Clinical Unmet Needs and Burden in Fragile X Syndrome: Results of a Targeted Literature Review

Melissa Raspa,[1] Patricia Sacco,[2] Donald B. Bailey, Jr.,[1] Jeannie Visootsak,[3] Raquel Cabo[3]

[1]RTI International, Research Triangle Park, NC, United States; [2]RTI Health Solutions, Research Triangle Park, NC, United States; [3]Ovid Therapeutics, New York, NY, United States

BACKGROUND

- Fragile X syndrome (FXS) is caused by an expansion of the CGG trinucleotide repeat on the 5' untranslated region of the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome.[1,2]
- FXS is the leading inherited cause of intellectual disability, with impact on behavior and functional abilities (e.g., daily living skills, communication, and social-emotional skills).

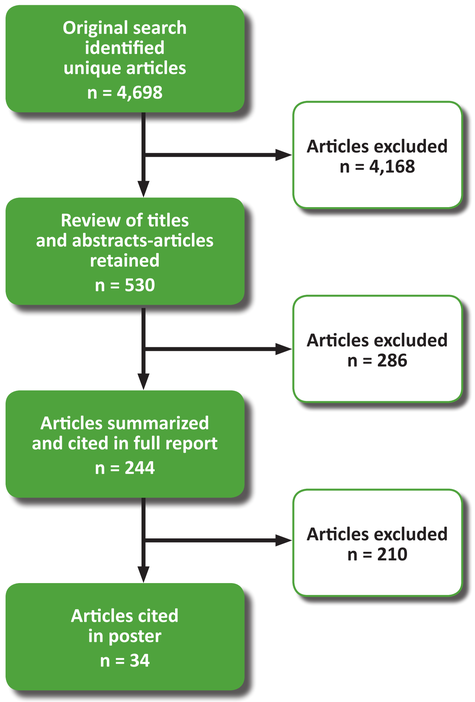
OBJECTIVE

- A targeted literature review was conducted to characterize the clinical unmet needs and burden associated with FXS.

METHODS

- PubMed served as the primary database for the electronic literature search.
- Abstracts were reviewed for relevance based on predefined criteria, including publications from 2006 to 2016, focusing on the epidemiology of FXS, genetics of FXS, natural history and description of the phenotype, caregiver burden and impact on family, treatment approaches, and guidelines.
- Search results are shown in Figure 1.

Figure 1. Review and Selection Process for Cited Literature



RESULTS

Prevalence and Diagnostic Procedures

- No large-scale, population-based screening studies have been conducted to determine the prevalence of FXS, so rates vary dramatically across studies.
  - Early studies found prevalence rates of 1:4,000 for males and 1:8,000 for females.[3,4]
  - Recent meta-analyses reported a rate of 1:7,143 for males and 1:11,111 for females.[5]
- FXS is typically diagnosed around 36 months, with concerns by parents starting around 12 months and a developmental delay confirmed by a professional at approximately 20 months.[6]

Clinical Presentation

- The impact of FXS on functioning and behavior over an individual's life span is presented in Figure 2.

Figure 2. Clinical Presentation of FXS

Infancy/early childhood

- Parents typically express concerns about their child's development before 12 months of age.[6]
- Males with FXS have expressive language impairments that begin with delayed first words.[7]
- Delays in all motor milestones reported for boys—including sitting, crawling, and walking.[8]

Middle childhood/adolescence

- More than 90% of males and 50% of females with FXS meet the criteria for intellectual disability by age 9.[9]
- Majority of males 6 or older have co-diagnosis of development delay (96%), attention problems (84%), hyperactivity (66%), and anxiety (70%).[10]
- Between 15% and 52% receive a co-diagnosis of autism, which results in a more severe phenotype.[11]
- About 18% experience seizures with the first occurring between 4 and 10 years of age.[12]

Adulthood

- Approximately 95% of adult males with FXS have an IQ below 70,[13] and 70% of women with FXS have some degree of cognitive impairment.[14]
- Most adult males and females are verbal and independently use the toilet, bathe, dress themselves, and eat.[15]
- As males age, the hyperactivity, irritability[16], and impulsiveness diminishes. Shy behavior and poor eye contact, however, remain constant throughout the lifecourse.[17]
- Irritability in females with FXS decreased with increasing age.[16]

Figure 3. Behavioral Symptoms in Males and Females With FXS

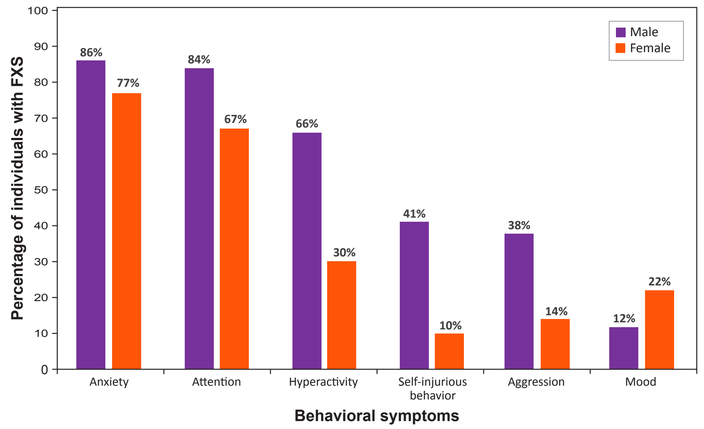
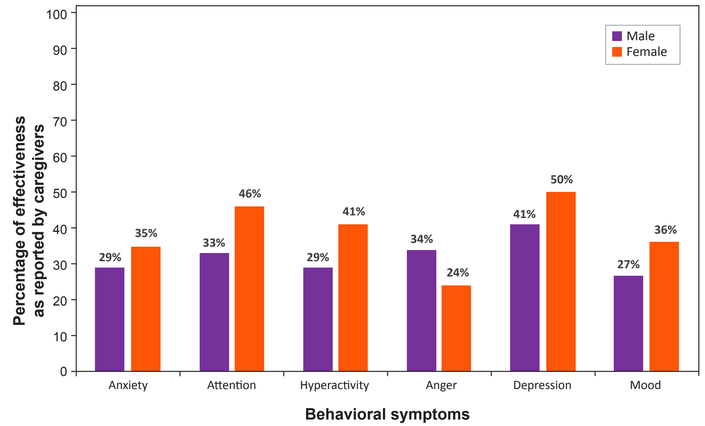


Figure 4. Caregiver Report of Medication Effectiveness by Behavioral Symptom



Intellectual Disability

- Most males with FXS present with a developmental delay or mild to moderate intellectual disability.

Functional Abilities

Adaptive Behavior

- Studies show increases in adaptive behavior through adolescence followed by a plateau over time.[15] Individuals with FXS who have lower cognitive functioning and more autism symptoms have lower adaptive behavior trajectories.[18]

Socio-emotional Skills

- Males, and females to a lesser degree, are likely to display deficits in social development and social interaction over time. Moreover, problem behaviors are more likely to occur during social situations as they may induce anxiety.[19]

Communication

- Expressive language tends to be more impaired than receptive language,[20] with delays in all domains.

Behavior

- A majority of individuals with FXS experience behavioral symptoms, with males having higher rates of prevalence than females.[10,21] See Figure 3.
  - Many of these behaviors manifest in early childhood and persist into adulthood, with some peaking in adolescence and others consistent over time.
  - Many of these behaviors cluster together with attention problems, anxiety, and hyperactivity most commonly presenting together.

Comorbid Conditions

- Reports of comorbidity of autism spectrum disorder diagnoses range from 15% to 52% in males with FXS,[11] with rates of approximately 16% in females.[10]
- Approximately 15% of males with FXS have been reported to experience seizures, with lower percentages reported for females.[12,22]
- Increased prevalence rates have also been reported for recurring otitis media, gastrointestinal problems, strabismus, and sleep problems.[23]

Symptoms and Disease Management

- Disease management is focused on a variety of symptom-specific medications and specialized therapies. Pharmacological intervention is primarily used to address behavioral symptoms and comorbid medical conditions (e.g., seizures).
- On average, 61% of males and 38% of females with FXS take at least one medication; half (50%) of males and a quarter (26%) of females took two or more medications.[24]
  - The most common symptoms being treated in males were anxiety (42%), attention problems (37%), hyperactivity (27%), and anger/aggression (24%).[24]
  - For females, the most common symptoms being treated were anxiety (26%), attention problems (23%), hyperactivity (11%), and mood swings (11%).[24]
- Depending on the behavioral symptom, between 20% and 30% of caregivers reported that medications for males had little or no effect (Figure 4).[24]
- Studies have suggested that a more careful examination of side effects and measures of effectiveness is warranted for those who are prescribed psychotropic medications.[25,26]

Quality of Life

Family Life

- In a large national survey, approximately one-third of families report that they had low levels of social support, and approximately half said that having a child with FXS had affected their family social life.[27]
- Parenting stress is higher and family adaptability is lower in families who have a child with FXS when compared with those with children with Down syndrome.[28-01]
- On average, families reported having to take 17.7 hours off work in the last month, 35% had someone quit working, 28% had turned down a job or promotion, 54% changed work hours, and 26% changed jobs.[31]

Caregiver

- Mothers of a child with FXS experienced elevated rates of stress, depression, anger, anxiety, with half scoring in the clinical range in these domains, and many taking medication to help with these symptoms.[32]

Patient

- A study of the health-related quality of life for individuals with FXS using a utility index derived from the Aberrant Behavior Checklist reported health states ranging from 0.16 to 0.92, with higher scores indicating better health.[33]
- An international study of health-related quality of life of adults with FXS reported mean utility scores ranging from 0.52 (France) to 0.73 (Spain).[34]

CONCLUSIONS

- FXS impacts several clinical domains; however, behavioral symptoms have the most profound impact on the individual. Although limited, the data suggest behavioral symptoms can be a mediating factor on family and caregiver quality of life.
- Several pharmacological interventions are available to address the various behavioral symptoms, but they are not helpful in all cases and the level of functional improvement or efficacy is not well characterized.
- There is a need for new treatment options to address the unmet clinical need and help minimize the impact on quality of life for patients, caregivers, and families.

REFERENCES

See handout for references.

CONTACT INFORMATION

Melissa Raspa, PhD
Senior Scientist

RTI International
3040 Cornwallis Road
Research Triangle Park, NC 27709

Phone: +1.919.541.8736
E-mail: mraspa@rti.org

AMCP Managed Care & Specialty Pharmacy Annual Meeting, April 23-26, 2018, Boston, Massachusetts

The authors do not have any information to disclose or any conflict of interest.