WITHDRAWN: Frontotemporal Dementia: A systematic review

Samar Khalifa (samarkhalifa@hotmail.com)
Kafrelsheikh University https://orcid.org/0000-0002-0759-4556

Systematic Review

Keywords: Frontotemporal Dementia, Frontal lobe, Temporal lobe, Dementia

Posted Date: December 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1156339/v1

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background:

Frontotemporal dementia is a common type of dementia and is a group of progressive neurodegenerative syndromes usually caused by the accumulation of pathological tau or TDP-43 proteins. The review is identifying the clinical measures including neuropsychological scores and functional measures.

Methods:

A systematic review was conducted covering the clinical trials done to investigate the Frontotemporal Dementia. The sample was taken from Pubmed library. 28 results were found in a range of time from 2016 to 2021. The excluded papers were 17.

Results:

A total of 10,349 articles were identified at the first stage of papers selecting. All records were screened in order to include and exclude by title/abstract and then based on full text. After excluding articles by year and type of papers, a total of 28 articles were identified through the databases. Following this, the irrelevant papers from databases were removed from original articles, and finally 11 articles were included based on their title/abstract. Full articles were then sourced for about 600 references. It included 732 patients and 195 controls as a total.

Conclusions:

The review describes the clinical and RCT trials for FTD in the last five years so it can be very updated information for the researchers to cover information required for their researches in the future ones.

Introduction

Frontotemporal Dementia (FTD) tends to start at a younger age than 65 in the contrary to general Dementia. Most cases are diagnosed in people aging 45-65, although it can also affect younger or older people [1]. Frontal and temporal lobes are affected in case of frontotemporal dementia with progressive syndromes caused by the accumulation of TDP-43 proteins [2]. Symptoms of FTD includes personal and behavioral changes as impulsivity and loss of motivation, language problems as speaking slowly, and mental abilities and memory problems [1].

FTD was studied in a longitudinal multimodal imaging and clinical endpoints clinical trials. Most imaging studies in frontotemporal dementia have been cross-sectional, and few have compared longitudinal changes in cortical volume with changes in other measures such as perfusion and white matter integrity. The goal of the study was to study stated longitudinal changes in 161 patients with three frontotemporal dementia syndromes: behavioral variant frontotemporal dementia (n = 77) and the semantic (n = 45) and non-fluent (n = 39) variants of primary progressive aphasia. Visits included comprehensive neuropsychological and functional assessment, structural MRI (3 T), diffusion tensor imaging, and arterial spin labelled perfusion imaging. identify measures that are appropriate as clinical trial outcomes for each group, as well as those that might be appropriate for trials that would include more than one of these groups [2].

Imaging changes were significantly correlated with the change in most clinical measures. Perfusion and diffusion tensor imaging accounted for variation in clinical decline beyond volume alone. Corpus callosal fractional anisotropy led to the least sample size estimates for all three syndromes. These findings provide further guidance on selection of trial endpoints for studies in frontotemporal dementia and support the use of neuroimaging, particularly structural and diffusion weighted imaging, as biomarkers. Diffusion and perfusion imaging appear to offer additional utility for explaining clinical change beyond the variance explained by volume alone, arguing for considering multimodal imaging in treatment trials [2].

A study was conducted using blood fluids of FTD patients as they have been analyzed using conventional lipid assays based on enzymes, and these have shown that triglyceride (TG) levels are increased in FTD compared to controls. Global lipid analysis has also shown that TG levels are increased in FTD compared to controls, along with changes in other lipids. The study undertook lipidomics analysis of FTD serum to investigate three key aspects of FTD pathophysiology relevant to neurodegeneration: mitochondrial dysfunction, inflammation, and oxidative stress. It analyzed cardiolipin and acylcarnitine, both of which are involved in mitochondrial energy production. Individuals diagnosed with bvFTD (N = 40) and healthy controls (N = 22) were recruited at Neuroscience Research Australia in Sydney from FRONTIER, the frontotemporal dementia clinical research group, and from a panel of healthy study volunteers [3].

Frozen post-mortem brain tissue samples were obtained from Sydney Brain Bank and NSW Brain Tissue Resource Centre following appropriate ethical approvals (University of New South Wales Human Research Ethics approval number: HC15789). Frozen samples from the superior frontal cortex from 10 FTD cases, 10 AD cases and 11 controls without neurological, psychiatric or neuropathological diagnoses were used in this study. The mean age of the three groups were 72.9 ± 13.0, 73.7 ± 7.5 and 79.5 ± 12.1 years, respectively [3].

Statistical analyses were performed using SPSS Statistics software (IBM, Chicago, Illinois). For comparisons between FTD and control groups, either univariate analysis (general linear model) or Student's t-test was used and statistical significance set at $p < 0.05$. When univariate analysis was performed, age

and gender were included as covariates. Pearson's correlations were used to determine if changes in lipid levels were associated with each other with statistical significance set at $p < 0.05$. Graphs were generated using GraphPad Prism 7 [3].

The Tailored Activity Program is an occupational therapy based intervention that involves working collaboratively with family carers (dyads) and prescribes personalized activities for behavioral management in people with dementia. Twenty dyads randomized into the study (Tailored Activity Program: $n = 9$; Control: $n = 11$) were assessed at baseline and 4-months [4]. Qualitative analyzes evaluated feasibility and acceptability of the program for the frontotemporal dementia cohort, and quantitative analyzes (linear mixed model analyzes, Spearman's rho correlations) measured the impact of the program on the dyads [4].

Previous research has proved that odor identification is impaired in the frontal variant of FTD. According to the Spanish Law 14/2007 of Biomedical Research, inform written consent forms of the Neurological Tissue Bank of Navarra Health Service, Brain Bank of IDIBELL, and Neurological Tissue Bank of IDIBAPS-Hospital Clinic (Barcelona, Spain) was obtained for research purposes from relatives of patients included in this study. The study was conducted in accordance with the Declaration of Helsinki and all assessments, post-mortem evaluations, and procedures were previously approved by the Clinical Ethics Committee of Navarra Health Service. For the proteomic phase, 4 FTLD-TDP43 and 4 FTLD-Tau (PSP) cases were analyzed. Four cases from elderly subjects with no histological findings of any neurological disease were used as a non-FTD group. All human brains considered in the proteomic study had a post-mortem interval (PMI) lower than 16 h. Proteomics was complemented with a follow-up phase in which protein changes and activation dynamics where checked by Western-blotting across all samples included in the study ($n = 27$ OB samples) [6].

Another study was conducted to determine whether intranasal oxytocin, alone or in combination with instructed mimicry of facial expressions, would augment neural activity in patients with frontotemporal dementia (FTD) in brain regions associated with empathy, emotion processing, and the simulation network, as indexed by blood oxygen-level dependent (BOLD) signal during fMRI [7].

A study was done to determine the effect of tolcapone, a specific inhibitor of Catechol-O-Methyltransferase (COMT), in patients with bvFTD. The most frequent treatment-related adverse event during tolcapone treatment was elevated liver enzymes (21%). There were no significant differences between tolcapone treatment and placebo in the primary or imaging outcomes [5].

Another study was conducted to compare hydromethylthionine treatment effects at two doses and to determine how drug exposure is related to treatment response in bvFTD. A population pharmacokinetic exposure-response analysis was undertaken in 175 of the patients with available blood samples and outcome data using a discriminatory plasma assay for the parent drug [8].

Behavioural variant frontotemporal dementia (bvFTD) is a form of frontotemporal degeneration characterized by early changes in personality, emotional blunting, and/or loss of empathy. Recent research has highlighted that these features may be at least partially explained by impairments in the theory of mind. A study applied anodal tDCS over the MFC (Fpz site, with the cathode between Oz and Inion) to modulate ToM performance in bvFTD patients. We used an adapted version of a ToM task, measuring the ability to represent other people's private and communicative intentions from the observation of their daily actions. Three out of the 16 patients had monogenic FTD [10].

In order to study the brain networks oscillations in bvFTD, some collaborators used a promising new connectivity measure called Weighted Symbolic Mutual Information (wSMI). In particular, this method proves more sensitive than previous approaches to EEG connectivity (phase-locking value, phase-lag index, and power spectral densities) used to evaluate network abnormalities in other pathological samples. Moreover, wSMI has already proven sensitive to detect aberrant networks in other neurodegenerative conditions. Instead of measuring basic oscillatory correlations, wSMI assesses the non-linear coupling of information sharing among distant networks [9].

The last study describes a novel adaptive proof-of-concept, phase 2, placebo-controlled, randomized crossover trial repurposing the hormone and neuropeptide oxytocin as a potential symptomatic treatment for apathy/indifference and related empathy deficits in patients with FTD. The objectives of the study design are to (1) efficiently identify the most promising dose schedule of oxytocin, given potential habituation to daily dosing, and (2) permit efficacy analysis of the most promising dose compared with placebo to determine whether progression to a phase 3 trial is warranted. We propose that this approach may inform the design and conduct of other RCTs, particularly of symptomatic medications in FTD and related neuropsychiatric disorders [11].

Methods

The methodology to perform this systematic review was developed according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines. A systematic review was conducted covering the clinical trials done to investigate the Frontotemporal Dementia. The sample was taken from Pubmed library. 28 results were found in a range of time from 2016 to 2021. The excluded papers were 17.

Inclusion criteria:

The review included only clinical trials and randomized controlled trials.

Exclusion criteria:

The review excluded systematic reviews, meta-analysis, books and documents.

The following data were extracted:

1. Publication details: authors and year of publication;

2. Study design: type of study (clinical trials);

3. Participants: number of participants, and participant demographic characteristics (including age greater or equal to 65 years and gender);

4. Diagnosis information;

5. Clinical features;

6. Treatment.

Outcome:

The outcome of the review is covering the clinical trials about FTD updated on the widest range databased library Pubmed in the last five years. It allows the reader to collect the required data for the research about FTD and its concerns in the latest research done the last half decade.

Data Synthesis:

As there were no RCT or quasi-experimental observational studies available in this area, a meta-analysis was not conducted, nor was it possible to examine measures of treatment effects, as all the studies reviewed were case studies. Data were synthesized by a narrative approach.

PRISMA Flow Chart:

(Fig. 1: PRISMA Flow Chart)

Demographic data table:

Study details (author, year) Study type	Age (gender)	Diagnosis	Clinical features	Treatment	Outcome
(Adam M Staffaroni, Peter A Ljubenkov, John Kornak, Yann Cobigo, Samir Datta, Gabe Marx, Samantha M Walters, Kevin Chiang, Nick Olney, Fanny M Elahi, David S Knopman, Bradford C Dickerson, Bradley F Boeve, Maria Luisa Gorno-Tempini, Salvatore Spina, Lea T Grinberg, William W Seeley, Bruce L Miller, Joel H Kramer, Adam L Boxer, and Howard J Rosen, 2019) Clinical trial	Mean=64.4 years, controls = 63.41 years. (NA)	pathological or Alzheimer's disease biomarker data (n = 109), autopsy diagnosis (n = 34), amyloid imaging results (n = 53), or CSF results in those without autopsy or amyloid imaging results (n = 22).	Neuroimaging acquisition and analysis, Biomarkers and pathological analysis.	NA	Results confirm previous work (Knopman et al., 2008; Schubert et al., 2016; Ramanan et al., 2017); however, showing that behavioral variant bvFTD patients experience reliable decline in many domains of cognition, and that functional measures currently provide the best metric for tracking change in this syndrome.
Katherine Phan, Ying He, Russell Pickford, Surabhi Bhatia, Jared S. Katzeff, John R. Hodges, Olivier Piguet, Glenda M. Halliday, and Woojin Scott Kim, 2020) Clinical trial	Mean= 65 ± 8 years, controls= 71 ± 5 years. (NA)	Triglycrine TG was significantly increased in FTD serum /compared to controls, and Phosphatidylethanolamine PE was unaltered, Increased oxidative stress in FTD.	HPLC- MS and LipidSearch software.	NA	This is a relation between arising of some blood serums as TG and PE ,and FTD.
(Claire M O'Connor, Lindy Clemson, Henry Brodaty, Lee-Fay Low, Yun-Hee Jeon, Laura N Gitlin, Olivier Piguet, Eneida Mioshi, 2019) RCT	NA	Identified five themes: "carer perceived benefits", "carer readiness to change", "strategies used by carer to engage person with dementia", "barriers to the Tailored Activity Program uptake/implementation", and "person with dementia engagement". Quantitative outcomes showed an overall reduction of behavioral symptoms ($F_{18.34}$ = 8.073, p = 0.011) and maintenance of functional performance in the person with dementia ($F_{18.03}$ = 0.375, p = 0.548).	Qualitative analyzes cohort, and quantitative analyzes (linear mixed model analyzes, Spearman's rho correlations).	NA	There is a relation between activity based intervention and FTD.
(Mercedes Lachén-Montes, Andrea González-Morales, Domitille Schvartz, María Victoria Zelaya, Karina Ausin, Joaquín Fernández-Irigoyen, Jean Charles Sánchez, Enrique Santamaría, 2019) Clinical trial	Mean=78.3 years, controls=79.6 years. (NA)	Strong disarrangement in the OB proteostasis during AD and PD progression.	Reduction, alkylation, digestion and TMT labeling, Off-gel electrophoresis, LC-MS/MS, Protein identification, Protein quantification, Bioinformatics, Western-blotting, Statistical analysis.	NA	Molecular findings in PSP and FTLD-TDP43 are in agreement with the clinically mild olfactory deficit described for these two neurological disorders.
(Lindsay D Oliver, Chloe Stewart, Kristy Coleman, James H Kryklywy, Robert Bartha, Derek G V Mitchell, Elizabeth C Finger, 2020) RCT	NA	Oxytocin alone and in combination with instructed mimicry increased activity in regions of the simulation network and in limbic regions associated with emotional expression processing.	Placebo-controlled, randomized crossover design, fMRI.	NA	provides Class III evidence that a single dose of 72 IU intranasal oxytocin augments BOLD signal in patients with FTD during viewing of emotional facial expressions.

(Table.1: Demographic data table)

Study details (author, year) Study type	Age (gender)	Diagnosis	Clinical features	Treatment	Outcome
(Rachel Fremont, Masood Manoochehri, Nicole M Armstrong, Venkata S Mattay, Jose A Apud, Mary C Tierney, D P Devanand, Yunglin Gazes, Christian Habeck, Eric M Wassermann, Jordan Grafman, Edward D Huey, 2020) Clinical trial	NA	Tolcapone was well tolerated and no patients dropped out.	randomized, double-blind, placebo-controlled, cross-over study at two study sites, BOLD, fMRI. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Neuropsychiatric Inventory-Questionnaire (NPI-Q), and Clinical Global Impressions scale (CGI).	Tolcapone treatment.	no significant differences between tolcapone treatment and placebo in the primary or imaging outcomes. there were significant Differences between RBANS total scores ($p < 0.01$), NPI-Q total scores ($p = 0.04$), and CGI total scores ($p = 0.035$) between treatment conditions which were driven by differences between baseline and tolcapone conditions. Further, there was a trend toward significance between tolcapone and placebo on the CGI ($p = 0.078$).
(Helen Shiells, Bjoern O. Schelter, Peter Bentham, Thomas C. Baddeley, Christopher M. Rubino, Harish Ganesan, Jeffrey Hammel, Vesna Vuksanovic, Roger T. Staff, Alison D. Murray, Luc Bracoud, Damon J. Wischik, Gernot Riedel, Serge Gauthier, Jianping Jia, Hans J. Moebius, Jiri Hardlund, Christopher M. Kipps, Karin Kook, John M.D. Storey, Charles R. Harrington, and Claude M. Wischik, 2020). RCT	Mean=63.1, Controls=63.6. (NA)	Patients had been diagnosed with bvFTD for almost 2 years on average (median, 1.1 years; ranging up to 17.6 years). Severity of frontotemporal atrophy was predominantly Kipps stages 2 or 3 (82.3%) with 17.7% at Kipps stage 4.	52-week Phase III, randomized, controlled, double-blind, parallel-group trial.	Hydromethylthionine treatment.	There were no significant differences between the two doses as randomized. There were steep concentration-response relationships for plasma levels in the range 0.3–0.6 ng/ml at the 8 mg/day dose on clinical and MRI outcomes. There were significant exposure-dependent differences at 8 mg/day for FAQ, Modified-CGIC, and whole brain atrophy comparing patients with plasma slevels greater than 0.346 ng/ml with having minimal drug exposure. The exposure-response is biphasic with worse outcomes at the high concentrations produced by 200 mg/day.

(Table.1: Demographic data table)

Study details (author, year) Study type	Age (gender)	Diagnosis	Clinical features	Treatment	Outcome
(Maria Cotelli, Mauro Adenzato, Valentina Cantoni, Rosa Manenti, Antonella Alberici, Ivan Enrici, Alberto Benussi, Valentina Dell'Era, Elisa Bonetta, Alessandro Padovani &Barbara Borroni, 2018) RCT	*N* = 16, four males, age = 67.7 ± 7 years= 67.7 ± 7 years.	The bvFTD group was slower than the HC group.	Randomized, double-blind, sham-controlled study.	NA	Significant contribution to the emergent domain of investigation that uses tDCS to improve social cognition and to treat neuropsychiatric disorders.
(Martin Dottori, Lucas Sedeño, Miguel Martorell Caro, Florencia Alifano, Eugenia Hesse, Ezequiel Mikulan, Adolfo M García, Amparo Ruiz-Tagle, Patricia Lillo, Andrea Slachevsky, Cecilia Serrano, Daniel Fraiman, Agustin Ibanez, 2017) Clinical trial	Mean=69.31,Controls=70.40 (NA)	bvFTD patients presented reduced information sharing between left frontal and temporal ROIs ($p = 0.04$), and between right frontal and temporal ROIs ($p = 0.02$) (Fig. 1B), with large effect size as shown by Cohen's *d* index: 0.98 and 1.11, respectively. No significant connectivity differences emerged between the other ROIs	Neuropsychological tests, EEG, disease control group.	NA	The seed analysis revealed connectivity alterations involving frontal hubs, namely, between the right frontal ROI and contralateral frontal regions. This pattern remained after FDR correction.
(Flora T Gossink, Annemieke Dols, Welmoed A Krudop, Sietske A Sikkes, Cora J Kerssens, Niels D Prins, Philip Scheltens, Max L Stek, Yolande A L Pijnenburg, 2016) RCT	NA	NA	MINI-International Neuropsychiatric Interview, Longitudinal multicenter study.	NA	Define frequency and character of DSM-IV psychiatric disorders among patients with probable and definite bvFTD compared to possible bvFTD, other neurodegenerative diseases, and psychiatric diagnoses, using MINI-International Neuropsychiatric Interview.

(Table.1: Demographic data table)

Study details (author, year) Study type	Age (gender)	Diagnosis	Clinical features	Treatment	Outcome
(Elizabeth Finger, Scott Berry, Jeffrey Cummings, Kristy Coleman, Robin Hsiung, Howard H Feldman, Adam Boxer, 2018) Clinical trial	NA	The simulations assumed an SD of 3.3 between the placebo and active arms (based on prior published studies of mean differences and SD on the NPI for an individual patient).	placebo-controlled, randomised crossover trial.	NA	a sample of 20 patients per arm per sex provides power of 80% to detect a 1-point difference.

(Table.1: Demographic data table)

Results

A total of 10,349 articles were identified at the first stage of papers selecting. All records were screened in order to include and exclude by title/abstract and then based on full text. After excluding articles by year and type of papers, a total of 28 articles were identified through the databases. Following this, the irrelevant papers from databases were removed from original articles, and finally 11 articles were included based on their title/abstract. Full articles were then sourced for about 600 references. It included 732 patients and 195 controls as a total.

Conclusions

This is the first systematic review that covers the clinical trials and the randomized controlled trials in the last five years on Pubmed library. The review describes the clinical and RCT trials for FTD in the last five years so it can be very updated information for the researchers to cover information required for their researches in the future ones.

Declarations

I declare that the review has been composed by myself and that the work has not be submitted for any other degree or professional qualification or journal.

Competing interests: the author declares no competing interests

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Figures

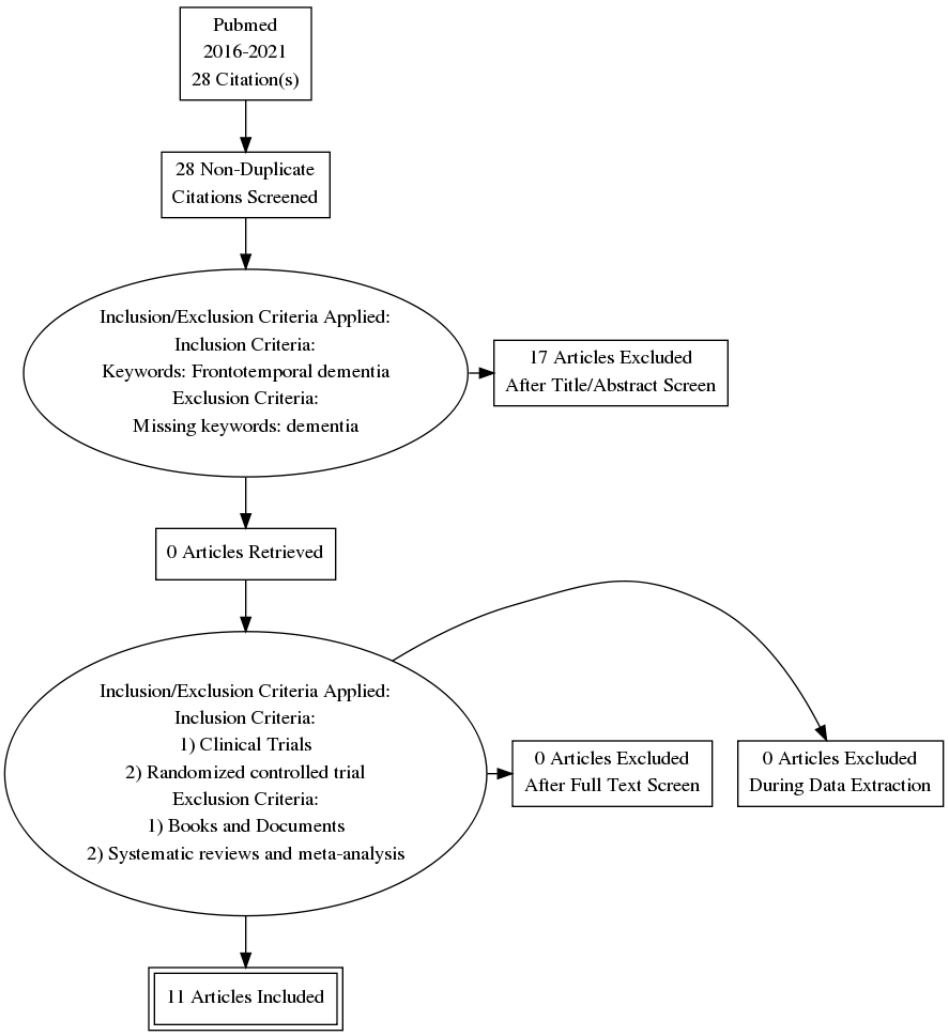

Figure 1

PRISMA Flow Chart