Drug Repurposing in Alzheimer's Disease: The Need of the Hour

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Abstract: Alzheimer's disease (AD) is a rapidly emerging disease worldwide and the production of new drugs is expensive, time consuming and often unsuccessful. Drug repurposing is an appealing approach used to explore new therapeutic uses of existing drugs with known safety and pharmacokinetic profiles. This paper discusses the current status of drug repurposing for AD, lists some of the most frequently mentioned repurposing candidates and their therapeutic category and discusses methods to validate drug repurposing hypotheses. The current evidence suggests a variety of potential treatments with no clear evidence of candidates to prioritize. There is inconsistent use of validation practices, and limited use of real world evidence. The lack of central nervous system penetration, preclinical limitations of blood–brain barrier models, uncertainty regarding effective dosing and safety, lack of standardized biomarkers, regulatory and commercial restrictions further limit the clinical translation. If this real-world data is integrated with computational screening, better disease models, validated biomarkers and collaborative research, these could help with more reliable candidate selection and could speed up effective AD treatments.

Keywords: Alzheimer's disease; drug repurposing; blood–brain barrier; real-world evidence; translational research.

1. Introduction

Alzheimer's disease (AD) is becoming increasingly prevalent worldwide. It is estimated that the number of people with AD dementia will increase from about 57 million today to 153 million by 2050. It is likely that this rise will have the greatest impact on low- and middle-income countries, which will have 71% of all dementia cases by mid-century. This burden is even higher when individuals with mild cognitive impairment or preclinical AD are taken into account.

But the rising tide of other neurodegenerative disorders is also being driven by population ageing. They are Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration and amyotrophic lateral sclerosis. While anti-amyloid monoclonal antibodies have been approved for the treatment of AD, this indicates a step forward in the treatment of AD, the drugs are only for the early stages of the disease and require diagnostic and treatment technologies that are not widely available. In addition, there are many biological mechanisms other than the amyloid that are involved in AD, providing further avenues for research into therapeutic interventions. New interventions that prevent or slow onset of disease, and that reduce the clinical rate of progression and enhance cognition, behavior, everyday functioning, and neurological symptoms are therefore much needed.

The development of drugs for AD and other neurodegenerative diseases is a long, expensive and risky procedure. It takes approximately 13 years to develop a typical program; many experimental therapies ultimately fail. Developments that shorten, decrease the cost, and minimize the uncertainty of development may help develop effective treatments faster for patients. A potential way forward is drug repurposing, which involves assessing existing drugs that have been approved for other, non-AD, neurodegenerative disorders, for potential therapeutic use in AD [1].

2. Related work

In an article published recently, 573 different drugs were mentioned, which were proposed to be used in the treatment of AD in the last decade. Of these, 17% were drugs acting on the nervous system, 16% were antineoplastic or immunomodulating drugs, and 12% were cardiovascular drugs. There was a wide variety of possible medications, and the most popularly suggested was clozapine, an atypical antipsychotic, which was only seen in six studies. Of the 124 studies reviewed, 76 used at least some type of validation. However, only 5 used real world data to justify their conclusions.

Overall, the report illustrates that a considerable number and diversity of repurposed medicines have been identified that could be developed for the treatment of AD. However, there is no consistent support for any single drug to be considered the most promising, so it is difficult to prioritize next steps for research. The authors also noticed that not all candidates proposed were validated and that real world evidence was not used much. The wider use of these kinds of evidence could enable scientists to compare various treatments, to identify what treatment(s) provide the best potential and to speed up the creation of new therapy treatments for AD (Table 1) [2].

Table 1. Frequently suggested AD repurposing candidates

Proposed drug	Studies supporting repurposing	Broad ATC category	Specific therapeutic subgroup
Clozapine	6	Nervous-system medicines	Antipsychotic agents
Adenosine	5	Cardiovascular medicines	Other treatments used for cardiac conditions
Aripiprazole	5	Nervous-system medicines	Antipsychotic agents
Pioglitazone	5	Alimentary and metabolic medicines	Non-insulin drugs used to lower blood glucose
Risperidone	5	Nervous-system medicines	Antipsychotic agents
Sunitinib	5	Anticancer and immune-modulating medicines	Protein kinase inhibitors
Tamoxifen	5	Anticancer and immune-modulating medicines	Hormone antagonists and related therapies
Vandetanib	5	Anticancer and immune-modulating medicines	Protein kinase inhibitors
Verapamil	5	Cardiovascular medicines	Selective calcium-channel blockers with direct effects on the heart
Vorinostat	5	Anticancer and immune-modulating medicines	Other antineoplastic agents

3. Translational Challenges

Drug repurposing is a very attractive approach in the area of AD, since already known drugs have a thorough safety as well as pharmacokinetic profile, but there are certain challenges against clinical translation. Many drugs lack adequate penetration of the CNS, and structural modification and delivery by nanocarriers, focused ultrasound, intracranial delivery add extra technical and regulatory complications [3], [4]. The biological nature of Blood-Brain Barrier (BBB) might not be adequately recapitulated in preclinical models, limiting the accuracy of clinical predictions [5]. Furthermore, dose reoptimisation, CNS pharmacokinetics, and CNS specific safety evaluation are needed to reach therapeutic CNS concentration without systemic side effects [6]. Limiting clinical development is the lack of standardisation of biomarkers, while soluble proteins and imaging, like DCE-MRI, hold promise for monitoring BBB damage and repair [7]. Regulatory regulations, restricted commercial monopoly, and poor financial returns also hinder investment [8], [9]. However, new developments in biomarkers, computer-based screening techniques, BBB mimetic models, and combined research probably can speed up clinical translation.

4. Key Contribution

This paper furthers the knowledge of this field by giving an extensive overview of the drug-repurposing research for AD. It compiles all the evidence from various studies and categorizes the suggested treatments in a systematic way based on treatment classifications. The analysis shows the variety of available drugs that could be used in AD treatment. It also points out that there is no well-defined process of identifying and prioritizing the best candidates. Existing validation practices are reviewed, with important weaknesses in the reliability and comparability of existing research identified. Specifically, it highlights the need to take advantage of real-world evidence to support the repurposing hypothesis. The paper thus offers useful guidance for enhancing both candidate assessment and validation approaches and future research. Overall it is helping to build a more systematic and evidence-based strategy for finding effective treatment for AD.

5. Conclusion

Drug repurposing offers significant potential for decreasing the time, cost and risk in the development of treatments for AD. But there are still a number of disjointed pieces of evidence, and there's no clear frontrunner as yet. Standardized candidate selection, validation and comparison should be achieved and real-world evidence should be used more in future research. Careful consideration of BBB penetration, CNS-effective dosing, toxicity, and clinical relevance will also be critical. Better preclinical models and validated biomarkers could facilitate the translation from preclinical results to clinical trials. Moreover, interdisciplinary cooperation between researchers, health care systems, regulatory agencies, and industry can help overcome financial and regulatory barriers. However, together with computational screening and advanced BBB-mimetic platforms, these activities could set the groundwork for a more systematic route to translate repurposed medicines into safe, accessible, and effective treatments for AD.

6. References

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