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Medical Management of Frontotemporal Dementias: The Importance of the Caregiver in Symptom Assessment and Guidance of Treatment Strategies

Gregory A. Jicha

Sanders-Brown Center on Aging and the University of Kentucky Alzheimer's Disease Center, University of Kentucky College of Medicine, Room 223, 800 South Limestone Street, Lexington, KY 40536, USA, gajich2@email.uky.edu

Abstract

There are no currently Food and Drug Administration-approved or proven off-label treatments for the frontotemporal dementias (FTD). Clinicians, care-givers, and patients struggle regularly to find therapeutic regimens that can alleviate the problematic behavioral and cognitive symptoms associated with these devastating conditions. Success is “hit or miss” and the lessons learned are largely anecdotal to date. Drug discovery in this area has been largely hampered by the heterogeneous clinical presentations and pathological phenotypes of disease that represent significant obstacles to progress in this area. Biologically, plausible treatment strategies include the use of antidepressants (selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitor and monoamine oxidase inhibitors), acetylcholinesterase inhibitors, *N*-methyl-D-aspartic acid antagonists, mood stabilizers, antipsychotics, stimulants, antihypertensives, and agents that may ameliorate the symptoms of parkinsonism, pseudobulbar affect, and motor neuron disease that can often coexist with FTD. These medications all carry potential risks as well as possible benefits for the person suffering from FTD, and a clear understanding of these factors is critical in selecting an appropriate therapeutic regimen to maximize cognition and daily functions, reduce behavioral symptoms, and alleviate caregiver burden in an individual patient. The role of the caregiver in tracking and reporting of symptoms and the effects of individual therapeutic interventions is pivotal in this process. This manuscript highlights the importance of establishing an effective therapeutic partnership between the physician and caregiver in the medical management of the person suffering from FTD.

Keywords

Frontotemporal dementia (FTD); Treatment; Caregiver

Introduction

Medical management of frontotemporal dementia (FTD) is complicated by the lack of currently available evidence supporting the efficacy of any therapeutic agent for this devastating disease (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al.

2010; Mendez 2009). Few rigorous clinical trials have been performed and only a handful of select agents have been tested in any paradigm (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009). The results of the few limited studies that have been published are often contradictory, even for the same agent studied. A web-based search of the US Food and Drug Administration's (FDA) "Orange Book" (<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>) identifies only 11 listings that all involve diagnostic testing. None of these listings focus on therapeutic approvals or applications for approval of therapeutic agents for the medical management of FTD. Further dismay can be invoked through perusal of the National Institute of Neurologic Disorders and Stroke information page on FTD (<http://www.ninds.nih.gov/disorders/picks/picks.htm>) that states verbatim, "No treatment has been shown to slow the progression of FTD. Behavior modification may help control unacceptable or dangerous behaviors. Aggressive, agitated, or dangerous behaviors could require medication. Anti-depressants have been shown to improve some symptoms." These four sentences represent the entire section on treatment for FTD, and while disappointing, do suggest a strategy for the medical management of FTD that relies on symptomatic improvement.

The present review outlines the barriers to drug discovery in FTD, existing data on medication usage in FTD, clinical trial findings in FTD, and plausible strategies for the medical management of FTD in the face of a clear lack of "best evidence" for any particular therapeutic approach. Recommendations and therapeutic considerations without citations should be considered anecdotal and based on the authors' personal experience with patients suffering from FTD rather than evidence-based conclusions. The role of the caregiver in identifying symptoms that guide therapeutic targeting, and in validating the efficacy or lack thereof for any treatment strategy attempted is critically important to this process, which is largely empiric, relying on a "hit or miss" approach that cannot be avoided at present in optimizing the medical management of FTD.

Barriers to Drug Discovery and Establishment of Clinical Efficacy in FTD

Primary issues that have thwarted drug discovery in FTD to date include: (1) relative rarity of this disorder, (2) clinical, genetic, and pathologic heterogeneity, (3) lack of appropriate assessment measures for the signs and symptoms of FTD for use as efficacy endpoints (Freedman 2007; Trojanowski et al. 2008). The epidemiology, clinical features, genetics, pathology, and assessment measures are described in detail in accompanying sections of this journal edition and will be described only briefly below.

The prevalence of FTD has been estimated at only 15 per 100,000 (Rosso et al. 2003; Gislason et al. 2003; Ratnavalli et al. 2002). Based on this estimate, Indianapolis, IN, USA (site of the 7th International Conference on FTD, 2010), the 14th largest city in the USA, has only 125 residents suffering from this disorder. While relatively rare compared to Alzheimer disease (AD) in the population >65 years of age, FTD may represent as much as 15% of total dementia cases in the population younger than 65 years of age (Rosso et al. 2003; Gislason et al. 2003; Ratnavalli et al. 2002). Increasing awareness of diagnostic misclassification, especially in younger populations, may change such estimates in the future. Generating large networks of clinical sites with established populations of FTD subjects eligible for participation in clinical trials is a critical obstacle to successful drug discovery and clinical trial implementation currently.

Clinical, genetic, and pathological heterogeneity subdivide this rare family of disorders (Table 1). To date, at least eight distinct clinical variants of FTD have been described including behavioral variant FTD, non-fluent primary progressive aphasia, semantic

dementia, FTD with Parkinsonism, FTD with motor neuron disease, FTD with inclusion body myopathy and Paget's disease of the bone, progressive supranuclear palsy, and corticobasal degeneration (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009). Mutations in at least seven different genes have all been shown to cause FTD in an autosomal dominant fashion including *TAU*, *PRGN*, *VCP*, *CHMP2B*, *TDP-43*, *FUS*, and an as of yet unidentified gene on chromosome 9 (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009; Froelich-Fabre et al. 2004; Galariotis et al. 2005b; Liscic 2009; Neumann et al. 2009; Rizzu et al. 1999; Seelaar et al. 2011). Pathological variants are classified according to eight different histological phenotypes including Pick's disease, tau-positive FTDP-17, TDP-43 positive FTD with or without motor neuron disease, FUS-positive, progressive supranuclear palsy, corticobasal degeneration, and ubiquitin-positive (tau/TDP43/FUS-negative) FTD (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009). While clearly some interrelationships exist between these clinical, genetic, and pathological phenotypes, the complexity of heterogeneity cannot be ignored, further complicating the design of clinical trials hoping to evaluate a given therapeutic in a homogeneous population of FTD subjects.

To date, clinical trials in FTD have relied on assessment measures developed and standardized for the assessment of AD (Freedman 2007; Kipps et al. 2008). Yet it is clear that FTD is clinically distinct from AD in terms of cognitive, behavioral, psychiatric, and motor signs and symptoms (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009; Chow et al. 2009; Kertesz et al. 2000; Lindau et al. 2003; Mathuranath et al. 2000a; Mioshi et al. 2007; Perry and Hodges 2000; Robles et al. 1999; Salmon et al. 2008). Behavioral variants of FTD may demonstrate intact cognition, while language variants may demonstrate severe deficits on even non-verbal tasks related to impaired comprehension of instructions or response expression (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009). Motor performance and visual tracking can be problematic for variants of FTD, such as FTDP-17, FTD-MND, PSP and CBD when analyzing executive function with standardized batteries including the Stroop and Trailmaking tests, among others (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009; Kertesz 2003; Kertesz and Munoz 2004; Lillo and Hodges 2009; Mathuranath et al. 2000b; Merrilees et al. 2010; Mitsuyama and Inoue 2009; Padovani et al. 2007). Few measures have been developed to specifically assess FTD, and it should be recognized that the clinical heterogeneity of disease will require unique tests for unique variants of FTD (Freedman 2007). Further work in this area is clearly needed to develop the tools that are a prerequisite to effective clinical trial development.

Barriers to Symptomatic Management of FTD

As no convincing data is available for the development of an a priori approach to the management of FTD, an individualized, empiric approach must be employed by the caregiving team. This team approach presents many obstacles to effective treatment that can be overcome if a careful delineation of roles and responsibilities are assumed by the treating physician and primary caregiver. The treating physician must become expert at utilizing various pharmacological approaches to manage cognitive, behavioral, psychiatric, and

motoric symptoms. This may require additional training if not already versed in the treatment of the myriad symptoms that can be seen to different degrees in individual cases of FTD. The caregiver represents the primary contact with the patient and has almost exclusive knowledge of the symptoms requiring treatment and is uniquely positioned to evaluate the benefits and potential side effects of specific therapeutic interventions. This is complicated by the presence of often significant fluctuations in symptoms and function caused by environmental triggers and stressors. Often, the symptoms noted after a new medication is started or an existing medication is changed in dose may relate more to environmental factors than to the effects of the medication itself. Clarity in reporting changes associated with medication adjustments and temporally associated environmental experiences are critical in the rational management of FTD. While the physician's medical expertise and credentials are needed to implement therapeutics, they are unable in many cases to assess the effectiveness of such therapies beyond the reports of symptomatic improvements or decline given by the caregiver. It is essential that the physician and caregiver work as a team in the medical management of FTD. Specific strategies to maximize this collaborative effort will be presented after the following discussion of therapeutic options below.

Therapeutic Options for the Symptomatic Management of FTD

Symptomatic treatment of FTD needs to focus on the cognitive, behavioral, psychiatric, and motor impairments experienced by the individual patient with FTD. There are no hard and fast rules. Individual treatment options are categorized below by drug class, realizing that the same symptom may be effectively managed by medications falling into one or more drug classes. Medications that may prove effective in symptom management in FTD include medications approved for use in AD (cholinesterase inhibitors and *N*-methyl-D-aspartic acid (NMDA) antagonists), anti-depressants (the only class of medication commented on in the NINDS information page for FTD presented above), mood stabilizers, sedatives, antipsychotics, anti-Parkinsonian agents, stimulants, anti-hypertensives, agents for pseudobulbar affect and motor neuron disease (Bei et al. 2010; Chow 2005; Kaye et al. 2010; Mendez 2009) (See Table 2).

Agents Approved for Use in AD

The use of AD medications for FTD is biologically plausible, based on frontal cholinergic denervation (specifically the use of acetylcholinesterase inhibitors), and specific cortical dysfunction (NMDA-based treatment; memantine) seen in FTD (Ferrer 1999; Hansen et al. 1988; Odawara et al. 2003; Procter et al. 1999; Sparks and Markesbery 1991; Uhl et al. 1983; Weinberger et al. 1991; Wood et al. 1983). Deficits in both neurotransmitter systems have been demonstrated in FTD (Ferrer 1999; Hansen et al. 1988; Odawara et al. 2003; Procter et al. 1999; Sparks and Markesbery 1991; Uhl et al. 1983; Weinberger et al. 1991; Wood et al. 1983). Several studies have shown stabilization of cognitive function (language and executive function) with the use of such agents (Kertesz et al. 2008; Moretti et al. 2004). These agents may prove especially useful in language variants (non-fluent primary progressive aphasia subtypes) that often represent cortical variants of AD rather than underlying FTD pathology. Yet another study suggested worsening of cognition with the use of memantine in FTD (Diehl-Schmid et al. 2008). Several studies have demonstrated reductions in scores on the neuropsychiatric inventory (NPI; Moretti et al. 2004; Boxer et al. 2009; Swanberg 2007), suggesting improvement in behavioral and psychiatric symptoms, while another study demonstrated decline on a specific FTD battery related to a tendency for such agents to cause hyperactivity leading to more behavioral problems (Mendez et al. 2007). Parasympathetic activation by such agents may also worsen salivation and lead to choking and aspiration in FTD associated with MND or progressive supranuclear palsy although this has not been studied previously and is purely anecdotal.

Antidepressants

The best evidence for effective intervention in FTD involves the use of anti-depressants. While still short of conclusive, the observation of impaired serotonergic (and more broadly monoaminergic) activity in FTD again implies biologic plausibility for the use of such agents in FTD (Sparks and Markesbery 1991; Bowen et al. 2008; Franceschi et al. 2005; Kanazawa et al. 1988; Rinne et al. 2002; Sjogren et al. 1998; Sparks et al. 1991; Yang and Schmitt 2001). Clinical trials and case series demonstrate significant but variable improvement in total NPI scores, depression, agitation, irritability, compulsions, aggression, eating disorders, and speech and motor stereotypies in FTD (Adler et al. 2003; Lebert et al. 2004; Moretti et al. 2002, 2003; Prodan et al. 2009; Swartz et al. 1997). No reports of worsening of behavioral or psychiatric symptoms as a result of anti-depressant therapy can be found in the literature. While a single trial of paroxetine demonstrated worsening of cognitive symptoms (Deakin et al. 2004), several other trials variably demonstrated enhanced cognitive function manifest as improvements in problem solving, executive function (Stroop test), and sustained attention (paced serial addition task; Adler et al. 2003; Moretti et al. 2002).

Mood Stabilizers

Many of the behaviors noted to be problematic in FTD such as motor restlessness, agitation, irritability, and depression are commonly seen in bipolar disorder. As such, mood stabilizers might prove beneficial in the treatment of such behavioral and psychiatric disturbances. There exists only a single case report in the literature on the effectiveness of topiramate, an AED with potential mood stabilizing properties, in FTD (Cruz et al. 2008). Topiramate reportedly reduced alcohol abuse in this single subject but did not impact other obsessive tendencies; as such, the applicability of such a finding may be called into question. Despite the lack of evidence, clinicians and researchers are intrigued by the potential of certain mood stabilizers, such as valproic acid and lithium to inhibit glycogen synthase kinase-3 β , a key enzyme responsible for the hyperphosphorylation of tau seen in degenerative disease states (Allain et al. 2003; Galariotis et al. 2005a; Mendez 2009; Trojanowski et al. 2008; Gozes 2010; Mudher et al. 2004). Further investigations in this area are needed to establish the potential for disease modification with these agents.

Sedatives

Sedatives, such as the benzodiazepines alprazolam (Xanax), lorazepam (Ativan), and diazepam (Valium) and the antihistamines such as benedryl and vistaril, are used widely in the field of psychiatry to quell anxiety, agitation, irritability, aberrant motor behaviors, and sleep disturbances. Such clinical features are common problems in FTD (Allain et al. 2003; Arvanitakis 2010; Bei et al. 2010; Boxer and Boeve 2007; Chow 2005; Galariotis et al. 2005a; Graff-Radford and Woodruff 2007; Kaye et al. 2010; Mendez 2009), and so the potential for intervention with sedative compounds is great. No studies exist of such agents in FTD; however, and so their use is purely empiric. One caveat is that, as sedatives, they will impair cognition, and if the symptoms targeted are the result of cognitive decline, they could worsen. Future studies examining the efficacy of such interventions in FTD are clearly needed.

Antipsychotics

Antipsychotics, especially the newer atypical antipsychotics, have been commonly used in dementia care for the management of extreme behavioral or psychiatric symptoms. Their use has been discouraged of late secondary to studies demonstrating a 1.6–1.7-fold increased risk of death in such associated with their use in elderly patients with dementia (Dorsey et al. 2010; Jeste et al. 2008; Kirshner 2008; Recupero and Rainey 2007; Salzman et al. 2008;

Wang et al. 2006). As many FTD patients are younger than the typical elderly AD patient, the risk for these subjects is unclear at present. Nonetheless, the finding of an increased risk of death over an average 10-week trial period from 2.6% with placebo to 4.5% with the use of an antipsychotic has led to a FDA “Black box” warning regarding this risk. Of note, observational studies suggest the risk is similar or even increased with the use of traditional antipsychotic agents such as haloperidol (Haldol) and thioridazine (Thorazine) among others. This has led to the expansion of the FDA “Black box” to include all antipsychotics rather than restricting the warnings to the newer atypical agents. Several case reports in the literature have demonstrated improvement in behavioral symptoms and even restoration of frontal glucose hypometabolism with the use of atypical anti-psychotics in FTD (Curtis and Resch 2000; Fellgiebel et al. 2007). Another study has shown an increased risk of Parkinsonian symptoms with antipsychotic use in FTD suggesting that such patients may be more susceptible to the deleterious effects of these medications than the standard patient population treated with such agents (Czarnecki et al. 2008). As the risk/benefit ratio may clearly be altered in individual cases, the use of antipsychotic therapy needs to be discussed with the caregiver and patient if they retain capacity with full and open disclosure on the risks associated with such treatment. Despite these caveats, at times the behaviors associated with FTD may pose a more serious risk to safety and well-being than the use of an antipsychotic would, and so they may serve as necessary therapy in certain cases and situations.

Antihypertensives

Given considerations regarding sedative and antipsychotic use in FTD, clinicians have been placed in a quandary as to how to safely alleviate many of the behavioral and psychiatric symptoms seen in FTD. Antihypertensives including alpha- and beta-blockers may prove to be suitable alternatives. These agents are useful for the treatment of anxiety and agitation in other disease states and so their plausible use in FTD is warranted. No data exists, however, on the utility of these agents in FTD at present. Care needs to be exercised to ensure that vital signs such as blood pressure and heart rate remain stable, and that medication adherence with the use of alpha-blockers, such as clonidine, that can cause extreme rebound hypertension with withdrawal, be assured.

Stimulants

A single randomized placebo-controlled clinical trial of methylphenidate (stimulant) has been reported with positive results in the literature (Rahman et al. 2006). In this study, risk-taking behavior as assessed by the Cambridge Gambling Task was reduced; however, no other benefits were observed. An additional case report demonstrated partial normalization of frontal electroencephalographic rhythms with methylphenidate use (Goforth et al. 2004). The rationale for use of stimulants in FTD draws parallels from its use in attention deficit hyperactivity disorder, and the observed attention deficits and hyperactivity seen in many persons with FTD. Again, further study is needed to clearly define the patient populations in which such an approach may prove fruitful.

Anti-Parkinsonian Agents

Symptoms such as Parkinsonism, motor neuron disease (amyotrophic lateral sclerosis or Lou Gehrig’s disease), and associated pseudobulbar affect may also be treated empirically if they are creating significant problems with daily function. Parkinsonism in FTD can be extremely debilitating (Padovani et al. 2007). Unlike classic Parkinson’s disease (PD), the symptoms typically arise from dysfunction of the basal ganglia rather than the degeneration of the dopamine-producing neurons in the substantia nigra of the midbrain (Kanazawa et al. 1988). As such, the typical Parkinsonism of FTD may represent striato-nigral rather than nigro-striatal degeneration and may not be amenable to treatment with agents such as

carbidopa/levodopa (Sinemet) or other dopaminergic agonists that can alleviate the symptoms of classic PD associated with nigro-striatal degeneration. Arguing against this notion is the clear demonstration of reduced dopaminergic activity in FTD compared to controls or AD subjects (Kanazawa et al. 1988; Rinne et al. 2002; Frisoni et al. 1994). A second consideration is the potential for dopaminergic agents to trigger or exacerbate psychiatric disturbance such as agitation, delusions, paranoia, and even frank hallucinations. Parallels drawn from the use of monoamine oxidase inhibitors (Selegiline and meclbomide described above as antidepressants) may suggest that the utility of such agents extends beyond alleviation of the motor symptoms of Parkinsonism that can be associated with FTD. Indeed, a single study of bromocriptine in FTD demonstrated improvement in fluency (measured as an increase in mean utterance length) in language variants of FTD (Reed et al. 2004).

Agents for Motor Neuron Disease

Treatments targeting motor neuron disease symptoms are limited. Persons afflicted with FTD that have the signs and symptoms of motor neuron disease have a reduced lifespan related to the physical incapacity of this comorbid disease state. Riluzole (Rilutek) is the only agent shown to prolong lifespan in motor neuron disease (Bedlack 2010; Bellingham 2011; Cheah et al. 2010; Miller et al. 2009). The use of riluzole increases the probability of surviving 1 year by only 9%. Its utility in the treatment of MND associated with FTD is unclear. Other symptomatic treatments include phenytoin or baclofen for spasticity, anticholinergics such as scopolamine for hypersalivation, and the unproven potential for supplements such as creatine and coenzyme Q-10 for maintenance of muscle mass and strength. Again, such agents have not been tested or proven in the treatment of FTD associated with MND, but their rationale use should not be excluded on the basis of absence of data where there is scientific and medical plausibility to support their use.

Agents for Pseudobulbar Affect

Pseudobulbar affect reflects emotional incontinence, where brainstem involvement such as that seen in FTD-MND and progressive supranuclear palsy, leads to inappropriate and uncontrollable pathological laughter and crying. Such symptoms can be extremely debilitating for persons with these disorders. Previous strategies for treatment of such conditions included the use of carbidopa/levodopa, amantidine, amitriptyline, and fluoxetine (Schiffer and Pope 2005). More recently, a combination therapy of dextromethorphan and quinidine has been developed and tested for the treatment of pseudobulbar affect in MND and multiple sclerosis patients, leading to approval by the FDA for these indications (Brooks et al. 2004; Miller 2006; Panitch et al. 2006; Rosen and Cummings 2007). Its use in pseudobulbar affect related to FTD-MND and progressive supranuclear palsy remains unclear, but medically plausible.

In summary, it is clear that the clinical data supporting the use of any single agent in FTD is lacking. Our best data supports the rationale use of antidepressants for the treatment of behavioral and psychiatric features that exist within and beyond the spectrum of affective disorders such as depression. The additional use of medications approved for use in AD (cholinesterase inhibitors and NMDA antagonists), mood stabilizers, sedatives, antipsychotics, anti-Parkinsonian agents, stimulants, anti-hypertensives, agents for pseudobulbar affect and motor neuron disease is medically and scientifically plausible, but requires caution and empiric testing of efficacy in each individual patient with FTD. The opposing actions of some of these agents (i.e., monoaminergic stimulators such as antidepressants and anti-Parkinsonian agents vs. monoaminergic depressants such as antihypertensives) attest to these concerns.

Building a Rational Strategy for Physician/Caregiver Interactions in the Empiric Management of FTD

As no clear algorithm for the management of FTD exists, given the lack of available evidence supporting any individual rationale strategy, the caregiving team comprised of the treating physician and the primary caregiver must devise an individualized treatment plan that targets the most bothersome and debilitating symptoms occurring at any given time. This requires a rational empiric strategy. Effective implementation of such a strategy is dependent on several key considerations for both the clinician as well as the caregiver.

While the physician has the ultimate responsibility of selecting appropriate medications to target current symptoms that are impairing quality of life and ensuring that the medications are being used at appropriate doses for sufficient periods of time to evaluate effectiveness of the therapeutic intervention, the physician's own experience of the symptoms, in the context of relatively short clinic visits in a foreign environment (typical office encounter) is insufficient to fully evaluate the repertoire of symptoms that may need to be targeted. Thus, the caregiver must play a primary role in the guidance of therapeutic intervention by accurately reporting problematic symptoms, identifying environmental triggers, and analyzing changes in these symptoms with the initiation or withdrawal of medications that be affecting such symptomatology. Additionally, the caregiver is almost solely responsible for identifying potential side effects or adverse effects on the targeted or other associated problematic symptoms.

Many caregivers of persons with FTD can be stressed by simple everyday interactions disrupted by cognitive, behavioral, psychiatric, or motoric symptoms of the disease. Without a defined strategy to track the critical information needed to make therapeutic decisions, clear targets for intervention at any given time cannot be reliably determined. Many caregiver-physician dyads benefit from the use of simple symptom diaries that track symptoms, time of day of occurrence, possible environmental triggers, degree of concern over symptoms, disruption of daily activities, alleviating or aggravating features, and response to therapies (Fig. 1). Such a tool helps organize symptoms into a hierarchical classification that can be based on objective tabulations of subjective observations. Such diaries are used routinely by neurologists and other physicians for optimal management of headaches and can be easily adapted for use in the setting of FTD.

Once such information is collected, the physician can easily review at office visits and obtain insights into the daily repertoire of problematic symptoms the patient is experiencing. Furthermore, the information in such a diary can be used to objectively evaluate the utility of any individual therapeutic strategy. Many therapeutic interventions may fail to fully control any individual symptom in FTD, and the continued presence of a symptom such as motor pacing can often be interpreted as a failure of the intervention. If, however, the symptom diary demonstrates a reduction in time spent pacing from 6 to 2 h per day, this might actually represent therapeutic success, rather than failure. Without a system for the rational tracking of symptoms, such valuable information would be lost and not available to the clinician when deciding on whether to increase the dose or discontinue this "failed" medication and try an alternative.

A few simple common sense rules can help maximize the therapeutic process and need to be conveyed to the caregiver for effective partnership (Table 3). The caregiver must be educated on the importance of obtaining such valuable information. They must also be clearly informed of the need for patience. Targeting one symptom at a time with a single medication adjustment is critical if an empiric approach to symptom management is to be successful. Simultaneous changes in more than a single medication will confuse our

interpretation of the effects of any given intervention. The caregiver also needs to realize that some medications, such as antidepressants, may have a several week delay in therapeutic efficacy, and that they need to wait this period of time to fully evaluate the potential efficacy of some interventions. Other medications, such as mood stabilizers, may need to be started slowly and escalated in dose over time to avoid potential adverse events. Achieving an optimal therapeutic dose is critical before deciding on the failure or success of a given therapeutic strategy. It should also be clearly understood that the medications will need to change in type and dose as the brain changes throughout the course of the disease. A medication that has “failed” previously may work wonders at a later time point in the disease. Conversely, a medication that helped to control symptoms early in the disease may prove detrimental if continued in the later stages of disease when the symptoms of FTD have changed, often dramatically. Stopping certain medications in an empiric test can be as useful as adding a new medication and can help prevent the polypharmacy seen in many of these patients as we strive for symptomatic benefit.

Conclusion

In summary, the role of the caregiver in the therapeutic partnership with the treating clinician cannot be overstated. Therapeutic intervention for symptom management can only be successful when the caregiver–clinician dyad is working in unison, combining the medical experience of the clinician with the actual phenomenal experience of the caregiver. Successful treatment of the symptoms of FTD is achievable for most at any given time in the course of the illness, but often does not come easy.

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Dementia Symptom Diary

DATE: _____

Name: _____

DOB: _____

Symptom	Time started	Time ended	Triggers (what were they doing when symptom started?)	How bothersome is symptom to patient (rate on scale of 1 to 10)	How bothersome is symptom to caregiver (rate on scale of 1 to 10)	What makes symptom better?	What makes symptom worse?	Medication effects?

RATING SCALE: 1 to 10 for symptom severity with 1 being the least severe, and 10 being the most severe

*Use additional sheets as necessary to record all events of concern

Fig. 1.
Example of caregiver diary for hierarchical categorization and effective targeting of symptoms of FTD, as well as monitoring of medication effects

Table 1

Clinical, genetic, and pathological heterogeneity in FTD

Clinical subtypes	Genetic mutations	Pathological subtypes
• Behavioral variant FTD	• <i>TAU</i> (coding for the microtubule associated protein tau)	• Pick's disease
• Non-fluent primary progressive aphasia	• <i>PRGN</i> (coding for progranulin)	• Tau-positive FTDP-17
• semantic dementia	• <i>VCP</i> (coding for the valosin-containing protein)	• TDP-43 positive FTD with or without motor neuron disease
• FTD with Parkinsonism	• <i>CHMP2B</i> (coding for the charged multivesicular protein 2B)	• FUS positive
• FTD with motor neuron disease	• <i>TDP</i> (coding for the tar-DNA binding protein 43)	• Progressive supranuclear palsy
• FTD with inclusion body myopathy and Paget's disease of the bone	• <i>FUS</i> (coding for the fused in sarcoma protein)	• Corticobasal degeneration
• Progressive supranuclear palsy	• Unidentified gene on chromosome 9	• Ubiquitin-positive (tau/TDP43/FUS-negative) FTD
• Corticobasal degeneration		

Table 2

Medications that may prove effective in symptom management in FTD (references cited in text and table where available)

Medication by class	Available clinical evidence, caveats, and considerations for use in FTD
Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)	<ul style="list-style-type: none"> May stabilize of language and executive functions (Kertesz et al. 2008; Moretti et al. 2004) May improve neuropsychiatric symptoms (Moretti et al. 2004) May aggravate neuropsychiatric symptoms (Mendez et al. 2007)
NMDA antagonists (memantine)	<ul style="list-style-type: none"> May improve neuropsychiatric symptoms (Boxer et al. 2009; Swanberg 2007) May worsen cognitive function (Diehl-Schmid et al. 2008)
Antidepressants (trazodone, paroxetine, fluoxetine, sertraline, selegiline, meclizemide)	<ul style="list-style-type: none"> May improve neuropsychiatric symptoms (Adler et al. 2003; Lebert et al. 2004; Moretti et al. 2002, 2003; Prodan et al. 2009; Swartz et al. 1997) May worsen cognitive function (Deakin et al. 2004) May improve cognitive function (Adler et al. 2003; Moretti et al. 2002)
Mood stabilizers (topiramate, lithium, valproic acid)	<ul style="list-style-type: none"> Only topiramate evaluated and shown to have efficacy for reducing compulsive alcohol use, but not other behaviors (Cruz et al. 2008) Lithium and valproic acid inhibit GSK-3B and may prevent tau mediated degeneration although unproven in vivo (Allain et al. 2003; Galaritis et al. 2005a; Mendez 2009; Trojanowski et al. 2008; Gozes 2010)
Sedatives (benzodiazepines and antihistamines)	<ul style="list-style-type: none"> Not tested in FTD May worsen cognition, exacerbate psychiatric symptoms and increase sleepiness limiting functional performance based on mechanism of action
Antipsychotics	<ul style="list-style-type: none"> May increase risk of stroke or death (FDA) (Dorsey et al. 2010; Jeste et al. 2008; Kirshner 2008; Recupero and Rainey 2007; Salzman et al. 2008; Wang et al. 2006) Restoration of frontal glucose hypometabolism (Curtis and Resch 2000; Fellgiebel et al. 2007) Aggravation of extrapyramidal signs and symptoms (dystonia and torticollis) (Czarnecki et al. 2008)
Stimulants (methylphenidate)	<ul style="list-style-type: none"> May reduce compulsive risk taking (Rahman et al. 2006) May partially normalize frontal electroencephalographic rhythms (Goforth et al. 2004) May hyperactivate based on mechanism of action
Antihypertensives (α & β blockers)	<ul style="list-style-type: none"> Not tested in FTD May be effective in controlling anxiety, agitation, and combative behavior
Anti-Parkinsonian agents (carbidopa/levodopa, dopaminergic agonists, bromocriptine)	<ul style="list-style-type: none"> Only bromocriptine tested, which may increase speech production in language variants of FTD (Reed et al. 2004) Other agents may help treat associated parkinsonism in FTD, but effectiveness is untested
Agents for pseudobulbar affect (amitriptyline, amantidine, dextromethorphan/quinidine)	<ul style="list-style-type: none"> Not tested in FTD May help treat associated pseudobulbar palsy in FTD, but effectiveness is untested
Agents for motor neuron disease (riluzole, phenytoin, baclofen)	<ul style="list-style-type: none"> Not tested in FTD

Medication by class	Available clinical evidence, caveats, and considerations for use in FTD
	<ul style="list-style-type: none">• May help treat associated motor neuron disease symptoms in FTD, but effectiveness is untested

Table 3

Common sense tips and strategies for the caregiver in order to maximize the effectiveness of empiric treatment strategies in FTD

Ten common sense rules for maximizing empiric treatment of FTD	
1	The caregiver should keep a diary of symptoms (Fig. 1)
2	Identify the key target symptom for intervention from diary
3	The caregiver should be careful not to attribute disease fluctuations with medication side effects or lack of efficacy
4	Target one symptom at a time with a single medication adjustment
5	Simultaneous changes in more than a single medication will confuse our interpretation of the effects of any given intervention
6	Allow for expected delays in therapeutic efficacy (i.e. antidepressant that may take several weeks to demonstrate efficacy)
7	Achieving an optimal therapeutic dose is critical before deciding on the failure or success of a given therapeutic strategy
8	A medication that has “failed” previously may work wonders at a later time point in the disease
9	A medication that helped to control symptoms early in the disease may prove detrimental if continued in the later stages of disease when symptoms have changed
10	Stopping a medications can be as useful as adding a new medication and also helps prevent unneeded or detrimental polypharmacy