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The VOICE of FTD

SPRING 2021

FEATURED STUDY: FOXY

Intranasal Oxytocin for Frontotemporal Dementia (FTD)

Having a specific treatment to address behavioral issues in persons diagnosed with frontotemporal degeneration (FTD) would provide some much-needed relief and may help return quality of life to those affected and their caregivers.

FOXY: A Phase 2 Clinical Trial of Intranasal Oxytocin for Frontotemporal Dementia seeks to assess the safety, tolerability, and effectiveness of one such potential treatment by targeting apathy, loss of interest, and lack of empathy.

"Doctors do borrow other medications and use them off-label to address symptoms in FTD, and some of those treatments have offered benefit. But right now we don't have any symptomatic treatments that are specifically approved for behavioral symptoms in FTD," said Elizabeth Finger, M.D., associate professor of **neurology** in the Department of Clinical Neurological Sciences at Western University in London, Ontario, Canada. "If oxytocin did look effective for primary **outcome measures** of empathy deficit and apathy, then it would be the first treatment specifically for those symptoms in FTD."

Oxytocin is a hormone that is naturally found in the brain of men and women. It acts as a neurotransmitter and appears to play an important role in social behavior.

Please note that this glossary is available to help you understand the scientific terms used in this article. Glossary terms are shown in bold the first time they appear.

The FOXY trial specifically seeks to address apathy, loss of empathy, and related issues including:

- Social apathy
- Lack of interest or motivation or initiation of conversations with others
- Offering to help or considering others' needs
- General apathy for activities, including the loss of engagement in hobbies, chores, sports or other interests that a person used to enjoy
- Empathy deficits
- Lack of engagement

"Social apathy overlaps to some extent with empathy deficits because you may look unempathetic if you just aren't engaging with someone else and their situation at all," said Dr. Finger, who is the study's **principal investigator**. "This is why we are looking at both of those as our main symptoms of interest in this study."

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OUTCOME MEASURES

Success of the FOXY trial's primary outcome measure will be a change in a person's Neuropsychiatric Inventory (NPI) apathy/indifference domain score. The NPI was developed in 1994 to assess dementia-related behavioral symptoms. It looks at 12 subdomains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities.

Secondary outcome measures include other behavioral symptoms seen in FTD. These include a change in emotional facial expression recognition performance, a change in the Revised Self-Monitoring Scale score, and a change in modified Clinical Global Impression of Change (apathy) scores.

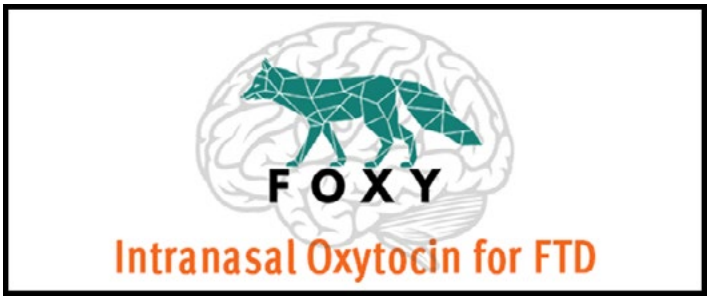
Additionally, there is particular interest in whether it would provide benefits for sleep issues, overeating (hyperphagia), or repetitive behaviors that some patients with FTD experience, Dr. Finger said.

"The primary focus on our outcome measure was selected based on the signals we were getting about oxytocin from data in two earlier pilot studies in FTD," she said.

HISTORY

In the early 1990s, researchers identified differences in social behavior in mammals related to the level of oxytocin. Several studies showed that acute doses of oxytocin increased behaviors such as social recognition, pair bonding, and grooming while decreasing anxiety.

For people with autism, oxytocin improved their reaction to social cues, processing of facial expressions, and cooperative decision-making. Studies of people



with schizophrenia showed promising results from acute dosing or single dosing of oxytocin. But there were also negative results, and it not currently used for these disorders.

Dr. Finger's team conducted two brief studies of oxytocin prior to initiating the FOXY trial. The first was a single-dose study looking at different measures of behavior and emotion processing of persons diagnosed with FTD. It was a **crossover study** where each participant was given the drug and a **placebo**.

The second study focused on the safety and effectiveness of dosing for one week. Improvement in behaviors was noted, with changes related to apathy and indifference.

"Although neither of those studies was to look at efficacy, we saw hints of efficacy," Dr. Finger noted. The results of these studies were used as the basis for developing FOXY.

Also influencing the development of FOXY was a **functional MRI (fMRI)** study that showed increased BOLD signal in the brain regions for emotional processing in participants when they were given oxytocin compared to when they received a placebo.

The FOXY trial was set up with a two-stage adaptive design. This was done because oxytocin had not been studied for tolerance in humans, meaning the loss of effect with continued use.

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"Nobody had addressed the question in humans of whether there would be any habituation to chronic dosing or tolerance that would reduce effectiveness," Dr. Finger said.

The trial's design hopes to avoid these issues and find the best treatment by looking at three different dosing schedules. For persons diagnosed with FTD who deal with behavioral symptoms, along with their families and caregivers, these answers come painfully slow.

UNKNOWNS

FOXY is a multi-center, **randomized, double-blind**, placebo-controlled **clinical trial**. The 11 sites are located across the United States and Canada, and the study will take five to six years to complete.

The first stage will examine which of three different doses of oxytocin may be more effective. In the second stage, patients entering the study will be randomized to the oxytocin dose that appeared most effective in the first stage.

Patients do not know the dosage level of oxytocin that they are receiving, the clinicians they visit periodically do not know the dosage level of the drug that their patients are receiving, and even the principal investigator does not know.

"As we started the study, we didn't appreciate that we would not have any idea of whether the treatment looked promising until many years after we started," Dr. Finger noted. "Now we've come to accept that reality of doing a double-blind study."

A **Data and Safety Monitoring Board**, composed of an independent group of experts, oversees and monitors the trial to ensure participant safety as well as the validity and integrity of the data.

DOSAGING

Oxytocin (Syntocinon), administered by a spray into the nostrils, is being compared to placebo (an inactive saline substance that contains no medication) in participants with FTD.

Patients receive a box with a separate nose spray bottle for each day. There may be contents still remaining in a day's bottle, but the following day the next bottle is used. While all participants use the nose spray twice a daily; the bottle's contents vary.

To maintain the study's blind, the dosage amount is referred to as low-dose; medium dose; and high dose.

"Even though the dose in which someone receives oxytocin varies, for outward appearances it is the same," she said, since all patients get two rounds of nose spray treatments every day for 42 days. In the crossover design, patients will also receive saline nasal sprays during their six placebo weeks.

While neither the participants nor the researchers know which treatment is being received, members of the Data and Safety Monitoring Board will review the unblinded data at the end of stage 1. They will select the most promising dose of oxytocin to be given to the remaining 40 percent of participants who will be recruited for stage 2.

"We at least can see the safety data and the data points for the participants in the trial," Dr. Finger explained. "At this time we just have no idea whether those were collected when they were receiving the oxytocin or the placebo."

Western University in London is also a trial site with 12 participants in stage 1. While this is only 20 percent of

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the study's total enrollment, these are people who Dr. Finger sees on a regular basis. But the cross-over design still makes it difficult to try to guess which dosage might be working the best.

"We don't look back at the visit before to see what that rating was," she said. "We don't want to bias the results by guessing. So in my mind, I don't have any inclination yet as to whether we are seeing effects or not."

As lead investigator, Dr. Finger takes comfort in knowing that the study is running as planned and as hoped.

"I can say from our site, and certainly from the overall trial safety data, that we're not seeing any worrisome side effects or safety concerns that appear to be caused by the oxytocin," she added.

The study began recruiting participants in 2017, and enrollment is expected to finish in 2022. Total enrollment during this time is estimated to be 112 people. The estimated date to see the results is in fall 2023.

"For stage 1 we planned to enroll 60 participants and have done that," Dr. Finger said. "We had a few dropouts, some due to the pandemic, but we are confident that we have enough completers. Then for stage 2, there will be 40 enrolled."

Eligibility criteria for the study include:

- Between 30-80 years of age
- Diagnosis of probable FTD (behavioral variant FTD, FTD-semantic subtype or FTD-Progressive Nonfluent Aphasia) with supportive brain imaging or known FTD causing genetic mutation.68
- Current symptoms of social apathy/indifference as measured by NPI apathy/indifference severity subscale
- Study partner who consents to study participation, cares for/visits the patient daily for at least 3 hours a day, and administers all trial medications.
- Stable baseline medications related to **cognition** or behavior

The Data and Safety Monitoring Board should have the results from stage 1 analysis this May, she said, with stage 2 enrollment beginning in June or July 2021.

"It is competitive enrollment; we enroll participants as we have them," explained Dr. Finger. "At this point we don't have a calendar date to cut off enrollment. It would simply be when we get to patient 40."

Upon completion of FOXY Phase 2 and after learning the results in 2023, Dr. Finger will then decide whether to move to Phase 3 and conduct a full, randomized clinical trial in the hope that results will show oxytocin as being effective in managing apathy and loss of empathy in FTD.

LEARN MORE ABOUT FOXY

READ MORE ABOUT DR. FINGER

Intranasal Oxytocin for Frontotemporal Dementia (FOXY)

Official Title: A Phase 2 Clinical Trial of Intranasal Oxytocin for Frontotemporal Dementia

Actual Study Start Date: January 31, 2018
Estimated Primary Completion Date: September 1, 2023

Recruitment Status: Recruiting

Brief Summary:
The purpose of this study is to assess the safety, tolerability, and effects on behavior of Syntocinon given intranasally (by a spray into the nostrils) compared to placebo (an inactive saline substance that contains no medication) in participants with frontotemporal dementia/Pick's disease. This study will take place in approximately 15 centers across Canada and

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the United States. Approximately 112 patients in total will be enrolled in this study. In the first phase, we will examine which of three different dosing schedules of oxytocin may be more effective. In the second phase of the study, patients entering the study will be randomized to the oxytocin dosing schedule that appeared most effective in the first phase.

Study type: Interventional (Clinical Trial)
Estimated Enrollment: 112 participants
Allocation: Randomized
Intervention Model: Crossover Assignment
Intervention Model Description: A Proof-of-Concept, Double-Blind, Randomized Controlled, Cross-Over Adaptive Design Trial
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description: Double Blind
Primary Purpose: Treatment

Arms and Interventions
Drug: Syntocinon (Intranasal Oxytocin)
Experimental:
- Low Dose
- Medium Dose
- High Dose

Outcome Measures
Primary:
1. Change in Neuropsychiatric Inventory (NPI) apathy/indifference domain score *[Time Frame: Up to 20 weeks]*

Pilot data from our two prior studies of oxytocin in FTD have driven the selection of the NPI as the primary outcome measure.

Secondary:
1. Change in emotional facial expression recognition performance *[Time Frame: Up to 20 weeks]*
2. Change in the Revised Self-Monitoring Scale score *[Time Frame: Up to 20 weeks]*
3. Change in modified Clinicians Global Impression of Change (apathy) scores *[Time Frame: Up to 20 weeks]*

Eligibility Criteria:
- **Ages:** 30 Years to 80 Years
- **Sexes:** All
- **Accepts Healthy Volunteers:** No

Inclusion Criteria:
- Diagnosis of probable FTD (behavioural variant FTD, FTD-semantic subtype or FTD-Progressive Nonfluent Aphasia) with supportive brain imaging (centrally rated frontotemporal atrophy score of 2 or greater on brain MRI or CT) or known FTD causing genetic mutation.68
- Current symptoms of social apathy/indifference as measured by NPI apathy/indifference severity subscale score >= 2 indicating the presence of moderate to marked levels of apathy/indifference.
- Study partner who consents to study participation and who cares for/visits the patient daily for at least 3 hours/day and who can administer all trial medications.
- FTLD-CDR score 0-2.
- MMSE >10.
- Stable baseline medications related to cognition or behaviour for >=30 days such as acetylcholinesterase inhibitors, memantine, antidepressants, antipsychotic agents, other mood stabilizers, benzodiazepines.
- Written informed consent must be obtained and documented (from the patient or, where jurisdictions allow it, from their substitute decision-maker).

Exclusion Criteria:
- History of stroke, other neurologic or psychiatric disorder other than FTD that is considered to better account for behavioural symptoms.
- History of a myocardial infarction within the last two years or congestive heart failure.
- Current uncontrolled hypertension
- Current bradycardia (rate < 50 beats per minute/bpm) or tachycardia (rate > 100 bpm)
- Current hyponatremia (Na <135 mEq/L)
- Current use of topical prostaglandin medications applied to the cervix.
- Females who are pregnant or breastfeeding, or planning to conceive within the study period.
- Use of any investigational or experimental drug or device within the last 60 days prior to screening or within 5 half-lives of the experimental drug, whichever is longer.

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- Participant has speech difficulties that in the opinion of the investigator would be incompatible with neuropsychology and safety assessments
- History of cancer except:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Any clinically significant hematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal or neurological disease. If the condition has been stable for at least the past year and is judged by the investigator not to interfere with the patient's participation in the study, the patient may be included.
- For the CSF sub-study, current use of anticoagulant medications (warfarin, rivaroxaban, etc.).
- Plan for FTD patient to be placed into long-term care or plan for hospital admission for any kind of treatment within the study period or if caregiver plans for holidays/respite care > 3 days during the study period.

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- Canadian Institutes of Health Research (CIHR)
- Berry Consultants

LEARN MORE ABOUT THE FOXY STUDY

READ ABOUT DR. FINGER

Join the Registry. Tell Your Story. Advance the Science.

"Together, we can make a difference!"

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