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EXPERT OPINION

Is a potential Alzheimer's therapy already in use for other conditions? Can medications for hypertension, diabetes and acne help with the symptoms?

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There is an urgent need to develop and evaluate more effective pharmacological treatments for Alzheimer's disease (AD). This editorial explores the avenue of drug repositioning and outlines a number of existing treatments that show great promise as therapies, in addition to discussing the potential for high-throughput drug discovery techniques in this important field.

Keywords: Alzheimer's disease, pharmacological, repositioning

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Dementia affects 35 million people worldwide, the majority of whom have Alzheimer's disease (AD). This devastating condition incurs an enormous personal cost to those affected and a worldwide financial cost in 2010 estimated at $604 billion [1]. AD therefore represents a major and increasing public health concern and there is an urgent imperative to develop more effective therapies to treat and delay the onset of the disease. There are currently four pharmacological treatments licensed in the UK which provide symptomatic benefit in AD. Three acetylcholinesterase inhibitors (donepezil, rivastigmine, galanthamine) are licensed for the treatment of people with mild to moderate AD. Memantine, an NMDA receptor antagonist, is licensed for the treatment of people with moderate to severe AD. Meta-analyses and cost-effectiveness evaluations have demonstrated that these treatments confer moderate symptomatic benefit and are cost-effective [2]. The availability of these drugs has been a significant advance in the treatment of people with AD, but there is a pressing need to build upon our increasing understanding of pathogenesis to develop more effective symptomatic treatments and disease-modifying therapies.

Efforts to develop more effective therapies have so far been unsuccessful, with several high profile clinical trials failing to demonstrate benefit. In part this failure is probably due to an overemphasis on the amyloid cascade as a target for disease modification [3], despite the myriad other complex and inter-related other systems that are involved in AD pathology. Trials of treatments targeting this pathology have also focused on recruiting participants with advanced amyloid pathology which is now thought to limit the potential efficacy of the drug in trial. Furthermore, there is criticism of the trial design and heterogeneity of trial cohorts which likely introduce confounding factors that prevent any true treatment effect from being detected. As a result of these failures and a lack of interest in investment in the field, there are currently fewer than 25 in-progress Phase II or III clinical trials of disease-modifying therapies for AD registered on the NCT or ISRCTN clinical trial databases, compared to > 1700 trials of cancer therapies [4]. A small number of these have shown initial promising outcomes, for example preliminary findings indicate

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a slowing of AD progression with the immunotherapy solaneuzumab [5]. However, positive trial outcomes are rare and so far are limited to preliminary, early phase trials. The majority of treatments have failed in subsequent trials, often showing inconsistent outcomes which do not reach statistical significance. There is currently a great opportunity to address this significant gap in research through novel, innovative approaches to drug discovery.

Drug repositioning offers an alternative, cost-effective translational drug development route with the potential to bring new treatments to the bedside in a fraction of the time required to develop a treatment from scratch. It has been used with great success in many disease areas including cancer, stress incontinence, irritable bowel syndrome, obesity, smoking cessation, psychosis and attention deficit disorder [6]. The considerable advantages associated with drug repositioning include the established safety and tolerability profile of the candidates which reduces the need for costly and time-consuming testing and optimisation phases. Approaches to drug repositioning vary across the literature, with some studies focusing on the identification of novel therapeutic targets for established drugs and others utilizing a broader interpretation which includes the investigation of drugs that act on the same target as that for which they are already licensed.

A recent systematic review, which utilised an extensive Delphi-style iterative process involving expert and industry representatives, recommended some agents for fast-tracking to clinical trial [7]. These included antihypertensives, antibiotics, anti-diabetic treatments and retinoid therapy. The evidence to support the potential benefit of angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) in AD is extensive. Beyond the established link between the condition and hypertension, these agents possess proposed neuroprotective mechanisms which may have a direct impact on cognition. ARBs directly impact on the activity, processing and receptor pathways of centrally acting angiotensin, a key player in mediation of inflammation and inhibition of acetylcholine release [8]. Both ARBs and CCBs have an emerging body of evidence indicating an effect on amyloid processing and accumulation both *in vitro* and *in vivo*, and both possess good brain penetrance, a key factor in any agent to be considered for treatment of AD [9,10]. The CCB nimodipine also has clinical trial evidence to support its benefit in people with dementia. A Cochrane review reported significant benefit in cognition, but not function, in 15 trials involving over 3000 people [11]. Two further CCBs, amlodipine and nivaldipine have also shown promise through reduction of amyloid burden in *in vivo* models of AD and have been taken forward to Phase II trials [5]. The rationale for repositioning diabetes drugs in AD is based in the established role of insulin signalling in AD, and the potent neuroprotective activity of insulin and insulin growth factor. Diabetes is an established risk factor for AD and other dementias. This relationship is thought to be not only due partly to similar lifestyle risk factors such as obesity and hypertension, but also due to the known disruption of insulin signalling in the AD brain [12]. Glucagon-like peptide (GLP-1) analogues such as exenatide and liraglutide, which are licensed for treatment of type 2 diabetes therefore hold promise in AD as they promote insulin release in addition to influencing a number of pathways related to AD pathology including amyloid precursor protein processing, amyloid- and iron-mediated neuronal impairment and apoptotic pathways via key cellular proteins. There is promising *in vivo* data to support the use of GLP-1 analogues including evidence of direct impact on both pathology and symptomology in animal models [13]. Exenatide has now entered Phase II trials in 115 people with AD and MCI to establish the impact of treatment on cognition and AD biomarkers (NCT01255163-Jan2013). The antibiotic minocycline is also a promising candidate based on data from *in vivo* studies that show a direct impact on amyloid pathology and behaviour [14] and promising outcomes from open trials in Parkinson's disease [15]. The expert review also identified retinoid therapy as a potentially viable candidate for repositioning. This class of therapies have excellent potential mechanistic plausibility due to their impact on APP processing, amyloid clearance, insulin signalling and neurogenesis [16]. A main barrier to retinoid therapy in AD is tolerability in frail older people due to the side-effect profile of the drugs including impaired liver function, skin exfoliation, headache, myalgia and abnormal lipids. Interestingly however, consultation with people with AD and their carers revealed a willingness to accept a fairly high level of adverse effects [7]. Of particular note and in a very exciting development, clinical trials of candidate drugs within each of the identified classes of candidate drug are now underway or will be commencing within the next six months. Phase II clinical trials of GLP analogues liraglutide and exendin, the retinoid acicretin, the ARB losartan and the antibiotic minocycline will commence in the UK, US and Germany. The calcium channel blocker nivaldipine will also enter Phase III trial in Ireland, funded by the European Union.

It is perhaps indicative of a new attitude towards drug discovery in AD that all of the priority candidates identified by the recent review are now in clinical trials for the condition. A more open attitude to this approach has been fostered by increased dialogue about the potential benefit and great need for new therapies in AD. This landscape now offers the opportunity for a greater programme of drug repositioning in AD and other dementia types. High-throughput screening techniques and the use of transcriptional profiling and established experimental *in vivo* and *in vitro* assays raises the potential to rapidly screen large numbers of candidate compounds. A number of large compound libraries are now available, with associated safety data. Any screening programme would require access to key animal model and microarray systems to test hitherto unidentified compounds with the potential to modify the disease processes in AD. Due to the relatively limited datasets available for these compounds, a robust decision-making algorithm would be required to ensure that

only compounds with the most promising combination of activities in a range of assays were taken forward to clinical trial. However, such a high-throughput raises the opportunity to identify existing candidate treatments on a scale to match other disease areas, and to reach a critical mass at which the potential to find a true disease-modifying therapy becomes a reality.

Declaration of interest

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