosis. Lithium reduces apoptosis induced by  $A\beta$ , GSK-3 $\beta$ , aluminum, glutamate, NMDA receptor stimulation,  $MPP^+$ , rotenone, aging, quinolinic acid cerebral ischemia, C2 ceramide, and other models, but is often proapoptotic in malignant cell lines. Although findings have been mixed, carbamazepine has predominantly promoted apoptosis. Preliminary evidence indicates that oxcarbazepine induces apoptosis. Valproate generally inhibits apoptosis in neuronal models, including  $A\beta$ -, GSK-3 $\beta$ -, NMDA-, and rotenone-induced apoptosis, but appears to be proapoptotic in many malignant and immature cell lines. This, as well as proapoptotic effects in microglia, suggest possible beneficial effects on the pathophysiology of AD.

Imipramine has produced mixed effects on apoptosis, inhibiting it in hepatocytes and in colon cancer while promoting it in immature neurons, lymphoblasts, and leukemic cells. While desipramine induced apoptosis in rat glioma, it inhibited apoptosis in several cell lines and in multiple models, including glutamate-, 6-OHDA-, corticosterone-, and ceramide-induced apoptosis. Nortriptyline, desipramine, and maprotiline blocked glutamate-induced apoptosis in a HD transgenic mouse model. Clomipramine promoted apoptosis, particularly in malignancies and leukemias, but protected against serotonin-induced apoptosis.

Fluoxetine protects neural stem cells and hippocampal neurons from apoptosis and prevents serotonin-induced apoptosis, but promotes apoptosis in malignancies. Paroxetine also protected against serotonin-induced apoptosis, but otherwise promoted apoptosis in malignancies. Citalopram promotes apoptosis in several leukemic cell lines.

The 5HT<sub>1a</sub> partial agonist anxiolytic buspirone has inhibited apoptosis in several neuronal models. In contrast, the benzodiazepine diazepam has promoted several types of apoptosis in several neuronal models and in multiple malignancies. Clonazepam had mixed effects on apoptosis, but has produced neuronal apoptosis in immature rats, particularly in the frontal lobe.

The antihistamine H1 antagonist diphenhydramine has promoted apoptosis in several malignant cell lines.

The hormone melatonin has inhibited apoptosis, including apoptosis induced by  $A\beta$  and  $MPP^+$ , but findings conflict in neoplasia.

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**TABLE 1. Neuroprotective Properties of Anti-Apathy, Antipsychotic, and Mood Stabilizing Agents**

Agent	$\alpha$ Syn	A $\beta$	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
<b>Apathy Treatments</b>								
Pramipexole	Inhibited MPP <sup>+</sup> -induced $\alpha$ Syn aggregation in human dopaminergic SH-SY5Y neuroblastoma cells. <sup>8</sup>	s-Pramipexole reduced cybrid A $\beta$ secretion. <sup>9</sup>			Prevented A $\beta$ fibril- and A $\beta$ oligomer-induced free radical formation. <sup>30</sup> Inhibited MPP <sup>+</sup> -induced ROS in SH-SY5Y <sup>31,32</sup> and rat striatum, <sup>34</sup> and scavenged MPP <sup>+</sup> -induced free radicals in SH-SY5Y. <sup>32</sup> Reduced serum free radicals in ALS patients. <sup>35</sup> Inhibited PTP at clinical concentrations <sup>24</sup> and after exposure. <sup>10,16,25,26,25</sup> MPP <sup>+</sup> inhibitor) <sup>25</sup> in several cell lines including SH-SY5Y. <sup>18,25</sup> Inhibited H2O <sub>2</sub> -induced PTP in neuroblastoma cells. <sup>36</sup>	Inhibited A $\beta$ -induced apoptotic caspase activation. <sup>27</sup> Inhibited dopamine-induced apoptosis in dopaminergic MES 23.5 cells. <sup>28</sup> Inhibited MPP <sup>+</sup> -induced apoptosis <sup>18,22,25,27</sup> in SH-SY5Y cells. <sup>18,22,25</sup> Inhibited rotenone-induced apoptosis in dopaminergic SH-SY5Y cells and non-dopaminergic JK cells. <sup>25</sup> Inhibited H2O <sub>2</sub> -induced apoptosis in PC12 cells. <sup>26</sup>	Pramipexole may inhibit $\alpha$ Syn accumulation, A $\beta$ secretion, ROS activity, mitochondrial PTP opening, and several types of apoptosis, consistent with utility in NDDs including PD, AD, and ALS.	
Ropinirole								
Amantadine				Attenuated nucleus basalis cholinergic neuron mitochondrial failure similar to memantine and MfK-801. <sup>29</sup>			Inhibited H3N2 influenza virus-induced renal MDCK cells apoptosis <sup>30</sup> and influenza A virus-induced apoptosis. TNF $\alpha$ and NO in J774.1 murine macrophages. <sup>31</sup> Bromocriptine inhibited MPP <sup>+</sup> -induced apoptosis in SH-SY5Y cells. <sup>32</sup>	There were no relevant studies detected for this agent. Amantadine data in NDD are inadequate, but amantadine potentially may have mitochondrial protective and antiapoptotic properties.
Other dopamine agonists		A $\beta$ fibril formation dose-dependently inhibited by dopamine > selegiline > levodopa > pergolide > bromocriptine. <sup>32</sup>						Dopamine and dopamine agonists may inhibit A $\beta$ fibril formation, and bromocriptine may inhibit MPP <sup>+</sup> -induced apoptosis, but these findings should be confirmed.

TABLE 1. Continued

Agent	αSyn	Aβ	t	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Antipsychotics Haloperidol		Acutely elevated APP without significant chronic effect in rats. <sup>35</sup> Inhibited Aβ formation in cell culture <sup>38</sup> and attenuated Aβ-induced calcium imbalance in human fibroblasts. <sup>35</sup>	Increased t phosphorylation at M4 (Thr231/Ser235), <sup>36</sup> PS214 (Ser214), <sup>36</sup> tag-1 (Ser199/202), PHF-1 (Ser396/404), <sup>37</sup> and reduced protein phosphatase 2A (PP2A) <sup>36</sup> in rats.	May inhibit proteasomal activity by triggering protease inhibitor transcription, including increases in Zfh268 mRNA levels and altered expression of protease inhibitors Cystatin C and the chemokine Cxcl10.	Reduced Complex I activity in a number of models, <sup>40,41</sup> including rat <sup>42,43,44</sup> and mouse brain. <sup>45,46</sup> and human cerebral cortex. <sup>47</sup> Reduced Complex I in mouse frontal cortex, striatum, and midbrain. <sup>46</sup> Reduced Complex I, II, and V activity in rat brain. <sup>44</sup> Increased Complex IV activity in rat brain. <sup>45</sup>	Increased oxidative stress marker malondialdehyde <sup>37</sup> and cell membrane peroxidation, <sup>40</sup> and reduced superoxide dismutase. <sup>37</sup> Chronic treatment increased ROS in rat cortex, hippocampus, and striatum. <sup>48</sup> Synergized Aβ-induced PTP development in N2a neuroblastoma cells. <sup>49</sup> Released AIF from mitochondria in SH-SY5Y cells, rat striatum, and human striatum. <sup>50</sup>	Reduced viability of SH-SY5Y <sup>50</sup> and rotenone-exposed PC12 cells. <sup>51</sup> However, rescued dopamine-mediated decreased cell viability in rat pituitary cell lines, and GH3D21 cells, suggesting D2 mediation of apoptosis. <sup>52</sup>	Induced apoptosis in cultured neurons, <sup>53,54</sup> peripheral blood mononuclear cells, <sup>55</sup> PC12 and N2a cells, <sup>38,49</sup> rat striatum, <sup>37</sup> rat nigra, <sup>7</sup> B16 melanoma, <sup>38</sup> breast tumor cells, <sup>53</sup> through diverse apoptotic mechanisms. Reduced mitochondrial proapoptotic factors Bax, Bcl-X(L) ratios but increased proapoptotic Bcl-XS. <sup>38,60</sup> Synergized Aβ1-40 <sup>49</sup> and Aβ1-25-35 <sup>60</sup> in increasing Bcl-XS and induced apoptosis by the sigma-2 receptor. <sup>49</sup> Dose-dependently increased apoptosis in rotenone-exposed PC12 cells. <sup>51</sup>	While effects on Aβ may be neutral, haloperidol may hyperphosphorylate t, inhibit proteasomal function, impair mitochondrial function, reduce cell viability, and promote apoptosis (except in dopamine D2-mediated apoptosis), indicating caution in NDDs, especially AD. The nigrostriatal distribution of complex I inhibition and striatal AIF release suggests caution in Huntington's disease (HD) and PD. Diminished tumor cell viability and proapoptotic effects may indicate utility in cancer chemotherapy.
Fluphenazine			A calmodulin antagonist (see Trifluoperazine and Chlorpromazine below).	Shifted 20S proteasomal activity toward products ending in hydrophobic amino acids and away from those with acidic amino acids by antagonizing peptide:glutaryl peptide bond hydrolyzing activity more strongly than lysinolytic-like activity. <sup>61</sup> Inhibited cardiolipin-induced proteasome activation in rat liver. <sup>62</sup>	Inhibited Complex I in mouse <sup>45</sup> and rat <sup>43</sup> brain. Increased Complex IV (cytochrome c oxidase) in rat brain, especially in striatum and frontal cortex, <sup>43</sup> but inhibited Complex IV in mouse <sup>64,65</sup> liver and heart. <sup>64,65</sup>			Inhibited apoptosis in mouse B16 melanoma cells and rat glioma cells, but not in primary brain tissue. <sup>56</sup> Protected cultured lymphocyte apoptosis after exposure to genotoxic agents.	Fluphenazine may perturb proteasomal function, impair mitochondrial function and promote apoptosis, indicating the need for caution in NDDs.

**TABLE 1. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Trifluoperazine	Inhibits protein kinase C, <sup>66</sup> an enzyme promoting metabolism of APP to non-toxic A $\beta$ . <sup>69</sup>	Inhibits calmodulin, <sup>70/71</sup> promoting <i>t</i> binding to intermediate filaments, <sup>70</sup> promoting <i>t</i> dysfunction and, potentially, <i>t</i> aggregation. Inhibits phosphatase PP-2B, preventing tau-1, A18, and PHF-1 <i>t</i> dephosphorylation. <sup>72</sup>	Shifted 20S proteasomal activity toward products ending in hydrophobic amino acids and away from those with acidic amino acids by antagonizing peptidylglutamyl peptide bond hydrolyzing activity more strongly than chymotrypsin-like activity. <sup>81</sup>	Reduces ATP synthesis, <sup>73/74/75/76</sup> Inhibited succinate oxidation within the cytochrome b-c1 and c1-aa3 segments of the respiratory chain. <sup>81</sup> Inhibited mitochondrial oxygen uptake, and gluconeogenesis, and ketogenesis. <sup>82</sup>	Inhibited MPP <sup>+</sup> -induced oxidative stress <sup>83</sup> and ROS. <sup>84</sup> Reduced MGI32 proteasome inhibitor - induced ROS, <sup>85</sup> and loss of mitochondrial transmembrane potential after exposure to glutamate. <sup>86</sup> MPP <sup>+</sup> delta-aminolevulinate oxy-radicals and calcium, <sup>85</sup> and a large number of other ROS/generative agents. <sup>88,89,90/91</sup> and conditions, <sup>92</sup> whereas higher concentrations of trifluoperazine potentiated mitochondrial membrane depolarization after exposure to either diamide or butylhydroperoxide. <sup>90</sup> Inhibited PTP induced by glutamate in an HD transgenic mouse model. <sup>95</sup> MPP <sup>+</sup> and calcium, <sup>74,94</sup> and ganglioside GD2. <sup>95</sup> Inhibited mitochondrial dysfunction induced by rotenone, <sup>94</sup> H <sub>2</sub> O <sub>2</sub> , <sup>96</sup> and ethanol. <sup>96</sup>	Improved viability after MPP <sup>+</sup> , <sup>84</sup> MGI32, <sup>85</sup> and butylhydroperoxide. <sup>97</sup> effect on lymphocytes at clinically relevant doses, <sup>74,98</sup> but cytotoxic against leukemia cells, <sup>74</sup> and, at higher doses, reduced lymphocyte viability. <sup>98</sup>	Mixed effects, deterring apoptosis in many cell lines, yet promoting apoptosis in more undifferentiated malignant cell lines. Failed to induce apoptosis in normal lymphocytes. <sup>74</sup> Inhibited apoptosis after exposures to glutamate in HD transgenic mouse model. <sup>95</sup> MPP <sup>+</sup> in PC12 cells, <sup>83,84</sup> and MGI32. <sup>99</sup> Inhibits physopholipase A2, <sup>99</sup> important in benzodiazepine apoptosis (see Diazepam). Promoted apoptosis in undifferentiated PC12 cells exposed to MGI32. <sup>85</sup> Chinese hamster lung fibroblast mouse B16 melanoma cells, <sup>100</sup> and leukemic cells. <sup>74</sup>	Trifluoperazine may promote, theoretically, amyloid plaque formation through PKC inhibition, interfere with tau dephosphorylation and assembly, impair mitochondrial energy production and utilization, and modify proteasomal function, indicating a particular need for caution in the context of AD, but preliminary evidence suggests potential protective and antiapoptotic properties in normal tissues. More data are needed in regard to apoptosis in the context of NDDs, but preliminary evidence suggests potential utility in neoplastic disease. Diminished viability of poorly differentiated tumor cells may indicate utility in cancer chemotherapy.	
Thiothixene					Inhibited complex I in rat brain mitochondria, <sup>42</sup> and stimulated mitochondrial state 3 and state 4 respiration, producing complete loss of respiratory control accompanied only by slight alterations of oxidative phosphorylation. <sup>102</sup>				Thiothixene may impair mitochondrial function, indicating caution in the context of NDD.

**TABLE 1. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Chlorpromazine		Inhibits protein kinase C, <sup>105</sup> an enzyme that promotes metabolism of APP to non-toxic A $\beta$ . <sup>69</sup>	Inhibits PP-2B (but not PP-1 or PP-2A) from dephosphorylating hyperphosphorylated <i>t</i> by direct inhibition of calmodulin. <sup>72</sup> (See also Trifluoperazine.)		Inhibited complex I electron transfer activity in rat liver, <sup>41</sup> rat brain, <sup>70</sup> mouse human cerebral cortex. <sup>104</sup> Mitochondria. Increased energy charge and redox reaction velocity in rat liver, <sup>105</sup> and increased ATP production by 15-20% in normal leukocytes. <sup>74</sup> However, reduced ATP production in several leukemic cell types, <sup>74</sup> indicating differential effects in normal and neoplastic cells.	Prevented mitochondrial permeability transition in rat liver mitochondria exposed to calcium. <sup>106</sup> and A $\beta$ (25-35). <sup>107</sup> Released mitochondrial cytochrome c in leukemic cells, but not in normal lymphocytes. <sup>74</sup>	No effect on lymphocyte <sup>74</sup> or lymphoblastoid cell viability <sup>108</sup> at clinically relevant doses, but was cytotoxic against leukemic cells. <sup>73,98</sup> At higher doses, however, reduced both lymphocyte <sup>98</sup> and neutrophil <sup>109</sup> viability.	Did not inhibit apoptosis in serum-deprived cultured neurons, <sup>10</sup> but inhibited acetaminophen-induced apoptosis in mouse hepatocytes. <sup>111,112</sup> Inhibits endonuclease <sup>111</sup> and suppressed DNA fragmentation in several models. <sup>113,114</sup> Inhibits phospholipase A <sub>2</sub> , <sup>106</sup> important in benzodiazepine apoptosis (see Diazepam). In less differentiated cell types or under certain conditions, promoted apoptosis in Chinese hamster lung fibroblast V79 cells, <sup>100</sup> mouse B16 melanoma cells, <sup>115</sup> mouse fibrosarcoma 1929 cells, <sup>116</sup> rat thymus T cells, <sup>117</sup> photoaggravated HaCaT keratinocytes, <sup>118</sup> activated human lymphoblasts, <sup>119</sup> and leukemic cells, <sup>74</sup> but not in normal lymphocytes. <sup>74</sup>	While chlorpromazine reduces A $\beta$ -stimulated mitochondrial PTP opening, it may prevent <i>t</i> dephosphorylation and theoretically promote amyloid plaque formation, signaling the need for caution in AD. Chlorpromazine inhibits mitochondrial respiration, yet increases ATP generation, prevents mitochondrial PTP opening, and inhibits apoptosis in normal cells, indicating need for further study in the context of NDDs. ATP production inhibition, cytochrome c release, apoptosis, and diminished viability with chlorpromazine in tumor cells may indicate utility in cancer chemotherapy.

**TABLE 1. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment		
Thioridazine					<p>Reduced respiratory control<sup>10,21,20</sup> but did not inhibit Complex I.<sup>41</sup> Increased ATP production by 15-20% in normal leukocytes;<sup>74</sup> prevented ATP reductions after frostbite<sup>21</sup> and burns in rat skin;<sup>124</sup> but reduced ATP production in leukemic cell lines.</p>	<p>Reduced mitochondrial superoxide radicals, inhibited calcium - induced mitochondrial PTP formation, and prevented cytochrome c release from mitochondria.<sup>123</sup> Inhibited cytochrome c release in normal leukocytes, and calcium-induced cytochrome c release in leukemic cell lines.<sup>74</sup></p>	<p>No effect on lymphocyte viability<sup>74</sup> at clinically relevant doses, but was cytotoxic against leukemic cells including Burkitt's lymphoma (Daudi and Raji lines, myelogenous leukemia K562 cells, and acute lymphoblastic leukemia BALL-1, MOLT-4, HSB-ALL, and CCRF-HSB-2 lines.<sup>74</sup></p> <p>Improved viability of PC12 cells exposed to rotenone.<sup>91</sup></p>	<p>Did not promote apoptosis in normal mouse brain<sup>66</sup> or lymphocytes;<sup>74</sup> but increased caspase-3 levels 25-30 fold in human neuroblastoma cells,<sup>66</sup> promoted apoptosis in rat glioma cells,<sup>66</sup> and in leukemic cells,<sup>74</sup> and induced apoptosis in mouse B16 melanoma cells.<sup>113</sup></p>	<p>Reduced ATP, enhanced apoptosis, and diminished viability in neoplastic cells may indicate utility in cancer chemotherapy while enhanced energy metabolism and reduced free radicals and cytochrome c release may indicate neuroprotective potential in neurodegenerative disease. Thioridazine may be safer than other antipsychotics in regard to mitochondrial respiration, but more data are needed.</p> <p>Risperidone may be neutral in affecting A<math>\beta</math> concentrations and may be antiapoptotic especially in AD and PD models, indicating potential utility in NDDs; but it may impair mitochondrial complex I activity, especially in brain regions particularly relevant to AD and HD and potentially relevant to PD.</p>		
Risperidone		Did not increase in APP levels. <sup>33</sup>			<p>Reduced complex I activity in rat liver,<sup>41</sup> peripheral blood mononuclear cells,<sup>45</sup> mouse brain,<sup>45</sup> and human<sup>103</sup> cerebral cortex. Reduced Complex I activity in mouse frontal cortex, hippocampus, and striatum, but not in the<sup>46</sup> midbrain.</p>	<p>Protected PC12 cells from A<math>\beta</math>-induced overproduction of intracellular reactive oxygen species and reduction in mitochondrial membrane potential.<sup>724</sup> Prevented reductions in SOD1 mRNA expression<sup>127</sup> in PC 12 cells.</p>	<p>Improved viability of PC12 cells<sup>127</sup> and PC12 cells exposed to rotenone.<sup>91</sup></p>	<p>Inhibited apoptotic markers induced by A<math>\beta</math><sup>60,124</sup> and by MPP<sup>7,125</sup> in PC 12 cells. In rats, protected against methamphetamine - induced bcl-2 reductions<sup>28</sup> and phenacyclidine - induced frontal lobe apoptosis.<sup>129</sup> However, induced apoptosis at 1<math>\mu</math>M concentrations in neurotrophils.<sup>130</sup></p>	<p>Did not inhibit complex I in rat liver, unlike haloperidol, chlorpromazine, risperidone, and quetiapine,<sup>41</sup> but inhibited succinate dehydrogenase selectively in cerebellum, consistent with impaired energy metabolism.<sup>128</sup></p>	<p>Did not inhibit complex I in rat liver, unlike haloperidol, chlorpromazine, risperidone, and quetiapine,<sup>41</sup> but inhibited succinate dehydrogenase selectively in cerebellum, consistent with impaired energy metabolism.<sup>128</sup></p>	<p>Olanzapine may prevent A<math>\beta</math> and MPP<sup>7</sup> apoptosis and improve cell viability in some cell lines (although not in neurotrophils), indicating possible utility in NDDs.</p>
Olanzapine											

**TABLE 1. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment		
Quetiapine					Inhibited Complex I in rat liver. <sup>41</sup>	Protected PC12 cells against A $\beta$ -induced intracellular ROS production and mitochondrial membrane depolarization. <sup>124</sup>	Improved PC12 cell viability after rotenone exposure. <sup>51</sup>	In PC12 cells exposed to A $\beta$ , inhibited oxidative stress, <sup>124</sup> caspase-3 <sup>124</sup> activation, <sup>124</sup> mitochondrial translocation, <sup>60</sup> mitochondrial Bax/ $\beta$ 1-X(L) ratio, <sup>124</sup> and cell death. <sup>124</sup> However, increased caspase-3 activation in rats. <sup>26</sup>	Quetiapine may reduce mitochondrial morbidity and may be mainly antiapoptotic and promote cell viability in AD and PD models, indicating potential utility in NDD, although it may impair mitochondrial complex I function.		
Aripiprazole					Inhibited succinate dehydrogenase selectively in prefrontal cortex after 28 days administration (2-20mg/kg) in rats, consistent with impaired energy metabolism. <sup>126</sup>				No conclusions can be drawn about neuroprotective properties of this agent because of limited data.		
Ziprasidone					Reduced Complex I activity in peripheral blood mononuclear cells <sup>40</sup> and, weakly, in rat brain, <sup>42</sup> but not in other studies of rat striatum <sup>43</sup> and rat brain. <sup>45,46,51</sup> In mice, clozapine produced a loss of complex I in the hippocampus and frontal cortex, but not in striatum. <sup>46</sup> The antipsychotic inhibited complexes I and III in human cerebral cortex, but was two orders of magnitude less potent in doing so than haloperidol, chlorpromazine, and risperidone. <sup>104</sup> Clozapine increased complex IV activity in rat frontal cortex <sup>43</sup> and increased cytochrome c oxidase activity throughout the brain (especially in caudate,						
Clozapine	Weakly inhibited PP-2B, but not PP-1 or PP-2A, from dephosphorylating hyperphosphorylated $\tau$ .				Did not increase reactive oxygen species in cerebral cortex but did so in hippocampus and striatum in rats with chronic administration. <sup>48</sup>	No effect on SH-SY5Y cell viability. <sup>30</sup>	Prevented MPP <sup>+</sup> -induced apoptosis in PC12 cells. <sup>125</sup> However, in neurotrophils, clozapine induced apoptosis at 1 $\mu$ M. <sup>127,128</sup> Related to nitrenium ion formation, <sup>132</sup> and induced oxidative stress and proapoptotic gene expression (p53, bax, bkl) in patients with schizophrenia, potentially correlating with agranulocytosis. <sup>134</sup> On the other hand, 20-50 $\mu$ M clozapine rescued PMNs from spontaneous apoptosis. <sup>135</sup> In a rat study, clozapine did not change Bax and Bcl-2 concentrations, but rather increased caspase-3 <sup>56</sup> activation. Clozapine did not release AIF from human striatum, rat striatum, or SH-SY5Y cells, unlike haloperidol. <sup>50</sup>	There were no relevant studies detected for this agent. Clozapine may prevent tau phosphorylation, indicating efficacy in the context of NDD, especially AD. Although less pronounced in disruption of mitochondrial metabolism than other antipsychotics, clozapine is nevertheless associated with loss of complex I activity in the hippocampus and frontal cortex, and with ROS generation in the hippocampus and striatum. While it exhibits some antiapoptotic properties, nitrenium ion generation remains a concern. Clozapine appears to have mixed effects on apoptosis. Relative lack of complex I inhibition may, however, suggest a relative advantage in PD, and lack of striatal AIF release may suggest a relative advantage in HD.			

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
<b>Mood Stabilizers</b>									
Lithium		Inhibits glycogen synthase kinase-3 $\beta$ (GSK-3 $\beta$ ). <sup>136</sup> a regulator of APP transcription. Consistent with this, has inhibited A $\beta$ production in HEK293 cells transfected with Swedish APP and in the PDAPP (APP(V717F)) transgenic mouse brain, and abolished GSK-3 $\beta$ - mediated A $\beta$ increases in transgenic mice. <sup>137</sup> Specifically inhibited gamma-secretase cleavage to A $\beta$ in transgenic mice overexpressing APP. <sup>138</sup> A $\beta$ accumulation in APP transgenic mice, <sup>138</sup> and amyloid secretion in COS7 cells transfected with amyloid precursor protein, <sup>139</sup> suggesting the potential of lithium to inhibit A $\beta$ production at several different steps. However, lithium increased beta-secretase cleavage in cultured rat neurons and CHO cells. <sup>140</sup> In the 3xTg-AD Alzheimer's mouse model, lithium did not affect A $\beta$ load or improve working memory. <sup>141</sup> A case-control study found a higher risk of dementia in	nucleus accumbens, septum, and pons). <sup>63</sup> In rats, 28-day administration inhibited succinate dehydrogenase selectively in striatum, consistent with impaired energy metabolism. <sup>136</sup>	Enhanced tau ubiquitination in a tauopathic mouse model, <sup>175</sup> but reduced the function of the 20S <sup>176,177</sup> and proteasome and reduced proteasomal degradation by inhibiting GSK-3 $\beta$ . <sup>38</sup>	Decreased cytochrome oxidase activity in the cingulate cortex and nucleus accumbens in rats after 21 days treatment. <sup>175</sup> Increased mitochondrial mass and ATP production without increasing mitochondrial efficiency in endothelial cells. <sup>180</sup>	Reduced ROS and restored mitochondrial membrane potential in reperused ischemic rat kidney. <sup>181</sup> Blocked $\beta$ -bungarotoxin-induced mitochondrial depolarization in cultured CGN cells. <sup>182</sup> Antagonized mitochondrial permeability and reduced cytochrome c release <sup>183</sup> in cultured CGN cells exposed to glutamate. <sup>184</sup> Rabbits exposed to intracisternal aluminum, <sup>185</sup> and SH-SY5Y cells exposed to rotenone and H <sub>2</sub> O <sub>2</sub> . <sup>186</sup>	Improved CGN viability after exposure to C2-ceramide <sup>187</sup> and did not reduce neurophil viability. <sup>188</sup> In ischemic rat brain, induced an activation of Akt (protein kinase B) and CaM kinase II, and increased protein phosphatase 2A restoring tau phosphorylation, leading to neuroprotection. <sup>189</sup> In human NTera2/D1 cells that resemble CNS progenitor cells, increased cellular proliferation. <sup>190</sup>	Robustly increase Bcl-2 expression in the CNS in vivo and in ex vivo human neurons, activates the cell-survival signaling cascade (the extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase pathway), and increase gray matter content suggestive of a reversal of illness-related atrophy and an increase in neuropil volume. <sup>91</sup> Chronic lithium treatment down-regulates proapoptotic mediators (e.g., p53, Bax, caspase, cytochrome c release, protein phosphatase 2A [PP2A], Bcl-2 dephosphorylation, caspase-2 activation, and tau hyperphosphorylation) and up-regulates cell survival molecules (e.g., Bcl-2, cyclic AMP-responsive element binding protein, brain-derived neurotrophic factor, Gp78, Hsp70, and beta-catenin), preventing or even reversing neuronal cell death and neurogenesis. <sup>192,193</sup> Hence, lithium has usually inhibited	While lithium may inhibit proteasomal function and mitochondrial cytochrome oxidase activity, lithium often reduces A $\beta$ production, tau hyperphosphorylation, membrane depolarization, cytochrome c release, and apoptosis, and may enhance neuronal viability, indicating its potential utility in NDD, especially in AD, PD, HD, and cerebrovascular disease.

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment	
		patients receiving lithium (odds ratio 1.8, 95% CI 1.1-2.8) although lithium may have served as merely a marker of patients otherwise at risk to develop <sup>42</sup> dementia.	phosphorylation of juvenile tau in cultured hippocampal neurons <sup>13</sup> and inhibited insulin-induced GSK-3 $\beta$ - mediated tau hyperphosphorylation in primary cortical neurons. <sup>160</sup> In neurons treated to GSK-3 $\beta$ lithium specifically reduced GSK-3 $\beta$ - mediated tau phosphorylation at ser181 and Ser396/404 in SH-SY5Y neuroblastoma cells. <sup>161</sup> GSK-3-mediated tau hyperphosphorylation at ser396/404 and Ser262 in HEK293/tau441, GSK-3 - related tau phosphorylation at Ser199 in cerebellar granule cells. <sup>149</sup> GSK-3 $\beta$ - and tau - related phosphorylation of the PHF-1 epitope in transfect CHO-K1, COS-7, and SH-SY5Y cells, and phosphorylation of epitopes specifically associated with AD in transgenic mutant tau mice. <sup>14</sup> Inhibited stress-induced GSK-3beta - mediated Tau-1(Ser199/202) and Ser396 but not A18(Ser202/Thr205) tau hyperphosphorylation in mouse hippocampus. <sup>165</sup> In diabetic rats, reduced increased GSK-3 activity and tau hyperphosphorylation and improved memory. <sup>166</sup> Reduced tau phosphorylation in 3X1g-AD and hAPP tg. <sup>167</sup> AD transgenic mouse models. Of particular note in AD, markedly						apoptosis in most models employing mature cells, but has usually promoted apoptosis in poorly differentiated and neoplastic and immature cells, with some exceptions. For example, lithium induced apoptosis in immature CGN cells but promoted survival in mature CGN cells. <sup>194</sup> Lithium prevented apoptosis in CGN exposed to aging, NMDA agonists, <sup>195</sup> ethanol, <sup>196</sup> radiation, <sup>197</sup> C <sub>2</sub> ceramide, <sup>187,198</sup> colchicine, <sup>200,201</sup> phenytoin, <sup>199</sup> carbamazepine, <sup>199</sup> non-depolarizing medium, <sup>198</sup> and potassium deprivation, <sup>199,203,204</sup> the latter being PDK dependent. <sup>203</sup> Prevented, inhibited, or reversed apoptosis, <sup>205,206,207</sup> GSK-3b induced <sup>206</sup> and GSK-3b-mediated staurosporine-induced <sup>208</sup> apoptosis, and heat shock - induced apoptosis, <sup>208</sup> and reduced tumor suppressor p53 levels in SH-SY5Y cells. <sup>209</sup> Prevented A $\beta$ -induced apoptosis in several models. <sup>210,211,212</sup> Long-term lithium exposure protected cultured rat cerebellar, cerebral cortical, and hippocampal neurons subjected to glutamate-induced apoptosis. <sup>213</sup> Prevented	

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
			reduced A $\beta$ -induced <i>t</i> hyperphosphorylation <sup>143,168</sup> particularly at Tau 1 and PHF-1 <sup>168</sup> although not in rabbit hippocampus <sup>168</sup>					apoptosis of hippocampal neurons irradiated cultured HT-22 mouse hippocampal neurons <sup>214</sup> and rabbits exposed to intracerebral aluminum <sup>185</sup>	
			interstitial amyloid A $\beta$ (1-42) <sup>168</sup> Promoted tau dephosphorylation and cleavage <sup>170</sup> microtubule assembly <sup>148</sup> tau binding to microtubules <sup>146,148</sup> and reduced hyperphosphorylated tau aggregation <sup>164,171,172</sup> and tauopathic impaired <sup>170</sup> axonal transport, suggesting its potential to reduce <i>t</i> hyperphosphorylation and pathophysiological consequences in AD. In FAD <sup>17</sup> tau and GSK-3beta overexpressing mice, chronic lithium treatment prevented tau hyperphosphorylation and neurofibrillary tangle formation. <sup>174</sup>					Prevented MPP <sup>+</sup> neurotoxicity in mice and prevented reduced Bcl-2 and increased Bax. <sup>219</sup> Reduced rotenone- and H <sub>2</sub> O <sub>2</sub> -induced caspase-3 activation and increased Bcl-2 levels in SH-SY5Y cells. <sup>220,221</sup> platelet activating factor (PAF) - induced neuronal apoptosis. Inhibited caspase-3-mediated apoptosis in a <i>quinaldic acid</i> model of Huntington's disease, and	

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	$\tau$	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment	
Valproic Acid	Increased $\alpha$ Syn expression and prevented its nuclear translocation, <sup>235</sup> and valproate - induced $\alpha$ Syn protected rat CGN cells against glutamate excitotoxicity. <sup>236</sup>	Inhibited A $\beta$ production in HEK293 cells transfected with Swedish APP and in the PDAPP transgenic mouse brain. <sup>35</sup>	Failed to inhibit tau phosphorylation in rat neurons <sup>144</sup> and CGN <sup>149</sup> cultures, in contrast to lithium.	Valproate, a histone deacetylase (HDAC) inhibitor, augmented gene expression of the B66gamma regulatory subunits of PP-2A, leading to proteasome-mediated p300 degradation, <sup>237</sup> and induced proteasomal degradation of HDAC-2, possibly by inducing expression of E2	Can produce clinical deterioration in mitochondrial diseases, including MELAS episodes <sup>239</sup> and cortical blindness. <sup>240</sup> Has produced swollen mitochondria in cerebellar Purkinje cells, <sup>241</sup> and other stigmata of mitochondrial damage. <sup>242</sup> and, in rat hepatocytes, mitochondrial swelling, numeric	Associated with oxidative stress in rat hepatocytes, <sup>271</sup> Induced PTP but not mitochondrial depolarization in rat hepatocytes, <sup>272,273</sup> Induced ERK1/2 phosphorylation that inhibited cytochrome c release in endothelial cells, <sup>274</sup> but released cytochrome c in human leukemia cells. <sup>275</sup> Reduced	Enhanced rat cerebral cortical neuron viability, <sup>276</sup> and did not reduce rat hepatocyte viability. <sup>277</sup>	Acts antiaoptotically through a number of mechanisms, including ERK/ MAP kinase cell-survival pathway activation, <sup>191,274,277</sup> Bcl-2 increases in human CNS, <sup>192,274,277,278</sup> cytochrome c release enhancing proteasomal function and neuronal inhibition, <sup>274</sup> caspase-3 activity suppression, <sup>195</sup> heat shock protein 70 (HSP70) <sup>195,277</sup> activation,	stimulated neuronal and astroglial progenitor proliferation in rat striatum, <sup>223</sup> In human glioblastoma cells, lithium increased the expression of p21(WAF/Cip1) and survivin and antiapoptotic proteins in human glioblastoma cells, <sup>223</sup> and lithium-induced CSK-3b inhibition conferred resistance to chemotherapy-induced apoptosis. <sup>225</sup> However, lithium-induced <i>tau</i> dephosphorylation promoted staurosporine - induced apoptosis in one study, <sup>170</sup> and lithium increased Fas activation-induced apoptotic signaling in differentiated immortalized hippocampal neurons and Jurkat cells. <sup>226</sup> Promoted apoptosis in rat hepatocytes, <sup>277</sup> in CGN cells, <sup>228</sup> K562 leukemia cells, <sup>258,260</sup> HL-60 cells, <sup>231,232</sup> CO37, and 293 cells, human prostate cancer cells, <sup>233</sup> but not in PCL1.	Although valproate does not inhibit $\tau$ phosphorylation and promotes $\alpha$ Syn accumulation, mitochondrial dysfunction, and mitochondrial PTP opening, valproate may inhibit A $\beta$ production, cytochrome c release, and, variably, apoptosis while enhancing proteasomal function and neuronal viability, suggesting some utility in NDD under particular circumstances. Whether effects on $\alpha$ Syn, A $\beta$ , and microglial

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	t	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment	
				and E3 enzymes in the ubiquitin ligase system. <sup>238</sup> This suggests the ability of valproate to enhance proteasomal function at both the proteasome itself and in ubiquitinating proteins for degradation. <sup>239</sup> CSK-3 $\beta$ inhibitor (see lithium, Proteasome).	increase, degeneration of matrix and disruption of the outer membrane in vivo. <sup>244,245,246,247</sup> Associated with reduced cytochrome aa3, <sup>245,248,249</sup> cytochrome oxidase activity, <sup>248,249</sup> carnitine concentrations, <sup>250,251,252</sup> aberrant carnitine metabolism, <sup>253,254,255,256</sup> reduced hepatic mitochondrial beta-oxidation. <sup>253,255</sup> 260,261, 262,263,264, and reduced oxidative phosphorylation <sup>265,266,267</sup> primarily in liver but also in brain. <sup>265,266,268</sup> Some studies have not found carnitine reductions <sup>269</sup> or reduced oxidative phosphorylation. <sup>253</sup> Valproate metabolites inhibit dihydrodipolyl dehydrogenase activity and impairs 2-oxoglutarate-driven oxidative phosphorylation. <sup>270</sup>	rotenone and H2O <sub>2</sub> -induced cytochrome c release in SH-SY5Y. <sup>271</sup>			CSK-3 $\beta$ inhibition <sup>279</sup> a PI3K dependent pathway, <sup>283</sup> and Akt (protein kinase B) induction <sup>277</sup> and is associated with neurofil volume and gray matter content increases consistent with a reversal of A $\beta$ pathology. GABA agonist, GABA-A agonists protect against A $\beta$ -induced neurotoxicity, <sup>280</sup> while GABA-A antagonists enhance neurotoxicity. <sup>281</sup> Antidopaminergically <sup>136</sup> inhibits GSK-3 $\alpha$ and $\beta$ , <sup>282</sup> and inhibits histone deacetylase activity. <sup>285</sup> The drug has mixed effects upon apoptosis in various models, but is antiapoptotic in many CNS models, including in SH-SY5Y cells exposed to GSK-3 $\beta$ , <sup>286</sup> rotenone <sup>287</sup> and H2O <sub>2</sub> , <sup>288</sup> and potassium depletion, <sup>289</sup> CGN cells exposed to NMDA, <sup>290,291</sup> agonists and platelet activating factor, <sup>292</sup> rat hippocampal neurons exposed to A $\beta$ and glutamate, <sup>286</sup> a rat intracerebral hemorrhage model, <sup>293</sup> and hypoxic ischemic neonatal rat brain. <sup>294</sup> Induces caspase 3-mediated apoptosis in microglia, of importance in AD and PD where activated microglia lead to inflammatory neurodegenerative responses. <sup>295</sup> However, can enhance apoptosis in	apoptosis confer advantages or disadvantages in PD clarification. Valproate is proapoptotic in neurodegenerative disease, suggesting potential utility in cancer chemotherapy.

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
								certain apoptosis models and in immature, differentiating, inflamed, or neoplastic tissues; valproate can enhance apoptosis, including yeast, <sup>290,291</sup> porcine ovarian follicular cells, <sup>292</sup> six different endometrial cell lines, <sup>293</sup> mouse experimental colitis, <sup>294</sup> mouse BV-2 microglia, <sup>289</sup> CCGN exposed to colchicine, <sup>290</sup> and C2-ceramide, <sup>198</sup> newborn rat brains at clinically-relevant valproate doses, <sup>295,296</sup> young rat brains, <sup>297</sup> a sheep leukemia/lymphoma model, <sup>298</sup> human cancer cells, <sup>299</sup> lymphoma cells infected with herpesvirus-8, <sup>300</sup> human leukemia cells, <sup>275</sup> several leukemic cell lines, <sup>301</sup> including HL-60 cells, <sup>302</sup> Philadelphia chromosome-positive acute lymphatic leukemia, <sup>303</sup> chronic lymphocytic leukemia cells, <sup>304</sup> human melanodysplastic MUTZ-1 cells, <sup>305</sup> acute myeloid leukemia K562 cells, <sup>306</sup> chronic myeloid leukemia cells, <sup>307</sup> multiple myeloma cell lines, <sup>308</sup> rat and human hepatoma cells, <sup>309,310,311</sup> prostate cancer LNCaP cells, <sup>312,313</sup> ovarian carcinoma cell lines, <sup>314</sup> thyroid cancer cells, <sup>315,316</sup> medulloblastoma cell lines, <sup>316</sup> human BGC-823 gastric cancer cells, <sup>318</sup> human neuroblastoma cells, <sup>307,319</sup> and some (but not all) melanoma <sup>307,320</sup> cell lines. <sup>307,321</sup>	

TABLE 1. Continued

Agent	$\alpha$ Syn	A $\beta$	t	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Carbamazepine		Failed to inhibit tau phosphorylation or GSK-3 $\beta$ in rat neurons; <sup>44</sup> suggesting a lack of benefit in preventing tau hyperphosphorylation in AD. However, carbamazepine and phenytoin suppressed glutamate-induced alterations in tau. <sup>286</sup>		Did not reduce ATP production. <sup>322</sup> Carbamazepine induced loss of mitochondrial activity of CGN cells was inhibited by pretreatment with N-methyl-D-aspartate or cycloheximide, a protein synthesis inhibitor. <sup>323</sup>	Did not increase ROS or reduce mitochondrial membrane potential in primary rat hippocampal neurons. <sup>325</sup> but induced oxidative stress in primary rat astrocyte. <sup>324</sup> cultures. <sup>324</sup>	Increased lymphocyte death in one study, <sup>325</sup> but no effect in another, although its metabolite 9-acridine carboxaldehyde increased cell death. <sup>325</sup>	Did not protect SH-SY5Y cells from GSK-3 $\beta$ -induced apoptosis. <sup>206</sup> Protected cultured rat hippocampal neurons from A $\beta$ - and glutamate-induced injury at clinically relevant doses, <sup>286</sup> but increased caspase-3 and apoptosis in another study in the same cells. <sup>327</sup> and in CGN cells. <sup>322</sup>	Carbamazepine did not inhibit tau phosphorylation, promoted oxidative stress and mitochondrial dysfunction in some neural tissues, and while it prevented A $\beta$ -induced neuronal injury in one model, it promoted apoptosis in other neuronal models. This suggests doubtful benefit in NDD, particularly AD, but more data are needed.	
Oxcarbazepine				Diminished ATP production in rat primary hippocampal neurons. <sup>328</sup>	Increased ROS production and reduced mitochondrial membrane potential in rat primary hippocampal neurons. <sup>328</sup> Induced oxidative stress in rat primary astrocyte. <sup>324</sup> Beta-oxidation of valproate may deplete glutathione. <sup>328</sup>	Increased caspase-3 and apoptosis in cultured rat hippocampal neurons. <sup>328</sup>	Oxcarbazepine seems to promote mitochondrial dysfunction and apoptosis in neuronal models, suggesting no value in NDD but potential for neoplastic disease although the data are minimal.		

Properties relevant to neuroprotection as demonstrated in *in vitro*, *ex vivo*, and *in vivo* preclinical studies involving treatment with apathy treatments, antipsychotic, and mood stabilizing agents.

A $\beta$ =beta-amyloid; AD=Alzheimer's disease; AIF=apoptosis inducing factor; ALS=amyotrophic lateral sclerosis; AMP=adenosine mono-phosphate; APP=amyloid precursor protein;  $\alpha$ Syn alpha-synuclein; ATP=adenosine triphosphate; BDNF=brain derived neurotrophic factor; CGN=cerebellar granule neuron; CHO=Chinese hamster ovary; CNS=central nervous system; D2=dopamine D2 receptor; DNA=deoxyribonucleic acid; ERK=extracellular signal-regulated kinase; FTDP-17=frontotemporal dementia with parkinsonism linked to chromosome 17 mutations in the tau gene; GABA=gamma-amino-butyric acid; GABA-A=gamma-amino-butyric acid A receptor; GSK-3 $\beta$ =glycogen synthase kinase 3-beta; H<sub>2</sub>O<sub>2</sub>=hydrogen peroxide; HD=Huntington's disease; HDAC=histone deacetylase; HSP=heat shock protein; MAP=mitogen-activated protein; MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MPP<sup>+</sup>=1-methyl-4-phenylpyridine ion; mRNA=messenger ribonucleic acid; NDD=neurodegenerative disease; NMDA=N-methyl-D-aspartate; NO=nitric oxide; PAF=platelet activating factor; PD=Parkinson's disease; PI3K=phosphatidylinositol-3 kinase; PKC=protein kinase C; PMNs=polymorphonuclear granulocytes; PPI=protein phosphatase 1; PP2A=protein phosphatase 2A; PP2B=protein phosphatase 2B; PTP=mitochondrial permeability transition pore; ROS=reactive oxygen species; SOD1=superoxide dismutase 1; t=tau; TNFa=tumor necrosis factor alpha.

**TABLE 2. Neuroprotective Properties of Antidepressant Agents**

Agent	$\alpha$ Syn	A $\beta$	t	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
<b>Antidepressants</b>									
<b>Amitriptyline</b>						<p>Monamine oxidase B inhibition (MAOBI) can deter ROS generation, MAO competitive MAOBI has been observed with amitriptyline in mouse and rat brains.<sup>330</sup> However, in rat dorsal root ganglia, amitriptyline incubation dose-dependently reduced mitochondrial membrane potential and released cytochrome C.</p>	<p>Reduced viability in human HT29 colon carcinoma cells.<sup>332</sup> One millimolar amitriptyline killed human polymorphonuclear neutrophils.<sup>333</sup> Rat dorsal root ganglia incubated with 100<math>\mu</math>M amitriptyline was associated with reduced neuronal count and demyelination.<sup>334</sup></p>	<p>In rat dorsal root ganglia, amitriptyline incubation dose-dependently activated caspase-3 apoptosis.</p>	<p>Amitriptyline may be apoptotic and reduces neuronal viability in rats, and reduces the viability of human carcinoma cells and neutrophils.</p>
<b>Imipramine</b>						<p>Imipramine exhibits noncompetitive MAOBI in the brains of mice,<sup>329</sup> rats,<sup>30,33</sup> dogs,<sup>36</sup> and monkeys.<sup>336</sup> Nevertheless, induced ROS and mitochondrial membrane depolarization in human acute myeloid leukemia HL-60 cells.<sup>337</sup> However, inhibited acid sphingomyelinase, an enzyme responsible for producing proapoptotic ceramide, in mice, associated with reduced cytochrome c release in hepatic ischemia-reperfusion injury.<sup>338</sup></p>	<p>Reduced cell viability in human cell lines including acute myeloid leukemia HL-60 cells,<sup>337</sup> HT29 colon carcinoma cells,<sup>332</sup> and, at 1 millimolar concentration, polymorphonuclear neutrophils.<sup>333</sup></p>	<p>Did not cause apoptosis in glioma and neuroblastoma cell lines.<sup>339</sup> Imipramine inhibition of acid sphingomyelinase resulted in inhibition of cisplatin-induced clustering of CD95 death receptors in human HT29 colon cancer cells<sup>340</sup> and reduced apoptosis in hepatic ischemia-reperfusion injury.<sup>338</sup> This tricyclic inhibited TNF<math>\alpha</math>-induced apoptosis and C16-ceramide in rat and mouse primary hepatocytes.<sup>341</sup> In rat hippocampal neural stem cells, 3<math>\mu</math>M imipramine reduced lipopolysaccharide-induced apoptosis, and increased survival rate through BDNF and MAPK/ERK pathways.<sup>342</sup> However, imipramine induced apoptosis in U-937 macrophages,<sup>343</sup> human lymphocytes, and Jurkat cells,<sup>346</sup> human acute myeloid leukemia HL-60 cells,<sup>337</sup> and increased dentate gyrus apoptosis in newborn mouse hippocampal neurons.<sup>349</sup></p>	<p>The data on mitochondrial function are inconclusive, but imipramine reduces viability in a number of cell lines, suggesting utility in cancer chemotherapy. The data are also mixed for apoptosis, suggesting oncological potential, but studies of mature neural tissue are needed to allow conclusions regarding NDD.</p>

TABLE 2. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Nortriptyline						Noncompetitive MAOBI observed in mouse brain. <sup>359</sup> Blocked glutamate-induced PTP opening in a yeast artificial chromosome transgenic mouse model of HD. <sup>35</sup> Inhibited PTP development and cytochrome c release in a mouse model of ALS. <sup>350</sup>	Killed human polymorphonuclear neutrophils <sup>353</sup> but, in a mouse model of ALS, protected motor neurons from death, reduced ventral horn atrophy, delayed disease onset, and prolonged mouse lifespan. <sup>350</sup>	Blocked glutamate-induced apoptosis in a yeast artificial chromosome transgenic mouse model of HD <sup>35</sup> and inhibited caspase-3 activation in a mouse model of ALS. <sup>350</sup>	Nortriptyline appears to inhibit PTP development and cytochrome c release and blocked apoptosis in mice models of HD and ALS. Neuronal viability was improved in the ALS mouse model, but apoptosis of neutrophils has also been demonstrated with this drug. Did not affect <i>t</i> phosphorylation and may have antioxidant, protective, and predominantly neurotrophic activities, suggesting essential utility in HD. Evidence for oncologic utility is mixed.
Desipramine	Chronic desipramine treatment did not alter <i>t</i> phosphorylation and tubule assembly in rats.			Induced the activity of mitochondrial succinate dehydrogenase in rat amygdala. <sup>352</sup>	Inhibits sphingomyelinase and inhibited TNF $\alpha$ -induced ceramide and mitochondrial ROS production in cultured human umbilical vein endothelial cells. <sup>353,354</sup> Attenuated HDAC inhibitor/perifosine-induced ceramide and ROS production in human leukemia cells. <sup>355</sup> Reduced hydrophobic taurothocholylsulfate-induced hepato <sup>356</sup> oxidative stress. <sup>356</sup> Blocked glutamate-induced mitochondrial PTP opening in a yeast artificial chromosome transgenic mouse model of HD. <sup>35</sup> However, potentiated morphine-induced mitochondrial membrane depolarization. <sup>357</sup>	Reduced cell viability in human HT29 colon carcinoma cells. <sup>352</sup>	Inhibited apoptosis in mouse thymocytes, <sup>358,359</sup> ischemic rat heart, <sup>360</sup> and CHO cells, <sup>361</sup> and inhibited proapoptotic ceramide production in cultured human umbilical vein endothelial cells. <sup>353,354</sup> UV irradiated renal 293 cells, <sup>362</sup> ascular smooth muscle exposed to nitric oxide, <sup>363</sup> and HDAC inhibitor/perifosine treated human leukemia cells. <sup>355</sup> Blocked apoptosis induced by glutamate in a yeast artificial chromosome transgenic mouse model of HD <sup>35</sup> and cerebroside <sup>364,365</sup> and 6-OHDA <sup>366,367</sup> in PC12 cells, but not by -OHDA cells. <sup>367</sup> Protected against lipopolysaccharide-induced apoptosis in cultured rat hippocampal neural stem cells and increased production of serotonin and norepinephrine. <sup>368</sup> Reduced Bax – to – Bcl2 ratio in prefrontal cortex in rats with myocardial infarctions. <sup>369</sup> However, induced apoptosis in rat glioma C6 cells and human HT29 colon carcinoma cells. <sup>367</sup>	There are insufficient data to reach any conclusions.	
Clomipramine				Inhibited complex III in rat mitochondria. <sup>371</sup>	MAOBI activity in rat brain, <sup>358</sup> which may deter ROS generation. Reduced mitochondrial depolarization, mitochondrial swelling and vacuolation. <sup>371</sup> However, released cytochrome c in rat glioma and human neuroblastoma cell lines, but may not in primary brain tissue. <sup>359</sup> Nevertheless, induced ROS and loss of membrane potential in mitochondrial leukemia HL-60 cells. <sup>357</sup> MAOBI activity in rat brain, <sup>350</sup> which may deter ROS generation.	Reduced cell viability in human acute myeloid leukemia HL-60 cells. <sup>357</sup>	Induced apoptosis in both quiescent and proliferating human lymphocytes as well as in lymphoblastoid cell line neuroblastoma, <sup>359</sup> and human acute myeloid leukemia HL-60 cells. <sup>357,371</sup> However, inhibited serotonin-, fenfluramine-, and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy")-induced apoptosis in B cell malignancies including acute lymphoblastic leukemia, mantle cell lymphoma, diffuse large B cell lymphoma, and multiple myeloma. <sup>373</sup>	Clomipramine appears to compromise mitochondrial function and cell viability and may promote apoptosis, warranting caution in NDD. Certain data indicate potential therapeutic utility in selected malignancies. Data regarding apoptosis in non-neoplastic neural tissue are needed.	
Trimipramine									There are insufficient data to reach any conclusions.

**TABLE 2. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Doxepin						MAOBI activity in rat brain, <sup>350</sup> which may deter ROS generation.			There are insufficient data to reach any conclusions.
Protriptyline									There were no relevant studies detected for this agent.
Maprotiline	Did not alter tau phosphorylation on microtubule assembly in rats. <sup>351</sup>				Noncompetitive MAOBI in mouse brain, <sup>335</sup> dogs, <sup>336</sup> and monkeys, <sup>336</sup> which may deter ROS generation. Blocked glutamate-induced mitochondrial PTP opening in a yeast artificial chromosome transgenic mouse model of HD.		Blocked glutamate-induced apoptosis in a yeast artificial chromosome transgenic mouse model of HD.	Maprotiline did not affect tau phosphorylation, indicating possible safety in the context of AD, and may have mitochondrial protective and antiapoptotic properties, but evidence for neuroprotection relies on a single study and more data are needed.	
Bupropion								May be pro-apoptotic in malignancies (15928583,15964626).	Data regarding the safety of bupropion in NDDs is needed although preliminary data suggest potential utility in cancer chemotherapy.
Fluoxetine	Improved contextual memory and cell proliferation in A $\beta$ transgenic Tg2576 mice. <sup>374</sup>			Inhibits electron transport and F1F0-ATPase activity. <sup>375</sup> Uncoupled oxidative phosphorylation and stimulated mitochondrial state 4 respiration. <sup>376</sup>	MAOBI activity in rat brain, thought to deter ROS generation. <sup>30</sup> Decreased voltage-dependent anion channel conductance and inhibited PTP opening and cytochrome c release in a staurosporine model. <sup>377</sup> However, depolarized mitochondrial membrane in Burkitt lymphoma cells <sup>378</sup> and released mitochondrial cytochrome c in rat glioma and human neuroblastoma cell lines, suggesting benefit in brain tumors. <sup>339</sup>	Reduced viability in human HT29 colon carcinoma cells <sup>382</sup> and killed human polymorphonuclear neutrophils. <sup>333</sup>	Protected against staurosporine <sup>377</sup> - and lipopolysaccharide <sup>379</sup> - induced apoptosis. Upregulated anti-apoptotic mediators, <sup>379,380</sup> and inhibited pro-inflammatory and pro-apoptotic cytokines in neural stem cells. <sup>379</sup> Prevented apoptosis in neural stem cells, <sup>379</sup> cultured rat hippocampal neural stem cells, <sup>381</sup> dentate gyrus of maternally separated rats, <sup>382</sup> rat hippocampus, <sup>380</sup> rat frontal cortex, <sup>380</sup> rat cingulate gyrus, <sup>380</sup> central nucleus of the amygdala. <sup>380</sup> Inhibited serotonin-induced apoptosis in Burkitt lymphoma cells unlike serotonin receptor antagonists. <sup>383</sup> fenfluramine-induced apoptosis in human placental choriocarcinoma cells, <sup>384</sup> serotonin-, fenfluramine-, and 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy")-induced apoptosis in B cell malignancies including acute lymphoblastic leukemia, mantle cell lymphoma, diffuse large B cell lymphoma, and multiple myeloma. <sup>373</sup> However, increased apoptosis <sup>378</sup> in newborn mouse dentate gyrus hippocampal neurons, <sup>349</sup> glioma and neuroblastoma cell lines, <sup>335</sup> and Jurkat cells. <sup>348</sup>	Fluoxetine has reversed A $\beta$ functional impairments, impaired oxidative phosphorylation, and reduced mitochondrial PTP opening, and reduced cell viability, indicating mixed evidence for possible utility in NDD. Nevertheless, fluoxetine has antiapoptotic properties in some neural tissues and can prevent serotonin-induced apoptosis while promoting apoptosis in neoplastic cell lines. Proapoptotic properties in immature and malignant cells suggest that fluoxetine may have utility in brain tumor chemotherapy.	

**TABLE 2. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Scrraline									There were no relevant studies detected for this agent.
Fluvoxamine						MAOBI in rat brain, <sup>330</sup> and may deter ROS generation.			The data are inconclusive.
Paroxetine	Preserved cognitive performance and reduced hippocampal A $\beta$ levels in 3xTgAD mouse model of AD. <sup>385</sup>	Reduced <i>t</i> pathology in male, but not in female transgenic 3xTgAD mice. <sup>385</sup>			Depolarized mitochondrial membrane in Burkitt lymphoma cells. <sup>378</sup>	Released mitochondrial cytochrome c in rat glioma and human neuroblastoma cell lines. <sup>339</sup>		Promoted apoptosis in cultured MCG3 human osteosarcoma cells, <sup>386</sup> glioma and neuroblastoma cell lines, <sup>339</sup> and Burkitt lymphoma cells. <sup>378</sup> Nevertheless, antagonized serotonin-induced apoptosis, in contrast to serotonin receptor antagonists. <sup>387</sup>	The data on cell viability and apoptosis are inconclusive, but paroxetine may have utility in brain tumor and osteosarcoma chemotherapy. While inhibition of the serotonin transporter may confer antiapoptotic properties to paroxetine, data in non-neoplastic neural tissue are needed to determine its safety in NDDs. Preliminary evidence suggests that paroxetine may reduce hyperphosphorylated tau in a transgenic mouse model of AD.
Citalopram		Did not alter tau phosphorylation or microtubule assembly in rats. <sup>381</sup>				MAOBI activity, thought to deter ROS generation, in rat brain, <sup>336</sup> but increased ROS and mitochondrial depolarization in human acute myeloid leukemia HL-60 cells. <sup>337</sup> and depolarization in Burkitt lymphoma cells. <sup>378</sup> although leukemia cells are more susceptible than normal lymphocytes. <sup>74</sup>	Reduced cell viability in human acute myeloid leukemia HL-60 cells. <sup>337</sup>	Promoted apoptosis in quiescent human lymphocytes, proliferating human lymphocytes, <sup>344,345,346,347</sup> acute myeloid leukemia HL-60 cells, <sup>337</sup> and Burkitt lymphoma cells. <sup>378</sup> but citalopram antagonized serotonin-induced apoptosis in Burkitt lymphoma cells, in contrast to serotonin receptor antagonists. <sup>383</sup>	Citalopram did not affect tau phosphorylation, but promotion of apoptosis signals the need for caution in NDDs. Data regarding mitochondrial function, cell viability, and apoptosis are lacking in NDD but extant findings suggest the potential utility of citalopram in cancer chemotherapy.
Trazodone									There were no relevant studies detected for this agent.
Nefazodone									There were no relevant studies detected for this agent.
Venlafaxine									There were no relevant studies detected for this agent.
Duloxetine									There were no relevant studies detected for this agent.
Mirtazapine							500-1000 $\mu$ M, killed 30% and 60% of MCG3 osteosarcoma cells, respectively. <sup>388,389</sup>		No conclusions can be drawn about neuroprotective properties of this agent because of limited data.

Properties relevant to neuroprotection as demonstrated in *in vitro*, *ex vivo*, and *in vivo* preclinical studies involving treatment with antidepressant agents.

A $\beta$ =beta-amyloid; AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis;  $\alpha$ Syn=alpha-synuclein; ATP=adenosine triphosphate; BDNF=brain derived neurotrophic factor; CHO=Chinese hamster ovary; ERK=extracellular signal-regulated kinase; HD=Huntington's disease; HDAC=histone deacetylase; MAO=monoamine oxidase; MAOBI=monoamine oxidase B inhibitor; MAPK=mitogen-activated protein kinase; MDMA=3,4-methylenedioxymethamphetamine; NDD=neurodegenerative disease; 6-OHDA=6-hydroxy-dopamine; PTP=mitochondrial permeability transition pore; ROS=reactive oxygen species; *t*=tau; TNFa=tumor necrosis factor alpha; UV=ultraviolet.

**TABLE 3. Neuroprotective Properties of Anxiolytic, Antihistaminic, Anticholinergic, Wake Promoting, and Hypnotic Agents**

Agent	$\alpha$ Syn	A $\beta$	$\tau$	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Anxiolytics Buspirone									Buspirone had antiapoptotic properties in several studies of neurons and may have potential in NDD.
Diazepam	Inhibited PKC activation-related cell protection in cultured chick embryonic cardiomyocytes, <sup>391</sup> and PKC inhibition has been associated with GSK-3 activation and A $\beta$ increases. <sup>137</sup>	Inhibited PKC activation <sup>391</sup> may potentially lead to tau hyperphosphorylation, related to GSK-3 activation in the context of PKC inhibition. <sup>150</sup>		Binds the mitochondrial peripheral benzodiazepine receptor (PBR), important for steroidogenesis, cell proliferation, mitochondrial respiratory chain, membrane potential, voltage-dependent calcium channels, responses to stress, and microglial activation. <sup>392</sup>	Mitochondrial PBR stimulation is involved in opening. <sup>393</sup> Diazepam produced dose-dependent swelling consistent with PTP opening in cardiac mitochondria. <sup>398</sup> CD95 antibody-induced apoptosis in Jurkat cells, <sup>368</sup> and released cytochrome c and apoptosis induced by colchicines in CCGNs. <sup>395</sup> Beta-carbolines, PBR receptor inverse agonists inhibited reactive oxygen species S1N-1 glutathione depletion mitochondrial depolarization, and cytochrome c release in PCI2 cells exposed to reactive nitrogen species. <sup>401</sup> However, diazepam prevented cytochrome c release in ischemic hippocampal slices. <sup>396</sup>	Did not reduce cell survival in rat C6 glioma cells. <sup>402</sup>	Reduced apoptosis in fetal rhombencephalic neurons. <sup>388,389</sup> 5HT1a agonists, <sup>389</sup> Bay X-3702, <sup>390</sup> and 8-OH-DPAT <sup>110</sup> inhibit apoptosis in serum-deprived cultured neurons, possibly by PI3K apoptotic and MAPKK survival pathway. <sup>389</sup>	Despite favorable findings in a single study of ischemic hippocampus, diazepam impairs mitochondrial function and promotes mitochondrial PTP development and apoptosis, indicating the need for caution in NDD but a possible potential benefit in stroke. Diazepam may also have some utility in cancer chemotherapy.	

**TABLE 3. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Chlordiazepoxide					<p>Did not bind to mitochondrial PBRs in rat pituitary GH3 cells.<sup>409</sup> Did not induce cholesterol side-chain cleavage in adrenocortical mitochondria,<sup>410</sup> unlike diazepam.<sup>410</sup> A GABA-A agonist, agents that protect against A<math>\beta</math>-induced neurotoxicity,<sup>280</sup> whereas GABA-A antagonists enhance picrotoxin neurotoxicity.<sup>281</sup></p>		<p>hypericin-induced apoptosis in human glioblastoma U-87 MG but not U373 MG cells.<sup>407</sup> Caspase-independent apoptosis was activated by diazepam-induced mitotic failure in HeLa cells, but not in human primary fibroblasts.<sup>408</sup> However, diazepam is a GABA-A agonist, and such drugs protect against A<math>\beta</math>-induced neurotoxicity,<sup>280</sup> while GABA-A antagonists enhance picrotoxin neurotoxicity.<sup>281</sup> Diazepam therefore appears to have mixed apoptotic effects in neural tissue, enhances neural tissue apoptosis induced by some agents, can inhibit apoptosis in neutrophils, and often promotes apoptosis in neoplastic tissues.</p>	<p>Chlordiazepoxide may not influence mitochondrial function, suggesting potential safety in NDD.</p>	
Flurazepam									<p>There were no relevant studies detected for this agent.</p>
Temazepam									<p>There were no relevant studies detected for this agent.</p>
Chlorazepate									<p>There were no relevant studies detected for this agent.</p>
Clonazepam					<p>Blocked increased mitochondrial calcium concentrations in hypoxic rat cardiomyocytes<sup>411,412</sup> and reduced mitochondrial calcium overload in neuroblastoma cells and cardiomyocytes.<sup>413</sup> Inhibits mitochondrial sodium/calcium ion exchange.<sup>388,414,415,416,417,418</sup> and normalizes</p>	<p>Attenuated mitochondrial depolarization induced by H<sub>2</sub>O<sub>2</sub> in post-hypoxic rat cardiomyocytes<sup>416,420</sup> and did not produce mitochondrial swelling indicative of opening in de-energized rat cardiomyocytes, in contrast to diazepam.<sup>398</sup> Studies of mitochondrial calcium release suggest that</p>	<p>Did not reduce cell survival in rat C6 glioma cells<sup>402</sup> or adult rats<sup>423</sup> and prevented cellular necrosis in neuroblastoma cells and cardiomyocytes,<sup>413</sup> but produced neurodegeneration in immature rats.<sup>423</sup></p>	<p>Unlike PBR ligands, did not induce apoptosis in esophageal cancer cell lines<sup>424</sup> and the human lymphoblastoid cell line U937,<sup>377</sup> but was no different in newborn rat<sup>395,397</sup> and immature rat brain apoptosis.<sup>423</sup> Clonazepam and other central benzodiazepine receptor (CBR) agonists did not inhibit apoptosis in rat mitochondria exposed to noise<sup>387</sup> or induced injury<sup>387</sup> or in the human lymphoblastoid cell line</p>	<p>Clonazepam may improve mitochondrial functioning in complex I deficiencies such as PD and inhibit mitochondrial PTP opening, however this drug has also produced neuronal apoptosis</p>

**TABLE 3. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Lorazepam					intramitochondrial calcium concentrations and subsequent ATP production in human complex I deficiency. <sup>418</sup>	clonazepam blocks the mitochondrial PTP <sup>415</sup> and calcium efflux. <sup>411,413,421,422</sup>		U937, <sup>423</sup> Clonazepam is a GABA-A agonist, and GABA-A agonists have been demonstrated to protect against A $\beta$ -induced neurotoxicity, <sup>280</sup> while GABA-A antagonists enhance picrotoxin neurotoxicity. <sup>281</sup>	There were no relevant studies detected for this agent.
Okazepam									There were no relevant studies detected for this agent.
Alprazolam									There were no relevant studies detected for this agent.
Zolpidem						In contrast to alpidem and other PBR inhibitors, did not increase calcium-induced mitochondrial permeability transition in rat liver. <sup>426</sup>			Zolpidem may not influence mitochondrial PTP opening, suggesting potential safety in NDD, but the relative absence of data precludes any conclusions.
Zopiclone									There were no relevant studies detected for this agent.
Zaleplon									There were no relevant studies detected for this agent.
<b>Antihistamines</b>									
Cyproheptadine									There were no relevant studies detected for this agent.
Diphenhydramine					Induced pre-malignant mitochondrial lamellar bodies in cultured rat liver epithelis, correlating with H1- but not H2-antagonists. <sup>427</sup> Reversed histamine-related uncoupling of oxidative phosphorylation in canine myocardial hypoxia. <sup>428</sup>		Induced apoptosis in several cell lines, including human acute T lymphocytic leukemia but not normal peripheral blood mononuclear cells, <sup>429</sup> and in four different human malignant melanoma cell lines, but did not adversely affect human melanocytes or murine fibroblasts. <sup>430</sup>	While diphenhydramine might possibly promote pre-malignant cell transformation, it may selectively promote apoptosis in malignant cell lines, suggesting potential utility in treating cancer. Improved mitochondrial oxidative phosphorylation in a single study offers the potential to improve post-hypoxic cell survival, but more data are needed.	
Hydroxyzine									There were no relevant studies detected for this agent.

**TABLE 3. Continued**

Agent	$\alpha$ Syn	A $\beta$	<i>t</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Anticholinergics Benzotropine									There were no relevant studies detected for this agent.
Trihexyphenidyl		Did not inhibit BA fibril formation, in contrast to dopamine and dopaminergic agonists. <sup>32</sup>							Data are insufficient to allow any conclusions for this agent.
Modafinil									There were no relevant studies detected for this agent.
Melatonin Agonists Melatonin	Reduced $\alpha$ Syn aggregation in rats, <sup>437</sup> SK-H-SH neuroblastoma cells treated with D-amphetamine, <sup>432</sup> and PC12 pheochromocytoma cells treated with maneb. <sup>433</sup>	Inhibited A $\beta$ fiber formation, <sup>434,435</sup> aggregation, <sup>437</sup> A $\beta$ deposition, <sup>435,436</sup> and improved AB(25-35)-in mice, <sup>438</sup> but did not reduce A $\beta$ burden in transgenic mice. <sup>439</sup> In two monozygotic twins with a similar age of onset of Alzheimer's disease, the twin taking melatonin had slower progression of functional disability than the twin not taking melatonin. <sup>440</sup>	Inhibited tau hyperphosphorylation, <sup>438</sup> including in SH-SY5Y cells exposed to mercury, <sup>441</sup> SAMPS senescent mice, <sup>442</sup> rat brain exposed to peroxynitrite <sup>443</sup> and in rat hippocampal pyramidal neurons <sup>444</sup> and human Alzheimer's neurons <sup>445</sup> exposed to wortmannin, a PI3K inhibitor. <sup>444,445</sup> Melatonin specifically protected rat neurons against tau hyperphosphorylation induced by wortmannin at the PHE-1 site, <sup>444</sup> isoproterenol at PHE-1 and tau-146, <sup>447</sup> and haloperidol at PHE-1 (Ser396/Ser404), <sup>37</sup> (Ser199/Ser202), <sup>37</sup> M4 (Thr231/Ser235), <sup>36</sup> and P5214 (Ser214), <sup>36</sup> and improved memory in rats. <sup>37</sup> Inhibits GSK-3 $\beta$ and reduces haloperidol-induced protein kinase A activation, <sup>36,37</sup> activates the protein phosphatase Pp-2A, <sup>37</sup> thereby attenuating tau phosphorylation. <sup>435</sup> Regarding phosphatases, melatonin inhibited calyculin A (a PP-2A and PP-1 inhibitor)-induced tau hyperphosphorylation in neuroblastoma N2a cells. <sup>448</sup> Restored suggesting the ability to alter neurofibrillary tangle (NFT) development in AD. Melatonin's	Inhibited beta-glutamyl peptide hydrolyase activity, <sup>450</sup> proteasomal proteases activation, <sup>451</sup> or impeding metabolic activity in SH-SY5Y cells, <sup>453</sup> Loss of complex I and melatonin activity occurs in PD $\alpha$ and stimulates complex I activity. <sup>457,458,459</sup> and has protected against its loss induced by 6-hydroxydopamine <sup>454</sup> and MPP <sup>+</sup> <sup>460</sup> in animal models of PD. Melatonin stimulated complex IV activity, <sup>457,461,462</sup> and protected complex III activity from oxidative damage in rat cardiomyocytes. <sup>463</sup> Stimulation of complex I and IV activities enhances oxidative phosphorylation, <sup>459</sup> adenosine triphosphate synthesis, <sup>466,459,464</sup> and mitochondrial glutathione levels. <sup>464</sup> Consistent with this, restored ATP production in septic mouse heart <sup>465,466</sup> and in SK-H-SH neuroblastoma cells exposed to D-amphetamine, <sup>432</sup> and increased glutathione levels in peripheral blood mononuclear cells. <sup>467</sup> Restored mitochondrial viability in rabbit corneal epithelial cell	Reduced free radical <sup>469</sup> and superoxide formation, <sup>468,470,471,472</sup> oxidative stress, <sup>37,432,445,448</sup> lipid peroxidation, <sup>469,475,476</sup> mitochondrial oxidative damage, <sup>468,477</sup> and oxidative alterations to complex I and III and cardiolipin, <sup>465</sup> reperfusion ischemic rat heart, <sup>463</sup> rat liver exposed to Adriamycin, <sup>476</sup> infant rat intestine exposed to lipopolysaccharide, <sup>475</sup> hyperglycemic kidney cortex tubule injury, <sup>469</sup> reperfusion arterial wall, <sup>474</sup> and ischemic neuroblastoma N2a cells. <sup>473</sup> N2a cells exposed to calyculin A, <sup>448</sup> embryonic chick telencephalon, <sup>470</sup> brain, <sup>471</sup> SAMPS HT22 mouse hippocampal cells exposed to glutamate, <sup>472</sup> human Alzheimer's neurons exposed to wortmannin, <sup>445</sup> brain cells exposed to haloperidol, <sup>37</sup> SK-H-SH neuroblastoma cells exposed to D-amphetamine, <sup>432</sup> hemiparkinsonian rats exposed to rotenone, <sup>478</sup> and rabbit corneal epithelial cell culture stimulated	Enhanced peripheral blood mononuclear cell viability and proliferation, <sup>467</sup> Improved N2a neuroblastoma cell viability after exposure to calyculin A <sup>448</sup> and reduced A $\beta$ cytotoxicity. <sup>280,435,499</sup>	Antagonized apoptosis through melatonin receptor dependent mechanisms <sup>500</sup> and inhibited 3-morpholinodimethylamine-induced caspase-3 activity. <sup>501,502,503</sup> and Bax translocation to the mitochondria. <sup>485</sup> Hypothesized to modulate the intrinsic apoptotic pathway by reducing intramitochondrial free radicals and by increasing complex I and IV activity, thereby reducing mitochondrial depolarization and PTP opening, assisted further by modulation of mitochondrial PTP currents. <sup>490,493</sup> Attenuated lipopolysaccharide-induced hepatic apoptosis in D-galactosamine-sensitized mice. <sup>504</sup> Reduced apoptosis in rat hepatoma cells, <sup>481</sup> UVB-irradiated HeCaT keratinocyte cells, <sup>505</sup> infant rat intestine induced by lipopolysaccharide, <sup>473</sup> SH-SY5Y human neuroblastoma cells induced by lead, <sup>506</sup> UVB irradiated U937 cells, <sup>496,507</sup> dinitrobenzene sulfonic acid-induced colitis in rats, <sup>508</sup> trinitrobenzene sulfonic acid-induced colitis in rats, <sup>509</sup> reperfusion skeletal muscle, <sup>374</sup> rat liver exposed to carbon tetrachloride, <sup>510</sup> rat thyroid follicular cells exposed to aflatoxin B <sub>1</sub> , <sup>511</sup> reperfusion ischemic rat pancreas, <sup>512</sup> oxygen and glucose deprived cerebellar	Evidence of inhibition of $\alpha$ Syn aggregation and A $\beta$ formation and deposition in most models, prevention of <i>t</i> phosphorylation at sites relevant to AD, activation of <i>t</i> -dephosphorylation by phosphatase PP-2A, protection of mitochondrial function, inhibition of free radicals, mitochondrial PTP development, and cytochrome c release especially in AD and PD models, improved cellular viability, and inhibition of apoptosis particularly in PD models, suggest significant potential in NDD, especially AD and PD. Data on cell viability remains inconclusive, but initial evidence suggests that melatonin may promote mitochondrial function and cell survival and inhibit apoptosis in some forms of neoplastic disease while impairing mitochondrial function and promoting apoptosis in others.	

TABLE 3. Continued

Agent	$\alpha$ Syn	A $\beta$	<i>f</i>	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Melatonin			effects on tau hyperphosphorylation might involve mechanisms other than the melatonin-1 receptor (MT1) since the MT1 antagonist luzindole did not reverse olivacetic acid-induced cytoskeletal abnormalities. <sup>459</sup>		culture exposed to stimulated macrophages. <sup>468</sup> In MCF-7 breast tumor cells, melatonin uncoupled oxidative phosphorylation, an effect that appeared to be melatonin receptor-dependent. <sup>461</sup>	mitochondrial NO-concentrations, <sup>459</sup> and induced mitochondrial damage by the activity of the mitochondrial nitric oxide synthase. <sup>459,481,482</sup> Prevented mitochondrial PTP development in hypoxic rat brain, <sup>483</sup> H <sub>2</sub> O <sub>2</sub> -stressed brain astrocytes, <sup>484</sup> hypoxic HL-1 cardiomyocytes, <sup>485</sup> and electrically stimulated canine muscle. <sup>486</sup> During oxidative stress in rat brain astrocytes, reduced mitochondrial swelling, calcium overload, membrane depolarization, mitochondrial PTP opening, and cytochrome c release. Prevented mitochondrial depolarization in doxorubicin-exposed myocytes. <sup>487</sup> Inhibited mitochondrial ROS, depolarization, and PTP development after a large mitochondrial DNA deletion of 4977 base pairs affecting the respiratory chain. <sup>488</sup> Inhibited mitochondrial cytochrome c release and current flows through the mitochondrial PTP, including cytochrome c release in $\alpha$ -synuclein-expressing rats. <sup>489,490</sup> Oxygen- and glucose-deprived cerebellar granule cells, <sup>491</sup> and rat substantia nigra exposed to arsenite. <sup>491</sup> Inhibited cytochrome c release in rat hippocampal neurons and oxygen- and glucose-deprived cerebellar granule neurons. <sup>494</sup> In non-neural malignancies, attenuated mitochondrial depolarization, and release of cytochrome c, in small cell lung	granule cells. <sup>494</sup> formaldehyde-exposed rat prefrontal cortex, <sup>513</sup> and anesthetized rat brain. <sup>514</sup> Reduced apoptosis in rat astrocytoma C6 cells. <sup>515</sup> NDA used ischemic cells, <sup>473</sup> and inhibit spinal cord-inhibited caspase-3 activation, cytokrome release, and DNA damage in cerebellar granule neurons deprived of oxygen and glucose, and induced Bcl-2 expression and arrested apoptosis in immunized pineal cells exposed to nitric oxide. <sup>488</sup> Reduced Bax/Bcl-2 relative expression, caspase-3 activation and apoptosis in aging rat liver. Although it did not decrease oxidative damage in the Ig-257 transgenic mouse model of AD, in other models it reduced $\beta$ -induced activation of caspase-3 and apoptosis. <sup>484,495</sup> Reduced MPP+ - induced apoptosis and caspase-3 activation in SK-H-SH human neuroblastoma cells. MPP+ - induced apoptosis, cdk5 expression, and p35-p25 cleavage in cerebellar granule cells, <sup>496</sup> and caspase-3 activation in rat substantia nigra exposed to arsenite. <sup>491</sup> Did not reduce apoptosis in irradiated cultured rat lymphocytes. <sup>500</sup> Increased apoptosis in keratinocytes and A-549 lung cancer cells, <sup>501</sup> rat pituitary prolactinoma cells, <sup>502</sup> HL-60 human myeloid leukemia cells, <sup>503</sup> human umbilical vein cells, <sup>504</sup> and human neuroblastoma SK-N-MC cells. <sup>505</sup> Although it reduced apoptosis in promonocytic leukemia cells, <sup>498</sup> it downregulated Bcl-2, activated caspase-3, and promoted apoptosis in human B-lymphoma cells. <sup>498</sup>		

**TABLE 3. Continued**

Agent	$\alpha$ Syn	A $\beta$	t	Proteasome	Mitochondrion	PTP	Cell Viability	Apoptosis	Comment
Ramelteon						cancer cells induced by mitomycin c <sup>105</sup> and reduced cytochrome c release in promonocytic leukemia cells. <sup>106</sup> However, increased reactive oxygen species in human leukemia cells <sup>107</sup> and, in human B-lymphoma cells, led to mitochondrial membrane depolarization, and cytochrome c release. <sup>108</sup>			There were no relevant studies detected for this agent.

Properties relevant to neuroprotection as demonstrated in *in vitro*, *ex vivo*, and *in vivo* preclinical studies involving treatment with anxiolytic, antihistaminic, anticholinergic, wake promoting, and hypnotic agents.

A $\beta$ =beta-amyloid; AD=Alzheimer's disease;  $\alpha$ Syn=alpha-synuclein; ATP=adenosine triphosphate; DNA=deoxyribonucleic acid; GSK-3 $\beta$ =glycogen synthase kinase 3-beta; H<sub>2</sub>O<sub>2</sub>=hydrogen peroxide; MPP<sup>+</sup>=1-methyl-4-phenylpyridine ion; MT-1=melatonin 1 receptor; NDD=neurodegenerative disease; NFT=neurofibrillary tangle; NO=nitric oxide; PD=Parkinson's disease; PI3K=phosphatidylinositol-3 kinase; PP1=protein phosphatase 1; PP2A=protein phosphatase 2A; PTP=mitochondrial permeability transition pore; ROS=reactive oxygen species; SIN=3-morpholinohydronimine; t=tau; UVB=ultraviolet B.

**TABLE 4. Effects of Psychotropics on Ubiquitin**

Drug	Effect
<b>Dopamine Agonists</b>	
Levo-dopa	Pulsatile levodopa administration led to ubiquitin-positive striatal ultrastructural changes associated with dyskinesia in dopamine depleted, norepinephrine deficient rats <sup>526</sup>
Pramipexole	Reduced ubiquitin immunoreactivity upregulation induced by lipopolysaccharide in rat substantia nigra <sup>527</sup>
<b>Antipsychotics</b>	
Haloperidol	Increased striatal and nucleus accumbens parkin E3 ligase mRNA <sup>528</sup> and nigral Pael-R mRNA, <sup>529</sup> the substrate of parkin, in rats treated with supratherapeutic doses (2mg/kg) Reduced ubiquitin – related systems mRNA expression in mice treated for 14 days with haloperidol and biperiden, an effect not seen with either drug by itself <sup>530</sup>
<b>Mood Stabilizers</b>	
Lithium	Promoted ubiquitination of tau in an Alzheimer’s transgenic tauopathic mouse model <sup>175</sup>
Valproate	Induced Ubc8 gene expression, the E2 ubiquitin ligase <sup>238</sup> Associated with increased expression of Ube2D1 and SKP1A, an E2 ubiquitin conjugase and a subunit of the E3 ubiquitin ligase <sup>531</sup>
<b>Antidepressants</b>	
Citalopram	Dysregulated the expression of ubiquitin-like protein genes in frontal and temporal cortex both at 96 hours and 4 weeks of administration to rats at therapeutic doses <sup>532</sup>
<b>Hypnotics</b>	
Melatonin	Decreased the expression of ubiquitin-conjugating enzyme E2M in keratinocytes exposed to ultraviolet B radiation <sup>505</sup>
<b>Antimuscarinic Agents</b>	
Biperiden	Reduced ubiquitin-related systems mRNA expression in mice treated for 14 days with haloperidol and biperiden, an effect not seen with either drug by itself <sup>530</sup>

The relations of psychotropics to ubiquitin and ubiquitin related genes and systems.

**TABLE 5. Quality of the Preclinical Data**

Finding	Replicated Within a Single Model	Replicated in an Additional Model	Demonstrated in Neural Tissue
<b>Pramipexole</b>			
Inhibits reactive oxygen species	X	X	X
Inhibits PTP development	X	X	X
Inhibits apoptosis	X	X	X
<b>Amantadine</b>			
Inhibits apoptosis		X	
<b>Haloperidol</b>			
<i>Reduces Complex I</i>	X	X	X
<i>Increases oxidative stress</i>		X	X
<i>Reduces cell viability</i>		X	X
<i>Induces apoptosis</i>	X	X	X
<b>Fluphenazine</b>			
<i>Inhibits Complex I</i>		X	X
<i>Increases brain Complex IV</i>		X	X
<i>Reduces visceral Complex IV</i>		X	
<b>Trifluoperazine</b>			
<i>Reduces ATP synthesis</i>	X	X	
<i>Reduces oxidative stress</i>		X	X
<i>Inhibits PTP development</i>		X	X
<i>Improved cell viability</i>		X	X
<i>Inhibits neural apoptosis</i>		X	X
<i>Promotes undifferentiated cell apoptosis</i>		X	X
<b>Chlorpromazine</b>			
<i>Inhibits Complex I</i>	X	X	X
<i>Inhibits PTP development</i>	X	X	
<i>Reduces leukemia cell viability</i>	X	X	
<i>Inhibits acetaminophen apoptosis in hepatocytes</i>	X	X	
<i>Promotes apoptosis in neoplasia</i>	X	X	
<b>Thioridazine</b>			
<i>Inhibits PTP development</i>	X	X	
<i>Promotes apoptosis in neoplasia</i>	X	X	X
<b>Risperidone</b>			
<i>Reduces Complex I activity</i>	X	X	X
<i>Inhibits apoptosis</i>		X	X
<b>Olanzapine</b>			
<i>Improves cell viability</i>		X	X
<i>Inhibits apoptosis</i>	X	X	X
<b>Quetiapine</b>			
<i>Inhibits apoptotic processes</i>			X
<b>Clozapine</b>			
<i>Promotes neutrophil apoptosis</i>	X		
<b>Lithium</b>			
<i>Reduces GSK-3<math>\beta</math> transcription</i>	X		X
<i>Inhibits A<math>\beta</math> production</i>	X	X	X
<i>Reduces t hyperphosphorylation</i>	X	X	X
<i>Reduces A<math>\beta</math>-induced t hyperphosphorylation</i>	X	X	X
<i>Reduces proteasomal function</i>	X	X	
<i>Inhibits PTP development</i>	X	X	X
<i>Promotes cell viability</i>	X	X	X
<i>Inhibits apoptosis</i>	X	X	X
<i>Inhibits A<math>\beta</math>-induced apoptosis</i>	X	X	X
<i>Inhibits glutamate-induced apoptosis</i>		X	X
<i>Inhibits hippocampal apoptosis</i>	X	X	X
<i>Inhibits apoptotic processes</i>	X	X	X
<i>Promotes apoptosis in neoplasia</i>	X	X	
<b>Valproic acid</b>			
<i>Increases aSyn expression</i>	X	X	X
<i>Inhibits A<math>\beta</math> production</i>		X	X
<i>Increases proteasomal function</i>	X	X	
<i>Exacerbates mitochondrial disease clinical symptoms</i>	X	X	X
<i>Induces mitochondrial swelling</i>	X	X	X
<i>Decreases oxidative phosphorylation</i>	X	X	X
<i>Induces PTP formation</i>	X		
<i>Reduced cytochrome c release</i>		X	X
<i>Inhibits apoptotic processes</i>	X	X	X
<i>Inhibits neural apoptosis</i>	X	X	X
<i>Promotes apoptosis in immature cell lines</i>	X	X	X
<b>Carbamazepine</b>			
<i>Inhibited hippocampal toxopathy</i>		X	X
<i>Increased caspase-3</i>	X	X	X

TABLE 5. Continued

Finding	Replicated Within a Single Model	Replicated in an Additional Model	Demonstrated in Neural Tissue
<b>Oxcarbazepine</b>			
<i>Increased oxidative stress</i>		X	X
<b>Amitriptyline</b>			
<i>Reduced cell viability</i>		X	X
<b>Imipramine</b>			
Reduced viability in neoplasia		X	
Promotes apoptosis in myeloid tissues	X	X	X
<b>Nortriptyline</b>			
Inhibits PTP development		X	X
<b>Desipramine</b>			
Inhibits oxidative stress		X	
Inhibits apoptosis	X	X	X
Promotes apoptosis in neoplasia		X	X
<b>Clomipramine</b>			
Promoted PTP development in neural neoplasia		X	X
Promotes apoptosis in myeloid tissues	X	X	X
<b>Fluoxetine</b>			
Promotes PTP development in neoplasia		X	X
<i>Reduces cell viability</i>		X	
Reduces apoptosis		X	X
Promotes apoptosis in immature cells and neoplasia		X	X
<b>Paroxetine</b>			
Promotes apoptosis in neoplasia		X	X
<b>Citalopram</b>			
Promotes mitochondrial depolarization in myeloid neoplasia		X	
Promotes apoptosis in myeloid tissue and myeloid neoplasia	X	X	
<b>Diazepam</b>			
<i>Inhibits mitochondrial respiration</i>		X	
<i>Promotes mitochondrial depolarization</i>		X	X
<i>Promotes apoptosis in nascent neural tissues</i>		X	X
<b>Clonazepam</b>			
Inhibits mitochondrial hypercalcemia		X	X
Inhibits mitochondrial Na/Ca exchange	X	X	X
Inhibits PTP development		X	
Inhibits mitochondrial Ca efflux	X	X	X
Prevents necrosis		X	X
Promotes apoptosis in immature brain	X	X	X
<b>Diphenhydramine</b>			
Promotes apoptosis in neoplasia		X	
<b>Melatonin</b>			
Reduces $\alpha$ Syn aggregation		X	X
Inhibits A $\beta$ fiber formation	X	X	X
Inhibits tau hyperphosphorylation		X	X
<i>Reduces proteasomal function</i>		X	X
Stimulates Complex I activity		X	X
Protects against Complex I loss		X	X
Stimulates Complex IV		X	X
Restores ATP production		X	X
Reduces superoxide formation		X	X
Reduces oxidative stress		X	X
Inhibits lipid peroxidation		X	X
Inhibits PTP development		X	X
Inhibits cytochrome c release	X	X	X
Improves cell viability		X	X
Reduces apoptosis		X	X
Reduces MPTP apoptosis		X	X
Increases oxidative stress in myeloid malignancies		X	
Inhibits cytochrome c release in malignancies		X	
Increases apoptosis in immature and malignant tissues		X	X

The quality of preclinical findings with respect to within-model replication, replication in at least one other model, and demonstration in neural tissue. "X" in the first column indicates independent replication of the finding in the same model by an independent group; "X" in the second column indicates replication of the finding in at least one other preclinical model; "X" in the third column indicates observation of the finding in neuronal tissue (neurons, glia, or immortalized neural cell lines including neuroblastomas) in at least one other study. Consequently, the more columns checked, the greater the validity and reliability of the finding. Italicized entries indicate findings in line with promoting neurodegeneration rather than neuroprotection, whereas non-italicized text indicates neuroprotective actions.

A $\beta$ =beta-amyloid;  $\alpha$ Syn=alpha-synuclein; ATP=adenosine triphosphate; GSK-3 $\beta$ =glycogen synthase kinase 3-beta; MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PTP=mitochondrial permeability transition pore; t=tau.

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**TABLE 6. Provisional Criteria Desirable for Determining Candidate Agents for Clinical Trial**

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**Pre-Clinical Criteria**

- Experimental evidence of a neuroprotective action using an established neuroprotective model at physiological drug doses (1-1000  $\mu$ M 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 A $\beta$  production, t 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 some day 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 flouroDOPA 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)

Putative criteria for assessing the probability that an agent will demonstrate translational neuroprotective effect in a clinical trial. Since the predictive utility of these factors remain 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.

A $\beta$ =beta-amyloid; AD=Alzheimer's disease; DOPA=di-hydroxy-phenylalanine; MMSE=Mini-Mental State Examination; MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD=Parkinson's disease; PTP=mitochondrial permeability transition pore; t=tau.

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**TABLE 7. Relative Weight of Preclinical Data for Actions of the Most Promising Neuroprotective Agents**

Agent	$\alpha$ Syn	A $\beta$	t	Proteasome	Mitochondrion	ROS & PTP	Cell Viability	Apoptosis
Pramipexole	+ (MPP <sup>+</sup> )	+ (A $\beta$ )				+++++ (A $\beta$ , MPP <sup>+</sup> , H <sub>2</sub> O <sub>2</sub> , ALS, striatum)		+++++ (MPP <sup>+</sup> , H <sub>2</sub> O <sub>2</sub> , rotenone)
Thioridazine					+++ - (cerebellum)	+++ (A $\beta$ , SOD1)	++ (rotenone)	+++++ (A $\beta$ , MPP <sup>+</sup> , frontal lobe) -
Olanzapine						+++ (A $\beta$ )	+	+++
Quetiapine		+++ (GSK-3 $\beta$ , gamma-secretase, AD APP transgenic mice)		--(GSK-3 $\beta$ , tauopathic AD transgenic mice)	+	+++++ (glutamate, H <sub>2</sub> O <sub>2</sub> , rotenone, cerebellar granule cells)	+++ (cerebellar granule cells)	+++++ (GSK-3 $\beta$ , A $\beta$ , cerebellar granule cells, cerebellum, cerebral cortex, hippocampus, striatum, aging, glutamate, NMDA agonists, ALS mouse model, HD model) ---- (tau dephosphorylation, hippocampus)
Lithium			+++++ (GSK-3, A $\beta$ , cerebellar granule cells, hippocampus, basal forebrain cholinergic neurons, AD transgenic mice, FTDP-17 transgenic mice)		+	+++ (rotenone, H <sub>2</sub> O <sub>2</sub> ) --	+	+++++ (GSK-3 $\beta$ , A $\beta$ , rotenone, H <sub>2</sub> O <sub>2</sub> , glutamate, NMDA receptor agonists, cerebellar granule cells, hippocampus, brain) ---- (microglia, cerebellar granule cells, young rat brain)
Valproic acid		+ (AD APP transgenic mice)			----- (brain)		+	+
Nortriptyline						++ (glutamate, HD and ALS transgenic mice)	+	+
Desipramine						+++++ (glutamate, HD transgenic mice)		+++++ (glutamate, 6-OHDA, HD transgenic mice, hippocampal neural stem cells)
Maprotiline						+		+
Fluoxetine						+		+
Paroxetine						+		+
Buspirone						+++ (H <sub>2</sub> O <sub>2</sub> )	+	+++++ (neurons)
Clonazepam						+		+
Diphenhydramine						+		+
Melatonin	+++	+++++	+++ (senescent mice, rat brain, rat hippocampal pyramidal neurons, human AD)	--	+	+++++ (glutamate, A $\beta$ , rotenone, H <sub>2</sub> O <sub>2</sub> ) (glutamate, hippocampal cells, human AD neurons, hippocampal cells, mouse hippocampal cells, human hippocampal cells, rat hippocampal cells, rat substantia nigra, rat brain astrocytes, aging rat, cerebellar granule cells)	+++++ (A $\beta$ )	+++++ (NO, A $\beta$ , MPP <sup>+</sup> , cerebellar granule cells, rat prefrontal cortex, rat brain, rabbit spinal cord, pineal cells)

The table shows the number of studies supporting a neuroprotective action ("+" and the number indicating an adverse effect on the neuroprotective function ("--"). This table does not record the number of studies failing to replicate the positive or negative findings, which are very few and are already recorded in Tables 1-3. All data in this table are abstracted from Tables 1-3. Models that are specifically relevant to major neurodegenerative diseases or specific central nervous system cells are also provided. The data in this table reflect studies in mature tissues and do not consider immature or neoplastic cell lines, except in the case of unexpected findings supporting neuroprotective actions demonstrable even in immature (one buspirone study of fetal rat rhombencephalic neurons) and neoplastic cell lines (multiple studies of antiapoptotic effects of melatonin).

A $\beta$ =beta-amyloid; AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; APP=amyloid precursor protein;  $\alpha$ Syn=alpha-synuclein; FTDP-17=frontotemporal dementia with parkinsonism associated with chromosome 17 mutations of the tau gene; GSK-3 $\beta$ =glycogen synthase kinase 3-beta; H<sub>2</sub>O<sub>2</sub>=hydrogen peroxide; HD=Huntington's disease; MPP<sup>+</sup>=1-methyl-4-phenylpyridine ion; NMDA=N-methyl-D-aspartate; NO=nitric oxide; 6-OHDA=6-hydroxy-dopamine; PD=Parkinson's disease; PTP=mitochondrial permeability transition pore; ROS=reactive oxygen species; SOD1=superoxide dismutase 1; t=tau.

TABLE 8. Side-B-Side Comparison Of Neuroprotective Profiles Of Promising Neuroprotective Psychotropics

Agent	aS	A $\beta$	t	Proteasome	Mitochondrion	ROS & PTP	Cell Viability	Apoptosis
Pramipexole	1+ PD	1+ AD				10+ AD, PD, ALS		8+ PD
Thioridazine				3+		4+		
Olanzapine				1-		2+ AD, ALS	2+ PD	5+ AD, PD
Quetiapine				1-		2+ AD	1+ PD	2+ 1-
Lithium		3+ AD	34+ AD, FTDP-17	2- AD	1+ 1-	5+ AD, PD, HD	3+	30+ AD, ALS, HD
Valproic acid	1+ AD	1+ AD		1-	20-	3+ PD 2-	1+	10+ AD, PD, HD
Nortriptyline						2+ HD, ALS	1+ ALS 1-	1+ HD
Desipramine						4+ HD		7+ PD, HD, AD
Maprotiline						1+ HD	1-	1+ HD
Fluoxetine		1+ AD	1+ AD		1+ 2-			2+
Paroxetine								
Bupirone								4+
Clonazepam						3+ PD	1+	
Diphenhydramine					1+			
Melatonin	3+	5+	11+ AD	2-	22+ PD, AD	36+ AD, PD	5+ AD	27+ PD

This table displays a side-by-side comparison of the different drugs regarded as promising for clinical neuroprotection. These comparisons are abstracted from TABLE 7, showing the number of studies supporting a neuroprotective action ("+" and the number indicating an adverse effect on the neuroprotective function ("-"). This table does not record the number of studies failing to replicate the positive or negative findings, which are very few and are already recorded in Tables 1-3. Where specific disease - relevant models have demonstrated neuroprotective or neurodegenerative actions, the relevant disease is mentioned. The data in this table reflect studies in mature tissues and do not consider immature or neoplastic cell lines, except in the case of unexpected findings supporting neuroprotective actions demonstrable even in immature (one bupirone study of fetal rat rhombencephalic neurons) and neoplastic cell lines (multiple studies of antiapoptotic effects of melatonin).

AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; FTDP-17=frontotemporal dementia with parkinsonism associated with chromosome 17 mutations of the tau gene; HD=Huntington's disease; PD=Parkinson's disease.

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