Published in final edited form as:
Dev Disabil Res Rev. 2009 ; 15(4): 353–360. doi:10.1002/ddrr.78.

Treatments for Fragile X Syndrome: A Closer Look at the Data

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Abstract

Research into the determinants and developmental course of fragile X syndrome (FXS) has made remarkable progress over the last 25 years. However, treatments to ameliorate the symptoms of FXS have been less forthcoming. While there is optimism in the field that the pace of intervention research is quickening, there has been a bias toward psychopharmacological approaches to treatment. A closer look at the data from those investigations reveals a paucity of evidence that medications can improve intellectual and adaptive functioning in FXS, or decrease associated behavioral and/or emotional issues. Work in other related disorders (e.g., autism) has shown that dramatic improvements in intellectual and adaptive functioning, as well as behavioral and emotional problems, can occur if intensive behavioral treatment is begun early in the child's life. It is hoped that future research efforts will evaluate these intensive early intervention strategies in children with FXS, perhaps in combination with pharmacological approaches.

Keywords

fragile X syndrome; psychopharmacology; behavioral treatment; FMR1 gene

In 1943, two British physicians, James Martin and Julia Bell, described several generations of boys with severe intellectual disabilities who all belonged to the same extended English family [Martin and Bell, 1943]. They speculated that because the intellectual impairment in these boys had been apparent in childhood and that it had remained “unchanged throughout life,” the disorder clearly differed from other inherited disorders such as Huntington or Tay-Sachs disease. Rather, they hypothesized that a single sex-linked gene could be responsible for the pattern of inheritance in this family. The disorder they had discovered, which we now know as fragile X syndrome (FXS), is the most common known form of inherited intellectual disability, affecting ~1 in 4,000 individuals worldwide [Turner et al. 1996; Crawford et al., 1999].

Since 1991, when the gene was identified [Verkerk et al., 1991], research into the biological and developmental features of the disorder has made remarkable progress. We now know, for example, that FXS is caused by a mutation to the FMR1 gene on the X chromosome at locus 27.3q, and is one of several known single-gene trinucleotide repeat expansion disorders (coincidentally, Huntington disease is another). An expansion of >200 CGG trinucleotide repeats in the promoter region of FMR1 results in methylation and transcriptional silencing of the gene such that its protein product (FMRP) is significantly reduced or absent. Research has shown that FMRP is an mRNA binding protein that has significant effects on brain development, namely, synaptic plasticity and dendritic spine maturation [Greenough et al., 2001]. As a result, children with FXS experience a cascade of developmental problems from

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birth leading to severe impairments in intellectual and adaptive functioning as well as manifesting specific behavioral and emotional problems (e.g., hyperactivity, social anxiety, and autistic features) [Reiss and Hall, 2007]. Because FXS is an X-linked disorder, males are usually more affected than females, with boys typically functioning in the moderate to severe intellectual disability range and girls functioning in the moderate to mild or borderline range.

Although extensive progress has been made toward understanding the genesis and nature of FXS, research into treatments that can prevent or ameliorate the symptoms of the syndrome has been slow. When and where does one begin to halt the progress of FXS? An obvious place to start would appear to be at the level of the gene. Unfortunately, gene therapy and FMRP replacement are simply not possible at this time and unfortunately could be decades away [Rattazzi et al., 2004]. As these authors and others have noted [Hagerman, 2002a], there are several hurdles that would need to be overcome before it can even begin to be realized. Given that gene therapy is not feasible at this time, investigators working in the field have therefore concentrated on developing pharmacological and/or behavioral treatments targeted to the "downstream" effects of reduced FMRP. These efforts will be the focus of this review. In this context therefore, "treatment" will refer to the management and/or amelioration of the symptoms of FXS (i.e., improvement in intellectual and/or adaptive functioning, and decreases in behavioral and/or emotional problems) using either pharmacological or behavioral approaches.

Pharmacological Approaches

It has been suggested that investigators working in the field of intellectual disability have a predisposition for choosing psychopharmacological interventions over behavioral interventions [Zarcone et al., 2008]. This may be particularly true for a genetic disorder such as FXS, as opposed to a behaviorally defined disorder such as autism, simply because FXS is characterized as a "medical" condition. Surveys of children and adults with FXS suggest that large number of individuals (both children and adults) are regularly prescribed psychotropic medications (e.g., stimulants, antidepressants, anticonvulsants, antipsychotics) by psychiatrists, pediatricians or primary-care physicians. For example, in a chart review of two FXS clinics operating in Chicago and Denver, it was reported that over 70% of boys aged 5–17 years were prescribed stimulant medications and over 60% of girls were prescribed antidepressant medications (selective serotonin reuptake inhibitors, SSRI's) [Berry-Kravis and Potanos, 2004]. Similarly, in a recent nationwide survey of medication use in FXS, it was reported that ~76% of individuals with FXS were currently taking or had taken a psychotropic medication in the past [Valdovinos et al., 2009]. These medications were used primarily to help with issues related to anxiety, hyperactivity, tantrums, and difficulty paying attention. Given the high percentage of medication use by individuals with FXS, it is important to ask the question: what is the evidence for their efficacy? Are psychotropic medications being over-prescribed in this population?

Although it is clear that a large proportion of individuals with FXS are taking psychotropic medications, there is surprisingly little research data to support the efficacy of doing so. While it appears stimulants, alpha2-agonists, antidepressants, anticonvulsants, and antipsychotic medications can all be helpful to some degree, the majority of evidence for their efficacy is largely based on reports from physicians and/or parents [Hagerman et al., 1994, 1995; Hagerman, 2002b]. For example, in their clinic survey, Berry-Kravis and Potanos [2004] reported that 75% of children taking stimulant medication and 50–60% of individuals taking SSRI's "responded" to these medications. Similarly, in a survey examining the efficacy of the alpha2-agonist, clonidine, 63% of parents described the medication as "very beneficial" [Hagerman et al., 1995]. However, given that these response rates were determined solely by reports from parents, teachers, and therapists, rather than being based on more

objective and unbiased measures of improvement, these reports should be interpreted cautiously.

It should be noted that many psychotropic medications can cause serious side-effects, ranging from weight gain, liver damage to cardiac anomalies and in a very small number of cases, even death [Berry-Kravis and Potanos, 2004]. In their nationwide survey, Valdovinos et al. [2009] reported that the most frequent side effect of medication use in FXS included loss of appetite (in the case of stimulant use), and sedation and weight gain (in the case of antipsychotic use). However, given that many children with FXS may have limited understanding and/or communication skills, other potential side-effects (e.g., hallucinations) may also go unreported. The risks must clearly be weighed against the potential benefits. Given that there is so little data available supporting the use of psychotropic medication use in FXS, parents and care-givers clearly face a difficult decision. It is important therefore to evaluate the efficacy of these medications in large double-blind placebo-controlled trials using objective outcome measures combined with careful side-effect monitoring.

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Double-Blind Placebo-Controlled Trials

There is a paucity of double-blind placebo-controlled studies evaluating pharmacological agents in FXS. For example, although stimulants are the most frequently prescribed psychoactive medication for FXS [Berry-Kravis and Potanos, 2004], only one controlled study has been conducted to date. In that study, Hagerman et al. [1988] administered methylphenidate (0.3 mg kg^{-1} twice daily), dextroamphetamine (0.2 mg kg^{-1} once daily) or placebo, each for 1 week, to 15 children with FXS (13 males, 2 females), aged 3–11 years. Outcome measures included two teacher and parent report behavioral checklists, direct behavioral observation, movement monitoring, a delay task, and a vigilance task. While the authors judged 10 of the 15 children to be "clinical responders," statistical examination of the data indicated that for the majority of the measures, there was no improvement in scores compared to placebo. Mean scores on the attention and social skills subscales of the teacher-report checklist did however appear significantly higher while the children were taking methylphenidate. However, inspection of the data contained in the report indicates that these effects appeared to be very small (a mean improvement on the scale of ~2 points). Side-effects included increased mood lability and irritability, although the number of patients experiencing these problems was not reported. Interestingly, seven children had been receiving stimulant medication prior to the trial, and eight patients were cotreated with folic acid during the trial, indicating that these participants were not medication naive.

During the 1980s, a number of investigators suggested that folic acid supplementation could improve cognitive and behavioral functioning in FXS, particularly in younger children [Brown et al., 1984; Lejeune et al., 1984; Gustavson et al., 1985]. These open-label studies were initiated primarily because folic acid inhibits the expression of the fragile X cytogenetic marker in vitro. In a sense, then, folic acid treatment could be considered the first treatment "targeted" specifically to the underlying genetic condition. Unfortunately, these open-label studies did not stand up to more rigorous testing in double-blinded trials [Brown et al., 1986; Froster-Iskenius et al., 1986; Gillberg et al., 1986; Fisch et al., 1988]. For example, in a double-blind placebo-controlled crossover trial, 25 males with FXS, aged 1 to 31 years, received 10 mg of folic acid or placebo, each for a 6-month period [Hagerman et al., 1986]. While parent reports of folic acid treatment suggested that four of the patients were "remarkably improved" and

nine patients were “mildly improved,” no significant improvements in IQ, language, or behavior were found when standardized testing was employed.

In the most recent study of folate supplementation in FXS conducted to date, 21 males with FXS, aged 2–22 years, received 15 mg day^{-1} Leucovorin® (a derivative of folic acid) or placebo for a period of 12 weeks each [Strom et al., 1992]. While several outcome measures were employed (including measures of adaptive, intellectual and behavioral functioning) no differences between those taking active medication and those taking placebo were found. For example, on the Vineland Adaptive Behavior Scales (VABS), mean scores were almost identical (51.0 on Leucovorin versus 50.9 on placebo). Again however, while no beneficial effects could be found on any of the outcome measures, parents of 10 of the children reported that their sons had benefited from the medication and elected to continue the treatment.

In a multicenter study conducted in Europe, Torrioli et al. examined the efficacy of administering L-acetylcarnitine, a metabolite that may have cytoprotective properties, to improve cognitive and adaptive functioning in children with FXS [Torrioli et al., 1999, 2008]. These authors suggested that this agent could be employed as an alternative to stimulant medication. Twenty-four children with FXS received 20–50 mg/kg/day L-acetylcarnitine for 12 months while 27 children received placebo for the same period. All children had a comorbid diagnosis of ADHD, and were aged 6–13 years (as well as being medication naïve). Results showed that in the first 6-months of the trial, scores on the VABS and Conner's Global Index improved in both active medication and placebo groups, suggesting that improvements were not medication-related [Torrioli et al., 2008]. Interestingly, by 12 months, improvements on the VABS appeared to be maintained in the active medication group (an improvement of 6.6 points on the Socialization domain of the VABS) but not in the placebo group. On the Conner's Global Index however, scores remained improved in both active medication and placebo groups (by 8.0 points vs. 4.4 points, respectively). Although the data were not reported, the authors stated that there was no effect of L-acetylcarnitine on intellectual functioning. It is therefore unclear whether L-acetylcarnitine supplementation is beneficial for children with FXS at this time.

Given the paucity of evidence concerning the efficacy of generic psychotropic medication use (and supplementation with folic acid or L-acetylcarnitine) in individuals with FXS, several investigators have begun to evaluate medications targeted specifically to the underlying pathology in FXS (i.e., the downstream effects of reduced FMRP). Research conducted on the fmr1 knock-out (KO) mouse has suggested that FMRP may be involved in the regulation of glutamatergic synaptic plasticity [Bear et al., 2004]. Berry-Kravis et al. [2006] hypothesized that treatment with CX516, an AMPA modulator that interacts with the glutamatergic system, could help to normalize glutamatergic functioning in FXS. In a 4-week randomized double-blind placebo-controlled trial, 24 adults with FXS (17 males, 7 females aged 18–49 years) received 600 mg of CX516 for 1 week with the dose increased to 900 mg for 3 weeks. A control group of 25 adults with FXS (21 males, 4 females) received placebo during the same time period. Following administration of a large battery of 10 memory tests and 4 behavior checklists at the beginning and end of the study, results showed that there were no differences in change scores between those taking CX516 and those taking placebo. Three individuals (12.5%) experienced a rash during the trial and 15 of the 24 participants were taking concomitant psychoactive medications during the trial.

In a recent double-blind placebo-controlled trial, Wirojanan et al. [2009] evaluated the efficacy of the hormone melatonin to improve sleep problems in children with FXS. Research has indicated that chronic treatment with melatonin can alleviate anxiety-related behaviors and learning problems in the KO mouse [Romero-Zerbo et al., 2009]. In this study, six boys with FXS, aged 2–7 years received 3 mg melatonin or placebo 30 min prior to bedtime, each for 3

weeks. The study also included several individuals diagnosed with autism (without FXS). Outcome variables included sleep duration, sleep-latency, sleep onset time, and counts of the number of night awakenings assessed using a combination of parental report and an activity monitoring device attached to the child's wrist or leg. Using a nonparametric statistical technique (and including the children who were diagnosed with autism), these authors reported that melatonin significantly increased sleep duration (by 21 min), decreased sleep-onset latency (by 28 min), and decreased sleep onset time (by 42 min) when compared to placebo. For the children with FXS however, visual inspection of the data contained in the report indicates that while mean sleep latency appeared to improve in five of the six boys, mean sleep onset time only improved in three of the six boys and there appeared to be no improvement in sleep duration in these boys.

Open-Label Studies

Several investigators have conducted smaller “open-label” studies to evaluate the efficacy of psychoactive medications. While this type of trial is clearly open to investigator bias and placebo effects, investigators have argued that these studies can still be quite useful to evaluate the safety and pharmacokinetics of medications before more rigorous controlled trials are conducted. To date, and not including the open-label studies that evaluated folic acid in the 1980s, several medications designed to target the downstream effects of reduced FMRP have been evaluated. Unfortunately, none of these studies have included a placebo control group.

Berry-Kravis et al. hypothesized that lithium, a commonly used mood-stabilizing medication for individuals with bipolar disorder, may “correct” excessive mGluR-mediated dendritic translation in FXS and hence improve cognitive and behavioral functioning. In a 2-month open-label trial, 15 individuals with FXS aged 6–23 years received lithium three times daily (with levels titrated until stable over 2 months) [Berry-Kravis et al., 2006]. These authors reported that on parent-report measures mean scores improved by 18.5 points on the total score of the Aberrant Behavior Checklist and by 1.7 points on the Personal subdomain of the Vineland Adaptive Behavior Scales. However, scores on a large battery of neuropsychological tests administered directly to the participants failed to find any improvement. A large number of patients were unable to complete the majority of these measures and only one of the measures (the RBANS list learning) showed improvements (by an average of 4.1 points), although no correction for multiple comparisons was made.

In another recent open-label study targeting possible glutamatergic dysfunction in FXS, Berry-Kravis et al. [2009] evaluated fenobam, an mGluR5 receptor antagonist and anxiolytic medication that has been shown to “rescue” the behavioral phenotype and neuronal protusion morphology in the fmr1 KO mouse [de Vrij et al., 2008]. Twelve adult patients with FXS aged 18–30 years, received a single dose (50, 100, or 150 mg) of fenobam on a single day. These authors reported that eight patients showed signs of “clinical improvement” in eye contact and/or social interaction. In addition, 6 of the 12 subjects were reported to show greater than 20% improvement on a prepulse inhibition (PPI) task. This figure compares favorably to 2/13 patients who were found to show >20% improvement on this measure without fenobam treatment.

Erikson et al. [in press] have recently hypothesized that the NMDA glutamate receptor antagonist, memantine, may be beneficial for reducing repetitive behavior, social impairment, anxiety, inattention and irritability in FXS. These authors examined the medical records of 6 individuals with FXS aged 13–22 years who had been receiving open-label 15–20 mg memantine over a period of 8–104 weeks. While four of the six subjects appeared to show “global clinical benefit,” statistical evaluation of the data on several parent-report behavioral checklists (Social Responsiveness Scale, Aberrant Behavior Checklist and the ADHD Rating Scale) indicated that these improvements were not significant.

While much attention has been given to the mGluR hypothesis, several investigators have speculated that other neurotransmitter systems may also be affected by reduced FMRP. For example, using magnetic resonance spectroscopy (MRS) Kesler et al. [2009] reported that levels of the neurometabolite, choline, were significantly reduced in dorsolateral prefrontal cortex—an area of the brain involved in learning and working memory. Given additional evidence indicating cholinergic dysfunction in the fmr1 KO mouse and *drosophila* (fruit-fly) models of FXS, these authors speculated that administration of the acetylcholinesterase inhibitor, donepezil, could help reregulate the cholinergic system in FXS. In a 6-week open-label trial, eight individuals (six males, two females) with FXS, ages 14–44 years, received a 5-mg dose of donepezil for 3 weeks that was increased to 10 mg for a further 3 weeks. Significant improvements were noted to occur on two parent-report scales (the Aberrant Behavior Checklist and the Child/Adult Behavior Checklist) as well as a direct measure of executive functioning (the Contingency Naming Task) at both doses. Again however, the clinical effects of these improvements appeared to be small (a mean of 12 points improvement on the total ABC score, and 4 points improvement on the C/ABCL at the 5-mg dose). An improvement of seven correct responses per minute was reported on the Contingency Naming Test at the 5-mg dose. However, the same version of this test was administered at each evaluation point and thus the possibility that improvements were due to practice effects cannot be ruled out.

In summary, caution must be exercised in interpreting the results of these open-label trials. First, the number of patients enrolled in these studies has been extremely small (ranging from 6–15 patients). The lack of appropriate comparison groups also limits the extent to which the various medications can be evaluated. A second issue concerns the timing and dosing of the medications. Most trials have been short-acting (ranging from 1 day to 8 weeks). The speed at which synaptic regeneration occurs in humans is unknown, as is the speed of learning once regeneration has occurred. Given that learning and cognition develop over time, it is possible that the full effect of these compounds may not be known for several years. A third issue concerns the monitoring and occurrence of side-effects. In the fenobam study, 3 of the 12 patients were reported to experience mild sedation effects and one patient demonstrated an increase in anxious behavior. In the lithium study, 7 of the 15 individuals showed increased polydipsia, 4 exhibited polyuria, and 5 showed increased bed-wetting during the trial. In the donepezil study, one participant experienced dizziness and shortness of breath at the 10-mg dose, while another participant experienced nausea also at the 10-mg dose. In the memantine study, two of the six patients showed increased irritability and therefore discontinued the medication. Fourth, all open-label studies published to date have included individuals who were taking concomitant psychoactive medications. Eight of the 12 subjects in the fenobam study, 14 out of the 15 participants in the lithium study, and 4 out of the 6 subjects in the memantine study for example were receiving stimulants, SSRI's, other antidepressants, anticonvulsants, and antipsychotics in addition to the study medication. In the donepezil study, five of the eight participants were also taking concomitant psychoactive medications [Lightbody, personal communication]. Interaction effects between medications could therefore have been quite common. Of the four subjects who were medication-free in the fenobam study, for example, only one was responsive to the PPI test.

A final issue concerns the outcome measures employed in the studies. Given the variable phenotype and large range of IQ's observed in individuals with FXS, investigators have struggled to find measures with proven reliability, sensitivity, and specificity as well as clinical utility [Berry-Kravis et al., 2008]. Many of the outcome measures employed to date have relied heavily on parent report (e.g., ABC and VABS) and hence these measures are subject to placebo effects and rater bias. Many low functioning boys are unable to complete directly administered measures of neuropsychological functioning (floor effects) while many high functioning girls may find these measures relatively easy to complete (ceiling effects). In the lithium study, for

example, Berry-Kravis et al. [2008] administered an extensive battery of neuropsychological tests to 15 individuals whose IQ's ranged from 47 to 61 but found that only one of the tests (the Peabody Picture Vocabulary Test) could be completed by all subjects. In other studies, the reliability and validity of the measures has been questionable. For example, in the fenobam study, the assessment of clinical response was neither made anecdotally by observations conducted by the primary investigator (i.e., clinical ratings that were not blinded) and the ratings were not subjected to a reliability assessment. Finally, some outcome measures have been employed (e.g., PPI) that measure extremely subtle changes in the brain that may or may not be indicative of changes in intellectual or adaptive functioning. There is therefore a critical need for reliable, objective, and clinically meaningful outcome measures of behavior change to be developed for individuals with FXS.

At a minimum, further double-blinded trials are warranted to evaluate the efficacy of psychotropic medications in FXS. Although many investigators have reported statistical effects in their data (i.e., improvement in mean scores on selected outcome variables), the “clinical” effects of improvement on those domains appears to be fairly small (e.g., 6–7 points on the Vineland Adaptive Behavior Scales). As Zarcone et al. [2008] pointed out, measurement of the social validity of treatment trials is an important issue here. For example, has the person's quality of life been improved as a result of taking the medication? Given that a variety of scales are often employed to measure the efficacy of medications, what represents a clinically meaningful change in the individual's level of functioning on these scales? These important questions will need to be answered in the future.

Behavioral Approaches

Few studies have been conducted evaluating the effects of behavioral treatment in individuals with FXS [Reiss and Hall, 2007]. This is unfortunate, particularly since behavioral approaches to the treatment and management of children and adults with intellectual disabilities has a long and rich history of success. For example, educational interventions designed to increase social skills and to improve intellectual and adaptive functioning have been shown to be highly successful in children with autism over the last few decades [Lovaas, 1987; McEachin et al., 1993; Remington et al., 2007]. Similarly, a large body of evidence has accumulated over the last 50 years showing that many behaviors of social importance (e.g., aggression, tantrums, self-injury, stereotypy) in individuals with and without autism can be successfully treated using basic operant conditioning techniques (i.e., differential reinforcement, punishment, and extinction) [Cooper et al., 1987; Martin and Pear, 2003].

To date, professionals working with children with FXS have employed a variety of behavior modification techniques, as well as other nonvalidated techniques, such as sensory integration therapy, to help ameliorate the symptoms of FXS [Braden, 2002; Epstein et al., 2002; Scharfenaker et al., 2002]. While an emphasis is often placed on sensory and/or anxiety issues related to FXS in these reports, suggesting that these interventions are somewhat “fragile X-specific,” unfortunately there is very little outcome data to support the efficacy of adopting these strategies for individuals with fragile X.

In one of several single-case reports, for example, Epstein et al. [2002] describe the case of a 5-year-old boy who showed severe aggressive behavior with his mother. Following direct observations of the child, the authors noted that aggression appeared to occur most often when the child was “frustrated with an object or bored with a situation” (p 349). In addition to initiating speech and language therapy, occupational therapy, and special education with the child, a treatment plan was devised that included “time-out” for aggression, reinforcement of appropriate attempts at obtaining attention, and modeling of appropriate touching. Two months after the implementation of the treatment plan, the child's mother reported that his aggression had decreased significantly, and that his teachers had reported few problems at school.

However, outcome data (e.g., counts made of the aggressive behaviors at baseline, during the intervention and at follow-up) were not presented to support the efficacy of the treatment.

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As Epstein et al. [2002] correctly point out, “time-out” (i.e., the contingent removal of the child from a situation) should not be applied without careful consideration of the purpose or “function” of the behavior. To use their example (p 348), if a child throws a math book on the floor to get out of completing a difficult math assignment, removing the child from the situation will only serve to make the behavior worse in the long-term. In this case, “time-out” is synonymous with reinforcement of the behavior (i.e., giving the child a break contingent on problem behavior). Conversely, if the child shows aggression to get attention from his mother, the removal of the child from the situation could be seen as a punisher, and this would be expected to decrease the behavior in the long-term. Clearly, a thorough understanding of behavioral principles is required to implement behavioral interventions appropriately. Herein lays the problem. There are few highly trained behavior therapists working in the field of intellectual disabilities and perhaps even fewer working with individuals with FXS.

Several pilot behavioral studies conducted in our laboratory and others have, however, shown that intensive behavioral programming in young children with FXS is at least possible to help reduce problem behaviors and build appropriate skills in their repertoires. For example, we have recently demonstrated that eye contact duration in children with FXS can be improved using a simple differential reinforcement technique [Hall et al., 2009]. While a large proportion of children with FXS show extremely high levels of eye gaze aversion in social situations, many professionals working in the field have argued that eye contact training should not be attempted [Dykens et al., 2000; Scharfenaker et al., 2002]. However, maintaining eye gaze with significant others appears to be an important “pivotal” skill for developing new skills. In this pilot study then, six boys with FXS, aged 8–17 years, underwent eye contact training in two, 1-hr sessions conducted over 2 days. During the sessions, the experimenter sat face-to-face with the participant, and on each trial, delivered a verbal prompt to make eye contact. When eye contact occurred, it was reinforced with social praise and edible reinforcers. At least 80 trials were conducted on each day and physical prompts were required for three of the children to augment the shaping process and eliminate the appearance of problem behaviors. Results showed that mean eye contact duration (recorded from direct observations of the participant) increased in four of the six boys without concomitant increases in social anxiety or behavioral problems occurring in children. It should be pointed out however that, in some cases, the gains in eye contact duration were quite small (e.g., from 2 to 4 sec per trial). Once again, it is important to ask questions concerning the social validity of the improvement. Was this treatment gain clinically meaningful? Further studies will be needed to determine whether these gains can be generalized and maintained, or indeed whether it is possible to make long-lasting improvements in eye contact in children with FXS using behavioral approaches alone.

In another pilot study, we determined whether children with FXS could learn basic math and geography skills using a matching-to-sample teaching procedure [Hall et al., 2006]. There is some evidence, for example, to suggest that children with FXS may benefit from teaching strategies that adopt a simultaneous stimulus presentation, as apposed to a sequential stimulus presentation [Braden, 2002]. Five adolescents (four boys, one girl), aged 12–19 years, were taught these skills using a self-paced computer program implemented intensively with the children over 2 days. In the math condition, children were taught to match fractions to pie charts (A = B matching) and then to match pie charts to decimals (B = C matching). Similarly, in the geography condition, children were taught to associate state names to their locations on a map (A = B matching) and to associate state locations on a map to their capitals (B = C matching). Results indicated that four of the five children successfully learned the math trained

relations and three of the five children successfully learned the geography trained relations. Further, two children demonstrated complete mastery of the math and geography relations at posttest (i.e., could associate decimals to their fractions and could associate state capitals to their state names). This indicated that these children were able to employ transitivity (if A = B and B = C, then A = C) to be able to correctly associate the new relations. These data indicate that computerized matching-to-sample procedures, even when conducted in time-limited sessions, may help individuals with FXS learn new skills.

Finally, Weiskop et al. [2005], attempted to decrease a variety of sleep-related problems (e.g., presleep disturbances, inability to fall asleep alone, night waking, and cosleeping) in five children with FXS aged 2–9 years using a combination of parent training, extinction and differential reinforcement techniques administered over a 7-week period. Inspection of the data contained in the report indicates that the number of presleep disturbances decreased significantly for two of the children, the number of nights falling asleep alone increased in four of the children, the number of night awakenings decreased in two of the children, and the number of cosleeping nights decreased in three of the children. These gains also appeared to be maintained at a 3 month and 12 month follow-up. Social validity data also indicated that all parents noticed at least “some improvement” in their son's sleeping. Interestingly, prior to the intervention, these authors conducted a behavioral assessment of possible factors maintaining the sleep problems (i.e., functional assessment) and determined that the majority of problem behaviors were being inadvertently reinforced by parental attention. This finding might help to explain why melatonin administration in the study conducted by Wirojanan et al. (described above) produced variable results in some children with FXS. If environmental factors (i.e., inadvertent reinforcement by parental attention) are still maintaining the child's sleep problems, it is unlikely that a medication could be powerful enough to counteract those effects. It seems likely, therefore, that treatment efficacy could be dramatically improved if pharmacological and behavioral approaches could work together synergistically.

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To this end, our laboratory has recently initiated a study in which the naturally occurring neuropeptide, oxytocin, is being evaluated as an augmentative therapy alongside social skills training. In this double-blind placebo-controlled trial, low functioning boys with FXS aged 13–21 years are randomized to receive either placebo, a moderate dose (24 IU) or high dose (48 IU) of Syntocinon® (a synthetic derivative of oxytocin) on three separate afternoons spaced 1-week apart. Intranasal dosing begins at 2:30 pm and social skills (i.e., eye gaze) training is implemented 1 hr later to coincide with peak uptake of oxytocin. Outcome measures include percentage eye gaze during a social challenge, heart rate monitoring, and activity counts using the Minilogger (MiniMitter, Co), as well as eye gaze duration during the social skills training. Following the double-blind phase, participants embark on a 2-week open-label trial of 48 IU daily syntocinon. Outcome measures in this part of the trial include parent ratings on the ABC, CGI, and SRS at baseline, 7 and 14 days into the trial. To date, we have found that intranasal administration of syntocinon has been well tolerated and has produced minimal side-effects.

Future Prospects

It is possible that behavioral approaches conducted with other populations of individuals with intellectual disabilities (e.g., autism, Down syndrome) may offer some insight into potential treatments for children with FXS. Over 20 years ago, Lovaas [1987] for example, reported that intellectual and adapting functioning in children diagnosed with autism could be dramatically

improved if intensive in-home behavioral treatment is applied early in the child's life. Each child received intensive (40 hr per week) individualized behavioral treatment conducted at home over a 2–3-year period by a team of highly trained behavior therapists. These behavior therapists employed discrimination learning techniques, also known as Discrete Trial Training, to increase adaptive skills in the child's repertoire (e.g., build compliance to verbal requests, imitation, appropriate toy play, expressive and early abstract language, interactive play with peers, appropriate and varied expression of emotions, as well as reading, writing, and arithmetic skills). The treatment also employed extinction and punishment techniques to prevent or decrease the appearance of problem behaviors in the child's repertoire (e.g., tantrums). While the results are still considered somewhat controversial, after 2 years of behavioral treatment, Lovaas [1987] demonstrated that 9 out of 19 children diagnosed with autism at ages 2–3 years had “recovered” by ages 5–6 years such that their levels of functioning were similar to their typically developing peers (i.e., IQ's ranged from 94 to 120). A further eight individuals required assignment to a special education class for language delay (their IQ's ranged from 56 to 95) while only two individuals failed to respond to the treatment (each of these children had an IQ of 30). Most importantly, these effects have now been replicated [Cohen et al., 2006; Remington et al., 2007]. As Lovaas et al. have pointed out, a major contributing factor to the success of this treatment was that it was begun early (at 2–3 years of age), presumably before the symptoms of the disorder (i.e., autistic behaviors) could have become entrenched in the child's repertoire.

While intensive behavioral treatment is clearly promising for children with autism, a major question concerns whether similar interventions could be beneficial to children with FXS (i.e., could similar gains in intellectual functioning occur in children with FXS)? Put another way, could behavioral intervention counteract the sustained effects of low levels of FMRP on brain development and the associated years of missed learning opportunities?

To begin to answer this question, we have recently initiated a study to evaluate a software-based learning tool for teaching basic cognitive skills to children with FXS using discrete trial training. The Discrete Trial Trainer (DTT) (Accelerations Educational Software, 2003) (http://www.dttrainer.com) has over 100 programs that support learning including classification, counting, identification, matching, math, money, sequencing, spatial relations, time, word analysis, written words, and “wh—” questions (who, what, when, etc.). The program filters allow the instructor to break programs within these topics down by developmental level (2 years to 4th grade), skill (money, letters, counting, etc.), and subject (life skills, language arts, math, etc.). During each session (which is typically programmed to last 10–20 min), auditory and visual prompts are utilized to increase the probability of a correct response. The learner can also work at his/her own pace over each session. After a block of trials, correct responses are reinforced with social/verbal praise and access to entertaining activities on the computer. We have found that many children with FXS are able to work independently for several hours per day on the DTT and have shown steady improvements in basic math and money skills. This type of intervention, if begun early in the child's life, offers promise to improve functional adaptive and intellectual skills in children with FXS.

Summary

Only modest gains in symptom reduction and no gains in intellectual functioning have been reported in FXS to date following treatment with pharmacological and/or behavioral approaches. Given that FXS is a disorder with a known biological cause, not surprisingly, investigators have primarily focused on pharmacological approaches to treatment. It is perhaps unlikely that a single medication could improve intellectual and adaptive functioning in FXS simply because the downstream effects of reduced FMRP in the developing human organism are extremely complex. Allied to this are the years of missed educational opportunities that

have occurred over the child's lifetime. Even if a medication could eradicate the deleterious effects of reduced FMRP in the brain, educational learning programs would still need to be set in place to develop basic skill sets that have been missed [Berry-Kravis et al., 2009]. Behavioral interventions clearly need to be begun early, to adopt teaching strategies to scaffold the building of new skills, to be implemented for longer periods of time (perhaps years), to include appropriate control groups, and to include outcome measures that assess intellectual and adaptive functioning, as well as behavioral and emotional problems associated with FXS.

Acknowledgments

The content is solely the responsibility of the author and does not necessarily represent the official views of the National Fragile X Foundation, the National Institute of Mental Health, or the National Institutes of Health. The author thanks Allan Reiss for his mentorship and for helpful discussions on this topic.

Grant sponsor: National Institute of Mental Health; Grant number: K08MH081998; Grant sponsor: National Fragile X Foundation.

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