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Therapy and clinical trials in frontotemporal dementia: past, present, and future

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Abstract

Frontotemporal dementia (FTD) is a common form of dementia with heterogeneous clinical presentations and distinct clinical syndromes. This article will review currently available therapies for FTD, its related disorders and their clinical evidence. It will also discuss recent advancements in FTD pathophysiology, treatment development, biomarker advancement and their relation to recently completed or currently ongoing clinical trials as well as future implications.

Keywords

frontotemporal dementia; clinical trials; treatment; 10th International Conference on Frontotemporal Dementia; behavioral variant frontotemporal dementia (bvFTD); primary progressive aphasia (PPA); progressive supranuclear palsy (PSP); tau; TDP-43; C9ORF72

Frontotemporal dementia (FTD) is a common form of dementia with heterogeneous clinical presentations encompassing dysfunctions in behavioral, language, motor, and cognitive domains. FTD typically comprises of three distinct clinical syndromes; behavioral variant frontotemporal degeneration (bvFTD), and two primary progressive aphasias (PPA): non-fluent variant primary progressive aphasia (nfvPPA) and semantic variant primary progressive aphasia (svPPA). FTD also frequently overlaps clinically with three additional neurodegenerative diseases with profound motor deficits: corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS) (Bang *et al.* 2015).

Each of the above clinical syndromes have established diagnostic criteria that identify the seminal features including: social dysfunction, executive, and behavioral changes for bvFTD (Rascovsky *et al.* 2011), agrammatic, effortful speech for nfvPPA, and impaired single-word comprehension, naming in svPPA (Gorno-Tempini *et al.* 2011). CBD, now referred to as

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corticobasal syndrome (CBS) for the syndromic presentation and CBD for the underlying neuropathology, can present with multiple subtypes encompassing motor, behavioral, or cognitive changes (Armstrong *et al.* 2013). Ophthalmoplegia and early falls are characteristic for the most common presentation of PSP (Richardson's) (Litvan *et al.* 1996), whereas ALS is a motor neuron disease with increasingly recognized cognitive and behavioral features (Ringholz *et al.* 2005). Despite such a wide range of clinical presentation, the above syndromes are generally recognized under the umbrella term frontotemporal lobar degeneration (FTLD) as the different clinical phenotypes often share underlying neuropathological substrates. The most common underlying forms of FTLD involve deposition of tau protein (FTLD-tau) or TAR DNA-binding protein 43 KDa (TDP-43; FTLD-TDP), whereas mutations in the microtubule-associated protein tau (*MAPT*) gene, progranulin (*GRN*) gene, and hexanucleotide repeat expansions in chromosome nine open reading frame 72 (*C9ORFT72*), were found to be responsible for a large fraction of familial FTD (Bang *et al.* 2015).

Currently there are no United State Food and Drug Administration (FDA) approved therapies for FTD, and there are no treatments that can stop or alter the course of disease progression. Pharmacological treatment to date has mostly involved off-label use of medications for symptomatic management. Because of the varied clinical presentations as mentioned above, clinical trials in the past may have included FTD syndromes with differing underlying pathology, many were not rigorous randomized, placebo-controlled, double-blind studies and were generally limited in number of cases. Thus there has been minimal evidence for efficacy to support currently available therapeutic management options.

Fortunately, there have been remarkable advancements in the understanding of FTLD pathophysiology, genetics, neuropathology as well as breakthroughs in neurodegenerative biomarkers recently. New cellular and animal models have allowed development of small molecules targeted toward the underlying FTLD pathology in hopes of achieving a disease-modifying effect. Biomarker development may improve diagnosis and recruitment accuracy, provide information on target engagement, improve sensitivity on pathophysiological changes and help improve clinical trial efficiency. Large clinical trials with previously hopeful disease-modifying agents have been recently completed for PSP, and although not successful, provided invaluable experience and evidence that large, multicenter international FTD clinical trials are feasible (Boxer *et al.* 2014). More clinical trials with potentially disease-modifying agents for PSP and FTD are currently underway, leading to a promising decade for therapy development for FTD.

This article will review currently available therapies for FTD, its related disorders and their clinical evidence. It will also discuss recent advancements in FTD pathophysiology, treatment development, biomarker advancement, and their relation to recently completed or currently ongoing clinical trials as well as future implications.

Currently available symptomatic treatments

Currently available medications commonly used for FTD were developed for use in psychiatric disorders or Alzheimer's disease (AD) and are not indicated (approved) for

treatment of FTD. The majority of these agents work by modulating the levels or downstream effects of various neurotransmitters, strategies that have been effective in AD or Parkinson's disease. Abnormalities in the cholinergic, serotonergic, dopaminergic, noradrenergic, and glutamatergic systems in FTD provide the rationale for these treatment efforts (Kaye *et al.* 2010). Unfortunately, the majority of available evidence is limited to small case series or open label trials. In some cases, initially promising agents failed to prove efficacious in further, more rigorous testing under randomized, double-blind, placebo-controlled conditions. The majority of these treatment efforts were aimed at improving behavioral, cognitive, or motor symptoms of FTD.

Behavioral symptoms management

Disinhibition, apathy, lack of empathy, compulsive behavior, and altered eating habits are cardinal features for bvFTD (Rascovsky *et al.* 2011). These behavioral symptoms are also prominent in PSP (Kobylecki *et al.* 2015), right temporal variant of svPPA (Seeley *et al.* 2005), have been described in nfvPPA (Gómez-Tortosa *et al.* 2015) and as a possible clinical presentation of CBD (Murray *et al.* 2007; Ling *et al.* 2010; Lee *et al.* 2011). Furthermore, depression is a commonly seen symptom in all neurodegenerative dementias. Neuropathological analyses have shown dysfunctional serotonergic systems with reduced 5HT1, 5HT2A receptors in orbital frontal, cingulate, frontal medial, temporal regions, and 40% loss of neurons in the serotoninergic raphe nuclei (Procter *et al.* 1999; Yang and Schmitt 2001; Franceschi *et al.* 2005). As selective serotonin reuptake inhibitors have historically been successful in managing mood symptoms in psychiatric and AD patients, a variety of serotonergic medications have seen use in FTD patients with mixed results.

In a case series and a 14-month open label trial without placebo, paroxetine was shown to improve repetitive behavior and neuropsychiatric index (NPI) respectively (Chow and Mendez 2002; Moretti *et al.* 2003a). However, the same drug failed to demonstrate significant differences in NPI or the Cambridge Behavioral Inventory in a randomized, double-blind, placebo-controlled crossover trial (Deakin *et al.* 2004). Sertraline has been shown to improve behavior in several open label trials in FTD patients (Swartz *et al.* 1997; Mendez *et al.* 2005) and improved the NPI in four svPPA subjects in another trial (Prodan *et al.* 2009). Citalopram has been shown in a 15 FTD patients open label trial to improve the NPI and frontal behavioral index (Herrmann *et al.* 2012), and a 12 week randomized, placebo-controlled, double-blind crossover trial demonstrated efficacy of trazodone in 26 FTD patients via improved NPI (Lebert *et al.* 2004). It is generally accepted that anti-depressants may help manage behavioral symptoms in FTD patients and are well tolerated.

While antipsychotics have long been used to control difficult behavior, evidence for their use in FTD comes mainly from case reports and uncontrolled series. Furthermore, all antipsychotic use carry the risk of extrapyramidal side effects, to which FTD patients are particularly vulnerable (Pijnenburg *et al.* 2003). In the US, there is also a FDA black box warning (drugs marketed in the US with special problems that lead to serious injury or death have warning information displayed within a box in the prescribing information) for all antipsychotics as use of atypical antipsychotics for dementia is associated with higher mortality than placebo, because of a higher cardiac- and infection-related mortality.

Quetiapine was shown in a case series to improve agitation (Chow and Mendez 2002) but failed to show significant changes in NPI in an eight FTD subject, double-blinded crossover trial (Huey *et al.* 2008). Risperidone and apriprazole have been described to improve agitation, inappropriate behavior in a series of case reports (Curtis and Resch 2000; Chow and Mendez 2002; Fellgiebel *et al.* 2007; Reeves and Perry 2013), whereas olanzapine was reported to improve NPI scores in 17 FTD patients in an open-label study (Moretti *et al.* 2003b). Other approaches to controlling behavioral symptoms in FTD involve use of anti-epileptics with mood stabilizing effects such as valproic acid, topiramate, carbamazepine, but evidence is mostly limited to case reports (Chow and Mendez 2002; Cruz *et al.* 2008; Nestor 2012; Poetter and Stewart 2012; Shinagawa *et al.* 2013; Singam *et al.* 2013).

Of note, other novel approaches to managing behavioral symptoms for FTD are currently being studied in placebo-controlled trials. The neuropeptide oxytocin, an important mediator of social behavior, was administered intranasally to 20 bvFTD and three svPPA patients in a double-blind, randomized, placebo-controlled, crossover trial over 1 week and demonstrated possible trend toward improved apathy and empathy (Finger *et al.* 2015).

Cognitive symptoms management

Cognitive symptoms are present in FTD and all its related disorders in varying degrees. Acetylcholinesterase inhibitors have been the mainstay of Alzheimer's treatment, and perhaps because of their success, acetylcholinesterase inhibitors have been studied extensively in the treatment of FTD, though all have produced disappointing results. Donepezil was studied in a 6 month, open label study of 24 FTD patients, with the treatment group resulting in worsening on the FTD inventory and four had worsening behavior. Discontinuation of donepezil resulted in abatement of behavioral symptoms, which was replicated in other recent studies (Mendez *et al.* 2007; Arciniegas and Anderson 2013; Kimura and Takamatsu 2013). In PSP, donepezil was tested with positive effects on memory but with more impaired motor function in a five patient series and a randomized, placebo-controlled, double-blind crossover trial of 21 PSP patients (Fabbrini *et al.* 2001; Litvan *et al.* 2001). Rivastigmine was studied in a 12-month open label study in FTD and showed some improvements in NPI but did not prevent cognitive deterioration (Moretti *et al.* 2004). In PSP, rivastigmine produced similar results compared to donepezil, where a five PSP case series resulted in positive effects on memory but decreased motor function (Liepelt *et al.* 2010). The third most commonly used acetylcholinesterase inhibitor, galantamine, was studied in 36 bvFTD and PPA patients. No significant differences were found in the bvFTD group, whereas the language function remained stable in the treated PPA group compared to placebo, although it is likely these subjects had the logopenic form of PPA which is typically caused by underlying Alzheimer's pathology and not FTLD (Kertesz *et al.* 2008). Currently, the evidence suggest cholinesterase inhibitors are not effective in FTD or PSP patients, and may worsen behavior or motor function respectively. Routine use is not recommended.

Memantine is a *N*-methyl-D-aspartate receptor antagonist with an indication for treatment in moderate to severe AD, with beneficial effects on activities of daily living and cognition (Reisberg *et al.* 2003; Tariot *et al.* 2004). Although AD and FTD differ in underlying pathology, excitotoxicity via over activation of *N*-methyl-D-aspartate receptors may be a

final common pathway for neuronal death. With this rationale in mind, memantine was studied in a small case series and open label study that suggested some improvements in NPI (Swanberg 2007; Boxer *et al.* 2009). Memantine was then tested in two rigorous, randomized, placebo controlled trials over 52 weeks and 26 weeks. Although both trials did not enroll the originally planned number of patients, both failed to demonstrate significant benefits on NPI or clinical global impression of change. Furthermore, the memantine group was associated with worsening cognitive function (Vercelletto *et al.* 2011; Boxer *et al.* 2013a). Experience with memantine in FTD stresses the limitations of extrapolating AD therapy to FTD and importance of randomized, placebo-controlled, double-blind trials to truly demonstrate efficacy.

Motor symptoms management

A substantial portion of FTD patients also present with parkinsonism. Frontotemporal dementia with parkinsonism (FTDP-17), an autosomal dominant form of FTD associated with mutations in the *MAPT* or *PRG* gene, is frequently characterized by progressive movement difficulties, including tremors, rigidity and bradykinesia. Furthermore, the FTD-related disorders PSP and CBD are defined by atypical parkinsonism, typically with substantial rigidity and infrequent tremors. Unfortunately, FTD, PSP, and CBD patients generally do not respond to dopaminergic therapy such as levodopa/carbidopa. A few cases of FTD with benefits from levodopa/carbidopa have been reported (Chow and Mendez 2002). In PSP, despite prominent parkinsonism, dopamine replacement therapy has seen limited benefit. This may be because of more widespread pathology involving additional basal ganglia, brainstem and cerebellar structures in PSP as opposed to limited involvement in dopaminergic output via the substantia nigra pars reticulata in Parkinson's disease. Clinical studies with levodopa in PSP were limited to open label case series without placebo control, and true benefits were difficult to determine (Klawans and Ringel 1971; Kompoliti *et al.* 1998; Birdi *et al.* 2002).

Non-pharmacological interventions

Non-pharmacological interventions in FTD and its related disorders remain an important corner stone of FTD management and should not be ignored. FTD patients with behavioral and cognitive difficulties often cause significant caregiver stress and may place the patient or caregiver in harm as well. Strategies to intervene in troublesome symptoms involving environmental, behavioral, and physical interventions have been discussed in a detailed review (Merrilees 2007). Physical therapy for gait, balance training, and home safety evaluation by occupational therapy is critical for FTD patients with movement dysfunction, PSP patients with high fall risk and CBD patients with limb, fine motor difficulties. Moreover, exercise has been shown to benefit cognition, mood, and overall health in dementia and should be recommended to all patients capable of performing exercise in a safe manner (Cheng *et al.* 2014). Speech therapy by speech pathologists experienced with neurodegenerative aphasias may be especially helpful in the primary progressive aphasias. (Kortte and Rogalski 2013; Tippett *et al.* 2015).

Potential disease-modifying treatments

Targets

Recent advancements in the understanding of the genetics, pathophysiology, and neuropathology of FTD and its related disorders have led to a new generation of therapeutics targeted towards potential underlying mechanisms in hopes of a disease-modifying effect. Table 1 displays available therapeutics and currently ongoing or recently completed clinical trials with potentially disease-modifying agents in FTD and its related disorders.

Tau

Tau is a microtubule-associated protein localized to neuronal axons that regulate the stability of microtubules by promoting tubulin polymerization and is a major component of axonal transport (Drechsel *et al.* 1992). In the human brain, alternative mRNA splicing of the *MAPT* gene produces six tau isoforms, either with three or four repeat domains in the C-terminal part (3R and 4R tau)(Andreadis *et al.* 1992). Tau is also subject to various post-translational modifications such as acetylation, phosphorylation that may affect its function. Mutations in the gene *MAPT* has been identified in familial FTD and encompass a wide range of clinical presentation and tau pathology (Ghetti *et al.* 2015). Abnormal tau, sporadic or familial, and whether it is because of loss of function, or gain of toxicity, has been implicated in many FTD-related neurodegenerative syndromes as well as AD.

Tau can exist as monomers, oligomers, filaments, and aggregated inclusions. Pathological tau inclusions, often hyperphosphorylated, contain predominantly 3R tau in Pick's disease (PiD), and 4R tau in PSP and CBD. Tau inclusions present with distinct pathological substrates; as dense, round inclusion bodies (Pick bodies) in ballooned neurons in Pick's disease, as globose neurofibrillary tangles in neurons, astrocytes (tufted astrocytes), oligodendrocytes (coiled bodies) in PSP, and as thread like neurofibrillary tangles, astrocytic plaques in CBD (Feany *et al.* 1996; Takahashi *et al.* 2002; Zhukareva *et al.* 2002). Further differences in tau structure reveals that PiD present with coiled, straight filaments, PSP has predominantly straight filaments, whereas CBD has twisted filaments (Buée and Delacourte 1999).

Over the past years, accumulating evidence has pointed to intercellular spread of tau aggregates and its ability to propagate further aggregation via conformational change in a prion like manner (Holmes and Diamond 2014). In addition, intracerebral injection of brain homogenates from pathologically confirmed tauopathies PSP, CBD, and PiD into tau transgenic and non-transgenic mice hippocampus and neocortex was able to recapitulate specific lesions resembling PSP and CBD, respectively, while forming inclusions in PiD. With the exception of PiD, filamentous tau pathology also propagated to neighboring or regions connected to the injection site (Clavaguera *et al.* 2013). The above suggests that for each FTLD syndrome, tau isoforms with 3R and 4R may be differentially expressed or post-translationally modified, distinct tau species may be responsible for each syndrome and abnormal tau may propagate and spread via a prion like mechanism along disease-specific networks of vulnerable cells, causing further pathologic aggregates. It is with these recent discoveries in mind that many tau directed therapies have entered clinical trials recently.

Therapies targeting tau aggregates

Experience from reducing amyloid burden in AD with immunotherapy has led to substantial efforts to develop immune therapies aimed at reducing endogenous tau levels. Active immunization in transgenic mouse models with human tau pathology have been shown to have reduced tau pathology and improved performance on sensorimotor testing (Asuni *et al.* 2007; Theunis *et al.* 2013). Two active tau vaccines have entered early stage clinical trials for AD. Passive immunization via antibodies has the advantage of high specificity and potentially fewer immune side effects. Over the past 4 years, multiple studies have demonstrated that injection of anti-tau antibodies to various tau epitopes in tau transgenic mouse models resulted in reduction in tau pathology, with three studies reporting cognitive or functional improvement (Boutajangout *et al.* 2011; Chai *et al.* 2011; d'Abramo *et al.* 2013; Yanamandra *et al.* 2013; Castillo-Carranza *et al.* 2014a,b; Collin *et al.* 2014). However, it is currently unclear whether certain tau conformations are better targets for immune clearance and whether there is a differential effect on neurotoxicity with the various tau conformations. Currently there are two ongoing phase I clinical trials utilizing anti-tau antibodies for patients with PSP as shown in Table 1.

Leuco-methylthioninium (LMTx) is a reformulated methylene blue compound that is thought to inhibit tau aggregation via selective blocking of a process required of tau to form filaments (Wischik *et al.* 1996). LMTx has recently published phase II clinical trial results in AD, showing improvements in cognition in the middle dose but not the highest dose cohort, where it was argued the drug suffered from impaired absorption (Wischik *et al.* 2015). LMTx is currently undergoing clinical trials for bvFTD as well, with results expected in 2016.

Therapies targeting tau aggregate formation

Modulation of post-translational tau modifications has been theorized to affect tau aggregation as well. As abnormal tau is hyper-phosphorylated, protein kinase inhibition may prevent phosphorylation, and glycogen synthase kinase (GSK-3) has been an early target of therapies meant to block tau phosphorylation. Clinical trials using lithium chloride for PSP was unsuccessful because of toxicity, and another GSK-3 inhibitor, tideglusib, recently completed trials for PSP without significant differences in primary outcomes (Tolosa *et al.* 2014). The tideglusib trial did report reduced brain atrophy in a treatment group subpopulation of uncertain clinical significance (Höglinger *et al.* 2014). Modulation of tau phosphorylation via enhancing phosphatase activity remains an interesting therapeutic possibility. In addition, other post-translational modifications such as acetylation may be an important step in tau aggregation (Min *et al.* 2010). Recently a non-steroidal anti-inflammatory drug salsalate was found to inhibit tau acetylation, and when given to transgenic mouse models of FTD, resulted in lowered levels of total tau, preserved hippocampal atrophy and improved memory deficits (Min *et al.* 2015). Salsalate is currently being tested in PSP patients in a small clinical trial (Table 1).

Tau loss of function therapies

Compromise of tau binding to microtubules leads to microtubule instability and may impair their function in transporting cellular constituents (Higuchi *et al.* 2002). Stabilization of

microtubules has been proposed as a way to make up for tau's loss of function. Davunetide, a peptide derived from a growth factor activity dependent neurotrophic protein, was theorized to promote microtubule stability and studied in an international, multi-center clinical trial with 313 PSP subjects. Despite no differences in all outcomes, the davunetide trial has shown that large, multicenter, international clinical trials in FTD are feasible (Boxer *et al.* 2014). Paclitaxel, from the taxane family of chemotherapy agents, works by interfering with the disassembly of microtubules, and the blood brain barrier permeable microtubule stabilizing agent, Epothilone D, has been shown to be efficacious in transgenic mouse models, but was abandoned after a small clinical trial in AD (Brunden *et al.* 2013). Paclitaxel itself has poor blood–brain barrier permeability but currently TPI-287, a synthetic, taxol-derived compound with good blood– brain barrier permeability developed for neuro-oncology has been repurposed for study in FTD and a phase I clinical trial for PSP and CBS is currently ongoing (Table 1).

Progranulin

Mutations in the *GRN* gene accounts for up to 5–10% of FTD cases with European ancestry (van Swieten and Heutink 2008). *GRN* mutations are associated with an underlying TDP-43 pathology. *GRN* mutation results in haploinsufficiency of GRN mRNA expression, resulting in readily measurable decreased levels of progranulin (PGRN) protein in serum and CSF (Ghidoni *et al.* 2008; Finch *et al.* 2009; Sleegers *et al.* 2009). In the CNS, PGRN may have neurotrophic and synaptic effects, though the exact function of PGRN remain an area of continued investigation. In addition, it has been demonstrated that patients with *GRN* mutation often have co-existing autoimmune disorders (Miller *et al.* 2013a). PGRN may also have a role in inflammation regulation, as it appears to antagonize the inflammatory effects of tumor necrosis factor alpha (TNF-alpha) (Tang *et al.* 2011). Despite incomplete understanding of the pathophysiological mechanism of *GRN* mutations, a readily measurable CSF and serum PGRN level can serve as not only a useful biomarker for diagnosis but also for target engagement and treatment response.

Because of the presence of haploinsufficiency in *GRN* mutation patients, it has been theorized that raising or restoring PGRN levels may be an effective therapy. Alkalilzing drugs such as chloroquine, bepridil, and amiodarone that affect endosomal sorting may stimulate PGRN production (Capell *et al.* 2011). Unfortunately, a recent pilot study using amiodarone in 5 FTD patients with *GRN* mutation failed to demonstrate any elevated granulin levels or change in disease course (Alberici *et al.* 2014). A recent phase I clinical trial utilizing the CNS-penetrant calcium channel blocker nimodipine in *GRN* mutation carriers was recently completed and results of its effects on serum and CSF PGRN levels should be available soon. A high throughput screen identified suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, was also shown to enhance PGRN expression, but this drug does not cross the blood brain barrier (Cenik *et al.* 2011). A phase 2 clinical trial utilizing FRM-0334, a proprietary histone deacetylase inhibitor that crosses the blood–brain barrier and enhances PGRN expression in preclinical models, is currently underway in *GRN* mutation carriers (Table 1).

As described above, patients with *GRN* mutation have a higher prevalence of systemic autoimmune conditions when compared when AD controls, normal controls, and the general population. Elevated TNF-alpha levels have been demonstrated in FTD, but without clear differentiation as to which pathological subtype (Sjögren *et al.* 2004). In addition, *GRN* knockout mice has been shown to develop inflammatory arthritis alleviated by PGRN, which shows antagonistic effects to TNF-alpha signaling (Tang *et al.* 2011). The above suggest a role for inflammation in the pathogenesis of FTD, especially in TDP-43 pathology subtypes or *GRN* mutations. A number of anti-TNF-alpha agents are already approved for systemic autoimmune disease, such as infliximab, adalimumab, etc. Clinical trials of such agents could potentially be pursued in FTD.

C9ORF72

FTD and ALS are both neurodegenerative processes, with up to 22% of ALS patients meeting FTD diagnostic criteria and 48% manifesting cognitive or behavioral abnormalities without meeting full criteria. An estimated 15% of FTD patients display signs of motor neuron disease and both disease have a 10% autosomal dominant pattern as well, suggesting some shared pathophysiology (Sha and Boxer 2012). In 2011, a hexanucleotide repeat expansion in the 5′ non-coding region of the *C9ORF72* gene was found to be the cause of FTD and ALS in a strongly chromosome 9p linked family (Boxer *et al.* 2011; DeJesus-Hernandez *et al.* 2011; Renton *et al.* 2011). This expansion is now thought to be the most common genetic cause of FTD-ALS, but also less commonly associated with CBS and nfvPPA presentations (Snowden *et al.* 2012; Anor *et al.* 2015). The pathology of C9ORF72 mutation carriers have been overwhelmingly TDP-43, but also with a unique p62 positive, TDP-43 negative polypeptide repeat inclusion in the cerebellum and hippocampus (Ash *et al.* 2013). Although recent studies have shown that specific dipeptide products are toxic in animal and cell models via cytoplasmic aggregates or nuclear inclusions and nucleolar stress, whether it is a major or exclusive pathogenic mechanism in humans remain to be elucidated (Mackenzie *et al.* 2015).

Although the precise function of *C9ORF72* remains unknown, expanded RNA transcripts may result in both loss of function or toxic gain of function. Recent studies have identified intranuclear RNA foci produced by abnormal localization of expanded *C9ORF72* transcription in FTD-ALS patients' motor cortex, spinal cord tissues (DeJesus-Hernandez *et al.* 2011). The nuclear RNA aggregation may sequester RNA-binding protein and is thought to disrupt RNA-binding protein function, resulting in abnormal RNA processing and may play a role in C9ORF72 pathophysiology (Echeverria and Cooper 2012).

In light of the above, antisense oligonucleotide (ASO) may be a viable strategy for FTD because of *C9ORF72* repeat expansions. ASO are synthetic nucleic acids that can inactive the mRNA of a target gene by direct binding or inducing RNAse H mediated cleavage via a DNA/RNA heteroduplex. ASOs have been successfully tested in ALS patients with super-oxide dismutase 1 mutation via intrathecal administration, and may serve as a roadmap for treatment development for FTD (Miller *et al.* 2013b). Several ASO candidates are in pre-clinical development and demonstrated reduction in RNA aggregation without toxic effects

in human C9ORF72 induced pluripotent stem cell neuron and fibroblast (Donnelly *et al.* 2013; Lagier-Tourenne *et al.* 2013; Sareen *et al.* 2013).

Future clinical trials considerations

Rapid development of successful FTD therapies will require close collaboration between academic laboratories, clinical research centers, pharmaceutical/biotechnology industry, and the FDA. The cooperation of the pharmaceutical industry will be critical with its large therapeutic compound libraries, clinical trial expertise, funding, and established infrastructure. The recent davunetide trial for PSP, although unsuccessful, has proven that large, multicenter, international trials for rare neurodegenerative disease are feasible. It has also provided a wealth of experience and natural history data that will be crucial for future clinical trial design. As a larger percentage of FTD cases are familial compared to AD, several recently launched treatment initiatives in preclinical and familial Alzheimer's disease; Dominantly Inherited Alzheimer's Network (DIAN) treatment unit, Alzheimer's prevention initiative, and Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) may serve as models for patient recruitment, data collection, multicenter collaboration, and clinical trial design. Efforts to develop research networks and biomarkers for FTD are underway via the Longitudinal Evaluation of Familial Frontotemporal Dementia project and Genetic FTD Initiative, focused on familial forms of FTD, and Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) project, focusing on all FTLD syndromes. Several additional topics relevant to FTD clinical trials development are discussed below.

Biomarkers

Differentiating between the various pathological subtypes of FTD will be important for proper patient selection in clinical trials, and biomarkers may help. Biomarkers can also provide evidence confirmation that a particular therapeutic candidate engages its intended target and exerts the predicted physiological effect (e.g., a pharmacodynamic effect).

The clinical trial environment for AD has undergone dramatic changes as the advent of β-amyloid positron emission tomography (PET) imaging with the ligands ^{11}C-Pittsburgh Compound B and ^{18}F-Florbetapir. The ability to detect β-amyloid pathology has led to an understanding of the limitations of a clinical diagnosis of dementia, as up to 16% of recruited patients in a previous AD trial did not have amyloid pathology by PET scan (Vellas *et al.* 2013). Beta-amyloid PET imaging is now a required part of most AD clinical trials to ensure proper patient recruitment, and is also being used for a CBS clinical trial to rule out Alzheimer's pathology presenting as a FTD-related syndrome.

With the broad understanding and experiencing from use of PET tracers in dementia, there is now increasing excitement and research into the possible use of tau PET tracers for FTD. Multiple tau-binding ligands are currently being investigated and was previously reviewed (Dani *et al.* 2015). ^{18}F THK5351 is one ligand that has been shown to bind to expected tau pathology distribution in AD patients and to tau deposits in postmortem AD tissue (Harada *et al.* 2016). Another ligand, ^{18}F-T807 appears to readily bind to tau pathology in AD, and regional uptake is correlated with cognitive impairment (Johnson *et al.* 2015). Its ability to

bind to tau pathology in FTD and its related disorders remains an important area of research (Marquié *et al.* 2015). Such agents could be immensely helpful for tau therapeutic studies in FTD.

Other imaging methods such as volumetric MRI to measure regional gray, white matter atrophy or diffusion tensor imaging for white matter tract integrity may also provide additional support for treatment efficacy. For example, recent work in PSP has demonstrated superior sample size estimates when using neuroimaging measures over standard clinical scales over 6 months (Whitwell *et al.* 2012).

Fluid biomarkers either from serum or cerebrospinal fluid are other options for FTD clinical trials. Cerebrospinal fluid β-amyloid and tau have been established in clinical use for AD diagnosis, but a similar biomarker for FTD and its related disorder is not yet available. The ratio of phosphorylate tau to total tau may help identify human cases of FTD with TDP-43 pathology (Hu *et al.* 2013). Neurofilament light chain is a non-specific marker of central nervous system injury, but serum levels has been shown to be a prognostic marker in ALS (Lu *et al.* 2015) and CSF levels reflect disease severity in FTD measured by clinical dementia rating scale, neuropsychology testing, and volumetric MRI (Scherling *et al.* 2014).

Additional research into biomarkers proven for diagnosis, prognosis or symptom severity in FTD will be crucial for future clinical trials. Diagnostic biomarkers, such as β-amyloid PET imaging in AD, can help to exclude atypical AD cases that may appear to have a FTD clinical syndrome but would not respond to FTD-specific therapies. Biomarkers that may predict disease prognosis can help homogenize the recruited study population to reduce the necessary size to detect treatment effects. Finally, a surrogate biomarker that closely reflects symptom severity, progression or recovery could greatly increase clinical trial efficiency, reducing time and sample size. While no such surrogate outcome biomarkers currently exist, their use could facilitate the design of more efficient clinical trials in this rare disease population.

Outcome measures

Because of the heterogeneous clinical presentation of FTD and its related disorders, encompassing motor, behavioral, language and cognitive symptoms, accurate clinical scales that capture disease progression and are sensitive to change will be crucial for clinical trial outcomes. A number of cognitive, behavior, and motor scales have been studied and validated in longitudinal studies of FTLD syndromes (Boxer *et al.* 2013b). For example, the Progressive Supranuclear Palsy Rating Scale, a six domain clinical scale encompassing history, mentation, bulbar, limb, gait, oculomotor function has been shown to have excellent sensitivity to disease progression and produces effect size, sample size estimates comparable to imaging outcomes over 12 months (Golbe and Ohman-Strickland 2007; Whitwell *et al.* 2012). Functional rating scales such as the FTLD-specific version of Clinical Dementia Rating may be more useful over time in bvFTD. A variety of neuropsychological tests are sensitive to change in FTLD (Knopman *et al.* 2008). The new ARTFL and Longitudinal Evaluation of Familial Frontotemporal Dementia projects (https://www.rarediseasesnetwork.org/cms/ARTFL) are using the National Alzheimer's Coordinating Center Uniform Data Set and FTLD module, including language testing and

may provide a wealth of longitudinal data for future clinical trial design. Ultimately rating scales should be sensitive in reflecting change over time, and facilitate translation and transport across sites as future FTD trials will likely be multinational and involve patients from various cultural backgrounds.

Conclusion

FTD and its related disorders are a spectrum of uniformly fatal neurodegenerative diseases with a finite number of pathophysiologies that are rapidly being elucidated. Currently there are no FDA approved treatments for FTD, and most treatments are symptomatic therapies for other disorders used off-label. Recent advancements in understanding the molecular and genetic basis of FTD, especially FTLD-tau have reached sufficient maturity for new drug targets to be identified, and several clinical trials based on these insights are underway. Development of novel biomarkers that can help with accurate diagnosis of FTD, prognosis and capturing disease progression are also being investigated. With such a road map in place, it may well be a promising decade for therapy for FTD and its related disorders.

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Abbreviations used

AD	Alzheimer’s disease
ALS	amyotrophic lateral sclerosis
ASO	antisense oligonucleotide
bvFTD	behavioral variant frontotemporal dementia
C9ORF72	chromosome 9 open reading frame 72
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CSF	cerebrospinal fluid
FDA	food and drug administration
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
GRN	progranulin
HDACi	histone deacetylase inhibitor
MAPT	microtubule-associated protein tau

MRI	magnetic resonance imaging
nfvPPA	non-fluent variant primary progressive aphasia
NPI	neuropsychiatric index
PET	positron emission tomography
PiD	Pick's disease
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
SSRI	selective serotonin reuptake inhibitor
svPPA	semantic variant primary progressive aphasia
TDP-43	TAR DNA-binding protein 43 KDa

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Table 1

(A) Clinical therapeutics for frontotemporal dementia (FTD) spectrum disorders and (B) ongoing or recently completed clinical trials with potentially disease-modifying agents

Drug class	Examples	Effect	Types of evidence
Panel (A)			
Treatments for behavioral symptoms			
Anti-depressants	Citalopram, paroxetine, sertraline, trazodone	May improve behavioral symptoms	Case reports & series, open label trials, randomized double-blind placebo-controlled trial
Anti-psychotics	Quetiapine, risperidone, apriprazole, olanzapine	May improve behavioral symptoms	Case reports & series
Anti-epileptics	Carbamazepine, topiramate, valproic acid	May improve behavioral symptoms	Case reports & series
Treatment for cognitive symptoms			
Acetylcholinesterase inhibitors	Donepezil, galantamine, rivastigmine	No improvements, may worsen behavioral symptoms	Open label trials, randomized, double-blind placebo-controlled trials
NMDA-antagonist	Memantine	No improvements, may worsen cognition	Case series, open label trials, randomized double-blind placebo-controlled trials
Treatment for movement symptoms			
Dopamine replacement	Carbidopa-levadopa	Modest to no benefits	Case series

Compound	Mechanism	Indication	Phase	Reference (identifier on clinicaltrials.gov)	Results
Panel (B)					
TRx0237 (LMTx)	Tau aggregation inhibitor	bvFTD	III	NCT01626378	Unavailable
TPI-287	Microtubule stabilizer	CBS, PSP	I	NCT02133846	Unavailable
C2N-8E12	Anti-tau antibody	PSP	I	NCT02494024	Unavailable
Davunetide	Microtubule stabilizer	PSP	II/III	NCT01110720	No effect (Boxer *et al.* 2014)
Tideglusib	Glycogen synthase kinase-3 inhibitor	PSP	II	NCT01049399	No effect (Tolosa *et al.* 2014)
BMS-986168	Anti-tau antibody	PSP	I	NCT02460094	Unavailable
Salsalate	Tau acetylation inhibitor	PSP	I	NCT02422485	Unavailable
FRM-0334	Increase progranulin expression	*GRN* carrier	II	NCT02149160	Unavailable
Nimodipine	Increase progranulin release	*GRN* carrier	I	NCT01835665	Unavailable

CBS, corticobasal syndrome; FTD, frontotemporal dementia; LMTx, Leuco-methylthioninium; PSP, progressive supranuclear palsy.