

# Frontotemporal Dementia and Psychiatric Symptoms

Elif Onur<sup>1</sup>,  
Pinar Dikmen Yalinay<sup>2</sup>

<sup>1</sup>Assoc. Prof. Dr., Dokuz Eylül University Medical School,  
Department of Psychiatry, Izmir - Turkey  
<sup>2</sup>Neurologist, Acibadem University Medical School,  
Department of Neurology, Istanbul - Turkey

## ABSTRACT

### Frontotemporal dementia and psychiatric symptoms

Frontotemporal dementia (FTD) is the second most common cause of early onset dementia and is clinically characterized by progressive behavioural change, executive dysfunctions, and language difficulties. FTD is frequently confused with Alzheimer's disease and psychiatric disorders. Clinical features of FTD include changes of personality, restlessness, loss of inhibition, apathy, social withdrawal and impulsiveness. Most patients with FTD display socially inappropriate behaviours, compulsive-like acts, poor insight and psychiatric features including hallucinations and paranoid delusions. These symptoms can lead to misdiagnosing FTD as a psychiatric disorder. The etiology of sporadic FTD is unknown. In hereditary FTD, a causative mutation in the tau gene has been identified. Three clinical FTD syndromes has been described; a behavioural variant of FTD, semantic dementia and progressive non-fluent aphasia. At the present time the term "FTD" is used to define clinical syndromes while "frontotemporal lobar degeneration" refers to underlying pathologies. A detailed history and psychiatric and neurologic examination with the usage of magnetic resonance imaging can help to distinguish FTD from other common forms of dementia and psychiatric disorders. Although no effective treatment for FTD exists, serotonin reuptake inhibitor drugs have been shown to improve behavioural symptoms.

**Key words:** Frontotemporal dementia, neuropsychiatric symptoms, treatment

## ÖZET

### Frontotemporal demans ve psikiyatrik belirtiler

Frontotemporal demans (FTD), erken başlangıçlı demanslar içinde ikinci sıklıkta görülmektedir; ilerleyici davranış değişiklikleri, yürütücü işlevlerdeki bozukluklar ve lisan problemleri ile karakterizedir. FTD, sıklıkla Alzheimer hastalığı ve psikiyatrik hastalıklarla karşı. Klinik olarak, kişilik değişiklikleri, huzursuzluk, inhibisyon kaybı, apati, sosyal geri çekilme ve impuls kontrolünde bozukluk görülür. Frontotemporal demanslı birçok hastada uygun-suz sosyal davranışlar, kompulsiyon benzeri hareketler, içgörü kaybı ve psikiyatrik hastalıklarda görülebilen var-sanılar ve paranoid sanılar gibi belirtiler nedeniyle hastalar sıklıkla psikiyatrik bozukluk tanısı alırlar. Sporadik FTD'nin etiyolojisi bilinmemektedir. Herediter FTD'de 17. kromozomda, tau geninde mutasyonlar olduğu saptanmıştır. Üç klinik FTD sendromu tanımlanmıştır: Davranış varyantı, semantik demans ve ilerleyici tutuk afazi. Günümüzde "FTD" terimi klinik sendromları kapsarken, "frontotemporal lob dejenerasyonu" ise altta yatan patolojiji tanımlamak için kullanılır. Ayrıntılı öykü, psikiyatrik ve nörolojik muayene, manyetik rezonans görüntüleme FTD'yi diğer sık görülen demanslardan ve psikiyatrik bozukluklardan ayırt etmeye yardım eder. Frontotemporal demansın etkin bir tedavisi olmamasına karşın, serotonin geri alım inhibitörlerinin davranışsal belirtilerin kontrolünde yararlı olduğu gösterilmiştir.

**Anahtar kelimeler:** Frontotemporal demans, nöropsikiyatrik belirtiler, tedavi

Address reprint requests to:

Assoc. Prof. Dr. Elif Onur, Dokuz Eylül  
Üniversitesi Sağlık Yerleşkesi. Psikiyatri Anabilim  
Dalı. İnciraltı 35340, İzmir - Turkey

Phone: +90-232-412-4162

E-mail address:  
elif.onur@deu.edu.tr

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## INTRODUCTION

Various clinical syndromes were described explaining primary degenerative processes related with frontal and/or temporal lobes: "Pick's Disease", "frontotemporal dementia (FTD) related with chromosome 17 and Parkinsonism", "Frontotemporal lobar degeneration (FTLD) with motor Neuron Disease (MND)". In recent years, FTD has been used to define clinical syndromes and FTLD is used to define pathological processes (1).

## EPIDEMIOLOGY

Studies about epidemiology of FTD is limited although it makes up 12.5-16.5% of degenerative dementias (2). In postmortem studies, prevalence among all types of dementia was found 3-10% (3). In population-based studies, prevalence of FTD was found 3.6-9.4/100.000 in Zuid-Holland study and 7.8/100.000 in North London study (5).

Gender distribution is equal in frontotemporal

dementia. Its onset is between 45 and 65 years of age and mean survey is 6-9 years (3,6).

## **PATHOPHYSIOLOGY**

Although it was focused on genetic mutations to bring out pathophysiology of frontotemporal dementia and important findings were achieved, pathophysiology of the disease has not been understood yet. Genetics of FTD is complicated with multiple genetic factors and more than 40% of cases are genetically inherited with 10% of them being autosomal dominant (7). Microtubule-related protein (MAPT), valosine-containing protein (VCP), chromatin-modifying protein 2 (CHMP2B) and TDP-43 (TARDP) are previously described mutations (8). After the role of “tau protein gene mutations” inherited at chromosome 17 in FTD cases were understood, more than 35 tau mutations were detected in familial FTD cases (5,9). Proportion of tau mutations in familial cases is around 30% (5). Tau is a microtubule-related protein with low molecular weight coded by a gene at Chromosome 17. Mutations in tau protein alter the structure of microtubules and affect neuronal transport and may even cause neuronal death. Cases of FTD without a mutation in tau protein lead to investigate different genetic mutations. “Progranulin gene mutations” at chromosome 17 were found to be related to FTD (5,6). Although there are FTD cases having “presenilin gene mutations” at chromosome 14, its direct relation to FTD is not clear (3,6,9).

In frontotemporal dementia, macroscopically there is atrophy in frontal and temporal lobes and microscopically there is superficial cortical spongy changes and gliosis in grey and white matters (10,11). Recent tendency is to classify FTD based on neuroanatomical, biochemical and molecular genetic changes. FTLT is histopathologically classified into two groups according to presence or absence of specific inclusion bodies: containing tau positive inclusion bodies (Pick, chromosome 17-related FTLT and Parkinsonism) and containing ubiquitin positive, tau negative inclusion bodies (6,7,12).

It was also proposed that autoimmunity has a role in

ethiopathogenesis of FTLT. However, it is not clear whether processes are primary or secondary (3).

## **Frontotemporal Dementia and Neurotransmitter Changes**

It was suggested that alterations in serotonergic, cholinergic, dopaminergic, glutamatergic and noradrenergic systems have roles in neuropathology of the disease especially in behavioral variant (13).

**Serotonin:** Impulsivity, depressive symptoms, change in eating habits and compulsive behaviors support presence of serotonergic dysfunction seen in frontotemporal dementia (13,14). Brain imaging and autopsy studies following decrease in number of serotonin receptors in temporal and frontal cortices shown by Procter et al. (15) showed anomalies of serotonin receptors. Yang et al. (16) showed decrease in raphe nucleus neurons in FTD patients and reported that serotonergic tracts ascending to forebrain may be affected. Decrease in 5-HT<sub>2A</sub> (17) and 5-HT<sub>1A</sub> receptors (18) were detected in orbitofrontal, medial frontal and cingulate cortices. These findings explain efficacy of selective serotonin reuptake inhibitors (SSRI) in FTD.

**Acetylcholine:** Neurons of Meynert’s basal nucleus was found preserved (19), cortical acetylcholine transferase levels were found normal (15,19) and postsynaptic muscarinic receptor binding was found to be normal (15) in the studies. These findings and inefficacy of acetylcholine esterase enzyme inhibitors suggest that there is not an evident pathology in the cholinergic system.

**Dopamine:** Levels of homovalinic acid (HVA) which is a dopamine metabolite in cerebrospinal fluid were reported to be low in patients with FTD (20). It was shown that presynaptic dopamine transporters in putamen caudate nucleus are decreased (21) and severity of extrapyramidal symptoms are related with secretase in striatal dopamine transport (22). HVA/5-hydroxyindolacetic acid (5-HIAA) ratios in cerebrospinal fluid were detected higher than other dementias (Alzheimer dementia (AD), mixed dementia, Lewy body dementia) and were found to be related with

aggressive behaviors in sub-group of FTD patients not receiving psychotropic drugs (23).

**Noradrenaline:** Studies which evaluated both number of noradrenergic neurons in locus ceruleus and levels of noradrenalin metabolite methoxy-hydroxy-phenyl-glycol (MHFG) did not find clear results (13).

**Glutamate:** Findings suggest that alterations in glutamatergic system may have roles in FTD. Studies showed that there is a decrease in the number of N-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (23) at cortical pyramidal cells of frontal and temporal cortex (24). There is need for further studies on the role of glutamatergic system.

### CLINICAL MANIFESTATIONS

Frontotemporal dementia is classified into 3 sub-types according to clinical and neuroanatomical localizations as “Behavioral variant (FTDbv)”, “Semantic variant (SD)” and “Progressive Non-Fluent Aphasia (PNA)” (25).

#### Behavioral Variant

Neuropsychiatric symptoms are more prevalent. “Personality and social behavioral changes” seen in initial period of the disease were described in Clinical Consensus Criteria” (25) (Table 1). These criteria may be inadequate especially at the early period due to a

group of patients called “phenocopy” which carry clinical characteristics of behavioral FTD but symptoms do not substantially progress over time. Criteria were revised (26,27). In newly formed criteria, behavioral variant were evaluated in 3 diagnostic accuracy level as possible, probable and definite. In the possible category, presence of three of basic behavioral or cognitive symptoms is mandatory; in probable category, these symptoms should substantially progress and supported by brain imaging findings and in definite category presence of neuropathological findings or genetic mutations is mandatory (Table 2) (26).

Loss of empathy, inappropriate affection, behavioral disinhibition, loss of social awareness, apathy/asponaneity, stereotypical behaviors and alterations in eating habits (addiction to food with a high carbohydrate content) can be seen. Slight cognitive changes and predominant psychiatric symptoms cause difficulties in differential diagnosis at early period. In this period, while clinical tests (working memory, planning, mental flexibility, response inhibition, concept formation) are within normal limits, it will be useful to evaluate neuropsychological functions related with ventromedial prefrontal cortex (28,29). Sub-types were defined according to assessment of grey matter and neuroanatomical features (predominantly frontal, frontotemporal, temporofrontoparietal, predominantly temporal) or behavioral characteristics and involvement of related neural tracts (apathetic type, disinhibited type, stereotypical) (30).

**Table 1: Neary Consensus Criteria in Diagnosis of Frontotemporal Dementia**

**Neary et al. (25), Consensus Criteria: Behavioral Variant of Frontotemporal Dementia (bvFTD) Basic Diagnostic Characteristics**

Insidious onset and slow progression  
 Impairment of interpersonal social relations in early period  
 Impairment in personal attitude in early period  
 Emotional blunting in early period  
 Loss of insight in early period

**Neary et al. (25), Consensus Criteria: Behavioral Variant of Frontotemporal Dementia (bvFTD) Supportive Diagnostic Characteristics**

Behavioral Characteristics	Language and Speech Characteristics	Physical Characteristics
Insidious onset and slow progression	Economical or suppressive speech	Primitive reflexes
Impairment of interpersonal social relations in early period	Stereotypical speech	Incontinence
Impairment in self-hygiene in early period	Echolalia	Akinesia, rigidity and tremor
Emotional blunting in early period	Perseveration	Low or labile blood pressure
	Mutism	

**Table 2: Rascovsky et al. (26) Behavioral Variant Revised Criteria**

**Possible Behavioral Variant.** Repetitive presence of at least 3 criteria.

- A Early (3 years) behavioral inhibition
- B Early (3 years) apathy or dullness
- C Early (3 years) loss of empathy or sympathy
- D Early (3 years) perseverative, stereotypical or compulsive /ritualistic behaviors
- E Hyperorality and alterations in eating habits
- F Neuropsychological profile: Memory and visuspatial -and to a minor extent- executive dysfunction

**Most Probable Behavioral Variant.** All criteria should be met.

- A Meeting possible behavioral variant criteria
- B Significant functional impairment
- C Brain imaging findings consistent with behavioral variant (frontal and/or temporal atrophy in computed tomography or magnetic resonance or hypoperfusion in SPECT or PET imaging)

**Definite Behavioral Variant.** Presence of B or C with criterion A.

- A Meeting possible or probable diagnostic criteria of behavioral variant
- B Histopathological diagnosis by post-mortem biopsy
- C Presence of pathogenic mutations

**Exclusion Criteria of Behavioral Variant.** A and B criteria negative, C criterion can be positive in possible behavioral variant but it should highly probably be negative in behavioral variant.

- A Pattern of deficits can be explained by other neurodegenerative dementia or medical conditions better.
- B Behavioral characteristics can be explained better by psychiatric disorders.
- C Biomarkers point out Alzheimer dementia or other neurodegenerative dementias.

#### **Additional Characteristics**

- A Presence of motor neuron findings lead to motor neuron disease.
- B Motor manifestations and findings point out corticobasal degeneration and progressive supranuclear palsy.
- C Word and object naming impairment
- D Motor speech defects
- E Significant grammar deficits

**Semantic Dementia:** Anterior temporal area is predominantly affected. When right temporal lobe is predominantly affected then problems in emotional perception and expression are seen and when left temporal lobe is affected, language impairment is predominant. There is insidious and slowly progressive language impairment (fluent aphasia) is present when left side is affected. Speech is fluent, empty and spontaneous. Place orientation and memory is relatively preserved in these patients different from AD. Behavioral symptoms can be seen in moderate-to-severe phases in patients with semantic dementia and obsessive-compulsive features are predominant (10,31).

**Progressive non-fluent aphasia:** This is an insidious, slowly progressive clinical picture with left frontal atrophy. Language disorder is predominant and non-fluent speech accompanied by at least one of the

features such as anomia, agrammatism or paraphasia. Behavioral symptoms occur late in the course (10,32).

## **PSYCHIATRIC SYMPTOMS**

Different psychiatric symptoms are seen according to affected neuroanatomical areas. Brain imaging studies showed that decrease in emotional processing, remoteness in interpersonal relations, hypomania-like behaviors are predominant when temporal areas are affected and apathy, and decrease in social activities are predominant when frontal areas are affected (33). Personality and behavioral changes, apathy, repetitive compulsive behaviors and lack of insight cause problems mainly in behavioral variant and especially at early periods and cause FTD cases misdiagnosed such as psychosis, schizophrenia, depression and late-onset

bipolar disorder (34-37). Although psychiatric symptoms are prevalent, number of studies investigating prevalence of psychiatric disorders in FTD is limited. Mild Behavioral Impairment (MBI) is the clinical syndrome in which disinhibition is the predominant symptom, and which does not meet dementia or major psychiatric disorder diagnoses according to DSM-IV diagnostic criteria and does not have behavioral and psychiatric symptoms (38). This definition also covers lack of severe cognitive disorder and maintenance of daily activities (38) and has risk of dementia, especially FTD. Taragano et al. (39) evaluated 119 MBI and 239 mild cognitive impairment (MCI) cases about development of dementia in their 5 year follow-up study. Dementia developed in 30% of patients with MCI and 70% of patients with MBI. However, FTD developed more in patients with MBI. It should be kept in mind that psychiatric-behavioral symptoms without cognitive impairment can be the prodromal phase of FTD.

Psychiatric symptoms in frontotemporal dementia can be evaluated under 3 main topics: Personality and behavioral changes, affective symptoms and psychotic symptoms.

### **Personality and Behavioral Changes**

Personality changes of insidious onset and impairment in interpersonal relations and mood are primary characteristics of behavioral variant. Brain imaging studies showed that especially right temporal involvement is related with personality changes (33,40). Socially inappropriate behaviors such as childishness, inappropriate jokes and sexual statements are present among behavioral symptoms. Impairment in emotional processing may cause not performing socially appropriate behaviors (41,42). Neglecting self-hygiene, collecting weird objects, alterations in eating habits, compulsions about punctuality, late-onset gambling and rarely excessive religious involvement can be seen in behavioral variant (43-45). In semantic dementia, there are compulsive symptoms such as oversensitivity for timing and excessive dependence on daily routine (46). When left frontal hypoperfusion is evident,

aggression, criminal behaviors, going away from friends, insensitivity to financial issues, pervert sexual behaviors are seen; when right frontal hypoperfusion is evident, political or religious ideologies and inconsistency in dressing and behaviors are seen (47).

Behavioral symptoms and severity of the disease is correlated and agitation, disinhibition and irritability are mainly seen in late stages (45). Presence of typical or atypical behavioral symptoms, lack of evaluating social clues during interview of FTD patients, limited eye contact and lack of interest on whether their responses are correct may help in differential diagnosis (48). Detailed interviews with patients' relatives and administering scales such as Neuropsychiatric Inventory, Frontal Behavior Questionnaire and Cambridge Behavioral Questionnaire are recommended to evaluate behavioral symptoms (45).

**Affective Symptoms:** Depression, apathy, irritability, anxiety and euphoria can be seen. "Apathy" has an important role among affective symptoms due to both its prevalence and importance in differential diagnosis of depression (45). FTD cases can be misdiagnosed as depression due to mental dullness, lack of motivation, lack of interest about previous hobbies and progressive social withdrawal. Behavioral symptoms such as euphoria, inappropriate joking, increase in self-confidence and irritability may cause misdiagnose as hypomania or mania as well (35,42,49). Depressive symptoms can be seen in three different ways (50,51): major depressive disorder, affective reactivity – lability and apathy. FTD should be considered in cases with late onset and treatment-resistant depression. Lack of sadness, anxiety, guilt, pessimism, insomnia and lack of appetite which are seen in major depressive disorder may help in differential diagnosis (50).

**Psychotic Symptoms:** Due to disinhibition, inappropriate social behaviors, repetitive compulsion-like behaviors and lack of insight, FTD cases may be misdiagnosed as late-onset schizophrenia or atypical psychosis (33,34,52,53). Psychotic symptoms are seen in 13-14% of cases with FTD (54). However, it was reported that psychotic symptoms are observed less than AD (FTD 2.3%, AD 17.4%) (52). Prevalence of

delusions is 14% and is predominantly seen in behavioral variant and bilateral of right-predominant involvement. It was reported that most prevalent delusions are of paranoid and somatic types and they are especially seen at early period (55). Emotional blunting, impairment of judgment, lack of insight, decrease in self-hygiene and impairment of social functions are among negative symptoms of schizophrenia and are also seen in FTD. Velakoulis et al. (54) compared FTD cases from National Neural Tissue Bank (n=72) and FTD cases from literature (n=751) according to presence of psychotic disorders. In the evaluation of neuropathological series, 17 FTD cases under 60 years old were evaluated from presence of psychotic disorders according to

DSM-III, DSM-IV and ICD-10 diagnostic criteria. Among 17 cases, 4 had schizophrenia and 1 had bipolar disorder diagnosis and it was reported that onset of FTD was earlier (28-43 years) in these cases. Pathological diagnoses of 5 cases were tau-negative and ubiquitin-positive. An interesting finding was presence of pathologically (TDP-43 positive) or clinically FTD and MND in 4 cases diagnosed schizophrenia. When literature is reviewed, it was reported that 13.3% of cases with FTD had psychotic symptoms at onset or during course of the disease and in 7.2% of cases psychotic symptoms started after FTD was diagnosed. Proportion of cases with psychotic disorder and FTD was 6% (n=46). Proportion of cases diagnosed as schizophrenia, schizoaffective disorder and bipolar affective disorder among the group was 4% (n=30) and psychotic symptoms started 2 years before FTD diagnosis in 1/3 of cases and 11-38 years ago in the remainder 1/3 and psychosis diagnosis declined by increasing age. It was reported that in 17% of cases, there was clinical or pathological FTD and MND. Clinicians may misdiagnose cases with early onset emotional blunting, social withdrawal and executive dysfunction as schizophrenia with or without presence of brain imaging findings. Authors mentioned that these cases diagnosed as schizophrenia or psychosis may actually be FTD and stated that due to neuroanatomically similar pathologies in both FTD and schizophrenia,

clinical phenotypes may also be similar in young adults (54). It was suggested that assessment of TDP-43 which is known to present in ubiquitin positive FTD cases in psychosis cases with advanced age onset (7,9,12) may clarify the relationship between FTD and psychosis (56). It is currently impossible to explain the relationship between schizophrenia and FTD. However, in presence of late-onset psychotic symptoms, it is important to consider FTD in differential diagnosis. Especially functional brain imaging may contribute to differential diagnosis (57). As for differential diagnosis of all neuropsychiatric symptoms, detailed history taking, utilization of diagnostic tools and follow-up is mandatory.

## TREATMENT

Frontotemporal dementia has not any specific treatment yet. Treatments towards control of behavioral symptoms constitute majority of treatment approaches. Slowing progression of the diseases is aimed with neuroprotective treatments. However, there is need for studies to evaluate the efficacy of these agents in the long-term treatment (6,13,14). Widely used agents in the treatment are antidepressants (AD). Other agents being used are acetylcholine esterase inhibitors, NMDA receptor antagonists, psychostimulants and antipsychotics (6,9,14,45).

### Antidepressants

**Serotonin Reuptake Inhibitors:** Serotonergic and dopaminergic dysfunction makes up the basis of SSRI use in the treatment (13,14). For controlling stereotypical behaviors, disinhibition, inappropriate sexual behaviors and especially excessive carbohydrate consumption present in the most of the patients in early period, SSRIs are used first-line. Fluoxetine, fluoxetine, sertraline and paroxetine are widely used (14,58-60). Evidence about efficacy of SSRIs in treatment are based either on open-label or few randomized controlled studies and their case numbers and follow-up durations are different (14,61). In an open-label study (n=11), it was reported that behavioral

symptoms were controlled in 82% of patients by paroxetine, fluoxetine and fluoxamine (62). Findings of two studies done with paroxetine are contradictory. In the placebo-controlled, randomized study, efficacy of 40 mg/day paroxetine for 6 weeks on behavioral and cognitive symptoms was not different from placebo (63). In another open-label study comparing paroxetine and piracetam, using paroxetine 20 mg/day for 14 months improved behavioral symptoms compared to 1200 mg/day piracetam (64). In open-label study of 12 weeks by fluoxamine, improvement in stereotypical behaviors was observed (65) and in a case with MND and FTD, inappropriate sexual behaviors were controlled by sertraline (66). There are not any studies with escitalopram and citalopram yet; however, their low anticholinergic side effects may be advantageous (61). In a meta-analysis evaluating combined activity of antidepressants (trazodone, selegiline, paroxetine and fluoxamine), mean 15.4 points decrease was reported in neuropsychiatric inventory scores (13). Level of evidence for efficacy of SSRIs on behavioral symptoms of frontotemporal dementia is II, no effect on cognitive symptoms were reported (67).

**Trazodone:** Trazodone increases extracellular serotonin levels in frontal cortex and has an antagonistic effect on 5HT<sub>2A</sub> receptors. In a placebo-controlled, randomized study, 12 weeks of trazodone use in 26 FTD cases decreased neuropsychiatric interview scores over 25% and in 10 cases over 50% mainly in irritability, agitation, eating habits and depression sub-topics (68). When investigators re-evaluated these cases 2 years later, they detected that improvement in behavioral symptoms is maintained but there was no significant effect on cognitive symptoms (69).

**Other Antidepressants:** Monoamine oxidase inhibitors are thought to be efficacious in FTD mainly by increasing dopaminergic neurotransmission. Limited number of open-label studies with low sample sizes showed that moclobemide and selegiline may be effective on behavioral symptoms (13,14,59). Although there are no studies available, venlafaxine can be effective on apathy and bupropion may be advantageous in Parkinsonism (7, 61).

## Antipsychotics

Although American Food and Drug Administration limited the use of atypical antipsychotics for controlling behavioral symptoms in dementia patients due to increased cardiac mortality, (70), use of antipsychotic drugs is quite prevalent. It was reported in a study evaluating off-label drug use, proportion of at least one antipsychotic in treatment was 4.5% (71). Antipsychotic drugs are used in FTD when SSRIs become inadequate to control behavioral symptoms and in the presence of psychotic symptoms (13,14). Case reports and open-label studies reported that aripiprazole, risperidone and olanzapine exert positive effects to control behavioral symptoms of FTD (72-74). Level of evidence is not sufficient for the efficacy of atypical antipsychotics. They should not be the first choice in treatment in elderly patients with dementia due to increased cardiac mortality and extrapyramidal and metabolic side effects. They are recommended to be used with care and in a limited fashion when SSRIs are not effective and to control psychotic symptoms (6,7,13,14,61).

## Cholinesterase Inhibitors

Results of studies evaluating effect of cholinesterase inhibitors on behavioral and cognitive symptoms are contradictory. They may improve cognitive symptoms (75) but may impair behavioral symptoms (76) as well. Acetylcholine esterase inhibitors are not efficacious in FTD and are not recommended for treatment (67).

## NMDA receptor antagonists - Memantine

There are case series, two open-label and one placebo-controlled studies evaluating the efficacy of memantine. Improvement in apathy, agitation and anxiety sub-scale scores of neuropsychiatric inventory in 3 FTD cases by 20 mg/day memantine for 3 months was observed (77). In the study done in 16 patients by using 20 mg/day memantine for 6 months, no difference between starting and endpoint in Neuropsychiatric Inventory and Frontal Behavior Questionnaire scores was reported (78). In the study done in 43 patients

whom 20 mg/day memantine was administered for 26 weeks, there was improvement of neuropsychiatric inventory scores at 16<sup>th</sup> week mainly in behavioral variant but it was reported that scores returned to the beginning at the end of the study (79). In a recent placebo-controlled, randomized study which evaluated the efficacy of 20 mg/day memantine for 1 year (n=23), no effect of memantine on behavioral and cognitive symptoms could be shown (80). There is not enough evidence for the efficacy of memantine and it does not exist in treatment guidelines like choline esterase inhibitors (67).

### Other Agents

Psychostimulants may be effective through noradrenergic and dopaminergic systems, especially on apathy and risky behaviors (59). In a case which methylphenidate was administered, behavioral improvement correlated with quantitative EEG (81) was seen and significant decrease in risk-taking behaviors was observed in 8 FTD cases with a single dose of 40 mg methylphenidate (82). A case was reported which topiramate was shown to be effective on controlling alcohol abuse but not effective on other compulsive behaviors (83).

### Non-Pharmaceutical Treatments

Importance of caregivers is already known in dementia. It was shown that level of exhaustion and stress are higher in caregivers of patients with FTD

compared to AD (45). Educating caregivers about behavioral symptoms will help their coping skills, increase quality of life of both patients and caregivers and delay nursing home placement. There is need for further studies investigating transfer to nursing homes and effective interventions at this period.

Security conditions of the environment in which patient lives is an important issue. Patients without any executive dysfunction may maintain their financial and planning skills in the early period of the disease. However, control of patients' spouses is necessary for patients with lack of insight and poor judgment. Providing training of caregiver, controlling environmental conditions and behavioral and physical precautions are recommended (6,7,45,58).

FTD, which is seen frequently second among early onset dementias, after dementia of Alzheimer's type, and thirdly seen among all degenerative dementias after dementia of Alzheimer's type and Lewy-body dementia, has a separate position with predominant neuropsychiatric manifestations. Different neuropsychiatric symptoms are seen in the disease and are similar to clinical psychiatric disorders. In diagnosis, differential diagnosis and treatment of the disease, neuropsychiatric symptoms should be evaluated in detail. There is still no treatment which can change the course of the disease. Treatment is mainly about controlling behavioral symptoms and SSRIs are the first-line treatments. Education of patients' spouses and caregivers and collaboration in treatment has an important role. There is need especially for developing behavioral interventions and their use in practice.

## REFERENCES

1. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001; 58:1803-1809.
2. Kaye ED, Petrovic-Poljak A, Verhoeff NP, Freedman M. Frontotemporal dementia and pharmacologic interventions. *J Neuropsychiatry Clin Neurosci* 2010; 22:19-29.
3. Sjögren M, Andersen C. Frontotemporal dementia - a brief review. *Mech Ageing Dev* 2005; 127:180- 187
4. Rosso SM, Donker Kat L, Baks T, Joosse M, de Koning I, Pijnenburg Y de Jong D, Dooijes D, Kamphorst W, Ravid R, Verheij F, Kremer HP, Scheltens P, van Duijn CM, Heutink P, van Swieten JC, Niermeijer MF. Frontotemporal dementia in the Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain* 2003; 126:2016-2022.
5. Stevens T, Livingston G, Kitchen G, Manela M, Walker Z, Katona C. Islington study of dementia subtypes in the community. *Br J Psychiatry* 2002; 180:270-276.



6. Arvanitakis Z. Update on frontotemporal dementia. *Neurologist* 2010; 16:16-22.
7. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. *CNS Drugs* 2010; 24:375-398.
8. Rohrer JD, Guerreiro R, Vandrovцова J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IR, Warren JD, de Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN. The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009; 73:1451-1456.
9. Kertesz A. Frontotemporal dementia topical review. *Cog Behav Neurol* 2008; 21:127-133.
10. Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol* 2005; 4:771- 780.
11. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM, Consortium for Frontotemporal Lobar Degeneration. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol* 2007; 114:5-22.
12. Neuman M, Tolnay M, Mackenzie IR. The molecular basis of frontotemporal dementia. *Expert Rev Mol Med* 2009; 11:1-22.
13. Huey ED, Karen T, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* 2006; 66:17-22.
14. Kaye ED, Petrovic-Poljak A, Verhoeff NP, Freedman M. Frontotemporal dementia and pharmacologic interventions. *Neuropsychiatry Clin Neurosci* 2010; 22:19-29.
15. Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999; 10 (Suppl.1):80- 84.
16. Yang Y, Schmitt HP. Frontotemporal dementia: evidence for impairment of ascending serotonergic but not noradrenergic innervation. Immunocytochemical and quantitative study using a graph method. *Acta Neuropathol* 2001; 101:256-270.
17. Franceschi M, Anchisi D, Pelati O, Zuffi M, Matarrese M, Moresco RM, Fazio F, Perani D. Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Ann Neurol* 2005; 57:216-225.
18. Bowen DM, Procter AW, Mann D, Snowden JS, Esiri M, Neary D, Francis PT. Imbalance of a serotonergic system in frontotemporal dementia: implication for pharmacotherapy. *Psychopharmacology (Berl)* 2008; 196:603- 610.
19. Hansen LA, Deteresa R, Tobias H, RD Terry. Neocortical morphometry and cholinergic neurochemistry in Pick's disease. *Am J Pathol* 1988; 131:507-518.
20. Sjögren, L, Minthon, U, Passant K, Blennow K, Wallin A. Decreased monoamine metabolites in frontotemporal dementia and Alzheimer's disease. *Neurobiol Aging* 1998; 19:379-384.
21. Rinne JO, Laine M, Kaasinen V, Norvasuo-Heilä M K, Nägren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. *Neurology* 2002; 58:1489-1493.
22. Sedaghat F, Gotzamani-Psarrakou A, Dedousi E, Arnaoutoglou M, Psarrakos K, Baloyannis I, Dimitriadis AS, Baloyannis SJ. Evaluation of dopaminergic function in frontotemporal dementia using I-FP-CIT single photon emission computed tomography. *Neurodegener Dis* 2007; 4:382-385.
23. Engelborghs S, Vloeberghs E, Le Bastard N, Van Buggenhout M, Mariën P, Somers N, Nagels G, Pickut BA, De Deyn PP. The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. *Neurochem Int* 2008; 52:1052-1060.
24. Ferrer I. Neurons and their dendrites in frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999; 10 (Suppl.1):55-60.
25. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S ve Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51:1546-1554.
26. Rascovsky K, Hodges JR, Kipps CM, Johnson JK, Seeley WW, Mendez MF. Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. *Alzheimer Dis Assoc Disord* 2007; 21:14-18.
27. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. *Neurology* 2009; 72:732-737.
28. Krueger CE, Bird AC, Growdon ME, Jang JY, Miller BL, Kramer JH. Conflict monitoring in early frontotemporal dementia. *Neurology* 2009; 73:349-355.
29. Hallam BJ, Silverberg ND, Lamarre AK, Mackenzie IR, Feldman HH. Clinical presentation of prodromal frontotemporal dementia. *Am J Alzheimers Dis Other Demen* 2007; 22:456-467.
30. Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, Senjem ML, Shiung MM, Boeve BF, Knopman DS, Parisi JE, Dickson DW, Petersen RC, Jack CR Jr, Josephs KA. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain* 2009; 132:2932-2946.

31. Yener G. Semantik demans: Bir olgu nedeniyle. *Demans Dergisi* 2002; 2:115-120 (Article in Turkish).
32. Mesulam MM. Primary progressive aphasia. *Ann Neurol* 2001; 49:425-432.
33. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2006; 77:4-7.
34. Panldar S, Bora E, Evyapan D, Özaşkın S. Frontotemporal demans: şizofreni benzeri psikoz tablosuyla giden bir olgu sunumu. *Klinik Psikofarmakoloji Bülteni* 2001; 11:116-120 (Article in Turkish).
35. Gökmen Z, Metin Ö, Cinemre B, Özkan Ç. Bir Olgu: Frontotemporal demans ve duygudurum bozuklukları. *Geriatri ve Geriatrik Nöropsikiyatri* 2010; 1:38-44 (article in Turkish).
36. Woolley JD, Wilson MR, Hung E, Gorno-Tempini ML, Miller BL, Shim J. Frontotemporal dementia and mania. *Am J Psychiatry* 2007; 164:1811-1816.
37. Blass DM, Rabins PV. Depression in frontotemporal dementia. *Psychosomatics* 2009; 50:239-247.
38. Schölzel-Dorenbos CJ. Mild behavioral impairment: a prodromal stage of frontotemporal lobar degeneration. *J Am Geriatr Soc* 2006; 54:180-181.
39. Taragano FE, Allegri RF, Krupitzki H, Sarasola D, Serrano CM, Lyketsos C. Mild behavioral impairment and risk of dementia: a prospective cohort study of 358 patients. *J Clin Psychiatry* 2009; 70:584-592.
40. Mychack P, Kramer JH, Boone KB, Miller BL. The influence of right frontotemporal dysfunction on social behavior in frontotemporal dementia. *Neurology* 2001; 56:11-15.
41. Kipps CM, Mioshi E, Hodges JR. Emotion, social functioning and activities of daily living in frontotemporal dementia. *Neurocase* 2009; 15:182-189.
42. Caycedo AM, Miller B, Kramer J, Rascovsky K. Early features in frontotemporal dementia. *Curr Alzheimer Res* 2009; 6:337-340.
43. Manes FF, Torralva T, Roca M, Gleichgerrcht E, Bekinschtein TA, Hodges JR. Frontotemporal dementia presenting as pathological gambling. *Nat Rev Neurol* 2010; 6:347-352.
44. Shinagawa S, Ikeda M, Nestor PJ, Shigenobu K, Fukuhara R, Nomura M, Hodges JR. Characteristics of abnormal eating behaviours in frontotemporal lobar degeneration: a cross-cultural survey. *J Neurol Neurosurg Psychiatry* 2009; 80:1413-1414.
45. Piguet O, Hornberger, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 2011; 10:162-167.
46. Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001; 70:323-332.
47. Assal F, Cummings JL. Neuropsychiatric symptoms in the dementias. *Curr Opin Neurol* 2002; 15:445-450.
48. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry* 2008; 69:60-73.
49. Woolley JD, Wilson MR, Hung E, Gorno-Tempini ML, Miller BL, Shim J. Frontotemporal dementia and mania. *Am J Psychiatry* 2007; 164:1811-1816.
50. Blass DM, Rabins PV. Depression in frontotemporal dementia. *Psychosomatics* 2009; 50:239-247.
51. Horstmann V, Gräsbeck A. Occurrence of depression in families with frontotemporal dementia: a family history study. *Neuroepidemiology* 2009; 33:124-130.
52. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: prevalence and review. *Dement Geriatr Cogn Disord* 2008; 25:206-211.
53. Passant U, Elfgren C, Englund E, Gustafson L. Psychiatric symptoms and their psychosocial consequences in frontotemporal dementia. *Alzheimer Dis Assoc Disord* 2005; 19 (Suppl.1):15-18.
54. Velakoulis D, Walterfang M, Mocellin, Pantelis C, McLean C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: clinicopathological series and review of cases. *Br J Psychiatry* 2009; 194:298-305.
55. Omar R, Sampson EL, Loy CT, Mummery CJ, Fox NC, Rossor MN, Warren JD. Delusions in frontotemporal lobar degeneration. *J Neurol* 2009; 256:600-607.
56. Velakoulis D, Walterfang M, Mocellin R, Pantelis C, Dean B, McLean C. Abnormal hippocampal distribution of TDP-43 in patients with late onset psychosis. *Aust NZJ Psychiatry* 2009; 43:739-745.
57. Duggal HS, Singh I. Frontotemporal dementia presenting with psychotic symptoms. *J Neuropsychiatry Clin Neurosci* 2009; 21:103-104.
58. Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal dementias: a review. *Ann Gen Psychiatry* 2007; 12:6-15.
59. Freedman M. Frontotemporal dementia: recommendations for therapeutic studies, designs, and approaches. *Can J Neurol Sci* 2007; 34 (Suppl.1):118-124.

60. Mendez MF. Frontotemporal dementia: therapeutic interventions. *Front Neurol Neurosci* 2009; 24:168-178
61. Vossel KA, Miller BL. New approaches to the treatment of frontotemporal lobar degeneration. *Curr Opin Neurol* 2008; 21:708-716.
62. Swartz JR, Miller BL, Lesser IM, Darby AL. Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1997; 58:212-216.
63. Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacology* 2004; 172:400-408.
64. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. A randomized, controlled, open 14-month study. *Eur Neurol* 2003; 49:13-19.
65. Ikeda M, Shigenobu K, Fukuhara R, Hokoishi K, Maki N, Nebu A, Komori K, Tanabe H. Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. *Dement Geriatr Cogn Disord* 2004; 17:117-121.
66. Anneser JM, Jox RJ, Borasio GD. Inappropriate sexual behaviour in a case of ALS and FTLD: successful treatment with sertraline. *Amyotroph Lateral Scler* 2007; 8:189-190.
67. O'Brien JT, Burns A. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol* 2010. (in press).
68. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 2004; 17:355-359.
69. Lebert F. Behavioral benefits of trazodone are sustained for the long term in frontotemporal dementia. *Therapy* 2006; 3:93-96.
70. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders>.
71. Bei Hu, Ross L, Neuhaus J, Knopman D, Kramer J, Boeve B, Caselli RJ, Graff-Radford N, Mendez MF, Miller BL, Boxer AL. Off-label medication use in frontotemporal dementia. *Am J Alzheimers Dis Other Demen* 2010; 25:128-133.
72. Fellgiebel A, Müller MJ, Hiemke C, Bartenstein P, Schreckenberger M. Clinical improvement in a case of frontotemporal dementia under aripiprazole treatment corresponds to partial recovery of disturbed frontal glucose metabolism. *World J Biol Psychiatry* 2007; 8:123-126.
73. Curtis RC, Resch DS. Case of Pick's central lobar atrophy with apparent stabilization of cognitive decline after treatment with risperidone. *J Clin Psychopharmacol* 2000; 20:384-385.
74. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: a 24-month follow-up of 68 patients. *Am J Alzheimers Dis Other Demen* 2003; 18:205-214.
75. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in frontotemporal dementia: an open-label study. *Drugs Aging* 2004; 21:931-937.
76. Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, Brashear R. Galantamine in frontotemporal dementia and primary progressive aphasia. *Dement Geriatr Cogn Disord* 2008; 25:178-185.
77. Swanberg MM. Memantine for behavioral disturbances in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord* 2007; 21:164-166.
78. Diehl-Schmid J, Förstl H, Perneczky R, Pohl C, Kurz A. 6-month, open-label study of memantine in patients with frontotemporal dementia. *Int J Geriatr Psychiatry* 2008; 23:754-759.
79. Boxer AL, Lipton AM, Womack K, Merrilees J, Neuhaus J, Pavlic D, Gandhi A, Red D, Martin-Cook K, Svetlik D, Miller BL. An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 2009; 23:211-217.
80. Vercelletto M, Boutoleau-Bretonnière C, Volteau C, Puel M, Auriacombe S, Sarazin M, Couratier P, Thomas-Antérion C, Verpillat P, Gabelle A, Golfier V, Cerato E, Lacomblez L. Memantine in Behavioral Variant Frontotemporal Dementia: Negative Results. *J Alzheimers Dis* 2010; 32:749-759.
81. Goforth HW, Konopka L, Primeau M, Ruth A, O'Donnell K, Patel R, Poprawski T, Shirazi P, Rao M. Quantitative electroencephalography in frontotemporal dementia with methylphenidate response: a case study. *Clin EEG Neurosci* 2004; 35:108-111.
82. Rahman S, Robbins TW, Hodges JR, Mehta MA, Nestor PJ, Clark L, Sahakian BJ. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology* 2006; 1:651-684.
83. Cruz M, Marinho V, Fontenelle LF, Engelhardt E, Laks J. Topiramate may modulate alcohol abuse but not other compulsive behaviors in frontotemporal dementia: case report. *Cogn Behav Neurol* 2008; 21:104-106.