Journal of Pharmacological Reports

Mehla, J Pharmacol Rep 2017, 2:1

Editorial Open Access

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

Jogender Mehla*

Canadian Centre for Behavioural Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada

***Correspondence author:** Jogender Mehla, Canadian Centre for Behavioural Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge-T1K3M4 Alberta, Canada, Tel: (1) 4039292361; E-mail: jsmehlaaiims@gmail.com

Received date: June 22, 2017; **Accepted date:** June 24, 2017; **Published date:** July 1, 2017

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*, *Chlamydophila 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 knew 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 β-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 Aβ deposition and fibrillation (Figure 1).

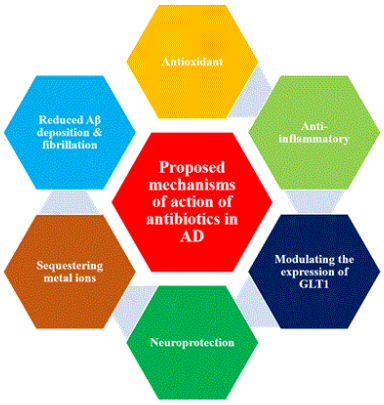

Figure 1: Mechanisms of action of antibiotics in Alzheimer's disease (AD). Aβ: Amyloid-β; GLT1: Glutamate Transporter 1.

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 drugs 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.

References

1. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297: 353-356.
2. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators (2016) "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388: 1545-1602.
3. Mawanda F, Wallace R (2013) Can infections cause Alzheimer's disease? Epidemiol Rev 35: 161-180.
4. Appleby BS, Nacopoulos D, Milano N, Zhong K, Cummings JL (2013) A review: treatment of Alzheimer's disease discovered in repurposed agents. Dement Geriatr Cogn Disord 35: 1-22.
5. Forloni G, Colombo L, Girola L, Tagliavini F, Salmona M (2001) Anti-amyloidogenic activity of tetracyclines: studies in vitro. FEBS Lett 487: 404-407.
6. Tucker S, Ahl M, Cho HH, Bandyopadhyay S, Cuny GD, et al. (2006) RNA therapeutics directed to the non-coding regions of APP mRNA, in vivo anti-amyloid efficacy of paroxetine, erythromycin, and N-acetyl cysteine. Curr Alzheimer Res 3: 221-227.
7. Kountouras J, Boziki M, Gavalas E, Zavos C, Grigoriadis N, et al. (2009) Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. J Neurol 256: 758-767.
8. Diomede L, Cassata G, Fiordaliso F, Salio M, Ami D, et al. (2010) Tetracycline and its analogues protect Caenorhabditis elegans from β amyloid-induced toxicity by targeting oligomers. Neurobiol Dis 40: 424-431.
9. Choi Y, Kim HS, Shin KY, Kim EM, Kim M, et al. (2007) Minocycline attenuates neuronal cell death and improves cognitive impairment in Alzheimer's disease models. Neuropsychopharmacology 32: 2393-2404.
10. Costa R, Speretta E, Crowther DC, Cardoso I (2011) Testing the therapeutic potential of doxycycline in a Drosophila melanogaster model of Alzheimer disease. J Biol Chem 286: 41647-41655.
11. Loeb MB, Molloy DW, Smieja M, Standish T, Goldsmith CH, et al. (2004) A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J Am Geriatr Soc 52: 381-387.
12. Molloy DW, Standish TI, Zhou Q, Guyatt G (2013) the DARAD Study Group. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. Int J Geriatr Psychiatry 28: 463-470.
13. Zumkehr J, Rodriguez-Ortiz CJ, Cheng D, Kieu Z, Wai T, et al. (2015) Ceftriaxone ameliorates tau pathology andcognitive decline via restoration of glial glutamate transporter in a mouse modelof Alzheimer's disease. Neurobiol Aging 36: 2260-2271.
14. Inaba T, Katayama Y, Ueda M, Nito C (2015) Neuroprotective effects of pretreatment with macrolide antibiotics on cerebral ischemia reperfusion injury. Neurol Res 37: 514-524.