● INVITED REVIEW

Six psychotropics for pre-symptomatic & early Alzheimer's (MCI), Parkinson's, and Huntington's disease modification

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Abstract

The quest for neuroprotective drugs to slow the progression of neurodegenerative diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), has been largely unrewarding. Preclinical evidence suggests that repurposing quetiapine, lithium, valproate, fluoxetine, donepezil, and memantine for early and pre-symptomatic disease-modification in NDDs may be promising and can spare regulatory barriers. The literature of these psychotropics in early stage and pre-symptomatic AD, PD, and HD is reviewed and propitious findings follow. Mild cognitive impairment (MCI) phase of AD: salutary human randomized controlled trial findings for low-dose lithium and, in selected patients, donepezil await replication. Pre-symptomatic AD: human epidemiological data indicate that lithium reduces AD risk. Animal model studies (AMS) reveal encouraging results for quetiapine, lithium, donepezil, and memantine. Early PD: valproate AMS findings show promise. Pre-symptomatic PD: lithium and valproate AMS findings are encouraging. Early HD: uncontrolled clinical data indicate non-progression with lithium, fluoxetine, donepezil, and memantine. Pre-symptomatic HD: lithium and valproate are auspicious in AMS. Many other promising findings awaiting replication (valproate in MCI; lithium, valproate, fluoxetine in pre-symptomatic AD; lithium in early PD; lithium, valproate, fluoxetine in pre-symptomatic PD; donepezil in early HD; lithium, fluoxetine, memantine in pre-symptomatic HD) are reviewed. Dose- and stage-dependent effects are considered. Suggestions for signal-enhancement in human trials are provided for each NDD stage.

Key Words: drug repositioning; neuroprotective agents; psychotropic drugs; neurodegenerative diseases; mild cognitive impairment; humans; animals; animal models

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Introduction

Disease modification remains elusive in neurodegenerative diseases (NDDs), including Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases. Successful interventions will be more likely made in early NDD stages, such as the mild cognitive impairment (MCI) phase of AD or, ultimately, even before clinical symptoms emerge. Pathogenic proteins, *e.g.*, beta-amyloid (Aβ) in AD, hyperphosphorylated tau in AD and tauopathies, alpha-synuclein (αSyn) in PD, and mutant huntingtin (HTT) in HD can be present years in advance of clinically-apparent disease. Although an over-simplification, these proteins can incite microglial activation and inflammation, generating and releasing free radicals and pro-inflammatory cytokines, promoting further pathogenic protein production. If not sufficiently disposed of by the proteasome or autophagy, proteins accumulate, triggering a neurodegenerative cascade including further inflammation, proteasomal and autophagic failure, mitochondrial membrane depolarization, mitochondrial transition pore development, and mitochondrial demise, releasing free radicals and cytochrome c, in turn inducing neuronal apoptosis. Neu-

ropsychiatric disorders, often present in the early stages of NDDs (Lauterbach, 2016), may clinically indicate psychiatric drugs (psychotropics) that simultaneously have therapeutic effects on the neurodegenerative cascade (**Figures 1**, **2**). These psychotropics are already approved by regulatory agencies. Repurposing them as NDD-modifying drugs spare regulatory and other barriers to development. This review considers existing data and the potential for six psychotropics in preventing or modifying the early course of several major NDDs.

Selected findings from neuroprotective studies of psychotropics are provided in **Tables 1–3**, indicating a basis for considering these drugs as disease prevention or modification candidates in prodromal and early NDDs. Together, the findings suggest disease-modifying potential in AD (quetiapine, valproate, lithium, valproate plus lithium, fluoxetine, donepezil, memantine), PD (quetiapine, valproate, lithium, fluoxetine), multiple system atrophy (MSA; quetiapine, valproate), frontotemporal dementia (FTD; lithium, fluoxetine), FTD with parkinsonism linked to chromosome 17 (FTDP-17; lithium), amyotrophic lateral sclerosis (ALS; lithium, valproate plus lithium, fluoxetine),

and HD (quetiapine, valproate, lithium, valproate plus lithium, fluoxetine), perhaps with differential efficacies at different NDD stages.

Preclinical animal and human clinical literature of the six most robust psychotropic attenuators of microglial activation in early NDD (Lauterbach, 2016), quetiapine, lithium, valproate, fluoxetine, donepezil, and memantine, in early-stage and pre-symptomatic AD (MCI stage), PD, and HD are reviewed here.

The literature of psychotropic trials administered *in vivo* in NDD preclinical animal and clinical investigations was reviewed from the perspective of disease-modification and disease-prevention in the early and pre-symptomatic stages of NDDs recorded in the NLM PubMed database for the six drugs and three diseases of interest. Studies were limited to those judged to consider a single psychotropic commenced during pre-symptomatic or very early model pathology, excluding studies involving multiple drugs where the effects of the psychotropic of interest could not be disentangled from other drugs. Studies and models where the stage of illness was ambiguous or uncertain were not included. Tauopathies and synucleinopathies other than PD are beyond the scope of this review and also tended not to distinguish early from late stage disease. All references to MCI apply specifically to the MCI of AD. Double-blind, placebo-controlled, randomized clinical trials are designated as "DBPCRCT."

Disease-Modification Potential in MCI of AD
Quetiapine
Although frequently prescribed in AD, quetiapine has not been studied in MCI. Quetiapine's antidepressant and anxiolytic properties are particularly germane to MCI but somnolence, cognitive impairment, and dose-related mortality risk in advanced AD that may diminish with increasing treatment duration (Schneider et al., 2005; Piersanti et al., 2014) but is unknown in MCI might be minimized by doses lower than those required for agitation and psychosis, absent in MCI.

Lithium
In APPSwe/PS1 amyloidopathic transgenic AD mice treated with lithium (0.65 ± 0.02 mM serum level) from 10 months of age (MCI stage) for 3 months, lithium treatment was associated with decreased APP gamma cleavage, Aβ, plaques, and autophagy and improved spatial learning and memory (Zhang et al., 2011). In contrast to a PCRCT of lithium 0.5–0.8 mM with negative findings in mild AD (Hampel et al., 2009), a 12-month DBPCRCT in amnestic MCI (aMCI) involving lithium 0.25–0.5 mM ($n = 45$; placebo $n = 24$) demonstrated better performance on the AD Assessment Scale-Cognitive subscale (ADAS-Cog) and attention tasks and a reduction in cerebrospinal fluid (CSF) phosphorylated tau (Forlenza et al., 2011) on lithium compared to placebo, suggesting that low-dose lithium may induce disease modification in MCI.

Micro-dose lithium 0.25 mg/kg/d in drinking water (0.006 mEq/kg, serum levels not apparent) was administered to 10-month old late MCI stage AD Cg-Tg (PDG-FB-APPSwInd) amyloidopathic transgenic mice for 8 months, with lithium-treated transgenic mice demonstrating preservation of spatial and aversive stimulus recall but lithium did not prevent senile plaque development or prefrontal cortical or hippocampal dentate neuronal loss (Nunes et al., 2015). This contrasts with neuroprotection evident when lithium was administered pre-symptomatically (see below). Interestingly, in advanced AD, this same group conducted a 15-month DB-PCRCT of 300 micrograms of lithium daily in 113 patients, finding a significant lack of deterioration with active treatment (-0.78 ± 0.9 *vs.* placebo 3.37 ± 1.33), with differences becoming significant by 3 months of treatment (Nunes et al., 2013).

Single findings of low-dose lithium in human patients and micro-dose lithium in transgenic mice await replication and mechanistic discovery before undertaking larger, well-designed, disease-modifying RCTs in MCI at these dose ranges.

Valproate
In APP23 amyloidopathic transgenic AD mice, valproate begun at 7 months of age produced a four-fold reduction in neuritic plaques after 1 and 2 months treatment, partially preserving spatial memory whereas later treatment reduced plaques significantly less, indicating a disease-modifying benefit of early treatment (Qing et al., 2008). This finding was replicated in double-transgenic APP23/PS45 amyloidopathic mice at the age of 1 month (Qing et al., 2008). Plaque reduction in these investigations correlated with reductions in Aβ_{40} and Aβ_{42} concentrations linked to gamma-secretase inhibition, related to valproate's inhibition of glycogen synthase kinase-3 beta (GSK-3β; Qing et al., 2008). Two weeks of valproate injections in 6 month-old APPswe/PS1dE9 amyloidopathic transgenic mice nearly completely restored contextual memory in treated mice, possibly through inhibition of histone deacetylases HDAC1, 2, 3, and/or 8 (Kilgore et al., 2010). In 5-month old Tg6799 transgenic AD mice, valproate increased hippocampal nerve growth factor (NGF) concentrations and decreased escape latencies in the Morris water maze paradigm (Noh and Seo, 2014).

These results, indicating the benefit of early treatment, suggest that the lack of slowing of cognitive, behavioral, and functional decline in the human 24-month DBPCRCT in moderately severe AD (Tariot et al., 2011) might have resulted from beginning treatment too late in the disease course, and that disease-modifying trials in MCI or pre-symptomatic AD may be warranted. In this DBPCRCT, greater hippocampal and whole brain atrophy (Fleisher et al., 2011; Tariot et al., 2011), possibly greater cognitive impairment on the Mini-Mental Status Examination (MMSE) not seen in other cognitive testing (Fleisher et al., 2011), and side-effects in the valproate group (Tariot et al., 2011) suggest the study of lower doses in future animal trials and human RCTs.

Fluoxetine
An 8-week fluoxetine DBPCRCT in 58 patients with MCI demonstrated improved MMSE and Wechsler Memory Scale III immediate and delayed logical memory scores, possibly related to hippocampal neurogenesis (Mowla et al., 2007), inviting longer term studies controlling for depression and
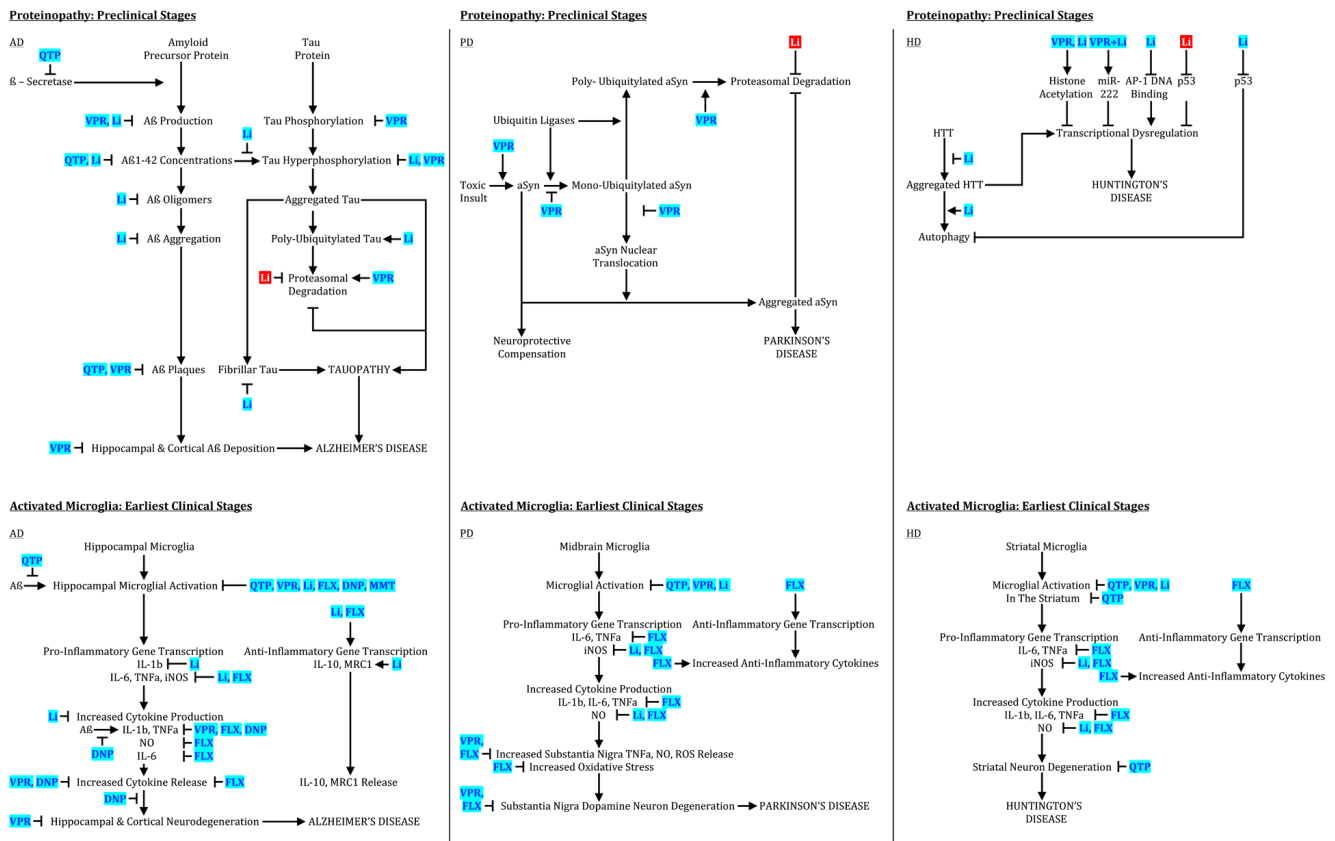
Figure 1 Psychotropic effects on proteinopathy and microglial activation.
The effects of quetiapine (QTP), valproate (VPR), lithium (Li), fluoxetine (FLX), donepezil (DNP), and memantine (MMT) are displayed for specific steps in the proteinopathic process (upper component of figure) and microglial activation (lower component of figure) derived from preclinical models relevant to Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Treatment of the proteinopathy may be best begun in pre-symptomatic disease stages whereas treatment of microglial activation is perhaps best begun in the late pre-symptomatic and earliest clinical stages. Therapeutic effects of psychotropic drugs are indicated by blue text on an aqua background while potentially adverse effects are indicated by white text on a red background. Arrowheads signify upregulation, facilitation, or promotion whereas lines ending in perpendicular bars signify downregulation, inhibition, or reduction. Aβ: Amyloid beta; AP-1: activator protein-1; αSyn: alpha-synuclein; HTT: huntingtin protein; IL: interleukin; iNOS: inducible nitric oxide synthase; miR: microRNA; MRC1: mannose receptor C-type 1; NO: nitric oxide; TNFα: tumor necrosis factor alpha.

employing biomarkers such as hippocampal volumetry or tau and Aβ biomarkers.

Donepezil

A 24-week DBPCRCT of donepezil 10 mg/d in 270 subjects with MCI indicated improvement of secondary efficacy measures (Salloway et al., 2004), but only improved ADAS-Cog scores on 48-week extension (Doody et al., 2009). A larger DBPCRCT in 769 aMCI patients randomized to donepezil 10 mg/d or vitamin E 2,000 I.U./d found reduced progression to AD at 12 months with donepezil but no difference in conversion from MCI to AD after 3 years, suggesting a symptomatic effect without a disease-modifying benefit (vitamin E was also without benefit) (Petersen et al., 2005). A secondary analysis of data from this study indicated that greater depression was associated with MCI conversion to AD and that donepezil reduced this conversion in this depressed group at 1.7 and 2.2 years of treatment (Lu et al., 2009). Another analysis of these data found that carriers of apolipoprotein E ε4 (APOE-ε4) and butyrylcholinesterase K* gene variants displayed an earlier age of AD onset and,

under donepezil treatment, progressed from MCI to AD significantly more slowly at 3 years of treatment (De Beaumont et al., 2016). MRI data from 131 subjects in this same study revealed a non-significant trend for slowing of hippocampal atrophy rates in APOE-ε4 carriers treated with donepezil, but there were otherwise no differences between treatment groups in atrophy of the hippocampus, entorhinal cortex, whole brain, and ventricles (Jack et al., 2008). While annualized hippocampal percentage change did not differ between the groups, MRI findings in a sub-study of the 48-week DBPCRCT involving 193 MCI subjects on donepezil and 199 on placebo revealed reduced decline in total, ventricular, and cortical volumes on donepezil (Schuff et al., 2011). A French 12-month study DBPCRCT in 216 subjects with very early MCI found hippocampal volume declined 45% less ($P < 0.001$) in the donepezil 10 mg/d group (annualized percent change of –1.89%) less than the placebo group (–3.47%) (Dubois et al., 2015) (This study was not sufficiently powered to determine neuropsychological performance). Thus, donepezil has a mild capacity to deter the progression of MCI to AD, but the effect is too small to be advisable as a clinically – meaningful strategy except in certain subgroups.

Figure 2 Psychotropic effects on neurodegeneration, neurogenesis, and behavior.
The effects of quetiapine (QTP), valproate (VPR), lithium (Li), fluoxetine (FLX), donepezil (DNP), and memantine (MMT) are displayed for specific steps in the neuropathic process, derived from preclinical models relevant to Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) regarding both pre-symptomatic and early clinical stages of these diseases. Therapeutic effects of psychotropic drugs are indicated by blue text on an aqua background while potentially adverse effects are indicated by white text on a red background. Arrowheads signify upregulation, facilitation, or promotion whereas lines ending in perpendicular bars signify downregulation, inhibition, or reduction. Aβ: Amyloid beta; APP: amyloid precursor protein; BDNF: brain derived neurotrophic factor; PS1: presenilin 1; RNS: reactive nitrogen species; ROS: reactive oxygen species.

Memantine

Nine month-old 3xTg amyloidopathic/tauopathic triple transgenic AD mice in the MCI stage were treated with memantine for 3 months at human-equivalent doses, resulting in improvements in cognitive impairment and tended to reduce insoluble Aβ, Aβ dodecamers, prefibrillar soluble Aβ oligomers, fibrillar Aβ oligomers, total tau, hyperphosphorylated tau, and cognitive decline in the mild pathology group but, interestingly, achieved robust statistical significance only in advanced AD stage animals (Martinez-Coria et al., 2010). A 2-year DBPCRCT involving memantine plus galantamine in MCI was halted due to galantamine safety concerns, yielding no disease-modifying data (Peters et al., 2012).

These data suggest stage-specific windows of neuroprotective potency, with memantine disease-modification potency in moderate-to-severe AD, and less efficacy in early disease including MCI. These findings should be studied further and replicated across AD models before considering disease – modifying trials in human MCI.

Future MCI trial design considerations

Enrichment of future samples with APOE-ε4 carriers (Jack et al., 2008) and depressed subjects (Lu et al., 2009) and employing multiple year trial durations and more sensitive cognitive ratings (Fleischer et al., 2007, 2008; Salloway et al., 2008) might increase the chances of finding efficacy against MCI progression in future disease-modifying RCTs. In RCTs of drugs increasing synaptic acetylcholine levels, enrichment with depressed patients (Lu et al., 2009), APOE-ε4

carriers (Fleisher et al., 2007; Jack et al., 2008; De Beaumont et al., 2016), female butyrylcholinesterase K* carriers (De Beaumont et al., 2016), and carriers of both these genes (De Beaumont et al., 2016) may increase the odds of finding a difference from placebo. Useful biomarkers will include CSF Aβ42, tau, and phosphorylated tau and positron emission tomography (PET) fibrillar amyloid (Albert et al., 2011), augmented by PET FDG and tau (Sperling et al., 2011), MRI medial temporal volume (DeCarli et al., 2007), and, possibly, hippocampal volumetry (Dubois et al., 2015).

Disease-Prevention Potential in Pre-Symptomatic AD

Quetiapine

Unstudied in human pre-symptomatic AD, in studies administering quetiapine beginning at 2 months in APP/PS1 mice, quetiapine decreased Aβ peptides, β-secretase expression and activity, APP C99 C-terminal fragment, cortical and hippocampal Aβ plaques, and nitrotyrosine, increased cerebral B-cell lymphoma 2 (Bcl-2), prevented memory impairment, and attenuated anxiety-like behavior at 6 and 9 months after 4 and 7 months of treatment (He et al., 2009). Findings of decreased Aβ peptides and plaques and improved memory were replicated in APP/PS1 mice treated from 4–12 months of age, in which quetiapine inhibited GSK-3β (Zhu et al., 2013). Quetiapine improved anxiety and increased cerebral BDNF at 10 months in APP/PS1 mice, suggesting a BDNF mechanism of neuroprotection (Tempier et al., 2013).

Quetiapine treatment attenuated hippocampal nitrotyrosine concentrations and object recognition memory impairment at 10 months, reflecting reduced oxidative stress in APP/PS1 AD mice (Luo et al., 2014). Again in APP/PS1 mice, quetiapine decreased cortical $A\beta_{40}$ (but not $A\beta_{42}$), almost reduced hippocampal $A\beta_{42}$ (P = 0.0504), decreased hippocampal microglial and cortical astroglial activation and cortical interleukin 1 beta (IL-1β) release, improved object recognition, and reduced anxiety, indicating slowing of progression, with inflammatory attenuation mediated through inhibition of the nuclear factor kappa B (NF-κB) p65 pathway and p65 nuclear translocation (Zhu et al., 2014). Thus, quetiapine administered pre-symptomatically in APP/PS1 AD transgenic mice reduced Aβ peptide species, Aβ plaques, reactive nitrosylation, impaired object recognition memory, and anxiety, possibly by inhibiting GSK-3β, glial activation, p65 nuclear translocation, and pro-inflammatory cytokines while increasing Bcl-2 and BDNF.

Lithium
Lithium prevented age-associated learning and memory impairments in *Drosophila* with attenuated PS1 function (McBride et al., 2010). In P301L, 4R0N tauopathic transgenic mice, lithium decreased both tau hyperphosphorylation at AD-relevant epitopes and tau aggregation and, if started during the early stages of tangle development, lithium also reduced axonal degeneration, consistent with GSK-3 inhibition-mediated neuroprotection (Noble et al., 2005). In APP intracellular domain (AICD) transgenic AD mice associated with GSK-3β over-activation, lithium prevented tau hyperphosphorylation, tau aggregation, neurodegeneration, and working memory deficits (Ghosal et al., 2009). In the scopolamine rat model, lithium activated choline acetyltransferase, inhibited acetylcholinesterase, and, through GSK-3β inhibition, regulated dendritic spine formation and arborization, indicating improved synaptic dysfunction that develops in the pre-symptomatic phase of AD (Wu et al., 2013). Data from a transgenic Arctic mutant $A\beta_{42}$ adult *Drosophila* AD model further indicate that $A\beta_{42}$ expression increases GSK-3 activity and lithium reduces $A\beta_{42}$ concentrations through GSK-3 inhibition (Sofola et al., 2010). In the PS1M146Lx-APPSwe-London transgenic AD mouse, lithium treatment in advance of neuropathology led to smaller Aβ plaques with reduced oligomeric halos, prevented hippocampal and entorhinal cortex neuronal loss, reduced axonal dystrophy, phosphorylated tau, autophagy, and ubiquitinated proteins, possibly related to astrocytic activation and the release of heat shock proteins (Trujillo-Estrada et al., 2013). Thus, lithium can deter incipient tauopathic, amyloidopathic, synaptopathic, and neurodegenerative progression in pre-symptomatic AD animal models through GSK-3 inhibition but these initial studies need replication.

Micro-dose lithium administered to pre-symptomatic 2-month-old Cg-Tg (PDGFB-APPSwInd) amyloidopathic AD transgenic mice at 0.25 mg/kg/d in drinking water for 16 months showed less senile plaques, an absence of hippocampal and cortical neuronal loss, evidence of increased cortical BDNF, reduced anxiety, and preserved spatial and aversive stimulus-related memory performance (Nunes et al., 2015).

The authors suggest that chronic lithium treatment may inhibit calcium influx through N-methyl-D-aspartate (NMDA) receptors, increase Bcl-2, stabilize endoplasmic reticulum homeostasis, regulate autophagy by inhibiting mammalian target of rapamycin (mTOR) or activating inositol monophosphatase, or inhibit GSK-3 and extracellular regulated protein kinases (ERK) cascades. Interestingly, lithium at these doses has been considered to be incapable of inhibiting GSK-3 in humans (Tariot and Aisen, 2009), suggesting the involvement of these other mechanisms. Additional mechanisms might include attenuated neuroinflammation (Lauterbach, 2016) and mitochondrial and oxidative stress stabilization (Morris and Berk, 2016). These micro-dose findings should be replicated, mechanisms confirmed, and micro-dose lithium should then be considered in a human clinical trial in pre-symptomatic AD.

Several human epidemiologic studies indicate that lithium administration lowers the risk of AD, including a Japanese retrospective chart review of 1,423 university psychiatric clinic outpatients age 60 or more that demonstrated better MMSE scores in patients previously receiving lithium *versus* age- and gender-matched controls never treated with lithium (Terao et al., 2006), a Brazilian case-control study of 66 euthymic bipolar disorder patients treated with lithium showing reduced AD prevalence relative to 48 age-, sex-, diagnosis-, and illness state-matched controls not currently so treated (Nunes et al., 2007), and a Danish study of 16,238 lithium-treated and 1,487,177 non-lithium-treated controls, revealing reduced risk of AD associated with lithium treatment (Kessing et al., 2008). These epidemiologic data collectively suggest that pre-symptomatic lithium may prevent or forestall AD in humans.

In summary, lithium ameliorated tauopathy in different animal models, reduced $A\beta_{42}$ in *Drosophila*, and can reduce synaptic dysfunction while micro-dose lithium reduced AD pathology and cognitive deficits in a transgenic mouse. Epidemiological studies found that previous lithium treatment preserved cognition (1 study) and reduced AD risk (several studies). However, a 3-week DBPCRCT of lithium (0.8 mmol serum levels) in 30 healthy subjects indicated worse performance on lithium than after discontinuation, and worse long term memory recall on lithium than in placebo (Stip et al., 2000), arguing for low- or micro-dose trials.

Valproate
In rats injected with ibotenic acid, chronic valproate increased brain histone H3 acetylation, protected nucleus basalis magnocellularis (NBM) cholinergic and gamma-aminobutyric acid-ergic (GABAergic) neurons from degeneration, and preserved cholinergic efferents to the cerebral cortex, consistent with valproate HDAC inhibition (Eleuteri et al., 2009). However, in contrast to 5-month-old Tg6799 transgenic AD mice, 1-month-old Tg6799 mice treated with valproate neither increased hippocampal NGF nor improved escape latency in the Morris maze (Noh and Seo, 2014). Further study is obviously needed to conclude any stage-dependent effects.

Fluoxetine
In a *Caenorhabditis elegans* model of AD, fluoxetine reduced

Aβ oligomers, delayed Aβ-induced paralysis, and extended life span, mediated through insulin signaling and the DAF-16/FOXO transcription factor (Keowkase et al., 2010). Fluoxetine prevented the loss of synaptophysin and microtubule associated protein 2, lowered brain soluble Aβ, and improved spatial memory, learning, and emotional behaviors in APP/PS1 mice, possibly by inhibiting APP T668 phosphorylation (Wang et al., 2014). More work is needed to follow-up these initial promising findings.

Donepezil
In the Tg2576 transgenic mouse, pre-symptomatic administration of donepezil for 6 weeks did not reduce Aβ plaque progression but improved contextual and cued memory although cued memory also improved in donepezil-treated non-transgenic controls (Dong et al., 2005). A follow-up study by this group demonstrated that donepezil treatment from 3–9 months decreased brain soluble $Aβ_{40}$ and $Aβ_{42}$ and Aβ plaques and increased synaptic density in the molecular layer of the dentate gyrus in a dose-dependent manner that correlated positively with higher doses (Dong et al., 2009). In 6-week-old APP23 mice treated before pathologic development, 2 months of donepezil followed by a 3-week washout demonstrated improved Morris water maze learning and retention equivalent to non-transgenic controls, suggesting disease-modification (Van Dam et al., 2008). In APP695 V717I transgenic mice, 6 months of donepezil decreased cortical acetylcholinesterase concentrations, increased acetylcholine transferase activity and hippocampal acetylcholine concentrations, and improved spatial learning and passive avoidance test memory (Cai et al., 2011). Again in APPV717I mice, donepezil administered pre-symptomatically for 4 months decreased cortical GSK-3β expression, suggesting a potential mechanism of donepezil (Shi et al., 2013). In APPswe/PS1dE9, donepezil administered pre-symptomatically for 6 months until 10.5 months of age revealed decreased Aβ concentrations, plaques, and memory impairment (Jeon et al., 2011). In rats receiving intra-cisternal $Aβ_{42}$, concomitant donepezil decreased amyloid deposition, prevented cholinergic dysfunction, and improved spatial and avoidance memory (Wu et al., 2014).

A 2-week DBPCRCT of donepezil 5 mg/d in 27 healthy adults showed no differences between groups on neuropsychological testing although the small sample size, low-dose, and minimal duration of treatment impede interpretation (Beglinger et al., 2004). Although long-term cognitive outcomes were not determined, an 8-week PCRCT of donepezil 5–10 mg/d in healthy men in their 7th decade of life revealed a 31% increase in insulin-like growth hormone and a doubling of growth hormone, reversing age-associated declines and suggesting possible mechanisms by which donepezil might reduce AD progression (Obermayr et al., 2005).

Pre-symptomatic donepezil treatment in AD animal model has demonstrated decreased Aβ and Aβ plaques and improved acetylcholine concentrations and memory outcomes across different models, but no adequate trials in humans have yet been conducted.

Memantine
In Wistar rats pretreated for 3 days with memantine before receiving intra-cerebroventricular $Aβ_{42}$ oligomer injections into the right NBM and frontal cortex, followed by memantine treatment for another 7 days until sacrifice, memantine attenuated microglial activation, preserved NBM cholinergic efferents to the neocortex, and decreased attention and memory impairments (Nyakas et al., 2011). APP23 mice treated pre-symptomatically for 2 months followed by a 3-week washout period dose-dependently improved learning and spatial recall consistent with disease modification (Van Dam and De Deyn, 2006). Memantine treatment for 6 weeks initiated 24 hours before Aβ and ibotenate injections to the bilateral hippocampi reduced microglial activation and hippocampal neuronal damage and prevented learning deficits in a dose-dependent manner (Nakamura et al., 2006). In rats undergoing intracerebroventricular $Aβ_{25-35}$, memantine prevented microglial and astrocytic activation and attenuated peptidylarginine deiminase 2 (Arif and Kato, 2009). Tg2576 mice treated with memantine for 6 months showed reduced Aβ plaque deposition and increased hippocampal and cortical synaptic density at 5 mg/kg yet without improvement in a fear conditioning paradigm, while 10–20 mg/kg doses had the same effects but were associated with increased neuronal degeneration (Dong et al., 2008). In APP/PS1 mice treated from ages 3–7 months, memantine was associated with reduced Aβ plaque burden and prevention of object recognition memory impairment (Scholtzova et al., 2008). In the 6-month old 3xTg mouse, 3 months of memantine reduced insoluble Aβ, Aβ dodecamers, prefibrillar soluble oligomers, fibrillar oligomers, total tau, hyperphosphorylated tau, and cognitive decline (Martinez-Coria et al., 2010). In Wistar rats treated with intrahippocampal okadaic acid and pretreated with memantine, CSF glutamate levels and spatial memory impairment were decreased compared to okadaic acid-exposed controls not treated with memantine, possibly by decreasing glutamate, tau hyperphosphorylation, and Cdk5/p25 signaling (Zimmer et al., 2012).

Future pre-symptomatic AD trial design considerations
Enhanced risk of progression from pre-symptomatic AD to MCI may be increased by enriching samples with patients with first-onset of anxiety, a predictor of incident cognitive impairment with a relative risk of 1.77, 95%*CI* 1.38–2.26 (Gulpers et al., 2016). Newer neuropsychological instruments are under development and may be more sensitive in detecting progression to MCI, such as the Loewenstein – Acevedo Scale for Semantic Interference and Learning (Loewenstein et al., 2016). Useful biomarkers in monitoring progression from the pre-symptomatic to MCI stage will include CSF $Aβ_{42}$, and PET amyloid and temporoparietal glucose metabolism (Sperling et al., 2011), augmented by CSF or PET tau, which progresses in this phase (Sperling et al., 2011) and, possibly, hippocampal/medial temporal volumetry (Dubois et al., 2015) and translocator protein (TSPO) receptor ligand PET (Lauterbach, 2016).

Disease-Modification Potential in Early PD

Studies of disease modification in early PD are limited to animal models for lithium and valproate, and human disease-modifying trials were not apparent for any of the psychotropics.

Quetiapine

Quetiapine doubled the 180-day mortality rate (hazard ratio of death 2.16, 95% confidence interval 1.88–2.48) in PD (Weintraub et al., 2016) and, if this risk also applies in early stage PD, lower doses than those applied in PD psychosis and agitation might avoid this concern, slow PD progression, and extend survival.

Lithium

In vitro evidence suggests that lithium enhances autophagy by inhibiting myo-inositol-1,4,5-trisphosphate (MITP) in PD (Motoi et al., 2014). A study of lithium carbonate given for 7 days after 7-day 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration revealed increased autophagy, substantia nigra dopamine neurons, and levels of striatal dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) and produced improvements in rolling bar latency, pole-climbing time, and spontaneous motor activity, perhaps related to increased autophagy (Li et al., 2013). These findings await replication but suggest disease-modification after early introduction of lithium in this model.

Valproate

Valproate was co-administered with MPTP for 5 days and 14 days afterwards to male FVBn mice throughout the period of active neurodegeneration, partially preventing striatal dopamine depletion with nearly complete protection of the substantia nigra against dopaminergic cell loss, possibly by HDAC inhibition (Kidd and Schneider, 2011). A study of valproate for 7 days following MPTP administration demonstrated increased autophagy, higher levels of substantia nigra dopamine neurons and striatal dopamine, and improved rolling bar latency, pole-climbing time, and spontaneous activity, possibly due to autophagic/lysosomal activation (Li et al., 2013). Valproate in rats undergoing unilateral striatal injections with 6-hydroxydopamine decreased HDAC, microcytic and astrocytic activation, tumor necrotic factor-alpha, striatal and dopaminergic mesencephalonic neuronal loss, and behavioral impairments, related to anti-inflammatory activity (Ximenes et al., 2015). The proteasomal inhibitor lactacystin was injected into the substantia nigra of rats in a model of PD and, 7 days later, valproate 200 mg/kg or 400 mg/kg daily was given for 28 days, dose-dependently reducing midbrain neurodegeneration and improving motor deficits, possibly by reversing histone hypoacetylation, and inducing neuroprotective and neurotrophic factors (Harrison et al., 2015). In this same intranigral lactacystin model under the same dosing conditions, valproate dose-dependently protected substantia nigra dopamine neurons and prevented spreading of neuronal degeneration to ventral tegmental area dopamine neurons

(Harrison et al., 2016).

Valproate is associated with reduced substantia nigra degeneration and improvements in histone hypoacetylation and behavioral impairments in these PD animal models. Within-model replication of all these findings should now be undertaken although the diversity of models tested suggests that a valproate clinical trial in early PD might be worth considering.

Future early PD trial design considerations

Enrichment of samples with elderly, men, occupational exposure to pesticides or solvents, life-long abstainers from caffeine and tea and smoking, with a history of REM behavior disorder (RBD), mild PD signs, olfactory loss, constipation, excessive daytime somnolence, hypotension, erectile dysfunction, urinary dysfunction, or depression, with siblings with early onset PD or first-degree relatives with PD will increase the likelihood of PD progression (Berg et al., 2015). The use of prodromal PD criteria (Berg et al., 2015) can assist diagnostic validity and sample homogeneity. Biomarkers might include fluoro-DOPA PET or dopamine transporter SPECT imaging and, perhaps, substantia nigra hyperechogenicity.

Disease-Prevention Potential in Pre-Symptomatic PD

No data were found for quetiapine, donepezil, or memantine in pre-symptomatic PD.

Lithium

Pretreatment of MPTP mice with lithium 4.4 g/kg (3.3 g/kg produced human therapeutic serum levels) for 4 weeks revealed dose-dependent protection against the depletion of striatal dopamine, DOPA, homovanillic acid, and Bcl-2 while decreasing apoptotic Bax, suggesting lithium's ability to prevent neuronal apoptosis (Youdim and Arraf, 2004). In the intranasal MPTP rat, lithium pretreatment for seven days prevented the loss of striatal dopamine and short-term memory impairment (Castro et al., 2012). Low-dose lithium (0.2 mEq/L blood level) prevented striatal microglial activation, astrogliosis, and further dopaminergic degeneration while preventing motor impairment in the aged parkin transgenic PD mouse model, possibly by anti-inflammatory effects (Lieu et al., 2014). In the A53T mouse model of PD also exposed to paraquat and maneb, lithium at human therapeutic concentrations prevented accumulation of oxidized/nitrated αSyn in the substantia nigra and striatum and oxidative stress-induced neurodegeneration (Kim et al., 2011). In the 6-OHDA rat, lithium did not reduce substantia nigra pars compacta dopaminergic degeneration despite inhibiting GSK-3β (Yong et al., 2011). These data, indicating prevention of nigrostriatal degeneration in different PD models, now await replication at specific doses.

Valproate

Nuclear αSyn prevents histone acetylation by histone acetyltransferase (Kontopoulos et al., 2006), possibly reversed

Table 1 Psychotropic effects on microgliosis, microglial activation, cytokine release, and associated cognitive performance

Effect	QTP	Li	VPR	FLX	DNP	MMT
Decreased microgliosis			+		+	
In hippocampus			+		+	
In cerebral cortex			+			
Decreased microglial activation	+	+	+	+	+	+
In hippocampus	+			+	+	
In cerebral cortex	+		+			
In midbrain substantia nigra			+	+		
In striatum	+					
Decreased cytokine release			+	+		
Decreased IL-1β concentrations			+	+	+	
Decreased IL-6 concentrations				+		
Decreased TNFα concentrations			+	+	+	
Improved object recognition					+	
Improved spatial memory		+	+		+	+

Psychotropic effects on microgliosis, microglial activation, cytokine release, and associated cognitive performance (from Lauterbach, 2016). DNP: Donepezil; FLX: fluoxetine; IL-1β: interleukin 1β; IL-6: interleukin 6; Li: lithium; MMT: memantine; QTP: quetiapine; TNFα: tumor necrotic factor alpha; VPR: valproate.

Table 2 Epigenetic and transcriptional effects of psychotropics

Effect	QTP	Li	VPR	FLX
Epigenetic Effects				
Upregulated histone acetylation		[4]	[4]	
(H3 and H4 are hypoacetylated in HD)				
Downregulated AP-1 DNA binding		[4]		
(low CpG region hypomethylated in HD)				
Transcriptional Effects				
Upregulated CLU (clusterin) transcription				[1]
(AD risk gene)				
Upregulated GRN (granulin) transcription				[1]
(some fronto-temporal dementias)				
Upregulated CCDC62 transcription				[2]
(PD risk gene)				
Upregulated SKP1A transcription				[3]
(gene linked to PD delayed onset)				
Upregulated BDNF transcription	[3]			[3]
In cerebral cortex		[3]		
Downregulated BDNF transcription				
In hippocampus		[3]		
Upregulated ALDH1A1 transcription				[3]
(gene linked to PD delayed onset)				
Downregulated MAPT transcription				[2]
(PD risk gene)				
Downregulated MCCC1 transcription				[2]
(PD risk gene)				

Epigenetic and transcriptional effects of psychotropics. Numbers 1–4 in table correspond to the references: [1] Lauterbach, 2012a; [2] Lauterbach, 2012b; [3] Lauterbach, 2013a; [4] Lauterbach, 2013b. AD: Alzheimer's disease; AP-1: activator protein-1; FLX: fluoxetine; H3: histone protein H3; H4: histone protein H4; HD: Huntington's disease; Li: lithium; PD: Parkinson's disease; QTP: quetiapine; VPR: valproate. Genes in capital letters are official gene symbols.

by valproate-inhibition of HDACs. Valproate protected dopaminergic neurons in *Caenorhabditis elegans* over-expressing αSyn, attributed to ERK-MAPK inhibition (Kautu et al., 2013). Chronic valproate decreased nigral and striatal monoubiquitinated αSyn nuclear translocation and preserved substantia nigral neurons, nigral and striatal tyrosine hydroxylase, and striatal dopamine levels in the rotenone rat PD model, presumably by valproate HDAC inhibition, increasing histone H3 acetylation (Monti et al., 2010). In another rotenone rat study, chronic valproate

Table 3 Replicated psychotropic effects on protein, proteasome, autophagy, mitochondria, apoptosis, neurodegeneration, neurogenesis, and animal cognition and behavior

Effect	QTP	Li	VPR	FLX
Effects on pathogenic proteins				
Decreased APP		[3]		
In amyloidopathic Tg AD mice		[3]		
Decreased β-secretase activity	[3]			
In amyloidopathic Tg AD mice	[3]			
Decreased β C-terminal fragment		[3]		
In amyloidopathic Tg AD mice		[3]		
Decreased $A\beta_{40}$ production	[3]	[3]	[2]	
In amyloidopathic Tg AD mice	[3]	[3]		
Decreased $A\beta_{42}$ production	[3]	[3]	[2]	
In amyloidopathic Tg AD mice	[3]	[3]		
Decreased Aβ oligomers		[1]		
Decreased Aβ aggregation		[1]		
Decreased Aβ deposition			[1]	
Decreased Aβ plaques	[3]	[3]	[3]	
In amyloidopathic Tg AD mice	[3]	[3]	[3]	
Decreased neuritic plaques			[3]	
In amyloidopathic Tg AD mice			[3]	
Decreased tau		[3]		
In amyloidopathic-tauopathic Tg AD mice		[3]		
In tauopathic htau23 Tg mice		[3]		
In FTDP-17 Tg mice		[3]		
Decreased fibrillar tau		[3]		
In FTDP-17 mouse models		[3]		
Decreased tau phosphorylation		[3]	[3]	
Increased tau ubiquitylation		[2]		
Increased αSyn			[3]	
Decreased mono-ubiquitylated αSyn			[3]	
Prevented αSyn nuclear translocation			[3]	
Decreased αSyn aggregation		[3]		
Decreased huntingtin aggregation		[4]		
Effects on proteasome and autophagy				
Increased proteasomal function			[2]	
Decreased proteasomal function		[2]		
Increased autophagy		[3]		
Of huntingtin protein		[4]		
Downregulates p53	[4]			
(decreased p53 disinhibits autophagy)				
Mitochondrial effects				
Decreased mitochondrial depolarization	[2]			
Induced by Aβ	[2]			
Decreased mitochondrial permeability transition pore development	[2]	[2]		
Increased mitochondrial permeability transition pore development			[2]	
Decreased cytochrome c release		[3]	[2]	
Decreased reactive oxygen species	[2]			
Decreased reactive nitrogen species	[3]			
In amyloidopathic Tg AD mice	[3]			
Decreased free radical damage			[3]	
Effects on apoptosis				
Increased antiapoptotic Bcl-2			[1]	
Decreased apoptosis	[2]	[3]	[3]	[2]
Aβ-induced		[2]		
Glutamate-induced		[2]		
In quinolinate HD rat striatum		[3]		
Decreased neuronal apoptosis		[3]		
In hippocampus		[2]		

Table 3 Continued

Effect	QTP	Li	VPR	FLX
Neuronal effects				
Neuroprotective			[1]	
In hippocampus	[1]		[1]	
In cerebral cortex	[1]			
In striatum	[1]			
Decreased neuronal loss		[3]		
In MPTP PD mice		[3]		
In nigrostriatal neurons		[3]		
In rotenone PD mice			[3]	
In nigrostriatal neurons			[3]	
In PC12 neuroblastoma cells	[2]			
In quinolinate HD rat		[3]		
In striatum		[3]		
Decreased neuronal degeneration			[1]	
In substantia nigra				[1]
Effects on neurogenesis				
Increased BDNF		[4]	[4]	[4]
Increased neurogenesis		[4]	[4]	[4]
Increased hippocampal neural stem cells				[3]
Decreased hippocampal neural stem cell apoptosis				[3]
Increased striatal neuronal proliferation		[3]		
Cognitive, motor, and survival effects				
Improved memory	[3]		[3]	
In amyloidopathic Tg AD mice	[3]	[1]	[3]	
In HD mouse				[4]
Improved motor status in HD mouse		[4]	[4]	
Extended survival in HD mouse		[4]	[4]	

Replicated psychotropic effects on protein, proteasome, autophagy, mitochondria, apoptosis, neurodegeneration, neurogenesis, and animal cognition and behavior at the time of the corresponding review (it is likely that there have been additional replicated findings since that time). Numbers 1–4 correspond to review articles in which the primary references can be found: [1] Lauterbach, 2016; [2] Lauterbach et al., 2010; [3] Lauterbach et al., 2011; [4] Lauterbach, 2013b. Aβ: Amyloid beta; AD: Alzheimer's disease; AP-1: activator protein-1; APP: amyloid precursor protein; αSyn: alpha-synuclein; BDNF: brain-derived neurotrophic factor; FLX: fluoxetine; FTDP-17: frontotemporal dementia with parkinsonism associated with chromosome 17 mutations; H3: histone protein H3; H4: histone protein H4; HD: Huntington's disease; Li: lithium; PD: Parkinson's disease; QTP: quetiapine; Tg: transgenic; VPR: valproate.

prevented loss of nigral dopamine neurons, nigral and striatal tyrosine hydroxylase, and contralateral forelimb disuse (Carriere et al., 2014). In the intranasal MPTP rat, seven days pretreatment with valproate prevented striatal dopamine loss (Castro et al., 2012). Replication of these pre-lesion valproate studies will be desirable across animal models of PD.

Fluoxetine
In the MPTP mouse, fluoxetine injections beginning when nigrostriatal dopamine neurons had been depleted by 15% prevented further degenerative depletion and increased striatal dopamine levels producing partial motor recovery, related to attenuated microglial activation (Chung et al., 2011). In 4–5 month-old transgenic A53T αSyn mice, chronic fluoxetine reversed hippocampal dysfunction and neurogenesis impairment, increasing hippocampal dentate gyrus neural precursor cell proliferation and differentiation into neurons, ascribed to increased BDNF and GDNF levels (Kohl et al., 2012). These findings await replication.

Future pre-symptomatic PD trial design considerations
Sample enrichment with subjects having reduced dopaminergic markers on functional imaging, substantia nigra hyperechogenicity, hyposmia, constipation, history of RBD (Mahlknecht et al., 2015), and other features listed in "Future early PD trial design considerations" may enhance the probability of PD progression. Biomarkers include dopaminergic functional imaging and, possibly, tegmental diffusion tensor imaging, supplementary motor area functional magnetic resonance imaging, and dorsolateral substantia nigra T2-weighted 7 Tesla MRI (Mahlknecht et al., 2015).

Disease-Modification in Early HD
There were no data relevant to disease modification in early HD for quetiapine or valproate.

Lithium
R6/2 HD transgenic mice treated with lithium demonstrated improved rotarod motor performance but not prolonged

survival (Wood and Morton, 2003).

Several early DBPC studies of lithium in 6 HD patients each showed no symptomatic benefit for chorea over 3–6 weeks but did not observe for HD progression (Leonard et al., 1975; Vestergaard et al., 1977). A clinical case series of 3 patients documented HD non-progression over 3–4 years with low-dose lithium 150–300 mg/d along with carbamazepine (Danivas et al., 2013). These findings suggest a disease-modifying effect without symptomatic benefit.

Fluoxetine
A 4-month DBPCRCT of fluoxetine in 30 non-depressed HD patients found no difference in neurological, cognitive, behavioral, or functional outcomes in this small study of brief duration (Como et al., 1997). Two HD patients treated with fluoxetine experienced non-progression over the subsequent 2 and 6 years, respectively (De Marchi et al., 2001). These findings suggest a disease-modifying effect without symptomatic benefit.

Donepezil
A 12-week DBPCRCT in 30 adults with HD lacking depression and dementia, with other medications held constant during the trial, showed no improvement in chorea, cognition, or quality of life with donepezil at 12 weeks, although chorea, symbol digit, ADAS-Cog, and WAIS-III symbol searching did not progress, in contrast to placebo group deteriorations (Cubo et al., 2006), suggesting disease-modification potentially detectable in a larger and longer trial.

Memantine
A patient with HD experienced non-progression over 6 months after adding memantine to the regimen (Cankurtaran et al., 2006). A 3-month un-blinded memantine trial in 12 patients showed improvement only in chorea but did not observe for disease-modification (Ondo et al., 2007). An un-blinded memantine trial in 4 patients showed neuropsychological non-progression at 18 months in one patient whereas the other 3 patients, who had discontinued memantine after 3–4 months, showed minor progression at 12 months (Hjermind et al., 2011). A two-year, un-blinded, flexible-dose trial of memantine in 27 patients suggested slowing of HD progression relative to historical controls (Beister et al., 2004). Blinded controlled clinical trials of suitable durations are now needed.

Future early (prodromal) HD trial design considerations
Pre-specified criteria (Reilmann et al., 2014) and HD gene repeat number may enhance sample homogeneity. Subjects can be followed for progression to end-points that may include motor, cognitive, and striatal volume outcomes.

Disease-Prevention in Pre-Symptomatic HD
There were no data for quetiapine or donepezil. Preliminary HD animal model data support the notion that lithium may prevent, valproate may delay, and memantine may slow HD emergence during the pre-symptomatic phase but replica-

tions are needed.

Lithium
Lithium protected against optic neurodegeneration in an N171-120Q *Drosophila* transgenic HD model (Sarkar et al., 2008). Lithium dose-dependently increased neuronal survival in N171-150Q *Caenorhabditis elegans* (Voisine et al., 2007). Lithium pretreatment increased Bcl-2 and reduced striatal neuronal apoptosis and lesion volume in the HD quinolinate rat model (Wei et al., 2001). In the 3-nitropropionic acid (3-NPA) HD rat, lithium prevented oxidative stress, cellular pathology, motor impairments, and weight loss, potentiated by hemin, with this synergy reversed by protoporphyrin, suggesting hemeoxygenase-1 and GSK-3β involvement in HD pathophysiology (Khan et al., 2015). *In vitro* evidence suggests lithium may enhance autophagy in HD by inhibiting MITP (Motoi et al., 2014).

Pre-symptomatic N171-82Q transgenic HD mice fed lithium at human therapeutic levels showed increased cortical GSK-3β inhibition, cortical and striatal HDAC inhibition, cortical and striatal BDNF increases, and reduced behavioral depression but neurological status, motor skill learning, and lifespan did not improve, in contrast to synergistic beneficial effects with combined lithium and valproate treatment (Chiu et al., 2011). The same findings obtained in similarly-treated YAC128 mice although neurological status and anxiety did not improve, in contrast to synergistic beneficial effects with combined lithium and valproate treatment (Chiu et al., 2011).

Pre-symptomatic micro-dose lithium in YAC128 transgenic HD mice normalized caspase-6 activation and BDNF levels, prevented loss of striatal neurons and volume, and improved neurological dysfunction (Pouladi et al., 2012).

Valproate
In N171-82Q transgenic HD mice, high dose valproate improved motor activity and survival, delaying symptom onset by 31% (Zádori et al., 2009). In another N171-82Q mouse study, dietary valproate producing human therapeutic serum levels inhibited cortical GSK-3β and cortical and striatal HDAC, increased cortical and striatal BDNF, the molecular chaperone HSP70, and lifespan, and improved behavioral depression but did not improve neurological status or motor skill learning, in contrast to synergistic beneficial effects in mice treated with combined lithium and valproate treatment (Chiu et al., 2011). In similarly-treated YAC128 mice, valproate produced the same positive effects but did not improve neurological status or anxiety, in contrast to synergistic beneficial effects of combined lithium and valproate treatment (Chiu et al., 2011).

Fluoxetine
In R6/1 HD transgenic mice, fluoxetine increased hippocampal neurogenesis, preserved dentate gyrus volume, preserved spatial memory, and improved depressive behavior (Grote et al., 2005).

Memantine
Memantine co-administered with 3-NPA in rats resulted in partially preserved striatal cells and striatal volume, increased Bcl-xl concentrations, and decreased huntingtin proteolytic fragments, Bax levels, apoptosis, degenerating neurons, weight loss, and micro-calpain levels (Lee et al., 2006), suggesting memantine attenuates NMDA receptor-related calcium-mediated apoptosis in this model.

Future pre-symptomatic HD trial design considerations
Future human trials should ideally involve blinding, placebo-treated controls, and adequate duration in disease-modifying or preventive designs. Pre-symptomatic trials can enlist family members with known genotype and CAG repeat number to approximate time of disease onset. Pre-specified criteria, *e.g.*, Reilmann et al. (2014), may enhance sample selection and homogeneity. Progression to motor, cognitive, and striatal volume end-points might increase signal detection.

Summary
Failed clinical trials in advanced NDDs should not deter consideration of the above psychotropics for trials in pre-symptomatic and early NDDs since pathophysiologies and drug effects vary between disease stages and therapeutic failure in late disease does not necessarily mean failure in early disease.

In MCI, clinical trials suggest disease-modifying potential for low-dose lithium and, in selected patients, donepezil, findings that await replication, while replicated transgenic animal data encourage further study of valproate in AD MCI, especially at subclinical doses; quetiapine awaits study while fluoxetine animal and memantine human studies are presently inconclusive; a memantine animal study suggested less disease-modifying potency in MCI than in later AD and should be replicated before considering further human trials. *In pre-symptomatic AD*, quetiapine has consistently reduced Aβ peptides, Aβ plaques, reactive nitrogen species, and improved object recognition memory and anxiety in APP/PS1 mice. Epidemiological data indicate lithium reduces human AD risk and, in animal models, ameliorates tauopathy and improves cognition but several amyloidopathic benefits await replication, as do animal findings for valproate and fluoxetine. In animal models, donepezil treatment has decreased Aβ and plaques, increased acetylcholine levels, and improved memory, awaiting exploration in humans. Memantine has consistently reduced microglial activation, Aβ plaques, hippocampal degeneration, and memory impairment in several animal models.

In early PD, valproate reduced substantia nigra degeneration and improved motor performance in animals. Other drugs await study and preclinical lithium findings await replication. *In pre-symptomatic PD*, lithium and valproate each prevented both substantia nigra degeneration and striatal dopamine depletion in animals. Additional findings for lithium, valproate, and fluoxetine await replication and human studies are needed. Donepezil and memantine await investigation.

In early HD, uncontrolled clinical data indicate non-progression with lithium, fluoxetine, donepezil, and, especially, memantine, urging blinded controlled clinical trials. Animal data are limited to a single (positive) study of lithium. *In pre-symptomatic HD*, animal studies of lithium at varying doses indicate preserved striatal volume and neurological function but other positive findings for lithium, valproate, fluoxetine, and memantine await replication. Clinical data in humans are needed for all six drugs.

Conclusion
Substantial data suggest promising potential for these psychotropics as disease-modifiers in pre-symptomatic and early-stage NDDs. Preclinical findings should be replicated across a variety of disease-specific animal models, especially at subclinical doses, subsequently confirmed in blinded, controlled clinical trials employing appropriate disease-modifying designs (delayed-start, randomized withdrawal, *etc*.) and methodological refinements detailed above for each disease and stage. Microglial activation, important in early NDDs, might additionally be tracked by serial PET quantitation using TSPO receptor ligands (Lauterbach, 2016). The findings summarized here offer the exciting prospect of minimizing NDD progression and, ultimately, the potential for arresting these diseases before signs and symptoms even begin.

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