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Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration

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Abstract

This review of pharmacotherapy for frontotemporal lobar degeneration describes the chemical rationale for agents used and reports observed responses to psychotropic medications. Paroxetine addressed anxiety and repetitive, ritualistic behaviors. Depression was resistant to treatment. Valproic acid and quetiapine calmed agitated subjects without exacerbating Parkinsonism. Donepezil has not emerged as a beneficial medication for this group of subjects. Behavioral disturbances can be alleviated pharmacologically, but further research might determine guidelines for management of this non-Alzheimer's dementia syndrome that could decrease the frequency of adverse drug events.

Keywords

frontotemporal dementia; pharmacotherapy; valproic acid; paroxetine; quetiapine; donepezil

Introduction

The caregiver and physician easily recognize marked changes in personality and behavior in patients with frontotemporal lobar degeneration (FTLD) as abnormal.¹⁻⁵ Frontotemporal lobar degeneration includes diagnoses of frontotemporal dementia (FTD), semantic dementia, and progressive nonfluent aphasia.^{6,7} Patients with FTD frequently require pharmacotherapeutic agents to address the neuropsychiatric manifestations of this early onset, non-Alzheimer's dementia. Mood disorders have been reported in 40 to 63.3 percent of FTD cases, and depressive episodes may predate progressive decline of cognitive function by many years.^{4,8} Abnormal oral behaviors range from a new preference for sweets to ritualistic meal habits to oral exploration of nonfood items. Most patients tend to gain weight, as opposed to the anorexia reported in many patients with Alzheimer's disease (AD). Seventy-five percent of FTD subjects in one study had obsessive thinking and repetitive or ritualistic behaviors.⁴ Psychosis is least frequently reported.

Patients with FTD suffer a decline in interpersonal skills that may be reflected in irritability, agitation, inflexibility, and disinhibited verbal or physical approaches. The neuropsychiatric symptoms usually prompt a referral to psychiatry as opposed to neurology clinics,⁹ and

some patients must be admitted to a psychiatric ward for urgent treatment of severe behavioral disturbances. Psychotropic medications play a large role in management of FTD. In most cases, there are major changes from baseline behavior patterns, but some patients manifest a worsening in severity of long-term behavior patterns. The severity of the neuropsychiatric symptoms usually warrants treatment and has, in some cases, led to incarceration.^{1,10} Although behavioral disturbance is not a dominant feature of progressive nonfluent aphasia or semantic dementia, behavioral changes are usually apparent after the first two years of illness.⁶ This paper is the first to review medication responses of a large group of subjects with FTLT.

Methods

The mental status of subjects was tested using a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol and neurological examination. Diagnosis of FTLT syndrome was then made according to consensus criteria by Neary *et al.*⁷ In many cases, presence of either unilateral or bilateral frontal or temporal hypoperfusion on 99Tc-HMPAO single photon emission computed tomography (SPECT) or abnormalities in similar areas seen with fluorodeoxyglucose positron emission tomography (FDG-PET) of the brain helped us minimize inclusion of subjects with possible AD.¹¹

Behavioral changes, as reported while taking a history of the presenting illness or on the neuropsychiatric inventory (NPI), helped to identify targets for pharmacotherapy. The NPI has established validity and reliability and consists of 12 subscales. In alphabetical order, they are: aberrant motor behaviors, agitation, anxiety, apathy, appetite changes, delusions, depression, disinhibition, euphoria, hallucinations, irritability, and sleep changes.¹² At the clinic specializing in FTLT at the UCLA Alzheimer's Disease Research Center, clinical nurses and the clinician administered the NPI to caregivers during baseline diagnostic evaluations.

Parkinsonism was detected on elemental neurologic examination as any combination of the following: rigidity, cogwheeling, bradykinesia, and festinating gait.

Medications were prescribed to 35 patients at the UCLA Frontotemporal Dementia Clinic for open-label usage from 1998-1999. Treating physicians included not only the author but also referring primary care physicians and referring neurologists. Some medications, particularly donepezil, were prescribed to patients by primary care physicians prior to the first evaluation at the FTD clinic.

Criteria for intervention were subjective and caregiver-driven; caregivers pursued intervention for behavioral disturbances that they could not tolerate emotionally or physically, and tolerance for a given symptom varied among caregivers. Either a caregiver's report of improvement or the clinician's objective observation of the subject's improvement qualified as a positive response. Unless intolerable adverse effects arose at initial doses, medications were continued for at least two months at initial or higher doses before discontinuation. Adverse effects were recorded and used to determine further dosage or discontinuation. Post-treatment NPI data are not consistently available for this sample.

Results

Table 1 lists ages, diagnoses, and target neuropsychiatric symptoms for 35 subjects in this sample. More than half of subjects treated had progressive nonfluent aphasia (NF-PPA) or semantic dementia. Repetitive motor behaviors and agitation were the most common behavioral disturbances among the subjects. Table 2 lists responses to medication and dosages.

Paroxetine was beneficial for 75 percent of subjects who took it, in that it decreased or eradicated repetitive, ritualistic behaviors. For example, a woman with FTD who compulsively stopped to rub or walk around certain trees while on daily walks with her dog was able to streamline the walks with less frequent stops. Trichotillomania also responded to paroxetine. The drug was much more effective against repetitive behaviors than as an antidepressant or anxiolytic. Often, as subjects progressed, repetitive motor behaviors subsided, and in three subjects, paroxetine was successfully tapered to lower doses or discontinued completely.

Adverse effects with paroxetine included stomach upset at 10 mg in a 64-year-old man with semantic dementia, and exacerbation of anxiety and depression in a 76-year-old woman with FTD. She also suffered decreased speech output at the starting dose of 10 mg/day. There was no complaint of headache or insomnia in 12 subjects, although these are common side effects among patients treated with selective serotonin reuptake inhibitors (SSRIs).¹³ Clomipramine caused hyperhidrosis in a 64-year-old man with semantic dementia when given for anxiety and obsessive-compulsive toileting behaviors. The same subject could not tolerate any SSRI drugs.

The author and other clinicians frequently prescribed SSRIs for depression and anxiety. Depressive symptoms did not respond, but anxiety was reduced. No clear antidepressant or anxiolytic effects were achieved with mirtazapine, bupropion, or buspirone. Buspirone had been prescribed by a primary care physician prior to evaluation in the FTD clinic for symptoms of separation anxiety.

Agitation was most often treated with neuroleptic drugs. The least sedating and most effective neuroleptic medication was quetiapine. One subject developed moderate parkinsonism on risperidone, which resolved after changing to quetiapine. Another subject made the same change to quetiapine after taking haloperidol, which had caused moderate rigidity and blunted consciousness. Once on quetiapine, he was much more mobile, arrived at clinic ambulatory rather than by wheelchair, and was able to recognize close family members. Two subjects had to transition from olanzapine due to sedating effects; one of these subjects experienced recurrence of seizures. Valproic acid was also effective in addressing agitation.

Parkinsonism in these subjects was addressed with three medications: carbidopa/levodopa, amantadine, and pramipexole. One subject with FTD featuring early parkinsonism had relief of rigidity and bradykinesia with carbidopa/levodopa 25/100 twice daily. Another subject with both NF-PPA and parkinsonism has had improvement in both speech and bradykinesia with a low dose of carbidopa/levodopa; psychosis and vivid dreams prohibited higher

dosing. Amantadine improved alertness and transiently increased speech fluency for a subject with early onset of parkinsonism in FTD. Adverse effects of amantadine included livedo reticularis resolving after decrease to 100 mg/day in one man; exacerbation of gastroesophageal reflux disorder in one woman who also refused bupropion and buspirone; dry mouth and constipation at 300 mg in one woman; and nightmares in one woman taking 300 mg/day. Livedo reticularis was more frequent when subjects attempted to increase beyond 200 mg total per day to 300 mg. On the strength of caregivers reporting increased alertness and motivation, two women with FTD tried amantadine up to 200 mg/day. No clear benefit was demonstrated, and in one case, confusion was increased. All subjects with NF-PPA demonstrated a transient improvement in speech fluency that was not detectable with objective timed tests of fluency.

Another subject with relatively early onset of parkinsonism experienced worsening of gait with pramipexole at .25 mg PO four times/day but has continued the medication at .25 mg PO daily at the caregiver's request.

Six subjects with NF-PPA or semantic dementia (32 percent of subjects with a language presentation of FTLD) came from primary providers who had already tried donepezil. The drug had no direct effect on aphasia or the target symptoms listed in Table 1. Side effects included stomach upset and vivid nightmares in two individuals. Both symptoms resolved with discontinuation of the medication.

Premarin .625 mg PO/day ended inappropriate sexual advances from one disinhibited man with NF-PPA. The sexual dysfunction caused by SSRIs has also curbed sexual disinhibition in demented patients. This was noted in another man with NF-PPA.

Discussion

The neurochemistry of FTD indicates primary roles for serotonergic and dopaminergic treatments but not cholinergic preparations as in AD. Autopsy results show no cholinergic deficit in FTD¹⁴ and normal choline acetyltransferase levels.¹⁵ Instead, there is a loss of serotonergic pre- and postsynaptic sites in frontal and temporal poles.¹⁵ Cerebrospinal fluid results from a different study on living FTD subjects show that 5-HIAA levels are similar to those found in AD subjects,¹⁶ but when FTD subjects are depressed, their serotonin substrate levels are further reduced.¹⁶ It was not clear how this reduction related to their concurrent antidepressant therapy. Responses to medication also support a serotonergic deficit in FTD that correlates with symptoms. Swartz *et al.* reported successful treatment of neuropsychiatric symptoms in FTD subjects with SSRIs.¹⁷

Cerebrospinal fluid levels of homovanillic acid, the substrate for dopamine, are significantly lower in FTD subjects than in AD.¹⁶ Functional neuroimaging shows decreased binding of D2 postsynaptic ligand in superior frontal regions of subjects with FTD.¹⁸ Selective serotonin reuptake inhibitors (SSRIs) or serotonergic transport inhibitors and dopaminergic medications may allow FTD patients to compensate for chemical imbalances brought on by the disease.

Consistent with this rationale, the SSRI paroxetine was successful most of the time for treatment of repetitive, ritualistic behaviors and anxiety. This study was not a head-to-head comparison of SSRIs, however, and other SSRIs may have shown similar efficacy in this population. Effective antidepressant therapy, on the other hand, has not been identified among the SSRIs for this group of FTD subjects. Even without the indirect evidence for use of SSRIs in FTD stated above, the side effect profile of SSRIs for older patients with depression compares well against that of tricyclic antidepressants.¹⁹

Paroxetine, quetiapine, and valproic acid adequately treated most cases of agitation. Of the limited drugs used to treat agitation in this sample, all drugs seem equally effective. Quetiapine replaced other typical and atypical neuroleptics when patients developed parkinsonism.

The tendency of FTD patients to develop parkinsonism over time complicates treatment of psychosis or agitation. One should avoid exposure to extrapyramidal side effects from neuroleptics. In addition, patients with dementia are not immune to dystonic reactions after receiving antipsychotic medication. Magnuson *et al.* reported that these subjects develop both acute and tardive torticollis.²⁰ One woman with FTD in this series developed tardive dyskinesia six weeks after stopping haloperidol. Quetiapine replaced other typical and atypical neuroleptics when subjects developed parkinsonism. Based on this study, neuroleptic use should be minimized and restricted to atypical neuroleptics in order to avoid exacerbating the parkinsonism that commonly develops in later stages of FTD. On the other hand, dopamine agonists induced psychosis occasionally in this sample, which justifies frequent monitoring for adverse drug effects.

Despite the lack of a cholinergic deficit in subjects with FTD, many clinicians have prescribed donepezil to patients before they were referred to the FTD clinic. It is not clear whether this was due to diagnosis as an atypical presentation of AD or an attempt to try a cognitive-enhancing agent in the absence of other disease-modifying medications for FTD, but donepezil has not benefited subjects who meet clinical diagnostic criteria for frontotemporal dementia syndrome. Neuropsychiatric symptoms in AD subjects who demonstrate frontal lobe perfusion deficits on SPECT have responded to cholinesterase inhibitor therapy, particularly disinhibition and irritability.²¹ These frequent behavioral disturbances localize to similar perfusion deficits on SPECT of brain in subjects with FTD, yet donepezil did not play a positive role for subjects with FTD in this sample.

The clinical syndrome of semantic dementia may be caused by either AD or FTD. It can be very difficult to differentiate between these two underlying etiologies without post-mortem neuropathology. For this study, we used functional neuroimaging (PET or SPECT of brain) to help hone FTD diagnoses. Semantic dementia due to FTD was only diagnosed if subjects had selective temporal but not parietal abnormalities in order to exclude as many AD subjects as possible, but it is possible that some of the semantic dementia subjects in this group actually had AD. One subject with semantic dementia had temporal hypoperfusion on SPECT, but postmortem neuropathology was consistent with AD; he was excluded from this sample. Subjects with semantic dementia due to AD are more likely to respond to donepezil

than subjects with frontotemporal degeneration, but it is probably incorrect to accept the converse: that subjects who respond to donepezil have AD.

Tanaka *et al.* reported effectiveness of another cholinesterase inhibitor, bifemaline, in their group of semantic dementia subjects.²² Patients with semantic dementia may deserve a trial of donepezil for possible AD, but they should be warned that donepezil can intensify irritability and restlessness in patients with FTD.²³ Pooling of data from multiple centers might lend more validity to the observations documented here. This may, in turn, form the basis of a prospective, multicenter, double-blind, placebo-controlled study of pertinent psychotropic medications. Collaborations between centers will need to agree on subgroup classifications of FTLT.

Questions remain as to how to treat depressive symptoms in this population, and the long-term implications of SSRI use with regard to 5-HT₂ heteroreceptor effects on presynaptic dopamine release in a dementing illness that features parkinsonism in its late stages are not yet known.²⁴

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Table 1

Demographics and diagnoses of 35 cases of frontotemporal lobar degeneration followed at the UCLA Frontotemporal Dementia Clinic from 1998 – 1999

	Frontotemporal dementia (n = 16)	Progressive nonfluent aphasia (n = 10)	Semantic dementia (n = 9)
Mean age during treatment, in years (range)	70.5 (55 – 79)	65.3 (65 – 84)	71.6 (65 – 79)
Mean age at onset, in years (range)	65.5 (51 – 76)	61.5 (51 – 81)	66.4 (61 – 78)
Female (%)	69	70	22
Target neuropsychiatric symptoms			
Obsessive-compulsive behaviors (%)	37.5	10	33.3
Depression (%)	18.8	10	44.4
Anxiety (%)	18.8	0	22.2
Agitation (%)	43.8	20	11.1
Parkinsonism (%)	12.5	10	0

Table 2

Responses to treatment (maximum doses reached are listed)

	Number of responders (age, gender, diagnosis)
Obsessive-compulsive behaviors	
paroxetine, 40 mg bid	8/11
clomipramine, 25 mg/day	0/1; Not well tolerated by 66 M SD *
Depression and anxiety	
fluoxetine, 20 mg/day	1/3
sertraline, 150 mg/day	1/3
paroxetine, 40 mg bid	1/2
mirtazapine, 30 mg/day	0/1; 65 yo M SD: improved sleep, but no effect on irritability, depression, anxiety
bupropion, 150 mg bid (SR)	1/4
buspirone, 10 mg tid	0/2; Suicide attempt in 67 F with NF-PPA * & seizures
Agitation	
risperdone, 1 mg bid	1/3
quetiapine, 250 mg qAM + 500 mg qHS	3/3
valproic acid, bid dosing to 1,125 mg daily	3/3
lorazepam, 1 mg qid	1/1; 65 NF-PPA F for seizure prophylaxis and for agitation
Parkinsonism	
carbidopa/levodopa, 25/250 qid	2/3
amantadine, 100 mg tid	5/5 NF-PPA; 1/4 SD
Miscellaneous	
donepezil, 10 mg/day	2/7; Both responders had SD

* NF-PPA = progressive nonfluent aphasia; SD = semantic dementia.