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Placebo Response in Fragile X-associated Tremor/Ataxia Syndrome

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ABSTRACT: Background: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder characterized by intention tremor, cerebellar ataxia, and executive dysfunction in carriers of a CGG repeat expansion premutation (55–200 repeats) in the fragile X mental retardation 1 (*FMR1*) gene. Given reports of poor insight in FXTAS, we postulated that patients with FXTAS would be less likely to exhibit placebo response.

Objective: To analyze placebo response from the first randomized controlled trial in FXTAS that evaluated cognitive and motor outcomes after 1 year of treatment with memantine.

Methods: Data from the placebo arm of the first randomized controlled trial in FXTAS were analyzed. There were 2 coprimary outcomes. Based on studies in Parkinson's disease, placebo responders were defined as individuals with an improvement of at least 50% in the coprimary outcomes. Improvements of 20% and 30% served as secondary cutoff values based on the suggested magnitude of placebo response in other movement disorders.

Results: A total of 36 participants in the placebo group completed baseline and follow-up evaluations. The average age was 66 ± 7 years, and 60% were men. Average CGG repeat size was 86 ± 18. A total of 19 participants had stage 3 disease. Only 1 patient showed 50% improvement in both coprimary outcomes. At 30% and 20% improvement, there were 2 and 3 patients showing placebo response in the coprimary outcomes, respectively.

Conclusions: Patients with FXTAS exhibited low rates of placebo response in a randomized controlled trial. Further studies on the relationship between baseline insight and placebo responsivity are applicable to FXTAS and other disorders exhibiting cognitive impairment.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disorder seen in aging individuals who carry a premutation (55–200 CGG repeats) in the fragile X mental retardation 1 (*FMR1*) gene. A full mutation of the *FMR1* gene (>200 repeats) is responsible for fragile X syndrome, the most common inherited cause of intellectual disability in boys.[1] Motor features of FXTAS include cerebellar ataxia, intention tremor, and parkinsonism. Cognitive deficits typically begin with executive dysfunction and progresses to include impaired short-term memory and more global cognitive impairments.[2] Up to 40% of carrier men older than age 50 are symptomatic, with disease penetrance increasing with age.[3] Up to 16% of premutation carrier women develop FXTAS, and the phenotype is milder as a result of X-inactivation.[4] FXTAS is generally slowly progressive with a median survival of 21 years after the onset of symptoms, although some patients have a more precipitous decline in function, often after an illness.[5]

There are currently no approved treatments for FXTAS. Symptoms are managed with medications shown to be helpful in other diseases with similar symptoms or those with anecdotal evidence from case reports.[6] Memantine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist approved for use in Alzheimer's disease.[7] Case reports of improvement in the motor and psychiatric symptoms of FXTAS with open label use of this

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TABLE 1 *Diagnostic criteria for fragile X-associated tremor ataxia syndrome*

Diagnostic criteria		
Molecular	Required	55-200 CGG repeats in the *FMR1* gene
Clinical	Major	Intention tremor
	Major	Cerebellar gait ataxia
	Minor	Parkinsonism
	Minor	≥ Moderate short term memory deficit
	Minor	Executive function deficit
Radiological	Major	MRI white matter lesions in the MCP's or brainstem
	Minor	MRI cerebral white matter lesions
	Minor	≥ Moderate generalized brain atrophy
Neuropathological	Major	Ubiquitin-positive intranuclear inclusions
Diagnostic categories		
Definite	One clinical major + one radiological or neuropathological major	
Probable	Two clinical major OR One clinical minor + one radiological major	
Possible	One clinical major + one radiological minor	

Table displays the current diagnostic criteria for FXTAS as adapted from Jacquemont and colleagues.[2]
FMR1, fragile X mental retardation 1; MRI, magnetic resonance imaging; MCP, middle cerebellar peduncle.

medication[8,9] prompted the first randomized placebo-controlled trial (RCT) in patients with FXTAS.[10] This study compared cognitive and motor symptoms of FXTAS after 1 year of treatment with memantine. Outcomes included both motor and neuropsychiatric measures. The primary outcomes were the Behavioral Dyscontrol Scale (BDS-II) and intention tremor severity. There was a trend toward improvement in intention tremor severity only.

Given the limited treatment options for FXTAS, the need for more clinical trials is urgent. The design of future RCTs, including planning sample size and outcome selection, requires an understanding of the tendency for placebo response in this syndrome.[11] There are reports of impaired insight in FXTAS,[12] which may lead to low rates of placebo response in this syndrome. As there has only been 1 RCT published in this population to our knowledge, placebo response in FXTAS has not been thoroughly studied. The aim of our study was to analyze raw data from the placebo arm of this trial to evaluate magnitude of placebo response and determine how often patients met the criteria for placebo response as defined in Parkinson's disease (PD). We predicted that patients with FXTAS would exhibit low rates of placebo response.

Methods

Our study involved the additional statistical analysis of data previously obtained as part of an institutional review board–approved RCT. An amendment to the research protocol of the RCT was approved by the same institution's institutional review board for this post hoc analysis of de-identified data. Raw data from the 36 patients who completed all assessments in the placebo arm were analyzed. Inclusion criteria for the original trial were definite, possible, or probable FXTAS based on published diagnostic criteria (Table 1).[2] Exclusion criteria were prior adverse effect associated with memantine use, renal insufficiency, unwillingness to participate in the study, and current memantine treatment.

In the original study, the predetermined coprimary outcomes were intention tremor severity and the BDS-II. The BDS-II is a 9-item neuropsychological test including a manual sequencing task and a go–no-go task to measure behavioral control, sequencing, and insight. A maximum score of 27 is possible.[13] A score of ≤14 has been used as cutoff for impairment in FXTAS.[14] The study's secondary outcomes included 3 other cognitive tests (Controlled Oral Word Association Test [COWAT], California Verbal Learning Test [CVLT], and the Weschler Memory Scale [WMS]) as well as 2 other tremor measures (postural tremor severity and writing tremor severity) and 2 bradykinesia measures (hand-tapping and finger-tapping frequencies). Tremor severity and the bradykinesia measures were assessed using a computerized system (CATSYS Tremor Pen, Danish ProductDevelopment Ltd., Denmark). This device uses tremor acceleration as a function of frequency to generate a tremor severity score. Bradykinesia was

TABLE 2 *Clinical characteristics of participants randomized to placebo, n = 36*

Variable	n	Mean or %	SD
Age, y	36	66.3	7.0
Education, y	36	15.1	2.9
CGG repeats	36	86	18
MMSE	36	28.9	1.4
BDS-II	34	15.4	3.7
Sex			
Female	12	40.43%	
Male	24	59.57%	
Race, white	36	100%	
Ethnicity			
Hispanic	4	11.1%	
Non-Hispanic	32	88.9%	
FXTAS diagnosis			
Possible	8	22.2%	
Probable	8	22.2%	
Definite	20	55.6%	
FXTAS stage			
1	2	5.6%	
2	7	19.4%	
3	14	38.9%	
4	11	30.6%	
5	2	5.6%	

Modified from Seritan and colleagues.[10] Table includes the clinical characteristics of the participants randomized to the placebo group who completed the study in the original randomized controlled trial.
MMSE, Mini-Mental State Examination; BDS-II, Behavioral Dyscontrol Scale II; FXTAS, fragile X-associated tremor/ataxia syndrome.

TABLE 3 *Number of participants exhibiting placebo response on the coprimary outcomes, n = 36*

Outcome	Improvement, n (%)			Mean Change, *P* Value
	50%	30%	20%	
Intention tremor severity + BDS-II	1 (3)	2 (6)	3 (8)	
Intention tremor severity	5 (14)	5 (14)	10 (28)	0.94
Behavioral Dyscontrol Scale II	1 (3)	3 (8)	8 (22)	0.19

Table displays the results of the analysis of placebo response with the number of participants who showed an individual improvement of 50%, 30%, and 20% on the 2 coprimary outcomes considered together and individually.

TABLE 4 *Number of participants with placebo response on secondary outcomes, n = 36*

Outcome	Improvement, n (%)			Mean Change, *P* value
	50%	30%	20%	
Postural tremor severity	3 (8)	3 (8)	8 (22)	0.85
Writing tremor severity	1 (3)	1 (3)	3 (8)	0.02
Hand-tapping frequency	0	1 (3)	4 (11)	0.14
Finger-tapping frequency	2 (6)	3 (8)	3 (8)	0.47
COWAT	4 (11)	6 (17)	12 (33)	0.16
CVLT	0	4 (11)	6 (17)	0.77
WMS	0	0	0	0.31

Table displays the results of the analysis of placebo response with the number of participants who showed an individual improvement of 50%, 30%, and 20% on the secondary outcomes considered individually.
COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; WMS, Weschler Memory Scale.

measured in taps per second (hertz) during a scripted motor protocol.

Baseline and 1-year follow-up scores were compared for each participant in the placebo arm for all outcome measures. Individual changes in scores were calculated and expressed as percent improvement. An individual improvement of at least 50% when compared with the baseline score was used as an initial cutoff for placebo response based on studies in PD.[15] Individual improvement of 30% and 20% when compared with the baseline score served as secondary cutoff values based on the proposed placebo response magnitudes in another parkinsonian syndrome, progressive supranuclear palsy.[16] A paired sample *t* test was also performed on the baseline and follow-up scores in each outcome. We next investigated possible patterns in placebo response by dividing the outcomes into symptom domains representing components of the FXTAS syndrome. The 9 outcome measures were considered as 3 categories: cognitive tests (COWAT, CVLT, WMS, BDS-II), action tremor measures (intention tremor severity, postural tremor severity, and writing tremor severity), and bradykinesia measures (hand-tapping and finger-tapping frequencies). We looked for individuals who responded to placebo on multiple tests within a symptom domain. All calculations were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Results

Of the 47 participants with FXTAS randomized to placebo, 36 completed both a baseline and follow-up evaluation and were included in the final analysis. Their demographics are summarized in Table 2. Of the participants, 40% were women and 60% were men. Their average age was 66 ± 7 years old. The average CGG repeat size was 86 ± 18. There were 19 participants with stage 3 FXTAS (moderate tremor and/or balance problems, occasional falls, and significant interference with activities of daily living). A total of 13 participants had stage 4 disease (severe tremor and/or balance problems, at least intermittent use of a cane or walker), and 11 had stage 2 disease (clear tremor and/or balance problems and minor interference with activities of daily living). The patients were nondemented on average, with a Mini Mental State Examination score of 29 ± 1.4.

Using the definition of placebo response as 50% improvement, 1 of 36 patients (3%) exhibited placebo response on the 2 coprimary outcomes (Table 3). Considering the more sensitive cutoffs for placebo response, only 1 participant was added per reduction in percent improvement. That is, at 30% improvement, there were 2 total participants exhibiting placebo response on the coprimary outcomes (6%), and at the still lower cutoff of 20% improvement, there were 3 participants (8%). Evaluating the primary outcomes individually as well as each of the secondary outcomes individually revealed overall low rates of placebo response (Tables 3 and 4). The mean change in writing tremor was the only outcome to show a significant difference from zero ($P = 0.02$). There were several individuals who responded to placebo in multiple outcomes. There was only 1 participant who responded to placebo within a symptom domain. This individual did so in the bradykinesia measures and only at the lowest cutoff of 20% improvement.

Discussion

Placebo response rates were low in the first RCT studying patients with FXTAS, with few participants responding to

placebo on the coprimary outcomes. Even with inclusion of more sensitive cutoffs for placebo response, there remained low numbers of placebo responders. Of the coprimary outcomes, there were higher rates of placebo response in intention tremor severity than the BDS-II. Of the secondary outcomes, the COWAT showed the highest rates of placebo-associated improvement.

The study of placebo response in movement disorders is unique given the implication of dopamine in both the brain's motor pathways and the reward response pathways.[17] This is especially true in PD where placebo response has been shown to be robust and long-lasting. Marked reductions in Unified Parkinson Disease Rating Scale scores can be seen up to 6 months from the application of placebo.[15] As a result of these studies, a cutoff of 50% improvement in symptoms has been regarded as the standard for placebo response in other movement disorders, including progressive supranuclear palsy,[16] Huntington's disease (HD),[18] and tic disorders.[19] FXTAS includes parkinsonism as a motor feature and could reasonably be added to the list of movement disorders to hold to this standard. However, the neuropsychiatric profiles of PD and FXTAS are quite different, with cognitive impairment occurring earlier in the disease course and characterized by more prominent executive dysfunction in FXTAS than in PD.[20]

Abnormal executive functioning is associated with inaccurate self-report of functional impairment, even in otherwise healthy adults.[21] It is therefore not surprising that patients with PD and HD differ in self-awareness for abnormal movements. This was shown in a study evaluating self-reports of choreiform dyskinesia in patients with PD and chorea in patients with HD.[22] Self-awareness of choreic movements was significantly more limited in HD patients than in PD patients despite comparable severity of movements and cognitive status. These 2 disorders also differ in their rates of placebo response. One study of placebo response in HD during an RCT testing riluzole found that the rates of placebo response were low. Using the definition of 50% improvement, patients with HD exhibited placebo response in only the behavior domain of the Unified Huntington Disease Rating Scale, but not in cognition, function, and overall motor scores.[18] Without sufficient awareness of their motor or cognitive symptoms, the patients did not have the necessary expectation of reward (ie, expectation of improvement in symptoms) for a placebo effect.[23]

A similar lack of insight into symptoms is seen in FXTAS.[24] Data presented by 1 of the investigators (D.A.H.) evaluated the self-report of symptoms in 18 nondemented patients with FXTAS compared with the examination findings by a blinded movement disorders specialist.[12] The participants were asked if they had "unsteady walking," "shakiness of the hands with action or at rest," and if they had "slowness or stiffness." Their responses were then compared to items on the FXTAS Motor Rating Scale corresponding to ataxia, action tremor, and parkinsonism. There was significant discordance between patient report and examination for ataxia and parkinsonism. All 18 patients had ataxia on examination. However, 9 patients answered "no" to the survey question, reporting that they did not have unsteady walking ($P = 0.02$). Although 15 of 18 patients exhibited parkinsonism on examination, 9 reported that they did not have any tremor at rest, slowness, or stiffness ($P = 0.02$). Patients overall accurately reported the presence or absence of action tremor, with 11 of the 15 patients who had action tremor on exam answering "yes" correctly to the survey question ($P = 0.25$). This restriction of insight into symptoms is consistent with the low placebo rates found in our study. Interestingly, we found more placebo responders on measures of intention tremor and postural tremor severity than in measures of bradykinesia. This would be consistent with some patients having awareness of baseline action tremor, but not of their parkinsonism as in this self-report study. The higher rates of placebo response on the COWAT test may be related to factors other than true placebo effect. This test has been shown to be susceptible to practice effect in healthy adults with improved scores on repeat testing up to at least 3 months later.[25,26] The CVLT has also been shown to exhibit practice effect in patients with mild cognitive impairment.[27]

One key limitation of our study is that the data available did not include the FXTAS rating scale as an outcome measure. The FXTAS rating scale, serving as a summary of signs and symptoms, may have better answered the question of whether the full syndrome of FXTAS improves with exposure to placebo in individual patients.[28] An evaluation of change in response to placebo is also important to consider in the context of natural history of the disease. Although these outcome measures have not been studied longitudinally in FXTAS to our knowledge, with this duration of follow-up, marked increase in tremor or decline in the BDS-II score would not be expected for most patients. However, writing tremor severity was significantly worse on average ($P = 0.02$). It is possible that the lack of change seen in the other tremor measures represents some degree of placebo response. For future studies, interval measures of placebo response will be important to include as it has been shown that placebo response can vary over time.[29]

Overall, our finding of low placebo response rates in patients with FXTAS should inform future clinical trial design in this population as lower sample sizes may achieve adequate power. Further studies on the relationship between baseline insight and placebo responsivity are applicable to FXTAS and other disorders exhibiting cognitive impairment.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

E.J.H.: 1B, 1C, 2A, 2C, 3A

C.G.G.: 2A, 2C, 3B
G.T.S.: 2A, 2C, 3B
R.H.: 1B, 1C, 3B
B.O.: 1B, 1C, 2A, 2B
D.A.H.: 1A, 1B, 1C, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the institutional review board at Rush University Medical Center. An amendment to the research protocol of the original study was also approved by the institutional review board at the University of California Davis for this post hoc analysis of de-identified data. Informed consent was obtained from each participant as part of the original trial at University of California Davis for the acquisition of the data, but was not obtained for this post hoc analysis of de-identified data. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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