● REVIEW

Selective serotonin reuptake inhibitors and Alzheimer's disease

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Abstract

Given the failure to develop disease-modifying therapies for Alzheimer's disease (AD), strategies aiming at preventing or delaying the onset of the disease are being prioritized. While the debate regarding whether depression is an etiological risk factor or a prodrome of AD rages on, a key determining factor may be the timing of depression onset in older adults. There is increasing evidence that untreated early-onset depression is a risk factor and that late-onset depression may be a catalyst of cognitive decline. Data from animal studies have shown a beneficial impact of selective serotonin reuptake inhibitors on pathophysiological biomarkers of AD including amyloid burden, tau deposits and neurogenesis. In humans, studies focusing on subjects with a prior history of depression also showed a delay in the onset of AD in those treated with most selective serotonin reuptake inhibitors. Paroxetine, which has strong anticholinergic properties, was associated with increased mortality and mixed effects on amyloid and tau deposits in mice, as well as increased odds of developing AD in humans. Although most of the data regarding selective serotonin reuptake inhibitors is promising, findings should be interpreted cautiously because of notable methodological heterogeneity between studies. There is thus a need to conduct large scale randomized controlled trials with long follow up periods to clarify the dose-effect relationship of specific serotonergic antidepressants on AD prevention.

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Introduction

Per the 2018 worldwide estimates, around 50 million individuals are living with dementia and every three seconds, one new person will develop the disease. Numbers are expected to increase 1.6 and 3 times by 2030 and 2050 respectively. The corresponding cost of care is also estimated to exponentially increase from one trillion US dollars in 2018 to three trillion by 2050. Alzheimer's disease (AD) is by far the most common type of dementia constituting 60–80% of all cases, and thus carrying the heaviest societal and economic burden (Alzheimer's Disease International, 2018).

AD is conceptualized as a biological and clinical continuum of three different stages. In the first, pre-clinical stage, the individual is asymptomatic but carries biomarkers of the disease including β-amyloid (Aβ) and/or pathologic tau deposition. The individual then progresses to the second stage of mild cognitive impairment with limited functional impact. By the third and final stage, the individual ultimately develops AD dementia, which is characterized by cognitive and pathophysiological changes as well as impairment in activities of daily life (Aisen et al., 2017). Given the multiple failures in developing disease-modifying therapies for AD, early interventions aiming at preventing or delaying its onset are promising strategies to decrease the substantial burden of the disease (Zissimopoulos et al., 2014).

Among modifiable risk factors for AD, depression stands out as a significant one, contributing to up to 15% of all AD cases (Barnes and Yaffe, 2011). A history of depression may be associated with an increased risk of developing mild cognitive impairment by 2.6 times and an increased risk of developing AD by 3.7 times (Burke et al., 2018). However, there is an ongoing debate regarding whether depression is an etiological risk factor (Ownby et al., 2006) or rather a prodrome/early manifestation of AD (Panza et al., 2010).

The articles used in this review were the result of an electronic search of the PubMed database for articles published up to April 2019, using the following keywords: "antidepressant"; "SSRI", "selective serotonin reuptake inhibitor", Alzheimer's disease". We included studies done in animal models with AD looking for the impact of SSRIs on the pathophysiological hallmarks of the disease, in addition to original investigations conducted in non-demented humans which explored the impact of SSRIs on the disease onset as a primary outcome.

Depression and Alzheimer's Disease: A Complex Relationship

Late-life depression can be either late-onset (defined in most studies as occurring for the first time after the age of 60 years) or early-onset (before the age of 60 years) recurring in later years of life (Driscoll et al., 2005). It has been argued that early-onset depression characterized by a chronic recurring-remitting course with increasing duration and severity of episodes across the lifespan is an etiological risk factor for AD (Green et al., 2003; Gracia-Garcia et al., 2015).

The underlying neurobiological correlates include activation of the hypothalamus-pituitary axis, hypersecretion of glucocorticoids leading to a reduction of hippocampal

volume (Sheline et al., 2003). Late-life depression is also associated with downregulation of neurotrophins (particularly brain-derived neurotrophic factor) (Neto et al., 2011), activation of neuroinflammatory pathways, increased secretion of pro-inflammatory cytokines and C-reactive protein (Herbert and Lucassen, 2016), and increased cortical amyloid burden (Chung et al., 2015); all these effects ultimately lead to neurodegeneration.

Other studies demonstrated that developing depression for the first time later in life and within 5 years of dementia onset as opposed to early life depression is a heralding sign of rather than a risk factor for AD (Brommelhoff et al., 2009; Li et al., 2011). This supports the hypothesis that late-onset depression is a prodrome of AD. Hence, the construct of mild behavioral impairment was developed by the International Society to Advance Alzheimer's Research and Treatment (ISTAART) to increase awareness about later-life onset of neuropsychiatric symptoms including affective and emotional dysregulation as precursors for cognitive decline (Ismail et al., 2017). Cognitively intact patients are four times more likely to develop clinically significant depressive symptoms, if they have Aβ brain deposits, which are positive biomarker of AD (Harrington et al., 2017).

Given these conflicting findings, we conclude that the relationship between depression and AD is very complex, with substantial evidence supporting both hypotheses. This has led some researchers to believe that AD and depression coexist synergistically across heterogeneous patient populations. Butters and colleagues propose a multiple pathway explanatory model by which depression, regardless of whether it is the result of accumulating neuropathological hallmarks of AD, causes neuronal injury, leading to a reduction in cognitive reserve and an earlier and more severe manifestation of cognitive impairment (Butters et al., 2008). This integrative approach highlights the necessity of earmarking depression as a catalyst of cognitive decline.

Targeting Serotonin in Alzheimer's Disease

Cholinergic dysfunction was long thought to be the sole contributor to AD symptomatology. However, there is growing evidence supporting the contributory role of a dysfunctional monoaminergic system. The serotonergic system seems to play a pivotal role in memory retention and learning by interacting with the cholinergic, dopaminergic, γ-aminobutyric acid (GABA)ergic and glutaminergic systems. 5-Hydroxytryptamine (5-HT)1, 5-HT4, 5-HT6 and 5-HT7 receptor classes are of particular interest for cognitive enhancement (Geldenhuys and Van der Schyf, 2011; Ramirez et al., 2014). Data from pre-clinical studies have shown that specific ligands for these subtypes of receptors not only increase cholinergic neurotransmission but also seem to increase neurogenesis, neuronal plasticity and reduce amyloid burden in the brain (Geldenhuys and Van der Schyf, 2011; Baranger et al., 2017; Hashemi-Firouzi et al., 2017; Shahidi et al., 2018).

Amyloid precursor protein (APP) is a transmembrane protein that is proteolyzed rapidly by secretases. Under normal circumstances, APP is metabolized by α-secretase to soluble APPα, a soluble non-toxic protein (non-amyloidogenic pathway). But in AD pathology, APP is processed by β-secretase then γ-secretase, yielding Aβ products or senile plaques that accumulate in the extracellular space (O'Brien and Wong, 2011). The other hallmark lesion of AD is the intracellular accumulation of neurofibrillary tangles or hyperphosphorylated tau proteins (Iqbal et al., 2010). Both proteins are believed to begin to accumulate decades before the manifestation of clinical symptoms. Evidence has been accumulating about the role of serotonin signaling on Aβ and tau proteins accumulation in the brain (Cirrito et al., 2011; Ramos-Rodriguez et al., 2013).

Selective serotonin reuptake inhibitors (SSRIs) are approved as first-line treatment of depressive disorders and have a favorable side effect profile when compared to older antidepressants such as the tricyclics. They work by selectively targeting the solute carrier family 6 member 4 responsible for terminating the action of serotonin in the synaptic cleft, consequently increasing this neurotransmitter availability at the synapse (Sangkuhl et al., 2009).

Although they don't selectively bind to specific 5-HT receptors, they have emerged as promising strategies to delay the onset of AD. Almost all SSRIs have been investigated in animal and human studies with regards to their impact on the trajectory of AD.

Implications of SSRIs on AD: insight from animal studies

Research in this field was first led by Cirrito and colleagues who explored the effect of antidepressants on the amyloid load in APP/presenilin-1 (PS1) transgenic mice. Fluoxetine (10 mg/kg) and citalopram (5 and 10 mg/kg) were shown to reduce Aβ levels in the interstitial fluid (ISF), with significant decrease starting 12–24 hours after administration. This reduction was found to be the result of the activation of extracellular signal-regulated kinases leading to decreased production of senile plaques. The finding was reproduced by the direct injection of serotonin into the hippocampus, but not by the administration of a non-SSRI antidepressant (tianeptine) (Cirrito et al., 2011). Chronic administration of citalopram in drinking water for 4 months was also shown to significantly decrease cortical and hippocampal plaque load on autopsy brain tissue, as well as cerebrospinal fluid (CSF) and ISF Aβ levels (Cirrito et al., 2011). It was also shown to decrease the formation and growth of novel-appearing plaques rather than clear already existing ones (Sheline et al., 2014b).

A dose-dependent relationship between citalopram and the decrease in Aβ levels was first demonstrated by Cirrito et al. (2011). It was then successfully replicated in another study, showing a statistically significant effect starting 5 mg/kg up to 10 mg/kg, with no additional effect with 20 mg/kg at 24 hours of administration (Sheline et al., 2014b). In addition to reducing the amyloid load by increasing α-secretase activity (Cirrito et al., 2011), citalopram was found to have an anti-inflammatory effect in decreasing microglial proliferation. It was also associated with an increase in GABA-secreting parvalbumin neurons in the cortex (Zhang et al., 2018), as

well as an improvement in synaptic plasticity as reflected by a reversal of long-term potentiation impairment (Wei et al., 2017).

Fluoxetine (doses 5–10 mg/kg per day) was associated with decreased soluble $A\beta_{40}$ and $A\beta_{42}$ levels through several mechanisms. It attenuates astrocytic activation and significantly reduces glial fibrillary acidic protein levels in APP/PS1 mice (Qiao et al., 2016), and alleviates APP phosphorylation (Wang et al., 2014). Furthermore, it was shown to promote neurogenesis and synaptic plasticity in the hippocampus (Jin et al., 2017; Ma et al., 2017). A dose-dependent relationship was also demonstrated with fluoxetine: doses equal or superior to 5 mg/kg per day had significantly positive effects on the behaviors of mice (Wang et al., 2014). Effects on the formation and accumulation of neurofibrillary tangles are however mixed (Wang et al., 2016; Jin et al., 2017).

There is limited evidence that 5 mg/kg per day of paroxetine may reduce the accumulation of tau proteins (Nelson et al., 2007) and senile plaques (Nelson et al., 2007; Olesen et al., 2017). However, paroxetine failed to mitigate $A\beta$ pathology in two other studies (Olesen et al., 2016; Severino et al., 2018). It was even associated with an increased risk of premature death in AD mice compared to controls, even at the lowest dose of 5 mg/kg per day which corresponded to therapeutic doses in humans and 86% serotonin transporter occupancy in the brain (Severino et al., 2018).

Although escitalopram (5 mg/kg per day; administered for 6 months) failed to significantly reduce $A\beta$ levels in the cortex and hippocampus of young APP/PS1 mice (von Linstow et al., 2017), it was associated with a reduction of tau hyperphosphorylation in hippocampal cultures of rats treated with $A\beta_{1-42}$ (Wang et al., 2016). **Additional Table 1** details the findings of the animal studies reviewed herein.

Impact of SSRIs on the onset of AD in humans
Based on evidence from animal studies regarding promising effects of SSRIs on both the amyloid cascade and tau hyperphosphorylation in AD (presented in **Figure 1**), researchers were encouraged to explore the role of serotonergic antidepressants in delaying the onset of AD in humans. Unfortunately, most studies conducted to date are observational and subject to methodological biases including confounding by indication and by severity. Moreover, only few of them focused on AD as opposed to the more generic diagnosis of dementia involving heterogeneous patient populations with distinct neurobiological and pathophysiological correlates (Khoury and Grossberg, 2019). Below, we review studies that focused on the effect of SSRIs on the outcome of developing AD.

In studies where a positive history of depression was an included variable, there is compelling evidence for a beneficial effect of SSRIs on delaying the onset of AD. In the AD neuroimaging initiative cohort, there were significantly lower conversion rates from mild cognitive impairment to AD in the subgroup of patients with a prior history of depression using SSRIs ($n = 67$) compared to those using other antidepressants ($n = 33$): $P = 0.002$. Interestingly, subjects who received SSRIs for more than 1610 days (defined by the authors as long term use) had a delay of 3 years in conversion to AD compared to subjects who took SSRIs for less than 1610 days: $P = 0.008$ (Bartels et al., 2018).

Similarly, Burke and colleagues explored the effect of anti-

Figure 1: Sites of action of SSRIs on pathophysiological hallmarks of Alzheimer's disease (AD) in animal models

FLX = Fluoxetine   CIT = Citalopram   S-CIT = Escitalopram   PRX = Paroxetine   ⊖ Decrease   ⊕ Increase   5HT-R   5HT

LTP long term potentiation   CTX cortex   HIP hippocampus   GSK3β Glycogen synthetase 3 β   SSRI Selective Serotonin Reuptake Inhibitors   APP Amyloid Precursor Protein   APP-● Phosphorylated Amyloid Precursor Protein
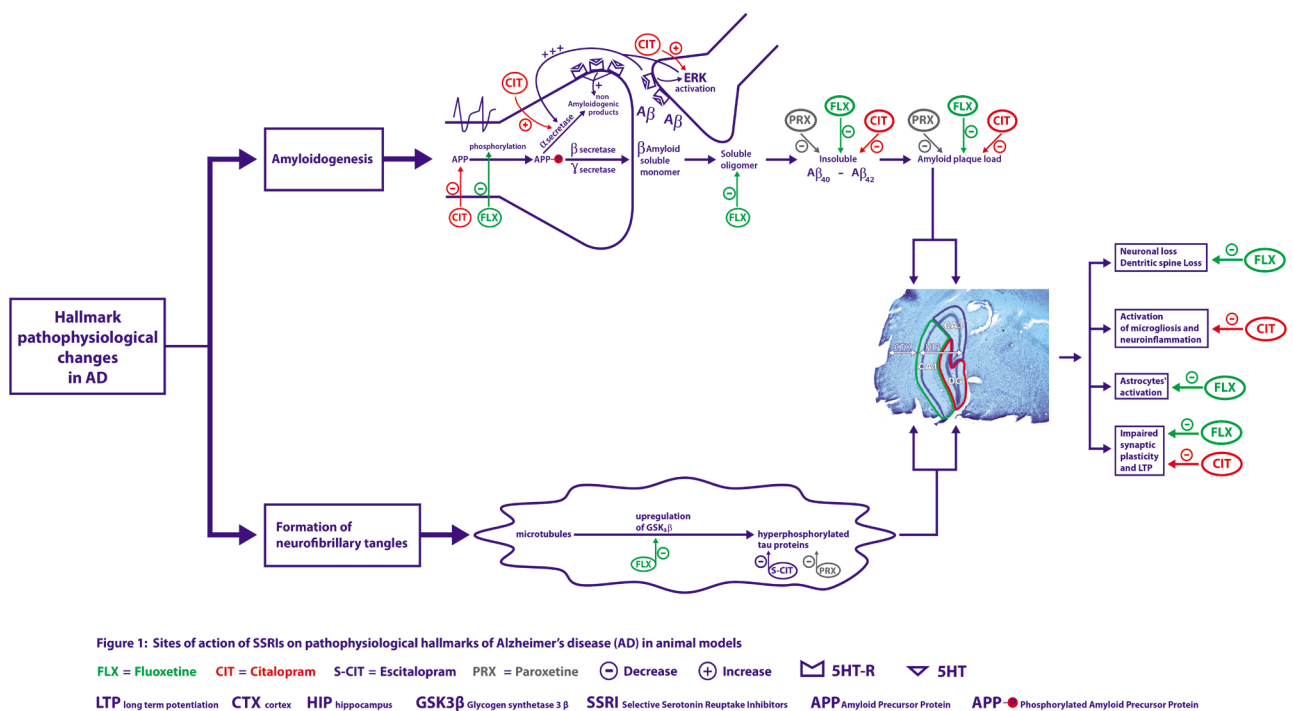
Figure 1 Sites of action of selective serotonin reuptake inhibitors (SSRIs) on pathophysiological hallmarks of Alzheimer's disease (AD) in animal models.

depressant use (mostly SSRIs) on the risk of developing AD in a large cohort of around 8000 cognitively intact subjects [Clinical Dementia Rating = 0], with a prior history of depression, followed for up to 9 years. In those with a remote history of depression (more than 2 years prior to the beginning of the study), the increased risk of developing AD was neutralized with both escitalopram and paroxetine compared to untreated subjects, after adjustment for apolipoprotein E4 carrier status. Sertraline in particular was shown to have a protective effect against developing AD as evidenced [hazard ratio [HR]; (95% confidence interval (CI)) = 0.17 (0.03–0.97)]. Additionally, in those with a more recent history of depression (within 2 years of the beginning of the study), citalopram, escitalopram, paroxetine and sertraline were all associated with a neutralization of the increased risk of developing AD compared to untreated subjects (Burke et al., 2018).

In a retrospective study looking at patients with Down syndrome (who are at higher risk of developing AD) who had previous history of depression, SSRI use for more than 90 days was associated with a statistically significant delay in the age of dementia onset (53 ± 5 years in those treated *vs.* 52 ± 5 years in untreated; $P = 0.04$). However, SSRIs didn't significantly increase longevity after the onset of dementia ($P = 0.35$) (Tsiouris et al., 2014). In another prospective cohort [the Adult Changes in Thought study] with a mean duration of follow-up of nearly 8 years, paroxetine use was associated with a higher risk of developing AD (28%) compared to other SSRIs or no use (around 20%) (Heath et al., 2018). When analysis was restricted to patients with a prior history of depression, cumulative doses of paroxetine were associated with a statistically significant increased risk of AD [HR (95% CI) = 1.94 (1.06–3.57)], whereas other SSRIs did not increase the risk of developing the disease [HR (95% CI) = 1.23 (0.83–1.83)].

On the other hand, studies that did not assess for status, history or severity of depression prior to subjects' inclusion yielded contradictory findings with respect to the impact of SSRIs on AD onset. In their large Danish population-based cohort (Kessing et al., 2009), Kessing and colleagues found that, compared to subjects exposed to one prescription of SSRIs, there was an increased risk of developing AD in subjects exposed to two prescriptions of SSRIs [relative risk (RR) (95% CI) = 1.55 (1.40–1.72)], and those exposed to 6–9 prescriptions of SSRIs [RR (95% CI) = 2.22 (2.03–2.43)]; unexposed subjects were found to be protected [RR (95% CI) = 0.32 (0.29–0.34)].

The effect of SSRIs on the neurobiological markers of AD were also explored in humans. Brendel and colleagues investigated the influence of SSRIs on grey matter volume and amyloid burden in 73 subjects with mild cognitive impairment or AD who were endorsing depressive symptoms assessed via the neuropsychiatric inventory. At 2 years of follow-up, depressed subjects who were treated with an SSRI had a statistically significant reduction in grey matter atrophy ($P < 0.05$), notably in the fronto-temporal cortex, compared to untreated depressed subjects. There was also a slight trend towards a reduction in amyloid deposition rate in the

SSRI group, notably in the frontal cortex, but the trend didn't reach statistical significance ($P = 0.64$) (Brendel et al., 2018).

In another study, CSF levels of $A\beta_{1-42}$, total tau and phosphorylated tau were found to be unaffected by SSRI treatment; this finding suggests that the pro-cognitive effect of SSRIs may not be mediated through the amyloid cascade (Bartels et al., 2018), but rather through other pathways like neuroinflammation. Limitations of this study included the unknown severity of depression at baseline, number of previous depressive episodes and any history of previous antidepressants use prior to study entry.

Contrary to those findings, a double-blind placebo-controlled trial of healthy cognitively intact individuals aged 18–50 years found that the one-time administration of two 30 mg doses of citalopram in one day resulted in a 38% decrease in $A\beta$ concentrations on serial CSF measurements. In addition, it lowered the concentration of newly formed $A\beta$ compared to baseline levels (Sheline et al., 2014b). Cirrito and colleagues, using amyloid positron emission tomography imaging with the Pittsburgh compound B, demonstrated a decrease in senile plaque formation in cognitively intact individuals who received any of sertraline, fluoxetine, citalopram or escitalopram (Cirrito et al., 2011).

Discussion/Conclusions

Data from animal models, while promising, needs to be interpreted with caution. Those studies are characterized by a high variability in the doses of SSRIs used, duration of administration, and the age, gender and model of studied animals. Evidence points to the possibility that a relatively longer period of treatment (months rather than days) using higher doses in relatively younger mice was associated with the most statistically significant findings with respect to alleviating neurobiological markers and behavioral manifestations of AD. Researchers need to be vigilant about methodological differences between studies, particularly the time of sampling of biological fluids (CSF/ISF/blood) with respect to each SSRI's half-life and peak concentrations in the respective fluids (Sheline et al., 2014a). An additional concern is related to SSRI dosing equivalence between animals and humans. For instance, citalopram used at the dose of 10 mg/kg in mice is equivalent to 50 mg in humans (Sheline et al., 2014b; Wei et al., 2017), a dose that is beyond what is approved for the treatment of depression in the elderly given its association with increased QTc interval and mortality in humans.

The impact of SSRIs on plaque formation rather than plaque clearance highlights the need to use those antidepressants as early as possible in cognitively intact individuals, optimally before the beginning of plaque deposition. This has been effectively demonstrated in human studies showing that a longer duration of SSRI treatment alleviated the risk of developing AD the most, and ascertaining the need to aggressively treat depression as a risk factor for AD. Nevertheless, robust large randomized controlled trials are still needed to better account for the effect of SSRIs and their optimal doses and duration of use on the disease's onset and biomarkers. Moreover, among all SSRIs, paroxetine is the

most anticholinergic carrying deleterious cognitive effects in the elderly population (Nevels et al., 2016). Given that paroxetine may be associated with increased odds of developing AD, properties of SSRIs (serotonergic *vs.* anticholinergic) need to be further explored in future trials (Harrington et al., 2017). Newly developed serotonergic antidepressants like vortioxetine modulate serotonin receptors (i.e., 5-HT7 antagonism), in addition to inhibiting serotonin transporter activity. In depressed patients diagnosed with mild AD, vortioxetine was shown to significantly improve cognition when compared to other conventional antidepressants (Cumbo et al., 2019). Future research needs to explore its impact on AD prevention or onset delay when used early in depressed *vs.* non-depressed cognitively intact individuals.

Additional files:
Additional Table 1: Pathophysiological and behavioral outcomes of SSRIs in AD animal models.
Additional file 1: Open peer review reports 1 and 2.

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