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TO FILL IN THE GAPS IN ALZHEIMER'S DISEASE MEDICATIONS THAT PENETRATE THE BLOOD-BRAIN BARRIER BY PUTTING FORWARD A TRANSLATIONAL PREDICTION

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ABSTRACT

Despite significant investment in drug discovery, Alzheimer's disease (AD) continues to be a significant unmet medical need. The effectiveness of CNS drugs is severely hampered by the blood-brain barrier (BBB), and many potential compounds fall short because of poor ADMET characteristics or insufficient brain exposure. Key research gaps on BBB-crossing compounds for AD are identified in this review: A strong dependence on in vitro or in silico predictors that do not generalize well in vivo; A limited integration of robust BBB permeability prediction with ADMET profiling, A translational gap between computational predictions and experimental/clinical validation; inadequate multi-target and mechanism-aware evaluation in repurposing studies. We point out antipsychotic repurposing candidates (like benperidol) as examples that lack thorough BBB/ADMET and free-energy or dynamics studies but have encouraging docking or preclinical signals. In order to identify candidates with genuine translational potential, we suggest a useful, integrated workflow that combines multi-task machine-learning BBB models, orthogonal in-vitro assays, ADMET pipelines, and conventional MD/MM-PBSA benchmarking. Closing these gaps will improve the success rate of AD treatments by speeding up the selection of agents with both target engagement and consistent brain exposure.

KEYWORDS: Alzheimer's disease, blood-brain barrier, BBB permeability, ADMET, drug repurposing, benperidol, molecular.

INTRODUCTION

There are few disease-modifying treatments for Alzheimer's disease (AD), a progressive neurodegenerative illness that is becoming more and more prevalent worldwide. Most candidate therapies have failed in late-stage testing, frequently due to inadequate efficacy or safety concerns, despite decades of research and multiple clinical trials.[1,2] The blood-brain barrier (BBB), which limits the therapeutic exposure of substances that otherwise exhibit in vitro potency against AD targets, is still one of the most enduring challenges. In order to improve translational success, modern drug discovery necessitates not only molecular potency but also verified proof of brain penetration and advantageous ADMET (absorption, distribution, metabolism, excretioxicity) profiles.[1,3]

Advances in BBB-targeting delivery methods (such as receptor-mediated transport and focused ultrasound) and the expanding use of computational BBB prediction models are documented in recent reviews; however, significant translational gaps and model limitations still exist.[1,4,5] Drug repurposing initiatives, which include computational screenings of FDA-approved medications, have concurrently identified potential candidates like Benperidol that exhibit preclinical effects or bind AD-relevant targets in silico, but Benperidol that exhibit preclinical effects or bind AD-relevant targets in silico, but a thorough evaluation of their BBB exposure and full ADMET liabilities is frequently lacking.[6,7] In order to prioritize BBB-crossing medications for AD, this re-synthesizes the literature to find recurrent gaps and suggests an integrated framework that combines orthogonal validation and predictive modeling.

2. Why BBB and ADMET matter for AD therapeutics

The blood-brain barrier (BBB) is a dynamic, selective interface that tightly controls the flow of molecules between the brain parenchyma and blood. Lipophilicity, polar surface area (PSA), molecular weight, H-bond donors/acceptors, and P-glycoprotein (P-gp) transport are some of the characteristics of small compounds that affect their ability to reach sufficient brain concentrations.[3,8] Crucially, despite encouraging target inhibition seen in vitro, treatment failure may result from insufficient unbound brain drug concentration; on the other hand, toxicity and CNS side effects can arise from unanticipated off-target brain exposure.[3,9] De-risking the election of candidates hence requires early inclusion of ADMET profile and

BBB permeability in the discovery pipeline.

According to recent AD pipelines and reviews, the pathophysiology of AD alters the BBB's integrity, and the behavior of complex compounds in healthy models may not transfer to disease situations where barrier function is disrupted.[2,10] This encourages orthogonal experimental evaluation even more.

3. Current approaches to assess BBB crossing & ADMET - strengths and limits

3.1 In vitro models

Low-cost permeability screening is made possible by common in vitro systems (such as PAMPA-BBB, cell monolayers, and hCMEC/D3). PAMPA-BBB lacks metabolic and active transport components, but it correlates rather well with in vivo brain permeation in large datasets (reported correlations of ~0.7-0.8 in some investigations).[11] Although cell-based models reflect tighter junction characteristics and active transport, their general utility is diminished by restricted scalability and lab-to-cell line heterogeneity.

3.2 In vivo methods

Microdialysis and rodent brain/plasma ratio testing are still the gold standards for direct brain exposure, but they require a lot of resources and have low throughput, and species differences make human translation.

3.3 In silico models

For predicting BBB permeability, QSAR, ML/DL, and hybrid mechanistic models have become increasingly popular. Compounds can be categorized by permeability using machine-learning techniques and traditional descriptors (logP, PSA, and MW). However, models frequently have poor interpretability, unbalanced datasets, and no standardized endpoints (e.g., LogBB vs. category permeability).[12,13] Deep learning and recent large-scale machine learning initiatives show promise, but they still need mechanical interpretability and thorough external validation before they can be extensively used for high-stakes or regulatory decision making.[5,12]

4. Gaps in current research on BBB-crossing AD drugs and ADMET

4.1 Fragmented workflows: siloed prediction or testing Numerous papers present data from a single approach (such as a single in vitro BBB assay or docking scores indicating target affinity) without incorporating cross-validated ADMET and BBB evidence. As a result,

hopeful applicants fall short when put through more rigorous testing. It is uncommon to find integrated pipelines that incorporate early in vivo exposure measurements, in vitro permeability tests, and orthogonal in silico forecasts.

Method	Strengths	Limitations
In vitro (PAMPA, Cell models)	Cheap, rapid, scalable; captures permeability	Lacks transporters, variability across labs
In vivo (Rodents)	Gold standard, captures full psychology	Expensive, Species differences
In silico (QSAR, ML/DL)	High throughput; Predicts permeability trends	Dataset imbalance, Endpoint inconsistency

Comparison of in vitro, in vivo, and in silico BBB models.

4.2 Over-reliance on docking / screening without exposure evaluation

Docking results (binding scores) are commonly reported by drug-repurposing screens for AD, but they are rarely accompanied by MD/MM-PBSA energetic validation or strong BBB exposure predictions (quantitative LogBB, P-gp substrate probability). The crucial proof of realistic brain concentrations is thus absent from a large number of repurposed candidates.

Benperidol, for instance, has been found to be a potent binder to AD targets in a number of in-silico screens; nevertheless, there are few thorough BBB/ADMET and sophisticated modeling studies.[6,7]

4.3 Insufficient attention to disease-specific BBB alterations

In AD, BBB permeability may alter due to transporter expression alterations and localized leakage. Brain exposure in sick brains may be mispredicted by standard permeability models that were trained under healthy conditions. Few studies employ models that reflect this changed physiology or account for disease-specific vascular alterations.[2,22]

4.4 Lack of standardization in BBB endpoints and benchmark datasets

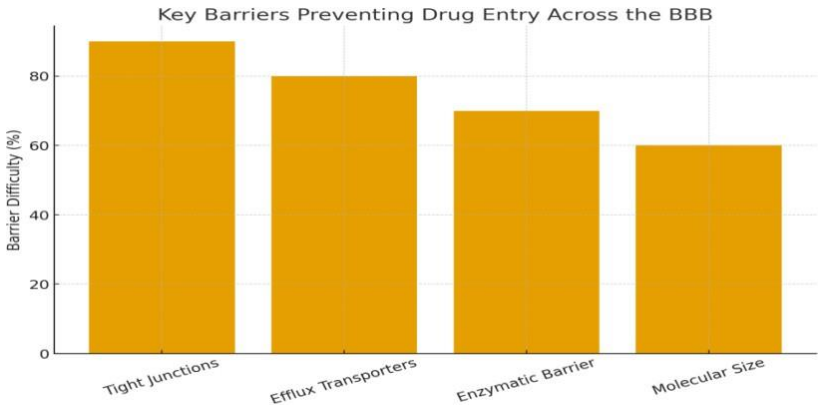
Building generalizable machine learning models is hampered by imbalanced or heterogeneous datasets and a variety of endpoints (LogBB, brain/plasma ratio, PAMPA permeability). To compare models fairly, the sector requires open datasets and community benchmarks.[12,16]

4.5 Sparse use of dynamics and free-energy calculations in repurposing

A poor substitute for binding affinity stability is docking alone. Few repurposing papers advance to MM-PBSA/MM-GBSA calculations or MD simulations, which would improve translational priority by better predicting complex stability and binding energetics.

5. Case example: Benperidol promise but missing translational data

Computational repurposing screens have shown that benperidol, an FDA-approved butyrophenone antipsychotic with potent CNS penetration, has good docking scores against ACHE, BACE-1, and other AD targets [6,20]. Although its exposure in the central nervous system implies the ability to cross the blood-brain barrier, there are no (a) quantitative LogBB or validated BBB permeability assays, (b) thorough ADMET profiling (P-gp substrate status, CYP liabilities, hERG risks) in the context of AD, or (c) MD/MM-PBSA benchmarking of predicted complexes in the published literature. In the absence of these, the hypothesis-generating claim is not translated into action.



6. Proposed integrated framework to fill gaps

We suggest the multi-tier approach below to enhance translational prioritizing of BBB-crossing AD candidates.

Tier 1 Computational prescreening (high throughput)

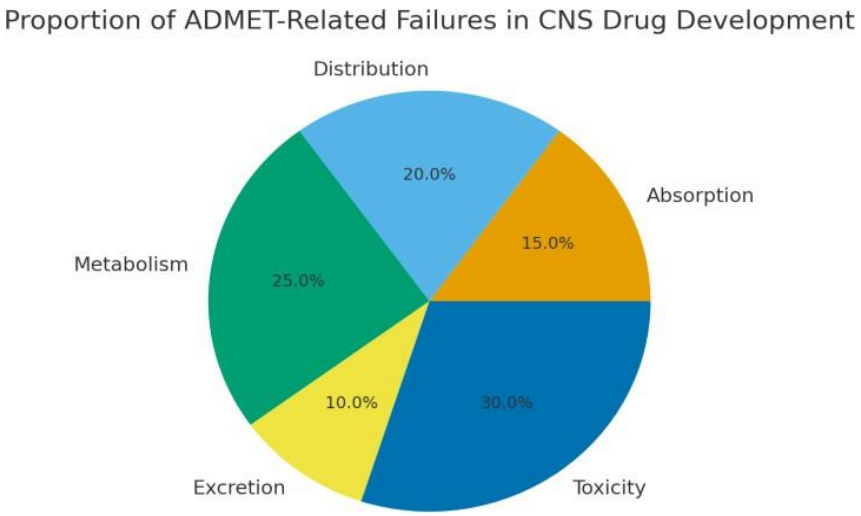
- Consensus scoring for multi-target docking (ACHE, BACE-1, tau kinases, and NMDA subunits).
- ADMET predictors (CYP, hERG, and P-gp) and predictive machine learning BBB models (ensemble of logBB regressors and categorical classifiers). Utilize models that have been verified on outside datasets.

Tier 2 - Mechanistic dynamic validation

- MD simulations of top complexes (50–100 ns); examine binding interactions, RMSD, and RMSF.
- Free-energy calculations using MM-PBSA/MM-GBSA to rank candidates according to thermodynamic stability.

Tier 3 - Orthogonal in-vitro BBB evaluation

- Transwell tests using PAMPA-BBB + cell lines to evaluate both active and passive transport.
- Assays for the P-gp transporter to identify efflux liabilities.



Tier 4 - Early in vivo exposure

The best options for measuring unbound brain concentrations (Kp,uu) are microdialysis or rodent brain/plasma PK.

Tier 5 - Safety and DDI risk assessment Off-target toxicity prediction using in vitro hepatocyte/CYP and cardiotoxicity panels.

In order to produce candidates with both target engagement and observable brain exposure, this integrated approach combines predictive speed with mechanistic confidence and experimental cross-checks.

7. Practical recommendations for researchers & journal reviewers

1. Repurposing claims of CNS drugs must include at least one orthogonal BBB estimate (e.g., both in-silico LogBB and a PAMPA or cell assay).

2. Promote MD and binding free-energy follow-up for the best docking hits before repurposing claims are published.
3. Standardize the reporting of ADMET flags (P-gp substrate status, major CYP interactions) and BBB endpoints (report LogBB or Kp,uu if feasible).
4. To facilitate model development and comparison, produce and distribute community benchmark datasets for brain exposure and the BBB.
5. As part of translational recommendations, a targeted ADMET and safety dossier should be required for repurposed CNS medications (such as benperidol).

CONCLUSIONS

ADMET and BBB permeability are key factors that determine how well Alzheimer's treatments work. Despite the quick advancements in computational repurposing and delivery strategies, there are still significant gaps, including siloed workflows, an excessive dependence on docking without exposure evidence, a lack of standardized benchmarks, and inadequate disease-specific modeling. Candidate molecules (including repurposed CNS drugs like benperidol) are more likely to progress to meaningful preclinical and clinical evaluation if the suggested integrated pipeline—coupling ensemble predictive models, dynamics/free-energy validation, orthogonal in-vitro assays, and focused in-vivo exposure studies—is put into practice.

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