



Behavioral benefits of trazodone are sustained for the long term in frontotemporal dementia

Florence Lebert

Centre Hospitalier
Universitaire,
Centre de la Mémoire,
Hôpital Roger Salengro,
Lille, 59037, France
Tel.: + 33 320 446 021
Fax: + 33 328 434 746
f-lebert@chru-lille.fr

Objective: Previously, a placebo-controlled cross-over trial of trazodone (300 mg/day) of 12-weeks duration showed behavioral improvement in a group of 26 patients with frontotemporal dementia. The long-term efficacy and safety of trazodone in frontotemporal dementia was unknown. **Materials & methods:** The placebo-controlled trial has now been followed by an open-label extension study. The 26 frontotemporal dementia patients with mild cognitive decline and severe behavioral troubles who entered the study had previously completed the double-blind study with trazodone. Patients were treated with 300 mg/day. They were followed for at least 2 years, after the end of the double-blind trial. The efficacy was evaluated by the neuropsychiatric inventory score. **Results:** The withdrawal rate was approximately 23% during the first year, two patients died due to unrelated causes, two patients were institutionalized and two refused the follow-up – none as a result of adverse events. The withdrawal rate was approximately 15% during the second year due to an increase dementia with a decrease in behavioral troubles. The mean duration of follow-up by the remaining 16 frontotemporal dementia patients was 36.7 months (± 11.5). In this group, no patient had an increase of final neuropsychiatric inventory score compared with baseline. The mean difference of neuropsychiatric inventory score between baseline and final was 20.5 (± 9.5). The neuropsychiatric inventory score was significantly lower at follow-up than at baseline ($p < 0.0005$). Regarding cognition, nine of the 16 had a decrease of mini mental state examination of more than three points compared with baseline score and 7/16 had no decrease or minor decrease in mini mental state examination. Hypotension was the single side effect, observed at long term follow-up in four patients. **Conclusion:** The follow-up trazodone study demonstrates that trazodone is well tolerated and is effective in the long-term control of behavioral difficulties associated with frontotemporal dementia.

Frontotemporal dementia (FTD) is a degenerative dementia; it is a disorder predominantly of the presenium. FTD is characterized by profound alteration of personality and social conduct, and mild cognitive decline distinct from Alzheimer's disease (AD). Estimates indicate that as many as 20% of adults presenting at memory disorder clinics with impaired cognition and behavior may suffer from FTD. The incidence in a geographically defined population has been estimated at 81 in 100,000 [1]. Behavioral disturbances in dementia increase the risk of institutionalization and morbidity, and are responsible for increased stress on caregivers. Pharmacologic research is needed to control these behavioral symptoms, which are the principal features of FTD. Moreover, of the dementia diseases, FTD is the most neglected by pharmacologic research. Since 1994, FTD has been correctly diagnosed using the criteria of Lund and Manchester [2]. The inter-rater agreement (0.75) of these criteria is similar to

that of the National Institutes of Health (NIH) Alzheimer's Association working group (NINCDS-ADRDA) criteria for AD.

There is little data on neurochemical deficits in FTD; however, there is an important difference between AD and FTD regarding the cholinergic system – acetylcholinesterase and cholinergic acetyltransferase activities are better preserved in FTD than in AD. Positive effects of cholinesterase inhibitors, the major treatment of AD, cannot be expected. Serotonergic changes in FTD are the most frequent biologic data reported in the literature. Neuropathologic data in FTD report decreases in;

- Metabolism of serotonin
- Hydroxyindoleacetic acid (HIAA) [3]
- Serotonin-binding in the frontal cortex
- 5-hydroxytryptamine (HT)2a receptors [4]
- The number of neurons in the nucleus raphe dorsalis [5]

Keywords: behavioral troubles, dementia, frontotemporal dementia, serotonin selective re-uptake inhibitors, trazodone, treatment



Future Drugs Ltd

In addition, using positron emission tomography (PET) reduced levels of 5-HT_{2a} receptors have been confirmed by Franceschi and colleagues [6].

Selective serotonin re-uptake inhibitors (SSRIs) have been logically proposed to manage behavioral troubles in FTD. Swartz and colleagues presented case reports of behavioral improvement with different SSRIs on disinhibition, carbonate-craving and compulsion [7]. These behavioral benefits have been confirmed by Chow in several case reports [8]. Recently, few trials with serotonin agents have been published. Moretti and colleagues proposed a double-blind study of paroxetine versus piracetam for FTD patients with moderate behavioral signs [9]. At 14 months, patients treated with paroxetine demonstrated a significant difference in behavioral disturbances compared with piracetam. Next, paroxetine was tested in a double-blind placebo-controlled trial on ten FTD patients. At 6 weeks, there was no significant difference between treatment or placebo on the neuropsychiatric inventory (NPI) [10]. Fluvoxamine, another SSRI, was administered to 16 FTD patients in an open 12-week trial. Stereotyped symptoms were significantly reduced [11].

Trazodone is an atypical serotonergic agent with original characteristics – moderate serotonin re-uptake inhibition and serotonergic antagonist effects with an active metabolite *m*-chlorophenylpiperazine (*m*-CPP). Trazodone is recommended in the American Psychiatric Association (APA) guidelines published in 1997 to manage behavioral signs in dementia [12]. An open trial with trazodone in 14 FTD out-patients has been carried out [13]. Trazodone reduced delusions, aggression, anxiety and irritability significantly with a 150-mg daily dose. To decrease depression, disinhibition and aberrant motor behavior, 300 mg of trazodone was necessary. No major side effects were observed. These promising results have been confirmed in a double-blind, cross-over, placebo-controlled trial including 26 patients. There was a significant decrease in the NPI total score after 6 weeks trazodone. A decrease of more than 50% in the NPI score was observed in ten patients. The improvement was mainly based on the improvement in four items of the NPI scale – irritability, agitation, depressive symptoms and eating disorders [14]. The aim of this study was to determine the long-term efficacy and safety of trazodone in

FTD. This descriptive open-label study followed the evaluation of 26 patients treated with trazodone over a maximum of 52 months. Patients were described mainly in terms of the change in neuropsychiatric symptoms.

Materials & methods

The 26 FTD patients who entered the study had previously completed a 12-week randomized, double-blind, placebo-controlled study with trazodone [14]. Patients were required by the double-blind study protocol to have an established diagnosis of FTD, according to the Lund and Manchester group criteria [2], with a score greater than 3 on the frontotemporal behavioral dysfunction scale [15], with a total score on the NPI of less than 8 [16] and a score of 4 or less for one of the following items;

- Delusion
- Hallucinations
- Aggression
- Depression/dysphoria
- Anxiety
- Disinhibition
- Irritability
- Abnormal motor behaviour
- Sleep disorders

Patients had no previous neurologic or psychiatric history. Exclusion criteria included major depression, evidence of addiction and whether neuroleptics or antidepressant agents had been taken. Patients were also excluded from the study if they had a poorly controlled concomitant illness.

At the start of the extension trial, all patients received 300 mg/day trazodone; this dose was continued throughout the study. They were followed for at least 112 weeks after the end of the double-blind trial, on a regular basis (two visits a year). The primary efficacy measure was the final NPI score. Safety was assessed at each visit by physical examination and cognitive assessment using the 30-point mini mental state examination (MMSE) score [17]. A significant decrease in cognition was defined by a decrease in MMSE score of 3 points or more. Hydroxyzine could be proposed for periods of less than 1 month if an increase of either agitation or restlessness was observed.

Ratings were compared using the Wilcoxon matched pair test, Mann and Whitney U-test and Spearman test.

Results

Among the 26 FTD patients, 14 women and 12 men were included. The average age was 60.0 years (± 9.3), mean MMSE score was 20.7 (± 8.6) and mean NPI score was 53.3 (± 18.7).

The withdrawal rate was approximately 23% ($n = 6$) during the first year; two patients died as a result of unrelated causes, two patients were institutionalized and two refused follow-up; however, none were as a result of adverse events. The withdrawal rate was approximately 15% ($n = 4$) during the second year after a decrease in dose of trazodone, as an increase of dementia occurs with a decrease in behavioral troubles. No patients were excluded as neuroleptics were never necessary. The comparison between patients who discontinued trazodone with those treated demonstrated one difference – the mean age of patients. Patients treated over a long-term period were found to be younger (57.5 years vs 65.7 years; $U = 38.5$, $p = 0.03$).

The mean duration of follow-up of the 16 FTD patients who had been \pm treated over 2 years was 36.7 months (± 11.5). In this group, no patient had an increase in final NPI score compared with the score at baseline. The mean difference of NPI score between baseline and final assessment was 20.5 points (± 9.5). The mean NPI score was significantly lower at final follow-up than at baseline (3.46; $p = 0.0005$). Neither age, sex nor MMSE score at baseline influenced the behavioral responsiveness.

Adverse events were mild. In terms of cognition, the mean difference in MMSE between baseline and final evaluation was 13.2 (± 12.9). Of the 16 patients, nine had a decrease in MMSE of more than 3 points compared with baseline score, and seven had no decrease or a minor decrease of MMSE. Neither age, sex, NPI score at baseline nor MMSE score at baseline influenced the cognitive decline. Hypotension was the single general side effect, observed at long-term follow-up in four patients, corrected by etilefrine or midodrine. Hydroxyzine was prescribed in seven patients for a period of less than a month.

Discussion

After the 3-year treatment period, the measurements of behavioral symptoms decreased significantly. In each patient, the reduction of behavioral symptoms was never temporary. These findings suggest that trazodone is effective in reducing behavioral symptoms in FTD in the long-term, as it is in a short period [14]. It is the longest trial in FTD published to date; a long-term benefit of

another serotonin agent, paroxetine, was reported from only 14 months follow-up, and the mean decrease of NPI score between baseline and final assessments was 8.25 points lower than with trazodone. Trazodone differs from other serotonin agents in two aspects – the 5-HT_{2a} antagonist effect and an agonist effect related to its metabolite, the m-CPP. The 5-HT_{2a} receptors are mainly present in frontal regions and decreased in FTD [6]. Drugs with 5-HT_{2a} receptor actions could be a good rationale for pharmacologic research in FTD.

Few data are available regarding the natural course of FTD in terms of survival and nursing home admission, and few pharmacologic studies provide information on the withdrawals from FTD trials. However, our data are in agreement with those of the literature or a little better. In 2003, Hodges and colleagues reported a retrospective survival study of 61 FTD patients with a confirmed diagnosis on neuropathology [18]. The median time-to-institutionalization was only 1 year after the diagnosis, whereas only 7% of our patients were admitted to a nursing home after a 3 year follow-up period with trazodone. Pasquier and colleagues reported a natural follow-up of 73 FTD patients with a mean follow-up of 5.3 years [19]. The percentage of institutionalizations was 15.9% at the end of the follow-up (5.3 years) vs 7% in our 3-year study and the percentage of death was 20 versus 7%, respectively. Our data are better than those of Scharre and colleagues [20] regarding the withdrawal from a FTD trial. For the percentage of withdrawal, in the recent 6-month open-trial with memantine in FTD [20], the withdrawal was 33%, whereas in our trial the dropout rate was 38%. The dropout rate of this study is similar to that seen in long-term trials (96 weeks) with rivastigmine in another non-Alzheimer dementia, the Lewy body dementia [21]. Trazodone has demonstrated a good safety and tolerability profile in patients with FTD at long-term follow-up. Hypotension was the unique side effect observed; however, no patients ceased treatment for this reason.

Interpretation of data from this long-term trial is limited, as it was of an open-label design without control group. However, there are ethical difficulties in maintaining patients with FTD on long-term placebo treatment because the patients have severe psychiatric symptoms. The behavioral troubles could be decreased over time, often with an increase in apathy. It is for this reason that four patients stopped trazodone; however, this cannot

explain the diffuse improvement on NPI observed throughout the 3-years. It is important to remember that Marczinski and colleagues reported a raise of behavioral troubles during thier 3-year observational study in FTD [22].

Acknowledgements

Supported by Grant EA 2691 from the Ministère de l'Éducation Nationale de la Recherche et de la Technologie (MNERT). Special thanks to Prof. Pasquier, Mrs Huyghes and Mrs Gheysen for their support with this trial.

Highlights

- There is no gold standard treatment of frontotemporal dementia.
- Serotonin re-uptake inhibitors are modestly effective in treating the behavioral troubles with frontotemporal dementia.
- A placebo-controlled cross-over trial of trazodone, an original serotonin agent, of 12-week duration demonstrated significant behavioral improvement.
- Trazodone should also be efficacious in the long-term (36.7 months) on behavioral signs of frontotemporal dementia.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 58, 1615–1621 (2002).
2. The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *J. Neurol. Neurosurg. Psychiatry* 57, 416–418 (1994).
3. Sjögren M, Minthon L, Passant U *et al.* Decreased monoamine metabolites in frontotemporal dementia and Alzheimer's disease. *Neurobiol. Aging* 19, 379–384 (1998).
4. Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. *Dement. Geriatr. Cogn. Disord* 10(Suppl.1), 80–84 (1999).
5. 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.* 101, 256–270 (2001).
6. Franceschi M, Anchisi D, Pelati O *et al.* Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Ann. Neurol.* 57, 216–225 (2005).
- **Provides information on serotonin receptors in frontotemporal dementia.**
7. Swartz JR, Miller BL, Lesser IM, Darby AL. Frontotemporal dementia: treatment response to serotonin selective re-uptake inhibitors. *J. Clin. Psychiatry* 58, 212–216 (1997).
8. Chow TW. Frontotemporal dementias: clinical features and management. *Sem. Clin. Neuropsych.* 8, 58–70 (2003).
9. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. *Eur. Neurol.* 49, 13–19 (2003).
- **Demonstrates benefits of paroxetine in frontotemporal dementia.**
10. 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* 172, 400–408 (2004).
- **Shows limitations of paroxetine in frontotemporal dementia.**
11. Ikeda M, Shigenobu K, Fukuhara R *et al.* Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. *Dement. Geriatr. Cogn. Disord.* 17, 117–121 (2004).
- **Demonstrates benefit of fluvoxamine receptors in frontotemporal dementia.**
12. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of Late Life. *Am. J. Psychiatry* 154(Suppl.), 1–39 (1997).
13. Lebert F, Souliez L, Pasquier F, Petit H. Trazodone in the treatment of behavior in frontotemporal dementia. *Hum. Psychopharmacol. Clin. Exp.* 14, 279–281 (1999).
14. Lebert F, Stekke W, Hasenbroeck Ch, Pasquier F. Frontotemporal dementia: a randomized, controlled trial with trazodone. *Dement. Geriatr. Cogn. Dis.* 17, 355–359 (2004).
- **First double-blind trial in frontotemporal dementia.**
15. Lebert F, Pasquier F, Souliez L, Petit H. Frontotemporal behavioral scale. *Alzheimer Dis. Assoc. Disord.* 1, 335–339 (1998).
16. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gorbain J. The neuropsychiatric inventory. *Neurology* 44, 2908–2314 (1994).
17. Folstein MF, Folstein SE, McHugh PR. 'Mini Mental State': a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198 (1975).
18. Hodges JR, Davies R, Xuereb J, Krill J, Halliday G. Survival in frontotemporal dementia. *Neurology* 61, 349–354 (2003).
19. Pasquier F, Richard F, Lebert F. Natural history of frontotemporal dementia: comparison with Alzheimer's disease. *Dement. Geriatr. Cogn. Dis.* 17, 253–257 (2004).
20. Scharre DW, Warner JL, Knich JA, Davis RA, Theado-Miller N. Memantine in frontotemporal dementia. *Neurology* 64(Suppl.1), A99 (2005).
21. Grace J, Daniel S, Stevens T *et al.* Long-term use of rivastigmine in patients with dementia with Lewy bodies: an open-label trial. *Int. Psychogeriatrics* 13, 199–205 (2001).
22. Marczinski CA, Davison W, Kertesz A. A longitudinal study of behavior in frontotemporal dementia and primary progressive aphasia. *Cogn. Behav. Neurol.* 17, 185–190 (2004).

Affiliation

Florence Lebert, PhD
Centre Hospitalier Universitaire,
Centre de la Mémoire, Hôpital Roger Salengro,
Lille, 59037, France
Tel.: + 33 320 446 021
f-lebert@chru-lille.fr