Advances in Treatment of Frontotemporal Dementia

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In this review, the authors explored the clinical features of frontotemporal dementia (FTD), focusing on treatment. The clinical features of FTD are unique, with disinhibition, apathy, loss of empathy, and compulsions common. Motor changes occur later in the illness. The two major proteins that aggregate in the brain with FTD are tau and TDP-43, whereas a minority of patients aggregate FET proteins, primarily the FUS protein. Genetic causes include mutations in *MAPT*, *GRN*, and *C9orf72*. There are no medications that can slow FTD progression, although new therapies for the genetic forms of FTD are moving into clinical trials. Once a diagnosis is made, therapies should begin, focusing on the family and the patient. In the setting of FTD, families experience a severe burden associated with caregiving, and the clinician should focus on alleviating this burden. Advice around legal and financial issues is usually helpful. Careful consideration of environmental changes to cope with abnormal behaviors is essential. Most compounds that have been used to treat dementia of the Alzheimer's disease type are not effective in FTD, and cholinesterase inhibitors and memantine should be avoided. Although the data are scant, there is some evidence that antidepressants and second-generation antipsychotics may help individual patients.

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Frontotemporal dementia (FTD) refers to a group of neurodegenerative brain disorders characterized by atrophy of the frontal and anterior temporal lobes (1) and is one of the most common forms of early-onset dementia (2). Clinically, there are three main syndromes of FTD that are generally recognized on the basis of their clinical presentations: a behavioral variant FTD (bvFTD) characterized by a progressive deterioration of personality, social comportment and cognition (3); and two language presentations, classified under primary progressive aphasia (PPA), in which an insidious decline in language skills is the primary feature (1). These PPAs are divided on the basis of the pattern of language breakdown into a nonfluent variant of aphasia (nfvPPA) and a semantic variant (svPPA). A third form of PPA, the logopenic variant (lvPPA), usually occurs in association with the pathology of Alzheimer's disease but can also be found in relation to FTD (4). There are forms of the disease that escape the descriptions of the main syndromes in FTD; an example of this is the right temporal variant, which is often associated with semantic memory impairment, prosopagnosia, and behavioral symptoms often associated with a socioemotional deficit (5). These syndromes have specific clinical symptoms and neuroimaging and pathological characteristics, although considerable heterogeneity and overlap exist in clinical practice, particularly as the disease progresses (1). In this article, pharmacological and nonpharmacological treatments for the neuropsychiatric aspects of FTD are reviewed. Promising advances in molecule-based therapies for the genetic forms are highlighted.

NEUROPATHOLOGY

Frontotemporal lobar degeneration (FTLD) is the term used to refer to a group of progressive brain diseases that predominantly affect the frontal and anterior temporal lobes. Thus, FTLDs include the clinical syndromes that are part of FTD: bvFTD, nfvPPA, and svPPA and also include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and bvFTD with motor neuron disease (FTD-MND). These diseases, although sharing similar anatomy, have diverse etiologic causes at the neuropathological and genetic levels. Pathologically, FTLD is subdivided according to the composition of the abnormal inclusions of misfolded proteins. There are three main subgroups: FTLD-tau, FTLD-TDP, and FTLD-FET. The first two, characterized by the accumulation of tau protein and TDP-43, account for 90%−95% of FTLD cases; the third, a consequence of FET protein accumulation, is related to the remaining 5%−10% of cases (6).

Tau is a microtubule-associated protein that has been linked to multiple molecular processes, including synaptic plasticity, cell signaling, and regulation of axonal stability (7). There are six isoforms of tau expressed in the brain from alternative mRNA splicing of a single gene, *MAPT*. What separates the longer forms of tau from the shorter forms is

the inclusion (or exclusion) of the 31 amino acids encoded in exon 10 at the carboxy-terminal end into three isoforms with four repeats (4R forms) and their exclusion into three isoforms with three repeats (3R forms) (8). The expression of tau is regulated throughout development, and in the adult brain, all six tau isoforms are present, with equal numbers of 3R and 4R forms. In Pick's disease, we mainly find 3R forms, whereas 4R forms can be related to PSP, CBD, nfvPPA, and other pathologies such as globular glial tauopathy (GGT); mixed 3R-4R forms can be found in Alzheimer's disease (AD) and chronic traumatic encephalopathy (9). In addition, the tau protein undergoes posttranslational changes, the most commonly described being phosphorylation, which can modify the affinity of tau for microtubules and lead to self-aggregation. There are 85 known putative phosphorylation sites (7), and tau posttranslational modifications characterize disease heterogeneity and stage in dementia (10).

FTLD-TDP is characterized by the accumulation of 43-kDa transactive response DNA binding protein (TDP-43), a multifunctional nucleic-acid-binding protein related to RNA metabolism to which other functions such as neurite outgrowth and axonal repair after injury have been attributed (11). TDP-43 loss from the nucleus leads to the up- and downregulation of more than 100 different proteins, including stathmin-2 (12). Upregulation of stathmin-2 is a proposed therapy for FTLD-TDP. In FTLD-TDP, abnormally phosphorylated and ubiquitinated versions of TDP-43 manifest with different morphology and are grouped according to the number of neuronal cytoplasmic inclusions, dystrophic neurites, and glial cytoplasmic inclusions into subtypes A, B, C, and D (13). Approximately 90% of svPPAs present TDP-43 type C, FTD-MND is almost exclusively related to type B, amyotrophic lateral sclerosis (ALS) is related to types B and D, and bvFTD and nfvPPA are related to types A and B (6, 14).

The FUS protein (fused in sarcoma) is one of several FET proteins (also including EWS and TAF15 proteins) associated with FTLD and ALS. FUS, like TDP-43, regulates mRNA and, in addition to being associated with bvFTD and PPA, is also a cause of ALS and neuronal intermediate filament inclusion disease (6). Functions linked to alternative splicing, transcription, and RNA transport are attributed to FUS. By affecting splicing, FUS dysfunction could affect normal *MAPT* expression, leading to an increased 4R-Tau–3R-Tau ratio (15).

GENETICS

FTD is strongly heritable. A positive family history is found in 30%−50% of cases, and in 10%−27%, the inheritance is autosomal dominant (2, 16–18). In comparison, in less than 1% of AD cases, the inheritance is autosomal dominant (19). Additionally, genetic causes are found in 1%−10% of sporadic bvFTD cases (20). Thus, genetics is of fundamental importance in the assessment of patients with FTD (21). Numerous genes are associated with FTD; however, the most commonly implicated genes are *MAPT*, *GRN*, and *C9orf72*.

MAPT, located on chromosome 17, is the gene encoding for the tau protein, whose function has been described previously. There are more than 50 known mutations for this gene. These mutations account for 5%−20% of familial FTD cases but are rarely found in sporadic forms of FTD (0%−2%) (21). Disease onset with these *MAPT* mutations varies but is often before 60 years of age. These mutations usually cause a bvFTD phenotype, but parkinsonism is often prominent.

Also located on chromosome 17 adjacent to *MAPT* is the *GRN* gene encoding for progranulin. This protein functions as a multifunctional growth factor in development, wound repair, neuroinflammation, autophagy, and lysosomal function (21, 22). More than 70 known *GRN* mutations lead to the generation of nonsense mRNA, which is subsequently eliminated by physiological surveillance mechanisms, leading to haploinsufficiency of the progranulin protein, which thus leads to FTLD-TDP pathology by an unclear mechanism (23, 24).

In 2011, it was described for the first time that the six-nucleotide noncoding repeat (G4C2) in the first intron of the *C9orf72* gene, located on the short arm of chromosome 9, could lead to FTD, ALS, and FTD-MND (25, 26). Up to 24 G4C2 repeats have been described in healthy control groups. Although there is no universally established cutoff point, it is suspected that more than 30 expansions increase susceptibility to neurodegeneration (26, 27). Although the mechanism of pathogenicity by which this nucleotide expansion leads to the development of FTD is not well defined, multiple hypotheses have been formulated, including haploinsufficiency of the homonymous protein; toxicity from the transcribed, expanded-repeat-containing RNA; up- and downregulation of numerous proteins, including stathmin-2; and toxic dipeptide repeat (DPR) proteins (21). Regardless of the pathological mechanism by which it produces the disease, the *C9orf72* mutation is the leading cause of familial FTD (20%−30% of cases) and the leading known genetic cause of sporadic FTD (6%) (21, 28–30). In addition, this expansion leads to the accumulation of DPRs that aggregate in the cerebellum and hippocampus (31) and TDP-43 type A and type B pathology (14). Clinically, this mutation can present as bvFTD, ALS, or both and is characterized by a shorter disease duration (6.4±4.9 years) relative to other genes such as *MAPT* or *GRN* (32). However, a group of carriers of this mutation may have extremely slow-evolving forms of the disease syndromically indistinguishable from bvFTD, categorized as "FTD phenocopies" (33). Moreover, between 10% and 50% of patients with this mutation may manifest psychotic symptoms (hallucinations, delusions, or both), which may lead to confusing this disease with psychiatric conditions such as schizophrenia, bipolar disorder, or obsessive-compulsive disorder (2, 27, 34).

There are recommendations for genetic testing for the three main bvFTD-related genes (*MAPT*, *GRN*, and *C9orf72*)

in patients with at least one affected first-degree relative. This recommendation extends to FTD or early-onset dementia relatives, but a history of ALS, Parkinson's disease, or unexplained late-onset psychiatric disorders should also be considered (2). Also, because of its association with sporadic cases of FTD, one should look for *C9orf72* mutations in cases of late-onset behavioral symptoms (even if they do not meet all criteria for bvFTD), and there are no neuroimaging abnormalities, as a diagnostic element (2). With a significant proportion of apparent sporadic cases that are due to unexpected mutations, several groups are moving toward genetic testing in all FTD cases, even without family history. This approach will become more routine when therapies become available.

Commonly, when mental health professionals explain the diagnosis of FTD to patients and their family members, they are often concerned about the heritability of the disease. Before obtaining genetic testing, the implications for the individual and their family unit should be discussed with a genetic counselor. Family members may also be interested in genetic testing. Genetic counseling has a cost and can have legal and, sometimes, ethical implications. Before testing a family member (or members), the ideal scenario is to have the affected gene identified and search for the mutation in those concerned. This is not always possible, for various reasons. For example, affected relatives may be deceased; the afflicted patient may refuse to be tested, and so forth. When the test for a single gene is negative, another gene may be responsible for the clinical syndrome (35). Even when the presence of a mutated gene is demonstrated, it is not possible to predict the exact age of onset, severity or type of symptoms, or the course of the disease (35). Also, there are numerous factors to consider when evaluating whether to perform genetic testing. For example, does the person understand what having the mutation implies, or will the genetic result affect the person's life decisions? Additionally, it is important to consider what psychological impact this information can have and whether the patient is prepared for this information (36). These decisions also have legal and economic consequences, including the possibility that the result affects the patient's health insurance coverage or the possibility that this information can be used by an employer to decide whether to hire the person. In the United States, in 2008, the Genetic Information Nondiscrimination Act, or GINA, was passed at the national level to prohibit information such as this from being used in the context of administrative decisions such as health insurance or employment decisions (37). However, many countries do not have similar legislation on this type of information, which could potentially expose mutation carriers to stigma and marginalization.

THE DIAGNOSTIC PROBLEM IN FTD

The diagnosis of bvFTD is particularly challenging because of the absence of molecular biomarkers except for imaging and, therefore, depends principally on clinical assessment (2). In addition, the symptomatic overlap with primary psychiatric disorders (PPDs) including major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, autism spectrum disorders, and even personality disorders (38) means that PPDs often constitute the main differential diagnosis of bvFTD (39). Around 50% of patients with bvFTD have received a previous psychiatric diagnosis (most frequently, major depression), and the average diagnostic delay is up to 5–6 years from symptom onset (40, 41).

BURDEN OF FTD

The years leading up to a patient's bvFTD diagnosis are often the most stressful period in the lifetime of a spouse and other family members (42). Marital strife; financial chaos, or even ruin; and estrangement from friends and family are common and may create resentment toward the patient that persists even after a neurologic diagnosis has been made (42). Caregiver emotional responses to a bvFTD diagnosis are often mixed (42). The diagnosis creates enormous grief because of the prognosis: progression to death within 5–7 years (43). The socioeconomic burden of FTD is high. FTD is associated with substantial direct and indirect costs, diminished quality of life, and increased caregiver burden (44). The economic burden for FTD in the United States is approximately twice that reported for AD (44).

LEGAL ASPECTS

Brain disorders have long been considered as a cause of criminal behavior (45). This seems to be particularly true in the case of FTD, where such behaviors can be found in up to 50% of cases (46, 47), up to five times more frequent than in patients with AD (48). One of the most prominent symptoms in FTD is behavioral disinhibition (3). These behaviors are often labeled as disinhibited because they break with social norms and frequently transgress legal boundaries (49, 50). There are at least two forms of disinhibition (51): impulsivity, acts involving general rule violations that are related to an impairment of cognitive control mechanisms (49); and person-based disinhibition, where the behavior is more related to disturbed interpersonal interactions violating social tact and personal boundaries (52), in which case behaviors may emerge because of the compromise of cognitive systems related to semantic knowledge (53) or personal salience (54). This type of behavior has been labeled as "acquired sociopathy" (55). Because antisocial behavior in patients with FTD arises as a result of compromised functioning of brain structures responsible for directly or indirectly modulating behavior, these cases present a challenge in defining the degree of autonomy in their actions, this being particularly true for the early stages of the disease (56). Thus, this disease presents a challenge for the criminal justice system.

NEUROPSYCHIATRIC SYMPTOMS AND MANAGEMENT

FTD is a devastating, progressive neurodegenerative disease characterized by changes in personality, behavior, and language. In this sense, bvFTD is the variant that produces the most profound and limiting behavioral changes, compromising social functioning through symptoms such as behavioral disinhibition, apathy, and loss of empathy (3). In both forms of PPA, language impairment is the predominant feature, leading to significant limitations in social interactions and activities of daily living. Moreover, both svPPA and nfvPPA are not exempt from manifesting, throughout their evolution, behavioral symptoms that are similar to those observed in bvFTD that further compromise the functionality and quality of life of these patients and their caregivers (57). Additionally, there is evidence that symptoms such as apathy and disinhibition can manifest across the entire FTLD spectrum (58). This makes the management of neuropsychiatric symptoms a priority for clinicians. No disease-specific treatment interventions for FTD exist, there are only symptomatic treatments that are partially effective. Consequently, treatment largely remains supportive and involves a combination of nonpharmacological and pharmacological measures aimed at reducing the effect of distressing symptoms (59).

Nonpharmacological Interventions

Behavioral management. Ikeda et al. (60) reported that troublesome behavioral symptoms were managed by reintroducing old hobbies and favorite games in six patients with FTD. They also reported that those methods were helpful for reducing social misconduct and disinhibition. They also reported that some patients who were treated with a behavioral therapy called "routinizing therapy"—in which stimulus-bound and stereotypic behaviors are replaced with appropriate behaviors—improved. This therapy was reported to help manage troublesome behaviors and contribute to a stable routine (61). The antecedent-behavior-consequence (ABC) model is a strategy often used in education for dementia caregivers, although there have been no studies of its effectiveness. The A, or antecedent, is the event or factors that initiate or contribute to the occurrence of the behavior. Antecedents are often called "triggers." The B, or behavior, is the specific behavioral symptom. The C, or consequences, are all the reactions and responses of others after the behavior (62). In the case of compulsive activities, substitutions may have positive results. It consists of offering a squeeze ball to hold, instead of touching strangers, or offering a lollipop to diminish repetitive and compulsive vocalizations (63, 64). Overall, behavioral management techniques that target disease-specific behaviors and preserved functions seem to be more effective than cognitive training in patients with FTD (65).

Environmental strategies. As each patient faces different situations, it is difficult to conduct clinical studies of the environmental strategies. As such, most are mainly based on narrative and clinical experience, and no clinical studies that provide evidence on these environmental strategies exist (65). Environmental strategies are the least restrictive to the patient and focus on modifying the environment of the patient. Examples may include limiting access to credit cards, changing the family schedule to meet the preferences of the patient, or posting reminder notes and signs (62). It is recommended that patients keep the same daily routine and that objects or furniture are kept in the same position around them. In addition, to minimize disruptions, caregivers may change their schedule to accommodate a patient's relatively harmless rituals, or a family may choose restaurants that the patient already knows (65). Reducing noise and stimulation, lessening clutter, turning off music, or simplifying social situations can help these patients to accurately focus on a designated task or response. Removing access to problematic items (e.g., credit cards, mail) or modifying public outings to reduce the opportunity for inappropriate interactions are examples of FTD-specific environmental manipulations (66). A supportive environment with normal lighting, moderate sound, a small number of people, and appropriate cueing were more likely to decrease behavioral symptoms in dementia (67). Exercise has been suggested to reduce behavioral symptoms (68), and aberrant motor behavior may respond to physical activity (69). Strategies for psychotic symptoms include environmental modifications such as removing mirrors or increasing lighting, which may reduce the propensity for misinterpretation (69).

Caregiver intervention. Caregiver intervention should be the most effective treatment within the context of dementia (70). Behavioral changes rather than level of disability seem to be correlated with caregiver distress and burden in bvFTD (71). The ABC strategy has shown a reduction in behavioral symptoms and improved caregiver outcomes for behavior management (72). The key to reducing caregiver stress seems to lie in increasing their understanding of the symptoms and ways of dealing with challenging behaviors (70). Programs such as The Savvy Caregiver have shown similar results in promoting caregiver mastery regarding behavior management and reduced caregiver stress (73–75).

Speech therapy. PPA is a debilitating disorder in which speech and language deteriorate as a result of neurodegenerative disease (76). Speech therapy is led by a language pathologist, who may offer a variety of interventions and compensatory strategies to patients with PPA (77). PPA interventions commonly tap strategies training individual word retrieval, trained scripts, and compensatory communication methods (78). A study by Henry et al. (76) included ten individuals with mild to moderate nonfluent-agrammatic variant PPA. They examined the immediate and long-term benefits of video-implemented script training for aphasia. They found that this treatment resulted in significant improvement in production of correct, intelligible scripted

TABLE 1. Level of evidence and strength of recommendation of frontotemporal dementia pharmacological treatments classified according to the American Hospital Formulary Service Drug Information[a]

Drug	Level of evidence	Grade of recommendation
Paroxetine	2	2
Citalopram	2	1
Sertraline	2	2
Fluvoxamine	2	2
Trazodone	2	1
Aripiprazole	3	2
Clozapine	3	3
Quetiapine	2	2
Olanzapine	3	3
Risperidone	3	4
First-generation antipsychotics	3	4
Anticonvulsants	3	3
Carbonate lithium	3	3
Methylphenidate	2	2
Dextroamphetamine	3	3
Oxytocin	2	3
L-DOPA	2	2
Dopamine agonists	2	4
Memantine	2	4
Cholinesterase inhibitors	2	4

[a] For further details on the American Hospital Formulary Service Drug Information, see reference 79. Level of evidence: 1=high strength or quality; 2=moderate strength or quality; 3=low strength or quality; 4=opinion/experience. Grade of recommendation: 1=recommended (accepted); 2=reasonable choice (accepted, with possible conditions); 3=not fully established (unclear risk or benefit, equivocal evidence, inadequate data or experience); 4=not recommended (unaccepted). L-DOPA=levodopa-3,4-dihydroxyphenylalanine.

words for trained topics, a reduction in grammatical errors for trained topics, and an overall increase in intelligibility for trained as well as untrained topics at posttreatment. Follow-up testing revealed maintenance of gains for trained scripts up to 1 year posttreatment on the primary outcome measure. Performance on untrained scripts and standardized tests remained relatively stable during the follow-up period, indicating that treatment helped to stabilize speech and language despite disease progression (76).

Pharmacological Interventions

Pharmacological interventions should be implemented after a careful analysis of the case, ideally after nonpharmacological approaches have been exhausted, or the magnitude of the symptoms requires these interventions to be implemented promptly. In addition, possible reactions and adverse effects to these medications should be monitored, and the relevance of their indication should be re-evaluated periodically. Table 1 summarizes the pharmacological interventions along with the level of evidence and recommendation for them (79).

Selective serotonin reuptake inhibitors (SSRIs). FTD has been shown to have serotonergic network disruption on the basis of autopsy, neuroimaging, and CSF studies (80, 81). Some studies suggest that SSRIs are effective in helping with various symptoms of FTD, including disinhibition, impulsivity, repetitive behaviors, and eating disorders (82), and they also suggest that the behavioral symptoms of FTD may improve after treatment with SSRIs (70, 83).

One study concluded that long-term treatment with paroxetine may influence noncognitive aspects of FTD, with improvements in behavior and social conduct as evidenced by a reduction in aggressiveness, agitation, weeping and depressed mood, social conduct, eating problems, and sleep disorders (84). A small study with paroxetine at doses of 20 mg/day for 14 months showed improvement in scores on the Neuropsychiatric Inventory (NPI) and was well tolerated (85). However, another study conducted with paroxetine versus placebo with doses increasing up to 40 mg/day reported that there was no significant improvement and that, moreover, it could worsen the cognitive profile of patients (86). The discrepancies between these studies are attributed to a better response to and tolerability of paroxetine at lower doses (20 mg/day) (87); however, an alternative hypothesis is that the worse performance, especially in the cognitive domain, with higher doses (40 mg/day) is due to the anticholinergic effect of paroxetine (88).

A study by Herrmann et al. (89) reported that citalopram treatment was effective in treating behavioral symptoms, with significant decreases in NPI total score, disinhibition, irritability, and depression scores over 6 weeks. The significant improvement in Frontal Behavior Inventory scores suggested that citalopram was also effective in treating FTD-specific behaviors (89). A more recent randomized, double-blinded, placebo-controlled study of 12 patients with doses of citalopram at 30 mg/day showed improved disinhibition and related cognitive functions. This effect was attributed to the restoration of impaired serotonergic neurotransmission in bvFTD (90).

There is limited information on the use of sertraline in FTD; in one study, eight patients showed improvement in stereotyped movements and compulsive behavior with doses of sertraline between 50 and 100 mg over a period of 6 months (91). A case report of a 53-year-old patient with ALS-FTD and inappropriate sexual behavior reported symptomatic improvement with sertraline at doses of 100 mg/day (92).

A 12-week open-label study of 16 patients with FTD and behavioral symptoms with fluvoxamine at doses of 50–150 mg/day showed improvement in stereotypic behavior, eating behavior, and roaming behavior (93). One paper reported two cases of FTD with symptoms of stereotypic behavior and compulsive complaint of abdominal pain where the use of fluvoxamine improved both symptoms (94).

Trazodone. Trazodone has been effective in treating agitation and aggression in FTD and may also function as a sleep aid, if necessary (82). In one study, it was also found that trazodone can reduce the behavioral symptoms of FTD that

were assessed by the NPI score, especially eating disorder, irritability, agitation, and depressive symptoms (95).

Second-generation antipsychotics. Although off-label use of antipsychotics in FTD is common (88), there are a few studies that support the use of these drugs for the control of behavioral symptoms in this disease. Concern about the association between the use of antipsychotics in older adults and increased risk of stroke led the U.S. Food and Drug Administration (FDA) in 2005 to issue a boxed warning for the use of this medication in dementia-related psychosis. Despite this, guidelines for the management of behavioral symptoms in dementia, such as the American Psychiatric Association guideline (96) and the International Psychogeriatric Association guideline in 2018, recommend the use of second-generation antipsychotics for symptoms such as agitation and psychosis in dementia. Because of the limited number of studies performed, it is unclear whether it is possible to translate these indications to FTD.

There is evidence that there is a deficit in dopaminergic neurotransmission across the spectrum of FTLD (97). Mesolimbic and mesocortical dopaminergic pathway involvement may be related to the manifestation of behavioral and cognitive symptoms (97). However, dopaminergic involvement in the nigrostriatal pathway may be related to the high prevalence of extrapyramidal symptoms observed in the course of the disease, making these patients particularly sensitive to the use of antipsychotics (98–100). Thus, if these drugs are used for the control of behavioral symptoms, antipsychotics with a lower D2 blockade profile (i.e., those with a lower incidence of associated extrapyramidal symptoms) are of choice. Among these drugs, quetiapine could be of particular relevance (101, 102). Quetiapine was observed in a case series to demonstrate improvements in agitation in three patients with FTD (103), but no difference in NPI scores was shown between baseline and quetiapine treatment in a separate double-blind, crossover study with dextroamphetamine and quetiapine involving eight patients with FTD showing behavioral symptoms (104).

Under the same logic, clozapine is an antipsychotic that could potentially be useful in FTD. Unfortunately, to date, there are no studies on its use in this population. However, a case report of a patient with a diagnosis of FTD, refractory psychosis, and frequent episodes of aggression describes significant clinical improvement after starting clozapine up to a dose of 400 mg/day. Aripiprazole, because of its effect as a partial D2 agonist, could also be presented as a drug with less adverse effects in FTD. However, there are currently only case reports of its clinical use. One report describes symptomatic improvement in a patient with frequent sexual remarks (105). Similarly, a case of FTD with sexual disinhibition reports symptomatic improvement within 2 weeks with aripiprazole at 18 mg/day (106). A study with 17 patients related the use of olanzapine to a substantial improvement in symptoms such as delirium, affective lability, wandering, and irritability (85). However, the use of olanzapine, because of its greater D2 blockade, may increase extrapyramidal symptoms, and it is associated with significant metabolic syndrome and higher mortality than quetiapine (88). The use of antipsychotics with greater dopaminergic blockade, such as risperidone or first-generation antipsychotics, is not recommended because of the high incidence of motor adverse effects and higher mortality in dementia (88).

Anticonvulsants. The use of anticonvulsants as mood stabilizers is common in the treatment of various psychiatric disorders, with bipolar disorder being one of its main indications in psychiatry. However, the use of anticonvulsants in treating patients with FTD is limited. Although there are several case reports where clinical utility is attributed to them, studies demonstrating this are lacking. Three case reports describe improvement in cases of FTD associated with hyperorality with topiramate, two of them in patients with binge eating (107, 108) and alcohol misuse (109). One case report recounts improvement in symptoms of hypersexuality with carbamazepine (110). Similarly, some case reports related the use of valproate to improvement of symptoms such as hypersexuality and agitation (103, 111). However, there is still little evidence to support anticonvulsants as a therapy in FTD.

Carbonate lithium. As with many anticonvulsants, the use of lithium carbonate as a mood stabilizer in the treatment of patients with bipolar disorder is widespread. However, the evidence for its use in treating patients with FTD is extremely limited. A case series published by Devanand et al. (112) describes three cases of patients diagnosed as having FTD, previously treated with a combination of antidepressants and antipsychotics, with symptoms such as hallucinations and agitation where the use of low doses of lithium (300–600 mg/day) led to clinical improvement. One of these cases reported lithemia values of 0.4 mmol/L for a dose of 450 mg/day of lithium, whereas another case of the same series recorded lithemia values of 0.8 mmol/L for a dose of 300 mg/day of lithium; similarly, another case recorded symptomatic improvement in agitation with a dose of 600 mg/day but developed tremor and sedation when increasing the dose to 1,200 mg/day. On the other hand, a case reported by Arciniegas (113) of FTD misdiagnosed as late-onset bipolar disorder reported marked impairment in cognitive, behavioral, and motor functions after reaching lithium levels considered therapeutic; these symptoms improved when lithium was discontinued. A phase 2 study is currently active with low doses of lithium versus placebo for the treatment of behavioral symptoms in patients with FTD (ClinicalTrials.gov identifier: NCT02862210). However, because of the current limited clinical evidence, the narrow margin of therapeutic safety and the risk of developing lithium toxicity, the use of this molecule should be considered with extreme caution by closely monitoring plasma lithium levels and closely evaluating cognitive, behavioral, or motor changes.

Stimulants. There is evidence that shows a deficit in dopaminergic transmission in FTD (97). Dopaminergic dysfunction has been related to the presence of extrapyramidal symptoms but also some behavioral symptoms such as agitation, disinhibition, and apathy (114–116). A small double-blind, placebo-controlled study in patients with bvFTD found that the use of methylphenidate, a dopamine and noradrenaline reuptake inhibitor, at doses of 40 mg was able to improve decision-making behavior of patients (117). A case report of a 72-year-old patient with FTD and symptoms of apathy, behavioral disinhibition, and irritability treated with 18-mg methylphenidate and 100-mg bupropion showed marked and sustained symptomatic improvement (118). A study in eight patients with FTD treated with dextroamphetamine versus quetiapine showed that the stimulant was effective in decreasing apathy and disinhibition on the NPI subscales (104). A limitation of these studies is that they were performed with small samples, so it is difficult to generalize these results. Moreover, the use of psychostimulants carries possible adverse effects that should be considered and monitored in case of their use.

Oxytocin. In a study by Jesso et al. (119), the effects of a single dose of intranasal oxytocin on neuropsychiatric behaviors and emotion processing were evaluated in patients with bvFTD. They designed a randomized, double-blind, placebo-controlled crossover design that included 20 patients with this diagnosis who received a 24-IU dose of intranasal oxytocin or placebo and then completed the emotion recognition tasks. Caregivers completed validated behavior ratings at 8 hours and 1 week after drug administration. There was a significant improvement in NPI scores on the night of oxytocin administration compared with placebo and baseline scores. Oxytocin was also associated with reduced recognition of angry facial expressions by patients with bvFTD. Jesso et al. (119) concluded that oxytocin is a potentially promising new symptomatic treatment candidate for patients with bvFTD and that further studies were needed. A phase 2 double-blind, randomized, multicenter study is currently active to test the safety, tolerability, and effects of intranasal syntocinon (synthetic oxytocin) versus placebo on behavioral symptoms of FTD (120).

Pharmacological treatment of motor symptoms. As described in the section on antipsychotics, it is common for FTD patients to manifest extrapyramidal symptoms during the course of the disease. Up to 70% of patients present symptoms of rigidity, gait dysfunction, or bradykinesia in their evolution (98–100, 121). The evidence on the use of pharmacological treatment for motor symptoms in FTLD focuses on PSP and CBD. In these cases, the use of L-dopa provides mild and transient improvement (122, 123). The use of dopaminergic agonists in FTD is often discouraged because of their incidence of dopaminergic dysregulation syndrome, which may worsen behavioral symptoms (88, 124). Within the monoamine oxidase inhibitors, there are data on three case reports that describe improvement in behavioral symptoms (125).

Memantine. Memantine is, together with cholinesterase inhibitors, one of the molecules approved by the FDA for the specific treatment of AD. It is postulated that its mechanism of action as a noncompetitive inhibitor of *N*-methyl-D-aspartate (NMDA) receptors could decrease glutamate-mediated cytotoxicity and thus slow the progression of the disease. Although the neuropathological changes in FTD are different from those in AD, it was believed that its protective effect on neuronal injury could be beneficial in FTD. Likewise, evidence that memantine could improve behavioral symptoms in AD made this molecule a target to explore in FTD. However, two separate double-blind, placebo-controlled studies found that there was no significant improvement between the placebo and memantine groups and that it may even worsen cognition (126, 127).

Cholinesterase inhibitors. Unlike AD, in FTLD, the cholinergic system is relatively preserved (97). Despite this, approximately 40% of FTD patients receive treatment with cholinesterase inhibitors (128). Numerous studies have attempted to study the therapeutic efficacy of cholinesterase inhibitors in FTD. Not only have these studies failed to demonstrate a benefit from the use of these drugs, but, on the contrary, there is also evidence that they may actually worsen cognitive and behavioral performance (59, 82, 87, 129).

CURRENT CLINICAL TRIALS AND BIOMARKERS

Molecule-based therapies are being considered for the genetic forms of FTD and to treat the symptoms of the disease (Table 2). For each of the major genetic subtypes, *MAPT*, *GRN*, and *C9orf72*, different approaches will be needed. Several advances have made it possible to consider such efforts. First, the discovery of powerful biomarkers such as the neurofilament light-chain protein (NfL) will make it possible to follow progression in a clinical trial, because NfL begins to rise during the transition from asymptomatic to mildly symptomatic FTD (130). Similarly, structural imaging can detect significant changes in atrophy over 6 months, making it likely that the magnetic resonance imaging (MRI) can also be used as a surrogate marker (131).

For *MAPT* carriers, the major emphasis of clinical trials will be to lower tau either by decreasing its production or by increasing its clearance. There is extensive evidence that lowering tau will ameliorate symptoms in animal models of AD and FTD (132, 133). Further, in humans, antibodies against tau have been demonstrated to reach the brain and bring tau into the plasma (134), but clinical trials using antibodies for both AD and FTD have been disappointing. These failures have probably occurred because of relatively low levels of the antibody that cross the blood-brain barrier. Therefore, technologies such as antisense oligonucleotides

TABLE 2. Active clinical trials in frontotemporal lobar degeneration (FTLD)[a]

Molecule	Indication	Mechanism	Phase	Status	ClinicalTrials.gov identifier
Therapies targeting C9orf72 expansion					
WVE–004	ALS-FTD	Antisense oligonucleotide	1b–2a	Recruiting	NCT04931862
Metformin	ALS-FTD	PKR pathway blockage	2	Recruiting	NCT04220021
Censavudine (TPN–101)	ALS-FTD	Nucleoside reverse transcriptase inhibitor	2	Not yet recruiting	NCT04993755
Therapies targeting GRN					
AL001	FTD	Antisortilin antibody	3	Recruiting	NCT04374136
PR006A	FTD	Gene therapy	1–2	Recruiting	NCT04408625
PBFT02	FTD	Gene therapy	1b	Recruiting	NCT04747431
Therapies targeting tau					
AADvac1	nfvPPA	Tau vaccine	1	Active	NCT03174886
Tolfenamic acid	PSP	*Sp1* transcription factor modulator	1–2	Not yet recruiting	NCT04253132
Bepranemab (UCB0107)	PSP	Antitau antibody (midregion)	1	Enrolling by invitation	NCT04658199
NIO752	PSP	Antisense oligonucleotide	1	Recruiting	NCT04539041
AZP2006	PSP	Tau aggregation inhibition	2	Recruiting	NCT04008355
Fasudil	PSP and CBD	Rho-associated protein kinase inhibitor	2	Recruiting	NCT04734379
RT001	PSP	Deuterium-stabilized linoleic acid	2	Recruiting	NCT04937530
Symptomatic treatment					
Lithium carbonate	FTD	Glycogen synthase kinase inhibitor	2	Recruiting	NCT02862210
Rotigotine	bvFTD	Dopamine agonist	2	Recruiting	NCT04937452
Suvorexant, zolpidem	PSP	Sleep disruption therapy	4	Recruiting	NCT04014387
Rivastigmine	PSP	Cholinesterase inhibition	3	Recruiting	NCT02839642
Syntocinon	FTD	Treatment of apathy or indifference	2	Recruiting	NCT03260920
Transcranial magnetic stimulation	nfvPPA and lvPPA	Magnetic stimulation	1	Recruiting	NCT03406429
High-definition transcranial direct current stimulation	nfvPPA and lvPPA	Direct current stimulation	2	Recruiting	NCT04046991

[a] ALS=amyotrophic lateral sclerosis; bvFTD=behavioral variant FTD; CBD=corticobasal degeneration; FTD=frontotemporal dementia; lvPPA=logopenic variant primary progressive aphasia; nfvPPA=nonfluent variant primary progressive aphasia; PKR=protein kinase R; PSP=progressive supranuclear palsy.

and CRISPR could lower tau in a highly effective manner. If *MAPT* carriers treated with effective tau-lowering therapies show slowing or progression or even halting of the disease, these approaches will next be used to treat other tau-related forms of FTD. Other efforts are focused on increasing the degradation of tau in the lysosome or the proteosome (135).

With *GRN*, different mechanisms and different approaches are being considered. *GRN* mutation carriers show markedly reduced brain and blood levels of progranulin, suggesting a haploinsufficiency mechanism with the deficiency of progranulin production on one chromosome sufficient to cause FTD. Many strategies are being considered to increase brain progranulin, with many focused on better ways to deliver progranulin into the brain. Arrant and colleagues found, when using an AAV vector (AAV-*Grn*) to deliver progranulin in $Grn^{-/-}$ mice, that lysosomal dysfunction and microglial pathology were both ameliorated (136). It is likely that, in the coming year, AAV transplantation studies will begin with *GRN* gene carriers, and others delivery systems are also being considered.

Finally, *C9orf72* mutations produce a long hexanucleotide repeat that is already the target for gene carriers with ALS, and therapies for FTD are being considered. As with all these gene-related therapies, multiple questions will need to be answered regarding delivery of the drug to the brain; timing of the therapy (presymptomatic versus symptomatic); the reliability of biomarkers; and, most importantly, efficacy. A new chapter in therapy for FTD and related conditions is beginning. Once the genetic forms of the disease have been effectively treated, new approaches to the sporadic form of the disease are likely to emerge.

CONCLUSIONS

FTD is frequently misdiagnosed, and when the diagnosis occurs, it often comes late in the course of the illness or is missed. Recognition that behavioral changes represent a neurodegenerative condition is difficult, leading clinicians to diagnose a primary psychiatric disorder. Also, diagnostic tools such as blood biomarkers or neuroimaging can be difficult to access, particularly in low- and middle-income

communities. Another barrier to its identification is the lack of knowledge and training for health care providers about FTD.

FTD treatment has been limited to the management of neuropsychiatric symptoms, these being the most prominent feature of the disease. Therapeutic strategies have focused on nonpharmacological interventions such as behavioral and environmental manipulation, caregiver interventions, and speech therapy for the language variants of FTD. Also, pharmacological treatment has also been used to treat these symptoms, with variable but sometimes positive results. With the advance of knowledge regarding the pathophysiology of FTD, pharmacological interventions such as the use of SSRIs, trazodone, or second-generation antipsychotics have a solid scientific basis for the treatment of FTD.

In the past 10 years, thanks to new techniques in neuroimaging, genetics, and biomarker analysis, much has been discovered about the phenomena underlying frontotemporal lobar degeneration. This has allowed the design of new molecule-based therapies that are still in the early stages of research but show promising results.

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