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Do anti-amyloid-β drugs affect neuropsychiatric status in Alzheimer's disease patients?

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ABSTRACT

In the Alzheimer's disease (AD) brain, accumulation of the amyloid-β (Aβ) peptide starts 15–20 years before clinical symptoms become apparent and is believed to be the initial event of the pathological process. Unfortunately, candidate drugs targeting production, clearance and deposition of Aβ have failed to show clinical benefit in patients with established or prodromal disease, or in cognitively normal subjects with high risk of developing AD. Surprisingly, several potent anti-Aβ drugs accelerated cognitive decline of AD and, in some cases, worsened neuropsychiatric symptoms (NPS) and triggered suicidal ideation. Clarifying the relationships between the AD-related pathology and NPS of AD patients may be useful for elucidating the underlying pathophysiological process. We believe that steady overproduction of Aβ in AD may represent an attempt of the brain to mitigate or repair neuronal damage/insult. Sudden reductions of brain Aβ levels with potent anti-Aβ drugs may worsen cognition and exacerbate NPS.

1. Introduction

Brain accumulation of the amyloid-β (Aβ) peptide is believed to be the initial event in Alzheimer's disease (AD). This starts 15–20 years before clinical symptoms occur and parallels cognitive decline (Villemagne et al., 2013). Dominant mutations causing early onset familial AD occur in three genes (*PSEN1*, *PSEN2*, and *APP*). These mutations alter the production of Aβ and this observation represents the foundation of the amyloid hypothesis of AD. However, familial AD represents less than 5% of all AD cases. For the remaining 95% of AD cases (late onset or "sporadic" AD), risk genes have been identified with that encoding for the apolipoprotein E ε4 allele (*APOE* ε4) being the most studied. In sporadic AD, there is an accumulation of brain Aβ although not strictly correlating with cognitive deficit. In normal aging, Aβ accumulation in the brain occurs in up to 44% of subjects, although without cognitive deficit (Jansen et al., 2015). On the other hand, tau pathology correlates with neuronal loss (Gómez-Isla et al., 1997) and both AD duration and severity (Arriagada et al., 1992), it mediates the association between brain Aβ load and AD occurrence (Bennett et al., 2004), and is visible in the entorhinal cortex in people with subjective memory complaints (Buckley et al., 2017).

During the last 25 years, intensive efforts have been made to delay or prevent such accumulation using compounds that decrease Aβ production, antagonize Aβ aggregation or increase Aβ clearance, but to date all have been clinically ineffective in subjects with established or early stage AD. The list of failed drugs includes Aβ aggregation inhibitors, Aβ antigens, anti-Aβ monoclonal and polyclonal antibodies, γ-secretase inhibitors and modulators, and β-secretase (BACE) inhibitors – and these multiple failures have raised questions about the validity of the Aβ cascade hypothesis of AD (Panza et al., 2019). Surprisingly, some anti-Aβ drugs caused worsening of cognition or clinical condition in treated patients compared to placebo recipients (Mullard, 2019). It is unclear whether this was due to non-specific adverse events masking any positive cognitive effects, or direct adverse effects on cognition itself. Indeed, Aβ is present throughout life and *in vitro* and *in vivo* evidence indicates that Aβ serves several important physiological functions, including preventing infection, maintaining the blood-brain barrier, promoting recovery from injury and regulating synaptic function (Brothers et al., 2018). Neuronal production of Aβ rapidly increases in response to physiological challenge and often diminishes

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Table 1
Principal clinical trials of anti-β-amyloid (Aβ) therapies in Alzheimer's disease (AD) and related disorders that reported the onset of neuropsychiatric symptoms (NPS) in treated patients.

Reference	Drug	Company	Mechanism of Action	Subject Population	Clinical Phase	Main NPS reported	Remarks
Salloway et al. (2011)	Scyllo-inositol	Transition Therapeutics/ Elan	Aβ Aggregation Inhibitor	Mild-to-Moderate AD	Phase II	Suicidal ideation and depression	Increases mortality. Inactivates Aβ oligomers
Doody et al. (2013)	Semagacestat	Eli Lilly	γ-Secretase Inhibitor	Mild-to-Moderate AD	Phase III	A dose-dependent worsening in the mean NPI score	Worsens cognition
Vandenberghe et al. (2016)	CAD-106	Novartis	Aβ Antigen	Mild AD	Phase II	Non-significant higher NPI scores worsening in the SSR group versus the placebo group	Borderline worsening in cognition
Lynch et al. (2018)	Elenbecestat	Biogen/ Eisai	BACE Inhibitor	Mild and prodromal AD	Phase II	Nightmares as a notable side effect on active drug	
Henley et al. (2019)	Atabecestat	Janssen/ Shionogi Pharma	BACE Inhibitor	Asymptomatic Aβ-positive subjects at risk of developing AD	Phase II/III	More frequent depression, anxiety and sleep disturbances	Worsens cognition
Egan et al. (2018)	Verubecestat	Merck	BACE Inhibitor	Mild-to-Moderate AD	Phase III	NPI scores worsened with 2 patients who completed suicide	Worsens cognition
Egan et al. (2019)	Verubecestat	Merck	BACE Inhibitor	Prodromal AD	Phase III	More frequent depression, anxiety, psychotic symptoms, sleep disturbances, suicidal ideation	Worsens cognition

NPI: Neuropsychiatric Inventory; SSR: strong serological response.

upon recovery (D'Andrea, 2016). Based on the observation that the 42-amino-acid form of Aβ ($A\beta_{1\text{-}42}$) is far more neurotoxic than the 40-amino-acid form ($A\beta_{1\text{-}40}$) and that patients with familial AD generally have an increased serum $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ ratio, drugs should selectively target the $A\beta_{1\text{-}42}$ species. However, studies using 3D super-resolution microscopy showed that $A\beta_{1\text{-}42}$ is present in the presynapse of hippocampal neurons in wild-type mice (Yu et al., 2018) and that picomolar concentrations of a preparation containing both $A\beta_{1\text{-}42}$ monomers and oligomers cause a marked increase of hippocampal long-term potentiation, and enhance both reference and contextual fear memory in normal mice (Puzzo et al., 2008). Furthermore, depletion of endogenous $A\beta_{1\text{-}42}$ impairs hippocampal synaptic plasticity and memory (Puzzo et al., 2011). Specifically, it has been shown that that maximal beneficial effects of $A\beta_{1\text{-}42}$ on long-term potentiation (LTP) in mouse hippocampal slices is observed at the 200 pM concentration (Puzzo et al., 2008). We do not know the hippocampal $A\beta_{1\text{-}42}$ levels in AD patients after BACE1 inhibitors, but we know that cerebrospinal (CSF) $A\beta_{1\text{-}42}$ levels in AD patients treated with verubecestat at the doses of 40 mg/day are around 60–70 pM (Kennedy et al., 2016). These biological findings are consistent with the detrimental outcomes of AD clinical trials aimed at Aβ depletion. Indeed, it has been hypothesized that Aβ pathology may be upregulated in the AD brain for reasons unrelated to disease progression – possibly as a protective function (Morris et al., 2018).

Neuropsychiatric symptoms (NPS) occur in the majority of persons with AD over the course of the disease. In a cross-sectional study involving 3608 participants, 43% of MCI subjects exhibited NPS in the previous month (29% rated as clinically significant) with depression (20%), apathy (15%), and irritability (15%) being most common. Among the subjects with dementia, 75% had exhibited a NPS in the past month (62% were clinically significant); 55% reported two or more and 44%, three or more disturbances in the past month. In participants with dementia, the most frequent disturbances were apathy (36%), depression (32%), and agitation/aggression (30%). These symptoms have serious adverse consequences (Lyketsos et al., 2002). Little is known about whether anti-Aβ drugs developed to treat AD have any effect on neuropsychiatric status (Rubin, 2018). We believe there is enough evidence to indicate that major Aβ perturbations caused by anti-Aβ drugs may induce or exacerbate NPS in AD patients and in prodromal AD syndromes.

2. Evidence coming from putative disease-modifying anti-amyloid – β therapies

Verubecestat, a potent BACE1 inhibitor, lowered CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in AD patients by around 70%, 80% and 90% compared to placebo after 12, 40 and 60 mg/day doses, respectively (Kennedy et al., 2016). In an 18-month, placebo-controlled study in which 1958 mild-to-moderate AD patients received verubecestat (12 or 40 mg/day) or placebo, adverse psychiatric effects were seen (Egan et al., 2018). Although the drug dose-dependently and robustly lowered Aβ concentrations in CSF, patients did not benefit in terms of either cognition (Alzheimer's Disease Assessment Scale–Cognitive Subscale, ADAS-Cog) or functionality (Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, ADCS-ADL) and the study was terminated early for futility. Adverse events leading to discontinuation of study medication were observed in 5.8%, 8.3% and 9.4% of patients in the placebo, 12-mg and 40-mg groups, respectively. There were 5 deaths in the placebo group (0.8%), 9 deaths in the 12-mg group (1.4%), and 12 deaths in the 40-mg group (1.8%), including 2 cases of completed suicide following worsening of previous suicidal ideation. In 18 months of treatment, mean (± SEM) Neuropsychiatric Inventory (NPI) scores worsened by 2.7 ± 0.5, 3.4 ± 0.5 and 3.8 ± 0.5 points in the placebo, 12-mg and 40-mg groups, respectively ($p > 0.05$). Statistically significant higher frequencies of psychotic symptoms [3.1%; 4.6% and 5.5% in placebo, 12-mg and 40-mg ($p < 0.05$) groups, respectively], sleep disruption [4.7%;

10.3% and 8.4% in placebo, 12-mg ($p < 0.05$) and 40-mg ($p < 0.05$) groups, respectively], and suicidal ideation [3.2%, 6.0% and 5.8% in placebo, 12-mg ($p < 0.05$) and 40-mg ($p < 0.05$) groups, respectively) were observed in the verubecestat-treated groups (Table 1).

In a 104-week, double-blind, placebo-controlled trial of verubecestat in 1454 subjects with prodromal AD, patients showed no cognitive or functional benefit, and the trial was terminated early for futility (Egan et al., 2019). Compared to placebo, the drug dose-dependently worsened cognition and daily functions, rate of hippocampal atrophy, and progression to dementia. Statistically significant increases in frequency of NPS were observed in the highest verubecestat dose group (40 mg once-a-day) compared to placebo: 10.3 *vs* 5.2% for depression ($p < 0.05$), 9.1% *vs* 4.3% for anxiety ($p < 0.05$), 9.1% *vs* 4.5% on sleep disturbances ($p < 0.05$), 5.6% *vs* 2.3% on psychotic symptoms ($p < 0.05$), and 9.3 *vs* 6.3% on suicidal ideation ($p < 0.05$). The worsening of the mean NPI score was also dose-dependent and reached statistical significance in the 40-mg dose group compared to placebo ($p < 0.05$).

A 54-month study of atabecestat (5 and 25 mg/day), another potent BACE1 inhibitor, in 1650 asymptomatic Aβ-positive subjects at risk of developing AD, was prematurely halted due to liver toxicity and cognitive worsening. The high-dose group significantly worsened compared to placebo on both the cognitive (Alzheimer's Disease Cooperative Study- Preclinical Alzheimer Cognitive Composite, ADCS-PACC, $p = 0.0001$ at 6 months and $p = 0.0004$ at 12 months) and the neuropsychological (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS, $p = 0.0007$ at 3 months) performance of the subjects. Subjects on 25 mg/day complained more frequently of depression, anxiety and sleep disturbance (Henley et al., 2019) (Table 1).

In an 18-month, placebo-controlled study with the BACE1 inhibitor elenbecestat in 70 mild and prodromal AD, discontinuation rates were 42% on the drug (22/53) *vs* 29% on placebo (5/17). Nightmares was a notable side effect on elenbecestat (Lynch et al., 2018) (Table 1).

Recently, two 5-year, placebo-controlled trials of umibecestat, a selective BACE1 inhibitor, in 3340 cognitively normal subjects at risk of developing AD (*APOE* ε4 allele and brain Aβ-positivity), were discontinued because the drug worsened cognition, brain atrophy and weight loss (Shugart et al., 2019).

Increased mortality and worsening of NPI scores have been observed with other anti-Aβ drugs (Table 1). In an 18-month double-blind, placebo-controlled study of semagacestat, a γ-secretase inhibitor, in 1537 mild-to-moderate AD patients there was a dose-dependent worsening in mean NPI score (+1.9, +2.9 and +3.7 NPI points on placebo, 100- and 140-mg semagacestat, respectively), with the effect of the highest dose reaching statistical significance ($p = 0.05$) (Doody et al., 2013). The trial was interrupted prematurely because of cognitive deterioration and serious adverse events (SAEs), including deaths. At termination, 10.2%, 23.9% and 27.3% of patients on placebo, semagacestat 100-mg and semagacestat 140-mg, respectively, had withdrawn because of adverse events.

Scyllo-inositol, a potent Aβ aggregation inhibitor, was shown to neutralize toxic effects of Aβ oligomers, including amelioration of oligomer-induced synaptic loss, long-term potentiation inhibition and memory deficits (Townsend et al., 2006). However, scyllo-inositol also increased mortality in an 18-month, double-blind, placebo-controlled study in 353 mild-to-moderate AD patients with 0, 1, 5 and 4 deaths in the placebo, 250, 1000 and 2000 mg twice-a-day groups, respectively (Salloway et al., 2011) (Table 1). One patient dying in the 1000 mg group had suicidal ideation and two patients who died in the 2000 mg group reported depression.

CAD106 is a potent Aβ antigen presently in Phase III studies in mild AD and in asymptomatic subjects with familial AD. In a 90-week, double-blind, placebo-controlled study in 121 patients with mild AD, SAEs were reported in 7% of placebo-treated patients and in 25% of CAD106-treated subjects. Cognitive decline on the Mini Mental State Examination over 78 weeks was 4.8 ± 3.6 in the CAD-treated patients with strong serological response (SSR) compared to 1.9 ± 3.3 the control group ($p = 0.052$). Mean NPI scores showed worsening of 6.3 ± 8.15 points in the SSR group versus 0.5 ± 10.59 points in the control group ($p = 0.171$) (Vandenberghe et al., 2016) (Table 1).

3. Relationship between neuropsychiatric symptoms and Aβ burden

A cross-sectional study in 1443 cognitively normal elderly subjects found that the frequency of NPS did not differ significantly based on cerebral Aβ burden status (24.9% *vs* 20.0%) (Krell-Roesch et al., 2019). However, when 270 cognitively normal older subjects were followed longitudinally for 1–5 years, early anxious-depressive symptoms were found associated with brain Aβ burden (Donovan et al., 2018). A cross-sectional study in 184 MCI patients found that NPS were significantly more frequent in subjects with brain Aβ burden (59.4%) compared to those without Aβ burden (34.6%) (Krell-Roesch et al., 2019). These observations imply that cerebral Aβ deposition is associated with both NPS and cognitive symptoms. Thus, a reduction in brain Aβ burden with potent anti-Aβ drugs should have resulted in a reduction rather than an increase in cognitive deficit and NPS. However, it has been proposed that the accumulation of Aβ during the long AD pathophysiology process does not trigger neuronal death but rather represents a protective response to neuronal insult (Lee et al., 2007). Longitudinal studies in middle-aged and older cognitively normal participants showed that increasing levels of tau most consistently relate to declines in cognition, suggesting that elevated Aβ alone may be insufficient to produce cognitive change in individuals at risk for AD (Aschenbrenner et al., 2018; Hanseeuw et al., 2019). Since Aβ and tau aggregates show different spatial and temporal patterns of progression within vulnerable brain regions, the existence of three distinct temporal phases in the AD process has been proposed (Jones et al., 2017). During the first phase in clinically unaffected individuals, tau-associated network disruption occurs in specific brain regions. During the second phase, this disruption can trigger Aβ-associated compensatory brain network changes. Finally, during the last phase, Aβ deposition marks the saturation of functional compensation and portends acceleration of the inciting phenotype-specific, tau-associated network failure (Jones et al., 2017) (Fig. 1). In this model, therapeutic intervention with potent anti-Aβ drug shutting down the production of native Aβ (γ-secretase or BACE1 inhibitors) may be detrimental because of the blockade of Aβ-associated compensatory brain network changes.

Preclinical studies seem to support the pejorative effects of anti-Aβ drugs observed in prodromal and AD patients. Studies in PDAPP and Tg2576 transgenic mice demonstrated that passive immunotherapy with Aβ-targeting antibodies (3D6 and β1) worsened abnormal neuronal hyperactivity and cognitive deficits (Busche et al., 2015). Aggravation of neuronal hyperactivity was found to be directly related to binding of the antibodies to Aβ rather than to non-Aβ-related properties of the antibodies. Since the pro-excitatory effect of anti-Aβ antibodies was not observed in wild-type animals, the increased hyperactivity was Aβ-dependent (Busche et al., 2015).

4. Conclusions

Potent anti-Aβ drugs, particularly β-secretase and γ-secretase inhibitors, may trigger NPS and suicidal ideation as a result of sudden reductions in Aβ. The neuropsychiatric effect size of anti-Aβ drugs may appear relatively limited but it refers, in most cases, to interrupted trials. It might have been greater if the trials had been completed. In addition, several anti-Aβ trials in which NPS emerged have still to be fully published. Although NPS are widely recognized as the most challenging manifestations of dementia, most clinical trials of potential AD treatments do not consider them as primary research targets (Canevelli et al., 2017). Since anti-Aβ drugs have repeatedly been

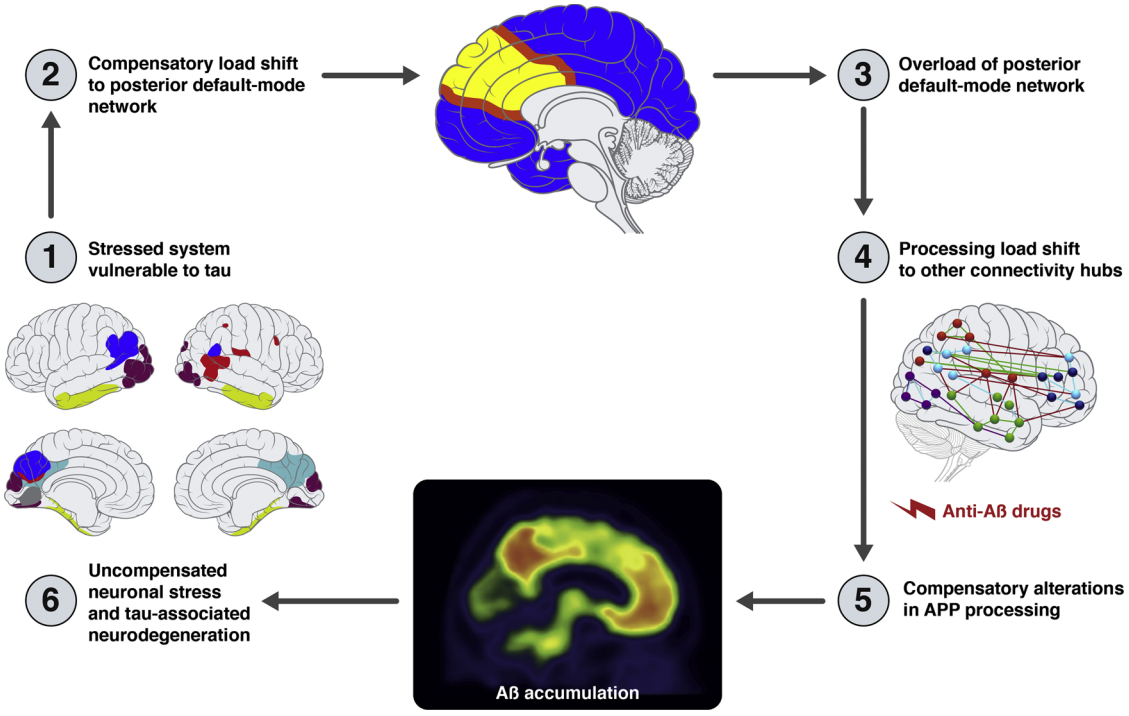

Fig. 1. Hypothesis of mechanism of action of anti-amyloid-β (Aβ) drug-induced cognitive and neuropsychiatric symptoms in AD patients. This figure is a modified scheme of the hypothetical model relating large-scale brain networks, Aβ, and tau across the AD spectrum proposed by Jones et al. (2017). 1) Five brain regions show spatially independent tau deposition; 2) in order to avert clinical impairment, posterior default-mode network is activated; 3) the posterior default-mode network becomes overloaded and shifts its processing load to other connectivity hubs (4). This increased load leads to Aβ hypersecretion in an effort to compensate for noisier synaptic activity (5). The altered amyloid precursor protein (APP) processing eventually leads to amyloid plaque formation and a saturation of synaptic and functional compensation. 6) The uncompensated neuronal stress leads to a rapid acceleration of tau-associated neurodegeneration. Anti-Aβ drugs, specifically β-secretase 1 (BACE1) inhibitors and γ-secretase inhibitors, could interfere with step 4 of the process thus precipitating the successive pathological steps.

associated with worsening of cognition and NPS in both AD and MCI patients, and even in cognitively unimpaired subjects, we conclude that both AD-associated neuronal death and neuropsychiatric disturbances cause an increase in brain Aβ levels and not *vice versa*.

Declaration of Competing Interest

None declared.

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