Modeling Path Importance for Effective Alzheimer's Disease Drug Repurposing (Supplementary Materials)*

Shunian Xiang[1†], Patrick J. Lawrence[1†], Bo Peng[1], ChienWei Chiang[1], PhD, Dokyoon Kim[4], PhD, Li Shen[4], PhD, FAIMBE and Xia Ning[1,2,3‡], PhD

[1]*Biomedical Informatics Department, The Ohio State University, Columbus, OH 43210, USA*
[2]*Computer Science and Engineering Department, The Ohio State University, Columbus, OH 43210, USA*
[3]*Translational Data Analytics Institute, The Ohio State University, Columbus, OH 43210, USA*
[4]*Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA 19104 USA*
[†]*Co-first author; authors contributed equally to this work*
[‡]*E-mail: ning.104@osu.edu*

S1. The Top-50 Drugs Identified by MPI and BSL

Table S1: Top-50 Drugs from MPI

Drug	MOA	Indication	Anti-AD	Evidence
varenicline	AChR-Ag	smoking cessation	N	-
fosinopril	ACE-INH	hypertension	Y	*in vivo*[1]
nicotine	AChR-Ag	smoking cessation	Y	clinical[2]
nizatidine	histamine receptor antagonist	duodenal ulcer disease	N	-
piroxicam	COX-INH	osteoarthritis	Y	other[3,4]
meloxicam	COX-INH	osteoarthritis	Y	*in vivo*[5–7]
galantamine	AChE-INH	Alzheimer's disease	Y	approved
bromfenac	COX-INH	inflammation	N	-
etodolac	COX-INH	osteoarthritis	Y	*in vivo*[8]
pyridostigmine	AChE-INH	myasthenia gravis	N	-
bupropion	dopamine reuptake inhibitor	depression	N	-
pentoxifylline	phosphodiesterase inhibitor	claudication	N	-
flurbiprofen	COX-INH	rheumatoid arthritis	Y	clinical[9]
zonisamide	sodium channel blocker	seizures	N	-
apixaban	coagulation factor inhibitor	stroke	Y	other[3,4]
rivastigmine	AChE-INH	Alzheimer's disease	Y	approved
ramipril	ACE-INH	hypertension	Y	clinical[10]
linezolid	bacterial 50S ribosomal subunit inhibitor	pneumonia	N	-
trandolapril	ACE-INH	hypertension	Y	*in vivo*[11]

*This project was made possible, in part, by support from the National Institute of Aging grant no. 5R01AG071470. Any opinions, findings and conclusions or recommendations expressed in this paper are those of the authors and do not necessarily reflect the views of the funding agency.

moexipril	ACE-INH	hypertension	N	-
quinapril	ACE-INH	hypertension	N	-
enalapril	ACE-INH	hypertension	N	-
benazepril	ACE-INH	hypertension	N	-
lisinopril	ACE-INH	hypertension	Y	*in vivo*[12]
hydralazine	vasodilator	hypertension	Y	*in vitro*[13]
rasagiline	monoamine oxidase inhibitor	Parkinson's Disease	Y	clinical[14]
ganciclovir	DNA polymerase inhibitor	cytomegalovirus	Y	*in vivo*[15]
naproxen	COX-INH	pain relief	N	-
fluvoxamine	selective serotonin reuptake inhibitor	obsessive compulsive disorder	Y	*in vivo*[16]
dapsone	bacterial antifolate	dermatitis herpetiformis	Y	other[17]
oxaprozin	COX-INH	osteoarthritis	Y	other[3,4]
ranitidine	histamine receptor antagonist	heartburn	N	-
donepezil	AChE-INH	Alzheimer's disease	Y	approved
memantine	glutamate receptor antagonist	Alzheimer's disease	Y	approved
empagliflozin	sodium/glucose cotransporter inhibitor	diabetes mellitus	Y	*in vivo*[18]
canagliflozin	sodium/glucose cotransporter inhibitor	diabetes mellitus	N	-
alogliptin	dipeptidyl peptidase inhibitor	diabetes mellitus	Y	*in vivo*[19,20]
oxiconazole	bacterial cell wall synthesis inhibitor	tinea pedis	N	-
rivaroxaban	coagulation factor inhibitor	stroke	Y	*in vivo*[21]
fluoxetine	selective serotonin reuptake inhibitor	depression	Y	*in vivo*[22]
azelastine	histamine receptor antagonist	conjunctivitis	N	-
sertraline	selective serotonin reuptake inhibitor	depression	N	-
ibuprofen	COX-INH	headache	N	-
labetalol	adrenergic receptor antagonist	hypertension	N	-
duloxetine	norepinephrine reuptake inhibitor	depression	N	-
quinine	hemozoin biocrystallization inhibitor	malaria	N	-
trihexyphenidyl	acetylcholine receptor antagonist	parkinsonism	N	-
ketoprofen	COX-INH	rheumatoid arthritis	N	-
selegiline	monoamine oxidase inhibitor	Parkinson's Disease	N	-
nortriptyline	tricyclic antidepressant	depression	N	-

In this table, the column "Drug" shows the identified top-50 ranked drugs; the column "MOA" shows the mechanism of action of each drug; the column "Indication" presents the indication of each drug; the column "Anti-AD " indicates if the drug has evidenced anti-AD effects; and the column "Evidence" presents the type of the evidence. In this table, ACE-INH represents the angiotensin converting enzyme inhibitor; COX-INH represents the cyclooxygenase inhibitor; AChE-INH represents the acetylcholinesterase inhibitor; and AChR-Ag represents the acetylcholine receptor agonist.

Table S2: Top-50 Drugs from BSL

Drug	MOA	Indication	Anti-AD	Evidence
tetracycline	bacterial 30S ribosomal subunit inhibitor	respiratory tract infections	Y	*in vitro*[23]
selegiline	monoamine oxidase inhibitor	Parkinson's Disease	N	-
ceftriaxone	bacterial cell wall synthesis inhibitor	gonorrhea	Y	*in vivo*[24]
ibuprofen	COX-INH	headache	N	-
levobunolol	adrenergic receptor antagonist	glaucoma	N	-
ketoprofen	COX-INH	rheumatoid arthritis	N	-
carbidopa	aromatic L-amino acid decarboxylase inhibitor	Parkinson's Disease	N	-
sulindac	COX-INH	osteoarthritis	Y	*in vivo*[25]
biotin	vitamin B	supplement	Y	*in vivo*[26]
lansoprazole	ATPase inhibitor	heartburn	N	-
itraconazole	cytochrome P450 inhibitor	onychomycosis	N	-
ketorolac	COX-INH	pain relief	N	-
quinidine	sodium channel blocker	malaria	N	-
terbinafine	fungal squalene epoxidase inhibitor	tinea pedis	N	-
labetalol	adrenergic receptor antagonist	hypertension	N	-
vilazodone	serotonin reuptake inhibitor	depression	N	-
ivermectin	benzodiazepine receptor agonist	gastrointestinal roundworms	N	-
oxiconazole	bacterial cell wall synthesis inhibitor	tinea pedis	N	-
dabigatran	thrombin inhibitor	stroke	Y	*in vivo*[27]
linezolid	bacterial 50S ribosomal subunit inhibitor	pneumonia	N	-
indomethacin	COX-INH	rheumatoid arthritis	Y	clinical[28]
donepezil	AChE-INH	Alzheimer's disease	Y	approved
levodopa	dopamine precursor	Parkinson's Disease	N	-
ketoconazole	sterol demethylase inhibitor	seborrheic dermatitis	N	-
loratadine	histamine receptor antagonist	allergic rhinitis	N	-
lovastatin	HMGCR inhibitor	coronary heart disease	Y	other[29]
triamterene	sodium channel blocker	hypokalemia	Y	clinical[30]
captopril	ACE-INH	hypertension	Y	*in vivo*[31]
naproxen	COX-INH	pain relief	N	-
methyldopa	adrenergic receptor agonist	hypertension	N	-
fluvoxamine	selective serotonin reuptake inhibitor	obsessive compulsive disorder	Y	*in vivo*[16]
zonisamide	sodium channel blocker	seizures	N	-
diflunisal	prostanoid receptor antagonist	rheumatoid arthritis	Y	*in vivo*[32]
sertraline	selective serotonin reuptake inhibitor	depression	N	-
rasagiline	monoamine oxidase inhibitor	Parkinson's Disease	Y	clinical[14]
verapamil	calcium channel blocker	hypertension	Y	*in vivo*[33]
metoclopramide	dopamine receptor antagonist	gastroparesis	N	-

diclofenac	COX-INH	rheumatoid arthritis	Y	other[34]
bupropion	dopamine reuptake inhibitor	depression	N	-
amiloride	sodium channel blocker	hypertension	Y	clinical[30]
vortioxetine	serotonin receptor agonist	depression	N	-
trazodone	adrenergic receptor antagonist	depression	N	-
losartan	angiotensin receptor antagonist	hypertension	N	-
trihexyphenidyl	acetylcholine receptor antagonist	parkinsonism	N	-
fluoxetine	selective serotonin reuptake inhibitor	depression	Y	*in vivo*[22]
azelastine	histamine receptor antagonist	conjunctivitis	N	-
nicotine	AChR-Ag	smoking cessation	Y	clinical[2]
dexamethasone	glucocorticoid receptor agonist	hypercalcemia	Y	*in vivo*[35]
doxazosin	adrenergic receptor antagonist	benign prostatic hyperplasia	Y	*in vitro*[36]
tramadol	centrally-acting opioid agonist	pain management	N	-

These columns have the same meaning as those in Table S1.

S2. BSL Survival Analysis

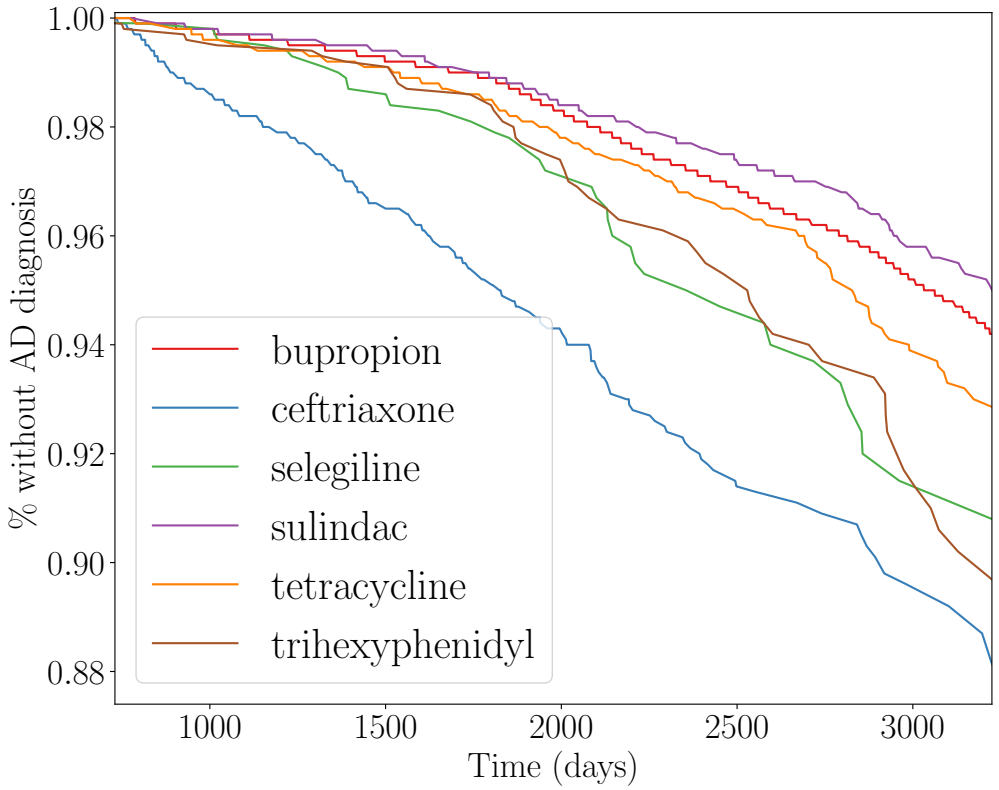

Fig. S1: Unadjusted Kaplan−Meier plots for BSL's top-ranked evidential drugs.

References

1. D. Deb, K. Bairy, V. Nayak, M. Rao et al., Comparative effect of lisinopril and fosinopril in mitigating learning and memory deficit in scopolamine-induced amnesic rats, Advances in Pharmacological and Pharmaceutical Sciences **2015** (2015).
2. P. Newhouse, K. Kellar, P. Aisen, H. White, K. Wesnes, E. Coderre, A. Pfaff, H. Wilkins, D. Howard and E. Levin, Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial, Neurology **78**, 91 (2012).
3. C. Zhang, Y. Wang, D. Wang, J. Zhang and F. Zhang, Nsaid exposure and risk of alzheimer's disease: an updated meta-analysis from cohort studies, Frontiers in aging neuroscience **10**, p. 83 (2018).
4. B. P. Imbimbo, V. Solfrizzi and F. Panza, Are nsaids useful to treat alzheimer's disease or mild cognitive impairment?, Frontiers in aging neuroscience **2**, p. 1517 (2010).
5. F. R. Ianiski, C. B. Alves, C. F. Ferreira, V. C. Rech, L. Savegnago, E. A. Wilhelm and C. Luchese, Meloxicam-loaded nanocapsules as an alternative to improve memory decline in an alzheimer's disease model in mice: involvement of na+, k+-atpase, Metabolic brain disease **31**, 793 (2016).
6. P. Guan, D. Zhu and P. Wang, Meloxicam inhibits apoptosis in neurons by deactivating tumor necrosis factor receptor superfamily member 25, leading to the decreased cleavage of dna fragmentation factor subunit α in alzheimer's disease, Molecular Neurobiology **60**, 395 (2023).
7. F. R. Ianiski, C. B. Alves, A. C. G. Souza, S. Pinton, S. S. Roman, C. R. Rhoden, M. P. Alves and C. Luchese, Protective effect of meloxicam-loaded nanocapsules against amyloid-β peptide-induced damage in mice, Behavioural Brain Research **230**, 100 (2012).
8. K. H. Elfakhri, I. M. Abdallah, A. D. Brannen and A. Kaddoumi, Multi-faceted therapeutic strategy for treatment of alzheimer's disease by concurrent administration of etodolac and α-tocopherol, Neurobiology of disease **125**, 123 (2019).
9. H. Geerts, Drug evaluation:(r)-flurbiprofen–an enantiomer of flurbiprofen for the treatment of alzheimer's disease, IDrugs: the investigational drugs journal **10**, 121 (2007).
10. W. Wharton, J. H. Stein, C. Korcarz, J. Sachs, S. R. Olson, H. Zetterberg, M. Dowling, S. Ye, C. E. Gleason, G. Underbakke et al., The effects of ramipril in individuals at risk for alzheimer's disease: results of a pilot clinical trial, Journal of Alzheimer's Disease **32**, 147 (2012).
11. J. Wang, Z. Zhao, E. Lin, W. Zhao, X. Qian, D. Freire, A. E. Bilski, A. Cheng, P. Vempati, L. Ho et al., Unintended effects of cardiovascular drugs on the pathogenesis of alzheimer's disease, PLoS One **8**, p. e65232 (2013).
12. J. Thomas, H. Smith, C. A. Smith, L. Coward, G. Gorman, M. De Luca and P. Jumbo-Lucioni, The angiotensin-converting enzyme inhibitor lisinopril mitigates memory and motor deficits in a drosophila model of alzheimer's disease, Pathophysiology **28**, 307 (2021).
13. M. Maheshwari, J. K. Roberts, B. DeSutter, K. T. Duong, J. Tingling, J. N. Fawver, H. E. Schall, M. Kahle and I. V. Murray, Hydralazine modifies aβ fibril formation and prevents modification by lipids in vitro, Biochemistry **49**, 10371 (2010).
14. Rasagiline rescue in alzheimer's disease clinical trial (r2) `https://classic.clinicaltrials.gov/ct2/show/results/NCT02359552`, Accessed: 2023-07-16.
15. L. Katsouri, A. M. Birch, A. W. Renziehausen, C. Zach, Y. Aman, H. Steeds, A. Bonsu, E. O. Palmer, N. Mirzaei, M. Ries et al., Ablation of reactive astrocytes exacerbates disease pathology in a model of alzheimer's disease, Glia **68**, 1017 (2020).
16. W. S. Kim, Y. Fu, C. Dobson-Stone, J.-H. T. Hsiao, K. Shang, M. Hallupp, P. R. Schofield, B. Garner, T. Karl and J. B. Kwok, Effect of fluvoxamine on amyloid-β peptide generation and memory, Journal of Alzheimer's Disease **62**, 1777 (2018).
17. J. H. Lee, B. Kanwar, C. J. Lee, C. Sergi and M. D. Coleman, Dapsone is an anticatalysis for

alzheimer's disease exacerbation, Iscience **25** (2022).
18. C. Hierro-Bujalance, C. Infante-Garcia, A. Del Marco, M. Herrera, M. J. Carranza-Naval, J. Suarez, P. Alves-Martinez, S. Lubian-Lopez and M. Garcia-Alloza, Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of alzheimer's disease and type 2 diabetes, Alzheimer's research & therapy **12**, 1 (2020).
19. S. O. Rahman, M. Kaundal, M. Salman, A. Shrivastava, S. Parvez, B. P. Panda, M. Akhter, M. Akhtar and A. K. Najmi, Alogliptin reversed hippocampal insulin resistance in an amyloid-beta fibrils induced animal model of alzheimer's disease, European Journal of Pharmacology **889**, p. 173522 (2020).
20. A. E. El-Sahar, N. A. Shiha, N. S. El Sayed and L. A. Ahmed, Alogliptin attenuates lipopolysaccharide-induced neuroinflammation in mice through modulation of tlr4/myd88/nf-κb and mirna-155/socs-1 signaling pathways, International Journal of Neuropsychopharmacology **24**, 158 (2021).
21. Z. Bian, X. Liu, T. Feng, H. Yu, X. Hu, X. Hu, Y. Bian, H. Sun, K. Tadokoro, M. Takemoto et al., Protective effect of rivaroxaban against amyloid pathology and neuroinflammation through inhibiting par-1 and par-2 in alzheimer's disease mice, Journal of Alzheimer's Disease **86**, 111 (2022).
22. K. Abu-Elfotuh, A. H. Al-Najjar, A. A. Mohammed, A. S. Aboutaleb and G. A. Badawi, Fluoxetine ameliorates alzheimer's disease progression and prevents the exacerbation of cardiovascular dysfunction of socially isolated depressed rats through activation of nrf2/ho-1 and hindering tlr4/nlrp3 inflammasome signaling pathway, International Immunopharmacology **104**, p. 108488 (2022).
23. G. Forloni, L. Colombo, L. Girola, F. Tagliavini and M. Salmona, Anti-amyloidogenic activity of tetracyclines: studies in vitro, FEBS letters **487**, 404 (2001).
24. M. A. Tikhonova, T. G. Amstislavskaya, Y.-J. Ho, A. A. Akopyan, M. V. Tenditnik, M. V. Ovsyukova, A. A. Bashirzade, N. I. Dubrovina and L. I. Aftanas, Neuroprotective effects of ceftriaxone involve the reduction of aβ burden and neuroinflammatory response in a mouse model of alzheimer's disease, Frontiers in Neuroscience **15**, p. 736786 (2021).
25. J. P. Modi, H. Prentice and J.-Y. Wu, Sulindac for stroke treatment: neuroprotective mechanism and therapy, Neural Regeneration Research **9**, p. 2023 (2014).
26. K. M. Lohr, B. Frost, C. Scherzer and M. B. Feany, Biotin rescues mitochondrial dysfunction and neurotoxicity in a tauopathy model, Proceedings of the National Academy of Sciences **117**, 33608 (2020).
27. M. Cortes-Canteli, A. Kruyer, I. Fernandez-Nueda, A. Marcos-Diaz, C. Ceron, A. T. Richards, O. C. Jno-Charles, I. Rodriguez, S. Callejas, E. H. Norris et al., Long-term dabigatran treatment delays alzheimer's disease pathogenesis in the tgcrnd8 mouse model, Journal of the American College of Cardiology **74**, 1910 (2019).
28. J. Rogers, L. Kirby, S. Hempelman, D. Berry, P. McGeer, A. Kaszniak, J. Zalinski, M. Cofield, L. Mansukhani, P. Willson et al., Clinical trial of indomethacin in alzheimer's disease, Neurology **43**, 1609 (1993).
29. G. Ransmayr, Cholesterol and statins in alzheimer's disease, Wiener Medizinische Wochenschrift **153**, 258 (2003).
30. Data analysis for drug repurposing for effective alzheimer's medicines (DREAM)- amiloride vs triamterene https://classic.clinicaltrials.gov/ct2/show/NCT05125237, Accessed: 2023-07-16.
31. Y. A. Abbassi, M. T. Mohammadi, M. S. Foroshani and J. R. Sarshoori, Captopril and valsartan may improve cognitive function through potentiation of the brain antioxidant defense system and attenuation of oxidative/nitrosative damage in stz-induced dementia in rat, Advanced pharmaceutical bulletin **6**, p. 531 (2016).
32. L. Rejc, V. Gómez-Vallejo, X. Rios, U. Cossio, Z. Baz, E. Mujica, T. Gião, E. Y. Cotrina,

J. Jiménez-Barbero, J. Quintana et al., Oral treatment with iododiflunisal delays hippocampal amyloid-β formation in a transgenic mouse model of alzheimer's disease: a longitudinal in vivo molecular imaging study, Journal of Alzheimer's Disease **77**, 99 (2020).

33. H. A. Ahmed and T. Ishrat, Repurposing verapamil for prevention of cognitive decline in sporadic alzheimer's disease, Neural Regeneration Research **17**, p. 1018 (2022).
34. O. Stuve, R. A. Weideman, D. M. McMahan, D. A. Jacob and B. B. Little, Diclofenac reduces the risk of alzheimer's disease: A pilot analysis of nsaids in two us veteran populations, Therapeutic advances in neurological disorders **13**, p. 1756286420935676 (2020).
35. Z. Hui, Y. Zhijun, Y. Yushan, C. Liping, Z. Yiying, Z. Difan, C. T. Chunglit and C. Wei, The combination of acyclovir and dexamethasone protects against alzheimer's disease-related cognitive impairments in mice, Psychopharmacology **237**, 1851 (2020).
36. B. P. Coelho, M. M. Gaelzer, F. dos Santos Petry, J. B. Hoppe, V. M. T. Trindade, C. G. Salbego and F. T. Guma, Dual effect of doxazosin: anticancer activity on sh-sy5y neuroblastoma cells and neuroprotection on an in vitro model of alzheimer's disease, Neuroscience **404**, 314 (2019).