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Diagnosis and Management of Behavioral Issues in Frontotemporal Dementia

Masood Manoochehri, BA[2] and **Edward D. Huey, MD**[1,2,3]

[1]Herbert Irving Assistant Professor of Psychiatry and Neurology

[2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain The Gertrude H. Sergievsky Center Columbia University 630 West 168th Street P&S Box 16 New York, NY 10032

Abstract

Frontotemporal lobar degeneration (FTLD) is an umbrella term for several different disorders. In behavioral variant frontotemporal dementia (bvFTD), patients show deterioration in cognition and social behavior. New diagnostic criteria proposed by the International Behavioral Variant FTD Consortium provide greater sensitivity in diagnosing bvFTD. Current pharmacological management of symptoms relies on medications borrowed from treating Alzheimer's Disease (AD) and psychiatric disorders. The evidence for using AD medications such as acetylcholinesterase inhibitors is questionable. Psychiatric medications can be helpful. Trazodone or SSRIs can have some efficacy in reducing disinhibition, repetitive behaviors, sexually inappropriate behaviors, and hyperorality. Small doses of atypical antipsychotics may be helpful in decreasing agitation and verbal outbursts. Non-pharmacological management includes caregiver education and support and behavioral interventions. While symptomatic treatments are likely to remain important behavior management tools, targeting the underlying pathology of bvFTD with disease-modifying agents will hopefully be the future of treatment.

Keywords

FTLD; frontotemporal lobar degeneration; bvFTD; frontotemporal dementia; diagnosis; differential diagnosis; treatment

Introduction

Frontotemporal lobar degeneration (FTLD) is an umbrella term for several different disorders. One of these disorders is behavioral variant frontotemporal dementia (bvFTD). BvFTD is characterized by a deterioration in cognition and social behavior. The diagnosis is made on the basis of clinical diagnostic criteria. In 1998, Neary and colleagues articulated diagnostic criteria, which included a set of "core" and "supportive" features [1]. Though widely used, in subsequent years clinicians noted the relative inflexibility of some of these features. Several studies suggested that these criteria were insufficient to capture early cases of bvFTD [2, 3]. In 2011, the International Behavioral Variant FTD Consortium (FTDC) used pathologically confirmed cases of FTLD to create a set of more sensitive and specific clinical criteria for diagnosing bvFTD [4]. These new criteria identified six behavioral and cognitive symptoms as central to the diagnosis of possible bvFTD. The presence of any three of these six symptoms, in the presence of a progressive deterioration of behavior and

[3]Corresponding author edh2126@columbia.edu Tel: 212-305-1134 Fax: 212-305-2426 .

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cognition, is sufficient for a diagnosis of possible bvFTD. Probable bvFTD can be diagnosed if, in addition, there is significant functional decline and imaging findings consistent with the disease. If the above criteria are met with the finding of FTLD pathology, a diagnosis of definite bvFTD can be made.

Diagnosing bvFTD

Lack of insight and gradual onset of disease are two of the hallmarks of FTD [1]. It is therefore imperative for clinicians to interview caregivers regarding changes in patient behavior and cognition. Below, we highlight the cluster of six behavioral and cognitive symptoms proposed by the FTDC for diagnosing bvFTD and remark on the methods and scales used to assess these symptoms.

Early apathy

A common and pervasive initial symptom is apathy and inertia [5]. Apathy refers to a general passivity and lack of spontaneity, and can be seen in the lack of motivation to pursue previously rewarding activities or hobbies. Inertia is the decreased ability to spontaneously generate actions and behaviors. Patients may require prompting to initiate conversations or reminders to continue activities they have started. The most recent study of pathologically-confirmed bvFTD cases found that over 85% of patients showed early apathy and inertia [4].

Early behavioral disinhibition

Behavioral disinhibition is a classic hallmark of bvFTD. Within the first several years of symptoms, patients can behave contrary to social norms. They may inappropriately touch or aggressively approach strangers, or even engage in theft or other criminal behaviors. Patients may also disregard subtler social norms to make offensive jokes or sexual remarks, encroach on the personal space of others, and exhibit childish behavior and a general lack of etiquette. Disinhibition may also be exhibited in the form of rash and impulsive actions like gambling or repeatedly falling for financial scams. The largest autopsy-confirmed study of bvFTD found 76% of patients exhibited behavioral disinhibition or impulsivity [4].

Early loss of sympathy or empathy

Patients can lose the ability to respond to the emotional expressions and needs of others and be distant, cold, and indifferent. They can be less socially engaged and fail to exhibit personal warmth, even with friends and family. Theory of Mind (ToM) is the ability to attribute mental states to one’s self and to others. Deficits in ToM ability have been hypothesized to be responsible for the lack of empathy and sympathy exhibited by bvFTD patients. A recent review used imaging data to suggest a link between the progressive degeneration of the anterior regions of the medial frontal cortex and the ToM deficits exhibited by bvFTD patients [6]. A study of 30 bvFTD patients found that levels of empathy were directly related to the volume of the subgenual cingulate/subcallosal gyrus in the inferior frontal cortex [7].

Early perseverative or compulsive behavior

Common ritualistic behaviors include counting rituals, hoarding objects, and wandering fixed routes. Patients may smack their lips, clap, or rub their hands repetitively. Some patients repeat stock words, phrases, or stories. There is a large literature linking inappropriate repetitive behaviors to dysfunction of a circuit involving the orbitofrontal and anterior cingulate cortexes, basal ganglia, and thalamus [8]. A disruption of normal mechanisms of reward learning has been implicated.

Hyperorality and dietary changes

Patients frequently exhibit altered food preferences, commonly craving sweets or carbohydrates, or expressing rigid preferences for particular foods [9]. In some cases, patients may engage in binge-eating. Oral exploration of inedible objects may also be seen [10]. While the etiology of these changes is not fully understood, the orbitofrontal-insular-striatal brain network has been implicated [11]. There is also emerging evidence that changes in the hypothalamus are involved. Piguet et al. found that bvFTD patients with severe eating disturbances exhibited significant atrophy in the posterior hypothalamus [12]. Drugs that stimulate the intact peptidergic pathways of the hypothalamus may present a new avenue for restoring normal eating habits.

Neuropsychological profile

According to diagnostic criteria, patients with bvFTD should show deficits in tests that assess executive and language function [4]. However, for these patients it can be difficulty to disentangle executive function from other cognitive functions, and cognitive impairment from behavioral symptoms. Executive dysfunction interferes with episodic memory performance. Much cognitive testing relies on patients adhering to certain norms of interpersonal behavior (e.g., following instructions, giving full effort, staying on task, etc.) that many bvFTD patients violate. Thus, interpreting neuropsychologists are often in the difficult position of attempting to determine whether poor performance in a cognitive domain is primary, or secondary to cognitive deficits in a different domain or due to behavioral abnormalities. However, poor performance on specific aspects of neuropsychological testing can clarify. For example, rule violations during testing appear to be more specific to bvFTD compared to healthy controls and patients with AD than overall performance on the Delis –Kaplan Tower Test [13].

A comprehensive neurological exam can aid in an accurate diagnosis of bvFTD. Gait abnormalities, frontal release signs, eye movement abnormalities, or evidence of motor neuron disease in the presence of behavioral symptoms are suggestive of bvFTD [14]. Several studies have contrasted the behavioral symptoms of bvFTD patients with those of patients with other types of dementias [15],. The Neuropsychiatric Inventory has been the most commonly used questionnaire used to assess 12 behavioral symptoms, including delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and eating abnormalities [16]. Using this measure obtained from a caregiver interview, bvFTD patients have consistently been found to show higher scores of apathy, euphoria, disinhibition, aberrant motor behavior, and eating abnormalities compared to AD patients. [5, 15, 17-19]. A recent meta-analysis of neurobehavioral measures concluded, however, that the NPI and other scales were not useful as diagnostic tools for clinicians. Instead, broadly used scales specifically developed to detect FTLD are the best aids in its differential diagnosis [20]. These include the Frontal Behavioral Inventory (FBI) and Middelhelm Frontality Scale (MFS). The FBI asks caregivers about symptoms associated with frontal dysfunction, such as apathy, personal neglect, and loss of insight and has been validated to be a useful measure for quantifying changes in behavior over time [21, 22]. The MFS is a clinician-administered scale that measures classic deficits due to frontal lobe damage including stereotyped behavior and emotional blunting [23]. Another useful behavioral scale is the Frontal Systems Behavioral Scale [24]. This measure has both caregiver and patient forms and has ratings for both pre-morbid behaviors and behaviors after onset of illness. This measure is useful to capture discrepancies between caregivers and patients and to contrast pre from post-morbid behaviors. Recently, the National Alzheimer's Coordinating Center (NACC) has developed a module of neuropsychological tests and symptom measures to be

administered in the Alzheimer's Disease Centers across the country [25]. A goal of this project is determine how well the components of this battery can distinguish FTLD from other types of dementia.

bvFTD vs Psychiatric Disorders

Often the behavioral symptoms upon presentation of bvFTD lead patients to be diagnosed with psychiatric disorders [3]. This causes frustration for caregivers [26]. Woolley et al. recently found that the behavioral changes seen in bvFTD lead to a psychiatric diagnosis more often than in the other neurodegenerative diseases [27]. There is currently a pressing need to better differentiate bvFTD from psychiatric disorders and to educate mental health practitioners how to detect bvFTD. This need will become even more urgent when disease-modifying treatments for FTLD become available as these treatments will most likely be most efficacious early in the course of the illness.

Although bvFTD patients often exhibit the apathy and decreased energy seen in Major Depressive Disorder, they usually do not show decreased appetite or experience depressed mood, guilt, suicidality, or feelings of worthlessness. In fact, bvFTD patients usually have hyperphagia and inappropriately preserved self-esteem (e.g., anosognosia for their symptoms and a belief that they are more functional than they actually are) [28]. There is evidence from lesion studies that damage to the dlPFC is associated with the entire syndrome of Major Depressive Disorder (MDD), while vmPFC damage is associated with a selective reduction of the cognitive/affective symptoms of MDD [29]. In this way, the depressive symptoms observed in bvFTD are similar to those observed with vmPFC damage.

Inappropriate giddiness and jocularity in bvFTD are sometimes interpreted as mania. True mania is not a stable mood state, and a prolonged and consistent course of this symptom should lead clinicians away from this diagnosis. On occasion, patients with bvFTD are also misdiagnosed with schizophrenia on the basis of disorganization [30]. Patients with bvFTD are much less likely to have auditory hallucinations and complex delusions than schizophrenics [31]. However, there is emerging evidence that the phenotype associated with C9ORF72 repeat expansions is more likely to be associated with psychotic symptoms [32]. Patients with bvFTD may engage in repetitive behaviors, but they generally lack the obsessions characteristic of Obsessive-Compulsive Disorder [8].

Few studies have examined the distinction between bvFTD and isolated psychiatric disorders in a systematic manner. Panegyres et al. used 13 patients to develop a profile of FTD vs. psychiatric patients and found that FTD patients exhibited neurological symptoms before psychiatric ones, showed frontal release signs and abnormal gait, and had a history of functional decline[33]. Psychiatric patients, in contrast, often had extensive personal and family psychiatric histories, normal neurological exams, and a fluctuating course. Recently, Rankin et al. used the Interpersonal Measure of Psychopathy (IMP) to identify specific in-clinic social behaviors that differentiated bvFTD from psychiatric diagnoses [34]. They found that bvFTD patients could be distinguished based on the presence of one of two sets of behaviors. One group of bvFTD patients showed unusual calmness during the clinical exam compared to those with psychiatric diagnoses. Another group of bvFTD patients readily crossed personal and professional boundaries, with little evidence of self-consciousness. These patients interrupted the examiner and became fixated on a topic, interfering with the clinical examination. The presentation of these behaviors during the clinical examination should lead clinicians to consider a referral to a dementia specialist.

Management of Behavioral Symptoms in FTD

There are currently no FDA-approved medications for treating bvFTD. Still, the majority of bvFTD patients receive medication treatment for their illness, usually either a psychiatric medication or a medication for Alzheimer's disease [35]. The psychiatric medications are usually used in an attempt to ameliorate the behavioral symptoms of bvFTD. This is an important goal; behavioral symptoms are a significant cause of distress for caregivers of bvFTD patients [4, 36]. Below, we review the pharmacological and non-pharmacological treatments currently used to treat bvFTD.

Pharmacological Treatments

Acetylcholinesterase inhibitors (AChIs) are prescribed in approximately 40% of bvFTD patients [35, 37]. In contrast to AD, the cholinergic system in FTD is relatively intact [38]. Perhaps unsurprisingly, clinical trials do not generally support the use of AChIs to treat bvFTD. One 12-month, open-label study of rivastigmine conducted by Moretti et al. reported reductions in NPI scores [39]. A case-control study of donepezil, however, showed a worsening of behavioral symptoms including disinhibition and impulsivity [40]. In 2008, the only double-blinded study of a AChI tested the use of galantamine in 36 patients with bvFTD and Primary Progressive Aphasia (PPA), an FTLD syndrome characterized by language symptoms. Behavioral symptoms did not significantly worsen or improve [41]. Taken together, these results have resulted in recommendations to avoid AChIs in treating bvFTD [42].

Memantine is a medication that has a small effect on slowing the cognitive decline of those with moderate AD [43]. Improved NPI scores in 3 bvFTD patients treated with memantine [44] spurred two open-label studies to examine its possible neuroprotective effects in FTD. In 2008, Diel-Schmind et al. conducted a 6 month study with 16 bvFTD subjects. Although the medication was well-tolerated, there was no evidence that it affected cognitive and behavioral decline [45]. Boxer et al. recruited 43 subjects, including 21 with bvFTD for a 26-week study in 2009. This study showed transient improvement of NPI scores for the bvFTD patients despite an overall behavioral and cognitive decline [46]. In light of these findings, Vercelletto et al. conducted a randomized, double-blind, placebo-controlled study with the largest group of bvFTD patients assembled to date [47]. Forty-nine patients were administered a battery of measures including the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIPIC-Plus), NPI, and FBI. One year after baseline, most measures showed no significant behavioral or cognitive differences between placebo and medication groups. One recent study reported that memantine increased metabolism in the insula and orbitofrontal cortex, but this did not correlate with any behavioral changes [48]. A larger double-blinded trial is currently underway and should yield results soon [49].

The neurochemistry of FTD suggests psychiatric medications can play a role in the symptomatic treatment of bvFTD. Most studies show abnormalities in the serotonergic system of FTD patients, with a decrease in 5-HT1A and 5-HT2A receptors in frontotemporal regions and neuronal loss in the raphe nuclei [38]. There is also evidence for a disrupted dopaminergic system in FTD, including low CSF levels of dopamine metabolites [50] and severely reduced pre-synaptic dopamine transporters in the putamen and caudate of FTD patients [51]. Psychiatric disorders treated with serotonin and dopamine augmentation also have some symptom overlap with bvFTD. The symptoms of Major Depressive Disorder and obsessive-compulsive disorder are ameliorated by serotonin augmentation. Dopamine augmentation can improve the executive function deficits of attention-deficit/hyperactivity disorder.

Serotonergic medications have been the most studied in bvFTD. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram have all been tested to treat the behavioral symptoms of FTD, albeit mainly in open-label studies. [52-56]. There is evidence that these drugs can have some efficacy in reducing disinhibition, repetitive behaviors, sexually inappropriate behaviors, and hyperorality. Amongst open-label studies, Swartz et al. first treated 11 subjects with fluoxetine, sertraline, or paroxetine and found improvement in disinhibition, apathy, carbohydrate cravings, and compulsive behaviors [54]. In another open-label study with 18 FTD patients, sertraline was found to significantly decrease verbal and motor stereotypies [56]. In a randomized study of paroxetine versus piracetam over 14 months, a group of 8 FTD patients treated with paroxetine showed an overall improvement in behavioral symptoms [53]. A 12-week open-label study of fluvoxamine showed improvements in the stereotypical behaviors and eating behaviors of FTD patients [57]. A daily 30 mg dose of citalopram over 6 weeks resulted in significant decreases in NPI scores as a result of lower apathy and disinhibition [55]. The most rigorous study of an SSRI was a double-blind, placebo-controlled study of 40 mg/day paroxetine [52]. After 6 weeks, there was no improvement of behavioral symptoms and a mild worsening of cognitive symptoms compared to placebo [52]. The only serotonergic drug that has yielded positive results in a double-blind, placebo-controlled trial has been trazodone. In this trial, conducted by Lebert et al., 26 bvFTD patients were treated with 300mg trazodone over the course of 12 weeks [58]. As measured by the NPI, patients showed significant improvement in behavioral symptoms, including agitation, depression, and eating abnormalities.

Despite the lack of rigorous clinical trials, the British Association for Psychopharmacology has given a B rating for the use of SSRIs for behavioral symptoms in bvFTD, indicating good overall clinical evidence [59]. A meta-analysis of studies using serotonergic drugs was conducted by Huey et al. in 2006 [38]. This study found an overall significant decrease in behavioral symptoms as measured by the NPI. These results lend further support to the use of these anti-depressant medications as symptomatic treatments for bvFTD.

Atypical antipsychotics are prescribed to treat severe disinhibition and verbal and physical outbursts in FTD [35]. These medications have been minimally studied in FTLD, and there have been no double-blind, placebo-controlled studies. However, the literature on the use of these medications in AD can inform their use in FTLD. A meta-analysis conducted by Maher et al. [60] found that atypical antipsychotics including risperidone, arepiprazole, olanzapine, and quetiapine all have a small but statistically significant effect in decreasing agitation, psychosis, and overall behavioral disturbances in dementia (mostly AD) patients. Case reports particular to FTD suggest that risperidone and arepiprazole can be effective in small doses [61, 62]. An open-label study found decreased agitation and delusions in 17 FTD patients treated with olanzapine over the course of 24 months.[63]. Clinicians should use caution in prescribing these drugs to bvFTD patients since they are particularly vulnerable to extrapyramidal side effects and weight gain [64, 65].

Non-pharmacological Interventions

FTD caregivers report the delay to proper diagnosis as one of the most frustrating aspect of their experience [26]. Non-pharmacological intervention should therefore begin with clinicians explaining to caregivers the diagnosis and the basis of the behavioral symptoms. This can help caregivers accept the altered behavior and shift their focus to implementing strategies for behavioral management.

There have been no systematic studies of behavioral and environmental interventions in FTD. However, case reports and the experience of clinicians suggest that some behaviors, including socially disruptive behaviors and stereotypical acts, are amenable to interventions.

Ikeda et al. reported that re-introducing old hobbies and favorite games reduced social misconduct and disinhibition amongst 6 FTD patients [66]. Another strategy is to use the Antecedent-Behavior-Consequence Model to specifically identify the triggers and consequences of particular behaviors [67]. Environmental strategies that minimize the worst results of these behaviors can then be implemented. For example, a caregiver's schedule may be changed to accommodate a patient's relatively harmless rituals, or a family may opt to go to restaurants where the patient is already known in order to minimize disruptions.

Other behavioral symptoms might require close supervision by the caregiver. The presence of hyperorality may require caregivers to provide dietary oversight to prevent binge-eating, excessive weight gain, or the dangerous placement of inedible objects in the mouth. Poor judgment and impulsiveness may necessitate limiting access to credit cards and bank accounts in order to prevent being taken advantage of by financial scams or making reckless purchases. Clinicians should encourage caregivers to keep detailed logs of behavioral symptoms. As bvFTD progresses, fewer inappropriate behaviors may be seen [65].

The behavioral changes of bvFTD including lack of empathy and interpersonal bonding, can be especially stressful for caregivers as these symptoms can increase feelings of isolation for the caregiver [68]. Social support of the caregiver can be crucial and includes support from family and friends, but also support from health professionals including physicians, nurses, and home health aides. Support groups with other caregivers of bvFTD patients can be very helpful. The Association for Frontotemporal Degeneration (AFTD) *(*www.theaftd.org) has many resources for patients and caregivers.

Future Treatments

A better understanding of the neurobiology of FTLD may lead to protein-specific therapies that can actually modify the course of the disease. Pathways involving tau and TDP-43 are potential targets of intervention. One approach involves preventing the aggregation of tau using agents like lithium and valproate, which may decrease the accumulation of hyperphosphorylated tau proteins [65]. Davunetide, an agent that has been linked to reduced tau pathology in a mouse model, is being tested in a Phase II/III clinical trial for the treatment of patients with the tauopathy progressive supranuclear palsy. Another approach may be to use agents that normalize levels of progranulin, a peptide that is linked to FTLD with TDP-43 pathology. Knopman et al. administered a modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC) and an FTLD-specific Clinical Dementia Rating Scale (FTLD-CDR) to FTLD syndrome patients, including 47 bvFTD patients. These scales were determined to be useful as potential outcome measures for medication trials for bv-FTD. They will hopefully aid researchers testing medications for bvFTD in the future. [69].

Investigations of new symptomatic treatments for bvFTD are based on a diversity of approaches. One strategy focuses on deficits in the dopaminergic system detected in bvFTD [38]. Rahman et al. [70] tested methylphenidate, which is known to increase synaptic concentrations of dopamine, in 8 subjects with bvFTD. Risk-taking behavior was reduced to normal levels as measured by the Cambridge Gamble Task, suggesting that decision-making and impulsiveness may be affected by dopaminergic augmentation. Recently, Gennatas et al. studied the effects of COMT $Val^{158}Met$, a single nucleotide polymorphism that affects synaptic dopamine concentrations, especially in the frontal cortex [71]. Differences in COMT genotype affected the volume of ventral mid-brain structures that predicted behavioral impairment, especially abnormal eating behaviors. A current clinical trial tests the effects of tolcapone, a drug that selectively increases pre-frontal dopamine concentrations, on the cognitive and behavioral symptoms of patients with FTD [72].

Molecular mediators of social behavior may have potential therapeutic roles in improving social cognition and empathy. Administration of the neuropeptide oxytocin has been shown to lead to better recognition of facial expressions, increased empathy, and increased cooperative behavior in normal adults [73]. A recent double-blind, placebo-controlled cross-over study tested the effects of a single dose of intranasal oxytocin in 20 bvFTD patients [74]. There was a significant improvement in behavioral symptoms as measured by the NPI and FBI, driven by small changes in many sub-items of these scales. A larger trial is underway [75].Vasopressin is a neuropeptide that is involved in regulating male social behavior. High levels of vasopressin have been linked to aggression in psychiatric patients and a vasopressin receptor subtype has been linked to differences in social behavioral traits [76, 77]. No studies to date have looked at the effects of vasopressin antagonists on social behavior, but this idea has drawn theoretical interest [73].

Conclusions

New diagnostic criteria may make it more likely that early cases of bvFTD will be correctly diagnosed. Given the frustration that diagnostic uncertainties so often present for bvFTD caregivers, this is a welcome development. The Frontal Behavioral Inventory, Middelhelm Frontality Scale, and Frontal Systems Behavioral Scale are all measures that will help clinicians considering a diagnosis of bvFTD.

The pharmacologic management of behavioral symptoms currently relies on medications borrowed from treating AD and psychiatric disorders. The evidence for using AD medications such as AchIs and memantine is lacking, but psychiatric medications can be helpful. Anti-depressants can have some efficacy in reducing disinhibition, repetitive behaviors, sexually inappropriate behaviors, and hyperorality. Small doses of atypical antipsychotics including risperidone, arepiprazole, olanzapine, and quetiapine may be helpful in decreasing agitation and verbal outbursts. Apathy, loss of empathy, and executive deficits have so far proven difficult to treat with medications, and require behavioral and environmental intervention. Support groups and the Association for Frontotemporal Dementia can be helpful for caregivers. While symptomatic treatments are likely to remain important behavior management tools, targeting the underlying pathology with disease-modifying treatments will hopefully be the future of bvFTD treatment.

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Table 1

Tailored Medication Treatment for bvFTD Symptoms

bvFTD Symptom	Current Treatment Options	Evidence for Current Treatments	Possible Future Treatment Options
Apathy	None	N/A	Dopaminergic medications?
Behavioral disinhibition	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs. Additional double-blind, placebo-controlled study supporting the use of paroxetine.	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone	Trazodone
	Atypical antipsychotics: risperidone, arepiprazole, olanzapine, and quetiapine	Case reports supporting use of antipsychotics	Atypical antipsychotics: risperidone, arepiprazole, olanzapine, and quetiapine
Loss of empathy	None	N/A	Oxytocin?
Perseverative behavior	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs. Additional double-blind, placebo-controlled study supporting the use of paroxetine.	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone	Trazodone
Hyperorality	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs. Additional double-blind, placebo-controlled study supporting the use of paroxetine.	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone	Stimulation of peptidergic pathways in hypothalamus
Executive dysfunction	None	N/A	Dopaminergic medications?
Neuroprotection	None	N/A	Medications that prevent tau hyperphosphorylation and accumulation Medications that increase progranulin levels