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HUMAN

Repurposed Drug Prioritisation Pipeline for an Alzheimer's Disease Multi-arm Platform Trial

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Abstract

Background: Despite recent developments in amyloid-clearing therapies for Alzheimer's Disease (AD), there remains a need for more effective, safe treatments. Funded by the UK National Institute of Health and Care Research, our aim was to establish a robust, systematic, and unbiased drug prioritisation pipeline to identify repurposed drugs with the greatest potential for sustained clinical effect in clinical 'real-world' AD (MMSE >17). These would then be considered for inclusion in a planned multi-arm UK platform trial.

Method: We invited the wider AD community to propose compounds by summarising their rationale and evidence in a prespecified drug proposal form. Fourteen proposals were received, and the drug proposers were invited to the first panel meeting. They presented a pre-clinical data focused rationale for each compound to an international expert panel comprised of AD clinicians, scientists, industry professionals, as well as both charity and patient/public representatives. In the context of a platform trial using prespecified primary outcome of cognition (ADAS-Cog, with neuropsychiatric symptoms and everyday activities as secondary outcomes), the panel ranked their top three compounds based on efficacy, biological plausibility, and safety in AD. Ten compounds were taken forward with two subsequently excluded due to lack of data in humans. We compiled extended drug curriculum vitae (CV) for the eight shortlisted compounds. This incorporated practical clinically relevant information and was supplemented by systematic clinical literature review using Repurposing Living Systematic Review (ReLiSyR), a machine learning tool that searches databases and screens studies to identify relevant publications.

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Result: Drug CVs were reviewed in a second panel meeting. Compound rankings were repeated with previous considerations and also practical clinical factors. The highest ranked compounds were atomoxetine (1st), metformin (2nd), isosorbide mononitrate and levetiracetam (joint 3rd). The pivotal determining factors across the top ranked compounds included scientific evidence of plausible mechanistic pathways in AD as well as evidence of substantial clinical data on safety and tolerability.

Conclusion: We present a practical approach to prioritising repurposed drugs to evaluate in the context of clinical AD. We would like to thank our patient and public contributors and the wider investigator team.