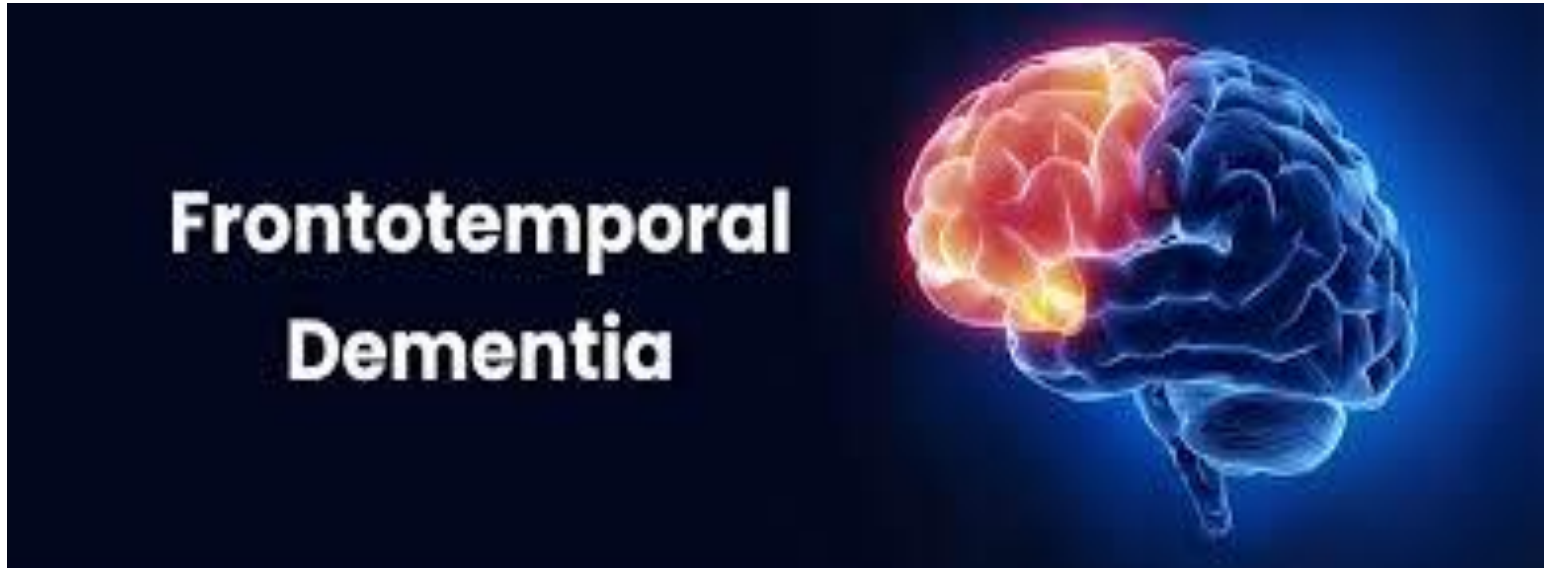

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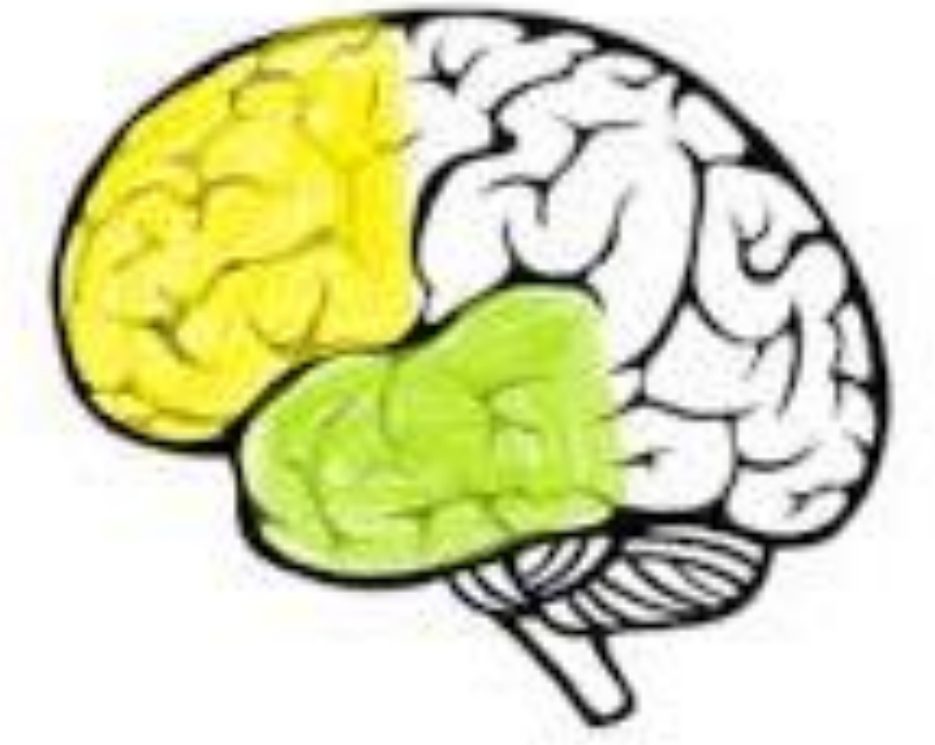
Contents

- Epidemiology
- Types
- Clinical features
- Diagnosis – Lab, Neuropsychological tests, Imaging
- Diagnostic Criteria
- Diagnostic approach and Challenges



EPIDEMIOLOGY

Epidemiology

- FTD is the second or third most common dementia in most meta-analytic studies, after Alzheimer's and dementia with lewy bodies.
- Affects approximately 2-10 per 100,000 people.
- 5% of all cases of dementia.
- The peak age of onset is between ages 45-70
- "presenile" onset compared to other dementias
- 10% of cases have onset before age 45 years
- 60% of cases have onset between 45-64 years
- 30% of cases occur in individuals older than 65 years
- More males are affected than females.

CLASSIFICATION

Histopathological classification

Frontotemporal lobar degeneration (FTLD)

- Refers to the histopathological substrate of FTD.
- The types FTLD-Tau and FTLD-“transactive response DNA-binding protein (TDP-43) are the most common ones.
- FTLD-Tau include several different pathological subtypes (pick, chronic traumatic encephalopathy, CBD, PSP, MAPT gene carriers).
- FTLD- TDP is also found in patients with genetic mutations in GRN,VCP and C9orf72 repeat expansion.
- bvFTD shows either FTLD-tau or FTLD-TDP neuropathology

FTD should be used for clinical descriptions and phenotypes, whereas **FTLD** should be used to describe the histopathological classification and not to refer to the clinical syndrome.

Types of FTD (Phenotypes)

1. Behavioral variant FTD
2. Primary Progressive Aphasia (PPA)
3. FTD overlaps with other tauopathies

The behavioral variant (bvFTD) is the most common phenotypic presentation of FTD.

CLINICAL PRESENTATION

Types of FTD - Behavioral Variant (bvFTD)

- There is relative preservation of recall, and behavior is usually the first change.

Disinhibition

- examples – touching or kissing strangers, public urination,
- flatulence without concern
- Make offensive remarks or invade other's personal space, playing with objects in their surroundings or taking other's personal items

Apathy and loss of empathy

- Losing interest and /or motivation for activities and social relationships
- Caregivers may describe patients as cold or unfeeling toward's others' emotions

Clinical Presentation

Hyperorality

- Hyperorality and dietary changes as altered food preferences such as carbohydrate cravings, sweet foods, binge eating, eating inedible objects, put excessive amounts of food in their mouths that cannot be chewed properly

Compulsive behaviors

- Perseverative, stereotyped or compulsive ritualistic behaviors include stereotypic speech, simple repetitive movements and complex ritualistic behaviors such as checking or cleaning
- Some develop new hobbies or interests, particularly those with a religious aspect, which are pursued obsessively.
- Lack insight into their behavioral changes

Types of FTD - Primary Progressive Aphasia (PPA)

a. Semantic variant primary progressive aphasia (svPPA, or PPA-S)/Temporal Variant)

- Patients have difficulty naming objects, difficulty with single-word comprehension, but speech production is spared along with repetition.
- The core features are impaired single-word comprehension and object naming in the setting of preserved fluency, repetition and grammar
- Word-finding difficulty ,ability to understand single object words is more affected than ability to understand complete sentence.

Types of FTD - Primary Progressive Aphasia (PPA)

b. Non-fluent (agrammatic) variant primary progressive aphasia (nfvPPA or PPA-G/PPA-NF/A)

- Patients are often stumbling for words and grammar is very poor.
- Hallmark is early ,progressive language disturbance leading to functional impairment with relative preservation of episodic memory and other cognitive domains
- Activities of daily living are maintained except those relating to language – effortful halting speech with inconsistent speech-sound errors and distortions and agrammatism in language production
- Memory, visual spatial skills, cognitive abilities are typically preserved at the time of presentation

Types of FTD - Primary Progressive Aphasia (PPA)

c. Logopenic variant primary progressive aphasia (lvPPA or PPA-L)

- usually rare in FTD, and more commonly seen in Alzheimer's.
- Patients have impaired naming and repetition, but grammar and single-word. comprehension is preserved.

Primary Progressive Aphasia (PPA)

Semantic variant primary progressive aphasia
Both of the following core features must be present 1. Impaired object naming 2. Impaired single-word comprehension
Of the following ancillary features, 3 must be present 1. Impaired object knowledge, particularly for low-frequency or low-familiarity items 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared grammaticality and motor aspects of speech
Non-fluent variant primary progressive aphasia
Of the following core features, 1 must be present 1. Agrammatism in language production 2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
Of the following ancillary features, 2 must be present 1. Impaired comprehension of syntactically complex (nonca nonical) sentences 2. Spared single-word comprehension 3. Spared object knowledge

Types of FTD – overlapped with other

FTD overlaps with other tauopathies

- Including progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), ALS.

DIAGNOSIS
Laboratory Investigations

Laboratory investigations

- Metabolic and/or infectious disorders (renal or liver failure, hypothyroidism, neurosyphilis and HIV infection, and so on) that cause neuropsychiatric manifestations can be ruled out through blood tests.
- All suspected cases of FTD (regardless of the phenotypic presentation) should undergo laboratory investigation to screen for reversible causes of cognitive-behavioral decline:

  (blood count, vitamin B12, folic acid, liver, kidney and thyroid functions, protein electrophoresis, and anti-HIV serology)

DIAGNOSIS
CSF Studies

CSF markers

- For patients who undergo lumbar puncture, the investigation of CSF biomarkers (beta-amyloid peptide, CSF AB42, Tau and P-Tau) is useful to rule out AD with a sensitivity and specificity of 80%, in cases of difficult differential diagnosis.
- NFL measurement is useful in differentiating FTD from other non-degenerative conditions such as primary psychiatric disorders.

DIAGNOSIS

Genetic Testing

Genetic Testing

- Most cases of FTD are sporadic. However, in about 40 - 50 %of cases, a family history of dementia is identified.
- In approximately 10 to 15% of patients, an autosomal dominant transmission pattern can be found.
- The most common pathogenic mutations include variants in *MAPT* gene (“microtubule-associated protein tau”), progranulin (*GRN*) gene and the C9orf72 repeat expansion.

DIAGNOSIS
Neuro-psychological Tests

Neuropsychologic Tests

- The Frontal Assessment Battery (FAB) is commonly used as a screening test.
- The Montreal Cognitive Assessment (MoCA) can also be used to screen for early mild cognitive changes.
- Since the Mini-Mental Status Exam (MMSE) does not include an assessment for impaired executive function, it cannot detect changes indicative of FTD.
- Good score on neurophysiologic testing early in the course of the disease.
- Memory and visuospatial functions are usually spared in bvFTD.

Cognitive profiles - AD : FTD

Cognitive domain	AD	Behavioral variant frontotemporal dementia
Episodic memory		
Free recall	+++	+-
Recognition	+++	-
Prompting	X	√
Intrusions	+++	+++
Semantic memory (naming)	++	+

Cognitive profiles - AD : FTD

Cognitive domain	AD	Behavioral variant frontotemporal dementia
Procedural memory	-	-
Working memory	++	+++
Insight	+++	+++
Attention	++	++
Executive functions	++ typical AD +++ frontal variant	+++
Visuospatial skills	++ typical AD +++ PCA	-

+++ Early and severe impairment
++ Moderate impairment
+ Mild impairment

AD : Alzheimer's disease, PCA : Posterior cortical atrophy

Cognitive profiles - AD : FTD

- Individuals with FTD have similar impairments in both **semantic** (i.e. - naming animals) and **letter fluency tasks** (i.e. - naming as many words as they can that start with the letter 'F') , due to frontal lobe retrieval deficits.

- On the other hand, patients with Alzheimer's disease are more impaired in **semantic than the letter fluency tasks** (consistent with impaired access to semantic information due to involvement of the temporal lobes instead)

DIAGNOSIS
Neuroimaging

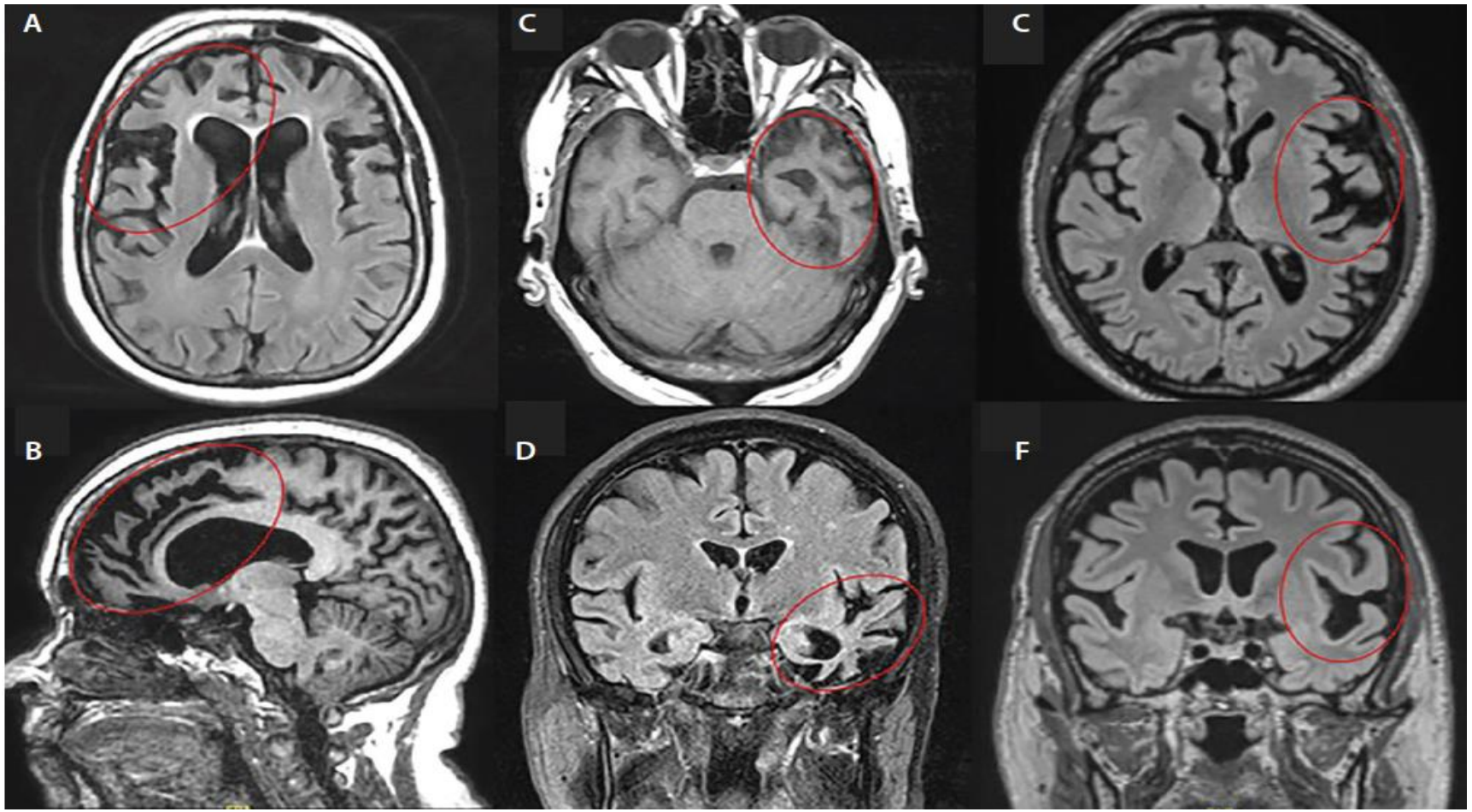
Neuroimaging

- A CT head or MRI head can show patterns of atrophy of the frontal lobes that can aid in the clinical diagnosis.

Variant	**Neuroimaging Findings**
Behavioral variant	**Both** frontal lobes (in particular the medial frontal lobes) and anterior temporal lobes have atrophy
Semantic variant	Middle, inferior, and anterior temporal lobes are atrophic bilaterally but asymmetrically, with the **left** side usually being more affected
Logopenic variant	Associated with predominantly **left** posterior perisylvian or parietal atrophy
Non- fluent variant	Associated with predominantly **left** posterior frontal-insular atrophy

Structural MRI in frontotemporal dementia (FTD) syndromes.

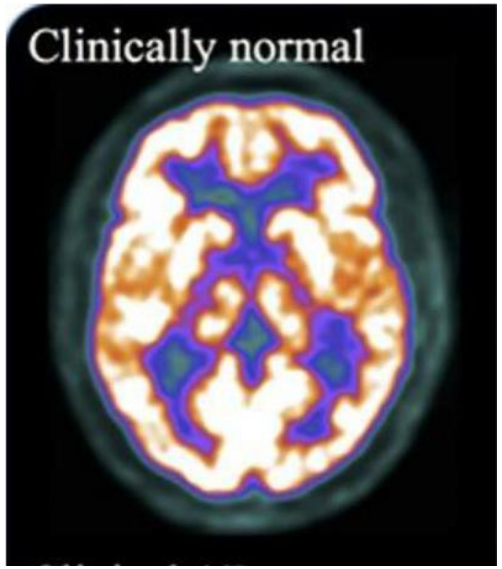
- In behavioral variant FTD (bvFTD), right frontal atrophy is characteristic (A), with relative sparing of posterior structures (B).
- In semantic variant primary progressive aphasia (svPPA) there is left anterior temporal atrophy (C, D)
- In nonfluent agrammatic variant primary progressive aphasia have degeneration in the inferior frontal gyrus and adjacent structures (E, F).

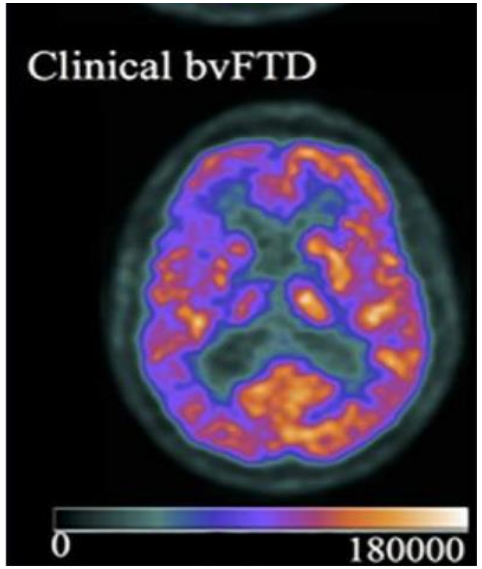


Neuroimaging (Functional Imaging)

- frontotemporal hypometabolism on ^{18}F-FDG-PET

- fluorodeoxyglucose (FDG)-PET has better sensitivity/specificity than structural MRI





uniform uptake throughout the brain as illustrated by the widespread intense bright colors.

asymmetric frontal and temporal hypometabolism in a person with bvFTD

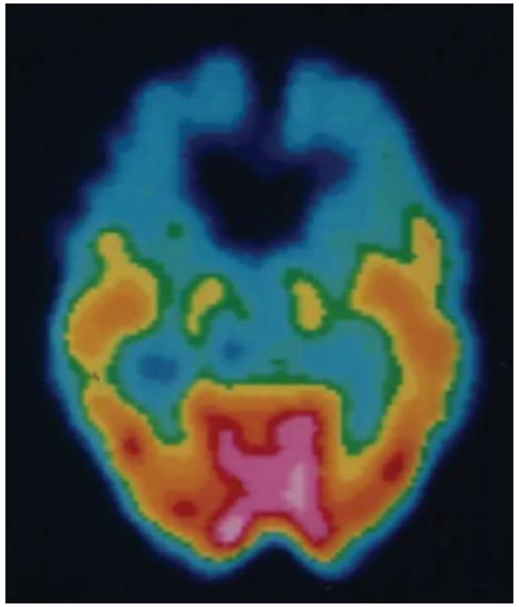
Ann Clin Transl Neurol. 2016 Aug 30;3(10):740–751.)

Neuroimaging (functional imaging)

- brain SPECT, amyloid, and tau PET are not as frequently utilized in clinical practice compared to MRI and FDG-PET.

- FTD findings in ^{99m}Tc-HMPAO-SPECT include bilateral hypoperfusion that targets the frontal lobes, with asymmetric hypoperfusion of the right frontal lobes.

- amyloid-PET imaging typically has no tracer retention in patients with FTD, negative amyloid PET rules out AD.



SPECT

MANAGEMENT

Management

- There are no approved treatments for FTD. All current treatments are thus off-label and used to manage symptoms of the disease, primarily behavioural symptoms.
- Antidepressants as a class have been shown to lead to some behavioural improvement.
- Behavioural Symptoms

For behavioural symptoms (such as disinhibition, impulsivity, repetitive behaviors and eating disorders) may respond to antidepressant class medications (response is thought to be due to loss of serotonergic neurons in FTD)

  - Trazodone has very good evidence for the treatment of behavioral symptoms related to FTD
  - Selective serotonin reuptake inhibitors such as Citalopram, fluoxetine and sertraline

Management

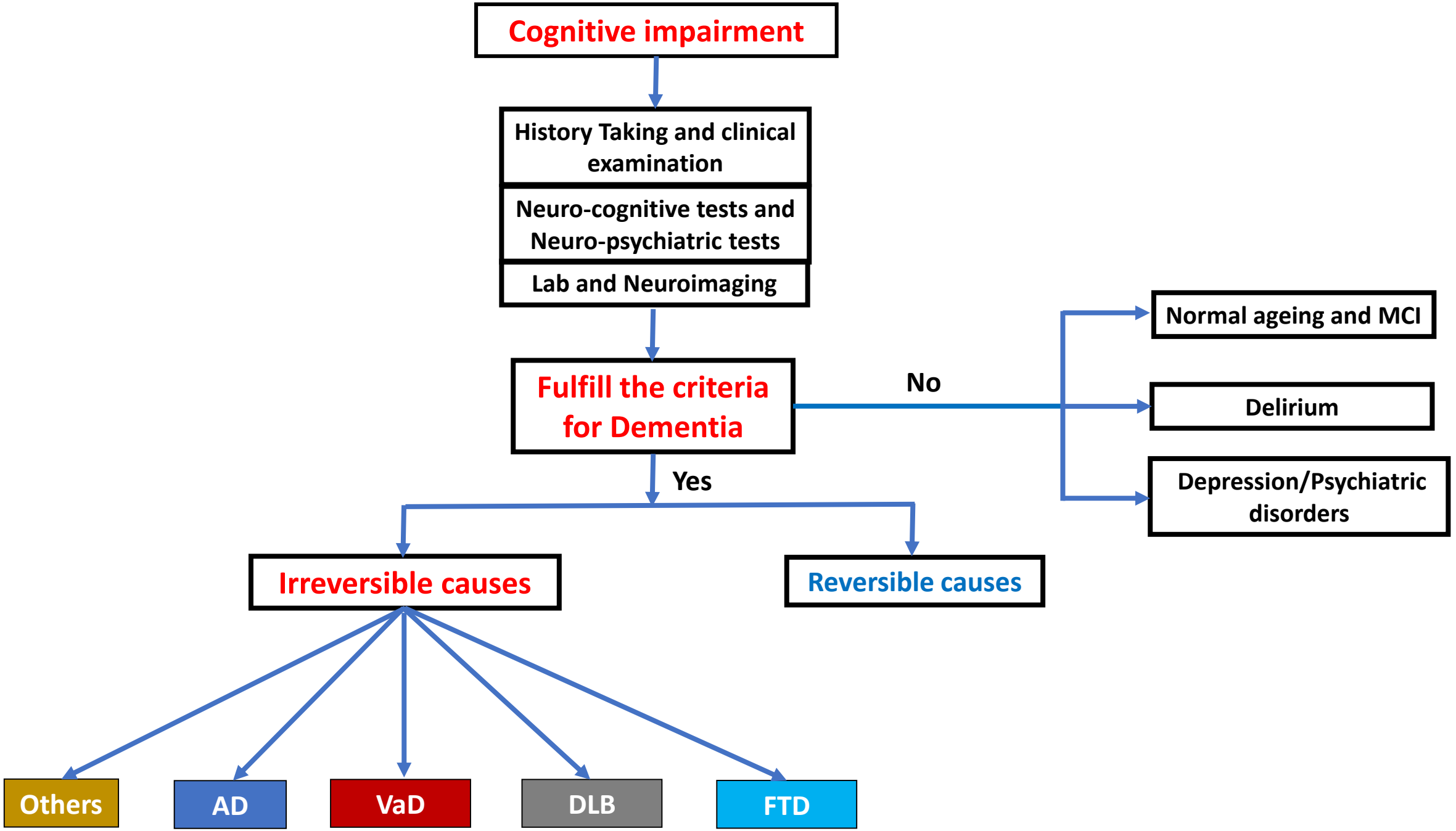
- Antipsychotics and anti-epileptics have also been shown to be effective in the management of behavioural symptoms but are limited in use due to their side effect profile.
- It is very important to rule out potential triggers for behavioural disturbances such as infections, electrolyte changes, medical issues, and environmental stressors prior to initiating psychotropic medications.
- Memantine is not effective.

Treatment approaches for behavior symptoms in FTD

Symptom	Current treatment options	Evidence for current treatments
Behavioral disinhibition	SSRIs (eg, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram); trazodone; and atypical antipsychotics (eg, risperidone, aripiprazole, olanzapine, quetiapine)	Open-label studies supporting use of SSRIs; double-blind, placebo-controlled study supports trazodone use
Perseverative behavior	SSRIs (eg, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram) and trazodone	
Hyperorality		
Symptom	**Future directions for symptoms without existing treatment**	
Apathy	Dopaminergic medications	
Loss of empathy	Oxytocin	
Executive dysfunction	Dopaminergic medications	
Neuroprotective	Prevention of tau hyperphosphorylation/ accumulation, increase progranulin levels, reduce C9ORF72 expanded repeat dipeptide production	

Abbreviations: SSRIs, selective serotonin reuptake inhibitors.

DIAGNOSIS PROCESS


Cognitive impairment
History Taking and clinical examination
Neuro-cognitive tests and Neuro-psychiatric tests
Lab and Neuroimaging
Fulfill the criteria for Dementia
No
Normal ageing and MCI
Delirium
Depression/Psychiatric disorders
Yes
Irreversible causes
Reversible causes
Others
AD
VaD
DLB
FTD

DSM5 Diagnostic Criteria for Dementia (Major & Mild Neurocognitive Disorders)

1. Major Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition)

B. The cognitive deficits interfere with independence in everyday activities

C. The cognitive deficits do not occur exclusively in the context of a delirium

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

2. Mild Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

B. The cognitive deficits do not interfere with capacity for independence in everyday activities

C. The cognitive deficits do not occur exclusively in the context of a delirium

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

DSM-5 Diagnostic Criteria of FTD

Criterion A

The criteria are met for major or mild neurocognitive disorder

Criterion B

The disturbance has insidious onset and gradual progression.

Criterion C - Either (1) or (2);

1.Behavioural variant

a. 3 or more of the following behavioral symptoms:

- Behavioral disinhibition
- Apathy or inertia
- Loss of sympathy or empathy
- Perseverative, stereotyped or compulsive/ritualistic behavior
- Hyperorality and dietary changes

b. Prominent decline in social cognition and/or executive abilities

2.Language variant

a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

Probable frontotemporal neurocognitive disorder

- if either of the following is present;

1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing.
2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging.

Possible frontotemporal neurocognitive disorder

If there is no evidence of a genetic mutation, and neuroimaging has not been performed.

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis

- **Primary psychiatric disorders**
  - Late-life depression
  - Late-onset psychosis or schizophrenia
  - Late-onset bipolar disorder
- **Neurodegenerative disorders**
  - Phenocopy syndrome of behavioural variant frontotemporal dementia
  - Alzheimer’s disease
  - Progressive supranuclear palsy (PSP)
  - Corticobasal degeneration (CBD)
  - Creutzfeldt-Jakob disease

Diagnostic Challenges & Approach

Challenges in diagnosis of FTD

- Complex clinical phenotype and its insidious presentation, especially in cases with non-specific behavioral features and without brain atrophy
- Several diagnostic barriers

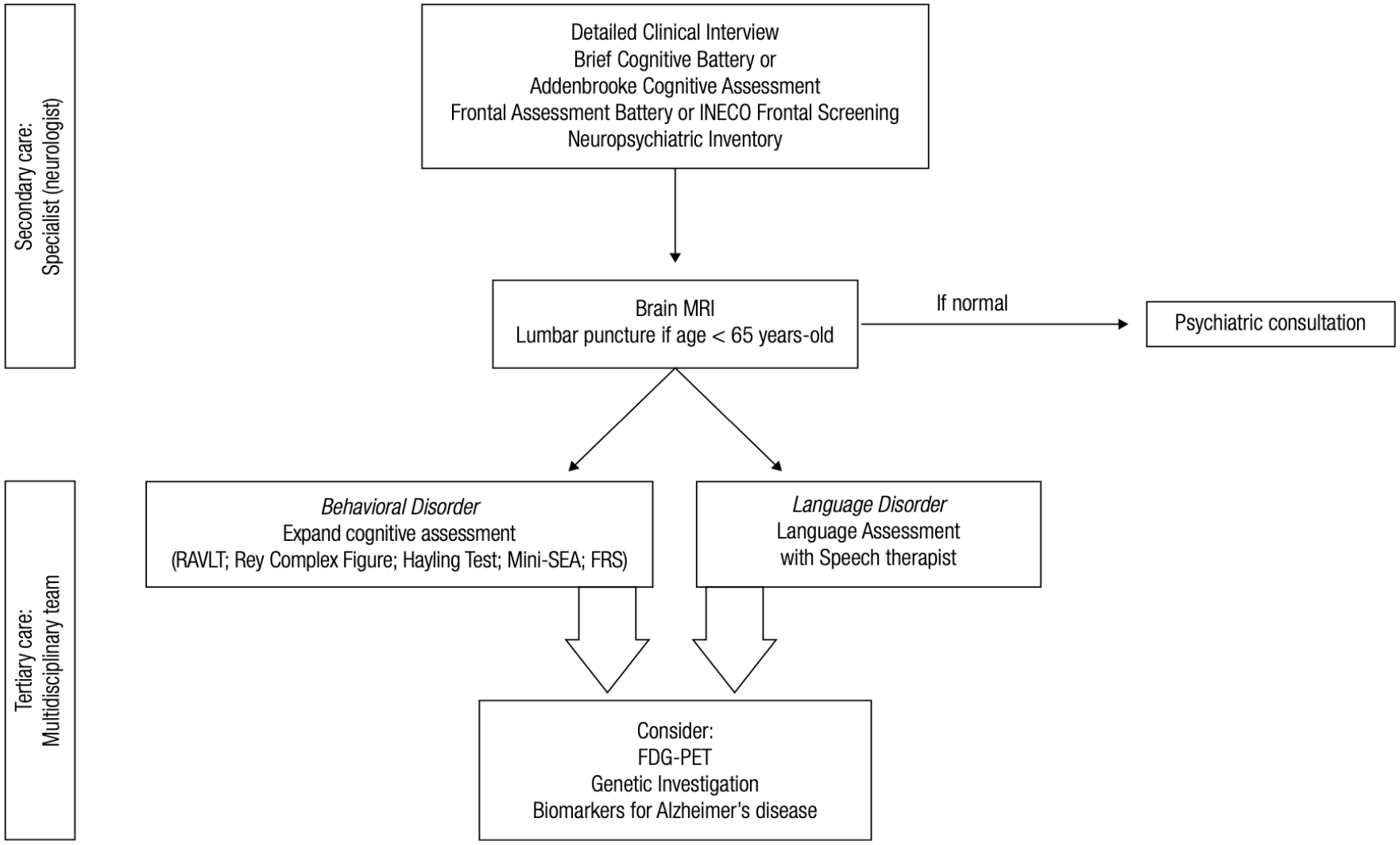
(i) The heterogeneity of FTD, whose clinical features frequently overlap with other neurological e.g., the behavioral/dysexecutive variant of AD or psychiatric disorders

(ii) Lack of knowledge and training of health professionals

(iii) Limited access to medical care, neuropsychological evaluations, and advanced neuroimaging facilities to support FTD diagnosis

(iv) Lack of validated instruments for the population that is capable of detecting and differentiating FTD from other pathologies.

Diagnostic Algorithm



Adapted from Dement Neuropsychol 2022 September;16(3 Suppl.1):36-48

Secondary level

Clinical assessment

At the secondary level, the patient will be evaluated by a neurologist.

- carry out a thorough history and neurological examination.
- look for
    - signs of parkinsonian syndrome,
    - changes in gaze (conjoined down-gaze palsy), which may evoke progressive supranuclear palsy.
    - signs of asymmetric muscle atrophy,
    - fasciculations and pyramidal signs (Babinski and Hofmann signs) should be looked for to identify signs of motor neuron disease.
    - presence of primitive signs (grasping, glabellar, snouting) that suggest severe frontal involvement.

Secondary level – Cognitive and behavioral assessment

Cognitive and Behavioral Assessment

- Brief Cognitive Screening Battery (BBRC) is recommended. The BBRC includes the Figure Memory Test, which requires naming and recalling ten figures to assess episodic memory. In this battery, executive functions are investigated with the Animal Verbal Fluency Test and the Clock Drawing Test.
- The Addenbrooke Cognitive Examination – Revised (ACE-R) is also an excellent tool for the global assessment of cognition.
- The Frontal Assessment Battery (FAB) and the INECO Frontal Screening (IFS) can identify executive dysfunction and help detect patients with bvFTD.
- The short version of the Neuropsychiatric Inventory (NPI), the NPI-Q, can be used in the investigation of neuropsychiatric symptoms. The NPI-Q can detect the behavioral symptoms of bvFTD.
- The Frontal Behavioral Inventory can also be used.

Cognitive and behavioral assessments at Tertiary Level

Behavioral variant (bvFTD)

- Verbal episodic memory – Rey Auditory-Verbal Learning Test. Scores within the expected range for age and education, or minor impairment, may be compatible with a diagnosis of bvFTD;
- Visual episodic memory – Rey Complex Figure. which requires the individual to copy a complex geometric figure, which is later drawn using visual memory.
- Attention and Executive Functions – Trail Making Test A and B assess visual attention and shifting. respectively: Wechsler Adult Intelligence Scale (WAIS-III) Forward and Backward Digit Span Test assess auditory attention and working memory. respectively; Wisconsin Card Sorting Test assesses working memory and mental flexibility.
- Inhibitory Control – The Hayling Test assesses the individual's ability to complete sentences with words that make sense or with words that prevent the logical sense of the sentence.

Cognitive and behavioral assessments at Tertiary Level

- Processing Speed – WAIS-III Digit Symbol Substitution test assesses visual attention and processing speed,
- Visuospatial Functions – Rey Complex Figure. The copy of the figure can be used as a parameter to assess planning and visuoconstructive skills;
- Language – the Boston Naming Test assesses the ability to perceive, interpret and name 60 common figures.
- Social cognition - Facial Emotion Recognition Test (FERT) and the *Faux-Pas* Test (which assesses theory of mind) are useful in the differential diagnosis between bvFTD and AD

Cognitive and behavioral assessments at Tertiary Level

- The Frontotemporal Dementia Rating Scale (FRS) is a useful scale for staging the disease.
- For behavioral changes, the Frontal Behavioral Inventory (FBI) is useful in the differential diagnosis between bvFTD and other dementias and has good psychometric properties.

Linguistic variants (PPA-NF/A and PPA-S)

- The investigation and characterization of language and speech impairments should encompass both spontaneous conversation and the testing of specific language skills, including phonological, lexical/semantic and syntactic levels.

SUMMARY

Summary

- FTD is a common cause of early onset dementia.
- FTD is clinically and neuropathologically heterogeneous disorder characterized by disturbances in behavior, personality and language with focal degeneration of frontal and or temporal lobes.
- Genetic factor association is present.
- Mainly 2 subtypes – bvFTD and PPA

Summary

- Diagnosis
  - diagnosis of different variants of FTD is mainly based on clinical history and the assessment of cognitive, linguistic and behavioral aspects.
  - Complementary tests (neuro- psychological tests, Functional neuroimaging) provide valuable information to support the diagnosis and to rule out causes that may be similar to FTD conditions.
  - The advent of new biological markers may provide greater diagnostic accuracy in the future.
- Late diagnosis is still the biggest challenge especially in the resource limited settings.
- No specific pharmacological option exists although SSRI may have modest benefits.


Thank You!