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Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia

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Abstract

There is no dedicated therapy for frontotemporal dementia (FTD). In order to treat the often devastating behavioral disturbances that interfere with both normal social functioning and the ability of caregivers to provide needed support, off-label medication usage is frequent. In addition to antidepressant and antipsychotic medications, which afford some benefits, US FDA-approved treatments for Alzheimer's disease are often used, including both cholinesterase inhibitors and memantine. Here, we review the various clinical manifestations of FTD, a general approach to treatment and the goals of any potential therapies. We review all of the existing literature on the use of cholinesterase inhibitors and memantine in FTD. While cholinesterase inhibitors do not currently have a place in FTD treatment, memantine may be helpful, although the results of two placebo-controlled trials with this agent are not yet available. Finally, we discuss our view that such approaches will probably become supplanted by rational, molecularly-based therapies currently in development.

Keywords

Alzheimer's disease; frontotemporal dementia; frontotemporal lobar degeneration; FUS; progressive nonfluent aphasia; semantic dementia; Tau; TDP-43

Frontotemporal dementia (FTD) is a common and devastating disease. Once thought to be rare, FTD is now recognized as being at least as common as Alzheimer's disease (AD) among middle-aged adults. Despite this wide prevalence, and the exacting toll of the disease on patients and their families, there is no US FDA-approved therapy for FTD.

To fill this void, off-label medication use in FTD is common [1]. Among the most frequently prescribed medications in FTD are the drugs FDA-approved for the treatment of AD, despite fundamental pathophysiological differences between the two diseases. Reviewed here are the possible benefits and pitfalls of this approach, including a survey of the existing literature and a discussion of what remains to be studied.

FTD: a family of three diseases

With rapid advances in knowledge, the nosology of FTD has undergone frequent revision. Before launching into a discussion of FTD treatment, it is important to define the terms that will be used. Although controversy remains with respect to nomenclature, two points are clear: FTD is distinct from AD, and it is not a sole entity. FTD encompasses a group of disorders unified by a proclivity to cause focal and often asymmetric cortical atrophy in anterior structures of the frontal and temporal lobes, typically sparing the parietal lobe structures that degenerate in AD [2]. FTD includes three clinical syndromes (Table 1) [3,4]: behavioral variant FTD (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA).

Behavioral variant FTD

Previously called ‘frontal variant FTD’ or simply ‘FTD’, bvFTD is a progressive behavioral condition characterized by apathy, disinhibition and loss of insight. Patients lose empathy, fail to recognize the needs or emotions of others and exhibit socially inappropriate and sometimes bizarre behaviors, resulting from a diminished capacity to consider the abstract consequences of concrete pleasures. Thus, individuals change their eating habits in favor of sweet and fatty foods, and they ignore personal hygiene. They become impulsive, careless and increasingly ritualistic, and inertia gradually replaces goal-directed behavior. On neuropsychological examination, bvFTD patients exhibit executive dysfunction with relative preservation of short-term episodic memory and visuospatial skills. Neuroimaging typically reveals focal, asymmetric atrophy of the nondominant (usually right) orbitofrontal, medial frontal and anterior insular cortex.

Unlike AD, which exhibits a relatively stable pattern of neuropathological manifestations, bvFTD – and FTD in general – is more complex. Frontotemporal lobar degeneration (FTLD) refers to the various neuropathological features of FTD. At the histopathological level, there are three main FTLD subtypes categorized according to the major protein aggregate observed [5]: FTLD-tau, where aggregates of the microtubule-associated protein tau predominate; FTLD-TDP, where intraneuronal inclusion bodies contain ubiquitinated deposits of TAR DNA-binding protein-43 (TDP-43) [6]; and FTLD-fused-in sarcoma protein (FUS), where similar ubiquitinated inclusion bodies instead contain the FUS [7]. As illustrated in Table 1, there is not a firm correlation between clinical and neuropathological phenotypes. In bvFTD, approximately half the cases exhibit FTLD-tau pathology; most of the remaining cases are FTLD-TDP, and a smaller percentage reveal FTLD-FUS pathology [5].

Semantic dementia

Semantic dementia (previously referred to as ‘temporal variant FTD’) features prominent word-finding difficulty, particularly for low-frequency nouns. As the symptoms progress, it becomes evident that the problem lies with loss of semantic meaning; as object and category knowledge degrade, along with confrontational naming skills. Additional symptoms may include impaired face recognition, ritualistic and inflexible behavior, and behavioral symptoms similar to, but typically not as severe as, those in bvFTD. Neuroimaging reveals asymmetric temporal pole atrophy that is worse in the dominant (usually left) hemisphere; in some cases, the process may begin on the right side before spreading to the left, in which case some of the behavioral symptoms may appear before the language deficits. In most cases, FTLD-TDP is the underlying pathological finding (Table 1).

Progressive nonfluent aphasia

Progressive nonfluent aphasia features slow, effortful speech that is hampered by dysarthria, sound distortions and inconsistent phonemic errors. Notably, grammar degrades in PNFA; patients begin to leave out articles and eventually verbs, and in severe cases, speech may simplify to a string of (poorly pronounced) nouns. Comprehension is generally preserved, but PNFA patients do have difficulty understanding grammatically complex phrases. To a variable extent, other motor and cognitive features may accompany expressive language deficits in PNFA. These include orobuccal apraxia, asymmetric limb apraxia (typically affecting the right hand and foot) and extrapyramidal motor features, including tremor or rigidity. A supranuclear eye movement abnormality may also develop, and together these symptoms may progress to corticobasal degeneration or progressive supranuclear palsy – two related neurodegenerative diseases that often overlap with FTD, both clinically and pathologically. Neuroimaging typically reveals asymmetric, dominant-hemisphere, frontal opercular and anterior insular cortical atrophy, with variable involvement of the ipsilateral striatum or other subcortical nuclei. In many cases, the neuropathology reveals FTLT-tau (Table 1).

Treatment considerations

Nonpharmacological treatment

Although this article will focus on pharmacological interventions, the first-line therapy for FTD should be nonpharmacological [8-10]. Treatment begins with education about the nature of the disease and its expected progression. Discontinuation of harmful agents may accomplish more than the introduction of new ones. It is imperative to review all medications that the patient is currently taking, including prescription drugs, nonprescription drugs, social drugs (caffeine, nicotine and alcohol) and/or alternative products (e.g., herbals, vitamin or minerals). Many psychotropic medications, such as stimulants, sedatives and anxiolytics, may exacerbate behavioral or cognitive symptoms.

Symptomatic therapy

There is an important conceptual distinction between therapies that target symptoms and those that target a disease process itself. Symptomatic therapy can enhance quality of life, and there is a need for these in FTD, especially when the behavioral abnormalities become so disruptive as to interfere with caregiving. In the absence of any FDA-approved medication for the management of behavioral symptoms in FTD, physicians routinely prescribe off-label psychoactive drugs in an attempt to provide relief to patients [1,11]. Among these, selective serotonin reuptake inhibitors (SSRIs) and antipsychotic medications are often used, probably reflecting the profound serotonergic and dopaminergic abnormalities in FTD [12-14].

Selective serotonin reuptake inhibitors have been used to treat a variety of behavioral symptoms in patients with FTD [15]. In an open-label study of 11 FTD patients treated with fluoxetine, sertraline or paroxetine, most patients experienced a reduction in disinhibition, depressive symptoms, carbohydrate craving or compulsions, and no subject worsened. Paroxetine may reduce repetitive, ritualistic behavior [16]. In a randomized, open-label study of 16 FTD patients comparing paroxetine to piracetam, improvements in behavioral symptoms occurred in the paroxetine group [17]. However, no effect of paroxetine emerged from a randomized, double-blind, placebo-controlled trial of ten FTD patients treated with paroxetine at a higher dose (40 vs 20 mg) [18]. Trazodone may be effective relative to placebo at controlling behavior in patients with FTD [19]. The serotonergic changes in FTD may be complex, and some have suggested the use of a serotonin antagonist [20].

Antipsychotic medications have also been used to treat the behavioral symptoms of FTD, especially agitation and disinhibition, although there is a general lack of supporting literature. A case report with risperidone [21] and an open-label uncontrolled study of olanzapine [22] provide some support for their use. Importantly, patients with FTD may be exceptionally sensitive to the motor side effects of antipsychotic medications, exhibiting high rates of extrapyramidal symptoms [23]. In addition, antipsychotic medications are associated with a higher risk of death in elderly patients [24]. Perhaps dopamine antagonism is not always the best approach. Selegiline, a MAO-B inhibitor that slows the metabolism of dopamine, may reduce neuropsychiatric symptoms [25]. Methylphenidate may also provide benefits [26,27].

Disease-modifying therapy

Treatment aimed at slowing or stopping disease progression remains an important and separate treatment goal. Such therapies often target the molecules that drive disease pathogenesis, and whereas symptomatic therapies designed for one indication (depression) may be helpful in another (FTD), disease-modifying drugs may be less portable. For instance, bapineuzumab, a monoclonal antibody designed to rid the brain of the β -amyloid peptide in AD [28], would almost certainly be ineffective in FTD. On the other hand, as addressed below, there is a possibility that multiple neurodegenerative diseases may share a common final pathway of cell death (e.g., NMDA receptor-mediated excitotoxicity), making a multipurpose neuroprotective agent conceivable (such as an NMDA receptor antagonist). Importantly, tau is implicated in both AD and some forms of FTD (Table 1), and new AD drugs targeting tau may be useful in diseases characterized by FTLD-tau pathology [29]. Indeed, such drugs may be even more efficacious in these forms of FTD than in AD, because unlike AD, there is an absence of other toxic proteins, such as amyloid, that may exert tau-independent effects on brain function. In the coming years, it is likely that a number of clinical trials of such tau-directed agents will be initiated for FTD and related disorders (see later).

Off-label use of AD medications in FTD

Cholinesterase inhibitors and memantine are symptomatic therapies for AD. As discussed here, a possible role for these agents in the treatment of FTD has been a matter of increasing attention in the literature.

Cholinesterase inhibitors

Cholinesterase inhibitors are first-line symptomatic therapies for AD. Their use in AD is rational, reflecting a profound cholinergic deficit arising from the early demise of neurons in the nucleus basalis of Meynert. Currently, there are four cholinesterase inhibitors that are FDA-approved for the treatment of AD: tacrine (Cognex[®]), donepezil (Aricept[®]), rivastigmine (Exelon[®]) and galantamine (Razadyne[®]). As successors to tacrine (a first-generation compound rarely prescribed because of the potential for hepatotoxicity), donepezil, rivastigmine and galantamine are approximately equally efficacious at providing symptomatic improvement of cognition and function at all stages of AD [30]. The clinical effects of these compounds are small and impermanent, and there is currently no conclusive data to support their use as disease-modifying agents (however, see [31,32]).

In FTD, there is a relative preservation of cholinergic neurons in the brain and no *a priori* reason to expect a benefit from cholinesterase inhibition [12-14,33]. On the other hand, there is evidence that cholinesterase inhibitors produce symptomatic improvements in behavioral and neuropsychiatric measures in patients with AD [34,35], raising the possibility that there could be similar benefits in FTD.

Data regarding the efficacy of cholinesterase inhibitors in FTD are mixed and difficult to interpret, owing to a lack of placebo-controlled studies: in one small open-label study [36], nine patients with bvFTD were given either donepezil or rivastigmine, and some (the four male patients) exhibited improvements in the Mini-Mental State Examination (MMSE) and a clock-drawing test, as well as unspecified improvements in SPECT. The others, women who were on average older than the men, demonstrated modest or no gains on these measures. There was no control group for comparison, and no statement regarding the effects on behavioral symptoms. Published in the same year was another open-label study of rivastigmine in 20 patients with bvFTD [37]. At 12 months, treated patients demonstrated improvements on the Neuropsychiatric Inventory (NPI), a common questionnaire-based assessment tool that evaluates the symptoms and other behavioral measures, and their caregivers reported less stress, relative both to baseline values and compared with a matched patient control group. Executive function, measured by a clock-drawing test and proverb interpretation, stabilized in rivastigmine-treated patients relative to controls, and there was no difference in MMSE, which declined in both groups. The NPI is frequently used as an outcome measure in FTD treatment studies; however, NPI scores for the many patients improve over time in the absence of therapy, probably reflecting increasing inertia and apathy that occur as the illness progresses [38].

A more recent study of galantamine in 40 patients with bvFTD or primary progressive aphasia (PPA; a general term encompassing SD, PNFA and logopenic aphasia) revealed no evidence for a beneficial effect of cholinesterase inhibition [39]. These patients were given escalating doses of galantamine during an 18-week open-label phase, and then randomized to drug or placebo during an 8-week double-blind phase. Galantamine produced no improvement in behavioral or language symptoms. A global severity score trended better in the treatment group among the subset of patients with PPA, but the authors did not characterize their PPA patients by phenotype; therefore, it is likely that some had logopenic aphasia, which is associated pathologically with AD rather than FTLN [40,41]. In any case, the authors found no clear evidence favoring cholinesterase inhibition in FTD. This is the largest and only double-blinded study of a cholinesterase inhibitor, and it was negative.

Donepezil may worsen behavior in bvFTD. In an open-label study of donepezil in 12 patients with bvFTD [42], the treated group exhibited no change in the MMSE or in a measure of overall functioning at 6 months, relative to 12 matched, untreated bvFTD patients. However, caregivers of the treated patients did endorse a higher level of disinhibition and compulsiveness that reversed upon discontinuation of donepezil. Taken together with the lack of compelling evidence for a benefit of galantamine or rivastigmine, these observations with donepezil have prompted a general recommendation to avoid cholinesterase inhibitors in FTD [11,43]. A further potential harm of cholinesterase inhibition is the risk of increasing oral secretions and contributing to aspiration in the significant subset of FTD patients who have associated motor neuron disease [44,45].

Memantine

Aside from the cholinesterase inhibitors, memantine is the only other medication approved by the FDA for treatment of AD. A low-affinity, use-dependent NMDA glutamate receptor antagonist, memantine, offers modest symptomatic improvement in cognition, function and behavior in moderate-to-severe AD [46].

Whereas the mechanism of action of cholinesterase inhibitors is conceptually straightforward, this is not the case for memantine [47]. Excessive activation of NMDA receptors by glutamate may contribute to neuronal death in a wide variety of acute and chronic neurological disorders [48,49]. However, high-affinity NMDA antagonists are problematic in humans, in part because they induce acute psychosis and neurotoxic side

effects of their own [50]. With an IC_{50} of approximately 1 μ m and an ability to bind only to open NMDA receptor channel pores, memantine offers the theoretical benefit of selectively blocking only overactive receptors. Nevertheless, despite a possibility that NMDA receptor overactivation may contribute to neurodegeneration in AD [49], memantine is not associated with any measurable disease-modifying effect [46]. Based in part on the growing belief that the symptoms of AD result from both cell death as well as loss of synapses [51] and consequent dysfunction of large-scale neuronal networks [52], one hypothesis to explain the observed symptomatic benefits of memantine is that the medication ‘dials down’ NMDA receptor transmission just enough to restore homeostasis to glutamatergic signaling [47]. This theory is attractive, but is complicated by the observation that memantine is less selective than expected and affects not only NMDA receptors, but also neuronal nicotinic acetylcholine receptors, serotonin 5-HT₃ receptors, catecholamine transporters and other nonselective CNS targets at pharmacokinetically relevant concentrations [47].

The hope that memantine may be beneficial in FTD stems less from mechanistic considerations than from the observation that improvement in agitation and other neuropsychiatric disturbances are among its more robust clinical effects in AD [53-56]. Improved NPI scores in three bvFTD patients treated with memantine [57] prompted more formal investigation. Two 26-week, uncontrolled, open-label trials of memantine in FTD have been completed: In a small study of 16 bvFTD patients [58], the drug had no effect on the primary behavioral end points, including the NPI. In a second trial, memantine was given to 21 patients with bvFTD, 13 with SD and nine with PNFA [59]. The bvFTD group responded with a transient improvement on the NPI, an observation that is hard to interpret in the absence of a control group and in light of the natural history of bvFTD (as mentioned above, see [38]); no other beneficial effect was observed. In both studies, patients tolerated memantine well at 20 mg per day (the same recommended dose for the treatment of AD) with no significant adverse reaction [58,59]. Two prospective, randomized, multicenter, double-blind, placebo-controlled trials of memantine for FTD are currently underway (Table 2): one is a 26-week Phase IV study in the USA (NCT00545974 [101]), and the other is a 52-week Phase II study in France (NCT00200538 [101]). Whether memantine may offer FTD patients symptomatic therapy, disease-modifying therapy, both or neither remains to be seen.

Expert commentary

Pending the results of the ongoing memantine trials, there remains guarded optimism that this medication may yet prove helpful in FTD. Even so, it would be surprising if anything more than a modest symptomatic improvement emerges.

Is there sufficient evidence to dismiss cholinesterase inhibitors? In practice, patients with FTD use cholinesterase inhibitors – mainly donepezil – frequently [1]. At least in part, this may reflect diagnostic uncertainty, particularly in the early stages of an apparently progressive dementia; AD and FTD frequently accompany each other on a differential diagnosis. Unfortunately, cholinesterase inhibitors cannot solve a diagnostic dilemma, as the absence of any robust, acute effect in either disease precludes their use as a litmus test.

There is a general pessimism regarding the usefulness of cholinesterase inhibitors in FTD [11,43]. This view is fueled mainly by donepezil’s association with worsened behavior in a small open-label study [42] and by the lack of any beneficial effect of galantamine in a larger, better-controlled trial [39]. There are two articles claiming that rivastigmine may be helpful [36,37], but these small, open-label studies are far from definitive.

In summary, patients with FTD should be treated conservatively, with an emphasis on symptomatic therapies and non-pharmacological approaches, as outlined above. Cholinesterase inhibitors should not be used. Although there is hope that off-label use of memantine may be helpful, this medication also cannot be recommended for use in FTD until the results of ongoing trials are available. Given the emergence of new potentially disease-modifying therapies for FTD, an important consideration for the field is whether additional clinical trials of symptomatic agents are warranted. Clinical trial recruitment in FTD can be challenging, given its lower prevalence, underdiagnosis and heavy concomitant use of other psychotropic medications compared with AD. Thus, researchers in the field of FTD therapeutics will need to work together to prioritize clinical trials that are most scientifically promising, so as not to create too much competition that could compromise enrollment across the board.

Five-year view

Much is likely to change in the treatment of FTD. Beyond completion of the ongoing memantine trials (Table 2), as well as possible clarification of the role of cholinesterase inhibitors, the most important changes are likely to include the introduction of rational drug therapies intended to slow or stop disease progression. These therapies will most likely be protein-specific, growing directly out of basic science studies of FTLD-tau, FTLD-TDP and FTLD-FUS.

One exciting example is the introduction of drugs aimed at preventing tau aggregation. Such therapy could potentially offer disease-modifying benefits in both AD and in a subset of FTD syndromes, including some cases of bvFTD and most cases of PNFA (Table 1). One such agent, the microtubule-interacting peptide NAPVSIPQ (NAP, also referred to as davunetide or AL-108) reduced tau neuropathology in a mouse model [60], and it is now in a Phase II randomized, double-blind, placebo-controlled trial for patients with predicted FTLD-tau pathology (NCT01056965 [101]). Methylene blue is another agent that has been investigated for its potential to reduce tau aggregation and slow AD [61]; a clinical trial of this agent in FTD is planned. Other potential therapeutic interventions include inhibition of enzymes that contribute to tau phosphorylation (glycogen synthase kinase-3 β [GSK3 β] or cyclin-dependent protein kinase 5), manipulation of tau-processing pathways (e.g., ubiquitination), reduction of tau expression and other approaches [29,62–64]. Lithium and valproic acid, both inhibitors of GSK3 β , have entered clinical trials as neuroprotective treatments for AD, FTD and other tauopathies (NCT00088387, NCT00703677, NCT01055392, NCT00385710 and NCT00071721 [101]).

Frontotemporal lobar degeneration-TDP neuropathology results in some cases from low levels of another protein, known as progranulin. Loss-of-function mutations in the progranulin gene result in a haploinsufficiency of the protein and cause familial, autosomal-dominant FTD with FTLD-TDP [65,66]. Although the exact function of progranulin is unknown, normalizing protein levels could be a potential therapeutic strategy. Recently, microRNA-29b was demonstrated to enhance progranulin expression *in vitro* [67]. Other possible therapeutic strategies include reducing TDP-43 hyperphosphorylation, ubiquitination, cleavage and translocation from nucleus to cytoplasm [6].

As protein-specific therapies emerge, accurate *in vivo* diagnosis will be essential. In particular, tools that can differentiate FTD-tau from FTD-TDP are needed, since most future disease-modifying agents are likely to be targeted towards one pathway or the other. Neuroimaging will play a critical role in this effort [68]. Recently, a large, longitudinal study patterned after and complementary to the Alzheimer's Disease Neuroimaging Initiative (ADNI) began recruiting patients with FTD to undergo sophisticated neuroimaging, with a

goal of characterizing the brain functionally and structurally over time, as well as developing spinal fluid biomarkers that may correspond to the underlying molecular pathogenesis. The hope is that this study will yield, not only new information on brain-behavior correlates, but also strategies for identifying the underlying proteinopathy in specific patients and to monitor the response to emerging treatments.

With luck, the vacuum that currently exists in FTD-dedicated therapeutics may begin to fill.

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Key issues

- The US FDA has not approved any medication for the treatment of frontotemporal dementia (FTD).
- Medications for Alzheimer's disease, as well as selective serotonin reuptake inhibitors and antipsychotics, are frequently used by patients with FTD in an effort to seek symptomatic therapy.
- Cholinesterase inhibitors, while often prescribed for FTD, produced mixed results in several small studies, including one study of donepezil demonstrating a possible adverse effect on behavior.
- Memantine did not exhibit any clear therapeutic effect for patients with FTD in two small, open-label, uncontrolled trials, but larger, randomized, double-blind, placebo-controlled trials are underway.
- While further clarification on the efficacy of off-label medications in FTD is expected in the coming few years, novel medications targeting the underlying molecular pathogenesis of FTD are likely to emerge.

Table 1

Frontotemporal dementia subtypes.

Syndrome	Features	Atrophy pattern	Neuropathology
Behavioral variant FTD	Personality change, disinhibition, apathy, loss of insight, impaired executive function	Right > left frontal	Tau $\approx$ TDP-43 > FUS
Semantic dementia	Deficits in naming and single word comprehension, preserved fluency, poor face recognition, impaired social behavior	Anterior temporal	TDP-43 $\gg$ Tau
Progressive nonfluent aphasia	Slow effortful speech, dysarthria, apraxias, impaired grammar, preserved comprehension and behavior	Left frontal	Tau $\gg$ TDP-43

>: More than; $\gg$: Much more than; FTD: Frontotemporal dementia; FUS: Fused-in sarcoma; TDP-43: TAR DNA-binding protein-43.

Table 2

Studies of Alzheimer's disease medications in patients with frontotemporal dementia.

Study (year)	Subjects	Study design	Findings	Ref.
<i>Donepezil</i>				
Lampl <i>et al.</i> (2004)	Nine bvFTD (five randomized to donepezil, four to rivastigmine)	Open-label, 6 months, uncontrolled	Of the five donepezil-treated patients, three improved on MMSE and clock-drawing, and two improved on SPECT	[36]
Mendez <i>et al.</i> (2007)	24 bvFTD (12 treated, 12 untreated controls, not randomized)	Open-label, 6 months, matched controls	Worsened disinhibition and compulsiveness in four of the 12 donepezil-treated patients compared with their own baseline; returned to baseline after discontinuation of treatment	[42]
<i>Galantamine</i>				
Kertesz <i>et al.</i> (2008)	17 bvFTD, 22 PPA (not separated by subtype)	18-week open-label galantamine treatment phase, followed by 8-week randomized, double-blind, placebo-controlled withdrawal	No change in any cognitive or behavioral end point	[39]
<i>Rivastigmine</i>				
Lampl <i>et al.</i> (2004)	Nine bvFTD (five randomized to donepezil, four to rivastigmine)	Open-label, 6 months, uncontrolled	Of the four rivastigmine-treated patients, three improved on MMSE and clock-drawing, and one improved on SPECT	[36]
Moretti <i>et al.</i> (2004)	40 bvFTD (20 treated, 20 matched controls)	Open-label, 12 months, matched controls	Improved scores on multiple behavioral assessments and on caregiver stress	[37]
<i>Memantine</i>				
Diehl-Schmid <i>et al.</i> (2008)	16 bvFTD	Open-label, 6 months, uncontrolled	No improvement on any behavioral or cognitive end point	[58]
Boxer <i>et al.</i> (2009)	21 bvFTD, 13 SD, nine PNFA	Open-label, 6 months, uncontrolled	Transient improvement on NPI in bvFTD patients, but no improvement on any other behavioral or cognitive end point	[59]
NCT00545974	–	Phase IV, 26-week randomized, multicenter, double-blind, placebo-controlled	Study in progress	[101]
NCT00200538	–	Phase II, 52-week, randomized, multicenter, double-blind, placebo-controlled	Study in progress	[101]

bvFTD: Behavioral variant frontotemporal dementia; MMSE: Mini-Mental State Examination; PNFA: Progressive nonfluent aphasia; PPA: Primary progressive aphasia; NPI: Neuropsychiatric Inventory; SD: Semantic dementia.