# Review Article
# Repurposing psychiatric medicines to target activated microglia in anxious mild cognitive impairment and early Parkinson's disease

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**Abstract:** Anxiety is common in the Mild Cognitive Impairment (MCI) stage of Alzheimer's disease (AD) and the pre-motor stages of Parkinson's disease (PD). A concomitant and possible cause of this anxiety is microglial activation, also considered a key promoter of neurodegeneration in MCI and early PD via inflammatory mechanisms and the generation of degenerative proinflammatory cytokines. Psychiatric disorders, prevalent in AD and PD, are often treated with psychiatric drugs (psychotropics), raising the question of whether psychotropics might therapeutically affect microglial activation, MCI, and PD. The literature of common psychotropics used in treating psychiatric disorders was reviewed for preclinical and clinical findings regarding microglial activation. Findings potentially compatible with reduced microglial activation or reduced microglial inflammogen release were evident for: *antipsychotics* including *neuroleptics* (chlorpromazine, thioridazine, loxapine) and *atypicals* (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone); *mood stabilizers* (carbamazepine, valproate, lithium); *antidepressants* including *tricyclics* (amitriptyline, clomipramine, imipramine, nortriptyline), *SSRIs* (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, and bupropion; *benzodiazepine anxiolytics* (clonazepam, diazepam); *cognitive enhancers* (donepezil, galantamine, memantine); and *other drugs* (dextromethorphan, quinidine, amantadine). In contrast, pramipexole and methylphenidate might promote microglial activation. *The most promising replicated findings* of reduced microglial activation are for quetiapine, valproate, lithium, fluoxetine, donepezil, and memantine but further study is needed and translation of their microglial effects to human disease still requires investigation. *In AD-relevant models*, risperidone, valproate, lithium, fluoxetine, bupropion, donepezil, and memantine have therapeutic microglial effects in need of replication. Limited clinical data suggest some support for lithium and donepezil in reducing MCI progression, but other drugs have not been studied. *In PD-relevant models*, lamotrigine, valproate, fluoxetine, dextromethorphan, and amantadine have therapeutic microglial effects whereas methylphenidate induced microglial activation and pramipexole promoted NO release. Clinical data limited to pramipexole do not as of yet indicate faster progression of early PD while the other drugs remain to be investigated. These tantalizing psychotropic neuroprotective findings now invite replication and evidence in AD-and PD-specific models under chronic administration, followed by consideration for clinical trials in MCI and early stage PD. Psychiatric features in early disease may provide opportunities for clinical studies that also employ microglial PET biomarkers.

**Keywords:** Microglia, cytokine, mild cognitive impairment, Alzheimer's disease, Parkinson's disease, anxiety, antipsychotic, mood stabilizer, antidepressant, anxiolytic

## Introduction

Microglial activation is a correlate of early Alzheimer's disease (AD) and early Parkinson's disease (PD). Activated microglia release proinflammatory cytokines and other molecules including interleukin-1 beta (IL-1b), IL-2, IL-6, IL-18, and tumor necrotic factor alpha (TNFa) [1-3], although there is a recent study suggesting that TNFa may be neuroprotective in hippo-

campal slices [4]. Activation of microglia and the subsequent release of proinflammatory molecules are considered to play an important role in mediating neurodegeneration [5, 6], particularly in the *early* stages of AD [7-10] and PD [5, 11, 12].

In AD, it is thought that inflamed activated microglia are prodegenerative and contribute to pathogenesis *early* in AD by releasing proin-

flammatory mediators but may mediate neuro-protection *later* in the disease course by clearing ß-amyloid (Abeta) [13], although some have argued the opposite [14]. There are several links between AD and inflammation, including the increased expression of inflammatory mediators and microglia evident in post-mortem brain, epidemiological evidence of benefit with non-steroidal anti-inflammatory drugs, symptomatic worsening in infectious and other systemic inflammatory states, and the association of AD with several inflammatory genes [14]. Activated microglia are associated with fibrillar Abeta plaques and microglia are activated either by Abeta itself [15] or by other factors operating in immediate proximity to some plaques but not others [16]. In patients with mild cognitive impairment (MCI), AD, or PD dementia (PDD) studied by positron emission tomography (PET) relative to normal controls, increased microglial activation correlated positively with Abeta and negatively with cerebral glucose metabolism and, in AD and PDD, with Mini-Mental State Examination (MMSE) scores [17] while a similar PET study did not find microglial activation in AD or MCI and concluded microglial activation to be a subtle phenomenon [18]. An earlier PET study of MCI relative to healthy controls found elevated cortical Abeta in 7 of 14 (50%) patients and frontal cortical microglial activation in 5 of 13 (38%), and 3 of the 5 cases with microglial activation had increased Abeta [19]. Consequently, microglial activation appears to be an early correlate of AD that contributes importantly to its pathogenesis.

Similar evidence exists in PD. There is evidence that alpha-synuclein (aSyn) activates microglia that in turn produce neurodegeneration [20]. In drug-naive patients with early stage PD studied by PET, contralateral midbrain microglial activation was significantly greater than in matched healthy controls, correlated inversely with putamenal dopamine transporters, and correlated positively with Unified Parkinson's Disease Rating Scale (UPDRS) motor severity scores, consistent with the concept that microgial neuroinflammatory responses contribute to neurodegenerative progression [11]. Another PET study found microglial activation in the pons, basal ganglia, frontal, and cortical regions in patients with PD relative to normal controls [5] while PD patients followed longitudinally over 2

years showed no changes in microglial activation on PET and a lack of correlation with putamenal dopamine uptake or clinical severity, suggesting to the authors that microglial activation occurs *early* in PD, remains static thereafter, and possibly drives the disease through the release of cytokines [5]. Thus, microglial activation appears to be an early correlate of AD as well as PD and it contributes significantly to their pathogeneses.

There is some evidence that anxiety is linked to microglial activation and its mediators in neurodegenerative diseases. Some of these proinflammatory cytokines have been associated with inducing the symptoms of anxiety including IL-1 [21], IL-1b in particular [22, 23], IL-2 [3], IL-6 [24, 25], IL-18 [22], and TNFa [23]. Anxiety itself has been linked to microglial activation in several different animal models and animal species [26-28]. Reductions in anxiety have been correlated with reduced microglial activation and other pathological hallmarks in transgenic mouse models of AD after continuous exercise [29] or rapamycin treatment [30] and in rats exposed to microglial-activating lipopolysaccharide (LPS) after anti-inflammatory treatment with candesartan [31] as well as in other neural paradigms [32, 33].

Anxiety is common in Alzheimer's disease (AD) and Parkinson's disease (PD), particularly in the early stages of these neurodegenerative diseases (NDDs). The prevalence of anxiety symptoms was 52% in a study of 161 subjects with mild cognitive impairment (MCI) [34]. MCI was strongly associated with Generalized Anxiety Disorder in men without depression (odds ratio 9.33, 95% CI 3.24-26.83) in a study of 2,414 community-dwelling elderly [35]. Studies generally indicate that anxiety nearly doubles the risk [36] and increases 1-5-fold the rate [35, 37-39] of MCI conversion to AD though not all studies agree [40]. Anxiety has been associated with accelerated cognitive decline in beta-amyloid (Abeta)-positive preclinical AD [39] and a tripling of Abeta 1-42 and total tau cerebrospinal fluid concentrations in MCI [41]. So, anxiety is common in MCI and there is evidence that it may promote the progression of MCI.

In PD, anxiety is prevalent and among the most common neuropsychiatric conditions present in the early stages of PD. In cross-sectional

studies, anxiety was present in 37.8% of 360 [42], 45% of 342 [43], and 56% of 117 [44] patients with PD using various methods of ascertainment. Formal anxiety disorders were found in 12.8% of 273 male Veteran's Administration (VA) patients with PD [45] and 34% in 342 patients with PD of either sex [43]. In 36 patients with early stage PD, anxiety symptoms exclusive of obsessive compulsive disorder were present in 27% and correlated inversely with MMSE scores and dopaminergic doses, but high somatization and obsessive compulsive scores in 67% and 53%, respectively, raise the possibility of underestimation of anxiety as ascertained in this study by the Symptom Check List 90 Revised (SCL-90-R) scale [46]. Among 292 drug-naive patients with early PD, anxiety was one of six non-motor symptoms in men and one of two in women that distinguished these patients from age-and sex-matched healthy controls [47]. Patients with early stage PD had higher anxiety scores that were associated with orbitofrontal and ventro-lateral prefrontal cortical, occipito-parietal, and striatal volume loss when compared to matched healthy controls [48]. In particular, anxiety has been found to be a predictor of MCI in early stage PD [49, 50]. Thus, anxiety is a common feature in the earliest stages of both AD and PD.

Microglial activation and anxiety appear to be concomitants of early NDD, particularly AD and PD, and microglial activation may contribute to neurodegenerative pathogenesis as well as anxiety in the early stages of AD and PD, as evidenced above. It is therefore possible that activated microglia might induce clinical anxiety by generating proinflammatory molecules that also promote neurodegeneration in AD, PD, or other NDDs. If so, it would then be worthwhile to reduce microglial activation to promote neuroprotection and deter the progression of NDDs beyond their early stages. This may hold particular promise for AD MCI and the pre-motor phase of PD, thereby stemming the devastating cognitive and motor disabilities engendered by these NDDs.

The rationale and advantages of repurposing already-approved drugs for disease-modifying indications for AD, PD, and other NDDs have been previously explained [51-54]. In light of the prevalence of psychiatric features in AD and PD, we have been interested in the neuroprotective potential and effects on neurodegeneration of commonly prescribed psychotropic agents with a view toward their repurpose as NDD neuroprotectants [55-64]. Neuroprotective actions of psychotropics are considerable and should be studied in well-designed prospective randomized controlled trials for their neuroprotective effects since retrospective studies are subjected to confounds that may preclude their elucidation [63].

In AD, research indicates that certain psychotropics exhibit neuroprotective effects on the transcription of genes linked to AD, glycogen synthase kinase-3 (GSK-3), Abeta, tau protein, proteasome, mitochondria, respiratory chain complexes I and IV, production of adenosine triphosphate (ATP), nitric oxide synthase (NOS), reactive oxygen species (ROS), other free radicals, antioxidant enzymes, mitochondrial permeability transition pore, apoptosis, glutamate excitotoxicity, Abeta toxicity, hippocampal neurons, brain derived neurotrophic factor (BDNF), neurogenesis, and other pathophysiological mechanisms [55-59].

In PD, findings reveal that a variety of psychotropics exert neuroprotective effects on H3 histone deacetylase, the transcription of PD risk genes, GSK-3, aSyn, proteasome, mitochondria, respiratory chain complexes I and IV, ATP production, mitochondrial permeability transition pore, NOS, reactive nitrogen species (RNS), ROS, other free radicals, antioxidant enzymes, dopamine autooxidation, mitochondrial permeability transition pore, apoptosis, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity, inflammation, dopamine neurons, trophic factors including glial derived neurotrophic factor (GDNF), BDNF, neurogenesis, and other pathophysiological mechanisms [55-57, 59-62]. Psychotropics that are already government regulatory body-approved, CNS-active and penetrant, intensively studied, and extensively prescribed are an obvious first choice for disease-modifying repurposing.

Here, the preclinical effects of psychotropics on microglial activation in MCI and early PD are considered. The literature of common first-line drugs used to treat common psychiatric disorders was searched for the effects of these psychotropics on microglial activation. The potential of these agents to effect neuroprotection

against the concomitants of microglial activation, the quality of the data, and the next investigative steps to be taken are considered. To the extent that microglial activation appears to play a major role in the progression of early MCI, AD, and PD as detailed above, some of the findings detailed here should be pursued and, when appropriate, advanced to human clinical randomized controlled trials using biomarkers and disease-modification designs (i.e., delayed-start, randomized withdrawal, etc.). The fact that these drugs are already Food and Drug Administration (FDA)-approved removes that barrier and speeds the process of determining their disease-modifying effects [51-54].

## Materials and methods

The literature of the National Library of Medicine PubMed medical literature database up to and including December 1, 2015 was searched. The literature of first-line psychotropics commonly used in treating psychiatric disorders for preclinical and clinical effects on activated microglia was examined using the following search terms: (activated microglia) AND (chlorpromazine OR haloperidol OR fluphenazine OR thioridazine OR thiothixene OR trifluoperazine OR aripiprazole OR asenapine OR clozapine OR iloperidone OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone OR pimavanserin OR tetrabenazine OR carbamazepine OR oxcarbazepine OR lamotrigine OR valproic acid OR lithium OR dextromethorphan OR quinidine OR amitriptyline OR clomipramine OR desipramine OR doxepin OR imipramine OR nortriptyline OR protriptyline OR trimipramine OR maprotiline OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR vilazodone OR duloxetine OR venlafaxine OR desvenlafaxine OR milnacipran OR levomilnacipran OR bupropion OR mirtazapine OR trazodone OR vortioxetine OR cyproheptadine OR diphenhydramine OR hydroxyzine OR alprazolam OR chlorazepate OR chlordiazepoxide OR clonazepam OR diazepam OR flurazepam OR lorazepam OR oxazepam OR temazepam OR buspirone OR zaleplon OR zopiclone OR eszopiclone OR zolpidem OR ramelteon OR modafinil OR armodafinil OR amantadine OR pramipexole OR ropinirole OR rivastigmine OR galantamine OR galanthamine OR tacrine OR donepezil OR memantine OR stimulant OR amphetamine OR lisdexamfetamine OR methylphenidate OR atomoxetine).

This resulted in 184 citations on December 1, 2015. Titles and abstracts of citations were searched for relevance to the intended topic and articles were selected for downloading and review. Relevant studies from this literature are detailed below. Evaluation of findings for acute administration, chronic administration, within model replication, replication in other models, and human trials are also considered.

## Results

There are several methods for activating microglia in experimental paradigms, including exposures to lipopolysaccharide (LPS), gamma-interferon, NMDA antagonists including ketamine and phencyclidine, the Toll-like receptor 2 ligand zymosan, the copper chelator cuprizone, ethanol, and Abeta, employed in the studies below. Drugs related to microglial activation are listed below. Drugs of the original search that produced no search citations are not mentioned.

### Chlorpromazine

Chlorpromazine (2.2 µM) and haloperidol each potently inhibited proton currents, important in generating ROS and perhaps inflammatory cytokines, in microglial BV2 cells studied by the whole-cell patch clamp method [65]. Chlorpromazine (0.2-20 µM) and loxapine (0.2-20) µM each were found to reduce microglial IL-1b and IL-2 secretion in mixed glial cultures activated by LPS [66]. Based only on a single cell culture study involving LPS stimulation, it is possible that chlorpromazine may reduce microglial cytokine release and might therefore have possible potential to reduce microglial activation.

### Haloperidol

In a recent study, haloperidol was administered chronically for 8 weeks via osmotic mini-pump at 2 mg/kg/day and was associated with microglial activation in secondary somatosensory cortex, anterior cingulate cortex, striatum, and hippocampus [67]. Although patch clamp experiments suggest an anti-inflammatory effect on microglia, haloperidol has weakly attenuated microglial activation induced by LPS, gamma-interferon, ketamine, and phencyclidine. Haloperidol (8.4 µM) and chlorpromazine potently inhibited proton currents in microglial

BV2 cells using the whole-cell patch clamp method, suggesting that these antipsychotics may reduce neuroinflammation and microglial activation [65]. However, in mouse N9 microglia activated by LPS, haloperidol did not significantly inhibit the release of nitric oxide (NO), in contrast to inhibition by olanzapine [68]. Similarly, in microglia activated by gamma-interferon, haloperidol was inferior to risperidone in inhibiting NO generation, inducible NOS (iNOS), and inflammatory cytokines including IL-1b, IL-6, and TNFa [69]. In a mixed culture of oligodendrocytes and microglia activated by gamma-interferon, haloperidol failed to suppress apoptosis of oligodendrocytes while aripiprazole and minocycline were effective for their suppression [70]. In rats administered the N-methyl-D-aspartate (NMDA) receptor antagonists ketamine or phencyclidine, haloperidol (1-10 mg/kg) administered intramuscularly (IM) 1 hour before NMDA antagonist treatment failed to prevent microglial activation in the posterior cingulate and retrosplenial cortex [71]. Thus, the evidence suggests that haloperidol is ineffective or, at best, only weakly effective in reducing provoked microglial activation and that haloperidol may actually induce microglial activation when acting by itself.

*Thioridazine*

Thioridazine, an inhibitor of NADPH oxidase-4 (NOX4), attenuated ROS production and glutamate release by rat microglia stimulated by zymosan, indicating possible potential to reduce microglial activation [72].

*Loxapine*

Loxapine 2-20 µM reduced IL-1b and IL-2 secretion in microglial cultures activated by LPS [66], indicating the possibility that loxapine might reduce microglial activation and inflammatory cytokines.

*Aripiprazole*

In microglia activated by interferon-gamma, aripiprazole inhibited NO and TNFa generation and suppressed elevated intracellular calcium concentrations [73]. In a mixed culture of oligodendrocytes and microglia activated by interferon-gamma, aripiprazole and minocycline each suppressed apoptosis of oligodendrocytes, reduced TNFa production from activated

microglia, and attenuated the phosphorylation of signal transducer and activator of transcription 1 (STAT1) in microglia [70]. Thus, aripiprazole reduced TNFa release in two cell culture studies, and NO release in one of these, in microglia stimulated by interferon-gamma, raising the possibility that aripiprazole might also reduce microglial activation, at least in glia exposed to interferon-gamma.

*Clozapine*

In microglial BV2 cells, clozapine 9.8 µM inhibited microglial proton currents, suggesting that clozapine may reduce microglial activation at doses that are therapeutic in schizophrenia [74]. However, in mouse N9 microglia activated by LPS, clozapine did not significantly inhibit the release of NO, in contrast to inhibition by olanzapine [68]. To date, clozapine has not reduced NO release from microglia activated by LPS.

*Olanzapine*

In a recent study, olanzapine administered chronically for 8 weeks via osmotic mini-pump at 10 mg/kg/day led to evidence of microglial activation in secondary somatosensory cortex, anterior cingulate cortex, striatum, and hippocampus [67]. However, in microglial BV2 cells, olanzapine 84 µM inhibited microglial proton currents [74]. In mouse N9 microglia activated by LPS, olanzapine significantly inhibited the release of NO [68]. Single studies suggest that chronic *in vivo* administration of olanzapine itself can activate microglia in brain regions relevant to AD and PD while the drug attenuated microglial NO release in an LPS cell culture model, but both findings need to be replicated within these paradigms and in other models.

*Quetiapine*

Quetiapine and perospirone each inhibited TNFa generation in microglia activated by interferon-gamma [75]. In the mouse experimental allergic encephalomyelitis MS model, quetiapine was found to suppress local microglial activation in the spinal cord [76]. Cuprizone was administered to mice in a model of oligodendroglial white matter pathology in schizophrenia and was found to activate microglia and astrocytes while reducing oligodendrocytes, reversed by treatment with dietary quetiapine

10 mg/kg for 5 weeks [77]. These same findings were replicated after 2 weeks of quetiapine within the same model in the cerebral cortex, corpus callosum, striatum, and hippocampus, along with quetiapine reversal of increased brain TNFa and IL-6 concentrations [78]. Thus, there is preliminary evidence in two different models that quetiapine can reduce microglial activation (including within-model replication in a cuprizone mouse model of schizophrenia) and TNFa concentrations, and this drug should now be studied in AD and PD models involving microglial activation, such as those employing Abeta, MPTP, and aSyn.

*Risperidone*

In microglial BV2 cells, risperidone inhibited microglial proton currents [74]. In microglia activated by gamma-interferon, risperidone inhibited NO generation, iNOS, and inflammatory cytokines including IL-1b, IL-6, and TNFa, indicating an anti-inflammatory effect on activated microglia [69]. Neonatal rats underwent intrahippocampal injection of LPS on postnatal day 7 and were then administered saline, risperidone (0.5 mg/kg), minocycline (40 mg/kg), or both risperidone and minocycline for 14 days beginning on postnatal day 42, finding that each of the active treatment arms rescued behavioral deficits and attenuated microglial activation in comparison to saline controls [79]. Single studies in different models suggest that risperidone may reduce microglial activation in a model of hippocampal LPS exposure and inhibit NO and cytokine production in cell culture, and these findings should now be replicated within these models and in AD and PD models involving microglial activation.

*Ziprasidone*

Ziprasidone inhibited NO generation in microglia activated by interferon-gamma [75], suggesting its possible potential for reducing microglial activation or, at least, NO release.

*Carbamazepine*

In mixed glial cultures of 70% astrocytes and 30% microglia from neonatal Wistar rats, carbamazepine reduced the amount of activated microglia, reduced glial viability, and increased the number of inactivated microglia [80]. Carbamazepine 5-20 μM strongly attenuated

NO and iNOS production by downregulating Akt phosphorylated activation, and reduced cyclooxygenase-2 (COX-2) expression and TNFa concentrations but did not reduce ROS production in BV-2 microglia activated by LPS [81]. If replicated, carbamazepine may have potential as a candidate to reduce microglial activation and NO and TNFa.

*Lamotrigine*

Lamotrigine 10 mg/kg p.o. for 7 days was noted to protect dopaminergic neurons against stereotactic 6-hydroxydopamine injection into the median forebrain bundle by a reduction in the number of activated microglia in Sprague-Dawley rats [82], suggesting lamotrigine may have potential to reduce microglial activation.

*Valproic acid*

In mixed glial cultures of 95% astrocytes and 5% microglia from neonatal Wistar rats, valproate itself substantially increased microglial activation at a variety of doses [80]. However, valproate at 500-1000 μM in mouse BV-2 microglia reduced microglial numbers and induced caspase 3 cleavage and apoptotic figures, suggesting that valproate may reduce microglia-secreted neurotoxins by killing microglia [83]. Valproate 0.6 mM for 48 hours was neuroprotective in a time- and concentration-dependent manner in a primary rat midbrain dopaminergic neuron and glia mixed culture exposed to LPS, mediated by a reduction in microglia and pro-inflammatory NO, ROS, and TNFa released from activated microglia [84]. Valproate suppressed microglial activation, reduced the number of microglia, and inhibited inflammatory markers including iNOS and COX2 while reducing infarct size and neurological deficits in rats sustaining middle cerebral artery occlusion [85]. In hippocampal slices, there is recent evidence that valproate exerted its neuroprotective action via an ATP-related purinergic-dependent activation of microglial P2X7 receptors mediating the release of TNFa [4]. A study in both BV-2 microglia and mouse primary microglial cells found that valproate induced microglial apoptosis through increasing phospho-p38 mitogen-activated protein kinase (MAPK) and subsequent activation of the mitochondrial caspase 3 pathway [86]. In rats with traumatic spinal cord injury due to severe contu-

sions, valproate 100-400 mg/kg IP daily for 7 days reduced microglial activation and local inflammation while increasing acetylated histones, microtubule-associated protein, BDNF, GDNF, and rapidity of recovery [87]. Minipump infusion of valproate treatment for 3 days attenuated microglial accumulation and improved hindlimb locomotion compared to controls in yet another spinal cord injury model [88]. In the APPswe/PS1 exon 9 deletion (APPswe/PS1ΔE9) transgenic mouse model of Alzheimer's disease (AD), valproate administered for 4 weeks at 7 months of age reduced microgliosis, IL-1b, and TNFa concentrations in the hippocampus and cortex, reduced neuronal degeneration and hippocampal p65 NFκB phosphorylation, and enhanced hippocampal acetyl-H3 histone, Bcl-2, and phospho-GSK-3ß concentrations while markedly improving spatial memory and decreasing Abeta deposition [89]. Evidence in multiple models including stroke, spinal cord injury, midbrain dopamine neurons, and an AD transgenic mouse model all indicate valproate-related reductions in activated microglia while it reduced cytokine release in the transgenic mouse model of AD and in rat midbrain microglia stimulated by LPS.

*Lithium*

Lithium, a GSK-3ß inhibitor, did not reduce microglial activation even though cortical caspase 3, apoptosis, and infarct volume were decreased in rats undergoing middle cerebral artery occlusion followed by post-ischemic lithium treatment [90]. However, in organotypic hippocampal slices exposed to LPS, lithium treatment was associated with downregulation of the pro-inflammatory genes iNOS, IL-1b, IL-6, and TNFa and upregulation of anti-inflammatory IL-10 and MRC1 through the inhibition of GSK-3 and enhanced the functional consequences of the microglial adaptive response on oligodendrocyte maturation [91]. In rat glial-enriched cortical cultures, GSK-3ß was expressed in microglia and astrocytes and increased in expression and activity in parallel with pro-inflammatory cytokines upon activation with LPS, whereas lithium chloride reduced LPS-induced cytokine concentrations [92]. Lithium reduced the expression of iNOS and RelA, a component of NFκB, in LPS-activated BV-2 microglia treated with lipoic acid [93]. Pretreatment with lithium, fluvoxamine, rebox-

etine, or imipramine each inhibited NO production in murine 6-3 microglial cells activated by interferon-gamma although, unlike these antidepressants, lithium did not inhibit IL-6 [94]. Lithium blocked ethanol-induced caspase 3 activation, phosphorylated tau increases, caspase-cleaved tau formation, and microglial activation in a developing mouse model of ethanol-induced neurodegeneration after acute administration [95]. In 4-month old APP/PS1ΔE9 transgenic mice, a model of AD, lithium and rosiglitazone for 12 weeks each reduced microglial and astrocytic activation, Abeta aggregates, Abeta oligomers, and Abeta-induced spatial memory impairments [96]. Thus, lithium has reduced microglial activation in an ethanol model in developing mouse brain and in an AD transgenic mouse model, and has reduced microglial NO and cytokine generation in several cell culture models.

*Dextromethorphan*

Dextromethorphan 1-10 μM pretreatment reduced inflammation-mediated degeneration of dopaminergic neurons through inhibition of microglial activation in a dose-dependent manner in rat mesencephalic neuron-glia cultures exposed to LPS [97]. Dextromethorphan pretreatment decreased NOX2 activity in activated microglia and, in vivo, 0.1 mg/kg ip (similar to the therapeutic dose range in humans) inhibited NOX2 expression of presumed microglial origin and decreased monocyte and lymphocyte infiltration, demyelination, and axonal loss of the spinal cord in an experimental autoimmune encephalomyelitis mouse model of MS [98]. Evidence is limited, but a single cell culture study involving mesencephalic dopamine neurons indicated that dextromethorphan inhibited microglial activation and was attended by neuronal preservation.

*Quinidine*

In rats pretreated with quinidine 70 mM, quinidine reduced spinal cord microglial activation as well as thermal hyperalgesia and mechanical allodynia in a spinal nerve ligation-induced peripheral neuropathic pain model [99], and this reduction in microglial activation now needs replication.

*Amitriptyline*

Amitriptyline has been found to be a potent microglial activator and stimulates 5'-nucleotid-

ase activity [100]. On the other hand, amitriptyline and its metabolite nortriptyline inhibited the release of IL-1b and TNF in rat mixed glial cell cultures at therapeutically relevant concentrations, but not in other types of mixed cell cultures [101]. Similarly, in rat microglial cell cultures activated by LPS, amitriptyline reduced IL-1b release at therapeutically relevant concentrations [101]. Amitriptyline 15 mg/hour infusion was associated with upregulated anti-inflammatory interleukin IL-10 concentrations in microgila in morphine treated rats and the drug's anti-inflammatory effects appeared to be mediated by the neuroinflammation-dependent IL-10 - p38MAPK - heme oxygenase-1 oxygenase-1 signaling pathway [102]. Intraperitoneal amitriptyline twice daily for 3 days was found to reduce microglial activation in the spinal dorsal horn of rats undergoing spinal nerve ligation [103]. Amitriptyline itself activated microglia yet, in a rat spinal nerve pain model, acute administration was found to reduce microglial activation, and it reduced IL-1b cytokine release in two different cell culture models.

### Nortriptyline

As mentioned immediately above, there is indirect evidence that nortriptyline might reduce microglial activation since it inhibited the release of IL-1b and TNF in rat mixed glial cell cultures at therapeutically relevant concentrations [101].

### Clomipramine

Clomipramine reduced NO and TNFa production, decreased their messenger ribonucleic acid (mRNA), and attenuated iNOS expression in microglia and astrocyte cultures, was neuroprotective, and, in LPS-activated microglia, inhibited IkappaB (IκB) degradation, nuclear translocation of the p65 subunit of NFκB, and phosphorylation of p38MAPK [104]. This indicates that clomipramine can reduce NO and TNFa production and indirectly suggests its possible potential to reduce microglial activation.

### Imipramine

Pretreatment with imipramine, fluvoxamine, and reboxetine each inhibited NO and IL-6 production in murine 6-3 microglial cells activat-

ed by interferon-gamma [94]. Imipramine reduced NO and TNFa production, decreased their mRNA, and attenuated iNOS expression in microglia and astrocyte cultures, was neuroprotective, and, in LPS-activated microglia, inhibited IkB degradation, nuclear translocation of the p65 subunit of NFκB, and phosphorylation of p38MAPK [104]. This indicates that imipramine can reduce NO (replicated across two studies), IL-6, and TNFa production and indirectly suggests a potential reduction in microglial activation.

### Citalopram

Several classes of antidepressants decreased the release of proinflammatory NO, TNFa, and IL-1b and citalopram and fluoxetine additionally reduced glutamate and D-serine release from primary microglia activated by LPS, with inhibited microglial glutamate and D-serine release leading to prolonged survival of oxygen-glucose deprived primary cortical neurons [105]. Citalopram pretreatment was found to inhibit both mRNA and protein expressions of TNFa and IL-1b as well as phosphorylation of p38-MAPK and c-jun N-terminal kinase (JNK) in BV2 microglial cells that were activated by LPS [106]. These studies indicate reduced production or release of TNFa and IL-1b in two different models and indirectly suggest that citalopram may have the potential to reduce microglial activation.

### Escitalopram

Escitalopram and fluoxetine were each found to inhibit mRNA and protein levels of inflammatory cytokines and upregulate anti-inflammatory cytokines in both activated mouse primary microglia and activated murine BV2 microglia [107], indirectly suggesting that escitalopram may hold promise for reducing microglial activation.

### Fluoxetine

In a study carried out in BV2 microglia, 1 μM fluoxetine itself increased IL-6, TNFa, NO production, iNOS (or NOS2) mRNA, NFκB, NFκB DNA binding activity, p38MAPK, and extracellular signal-related kinase (Erk)1/2MAPK [108]. However, in another study employing LPS as a microglial activator, fluoxetine reduced IL-6, TNFa, NO, the mRNA of TNFa, IL-6, and iNOS,

and the degradation of IkB-a, phosphorylation and nuclear translocation of the p65 subunit of NFκB, and phosphorylation of p38MAPK in activated microglia in both primary microglial cultures and BV2 microglial cells [109]. In another investigation of BV2 microglia activated by LPS, fluoxetine reduced IL-1b production, serotonin depletion, and phosphorylation of NFκB and p38MAPK [110]. In yet another study, fluoxetine inhibited mRNA and protein levels of inflammatory cytokines and upregulated anti-inflammatory cytokines in activated murine BV2 microglia and both activated mouse primary microglia [107]. Fluoxetine decreased the release of NO, TNFa, IL-1b, glutamate, and D-serine release from primary microglia activated by LPS, with enhanced neuronal survival in co-cultures resulting from inhibited microglial glutamate and D-serine release [105]. Fluoxetine inhibited IL-6, TNFa, NO, and phosphorylation of NFκB and transforming growth factor-beta-activated kinase 1 (TAK1) through a mechanism of enhanced beta-arrestin 2 with TAK1-binding protein (TAB1) and disrupted TAK1-TAB1 interaction in microglia activated by LPS [111]. In a model of spinal cord injury, fluoxetine 10 mg/kg i.p. daily inhibited microglial activation, associated with reductions in p38-MAPK and caspase 3 activations, oligodendrocyte cell death, axonal loss, and white matter demyelination 5 days post-injury [112]. In mice injected with LPS i.p. and 1 week later treated with fluoxetine 10 mg/kg for 28 days, fluoxetine was associated with reduced hippocampal microglial activation [113]. In LPS-activated microglia, fluoxetine treatment was associated with reduced loss of nigral dopamine neurons and suppression of microglial NADPH oxidase activation, iNOS upregulation, ROS generation, and oxidative stress 7 days after LPS injection into the substantia nigra in rats [114]. The preponderance of cell culture evidence indicates that fluoxetine inhibits NO, ROS, and cytokine production and release by activated microglia including in the substantia nigra, and reduces microglial activation in live animal models, including in the hippocampus after chronic treatment in one such study.

*Fluoxamine*

Pretreatment with fluvoxamine, reboxetine, and imipramine each inhibited NO and IL-6 production in murine 6-3 microglial cells activated by interferon-gamma [94], indirectly suggesting that fluvoxamine might potentially reduce microglial activation.

*Paroxetine*

Paroxetine and sertraline each inhibited NO and TNFa generation as well as elevations of intracellular ionized calcium, critical for the release of cytokines and NO from activated microglia, in 6-3 microglia activated by interferon-gamma [115]. Paroxetine pretreatment was found to inhibit IL-1b, TNFa, NO, and iNOS production, mRNA expressions of IL-1b and TNFa, JNK1/2 activation, and neurotoxicity, but not ERK1/2 activity, p38, or p65/NFκB, in both BV2 and primary microglial cells activated by LPS [116]. Paroxetine has also been documented to inhibit L-glutamate release from activated microglia, which, as a result, reduced the down-regulation of astrocyte L-glutamate transporters, thereby neuroprotectively decreasing ambient glutamate levels that might otherwise be neurotoxic [117]. In a study of rodent microglial cells that were pretreated with BDNF, paroxetine and sertraline each potentiated BDNF-induced increases in ionized calcium [118]. The evidence is thin, but two studies in 3 microglial cell lines indicate that paroxetine shuts down the production of NO and TNFa, although it remains to be demonstrated that this drug reduces microglial activation itself.

*Sertraline*

Sertraline inhibited NO and TNFa generation and elevations of intracellular ionized calcium, critical for cytokine and NO release from activated microglia, in 6-3 microglia activated by interferon-gamma [115]. In contrast, sertraline potentiated ionized calcium increases in rodent microglial cells pretreated with BDNF [118]. Evidence is at present limited to a single study indicating that sertraline reduces NO and TNFa production.

*Venlafaxine*

Venlafaxine reduced numbers of microglia, IL-6 and interferon-gamma release, and microglial activation in astroglia and microglia co-cultures [119]. Thus, evidence is limited to a single study showing reduction in microglial activation and cytokine release.

*Bupropion*

Bupropion 10 mg/kg pretreatment 30 minutes before kainic acid i.p. injection attenuated kainate-induced microglial activation, ERK1/2 phosphorylation, and neuronal cell death in the hippocampal CA3 region in a kainic acid-induced seizure model in rats [120], indicating reduction of hippocampal microglial activation in a single study.

*Clonazepam*

Clonazepam, diazepam, and the peripheral benzodiazepine receptor/translocator protein 18 kilo-Dalton (PBR/TSPO) ligand PK11195 each inhibited the release of NO and the benzodiazepines inhibited the proliferation and release of TNFa from microglia activated by LPS [121], indirectly suggesting that these drugs might potentially also reduce microglial, albeit in a single study.

*Diazepam*

Diazepam inhibited the release of TNFa and NO from microglia activated by LPS [121]. Co-administration of diazepam with allopregnanolone was noted to synergistically reduce microglial activation albeit in a tetramethylenedisulfotetramine model of epilepsy [122]. Preliminary evidence from single studies suggests that diazepam may reduce microglial activation and NO and cytokine release.

*Amantadine*

Amantadine inhibited the release of pro-inflammatory factors from microglia, increased the expression of neurotrophic factors such as GDNF from astrocytes, and protected dopaminergic neurons in mixed cell cultures exposed to either LPS or the neurotoxin MPTP [123]. Thus, a single cell culture study in two different models indicates that amantadine can inhibit the release of microglial cytokines.

*Pramipexole*

Microglia have recently been found to express D1-5 dopamine receptors and the D2/D3 agonist pramipexole enhanced NO secretion by cultured microglia subjected to proinflammatory stimuli [124], indicating a possibility that this drug might also activate microglia via D2 stimulation.

*Methylphenidate*

Methylphenidate 10 mg/kg induced microglial activation and enhanced sensitivity of dopaminergic neurons to MPTP in the substantia nigra pars compacta with chronic administration, and increased IL-6 and TNFa mRNA levels in the striatum with acute but not chronic dosing [125]. Thus, a single study indicates that methylphenidate can increase microglial activation and cytokine release in the substantia nigra with chronic dosing, of potential relevance to PD.

*Donepezil*

Donepezil decreased the microglial release of IL-1b, TNFa, NO, and PGE2 and reduced the upregulation of iNOS and COX-2 and diminished p38MAPK phosphorylation and NFκB translocation in microglia activated by Abeta oligomers [126]. In primary hippocampal cells, donepezil suppressed activated microglia-mediated toxicity [126]. In addition, donepezil 2 mg/kg/day for 5 days inhibited microgliosis and astrogliosis in mice injected intrahippocampally with Abeta oligomers [126]. In APP/PS1 transgenic mice chronically treated with donepezil (0.5-2.0 mg/kg/day for 4 weeks), improved object recognition and Morris water maze performance was related to inhibited microglial activation and reduced IL-1b and TNFa [127]. In single studies, donepezil diminished cytokine release provoked by Abeta oligomers in cell culture and, when administered acutely, reduced hippocampal microgliosis while chronic administration inhibited microglial activation and cytokine release in an AD transgenic mouse.

*Galantamine*

In a model of HIV-associated dementia, galantamine and nicotine pretreatment each attenuated TNFa and NO release through a mechanism involving the alpha7 nicotinic cholinergic receptor and p44/42 MAPK system in microglia activated by exposure to both interferon-gamma and the HIV-1 coat glycoprotein gp120 [128]. Thus, a single study demonstrated that galantamine reduced NO and TNFa release in an HIV model.

*Memantine*

Memantine 10 mg/kg/day intraventricularly for 28 days (plasma levels similar to therapeutic doses in humans) reduced microglial activation and improved hippocampal-dependent spatial memory impairments in rats undergoing chronic intraventicular LPS infusions [129]. In a study of APPswe/PS1 transgenic mouse retina, memantine reduced activated microglia and ERK1/2 phosphorylation after 10 mg/kg/day for 8 days [130]. In single studies, memantine reduced microglial activation after acute administration in an AD transgenic mouse and after chronic administration in rats receiving intraventricular LPS infusions.

**Discussion**

As detailed in the Introduction, microglial activation occurs early in the neuropathological course of AD and PD and correlates with anxiety. Activated microglia release proinflammatory cytokines including IL-1b, IL-2, IL-6, IL-18, TNFa, and other molecules that mediate neuroinflammation, activate other microglia, and also may produce anxiety symptoms that are especially prominent in early AD and PD. In AD, microglial activation correlates positively with Abeta and negatively with cerebral glucose metabolism and MMSE scores. In PD, midbrain microglial activation correlates positively with contralateral motor signs and overall motor severity in early stage PD and negatively with dopamine transporters in the putamen. In addition to its induction by cytokines, anxiety robustly correlates positively with microglial activation in animal models. Thus, microglial activation appears to be a correlate that may significantly drive both anxiety and the early pathogenesis of AD and PD. The current state of the data offers some replicated findings and a number of tantalizing as of yet un-replicated findings that are potentially relevant to AD MCI and early stage PD, deserving of further investigation.

For reducing microglial activation, the most promising *replicated* findings are for quetiapine, valproate, lithium, fluoxetine, donepezil, and memantine. For the inhibition of cytokine and other toxic inflammogen release, the most promising replicated findings are for quetiapine, aripiprazole, valproate, amitriptyline, imipramine, fluoxetine, paroxetine, donepezil, and amantadine. Further studies are needed, however, and the effects of these drugs on microglia have not yet been studied in humans, let alone in human MCI of AD and early PD. Of note in PD, *un-replicated* findings of *increased* microglial toxic NO secretion with pramipexole and *increased* microglial activation and cytokine release with methylphenidate signal caution and urge replication.

*Replicated findings for inhibiting microglial activation and microglial cytokine release by psychotropic class*

Among antipsychotics, replicated findings include quetiapine reduction of microglial activation (replicated within the same cuprizone model of schizophrenia and in a spinal cord model of experimental allergic encephalomyelitis) and aripiprazole inhibition of microglial TNF release (in two cell culture studies after interferon-gamma activation). The single findings observed for other antipsychotics remain to be replicated both within and across models. If the salutary hippocampal and striatal quetiapine findings can be replicated with chronic administration in AD or PD models, such as those employing Abeta, MPTP, and aSyn, followed by *in vivo* studies in AD and PD animal models under chronic treatment, this drug might then be studied in early human AD and PD, diseases in which it is already in clinical use in later stages. Such human clinical trials should employ PET biomarkers of microglial activation, such as the TSPO receptor ligands PK11195, Ro5-4864, or newer ligands [131]. The next steps for the development of aripiprazole as a potential neuroprotectant in AD and PD might include replication of the cell culture findings (inhibited TNF release) and observations on microglial activation itself in preclinical AD and PD live animal models undergoing chronic treatment.

For mood stabilizers, while single studies are mildly encouraging for carbamazepine and lamotrigine, replicated findings exist only for valproate and lithium. Valproate has reduced microglial activation in a midbrain dopamine neuron and glia mixed cell culture and in several live animal models including the AD APPswe/PS1ΔE9 transgenic mouse, stroke, and spinal cord injury although only the AD model involved chronic dosing, and it has also reduced cytokine release in the cell culture and

transgenic mouse models. Similarly, lithium reduced microglial activation in the AD APPswe/PS1ΔE9 transgenic mouse and an ethanol developing mouse brain model, however only the AD model employed chronic treatment. The next steps in developing these drugs as potential neuroprotectants should involve replicating reduced microglial activation and cytokine release with chronic valproate and lithium treatments in PD and additional AD models, as well as the needed within-model replications of each of these findings.

Single findings for dextromethorphan (reduced microglial activation in mesencephalic dopaminergic cell culture and reduced NOX2 expression in a mouse MS model) and quinidine (reduced microglial activation in a rat neuropathic pain model) await replication.

Replicated findings for tricyclic antidepressants, including amitriptyline reduction of IL-1b release and imipramine reduction of NO production in microglial cultures, now await within-model replication and extension to AD and PD animal models undergoing chronic treatment.

SSRI antidepressants with replicated findings include fluoxetine and paroxetine. Fluoxetine reduced microglial activation in two different *in vivo* models including hippocampal microglial activation after chronic 4-week treatment in one study, and reduced IL-1b, IL-6, TNFa, and NO concentrations in two different microglial cell line models activated by LPS as well as in an *in vivo* study in mouse substantia nigra. Similarly, for paroxetine, evidence in 3 different microglial cell lines activated by either interferon-gamma or LPS reveal the inhibition of NO and TNFa. The microglial activation findings for fluoxetine and the NO and TNFa findings for paroxetine still await within-model replications and these and the fluoxetine cytokine findings should now be studied in other models, especially AD and PD models involving chronic treatment. The encouraging single un-replicated findings for these drugs and the other SSRIs await replication.

There were no replicated findings for benzodiazepines, with single un-replicated salutary findings only for diazepam and clonazepam.

There were no replicated findings for the anti-apathy agents pramipexole and methylpheni-

date but amantadine inhibited the release of microglial pro-inflammatory factors and protected dopamine neurons in mixed cell cultures that were exposed to either LPS or MPTP, indicating across-model replication. The next steps in developing amantadine as a potential neuroprotectant include within-model replication and extension to AD and PD animal models with chronic treatment.

Donepezil reduced IL-1b and TNFa in a hippocampal cell culture exposed to Abeta oligomers and the APP/PS1 transgenic mouse model of AD, and reduced microglial activation in the transgenic mouse after *chronic* treatment as well as in mice injected with intrahippocampal Abeta oligomers after *acute* treatment. These findings for donepezil now need within-model replication and to be studied further in other animal models of AD and PD under chronic treatment. Single findings for galantamine, reduced TNFa and NO release, await replication.

Memantine reduced microglial activation after acute administration in an AD transgenic mouse and after chronic administration in rats receiving intraventricular LPS infusions. This finding, as well as cytokine release, should now be studied in other AD and PD animal models during chronic administration of memantine.

It will be important to study these drugs in AD and PD models since, in contrast to their salutary findings in studies using microglial activators (e.g., LPS, interferon-gamma, Abeta), some drugs (i.e., valproate, amitriptyline, and fluoxetine) have actually activated microglia when administered in isolation (i.e., in the absence of these exogenous microglial activators) while effects in this regard appear to be still unstudied for the other drugs with replicated findings. It also remains an open question whether these preclinical findings will translate to the inhibition of microglial activation or cytokine release in human patients with MCI and early PD.

*Findings particularly relevant to AD*

In AD-relevant models, single un-replicated findings suggest that risperidone, valproate, lithium, fluoxetine, bupropion, donepezil, and memantine may reduce microglial activation. Risperidone for 14 days was effective in reducing microglial activation and rescuing behavior-

al deficits in neonatal rats receiving intrahippo-campal injections of LPS [79]. *Chronic* valproate treatment for 4 weeks was associated with diminished hippocampal and cortical microgliosis, IL-1b and TNFa concentrations, Abeta deposition, and neuronal degeneration while markedly improving spatial memory in adult APPswe/PS1ΔE9 transgenic mice [89]. *Chronic* lithium treatment for 12 weeks also correlated with reduced microglial and astrocytic activation, Abeta oligomers, Abeta aggregates, and spatial memory impairments in 4-month old APP/PS1ΔE9 transgenic mice [96]. Though in mice previously injected with LPS, *chronic* fluoxetine treatment for 28 days was associated with reduced hippocampal microglial activation [113]. Though in a kainate-induced seizure model, bupropion pretreatment was associated with attenuated microglial activation and neuronal cell death in the hippocampal CA3 region in rats [120]. Donepezil was linked to decreased release of IL-1b, TNFa, and NO and upregulation of COX-2 in microglia activated by Abeta oligomers, as well as the suppression of activated microglia-mediated toxicity in primary hippocampal cells [126]. Donepezil administered for 5 days inhibited microgliosis and astrogliosis in mice injected intrahippocampally with Abeta oligomers [126]. In *chronically* treated APP/PS1 transgenic mice, donepezil for 4 weeks was found to inhibit microglial activation and IL-1b and TNFa release that was correlated with improved object recognition and maze performance [127]. Memantine reduced activated microglia in the retina after 8 days treatment in APPswe/PS1 mice [130]. Although in an intraventricular LPS infusion rat model, *chronic* memantine at human therapeutic plasma levels for 28 days reduced microglial activation and improved hippocampal-dependent spatial memory deficits. Each of these findings should now be replicated within their respective models, replicated in AD transgenic mouse models undergoing *chronic* treatment with the psychotropic, and, if confirmed, then observed for in clinical trials of patients with MCI, simultaneously following study subjects by PET measures of microglial activation (e.g., PK11195, Ro5-4864). While fluoxetine and bupropion may be indicated for anxiety and depression in MCI, it may be more difficult to clinically justify the use of risperidone, lithium, valproate, or memantine in MCI. Given some salutary findings for donepezil in MCI (see below), further

such trials will be more informative if accompanied by PET markers of microglial activation.

Concerning drugs with replicated evidence of inhibition of microglial activation in models that are not specific to AD or MCI, lithium and donepezil have some evidence for *clinical* utility in MCI while there do not appear to be any published trials (www.ncbi.nlm.nih.gov/pubmed) or trials in progress (https://clinicaltrials.gov) of quetiapine, valproate, fluoxetine, or memantine in MCI that are not complicated by the coadministration of other drugs. Similarly, there are no published trials for risperidone or bupropion, with single as yet un-replicated positive findings in AD-relevant models. A single 12-month randomized placebo-controlled trial of lithium in amnestic MCI found ADAS-Cog and attentional tasks to improve, along with reduced cerebrospinal fluid phospho-tau concentrations with lithium treatment [132]. Three randomized double-blind placebo controlled trials failed to demonstrate significant effects of donepezil on primary outcomes over 24 weeks [133], 48 weeks [134], and 3 years [135], although the ADAS-Cog13 had deteriorated less at 24 weeks [133] and 48 weeks [134] on donepezil, and the rate of progression was slower over the initial 12 months on donepezil [135]. In a secondary analysis of subjects with depression from the 3-year study, those with MCI and depression on the Beck Depression Inventory progressed more slowly to AD with donepezil than placebo over the first couple of years [136]. In a sub-study of the 48-week trial, although hippocampal volume was not different between treatment groups, total brain volume, cortical region volume, and ventricular volumes were significantly less atrophic in the donepezil group at 48 weeks [137]. Recently, a French double-blind, placebo-controlled, randomized trial of donepezil found a 45% reduction in the rate of hippocampal atrophy at 1 year with donepezil in 174 subjects with suspected prodromal AD [138]. These secondary findings lend construct validity to the potential of at least mild utility of drugs that inhibit microglial activation in reducing MCI progression.

*Findings particularly relevant to PD*

In PD-relevant models, only amantadine had replicated findings in two different cell culture models. Amantadine inhibited the release of

pro-inflammatory factors from microglia, increased the expression of neurotrophic factors such as GDNF from astrocytes, and protected dopaminergic neurons in mixed cell cultures exposed to either LPS or MPTP [123]. Single unreplicated findings indicate lamotrigine-related reduced microglal activation and the associations of valproate, dextromethorphan, and fluoxetine with the attenuation of microglial cytokines and free inflammogens, and possibly, microglial activation, whereas pramipexole might promote, and methylphenidate induce, microglial activation. Valproate protected rat midbrain dopaminergic neurons, reduced microglial NO, ROS, and TNFa release, and depleted microglial numbers in mixed cultures of primary rat midbrain dopaminergic neurons and glia exposed to LPS [84]. Dextromethorphan 1-10 µM dose-dependently diminished microglial activation and inflammation-mediated degeneration of dopaminergic neurons in rat mesencephalic neuron-glia cultures exposed to LPS [97]. Fluoxetine reduced the loss of nigral dopamine neurons and suppressed microglial NADPH oxidase activation, iNOS upregulation, ROS generation, and oxidative stress 7 days after LPS injection into the substantia nigra in rats [114]. Replication of these findings for valproate, dextromethorphan, fluoxetine, and amantadine within their respective models and validation and replication in MPTP and other PD models undergoing *chronic* treatment is now needed, as well as observations in clinical trials of patients with early PD where fluoxetine and amantadine may be indicated, preferably with PET markers of microglial activation. While fluoxetine and amantadine are clinically useful in early PD, it may be more difficult to clinically justify the use of dextromethorphan and valproate at this stage of illness.

In contrast, pramipexole increased NO secretion by cultured microglia subjected to proinflammatory stimuli, possibly mediated through dopamine D2 receptors [124]. Similarly, methylphenidate also induced microglial activation and enhanced sensitivity of dopaminergic neurons to MPTP in the substantia nigra pars compacta after *chronic* administration [125]. It may turn out that pramipexole does actually hasten progression selectively in *early* PD in contrast to its neuroprotective properties in *later stages* of PD, and that methylphenidate might best be

avoided in *early* PD, especially since apathy and hypotension are uncommon in this stage. However, these single findings must first be replicated both within and across models and, clinical trials of pramipexole in early PD (see below) have, so far, not demonstrated hastened progression.

Except for pramipexole, relevant *clinical* studies in early PD among published trials (www.ncbi.nlm.nih.gov/pubmed) or trials in progress (https://clinicaltrials.gov) were not apparent for drugs with replicated evidence of inhibiting microglial activation in models not specific to AD or MCI (quetiapine, valproate, lithium, fluoxetine, donepezil, and memantine), amantadine, or those with single, as yet un-replicated findings in models relevant to PD (valproate, dextromethorphan, fluoxetine, pramipexole, methylphenidate). For pramipexole, all potentially relevant studies in early PD in ClinicalTrials.gov have either been completed or terminated. Of published studies, 301 subjects with early PD and treated initially with pramipexole developed less levodopa motor complications than those treated initially with levodopa although the latter group had greater improvement in UPDRS score, and in 82 of these subjects evaluated by 123 2-beta-carboxymethoxy-3-beta-(4-iodophenyl)tropane (beta-CIT) uptake on single photon emission computed tomography (SPECT) imaging of the dopamine transporter, those begun on pramipexole showed less decline in the transporter than those initiated on levodopa over 23.5 months [139]. At 48-month follow-up however, initial treatment with pramipexole was associated with a higher incidence of freezing than with levodopa, whereas initial treatment with levodopa continued to be associated with greater incidences of dyskinesia and wearing off phenomena [140]. Over a 46-month follow-up period after initial treatment in this study, beta-CIT rates of dopamine transporter decrement were calculated as 7.1% (S.D. 9.0%) at 22 months, 10.9% (11.8%) at 34 months, and 16.0% (13.3%) for pramipexole versus 13.5% (9.6%), 19.6% (12.4%), and 25.5% (14.1%) for respective time points for levodopa [141]. However, in the PROUD study, a 15 month randomized double-blind, placebo-controlled, 6-9 month delayed-start investigation in 535 patients with early PD, initial treatment with pramipexole showed no significant differences from delayed-start pramipexole in

either UPDRS or striatal (123)I-FP-CIT imaging of the dopamine transporter (-15.1% initial vs. -14.6% delayed pramipexole treatment) in this sample where 58% had Hoehn and Yahr stage I disease and 42% had stage II in the initial treatment group, compared to 62% and 38% in the delayed treatment group [142]. One wonders if limiting enrollment to stage I disease, longer delay in treatment, or more protracted follow-up might produce a significant difference, but despite the group initially receiving pramipexole experiencing more freezing, there are no statistically significant findings at this point to evidence a faster progression of early PD with pramipexole.

*Investigating inhibited microglial activation in early neurodegenerative diseases*

As discussed above, inhibition of microglial activation is most likely to yield therapeutic results selectively in *early* neurodegenerative disease, at least in AD and PD. Upon consistent replication of therapeutic effects across AD models, clinical trials should utlimately be considered in subjects who are at risk to develop Alzheimer's, including amnestic MCI [143] and preclinical AD [144]. Patients with impairment in episodic memory attended by either low CSF Abeta-42 or elevated Abeta binding in brain on PET, coupled with elevated CSF total tau or phosphorylated tau might be selected for clinical trials in *amnestic MCI* [143]. For even earlier *preclinical AD*, patients with the same biomarkers but lacking current evidence of cognitive or behavioral impairment might constitute the best samples [144]. For prodromal PD, study patients might be selected by markers such as a history of REM behavior disorder along with dopaminergic abnormalities on PET or SPECT, substantia nigra hyperechogenicity, and olfactory loss [145]. Although evidence of microglial activation in anxiety and depression is presently only indirect, it might be possible to increase the chances of finding a difference with treatment by using anxiety as an inclusion criterion. Similarly, depression has also been related to microglia and is a prodromal feature or risk factor for AD [146] and PD [147, 148], suggesting the possibility that adding depression as an inclusion criterion might also enhance the possibility of finding a difference between treatment groups. In addition to AD and PD, microglial activation has been observed

in early frontotemporal dementia [149], progressive supranuclear palsy [150, 151], corticobasal degeneration [150], and multiple system atrophy [152-154]. As previously mentioned, clinical investigations into the capacity of inhibitors of microglia activation to afford neuroprotection in early neurodegenerative diseases should take advantage of disease-modifying methodological design coupled with TSPO PET ligands [131]. Further study of the suppression of microglial activation using selected psychotropics will establish their suitability for study in human disease, whereupon clinical trials including some of the above methodological features can be commenced.

*Limitations*

This review is subject to the limitations of a literature review including reporting biases and indexing irregularities. Not all relevant articles are necessarily indexed in the PubMed database, and not all relevant articles are appropriately indexed. The most inclusive search strategy was used although there is always the likelihood that a search strategy will miss some relevant citations. Most of the activated microglial data are from cell culture or acutely treated animal models, and few of these studies involve paradigms specifically pertinent to AD or PD. There is a paucity of studies involving chronic administration of psychotropics, especially in animal models of AD or PD. Some psychotropics have been demonstrated to promote microglial activation or cytokine release when administered alone, in contrast to their effects in models using exogenous microglial activating agents, necessitating the study of these drugs in AD and PD models to determine whether they will actually be beneficial as applied to these diseases. Further, findings from studies in animal models of AD and PD do not necessarily translate to humans or to the human diseases of AD and PD. Even if they do, such findings may or may not translate to the very *early* stages of AD and PD. These limitations notwithstanding, the findings reviewed above offer some tantalizing leads meriting further investigation with a view toward slowing AD and PD in their earliest stages.

**Conclusions**

Recent research indicates that Abeta and aSyn, or factors related to these proteins, serve

to activate microglia in AD and PD. Microglial activation correlates with and probably mediates neurodegeneration as well as anxiety in the early stages of both AD and PD. Some of the psychotropics identified in this review that appear to reduce microglial activation or microglial cytokine release already have clinical utilities in treating AD and PD, including anxiety, and the potential to simultaneously treat both clinical features and underlying pathobiology is certainly attractive. While repurposing psychotropics as neuroprotectants in early disease is appealing, and the early findings for certain psychotropics are encouraging, much further investigation into their microglial effects is needed, particularly in models relevant to AD and PD.

### Disclosure of conflict of interest

The author serves as a Consultant and Speaker for Otsuka America Pharmaceutical, Inc. and owns 101 shares of Pfizer Inc. with a value of less than $3500.00.

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