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Early investigational drugs targeting tau protein for the treatment of Alzheimer's Disease

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Abstract

Introduction—Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is a significant burden to society. With continual expansion of our understanding of the disease, novel therapies are emerging as potential therapeutics to either halt or reverse progression of the disease.

Areas Covered—This paper aims to provide an overview of current drug therapies aimed at targeting the tau protein. With this protein known to be a noted pathologic finding of the disease, trials of therapeutics aimed at this protein have been under investigation. This article is based on data obtained from PubMed searches, TauRx, ALZFORUM, and Clinicaltrials.gov with search terms including: anti-tau, tau therapeutic agents in Alzheimer's disease, phase 0, I, II, III trials in Alzheimer's disease, monoclonal antibodies, vaccines.

Expert opinion—Broad based treatments that target tau, including microtubule stabilization and tau aggregation inhibitors, appear to be of greatest promise. Immunotherapy appears relatively safe and efficacious but narrow while protein kinase inhibition has not demonstrated clinical benefit to date.

1. Introduction

Alzheimer's disease (AD), a stepwise neurodegenerative disorder, is known to be the most common cause dementia. This disease causes a significant disease of morbidity and mortality. Pathologic hallmarks of AD include an abundance of amyloid-beta plaques (aβ) and neurofibrillary tangles composed of tau, a microtubule associated stabilizing protein[1] The disease also requires a clinical deterioration depicted by decline in cognition, language, visuospatial skills, executive function, personality, and sleep among other signs and symptoms. This disease accounts for over 50% of diagnoses of causes of dementia and leads to death often within a decade of the time of diagnosis. With over 5 million cases of AD in 2010 in the US alone, the rate is projected to increase 3-fold by 2050[1]. This disease has many medical, social, financial, and emotional implications to the say the least with a

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significant burden placed on individuals, family members, caregivers, and health care providers. While a timely diagnosis may allow for a projected lifetime course for the patient, current therapies prove to only fail to abate the progression of the disease but only temporize the inexorable prognosis [2].

The mainstays of current therapeutics directed towards Alzheimer's Disease include cholinesterase inhibitors (ChEI) and N-methyl-D-aspartate (NMDA) receptor agonists such as memantine. Such therapeutic regimens are FDA and EMA approved. However the aforementioned therapeutics are only symptomatic and not curative or preventative.

The hyperphosphorylation of the tau protein forms conglomerates known as paired helical fragments whose deposits are that of the known neurofibrillary tangles[3]. Tau is associated with pathology in numerous diseases known as tauopathies including but not limited to AD, Progressive Supranuclear Palsy (PSP), Pick's Disease, corticobasal degeneration, post-encephalitic parkinsonism, frontotemporal dementia (FTP), and more[4]. With clinical trials previously showing limitations to the treatment of aβ, a focus on treatments of the other pathologic mechanisms of AD is worth investigation. With numerous protein kinase enzymes responsible for the phosphorylation of tau, this leads to multiple avenues for research for potential targets for intervention [5]. It has been noted that neurofibrillary tangles are more closely associated with cognitive decline versus amyloid beta and that reduction of these tangles in mice models results in improvement in overall cognitive function[6]. Therefore, a current movement to explore avenues for combating tau can prove to yield significant gains in altering the landscape for treatment of AD. Current ongoing and prospective efforts on therapeutics directed against tau are analyzed in the following.

2. Tau Based Drugs of Note

2.1 Immune Therapy

2.1.1 AADvac-1 (also known as Axon peptide 108 conjugated to KLH)—This form of therapy includes active immunization. A DC8E8 (pathologic regulatory domain) epitope was used to construct a vaccine trial for a transgenic rat model. The vaccine was constructed using an N-terminus peptide (Sequence: KDNIKHVPGGGS) involved in tau-tau interaction conjugated to the metalloprotein keyhole limpet hemocyanin (KLH). The results in this trial demonstrated a decrease of pathologic hyperphosphorylated tau in response to the vaccine that triggered a humoral response to discriminate between physiological and pathological tau. The results also demonstrated improved function of the rats with a favorable side effect profile. Currently, the AADvac-1 in phase 1 trial by Axon Neuroscience has been completed as of March 2015 with data pending[7].

2.1.2 Acl-35—This is a liposomal-based vaccine that also provides active immunization. The vaccine utilizes a synthetic peptide, which imitates phosphorylated tau protein at specific amino levels to induce a powerful antigenic response in Tau.P301L mice. The specific amino acid areas incorporated into the vaccine include phosphorylated S396 and S404 residues. The vaccine itself corresponded to residues 393–408 of the tau protein simulating the Tau 441 isoform. The study demonstrated efficacy with reductions in phosphorylated tau on pathology of brains, increased IgG titers in vaccinated mice, and

improved motor function of vaccinated mice. The vaccine also demonstrated safety with regard to decreased markers of inflammation as measured by immunohistochemistry for astrocytes, microglial activation, immunoglobulin levels, and the number of CD45 T and B cells[8]. Currently, a phase Ib trial is underway by AC Immune to assess for safety profile along with secondary outcomes including markers as well as phenotypic changes.

2.1.3 BMS 986168 (also known as IPN 007)—While not currently approved for Alzheimer's Disease, Bristol-Myers Squibb is currently testing a phase I trial with this monoclonal antibody directed towards extracellular tau (eTau)[9]. A study demonstrates a correlation between eTau and aβ both *in vitro* and two transgenic in vivo mice models. Of interesting note is the reduction in aβ that occurs when eTau is targeted with an antibody. The study notes that eTau and aβ may be involved in a feed forward cycle that may exacerbate the pathologic process. The study identified four types of eTau varying in the size of amino acid sequence. IPN 002 is an antibody specific to eTau in this study. This is an N terminal antibody encompassing amino acids 17–28. Treatment with this antibody was demonstrated to show reduction in amyloid *in vitro* and *in vivo*. [10].

2.1.4 RG7345—A human monoclonal antibody targeting a specific tau phosphorylated epitope at site pS422. This site was used to conduct a vaccine trial, which demonstrated that vaccination directed toward a specific epitope improves transgenic mice performance in the Y-maze test with also decreased levels of tau by immunohistochemical and biochemical testing [11]. A transgenic mouse trial involving passive administration of the antibody demonstrated clearance of tau with the proposed mechanism being intracellular clearance of antigen-antibody complexes [12]. Currently, a phase I trial for safety by Roche is underway.

2.2 Microtubule Stabilizers

2.2.1 Davunetide (also known as NAP, AL-108)—While there are currently only planned trials for the safety and efficacy of davunetide, this drug is derived from activity dependent neuroprotective protein (ADNP) to stabilize microtubules, which could offer a tau-based therapy for AD. The mechanism of action of davunetide is multidimensional and thought to not only affect tau aggregation but also involved in gene regulation and through interaction with other protein complexes. Newer hypothesized mechanisms postulate that davunetide and related compounds affect microtubule stabilization through interaction with microtubule severing proteins via expression of tau. A recently identified binding target for davunetide and ADNP are microtubule end binding proteins 1 and 3 (EB1 and EB3) which are directly implicated in neuronal plasticity and neuroprotection [13] A phase 2 trial in 2007–2008 demonstrated improvement in patients with mild cognitive impairment (MCI) with well tolerable side effects [14–15]. The results in the pure tauopathy, progressive supranuclear palsy (PSP) were unimpressive [16], suggesting intervention at early stages of the disease [17–18].

2.2.2 Epothilone D (also known as BMS-241027)—This is a small molecule microtubule-stabilizing drug. With phosphorylated tau leading to poor solubility and increased pathogenesis from poor microtubule function, stabilization of microtubules can prevent the pathogenic mechanism in AD. Two studies of PS19 tau transgenic mice treated

with Epothilone D demonstrated both behavioral and pathologic benefit. Mice treated represented decrease pathologic tau in the forebrain with preservation of neuronal framework in the hippocampus. Behavioral and cognitive deficits were reduced when mice were treated[19–20]. Bristol-Myers Squibb conducted a phase I trial to evaluate for safety with measurement of spinal fluid levels of tau and cognitive behavioral testing as secondary outcomes. The trial involved 40 mild AD subjects treated with IV BMS-241027 with three-week interval testing cognitively and measurement of CSF at the 70 day mark. Currently there is no data from the trial and no further trials to investigate the effects of Epothilone D on tau in AD [21].

2.2.3 TPI 287—Developed by Cortice Biosciences, this drug falls in the taxane class and is currently undergoing phase I testing to evaluate for safety in increasing doses. The mechanism of action involves microtubule stabilization along with affecting levels of phosphorylated tau. Preliminary data from a preclinical trial indicates that transgenic mice treated with TPI 287 demonstrated improvement in the Morris Water Maze and decreased in phosphorylated tau on brain gross histopathology [22].

2.3 Tau Aggregation Inhibitors

2.3.1 LMTX (also known as Methylthionium Chloride, Rember TM, Tau Aggregation Inhibitor (TAI), TRx-0014, TRx0237, Methylene Blue)—Currently being marketed by TauRx and initially as Rember TM, this drug is a tau aggregation inhibitor (TAI). This class of drugs is believed to reduce existing neurofibrillary tangles. The premise of the mechanism revolves around failure of intracellular processing by endosome-lysosome complexes leading to tau molecule self binding induced feed forward mechanisms propagating itself [23] Phase II trials of Rember demonstrated a decrease in the rate of cognitive decline by 90% through cognitive testing (Alzheimer's Disease Assessment Scale-cognitive subscale) and with functional SPECT/PET demonstrating improvement in regions of the brain affected by AD, most notably medial temporal and temporoparietal regions. Three different doses of the medications were used in this trial with 138 mg/day being deemed the safest minimum dose. The most commonly reported adverse effects included diarrhea, dysuria, and urinary frequency[24].

LMTX is a stabilized compound related to Rember through modification and reduction of the compound, which is thought to be better, tolerated and absorbed. Rember has the oxidized form of the chloride salt of the compound methylthionine, which resulted in dose dependent limitations. LMTX is currently undergoing three different Global phase 3 trials with reports to be expected in 2016.

2.4 Protein Kinase Inhibitors

2.4.1 Tideglusib (NP031112, Nypta®, Zentylor™, Glycogen synthase kinase 3 inhibitor, NP12)—Tideglusib functions as an inhibitor of glycogen synthase kinase (GSK-3). A phase2b trial was conducted in 30 patients with mild to moderate AD with varying increasing dose of tideglusib versus placebo with the main focus to assess for safety. Performance on numerous cognitive tests was used to measure other outcomes. The only concerning adverse effect was asymptomatic elevation of transaminases, which were

reversed, with withdrawal of the agent. The patients did demonstrate improvement in the cognitive tests but the small sample size precluded conclusions on significance for a general population [25]. A subsequent phase II trial known as ARGO was conducted to assess safety and efficacy. This was a double blinded, randomized trial in mild to moderate AD patients who were treated for 26 weeks. ADAS-cog15 was used to measure outcomes however the results demonstrated no statistically significant findings but the drug was well tolerated with diarrhea and asymptomatic transaminase elevations as the only side effects. The authors conclude that further studies of increasing dose and duration would be required to make deductions on efficacy of the drug [26]. There are no current FDA approved trials ongoing.

2.4.2 Lithium—While Lithium has played a role in mood and affective disorders, its implication in the treatment of tau-based disease, neurodegenerative disorders is of note. The mechanism involves regulation of GSK-3, a protein kinase. A trial of lithium of 12 months in patients with mild cognitive impairment (MCI) noted improvement in cognitive function as well as decrease in CSF related markers of p-tau[27]. However a study of chronic lithium administration in adults found that chronic use leads to decreased glucose uptake in the cerebellum and hippocampus however the low sample size precluded any significant conclusion[28]. A study of 10 weeks of lithium administration to patients with AD showed no significance with reduction of p-tau levels in CSF and GSK-3 activity in lymphocytes[29]. Lithium is also thought to mediate improvement in cognition through neutrotrophic mechanisms and with response to triggers including oxidative stress, inflammation, and responses to maintain homeostasis[30].

2.4.3 Valproic Acid—Like lithium, valproic acid's proposed mechanism of effect on reducing neurofibrillary tangles is through mediation of GSK-3 and CDK-5, two protein kinases. A study involving APP presenilin 1 transgenic mice treated daily for 12 weeks demonstrated reduced phosphorylation at three specific amino sites with also inhibitory effect on the kinases[31]. Valproic acid has been studied extensively as a treatment for agitation without significant benefit demonstrated. The design of the phase II study also looked at the potential to slow the rate of decline in subjects with AD as a means of testing an anti-tau effect. Administration of valproic acid was not associated with slower decline [32]. Another study demonstrated that chronic use reduces brain volumes as measured by MRI with patients showing poorer performance on cognitive testing at 12 months [33].

2.4.4 L-3-n-butylphthalide (L-NBP)—L-NBP, derived from seeds of Apium graveolens Linn or Chinese celery reduces tau phosphorylation in APP presenilin 1 transgenic mice treated daily for 3 months with reduced phosphorylation at specific sites and with an inhibitory effect on GSK-3 and CDK-5 with improvement in task function as compared to controls [34].

2.4.5 2-methyl-5-(3-{4-[(S)-methylsulfinyl]phenyl}-1-benzofuran-5-yl)-1,3,4-oxadiazole (MMBO)—An animal trial of this synthetic compound demonstrates that it inhibits GSK-3 leading to reduced tau phosphorylation in the hippocampus along with improvement in rat task function in the Y maze and object recognition [35].

2.5 Conclusion

Tau based therapy for AD has become a point of increasing focus in recent years. This recent shift in therapeutic and preventative approaches to AD appears to have great potential from limited data available to provide approaches for combating one of the main yet elusive pathologic mechanisms for AD. While the scope of evidence for the use of tau based therapy continues to grow, current and previous investigational therapies can be grouped into four categories: immune based therapy, microtubule stabilizers, tau aggregation inhibitors, and protein kinase inhibitors.

3. Expert Opinion

Anti-tau immunotherapy is the area of greatest ongoing clinical trials. Preliminary results as above have demonstrated great promise for their use. The two current vaccines undergoing trial investigation include AAD-vac1 and Acl-35. Preclinical trials demonstrating safety and efficacy are the rationale for current phase I clinical trials. The ability to trigger an immune response that can discriminate physiologic from pathologic tau has the potential to provide not only a therapeutic benefit but also a preventative benefit. Peptide based vaccines provide therapeutic benefit via gross evaluation along with behavioral benefits. Reductions in pathologic tau along with decrease in tau phosphorylation contribute to this benefit. Likewise, monoclonal antibodies targeting specific epitopes can effectively reduce levels of eTau in preclinical trials. The future implications of immune therapy include determining various epitopes to develop vaccines and monoclonal antibodies towards targeting tau as the heterogeneity of conformations of pathologic tau is numerous. Data from current clinical trials will shed light on safety, tolerability, and efficacy in humans.

Microtubule stabilizers are another class of drugs directed towards tau that have demonstrated promise. This class of drugs may demonstrate the greatest potential as it has the ability to target protein misfolding to prevent symptomatology related to pathologic tau irrespective of the underlying cause. With numerous pathological mechanisms postulated for the basis of neurofibrillary tangles, the root of this hallmark stems from protein misfolding and targeting this area to encompass all disease causing mechanisms can have large implications. Davunetide has had clinical data demonstrating improvement in patients with MCI. Epothilone D was conducted in patients with mild AD however data is still pending. The current clinical trial involving TPI 287 is ongoing. Future data will shed light onto the safety and efficacy of this drug. Of particular interest is to evaluate the gross density of neurofibrillary tangles, improvements in cognitive and behavioral testing, and the total tau and composite tau levels.

Methylene Blue in its current investigative formulation LMTX is the furthest advanced clinical trial to date. The premise revolves around inhibition of tau aggregation. With phase II data from Rember demonstrating relative safety and efficacy, TAIs in the form of methylthionium chloride have made large strides. With the ability of these drugs as well to be tolerated well along with inhibiting pathologic tau-tau aggregation leading to the formation of PHF while simultaneously allowing physiologic tau interaction, these drugs can provide a broad approach to tau therapy. As mentioned earlier, a broad based approach to tau therapy appears favorable due to the numerous pathologic mechanisms for tau pathology.

The proponents of TAI argue that the primary mechanism of pathology is from tau-tau aggregation through self-binding based on high affinity tau substrates. Notwithstanding, the therapeutic benefit that has been reported and data from current phase III trials will allow us to glean on the larger scale impact of LMTX and their therapeutic potential.

While numerous protein kinases can be implicated in the phosphorylation of tau, GSK-3 and CDK-5 have been studied in preclinical and clinical trials. While Tideglusib showed no significant benefits in a larger clinical trial. Lithium did show promise in patients with MCI however did not demonstrate any benefit in patients with AD. The remaining protein kinase inhibitors demonstrated efficacy in preclinical trials. While preclinical trials have been reassuring to implicate protein kinase inhibition as a mechanism to combat tauopathy, clinical trials unfortunately have not demonstrated this benefit. This may be attributed to the relatively narrow mechanism of focus for this class of drugs but further research on safety especially of the mood stabilizing agents along with efficacy of novel protein kinase inhibitors will allow us to see what future lies with this class of drugs.

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References

1. Querfurth HW, LaFerla FM. Alzheimer’s Disease. New England Journal of Medicine. 2010; 362(4): 329–344. [PubMed: 20107219]

2*. Berk C, Paul G, Sabbagh M. Investigational drugs in Alzheimer’s disease: current progress. Expert Opinion on Investigational Drugs. 2014; 23(6):837–846. (Discusses current progress of all drugs in AD therapy). [PubMed: 24702504]

3**. Grundke-Iqbal I, Iqbal K, Tung YC, et al. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proceedings of the National Academy of Sciences of the United States of America. 1986; 83(13):4913–4917. (Describes Tau Phosphorylation). [PubMed: 3088567]

4. Williams DR. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. Internal Medicine Journal. 2006; 36(10):652–660. [PubMed: 16958643]

5**. Boutajangout A, Wisniewski T. Tau-based therapeutic approaches for Alzheimer’s disease - a mini-review. Gerontology. 2014; 60(5):381–385. (discusses tau as a therapeutic target for treatment of AD). [PubMed: 24732638]

6. Giacobini E, Gold G. Alzheimer disease therapy–moving from amyloid-β to tau. Nature Reviews. Neurology. 2013; 9(12):677–686. [PubMed: 24217510]

7**. Kontsekova E, Zilka N, Kovacech B, et al. First-in-man tau vaccine targeting structural determinants essential for pathological tau-tau interaction reduces tau oligomerisation and neurofibrillary degeneration in an Alzheimer’s disease model. Alzheimer’s Research & Therapy. 2014; 6(4):44. (1st Tau Vaccine).

8. Theunis C, Crespo-Biel N, Gafner V, et al. Efficacy and safety of a liposome-based vaccine against protein Tau, assessed in tau.P301L mice that model tauopathy. PloS One. 2013; 8(8):e72301. [PubMed: 23977276]

9. Squibb, Bristol-Myers. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); May 18. 2015 A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study of Intravenously Administered BMS-986168 in Healthy Subjects. 2000-Available from: https://clinicaltrials.gov/ct2/show/NCT02294851. NLM Identifier: NCT02294851
10. Bright J, Hussain S, Dang V, et al. Human secreted tau increases amyloid-beta production. Neurobiology of Aging. 2015; 36(2):693–709. [PubMed: 25442111]
11. Troquier L, Caillierez R, Burnouf S, et al. Targeting phospho-Ser422 by active Tau Immunotherapy in the THYTau22 mouse model: a suitable therapeutic approach. Current Alzheimer Research. 2012; 9(4):397–405. [PubMed: 22272619]
12*. Collin L, Bohrmann B, Göpfert U, et al. Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer's disease. Brain: A Journal of Neurology. 2014; 137(Pt 10):2834–2846. (monoclonal antibody for treatment of tau). [PubMed: 25085375]
13. Oz S, Kapitansky O, Ivashco-Pachima Y, et al. The NAP motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through microtubule end binding proteins. Mol Psychiatry. 2014; 19:1115–1124. [PubMed: 25178163]
14. Gozes I. NAP (davunetide) provides functional and structural neuroprotection. Current Pharmaceutical Design. 2011; 17(10):1040–1044. [PubMed: 21524250]
15. Gozes I, Schirer Y, Idan-Feldman A, David M, Furman-Assaf S. NAP alpha-aminoisobutyric acid (IsoNAP). Journal of Molecular Neuroscience: MN. 2014; 52(1):1–9. [PubMed: 24458740]
16. Boxer AL, Lang AE, Grossman M, et al. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. Lancet Neurol. 2014; 13:676–685. [PubMed: 24873720]
17. Gozes I, Iram T, Maryanovsky E, et al. Novel tubulin and tau neuroprotective fragments sharing structural similarities with the drug candidate NAP (Davuentide). Journal of Alzheimer's Disease: JAD. 2014; 40(Suppl 1):S23–36. [PubMed: 24503616]
18. Gozes I. The cytoskeleton as a drug target for neuroprotection: the case of the autism- mutated ADNP. Biol Chem. 2015
19. Brunden KR, Zhang B, Carroll J, et al. Epothilone D improves microtubule density, axonal integrity, and cognition in a transgenic mouse model of tauopathy. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2010; 30(41):13861–13866. [PubMed: 20943926]
20*. Zhang B, Carroll J, Trojanowski JQ, et al. The microtubule-stabilizing agent, epothilone D, reduces axonal dysfunction, neurotoxicity, cognitive deficits, and Alzheimer-like pathology in an interventional study with aged tau transgenic mice. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2012; 32(11):3601–3611. (Description of Epothilone D in animal Tau model). [PubMed: 22423084]
21. Squibb, Bristol-Myers. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); May 23. 2015 Study to Evaluate the Safety, Tolerability and the Effect of BMS-241027 on Cerebrospinal Fluid Biomarkers in Subjects With Mild Alzheimer's Disease. 2000-Available from: https://www.clinicaltrials.gov/ct/show/NCT01492374 Identifier: NCT01492374
22. Cortice Biosciences Announces Results From Studies Evaluating Pipeline Candidates TPI 287 and CRT 001 in Preclinical Models of Tauopathies and Alzheimer's Disease. 2014 Nov 12. Retrieved May 23, 2015, from http://globenewswire.com/news-release/2014/11/12/682514/10107850/en/Cortice-Biosciences-Announces-Results-From-Studies-Evaluating-Pipeline-Candidates-TPI-287-and-CRT-001-in-Preclinical-Models-of-Tauopathies-and-Alzheimer-s-Disease.html
23*. Wischik CM, Harrington CR, Storey JMD. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochemical Pharmacology. 2014; 88(4):529–539. (A new Tau Inhibitor described). [PubMed: 24361915]
24*. Wischik CM, Staff RT, Wischik DJ, et al. Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease. Journal of Alzheimer's Disease: JAD. 2015; 44(2):705–720. completed phase 2 study regarding derivative of methylene blue. [PubMed: 25550228]

25. Del Ser T, Steinwachs KC, Gertz HJ, et al. Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: a pilot study. Journal of Alzheimer's Disease: JAD. 2013; 33(1):205–215. [PubMed: 22936007]

26. Lovestone S, Boada M, Dubois B, et al. A phase II trial of tideglusib in Alzheimer's disease. Journal of Alzheimer's Disease: JAD. 2015; 45(1):75–88. [PubMed: 25537011]

27. Forlenza OV, Diniz BS, Radanovic M, et al. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. The British Journal of Psychiatry: The Journal of Mental Science. 2011; 198(5):351–356. [PubMed: 21525519]

28. Forlenza OV, Coutinho AMN, Aprahamian I, et al. Long-Term Lithium Treatment Reduces Glucose Metabolism in the Cerebellum and Hippocampus of Nondemented Older Adults: An [(18)F]FDG-PET Study. ACS Chemical Neuroscience. 2014

29. Forlenza OV, de Paula VJ, Machado-Vieira R, et al. Does lithium prevent Alzheimer's disease? Drugs & Aging. 2012; 29(5):335–342. [PubMed: 22500970]

30. Forlenza OV, De-Paula VJR, Diniz BSO. Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders. ACS Chemical Neuroscience. 2014

31. Hu JP, Xie JW, Wang CY, et al. Valproate reduces tau phosphorylation via cyclin-dependent kinase 5 and glycogen synthase kinase 3 signaling pathways. Brain Research Bulletin. 2011; 85(3–4): 194–200. [PubMed: 21435383]

32. Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Archives of General Psychiatry. 2011; 68(8):853–861. [PubMed: 21810649]

33*. Fleisher AS, Truran D, Mai JT, et al. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. Neurology. 2011; 77(13):1263–1271. (demonstrates drawbacks of a specific alternative therapy used to target tau). [PubMed: 21917762]

34. Peng Y, Hu Y, Xu S, et al. L-3-n-butylphthalide reduces tau phosphorylation and improves cognitive deficits in AβPP/PS1-Alzheimer's transgenic mice. Journal of Alzheimer's Disease: JAD. 2012; 29(2):379–391. [PubMed: 22233765]

35. Onishi T, Iwashita H, Uno Y, et al. A novel glycogen synthase kinase-3 inhibitor 2-methyl-5-(3-{4-[(S)-methylsulfinyl]phenyl}-1-benzofuran-5-yl)-1,3,4-oxadiazole decreases tau phosphorylation and ameliorates cognitive deficits in a transgenic model of Alzheimer's disease. Journal of Neurochemistry. 2011; 119(6):1330–1340. [PubMed: 21992552]