

## Repurposing Clinically Used Antibiotics for the Treatment of Alzheimer's Disease

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### Editorial

Alzheimer's disease (AD), a chronic progressive neurodegenerative disease, is the leading cause of dementia in elderly which is pathologically characterized by deposition of amyloid plaques and formation of neurofibrillary tangles [1]. Approximately, 29.8 million people worldwide are diagnosed with AD [2]. Moreover, clinical and experimental studies have already been shown the involvement of several infectious microbes such as *Herpes Simplex Virus Type 1* (HSV-1), *Helicobacter pylori*, *Chlamydomphila pneumoniae*, and *Borrelia burgdorferi* in the cognitive decline [3]. Therefore, these infectious agents have been assumed as the possible cause of AD. Currently, available therapy provides only symptomatic treatment. There is an urgent need to develop a therapy which could slow the progression, delay the onset, prevent, reverse or improve the cognitive functions of AD patients. Various neuroscientists from academia and pharmaceutical/biotechnology companies are trying to find new therapeutic interventions for the treatment of AD.

Repurposing also known as repositioning, reusing, rediscovery means to study new uses of already approved or abandoned drugs. In the drug development process, the repurposing of existing drugs offers following advantages over the creation of new ones [4].

1. The safety profile has already been established.
2. The pharmacokinetic, formulation, and manufacturing issues have been resolved.
3. Repurposing can get drugs to the market cheaper and faster than de novo drug discovery program.

Numerous repurposed drugs have been tested in experimental and clinical studies [4]. Several antibiotics such as  $\beta$ -lactam, tetracyclines, and macrolides have shown the potential anti-Alzheimer activity in preclinical studies [5-8]. Moreover, treatment of *Helicobacter pylori* with antibiotics have shown improved cognitive parameters in AD patients [7]. Tetracycline and its derivatives (doxycycline and minocycline) have also shown the neuroprotective effect in various experimental models of AD [8-10]. However, treatment with doxycycline and rifampin orally daily for 3 months in mild to moderately severe AD patient demonstrated fewer declines on the Standardized Alzheimer's Disease Assessment Scale Cognitive Subscale at 6 months. However, no difference was observed between treatment and placebo groups at 3 and 12 months [11]. In another study, doxycycline alone or in combination with rifampin has not shown any positive effects on cognitive parameters [12]. Furthermore, ceftriaxone decreased the tau pathology and showed the improvement in cognitive functions through the restoration of glial glutamate transporter in a 3xTgAD mouse model of AD [13]. Additionally, the macrolide antibiotics such as roxithromycin, clarithromycin, erythromycin, azithromycin, or kitasamycin also showed the neuroprotective effect in

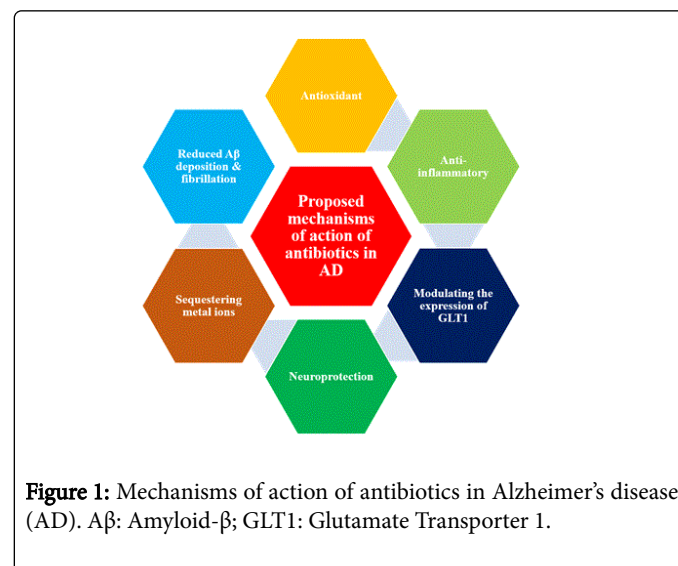
experimental model of ischemia [14]. Therefore, these antibiotics could be the potential therapeutic agents for AD.

The repurposed drugs for AD therapy should be selected based on the following criteria:

1. The drugs have already been shown the antioxidant and anti-inflammatory activities *in-vitro* and *in-vivo* models.
2. The drugs should have very good brain permeability.
3. Drugs with novel targets that show potential to delay, slow (or) prevent the progression of AD.

If more than one drug in class is available, then, detailed intra-class comparability data such as side effects, dose regimen, pharmacokinetic data, etc. are required.

A very little is known about the protective mechanism of action of these antibiotics in AD research. The antibiotics may exert the anti-Alzheimer effects via an antioxidant, anti-inflammatory activity, neuroprotection, sequestering metal ions, modulating the expression of Glutamate Transporter (GLT1) and reducing the A $\beta$  deposition and fibrillation (Figure 1).



**Figure 1:** Mechanisms of action of antibiotics in Alzheimer's disease (AD). A $\beta$ : Amyloid- $\beta$ ; GLT1: Glutamate Transporter 1.

The major concern about the repurposing antibiotics for AD treatment is safety. As we know that we need to administer the medications chronically for the treatment or management of AD. Therefore, chronic use of antibiotics at clinical dose may impose drug resistance as the results of which it becomes difficult to treat the common infection. The long-term use of antibiotics may make the patients more susceptible to infection. Additionally, chronic use of

antibiotics may also affect the beneficial microbes of the gut of the patients. We need to investigate the anti-Alzheimer potential of antibiotics at the dose lower than the dose used for the treatment of infection. If any antibiotics are showing Anti-Alzheimer potential either in experimental or clinical studies, then, long-term consequences of these antibiotics need to be evaluated. Moreover, no need to mention various classes of drugs such as anti-diabetic, anti-depressants, etc. other than those used for antibiotics are considered as potential drugs for AD treatment. Drug repurposing is one way for fast translation of existing therapeutic information into new indications. Hence, there is need to search the therapeutic potential of existing drugs for the better treatment or management of AD using repurposing approach.

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