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Oxytocin for frontotemporal dementia

A randomized dose-finding study of safety and tolerability

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ABSTRACT

Objective: To determine the safety and tolerability of 3 doses of intranasal oxytocin (Syntocinon; Novartis, Bern, Switzerland) administered to patients with frontotemporal dementia (FTD).

Methods: We conducted a randomized, parallel-group, double-blind, placebo-controlled study using a dose-escalation design to test 3 clinically feasible doses of intranasal oxytocin (24, 48, or 72 IU) administered twice daily for 1 week to 23 patients with behavioral variant FTD or semantic dementia (clinicaltrials.gov registration number NCT01386333). Primary outcome measures were safety and tolerability at each dose. Secondary measures explored efficacy across the combined oxytocin vs placebo groups and examined potential dose-related effects.

Results: All 3 doses of intranasal oxytocin were safe and well tolerated.

Conclusions: A multicenter trial is warranted to determine the therapeutic efficacy of long-term intranasal oxytocin for behavioral symptoms in FTD.

Classification of evidence: This study provides Class I evidence that for patients with FTD, intranasal oxytocin is not significantly associated with adverse events or significant changes in the overall neuropsychiatric inventory. *Neurology*® 2015;84:174–181

GLOSSARY

bvFTD = behavioral variant frontotemporal dementia; **FBI** = Frontal Behavioral Inventory; **FTD** = frontotemporal dementia; **IRI** = Interpersonal Reactivity Index; **NPI** = Neuropsychiatric Inventory.

Loss of empathy is a hallmark symptom of the most common subtype of frontotemporal dementia (FTD), behavioral variant FTD (bvFTD).[1,2] Presently, there are no treatments for the emotional blunting, lack of empathy, and social behavioral decline in FTD. Without treatments targeting these difficulties, physicians are unable to manage the symptoms most destructive and emotionally challenging to caregivers.[3,4]

Research suggests that the neuropeptide oxytocin is an important mediator of social behavior, potentially enhancing empathy and prosocial behaviors.[5] Oxytocin administration to healthy adults or patients with autism improves emotional expression processing,[6,7] empathy,[8] and cooperative behavior.[9] A single dose of intranasal oxytocin vs placebo was associated with a transient improvement in social and neuropsychiatric behaviors in patients with FTD.[10] Thus, upregulation of oxytocin-mediated mechanisms of empathy and prosocial behavior may be a potential treatment approach in FTD.

The optimal dosage and outcome measures for a clinical trial of oxytocin in FTD are unknown. Animal studies report increases in some forms of aggression after oxytocin administration, leading to concerns regarding potential adverse effects of extended dosing in humans.[11] Other potential dose-limiting toxicities include uterine contractions and hyponatremia. The objectives of this study were (1) to determine the optimum dosage of intranasal oxytocin based on safety, feasibility, and tolerability in patients with FTD; (2) to preliminarily evaluate the

Supplemental data at Neurology.org

From the Departments of Clinical Neurological Sciences (E.C.F., J.M., M.B., S.J., S.P., A.K.), Medicine (M.B., J.W.), Psychiatry (D.G.V.M.), and Anatomy and Cell Biology (D.G.V.M.), and Graduate Program in Neuroscience (L.D.O.), Schulich School of Medicine and Dentistry, Western University, London, Ontario; Tanz Centre for Research in Neurodegenerative Disease (M.C.T.), University of Toronto, Canada; Freie Universität Berlin (I.D.), Cluster of Excellence Languages of Emotion, Berlin, Germany; and Department of Neurology (K.R., A.B.), University of California San Francisco School of Medicine.

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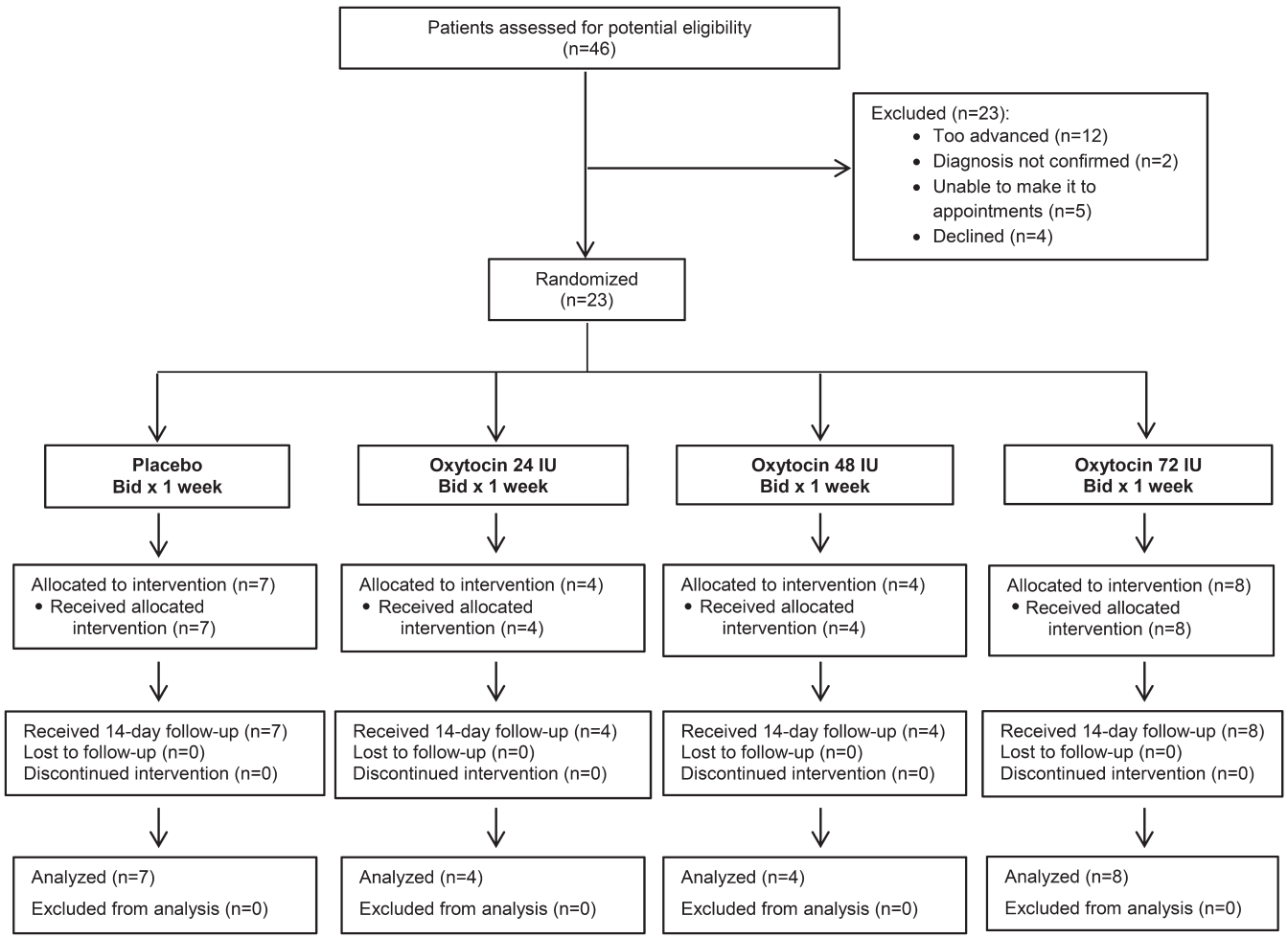
efficacy of repeated intranasal oxytocin dosing for improving empathic behaviors and neuropsychiatric symptoms in FTD; and (3) to identify which outcome measures are most sensitive to the effects of oxytocin in patients with FTD.

METHODS This was a randomized, parallel-group, double-blind, placebo-controlled trial of 3 doses of intranasal oxytocin (24, 48, and 72 IU) in patients with FTD based on a modified dose-escalation design.[12,13] Medication was administered twice daily for 1 week with telephone assessments after 1 week washout. The study was completed at the Cognitive Neurology and Alzheimer Research Unit at St. Joseph's Hospitals, London, Canada. Study visits occurred between June 2011 and October 2013. Primary outcome measures were safety and tolerability of each dose of oxytocin. Secondary measures explored the efficacy of oxytocin on ameliorating the behavioral symptoms and emotion deficits hallmark in FTD.

Participants. Forty-six patients known to our clinic or referred for the study were reviewed for potential eligibility (figure 1). For inclusion, participants had to meet the revised international consensus criteria for probable bvFTD[14] or Neary criteria for semantic dementia with concomitant behavioral features, and demonstrate significant deficits in empathy as reported by caregiver responses on the Frontal Behavioral Inventory (FBI).[15] Exclusion criteria included history of stroke, tumor, or brain lesion (see appendix e-1 on the *Neurology*® Web site at Neurology.org for detailed inclusion/exclusion criteria). While no specific cutoff scores to limit disease severity were used, on chart review, 12 patients (figure 1) were found to be too advanced to participate, based on their inability to follow basic instructions in prior clinical assessments.

Procedures. ***Screening visit.*** At the first visit, neurologic and psychometric assessments were completed to confirm the diagnosis of probable FTD, including symptoms of emotional blunting/empathy deficits (figure e-1). Caregivers completed patient baseline behavioral and severity ratings on the Neuropsychiatric Inventory (NPI),[16] Interpersonal Reactivity Index (IRI),[17] FBI,[15] Frontotemporal Lobar Degeneration–modified Clinical Dementia Rating,[18] and Frontotemporal Dementia Rating Scale[19] (see appendix e-1 supplemental methods for scale descriptions). The NPI was designated a priori as the main efficacy measure based on prior findings.[10] The IRI includes an "empathic concern" scale, which we predicted would capture increases in empathy after oxytocin treatment. Patients completed an exploratory baseline performance measure of empathy, the Multifaceted Empathy Task.[20] Vital signs and serum sodium levels were

Figure 1 Trial profile



Bid = twice a day.

measured before the first dose of oxytocin. Premenopausal women completed urine pregnancy tests on the screening visit and prior to the first dose of medication.

Randomization, masking, and dose escalation. This was a double-blind, parallel-group study. Because of the frequent occurrence of behavioral problems in FTD, which could confound attribution of adverse behaviors, we included a small placebo group (figure e-2). The intranasal oxytocin was manufactured by Novartis Switzerland (Syntocinon) and purchased from International Apotheke (Bern, Switzerland). The study drug and placebo (Salinex saline spray) were repackaged by our institutional research pharmacy (appendix e-1 supplemental methods). The dosages selected (24, 48, and 72 IU twice daily) are based on Fibonacci sequences recommended for dose escalation[12,13] and supported by (1) prior published studies of intranasal oxytocin on social cognition and neuropsychiatric symptoms, which indicate beneficial effects without significant safety concerns at these doses; and (2) the volume that can be absorbed intranasally. Optimal intranasal dose volumes are considered to be less than 0.5 mL per nostril; thus, for larger volumes (48 and 72 IU), doses were divided over 10-minute intervals to maximize absorption (i.e., 3 sprays per nostril every 10 minutes). The number of intranasal sprays was matched in the oxytocin and placebo groups. Based on the estimated duration of action of oxytocin in the CNS between 2 and 5 hours,[21,22] twice-daily dosing (8 AM/2 PM) was used to augment CNS levels of oxytocin during daytime hours. Caregivers administered the sprays and compliance was measured through logs recording administration times and measurement of remaining volumes on day 7.

Four cohorts were randomized to oxytocin or placebo (figure e-2). All randomization was conducted by the research pharmacy. The randomization ratio for the initial 3 cohorts was 4 treatment to 1 placebo. After identification of the highest dose tolerated, a final cohort of 8 patients was randomized in a 1:1 ratio to oxytocin or placebo at the maximum tolerated dose (72 IU) so that a total of 8 participants received the maximum dose.

On day 7, study drug was administered in the morning by the study physician. Twenty minutes after the administration of the nasal solution, safety assessments were completed, followed by patient- and caregiver-completed behavioral measures and physician-completed Clinician's Global Impression of Change (figure e-1). Caregivers were instructed to report on the average behaviors over the 7-day treatment period. Adverse events were assessed each visit through standardized medical symptom-based questionnaires, and heart rate, blood pressure, and serum sodium levels were monitored at baseline and posttreatment on day 7. A follow-up telephone assessment was conducted with caregivers on day 14, after 7 days of medication washout, to assess for any unanticipated effects of medication discontinuation.

Methods/primary research question: Is intranasal oxytocin safe and well tolerated when administered twice daily to patients with bvFTD?

Standard protocol approvals, registrations, and patient consents. The study was approved by the human ethics review board at Western University, London, Canada, and by Health Canada. The trial is registered at clinicaltrials.gov, registration number NCT01386333. Written informed consent was obtained from all patients and their caregivers.

Statistical analysis. The *t* tests were performed on descriptive data to determine any group differences at baseline (age, age at onset), and χ^2 analysis for sex. Because of the small sample size, brief duration of treatment, and multiple secondary outcome measures of interest, formal statistical testing is not reported for the secondary outcome measures.

RESULTS Twenty-three patients with FTD exhibiting prominent behavioral symptoms and emotional blunting met trial eligibility criteria and were enrolled (n = 20 bvFTD; with 2 of 20 also with features of progressive nonfluent aphasia and 3 with semantic dementia with prominent behavioral features) (table e-1 and figure e-3). For the 3 patients with semantic dementia, randomization resulted in one assigned to the placebo treatment, one to 24 IU oxytocin twice daily, and one to 72 IU oxytocin twice daily. All 23 participants were able to complete the study and were included in the analysis. According to the logs and caregiver reports, all patients received each scheduled dose of the study drug. This was confirmed with measurements of the volume of remaining medication.

Baseline demographics and screening material. Demographic information and neuropsychological testing are presented in table 1. There were no significant differences in baseline demographics, cognitive test scores, or disease severity between the combined oxytocin and placebo treatment groups.

Primary outcome measures: Safety and tolerability and adverse events. There were no serious adverse events during the course of the study (table 2). After a caregiver report of increased hypersexual behaviors, the hypersexuality item on the FBI was reviewed for all participants, and was increased in 31% of patients receiving oxytocin, compared with 14% of the placebo group ($\chi^2_1 = 0.73$, $p = 0.4$).

Safety measures. Comparison of heart rate, systolic and diastolic blood pressure, and serum sodium levels at baseline (pretreatment) and day 7 revealed no clinically relevant differences between treatment groups (table e-2).

Secondary outcome measures: Efficacy. Mean differences and 95% confidence intervals for the secondary efficacy measures are reported in table 3. Possible trends of improvement were observed for the oxytocin-treated group on the measures hypothesized to be sensitive to the effects of oxytocin including the NPI apathy and FBI apathy domains and the IRI empathic concern scale (figure 2), with the Addenbrooke's Cognitive Examination–Revised included as a nonsocial cognitive measure for comparison.

Classification of evidence. This interventional study provides Class I evidence that intranasal oxytocin at 24, 48, and 72 IU twice daily is safe and well tolerated in patients with FTD.

Table 1 Baseline characteristics

		Oxytocin		Oxytocin by dose subgroup					
	Placebo (n = 7)	Combined (n = 16)	*p* Value[a]	24 IU (n = 4)	*p* Value[b]	48 IU (n = 4)	*p* Value[b]	72 IU (n = 8)	*p* Value[b]
Characteristics									
Men, n (%)	3 (43)	8 (50)	0.75	2 (50)		2 (50)		4 (50)	
Age, y	61.1 (53.4-69.9)	66.0 (62.1-69.9)	0.17	60.5 (50.3-70.7)	0.70	69.5 (58.8-80.3)	0.11	67.0 (61.1-72.9)	0.13
Age at onset, y	56.57 (48.5-64.6)	59.6 (57.1-63.1)	0.17	55.8 (48.8-62.7)	0.45	58.0 (47.2-68.8)	0.57	62.4 (57.2-67.6)	0.20
Education, y	12.9 (8.9-16.8)	13.6 (12.4-14.9)	0.55	12.8 (8.0-17.50)	0.61	15.0 (10.0-20.0)	0.05	13.5 (11.0-16.0)	0.19
MMSE	20.0 (13.9-26.1)	22.2 (19.6-24.7)	0.40	21.3 (8.9-33.6)	0.71	22.8 (13.9-31.0)	0.39	22.4 (19.9-24.9)	0.68
ACE-R	47.9 (30.9-64.8)	55.1 (47.5-62.7)	0.30	47.5 (25.6-69.3)	0.78	54.8 (24.2-85.3)	0.35	59.1 (49.0-69.3)	0.27
Primary outcomes									
Heart rate, bpm	72.6 (59.4-85.8)	64.6 (59.5-69.8)	0.70	64.0 (42.7-85.3)	0.34	70.5 (50.8-90.2)	0.85	62.0 (57.3-66.7)	0.06
Systolic pressure, mm Hg	112.7 (99.6-125.8)	126.06[c] (120.9-131.2)	0.24	119.0 (104.0-134.0)	0.63	124.0 (117.2-130.8)	0.26	130.6 (122.2-139.0)	0.01
Diastolic pressure, mm Hg	75.5 (59.6-83.6)	75.8 (71.9-79.4)	0.11	75.8 (60.4-90.3)	0.57	75.7 (62.9-88.6)	0.45	71.6 (70.4-81.1)	0.35
Sodium, mEq/L	140.71 (137.0-144.0)	140.43 (137.0-144.0)	0.75	141.75 (140.0-144.0)	0.47	140.00 (137.0-143.0)	0.65	140.00 (139.0-142.0)	0.44
Secondary outcomes									
NPI	23.7 (7.2-40.2)	33.3 (24.3-42.4)	0.23	32.5 (3.9-61.1)	0.45	40.5 (4.0-77.0)	0.35	30.13 (17.9-42.4)	0.46
CGI severity	3.4 (2.9-3.9)	3.9 (3.5-4.3)	0.14	4.0 (2.2-5.8)	0.40	4.5 (3.6-5.4)	0.03	3.6 (3.2-4.1)	0.46
IRI	63.7 (49.1-78.3)	61.3 (54·3-68·2)	0.70	61.8 (53.3-70.2)	0.92	54·8 (45.4-64.1)	0.22	64.3 (49.8-78.7)	0.60
FBI	33.1 (24.0-42.3)	37.4 (33.2-41.5)	0.28	33.5 (16.3-50.7)	0.34	43.5 (30.1-56.9)	0.15	36.3 (32.7-39.8)	0.77
CDR-FTD	12.4 (9.6-15.2)	12.6 (10.2-15.0)	0.94	12.5 (2.3-22.7)	0.99	14.1 (5.3-22.9)	0.67	11.8 (8.3-15.3)	1.0
Exploratory measures									
FRS	34.8 (14.5-55.2)	24.6 (16.0-33.3)	0.23	26.4 (−8.8 to 61.8)	0.57	24.8 (2.9-46.8)	0.35	23.6 (10.0-37.3)	0.30
AES[c]	33.75 (18.3-49.3)	NA	0.68	NA		NA		31.5 (25.6-37.4)	0.77

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination-Revised; AES = Apathy Evaluation Scale; CDR-FTD = Clinical Dementia Rating for Frontotemporal Dementia; CGI = Clinician's Global Impression; FBI = Frontal Behavioral Inventory; FRS = Frontotemporal Dementia Rating Scale; IRI = Interpersonal Reactivity Index; MMSE = Mini-Mental State Examination; NA = not applicable; NPI = Neuropsychiatric Inventory.

Data are mean (95% confidence intervals) unless otherwise stated. Significant at $p < 0.05$.

[a] The *p* value for *t* test comparing placebo vs combined oxytocin group.

[b] The *p* value for Mann-Whitney pairwise comparison vs placebo.

[c] AES was only administered to highest dose group (n = 4 at 72 IU and n = 4 placebo).

Table 2 Adverse event summary by preferred term

		Oxytocin			
Adverse event	Placebo	Oxytocin combined	24 IU	48 IU	72 IU
Fatigue	0	1 (6.25)	0	1 (25)	0
Dry mouth	0	1 (6.25)	0	1 (25)	0
Shortness of breath	0	1 (6.25)	0	1 (25)	0
Dizziness	0	1 (6.25)	0	0	1 (12.5)
Headache	1 (14)	1 (6.25)	0	0	1 (12.5)
Inappropriate sexual behavior	1 (14)	5 (31.25)	2 (50)	3 (75)	0
Depression	0	1 (6.25)	1 (25)	0	0
Euphoric mood	0	1 (6.25)	0	1 (25)	0
Aggression	0	1 (6.25)	0	1 (25)	0

Data are number of patients (%).

DISCUSSION All 3 doses of intranasal oxytocin administered twice daily for 1 week were safe and well tolerated in patients with FTD. We identified convergent changes in subscales of the NPI, FBI, and IRI in oxytocin compared with placebo, suggesting that intranasal oxytocin may improve a subset of behavioral symptoms in FTD, namely, levels of apathy and expressions of empathy, resulting in improved patient–caregiver interactions (based on informant interviews). While there were no reported instances of increased aggression, one-third of patients receiving oxytocin had reported increases in hypersexual behaviors (vs 14% in placebo group). These increases were mild, but raise concerns that this effect could become a limiting side effect for some patients receiving oxytocin. While the small sample size and other factors precluded statistical analysis of the secondary efficacy measures, examination of performance suggests that intranasal oxytocin may improve a subset of behavioral symptoms in FTD, namely, levels of apathy and expressions of empathy. As anticipated, no trends of effects of intranasal oxytocin were observed on nonsocial aspects of cognition. Taken together, these results suggest a favorable benefit/risk ratio for chronic oxytocin treatment over 1 week in FTD. Because approximately 70% to 80% of caregivers of patients with FTD rate loss of empathy and apathy as particularly burdensome,[5] our findings strongly suggest that longer-term efficacy studies of intranasal oxytocin for treating social and behavioral deficits in FTD are feasible and should be pursued.

Although preliminary and requiring confirmation by a larger study powered for efficacy, the results indicate that effects of oxytocin on patients' outward empathic behaviors may best be captured by caregiver interview tools that include measures of apathy and empathy (the NPI, FBI, and IRI).

While we found all oxytocin doses to be safe and well tolerated, the efficacy data indicate the maximum feasible dose used (72 IU) may be most promising. We found a significant, dose-related improvement on the FBI apathy subscale, although the same dose response was not observed on the NPI. Inspection of the interaction between Clinician's Global Impression severity index by dose group suggests that the failed response in the 48 IU group may be confounded by greater disease severity in that cohort relative to the placebo group ($U = 3$, $p = 0.03$) or the 72 IU group ($U = 5$, $p = 0.04$) (table 1). While there was a correlation between the FBI and NPI apathy scores ($t = 0.32$, $p < 0.05$ 1-tailed, Kendall tau test), slight differences in results on these 2 apathy measures may be attributable to the differences in the interview prompts they contain; the FBI item focuses more on social interactions ("Has the patient lost interest in friends or activities") compared with the NPI ("Has the patient lost interest in the world around him/her?"). Supporting this hypothesis, a correlation was observed between the IRI empathic concern and the FBI apathy scores ($t = 0.46$, $p < 0.05$ 2-tailed), but not the NPI apathy and IRI empathic concern scores.

There are few data regarding the effects of repeated dosing of oxytocin on behavior and cognition, with suggestions of possible habituation in other populations.[8] In the present study, behavioral ratings were not collected after the first dose, and thus habituation to repeated dosing cannot be determined. However, day 7 caregiver reports indicate that at least some clinically apparent effects may be maintained over 1 week. Future clinical trials focused on efficacy may address this question with additional interim assessments. However, even if habituation occurs, the potential may remain for the use of intranasal oxytocin on an as-needed basis.

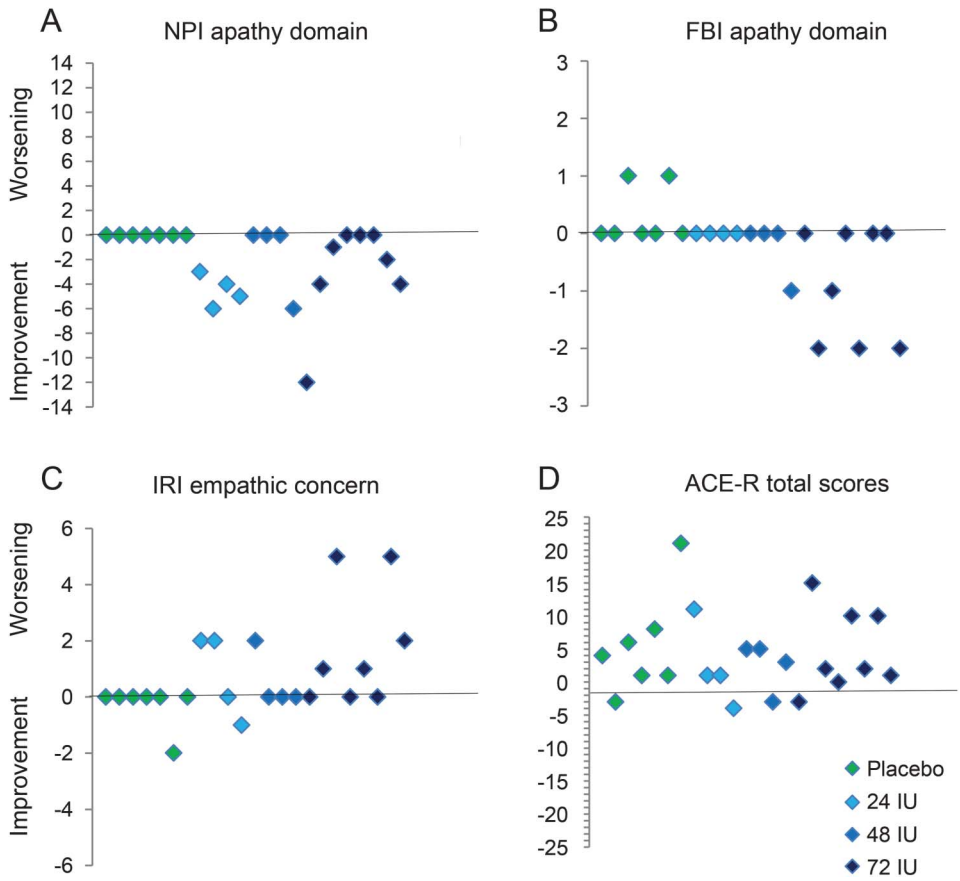
Table 3 Mean differences in change from baseline to day 7 of treatment

	Placebo	Combined oxytocin	24 IU	48 IU	72 IU
NPI					
Total	−1.71 (−4.42 to 0.99)	−5.81 (−10.06 to −1.55)	−3.75 (−6.47 to −1.03)	−2.75 (−11.50 to 6.00)	−8.38 (−17.03 to 0.28)
Delusions	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Hallucinations	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Aggression	0.50 (−0.38 to 1.38)	−0.42 (−1.61 to 0.77)	0.75 (−1.64 to 3.14)	0 (0 to 0)	−2.00 (−5.68 to -1.67)
Depression	−0.33 (−1.19 to 0.52)	−0.38 (−1.22 to 0.45)	0 (0 to 0)	−1.25 (−5.23 to 2.73)	0 (0 to 0)
Anxiety	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Elation	0 (0 to 0)	0.87 (−0.81 to 2.55)	0 (0 to 0)	0 (0 to 0)	1.86 (−2.22 to 5.94)
Apathy	0 (0 to 0)	−2.94 (−4.70 to −1.17)	−4.50 (−6.55 to −2.44)	−1.5 (−6.27 to 3.28)	−2.88 (−6.26 to 0.51)
Disinhibition	0 (0 to 0)	0.50 (−1.3 to 2.35)	0 (0 to 0)	0 (0 to 0)	1.17 (−4.16 to 6.49)
Irritability	−0.14 (−0.49 to 0.21)	−1.00 (−2.31 to 0.31)	0 (0 to 0)	0 (0 to 0)	−2.60 (−6.28 to 1.08)
Motor	−1.5 (−6.27 to 3.27)	−0.08 (−0.27 to 0.10)	0 (0 to 0)	0 (0 to 0)	−0.25 (−1.04 to 0.54)
Sleep	−0.60 (−2.27 to 1.06)	−0.33 (−1.07 to 0.40)	0 (0 to 0)	0 (0 to 0)	−1.00 (−4.18 to 2.18)
Appetite	−0.42 (−1.47 to 0.62)	−0.64 (−1.87 to 0.59)	0 (0 to 0)	0 (0 to 0)	−1.50 (−4.87 to 1.86)
FBI					
Total	−1.29 (−4.15 to 1.58)	−2.00 (−3.91 to −0.90)	0 (−1.30 to 1.30)	−0.50 (−1.42 to 0.42)	−3.75 (−7.50 to −0.20)
Apathy	0.29 (−0.17 to 0.74)	−0.50 (−0.94 to −0.06)	0 (0 to 0)	−0.25 (−1.05 to 0.54)	−0.88 (−4.87 to 1.87)
Indifference	−0.29 (−0.98 to 0.41)	−0.50 (−0.89 to −0.11)	−0.25 (−1.05 to 0.54)	−0.50 (−1.42 to 0.42)	−0.63 (−1.39 to 0.14)
Perseveration	−0.29 (−0.73 to 0.16)	−0.31 (−0.74 to 0.11)	−0.25 (−1.04 to 0.54)	0 (0 to 0)	−0.50 (−1.39 to 0.39)
Inappropriateness	−0.86 (−1.98 to 0.26)	−0.31 (−0.74 to 0.11)	−0.25 (−1.04 to 0.54)	0 (0 to 0)	−0.50 (−1.40 to 0.40)
Jocularity	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Impulsivity	0.14 (−1.21 to 1.49)	0 (−0.33 to 0.33)	0.25 (−0.54 to 1.05)	0 (0 to 0)	−0.13 (−0.82 to 0.57)
Irritability	0.14 (−0.21 to 0.49)	−0.19 (0.54 to 0.16)	0 (0 to 0)	0 (0 to 0)	−0.38 (−1.14 to 0.39)
Aggression	−0.29 (−0.98 to 0.41)	−0.25 (−0.55 to 0.05)	0 (0 to 0)	0 (0 to 0)	−0.50 (−1.13 to 0.13)
Hypersexuality	−0.14 (−0.49 to 0.21)	0.06 (−0.34 to 0.47)	0.50 (−1.09 to 2.09)	0.25 (−0.54 to 1.04)	−0.25 (−0.84 to 0.34)
IRI					
Empathic concern	−0.29 (−0.98 to 0.41)	1.20 (0.25 to 2.13)	0.75 (−1.05 to 0.55)	0.50 (−0.54 to 1.04)	1.75 (−0.64 to 0.14)
Fantasy	−0.14 (−0.98 to 0.68)	0.13 (−0.39 to 0.14)	−0.25 (−1.04 to 0.55)	0.25 (−0.55 to 1.05)	−0.25 (−0.64 to 0.14)
Perspective taking	−0.14 (−0.49 to 0.21)	0 (−0.78 to 0.77)	1.00 (−1.25 to 3.25)	0.75 (−3.13 to 1.63)	−0.13 (−1.25 to 1.00)
Personal distress	0.29 (−0.41 to 0.98)	−0.56 (−1.75 to 0.62)	−1.00 (−2.83 to 0.83)	1 (−2.18 to 4.18)	−1.13 (−3.24 to 0.99)
ACE-R					
Total	5.42 (−1.75 to 12.61)	3.50 (0.57 to 6.43)	2.25 (−7.76 to 12.26)	2.50 (−3.52 to 8.52)	4.62 (−0.58 to 9.38)

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination–Revised; FBI = Frontal Behavioral Inventory; IRI = Interpersonal Reactivity Index; NPI = Neuropsychiatric Inventory.
Data are mean (95% confidence interval). Mean difference is day 7 scores minus baseline scores.

How oxytocin may increase empathy and improve corresponding social behaviors in patients with FTD has yet to be determined. The integrity of oxytocin-producing neurons in the hypothalamic nuclei is preserved in patients with TDP-43 (TAR DNA-binding protein 43) frontotemporal lobar degeneration,[23] suggesting that disease pathology at the sites of afferent projections including the amygdala, orbitofrontal cortex, and insula may disrupt oxytocinergic systems, and that increased oxytocin receptor–dependent signaling to these regions may partially overcome deficits due to neuronal loss or dysfunction. In support of this hypothesis, intranasal oxytocin administration to mice increases levels of oxytocin in the amygdala and hippocampus after 30 minutes.[24] This and related work has led to the hypothesis that oxytocin may mediate prosocial behaviors by increasing positive social stimulus processing, reducing anxiety related to threat cues, and improving the capacity to attend to social cues.[25] Studies examining the neural response to oxytocin administration in FTD are under way to test this hypothesis.

Figure 2 Clinical efficacy measures



Scatter plots depicting individual patients' change in scores from baseline to day 7 of treatment according to treatment group in the combined oxytocin vs placebo groups for (A) NPI apathy domain, (B) FBI apathy domain, (C) IRI empathic concern scale, and (D) ACE-R. ACE-R = Addenbrooke's Cognitive Examination–Revised; FBI = Frontal Behavioral Inventory; IRI = Interpersonal Reactivity Index; NPI = Neuropsychiatric Inventory.

Limitations of the study were that escalation to higher doses of oxytocin was not feasible because of the oxytocin formulation commercially available, the small sample size, and the relatively short duration of follow-up. However, the lack of limiting safety issues suggests that follow-up clinical trials should consider inclusion of higher maximum doses should they become available.

Effect sizes from the present study used to estimate the sample size required for a definitive study of the efficacy of intranasal oxytocin in FTD indicate that approximately 22 patients per group would be required (appendix e-1). An efficacy trial would be further strengthened by powering for possible differential sex and oxytocin receptor genotype effects that might influence the response to exogenous oxytocin administration, because the distribution of oxytocin receptors is known to vary by sex, and variations in the oxytocin receptor gene have been associated with differential baseline empathic traits.

The current study indicates that repeated doses of intranasal oxytocin are safe and well tolerated at doses up to 72 IU twice daily in patients with FTD. The results suggest that a multicenter trial is warranted to determine the therapeutic efficacy of intranasal oxytocin for the difficult and currently untreatable loss of empathy and related social behavior changes in FTD.

AUTHOR CONTRIBUTIONS

E.C.F. obtained funding, designed and supervised the study, and wrote the report. A.B. participated in study conception and design, reviewed and made substantive comments on the report. A.K. participated in patient enrollment and made substantive comments on the report. M.C.T., J.W., M.B., and S.P. participated in patient recruitment and evaluation, and review and revision of the final report. I.D. and K.R. participated in study design and review and revision of the final report. S.J., J.M., and L.D.O. assisted with study conduct, data collection, cleaning, and analysis, and review and revision of the final report. M.B. assisted with statistical analysis and made substantive comments on the report.

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