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ORIGINAL ARTICLE

Results of a Nation-Wide Survey Evaluating Psychotropic Medication Use in Fragile X Syndrome

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Abstract Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. The behavioral phenotype associated with FXS includes hyperactivity, anxiety, and sometimes problem behaviors for which stimulants, antipsychotics, and SSRI antidepressants are prescribed. Little information, however, is known about the side effects individuals with FXS may experience as a result of taking these medications. Using a nation-wide survey, this study examined the prescription patterns of psychotropic medication use within the FXS population and the prevalence of side effects associated with psychotropic medication use by people diagnosed with FXS. Significant associations were found between the most commonly prescribed medications and side effects for our total sample. These findings give insight to the different dimensions of medication use in people diagnosed with FXS.

Keywords Fragile X syndrome · Psychotropic medication · Side effects

Fragile X syndrome (FXS), the most common inherited cause of mental retardation, is caused by the inactivation of the FMR1 gene, responsible for the production of the fragile X mental retardation protein (FMRP) (Sherman 2002). This inactivation and the subsequent adverse effect on the production of FMRP are significant as FMRP is involved in synaptic development. One hypothesized mechanism of action is that FMRP may regulate metabotropic glutamate receptor (mGluR) activity via a negative feedback system. Without FMRP production, mGluR remains unchecked and an enhancement in long term depression (LTD) is observed (Bear et al. 2004). As a result, synapses fail to mature presenting with an increased density of long,

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small, thin spines (Beckel-Mitchener and Greenough 2004). The over-activation of mGluR is thus hypothesized to account for some of the phenotypic characteristics associated with FXS - seizure activity (Berry-Kravis 2002; Chiurazzi et al. 2003; Yan et al. 2005), psychiatric issues (e.g., Attention Deficit Disorder, Social Phobia, Impulse Control Disorder, Obsessive-Compulsive Disorder (OCD), (Bear et al. 2004; Tsiouris and Brown 2004), and possibly behavior problems (e.g., hyperactivity, aggression) (Berry-Kravis and Huttenlocker 1992; Hagerman 2002a).

To treat the psychiatric and behavioral phenotype of FXS, psychotropic medications are often prescribed. These medications routinely include stimulants, antidepressants, and antipsychotics (Tsiouris and Brown 2004). Given their mood stabilizing effects, anticonvulsants have also been recommended (Hagerman 1997; Hagerman 2002b). Despite these common practices, limited clinical trial research has been conducted on the efficacy of these medications for the treatment of disorders associated with FXS. Hagerman and colleagues (1994) surveyed patients at their clinic who were taking fluoxetine, an SSRI antidepressant, and found that fluoxetine was beneficial for most of their sample; however, a large percentage of their sample also experienced some type of side effect as a result of the medication use.

Although little clinical trial research has been conducted to evaluate effectiveness of various psychotropic medications prescribed to those with FXS, even less research has been conducted on prescription patterns or the untoward effects of these medications in this population. Generally, evidence suggests that individuals with developmental disabilities are more likely to experience adverse side effects associated with psychotropic drug use than the general population (Kalachnik 1999). However, very little information exists on the types of side effects most often experienced by individuals with FXS. Given this possible increased risk for experiencing side effects and the sparseness of evidence regarding side effects of psychotropic medication in FXS, we felt it important to evaluate the side effects experienced by those with FXS using psychotropic medication. Hence, the aim of this study was to survey what psychotropic medications are being used by individuals with FXS and to explore/identify relationships between a particular medications and side effects.

Method

This study involved a nationwide survey of parents/care providers of individuals with FXS. A cover letter and questionnaire was mailed out nationally by the National Fragile X Foundation, to all individuals on their mailing list. There were 2896 packets mailed of which 216 packets were returned as undeliverable. From this distribution, 392 surveys were completed resulting in a 14.6% response rate.

The survey instrument developed for this study (See "Appendix A") was based on a version used by Valdovinos and Schroeder (2003) and contains items regarding age, gender, ethnicity (American Indian or Native Alaskan; Asian or Pacific Islander; Black, not of Hispanic origin; Hispanic; White, not of Hispanic origin; Other), co-existing health conditions (Seizure disorder, GERD, Hypertension, Insomnia/Sleep Disturbances, Diabetes, Other, None), Autism diagnosis, psychiatric diagnoses (ADHD, Depression, Anxiety disorder, OCD, Bipolar disorder, Impulse Control

disorder, Social Phobia, Other, None), level of functioning [No intellectual disability (mental retardation), Mild, Moderate, Severe, or Profound intellectual disability (mental retardation)], and behavioral issues (Hyperactive, Inattention, Aggression, Self-injurious behavior (SIB), Property destruction, Tantrums, Other, None). These items were on the questionnaire to determine if there are variables that were correlated with the occurrence of side effects of psychotropic drug use in individuals.

The form also contains questions about current and prior psychotropic medications use, specifically, the name of medication, dose, purpose, prescribing physician, date initiated, effectiveness, effect on target behavior, and changes in psychotropic medication in response to side effects. This information was included in an attempt to allow us to determine what the current trends and perceived efficaciousness of psychotropics are in prescribing these medications to those with FXS. With regard to side effects experienced, a list of the most common side effects associated with psychotropic drugs, as well as those most commonly experienced by people with Fragile X (Drowsiness, dizziness, tired, insomnia, headache, diarrhea, constipation, nausea, vomiting, weight gain, weight loss, increased appetite, decreased appetite, tremors, twitching, anxiety, decreased concentration, nervousness, strange movements, dry mouth, and hypotension) (Hagerman et al. 1994), were listed but respondents were also provided with the opportunity to list additional side effects not included in the list. The rationale for providing both direct and open-ended questions is to control for under-reporting and over-reporting.

Data were coded and entered into a database. As data were entered, each medication taken by a respondent was considered as one observation. So, if a person was on five different medications they were counted as five separate observations. Different levels of analyses were conducted. Since there were so many different medications (a total of 51 different psychotropics reportedly used) and combinations of medications reportedly used, it was impossible to conduct any type of meaningful analysis for our sample without being forced to combine medications into medication classes. Having divided medications into classes (anticonvulsants, stimulants, atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and alpha-adrenergics), we only conducted analyses for those classes with more than 40 observations (other classes had numbers too sparse to analyze). After evaluating those results, we further analyzed data for four medications: methylphenidate (Ritalin), dextroamphetamine (Adderall), risperidone (Risperdal), and sertraline (Zoloft). These were the only medications that were used by more than 50 individuals within our sample (see Table 1). We also assessed side effects in two manners, individually and grouped [gastrointestinal effects (Constipation, Diarrhea, Less Hungry, More Hungry, Nausea, Vomiting); neurological effects (Dizziness, Headache, Strange Movements, Tics, Tremors, Twitching); sedation effects (Drowsiness, Sleeps More, Tired); and overall health effects (Change In Blood Pressure, Weight Gain, Weight Loss, Dry Mouth)].

Results

Out of the sample, there were 299 people on medication or who had taken medication and 90 who were not nor had not ever been on medication (numbers do

Table 1 Medications used in analysis

Medication	Number of Current/Most Recent Observations (Total Observations)
Methylphenidate (Ritalin)	68 (181)
Dextroamphetamine (Adderall)	40 (85)
Risperidone (Risperdal)	39 (64)
Sertraline (Zoloft)	36 (56)

not add up to 392 as there were some individuals who did not correctly complete the questionnaire and thus the questionnaires were not be included in the analysis). Data presented in this paper are for those individuals who were taking psychotropic medication. For purposes of this analysis, respondents were grouped by age: Children under 13 years, Adolescents 13–18 years, and adults over 18 years of age. Of the 299 individuals who had been reported to have used psychotropic medication, 130 were children, 55 were adolescents, and 114 were adults. A large majority of the sample was Caucasian males (265 males and 34 females). Information was collected for both current and prior medication use. As such, data were analyzed for either current/most recent use or overall use (current/most recent + past).

Frequency for variables in sample. Grouping medications into classes of similar mechanisms of action the following are counts for overall medication use 338 counts of stimulants, 23 counts non-stimulants, 69 counts alpha-adrenergics, 165 counts of SSRIs, 10 counts of tricyclic antidepressants, 1 count of MAOI, 15 counts of other antidepressants, 120 counts of atypical antipsychotics, 14 counts of typical antipsychotics, 83 counts of anticonvulsants, 21 counts of anxiolytics, and 7 counts of beta-blockers.

With regard to level of functioning, most of our participants were diagnosed with either mild or moderate intellectual disabilities (mental retardation). Table 2 presents the number of current/most recent users and overall users of Ritalin, Adderall, Risperdal, and Zoloft by level of intellectual disability (level of retardation). (The numbers in the table do not total the number in parentheses as individuals may have been reported to be using medications other than the four listed here or multiple medication use may have been reported.) It appears that those diagnosed with less severe intellectual disabilities were more often reported to be using stimulants (Ritalin and Adderall) whereas those with more severe intellectual disabilities were more often reported to be using Risperdal and Zoloft.

Consistent with the literature, the most common psychiatric diagnosis for our sample was Attention Deficit Hyperactivity Disorder broadly defined followed by Anxiety disorders (Hagerman, 2002a). Also, one-fourth of the sample reported having a diagnosis of autism which is also consistent with previous research. Table 3 presents the number of psychotropic medications prescribed per psychiatric diagnosis. Ritalin, Adderall, and Risperdal were more often observed to be used

Table 2 Number of psychotropic medications by level of intellectual disability (mental retardation)

	Methylphenidate (Ritalin) C/O	Dextroamphetamine (Adderall) C/O	Risperidone (Risperdal) C/O	Sertraline (Zoloft) C/O
No MR (9/15)	1/2	1/2	0/0	1/1
Borderline Intelligence (5/6)	0/1	2/2	0/0	1/1
Learning Disability (45/67)	10/19	9/13	4/5	4/5
Mild MR (82/104)	21/51	11/26	8/12	15/21
Moderate MR (115/142)	27/54	15/24	15/25	9/15
Severe MR (26/26)	3/7	0/2	11/15	1/4
Don't know (15/30)	3/7	2/4	0/0	5/5

Numbers in parentheses indicate number of individuals (using psychotropics/total sample) with level of intellectual disability (mental retardation). Two respondents did not provide a response. C = Current/Most Recent Use; O = Overall Use

with those who had a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) (broadly defined), Anxiety Disorder, and Autism. Zoloft was most often reported as used by those with a diagnosis of ADD and Anxiety Disorder.

As to behavior problems, the most commonly reported behavioral issues were: anxiety, hyperactivity, tantrums, and difficulty paying attention. Fewer respondents reported self-injurious behavior (SIB), refusal/oppositional behavior, aggression, and withdrawal to be problems. And even fewer reported property destruction, other behaviors, or an absence of problem behaviors. When we compare the existence of problem behaviors in those using medication to the entire sample, it is observed that an overwhelming majority of those individuals with any given problem behavior use psychotropic medication which is not unexpected. Table 4 presents the number of psychotropic medications prescribed per problem behavior. Ritalin and Adderall

Table 3 Number of psychotropic medications by psychiatric diagnosis

	Methylphenidate (Ritalin) C/O	Dextroamphetamine (Adderall) C/O	Risperidone (Risperdal) C/O	Sertraline (Zoloft) C/O
Attention Deficit Hyperactivity Disorder (164/180)	50/141	29/57	17/30	20/28
Depression (26/31)	2/8	2/5	6/6	4/7
Anxiety (101/108)	22/59	8/24	13/21	20/29
Obsessive Compulsive Disorder (54/58)	12/29	3/10	10/17	6/11
Bipolar (4/4)	0/0	0/0	1/2	0/0
Impulse Control (44/47)	10/20	2/7	5/11	5/6
Social Phobia (24/29)	2/11	3/7	3/3	3/5
Autism (101/117)	15/48	14/28	18/26	9/12
Other (46/53)	9/23	4/10	9/12	7/8
None (41/90)	9/13	7/9	7/7	4/5

Numbers in parentheses indicate number of individuals (using psychotropics/total sample) with diagnosis. C = Current/Most Recent Use; O = Overall Use

Table 4 Number of psychotropic medications by problem behavior

	Methylphenidate (Ritalin) C/O	Dextroamphetamine (Adderall) C/O	Risperidone (Risperdal) C/O	Sertraline (Zoloft) C/O
Hyperactivity (302/330)	48/100	29/55	24/38	17/26
Difficulty Attention (254/310)	63/133	38/71	31/48	28/42
Aggression (134/141)	20/60	17/35	31/45	16/25
SIB (146/168)	24/69	23/43	24/38	19/27
Refusals Opposition (143/164)	27/66	20/39	27/38	16/24
Property Destruction (76/83)	12/32	6/14	22/28	10/15
Tantrum (304/317)	17/52	18/32	28/35	15/21
Anxiety (300/336)	45/107	26/54	26/42	33/46
Withdrawal (83/98)	17/39	8/19	12/16	16/22
Other (22/30)	2/7	4/5	2/7	2/3
None (4/20)	1/1	0/0	0/0	0/0

Numbers in parentheses indicate total number of individuals (using psychotropics/total sample) with behavior issue. C = Current/Most Recent Use; O = Overall Use

were most often reported for hyperactivity, difficulty with attention, and anxiety whereas Risperdal was most often reported for difficulty with attention, aggression, and anxiety. Finally, Zoloft was most often reported for difficulty with attention and anxiety. Unexpected were the number of individuals reported to have difficulty with anxiety who were prescribed stimulants. When we delved further into our data, we found that 67% of individuals with an anxiety disorder were also diagnosed with ADHD thus offering an explanation as to why so many with anxiety were using stimulants.

Data analysis for overall use. To analyze the relationship between reported side effect groups and psychotropic medications for our sample for overall medication use, we conducted Chi Square analyses ($p<.01$). Given the small number of items per cell, we were only able to provide information about the relationships between medication classes and side effect groups; however, we can postulate which specific side effects were driving the interactions (noted in parentheses). Positive associations were found for gastrointestinal effects and stimulants (loss of appetite), atypical antipsychotics and sedation (tired, drowsiness, and more sleep), and atypical antipsychotics and overall health (weight gain). There was also a positive interaction between sedation effects and alpha adrenergics (drowsiness, tired, and more sleep) (Table 5). At the $p<.05$ level, there was a relationship between the lack of experiencing side effects and atypical antipsychotics and overall health (weight loss and other side effects) and alpha adrenergics.

We were unable to determine which side effects were positively associated with worsening of problem behaviors. However, we did find that those who reported experiencing side effects were more likely to report problem behaviors worsening than those who did not [$\chi^2(1, N=740)=26.995, p<.0001$]. When we evaluated the four medications, we found that behaviors were reported to worsen when side effects were present for those individuals using Adderall and Ritalin [$\chi^2(1, N=181)=5.52,$

Table 5 Interactions between side effects and psychotropic medications

	df	*N*	x^2 Value	*p*
No side effects & Anticonvulsants	1	580	.0403	.8389
Gastrointestinal & Anticonvulsants	1	740	.0703	.7900
Neurological & Anticonvulsants	1	740	.7315	.3924
Sedation & Anticonvulsants	1	740	.0890	.7655
Overall health & Anticonvulsants	1	740	.2946	.5873
No side effects & Stimulants	1	580	3.59	.0580
Gastrointestinal & Stimulants	1	740	25.54	<.0001
Neurological & Stimulants	1	740	.7389	.3900
Sedation & Stimulants	1	740	1.24	.2646
Overall health & Stimulants	1	740	.0005	.9821
No side effects & Atypical Antipsychotics	1	580	5.09	.0241
Gastrointestinal & Atypical Antipsychotics	1	740	.2138	.6438
Neurological & Atypical Antipsychotics	1	740	.3170	.5734
Sedation & Atypical Antipsychotics	1	740	18.68	<.0001
Overall health & Atypical Antipsychotics	1	740	15.66	<.0001
No side effects & SSRI's	1	580	2.72	.0994
Gastrointestinal & SSRI's	1	740	1.37	.2423
Neurological & SSRI's	1	740	.2021	.6530
Sedation & SSRI's	1	740	.0135	.9075
Overall health & SSRI's	1	740	2.32	.1276
No side effects & Alpha Adrenergic Stimulants	1	580	.0170	.8963
Gastrointestinal & Alpha Adrenergic Stimulants	1	740	1.28	.2577
Neurological & Alpha Adrenergic Stimulants	1	740	.4352	.5095
Sedation & Alpha Adrenergic Stimulants	1	740	21.45	<.0001
Overall health & Alpha Adrenergic Stimulants	1	740	6.12	.0134

$p<.05$, $p<.01$

$p<.0188$]. Using logistic regression analysis we attempted to determine the relationship between age and worsening of problem behavior and side effects present and found that age was not a mitigating factor. Furthermore, we were unable to determine which side effects accounted for the worsening of any problem behavior.

Data analysis for current/most recent use. We also analyzed the interactions observed between side effect groups and medication classes across our age groups. For children there was a positive relationship observed between gastrointestinal effects and stimulants (weight loss) [$\chi^2(1, N=130)=4.20$, $p=.040$]. For adolescents the only positive relationship observed was between stimulants and gastrointestinal effects (loss of appetite) [$\chi^2(1, N=55)=9.36$, $p=.002$]. And finally, for adults we found the most number of significant interactions between side effect groups and medication classes. There were positive relationships between overall health effects and anticonvulsants [$\chi^2(1, N=114)=6.54$, $p=.0106$] and overall health effects and atypical antipsychotics (weight gain) [$\chi^2(1, N=114)=6.07$, $p=.0137$]; between sedation effects and atypical antipsychotics [$\chi^2(1, N=114)=11.90$, $p=.0006$] and alpha adrenergics and sedation effects (drowsiness, tired, and sleeps more) [$\chi^2(1, N=114)=3.88$, $p=.0489$]; and between gastrointestinal effects and stimulants (loss of appetite) [$\chi^2(1, N=114)=4.76$, $p=.0292$]. However, adults were also found to be less likely to experience a lack of side effects with atypical antipsychotic use as well [$\chi^2(1, N=93)=9.96$, $p=.002$].

To determine what might account for the differences in side effects experienced across age groups, we analyzed the type of medication class prescribed (using the classes with over 40 cases as the criterion for inclusion) and the total number of medications prescribed per age group. Although adults were more likely to be prescribed anticonvulsants, atypical antipsychotics, and SSRIs, these differences were not significant (see Table 6). To determine if adults were more likely to be prescribed more psychotropic medication (polypharmacy), and thus accounting for the increase in side effect/psychotropic medication class interactions, we conducted a regression analysis. However, the results of this analysis were insignificant (R^2=.03).

Although the sample size did not allow for analysis of the effects that interclass vs. intraclass polypharmacy may have on side effects experienced, we did examine patterns of prescribing. Very little intraclass polypharmacy was observed in this sample. There were eight individuals who were prescribed more than one anticonvulsant, five individuals who were prescribed more than one atypical antipsychotic, four individuals prescribed more than one stimulant, two individuals prescribed more than one non-SSRI, one individual prescribed more than one SSRI, and one individual prescribed more than one anxiolytic. With regard to interclass polypharmacy, there appeared to be more common prescription patterns although the number of combinations was relatively low (see Table 7). Specifically, there more individuals prescribed both SSRI and stimulant medications.

Looking at Ritalin, Adderall, Risperdal, and Zoloft and the side effects individuals were most likely to report, we found more individuals currently taking Ritalin reported decrease in appetite as a side effect (24 out of 68 individuals) or reported a lack of side effects experienced (22 out of 68 individuals). For those using Adderall, a majority of individuals reported drowsiness as a side effect (36 out of 41 individuals). Of the individuals taking Risperdal, the side effect most often reported was weight gain (15 out of 39 individuals). Few side effects were reported for those taking Zoloft (15 out of 36 individuals reported a lack of side effects experienced).

Finally, we attempted to determine which medications were more likely to be associated with behaviors improving and worsening; however, the sample size did not allow for the analysis. Instead, we examined which medications were more likely to be discontinued as a possible indication of medication efficacy. We found that a greater proportion of individuals reported discontinuing Ritalin (51.97%) and Adderall (43%) than Risperdal (30%) and Zoloft (32%). Essentially, what we determined is that the stimulant medication class, although

Table 6 Percentage of individuals taking medications

	Anticonvulsants	Stimulants	Atypical Antipsychotics	SSRIs	Alpha Adrenergics
Children	13.08%	48.46%	18.46%	26.92%	14.61%
Adolescents	16.37%	61.82%	21.82%	34.55%	14.55%
Adults	19.29%	36.84%	23.68%	39.47%	10.53%
Total Sample	16.72%	46.49%	21.07%	33.11%	13.04%

Table 7 Number of individuals prescribed more than one medication from each class

	Typical Antipsychotic	Atypical Antipsychotic	Tricyclic Antidepressant	SSRI	Non-SSRI	Anxiolytic	Stimulants	Beta-Blockers	Alpha Adrenergics	Lithium	Strattera
Anticonvulsant	0	18	1	11	1	9	8	1	5	0	2
Atypical Antipsychotic			0	20	5	10	18	1	7	1	2
SSRI					0	6	34	2	15	2	2
Non-SSRI						1	3	0	1	0	1
Anxiolytic							3	1	2	2	1
Stimulants								0	12	1	0
Alpha Adrenergics										1	0

most likely to be used, is the most likely to be discontinued over all other medication classes.

Discussion

This study attempted to measure various variables and their relationship to psychotropic medication use in individuals with FXS. Specifically, we examined individual characteristics (i.e., age, diagnosis, and problem behaviors), side effects, medications used, effectiveness of medication use, and changes in medication use. Responses obtained were incredibly varied suggesting that when it comes to pharmacologically treating psychiatric and behavioral symptoms of individuals with FXS there are no clear patterns that emerge making it difficult to assess efficacy of psychotropic medications for this population.

Ultimately, we determined that the side effect groups associated with reported medication classes were consistent with what is observed in the general population. For example, those taking atypical antipsychotics were reported to experienced sedation effects as is also observed in the general population. Unfortunately, we were unable to conclusively determine specific relationships beyond medication classes and side effect groups given the small sample size but were able to postulate which side effects within the group were most likely contributing to the associations.

In addition, we also observed that increased age was associated with more side effects experienced and not necessarily more of the same side effects experienced. That is to say, the types of side effects reported to occur seemed to change as a function of age not type of medication prescribed, as our analysis revealed that children, adolescents and adults were proportionally on comparable amounts of each psychotropic class. Furthermore, there was no evidence to support that that older, individuals were more likely to be reported to be taking multiple medications which may have possibly caused medication interactions that could account for the side effects reported.

This study is not without limitations. First, there was non-compliance with instructions for completing the questionnaire despite providing examples for completing the form making it difficult to code and enter all data or to complete all desired analyses. For example, some respondents were able to provide information about doses of prior medications used but not all respondents were able to provide that information. Therefore, we are unable to determine if side effects experienced were related to dose prescribed. Second, we had a low response rate. On average, the response rate for mailed surveys is 30% (Kaplowitz et al. 2004). Given the low rate this sample may not be representative of the larger FXS population. However, this study provides insight into psychotropic medication usage and side effect patterns of individuals with FXS and a rationale for conducting future research. Nonetheless, the low response rate made some analyses of data difficult to run. That is, we were only able to analyze data for those medications which had a large number of individuals reporting use and not all medications reportedly used. Additionally, given the various combinations of medications prescribed and the size of the sample, it was impossible to analyze which, if any, medication combination could account for the side effects experienced. By counting each medication as one observation, our analysis was not as sensitive as it might have been had we been able

to consider all medication combinations. A person could have been on more than one medication and the combination of medications could have been what resulted in side effects experienced. In other words, in instances when individuals were reported to be using multiple medications and experiencing more side effects, we are unable to determine if the side effects were a result of multiple medication use from the same class or different class.

Despite the small data set, these findings indicate areas in which further research is warranted. For example, future research should determine if adults with FXS are indeed more likely to experience side effects as a result of using psychotropic medication or if these findings are applicable to our sample only. If adults truly are more likely to experience side effects as a result of psychotropic medication use, does this result from older persons being prescribed more medications or is there some other variable, possibly physiological, that may account for this effect. Also, stimulants were the most reported psychotropic medication used with this population - not surprising given the phenotype of hyperactivity associated with FXS. Consistent with existing research, we found that stimulants were the medication class most likely to be discontinued and most often associated with behaviors worsening in the presence of side effects. The possibility that stimulants may not be effective for all or may worsen behavior or induce excessive side effects in those with FXS in not new (Berry-Kravis and Potanos 2004; Hagerman et al. 1988). For example, Hilton and colleagues (1991) reported a case in which a 6-year old boy with FXS had symptoms worsen when on methylphenidate but improved when on imipramine, tricyclic antidepressant. Given the frequency with which stimulants are prescribed to this population, further research needs to be conducted to determine if there are particular stimulants that are less/more effective than others at treating hyperactivity in those with FXS or if there are particular characteristics of individuals with FXS (e.g., levels of FMRP) that make them more or less likely to respond favorably to stimulants.

Additionally, although no clear pattern of side effects and problem behavior emerged that may have accounted for the positive relationship between side effects and the worsening of problem behavior for specific medications; it is not uncommon to hypothesize that side effects may affect behavior in adverse ways (Valdovinos and Kennedy 2004). Future research should evaluate the extent to which side effects of psychotropic medication may adversely affect the very behaviors they are intended to treat.

Finally, although we were unable to analyze data with any depth, we observed that anticonvulsants were commonly prescribed to these individuals despite the low number of individuals in the sample reported to have a seizure disorder. Because of their mood stabilizing properties, anticonvulsants are being prescribed in an off-label manner that is to say, more often prescribed to treat problem behaviors in individuals with intellectual disabilities (mental retardation) rather than seizure disorders. Also reported, although not analyzed, was the use of folic acid and melatonin. Future research should explore the prevalence and efficacy of the use of anticonvulsants and other substances to treat symptoms associated with FXS. Given the breadth of the types of medications reported to be used in this sample, some in an unconventional manner, there is a great need for randomized, clinical trails of psychotropic medications use in this population.

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Appendix A

Medication Side Effects Questionnaire **Today's Date:** _____

Instructions: Please, answer the questions about the individual with Fragile X as best as you can by either circling the correct answer or providing the information in the spaces below, if you cannot answer a question, leave it blank.

Who completed this form (mother, father, other caregiver, doctor, other):
_____

Age of Individual with Fragile X: _____ Gender: M F

1. **Ethnicity/Race:** American Indian or Native Alaskan
   Asian or Pacific Islander
   Black, not of Hispanic origin
   Hispanic
   White, not of Hispanic origin

2. **Does the individual have any of the following medical conditions? (circle all that apply):**
   a. Seizure disorder
   b. Reflux in stomach
   c. High blood pressure
   d. Sleep problems
   e. Diabetes
   f. Other: _____
   g. None

3. **Has the individual ever received any of the following diagnoses from a doctor?** (circle all that apply)
   a. Attention deficit disorder
   b. Depression
   c. Anxiety disorder
   d. Obsessive compulsive disorder
   e. Bipolar (manic depressive) disorder
   f. Impulse control disorder
   g. Social phobia
   h. Autism
   i. Other: _____
   j. None

4. **I.Q. level/level of functioning (circle best choice):**
   a. No Mental Retardation
   b. Borderline intelligence
   c. Learning disability
   d. Mild mental retardation
   e. Moderate mental retardation
   f. Severe mental retardation
   g. Don't know

5. **Has the individual had problems with any of the following behaviors? (circle all that apply)**
   a. Hyperactivity
   b. Difficulty paying attention
   c. Aggression
   d. Self-injurious behavior (SIB) (hand biting, skin picking, head hitting, etc.)
   e. Refusals/oppositional behaviors
   f. Property destruction
   g. Tantrums
   h. Anxiety
   i. Withdrawal
   j. Other: _____
   k. None

Table 8 Current medications

Medication	Dose	Purpose	Prescribed By	Date Started	Is the Medication helping?
Example (one med): Ritalin	20 mg twice a day	For ADHD	Pediatrician	June 2004	Yes
Example (multiple meds): Risperidone	2 mg daily	Impulse control	Psychiatrist	May 2005	Yes
Prozac	50 mg twice a day	Depression	Psychiatrist	April 2003	Yes
Example (multiple meds): Adderall	5 mg daily	Hyperactivity	Family Doctor	February 2001	Yes
Buspar	50 mg daily	Depression	Family Doctor	September 2003	Yes
Depakote	1500 mg a.m. 1000 p.m.	Seizure Disorder	Neurologist	January 2000	Yes

Please list current medications being taken and provide information for each medication (see examples)

Table 9 Side effects of current medications

Medication	Behaviors that got worse (List)	Behaviors that got better (List)	Side Effects (List)	Changes in Medication because of Side Effects
	Hyperactive Inattention Anxiety/ nervousness Aggression Self-injurious behavior Property destruction Tantrums Refusals/ oppositionality Withdrawal Other No Change	Hyperactive Inattention Anxiety/ nervousness Aggression Self-injurious behavior Property destruction Tantrums Refusals/ oppositionality Withdrawal Other No Change	Drowsiness, dizziness, tired, insomnia, sleeps more, headache, diarrhea, constipation, nausea, vomiting, weight gain, weight loss, more hungry, less hungry, tremors, tics, twitching, strange movements, dry mouth, changes in blood pressure, other, no side effects.	No Change Decrease dose Increase dose Add new Med
Example (one med): Ritalin	Tantrums	Hyperactivity Inattention	less hungry, irritable, anxiety	Decreased dose
Example (multiple meds): Risperidone	Withdrawal	Aggression	More hungry, sleeps more, weight gain	R-decreased dose
Prozac				P-no change
Example (multiple meds): Adderall	No change	Hyperactivity	No side effects	No change
Buspar		Depression		
Depakote				

Please choose which items listed in each column were true for each medication you listed in the table on page 2 (See examples)

Table 10 Past medication use

Medication and Dose	Purpose	Dates Used	Behaviors that got worse (List)	Behaviors that got better (List)	Side Effects (List)	Changes in Medication because of Side Effects
			Hyperactive Inattention Anxiety/ nervousness Aggression Self-injurious behavior Property destruction Tantrums Refusals/ oppositionality Withdrawal Other No Change	Hyperactive Inattention Anxiety/ nervousness Aggression Self-injurious behavior Property destruction Tantrums Refusals/ oppositionality Withdrawal Other No Change	Drowsiness, dizziness, tired, insomnia, sleeps more, headache, diarrhea, constipation, nausea, vomiting, weight gain, weight loss, more hungry, less hungry, tremors, twitching, tics, strange movements, dry mouth, changes in blood pressure, other, no change.	No change Stop use Decrease dose Increase dose Add new Med
Example (one med): Dexedrine 20 mg	ADHD	3/04–6/04	Tantrums	No change	Less hungry, irritable, anxiety	Stopped use Add new med
Example (multiple meds): Zoloft 50 mg	Depression	1/04–4/04	Anxiety	No Change	Weight loss	Stopped use
Buspar 30 mg		9/03–4/04	Tantrums			Increased dose

Please fill in the table listing any medications that were tried in the past (see example)

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