Community views on medication use in fragile X syndrome

Sarah Eley (s.eley@ed.ac.uk)
The University of Edinburgh https://orcid.org/0000-0001-8455-3670

Andrew G. McKechanie
University of Edinburgh Division of Medical and Radiological Sciences: The University of Edinburgh Division of Health Sciences

Andrew C. Stanfield
University of Edinburgh Division of Medical and Radiological Sciences: The University of Edinburgh Division of Health Sciences

Research Article

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Abstract

Objectives

The difficulties inherent in conducting clinical trials in fragile X syndrome (FXS) mean that investigators must be judicious in selecting which potential therapeutic interventions to trial. To inform the development of future trials we set out to examine what the attitudes of families are to taking medication, and to participating in medication trials, including what their priorities for intervention are.

Results

Seventy three people completed the questionnaire. The majority reported being interested in taking part in medication trials. Over 50% of respondents were either unaware or had no opportunity to participate in trials. The priorities for future trials were anxiety, learning, language, attention and social behaviour. Attention was more commonly listed as a priority for children, whereas social behaviour was more common in adults.

Introduction

Fragile X syndrome (FXS) has a prevalence of around 1.4 per 10,000 males and 0.9 per 10,000 females (1). The degree of intellectual disability (ID) in individuals with FXS can vary considerably ranging from mild to severe; with males typically more affected than females (2). Alongside the well-documented physical characteristics and ID (3) associated with FXS, there are often a wide range of behavioural features reported. Individuals with FXS are commonly diagnosed with anxiety, ADHD and autism and present with over-arousability, impulsivity, aggression, poor language development and seizures (4, 5). Medications are not always prescribed for individuals with FXS; instead it is often a multidisciplinary approach that is used (2) as not all individuals require medication, and behaviours exhibited in younger years may become less problematic as they get older (4).

In recent years, there have been a large number of clinical trials for FXS (6). These are primarily of new or repurposed medications targeted at the core pathophysiology of the condition. In addition to these studies there have been some trials of existing medicines which aim to treat symptoms which, although not core symptoms, may be associated with FXS, such as anxiety, sleep problems and features of ADHD. One trial showed a positive result in the use of stimulants in FXS for treating hyperactivity (7), and melatonin has also been trialled in FXS showing improvements in sleep disturbance (8). Low-dose sertraline (an SSRI) has also been trialled in young children; although anxiety was not directly assessed in this study, significant improvements were shown in cognition, visual perception and fine motor skills (9).

The difficulties inherent in conducting clinical trials in FXS (10) mean that investigators must be judicious in selecting which potential therapeutic interventions to trial. In order to inform the development of future

trials we therefore set out to examine what the attitudes of families affected by FXS are to taking medication, and to participating in medication trials, including what their priorities for intervention are.

Methods

Procedure

A questionnaire was completed by parents, carers and by people with FXS. Parents/carers were permitted to assist those with FXS to complete the questionnaire. The questionnaire was made up of 16 questions (supporting information). These examined current medication use, perceived need for medication, previous involvement in clinical trials, what they would like medication to help with and if they were interested in future clinical trials of medicine.

Recruitment

Recruitment proceeded through four sources. Firstly a link to an electronic copy of the questionnaire was emailed to families through the UK Fragile X Society, the main support organisation for families in the United Kingdom. In addition a link to the questionnaire was emailed to individuals registered with our research centre, the Patrick Wild Centre, at The University of Edinburgh. A link to the online version of the questionnaire was also advertised on the Patrick Wild Centre website, Facebook page and Twitter feed. Finally, 24 international Fragile X societies were contacted and 4 promoted the study on their social media platforms. In order to participate, all individuals had to be over the age of 18 and either be a family member or a carer of someone with a diagnosis of FXS or have FXS themselves.

Analysis

The analysis for the questionnaire data was conducted using IBM Statistical Package for SocialScience (SPSS) (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The primary results were considered using descriptive statistics. Chi-squared tests were used to determine whether age made a difference to medication use and motivation to take part in trials.

Results

Participants

A total of 73 People completed the questionnaire; 71 were parents of individuals with FXS, 1 was a carer, and 1 had a diagnosis of FXS. The age of people with FXS being discussed ranged broadly from infants to adults with the largest group (54.4%) being in the 16–29 bracket, of these 85.7% were male and 17.1% female. Results were collected from 10 countries; 71.8% UK, 15.5% USA and Canada, 8.5% rest of Europe and 4.2% other.

Use of, and attitudes towards, medication

Of the 73 respondents, 71 people gave responses about medication use. 43.7% (n = 31) were prescribed psychotropic medication; 22 people were prescribed an SSRI, 9 were prescribed a stimulant, 8 were prescribed melatonin and 8 were prescribed antiepileptic drugs. Other medicines prescribed include: cannabidiol (CBD), risperidone, other antipsychotics, metformin and minocycline. There was no significant difference in psychotropic medicine use between adults and children (47.8% vs 40.9%, χ^2 = 0.29, p = 0.59)

In the UK 52.9% people were on medication, compared to 81.8% in Canada/U.S.A, and 33.3% in the rest of Europe and other countries. Figure 1 shows medication use by country/region.

Of the 40 (56.3%) not on psychotropic medication, 17 (42.5%) said they felt the person they cared for would benefit from taking medication to help with their mental health or behaviours. Of those individuals not on medication, 47% of respondents reported wanting help with anxiety and 29% reported wanting medication to help with a variety of behaviours. Of note, 38 (52.8%) of all respondents stated they had not heard of any medicines which may have been helpful in treating mental health symptoms or certain behaviours associated with FXS. Interestingly, 29% of all respondents said they had been unable to start medication due to a healthcare professional being unwilling to prescribe or having difficulties accessing services; all of these responses came from the UK.

Attitudes towards trials

Of the collected responses, 55.6% had heard of clinical trials that had been conducted in FXS with 12.7% who had taken part in one. Participants were asked if they would be interested in the person they care for taking part in a trial. 68% of people reported being interested if it was a trial of an already-available medicine where more was known about side effects and 59% would still be interested in trials of novel medicines. There was no significant difference in interest in trials of novel medicines in adult vs children (52.3% vs 72.7% χ^2 = 2.5 p = 0.11) or interest in repurposed medicines in adult vs children (64.4% vs 77.3% χ^2 = 1.1 p = 0.29).

51.6% reported not taking part in previous trial due to not being aware of any or not being asked to take part, whilst 16.7% felt that distance/travel prevented them from participation, and 11.7% wanted to take part but did not meet the inclusion criteria. Other reasons noted for not taking part included not being willing to come off current medication, the added pressure/time commitment, concern about side effects and behaviour not severe enough.

Priorities for future trials

Figure 2 shows what respondents would like to see medication trials helping with. The top two priorities reported were help with anxiety and learning; with both being noted as priorities by over 80% of respondents. Over 50% of respondents wanted future trials to look at improving language, attention and social behaviour. Of those who endorsed the ‘other’ category, novel responses that were not covered elsewhere included seizure medication more suited for FXS or medication for gastrointestinal symptoms. Of these responses, two differed between children and adults; hyperactivity was rated significantly more

often by parent/carers of children than adults (59.1% vs 25% $\chi^2 = 7.3$ p = 0.01) whereas social behaviour was rated significantly more often by parents/ carers of adults (61.4% vs 31.8% $\chi^2 = 5{,}1$ p = 0.02)

Discussion

In this study we set out to examine medication use in people with FXS and to determine community priorities for future clinical trials. We found that over half of respondents were already prescribed medication, these were predominantly SSRIs, stimulants, melatonin and antiepileptic drugs. There was a greater percentage of people prescribed medication in USA/Canada than in other countries with stimulant prescriptions primarily accounting for this. These results are similar to those from trials looking at other neurodevelopmental conditions showing that people in the USA/ Canada are more likely to be prescribed medication than those from other parts of the world (11, 12). Just under half of those not taking medicine highlighted that they would like to have access to medicines, particularly to help with anxiety and difficult behaviour, and 29% of participants reported not being able to access medicine due to an unwillingness from healthcare professionals to prescribe – notably all of these responses came from the UK. Common co-occurring mental disorders (e.g. anxiety and ADHD) should be considerd in FXS and treated where they exist (13), but the current study shows clear geographical variation in prescription habits, as well as a perceived difficulty in accessing medication in the UK. While some studies do exist (7–9) the development of an evidence base in regard to the efficacy of existing treatments in fragile X syndrome is required in order to guide clinicians and ensure that treatments are received or withheld appropriately.

With regard to trials, it was interesting to note that only half of respondents had heard about medication trials in FXS despite almost two thirds being interested in taking part in a trial of an already available medicine. There therefore appears to be a clear appetite within the FXS community for medication trials to take place and highlights the need for trials to be well advertised, so that those who would like to take part can be given the opportunity. The reasons for not wanting to take part in trials were mainly not being aware of any, travel, concern about coming off current medication and side effects, findings which are similar to previous studies carried out in this area (10, 14, 15)

Anxiety and ability to learn were the two most frequently endorsed priorities highlighted for targeting by future trials, with language, attention and social behaviour also highlighted by more than half of participants. It is interesting that two of these five priorities (anxiety and attention) are areas for which medications already exist but, as mentioned above, there is a lack of strong evidence for their use in fragile X syndrome (16). A search of clinicaltrials.gov for fragile X syndrome shows 58 registered treatment trials for medication (8 of which are currently ongoing) (17); of these none employed existing treatments to target either anxiety or attention, suggesting that this is an unconsidered area in fragile X. The other priorities (learning, language and social behaviour) are more usually regarded as ‘core’ features of fragile X and do tend to be addressed by the identified studies on clinicaltrials.gov (which are primarily of treatments targeted at the underlying pathophysiology of the condition).

In summary, this study demonstrates that medication use is common within the fragile X community and that there is an appetite for clinical trials, especially targeting anxiety and learning. Almost all recent medication trials are targeted at core features of the condition, suggesting that there is a need for more studies to guide clinicians around the effective use of existing treatments for associated features.

Limitations

While there are responses from 10 countries worldwide, the results are still limited by a relatively small sample size. The survey was advertised via several routes, however there may be a degree of ascertainment bias, with those more actively engaged with FXS communities and thus more likely to see the adverts not being fully representative of the wider fragile X communities. We were unable to collect a representative sample of genders, which may have an impact on results as we know males with FXS are often more affected. The study did not specifically ask about side effects of medications - while side effects were not reported as a specific reason for not taking medications this would be interesting to study further.

Abbreviations

ADHD – attention deficit hyperactivity disorder

FXS – fragile X syndrome

SPSS - Statistical Package for Social Science

SSRI – Selective serotonin reuptake inhibitors

Declarations

Ethics approval and consent to participate

The questionnaire and methodology for this study was approved by the Edinburgh Medical School Research Ethics Committee on the 16th February 2021. REC Reference: 20-EMREC-017

Informed consent was not required. An information sheet was included on the first page of the questionnaire and consent was implied through its completion.

Consent to publish

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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No funding was obtained for this project.

Authors' Contributions

SE designed study, acquired data, analysed data and prepared first draft of paper

AM analysed data and modified paper

AS designed study, analysed data and modified paper

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Figures

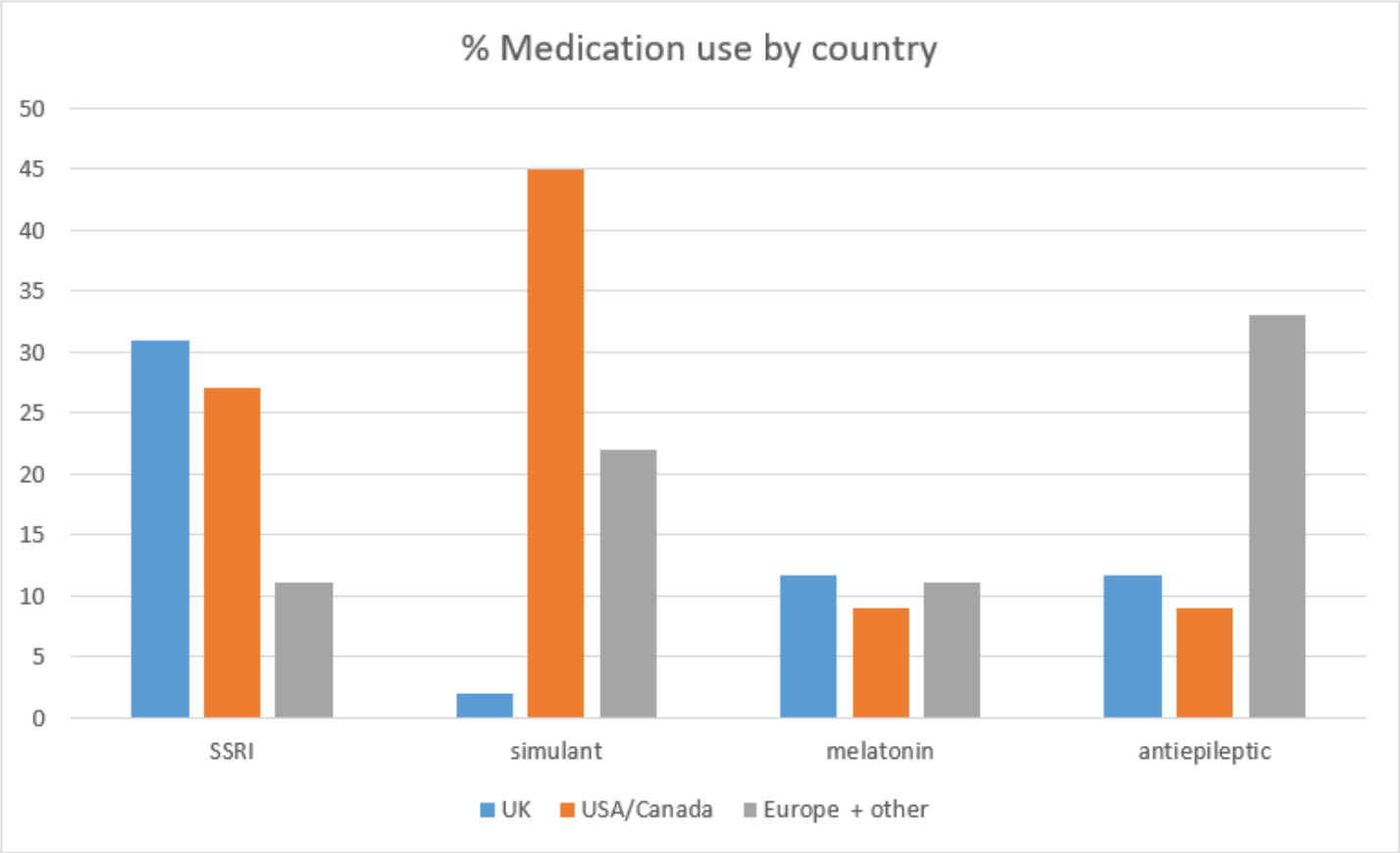

Figure 1

Number or respondents endorsing each prescribed medication per country

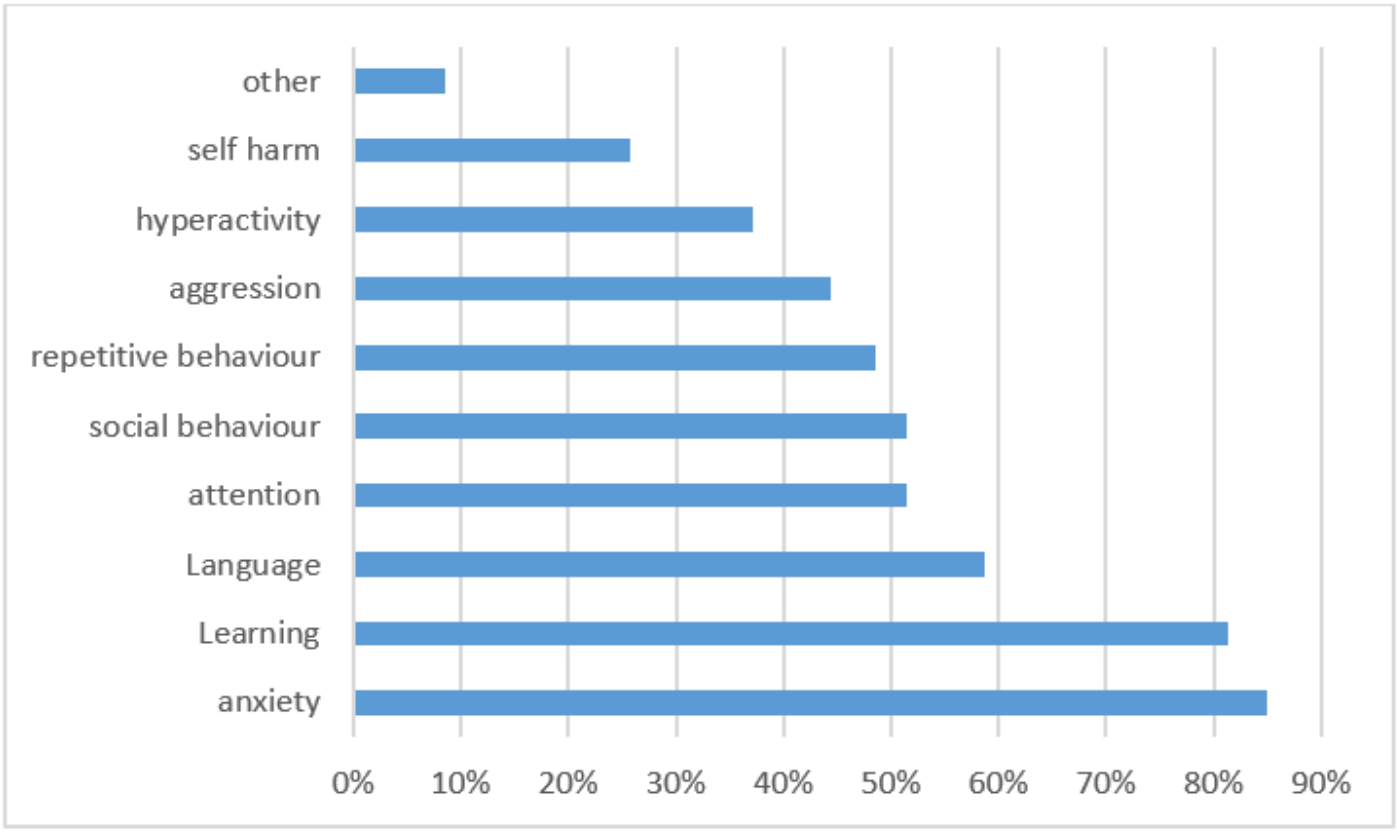

Figure 2

Number or respondents endorsing each item that they would like medication trials to help with.

Supplementary Files

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- STROBEchecklistv4combined.docx