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# Behavioral and Psychological Symptoms of Frontotemporal Dementia: A Review

Frontotemporal dementia (FTD) is commonly diagnosed in people younger than 65 years, and presents with various behaviors which could be unsafe for the patient and their caregivers. Many studies have been conducted to determine the behaviors' source and the possible treatments for the varied psychological symptoms, from agitation and aggression to eating disturbances.

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Once thought to be an infrequent cause of dementia, it is now estimated that FTD is found in 4% of the general dementia population,<sup>1</sup> and is present in 20% to 30% of dementia patients younger than 65 years.<sup>2,3</sup> This early-onset dementia can initially present in a variety of phenotypes, most commonly as a gradual change in

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behavior, personality and/or language ability.<sup>4</sup> Symptoms may worsen to the point of a loss of independence<sup>5</sup> and inappropriate social functioning.<sup>6</sup> There have been multiple attempts to clearly outline the key diagnostic features of the clinical variants.<sup>7-9</sup> Three distinct clinical variants have arisen: the behavioral-based (bv-FTD), and the language-based primary progressive aphasia (PPA) and semantic dementia (SD).

Bv-FTD is defined by an impairment in social functioning and emotional blunting in the patient, but may also include a decline in personal hygiene and mental rigidity, and distractibility.<sup>7,9</sup> PPA patients initially present with a progressive loss of speech without cognitive or behavioral impairment, while SD patients' fluency is intact (though the quality of speech is compromised and behavioral symptoms may be present at the onset of the disease).<sup>7,10</sup>

Although improvements have been made in the diagnosis of FTD, treatment options remain limited and have focused on the management of neuropsychiatric symptoms. Only a handful of treatment

trials in FTD patients have been conducted, using interventions including antidepressants,<sup>11-14</sup> antipsychotics<sup>15</sup> and cognitive enhancers.<sup>16-18</sup>

The numerous consensus have outlined the typical neuropsychiatric symptoms occurring in patients with FTD.<sup>7,9</sup> At early onset of the disease, many of the behavioral symptoms are present in the bv-FTD variant, and to a lesser extent in SD and PPA.<sup>19,20</sup> The most common neuropsychiatric symptoms associated with FTD, their neurobiological correlates and the treatment options currently available are outlined below.

## Neuropsychiatric Symptoms Associated with FTD

**Apathy.** This behavior is often mistaken for depression, but is considered a hallmark of FTD as it is present in 95% to 100% of FTD patients.<sup>21,22</sup> Typically, apathetic individuals present with a lack of effort for performing routine activities or starting new activities, indifference to their own personal problems and flat affect, a symptom where individuals do not respond

Table 1

**Treatment of Behavioral Symptoms in FTD**

<b>Study</b>	<b>Intervention(s)</b>	<b>Outcomes</b>	<b>Comments</b>
<i>Antidepressants</i>			
Swartz et al 1997 3-month open-label (n = 11)	<ul style="list-style-type: none"> <li>Fluoxetine (20 mg/d)</li> <li>Sertraline (50-125 mg/d)</li> <li>Paroxetine (20 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>NPI: 9/11 patients “improved,” not statistically significant</li> </ul>	<ul style="list-style-type: none"> <li>AEs: 2 withdrawals (1 sertraline-diarrhea, 1 paroxetine-agitation, psychomotor agitation)</li> </ul>
Morreti et al 2003 14-month open-label (n = 8)	<ul style="list-style-type: none"> <li>Paroxetine (20 mg/d) compared to piracetam (1200 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>Behavioral improvements</li> <li>Reduced caregiver stress</li> </ul>	<ul style="list-style-type: none"> <li>AEs: No dropouts</li> </ul>
Lebert et al 2004 6-week placebo-controlled (n = 26)	<ul style="list-style-type: none"> <li>Trazodone (titrated to a max 300 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>NPI: 10/26 “responder” to drug</li> <li>Improvement in irritability, agitation, depression and eating disorders</li> </ul>	<ul style="list-style-type: none"> <li>MMSE score unchanged after treatment</li> <li>AEs: 5 withdrawals (significantly greater in drug group vs. placebo)</li> <li>11 patients reported AEs (fatigue, dizziness, hypotension)</li> </ul>
Lebert et al 1999 6-week open-label (n = 14) in bv-FTD	<ul style="list-style-type: none"> <li>Trazodone (titrated to a max 300 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>NPI: Significant decrease from baseline in delusions aggression, anxiety and irritability with 150 mg/d</li> <li>Significant decrease in depression, disinhibition and aberrant motor behavior</li> </ul>	<ul style="list-style-type: none"> <li>MMSE score unchanged</li> <li>One AE reported: transient faintness (300 mg/d)</li> </ul>
<i>Antipsychotics</i>			
Huey et al 2008 3-week open-label (n = 8) in bv-FTD	<ul style="list-style-type: none"> <li>Quetiapine (150 mg/d) compared to dextroamphetamine (20 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>NPI: Significant decrease in score from baseline only with dextroamphetamine</li> </ul>	<ul style="list-style-type: none"> <li>AEs: 1 patient reported sedation with quetiapine. Sleep disturbance with both drugs</li> </ul>
Gafoor et al 2003 2 case studies of FTD + mania	<ul style="list-style-type: none"> <li>Olanzapine (27.5 mg/d) + clonazepam (0.5 mg/d)</li> <li>Haloperidol (5 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>Manic symptoms improved with all treatments</li> </ul>	<ul style="list-style-type: none"> <li>Secondary mania a rare occurrence</li> <li>Involvement of the right frontal lobe?</li> </ul>
Curtis et al 2000 1-week case study (n = 1) of Pick’s Disease + psychosis	<ul style="list-style-type: none"> <li>Risperidone (6 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>Psychotic symptoms improved after 1 week treatment.</li> <li>After 3 months of treatment, no delusions/hallucinations</li> </ul>	<ul style="list-style-type: none"> <li>AEs: Akathisia and mild parkinsonism</li> </ul>
<i>Cognitive Enhancers</i>			
Mendez et al 2007 6-month case-control study (n = 12) in bv-FTD	<ul style="list-style-type: none"> <li>Donepezil (10 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>No significant improvement on any outcome: MMSE, CDR, FTD checklist.</li> </ul>	<ul style="list-style-type: none"> <li>AEs: Caregivers reported increased disinhibition, compulsions</li> </ul>
Moretti et al 2004 12-month open-label (n = 20) in bv-FTD	<ul style="list-style-type: none"> <li>Rivastigmine (3-9 mg/d) vs. control (matched FTD patients taking antipsychotics, benzodiazepine, selegiline)</li> </ul>	<ul style="list-style-type: none"> <li>NPI: Significant improvement in total scores from baseline and vs. control on most items of NPI</li> <li>Reduction in caregiver burden</li> </ul>	<ul style="list-style-type: none"> <li>AEs: Nausea, muscle cramps, blood pressure changes</li> </ul>
Lampl et al 2004 3-month open-label (n = 9)	<ul style="list-style-type: none"> <li>Donepezil (10 mg/d)</li> <li>Rivastigmine (6-12 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>4/9 patients demonstrated clinical significant improvement + improvements on SPECT imaging</li> </ul>	<ul style="list-style-type: none"> <li>AEs: None reported</li> </ul>

### Treatment of Behavioral Symptoms in FTD (*continued*)

Study	Intervention	Outcomes	Comments
<i>All FTD subtypes</i>			
Kertesz et al 2008 18-week open-label (n = 36) in bv-FTD + PPA	• Galantamine (mean 21.5 ± 4.9 mg/d)	<ul style="list-style-type: none"> <li>• NPI: No significant improvement in behavioral or language outcomes (PPA patients showed trend)</li> <li>• Subjects demonstrated improvement in the withdrawal phase over placebo on CGI-S, results not significant after correction</li> </ul>	• AEs: nausea, diarrhea, headache (5 withdrawals)
Diehl-Schmid et al 2008 6-month open-label (n = 16) in bv-FTD + SD	• Memantine (20 mg/d)	<ul style="list-style-type: none"> <li>• NPI: No significant improvement in scores from baseline</li> <li>• SD subgroup improved significantly in FBI score from baseline</li> </ul>	• AEs: Depression, other reported but deemed unrelated to the medication
Swanberg M et al 2007 3-month open-label (n = 3) in bv-FTD	• Memantine (20 mg/d)	<ul style="list-style-type: none"> <li>• NPI: Improvement in apathy, agitation and anxiety</li> <li>• No improvements in cognition</li> </ul>	• AEs: None reported

emotionally.<sup>23</sup> While not considered an immediate danger to the patient, apathy may have significant negative implications. In addition to the decline of activities of daily living (ADL), poor quality of life and an increased probability of developing Parkinson-like symptoms,<sup>24-26</sup> patients may cease all social interactions and neglect personal hygiene.<sup>27,28</sup>

Apathetic behaviors have been most commonly linked to bv-FTD, but a significant portion of patients who initially present with PPA may develop this symptom as the disease progresses.<sup>29,30</sup> Reports have suggested that SD patients may also present with apathy, possibly linked to bilateral amygdala atrophy.<sup>31</sup> A recent MRI study, examining 62 FTD patients, linked the severity of apathy to the right dorsolateral prefrontal cortex.<sup>32</sup>

**Disinhibition.** Although less frequently reported at the onset of FTD than apathy, disinhibition remains a prevalent symptom and is found in 52% of FTD patients.<sup>21</sup> Most promi-

nent in bv-FTD, it is also present in SD manifesting as an inability to behave in a socially acceptable manner.<sup>33</sup>

Behaviors indicative of a loss of inhibition are wide ranging, with one study reporting shoplifting, exhibitionism, inappropriate contact with strangers and extramarital affairs among others. Of note, patients exhibiting moderate to severe disinhibition demonstrated hypoperfusion in the

right temporal lobe.<sup>34</sup> Neuroimaging data supports the right temporal lobe as an important site of degeneration, leading to a loss of inhibition. One MRI study associated increased disinhibition with grey-matter loss in the nucleus accumbens and the right mediotemporal region of the brain.<sup>32</sup> A recent PET imaging study, looking at 29 socially impaired FTD subjects (all three variants), found decreased glucose metabo-

lism in the right anterior temporal lobe, consistent with the previous finding that this region was responsible for “social” cognition, while another PET study singled out the orbitofrontal cortex.<sup>35-37</sup>

**Agitation and aggression.** The presence of agitation and aggression has been previously reported in FTD patients and poses a great risk not only to the patient, but also to caregivers.<sup>38,39</sup> It is not uncommon to see

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more dangerous behaviors, such as aggression, in severe cases, which could lead to incarceration or institutionalization.<sup>20,40</sup> A comparative study found a greater proportion of FTD patients (45%) than Alzheimer’s disease (AD) patients (5%) exhibiting antisocial behaviors, such as assault and death threats, which could be linked to hypoperfusion in the anterior frontal and temporal regions of the

brain.<sup>41</sup> A genetic study found a relationship between the apolipoprotein E4 allele and aggression in FTD, where patients homozygous for the allele displayed a significantly greater score in aggression outcomes.<sup>42</sup> An increase in dopaminergic neurotransmission and a disruption of the serotonergic pathway were recently suggested as contributors to aggression and agitation in FTD patients.<sup>43</sup>

**Eating disturbances.** Dramatic changes in diet may occur with high frequency at the onset of FTD and may steadily get worse as the disease progresses. Such changes early in the presentation may help differentiate

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FTD from other neurodegenerative diseases like AD.<sup>44</sup>

A comparative study between FTD subjects and AD patients found that 79% of FTD patients reported carbohydrate craving, while no AD patients exhibited this behavior.<sup>45</sup> Another study examining the eating patterns of bv-FTD and SD patients found that both subgroups had similar eating behaviors with both experiencing changes in food preferences and appetite at onset, and a decreasing swallowing ability as the disease progressed.<sup>46</sup> In an epidemiologic study of bv-FTD patients, eating disorders, including overeating, bulimia and food fads, were among the most common symptoms that progressed within a four-year period.<sup>47</sup> A recent study examining binge eating in the bv-FTD variant was linked to atrophy in the right ventral insular cortex, striatum and the orbitofrontal cortex.<sup>48</sup>

**Other behavioral features.** A number of other neuropsychiatric

symptoms may be present but may not necessarily represent true core features of FTD. Repetitive behaviors or obsessive-compulsive features have commonly been reported within the FTD population.<sup>49</sup> A study examining these behaviors found that, within a population of 90 FTD subjects, 21% displayed complex compulsive behavior and this was associated with temporal lobe atrophy, a degenerative pattern common to SD.<sup>50</sup> Another study found that both the frontal and the temporal variants of FTD demonstrated a significant number of stereotypical/repetitive behaviors, including verbal perseveration, hoarding and rituals.<sup>51</sup>

Psychotic symptoms have also been reported in FTD, although they are an uncommon occurrence. A study comparing the prevalence of psychotic symptoms in FTD and AD found that fewer FTD patients reported symptoms (2% vs. 17.4%), with both patient groups reporting delusions and paranoia.<sup>52</sup> A number of case studies have also reported the presence of psychosis in FTD patients.<sup>53-55</sup>

### **Treatment Options for FTD**

There are few effective treatment options for FTD, and the majority of clinical trials aim to treat symptoms associated with the disease, rather than focusing on disease modification. A number of pharmacologic interventions have been used in clinical trials and have demonstrated variable results. These data are summarized below and in Table 1.

**Antidepressants.** The selective serotonin reuptake inhibitor (SSRI) drug class has been the most studied.

There is a good rationale for SSRI use in FTD, as studies have indicated a disruption of the serotonergic system, including losses of 5HT-1A and 5HT-2A receptors.<sup>56,57</sup> Significant losses of these receptors in key brain regions may decrease the response to serotonin, which may confer the need for replacement and limit treatment effectiveness of SSRIs.<sup>58</sup>

A three-month open-label study examined fluoxetine, sertraline or paroxetine treatment in 11 FTD patients and found that more than half the subjects exhibited improvement in behaviors such as disinhibition, depression and compulsions.<sup>59</sup> Another open-label trial examined 20 mg/d of paroxetine in eight FTD subjects and found a significant improvement in behavioral symptoms following 14 months of treatment.<sup>11</sup>

In contrast, a randomized control trial (RCT) found no benefits in behavioral symptoms, and even worsened cognitive performance, in eight bv-FTD subjects who were titrated to a maximum of 40 mg/d paroxetine.<sup>14</sup> Two trials evaluating the efficacy of trazodone in FTD have been conducted, one a placebo-controlled crossover trial and the other an open-label study. In the six-week crossover trial of trazodone vs. placebo, 26 FTD patients with neuropsychiatric symptoms improved significantly on behaviors of irritability, agitation, depression and eating disorders.<sup>12</sup> The open-label study of trazodone in 14 FTD subjects found a dose-dependent improvement in delusions, irritability, aggression and disinhibition.<sup>60</sup> A recent review evaluated the drug trials that have been conducted for the management of behavioral symptoms in FTD. Those authors concluded that there was modest evidence to support the efficacy of paroxetine, fluvoxamine, selegiline and trazodone, as FTD patients were more likely to improve while taking

these medications.<sup>61</sup> These results must be interpreted with some caution, as only two of the studies were randomized clinical trials.

**Antipsychotics.** A number of case reports have shown variable results with antipsychotics. Potential therapeutic effects of this drug group may be related to dopaminergic antagonism, as one study found an association between increased dopaminergic neurotransmission and agitated and aggressive behaviors in 25 FTD patients.<sup>43</sup> One small study demonstrated improvement with olanzapine and haloperidol in the treatment of manic symptoms associated with FTD.<sup>62</sup> Another study (n = 8), found significant improvement in behavioral symptoms with dextroamphetamine treatment but not quetiapine.<sup>15</sup> A single case study reported the effectiveness of one week of risperidone 3 mg bid for an FTD patient with psychotic symptoms.<sup>63</sup>

**Cognitive enhancers** have also been investigated as possible treatment options. A deficit in cholinergic transmission has been a hallmark contributor to AD, yet a link to FTD is less convincing. Only one study has shown a disruption of this system, with decreases of muscarinic acetylcholinergic receptors in the temporal cortex of five SD patients.<sup>64</sup> Within the cholinesterase inhibitor (ChEI) class, studies have looked at treatment with donepezil, rivastigmine and galantamine. A small open-label study (n = 9) of recently diagnosed FTD patients found that four of the subjects taking either donepezil or rivastigmine showed clinically significant improvements after three months of treatment, and improvements in their SPECT scans after six months, although outcomes for this study were vaguely defined.<sup>65</sup> A six-month case-controlled

study of donepezil in FTD (n = 24) found conflicting evidence, suggesting no significant differences in cognition were observed between the drug and control groups, with the drug group experiencing significantly greater worsening of symptoms following treatment.<sup>66</sup>

A 12-month open-label study of rivastigmine found that subjects taking the drug experienced a significant improvement in behavioral symptoms and caregiver burden when compared to age-matched controls.<sup>16</sup> Similarly, an 18-week open-label study followed by an eight-week RCT (n = 36) looking at galantamine in the treatment of bv-FTD and PPA found no significant

improvement in behavior or language, but the language performance of PPA subjects taking the drug remained stable compared to subjects taking placebo.<sup>17</sup> Evidence for another cognitive enhancer, the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, is contradictory with regard to efficacy. The rationale for its use as a treatment option remains somewhat scarce, with a handful of studies suggesting a disruption of the glutamatergic system, with decreased NMDA receptors and glutamatergic neurons in the frontal and temporal brain regions of FTD patients.<sup>67,68</sup> A small case series suggested benefits in behavior and cognition,<sup>69</sup> while an open-label study (n = 16) found no statistically significant improvement in behavioral outcomes and a decline in cognitive performance.<sup>18</sup>

### What's the next step?

The behavioral symptoms associated with FTD appear wide-ranging and may overlap with other neurodegenerative diseases. This may contribute to misdiagnoses and leave patients untreated until behavioral symptoms reach an unmanageable level. A recent study in Norway and Sweden found that, on average, it took two to three years for a clinical diagnosis of FTD to be confirmed from the first physician visit.<sup>70</sup> It is for this reason that further research is warranted, with the goal of effective treatment at an early stage.

A number of therapeutic options have shown efficacy in the treatment

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of neuropsychiatric symptoms associated with FTD, but more must be done. An epidemiologic study has found that it would be feasible to conduct large-scale multi-centred clinical trials, since all the factors for a successful trial, including a large, testable FTD population and appropriate standardized outcomes, are readily available.<sup>71</sup> The potential of disease-modifying therapies are currently being investigated in AD and it is hoped that this will spread to the FTD field. In theory, drugs targeting tauopathies or ubiquitination of TDP-43 proteins may prove beneficial in reversing the localized damage to the frontal and temporal lobes of the brain. Until this happens, more therapeutic options to treat the debilitating neuropsychiatric symptoms of FTD are urgently required.

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