Medications in Fragile X

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Current Psychopharmacology

Treatment strategies for individuals with FXS are at this point supportive strategies designed to maximize functioning. No treatments are currently available that are directed specifically at the underlying neuronal defect caused by the absence of FMRP. As behavior in FXS can significantly impact functionality, symptom-based treatment of the individual's most problematic behaviors can be quite helpful. A survey of medications used in an FXS cohort showed responsiveness by clinical report to a variety of medications used clinically in an uncontrolled setting to target specific symptoms.[1]

Although medication management for behavior in FXS shows promise in the clinical setting, more controlled studies are needed to evaluate formally the effects of these medications in the FXS population. One small placebo-controlled cross-over study showed methylphenidate to be effective for hyperactivity and attention in about 70% of boys with FXS.[2] Indeed, stimulants are the most frequently used and most frequently helpful class of medication in boys with FXS. . Figure 1 shows medication classes used in a large Chicago FXS clinic[3] and the percentage report of positive response for the symptom being targeted. In this cohort, stimulants were targeted to symptoms of distractibility, hyperactivity and impulsivity; alpha2-agonists were targeted to hyperactivity, impulsivity, mild aggression, and hyperarousal and hypersensory behaviors; SSRIs and tricyclics were targeted to anxiety, perseverative and OCD behaviors and mood lability; and risperidone targeted aggression and other more severe aberrant behaviors. The response rate to stimulants for hyperactivity and attentional symptoms was 77% (Figure 1), similar to that seen in the one controlled study.[2] In some FXS patients, stimulants exacerbate anxiety, mood lability, or aggressive tendencies and must be abandoned. Stimulants (Adderall and methylphenidate) now come in many different long-acting forms, which may be quite useful in eliminating swings in mood and behavior during the day seen on multiple-dose regimens of fast-acting preparations. Stimulants may also induce excessive side effects or may not be effective in FXS children less than 5 or 6 years old, although they may be quite effective if re-introduced at an older age.

Anxiety, compulsive/perseverative and mood symptoms can be managed with antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs). SSRIs appear to be particularly helpful for social anxiety and withdrawal seen in females and high-functioning males with FXS. In the Chicago cohort, response rate to antidepressants was about 50% (Figure 1) for anxiety, mood or compulsive/perseverative symptoms. SSRIs can result in activation or disinhibition with increased impulsivity, which may require discontinuance. For patients who are too disinhibited on SSRIs, venlafexine (Effexor) or tricyclic antidepressants may be useful. Tricyclics may also help with sleep dysregulation.

Alpha 2-agonists, clonidine and guaneficine (Tenex), show about 50% efficacy (Figure 1) in treating hyperactive, hyperaroused, hypersensitive, impulsive, and aggressive behaviors in young boys with FXS. These medications may be particularly effective in children less than 5 years of age who do not tolerate or respond to stimulants. Risperidone (Risperdal) is effective for aggressive behavior and other aberrant and undesired behaviors (Figure 1), but may result in intolerable weight gain, especially at higher doses. Other more recently developed atypical antipsychotics such as quetiapine (Seroquel) and ziprasidone (Geodon) may be also be helpful for aggressive behavior if there are problems with weight gain on risperidone. Valproic acid and carbamazepine may help with mood cycling.

Psychopharmacology for the Future

As information regarding the neuronal functions of FMRP becomes available, more directed pharmacological interventions will be designed to address specific neurochemical deficits generated by the absence of FMRP. For instance, it has recently been shown that AMPA receptors and AMPA-mediated activity[4,5] are down-regulated in FXS cortex and mGluR5 activity is increased,[5] leading to abnormalities of synaptic long-term depression and long-term potentiation. Positive AMPA-receptor modulators, which act as cognitive and memory enhancers, may therefore improve cognitive functioning and behavior in individuals with FXS. Several of these compounds are already in development and the first trial of an AMPA-receptor positive modulator (ampakine, CX516) in adults with FXS is underway. It is expected that more directed cognitive pharmacotherapy for FXS, such as mGluR5 receptor antagonists, will be available in the near future.

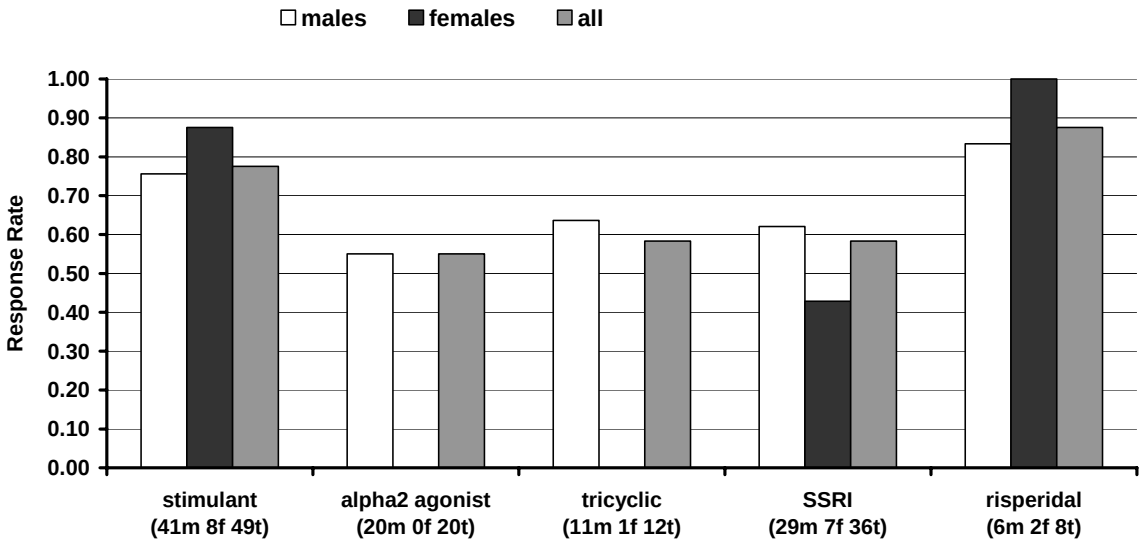

Figure 1. **Response rates to various classes of medications in a Chicago FXS cohort.[3]** Response was determined clinically based on feedback from parents, teachers, and therapists, regarding target behaviors. Stimulants included methylphenidate preparations, Adderall, and dextroamphetamine preparations. Alpha2-agonists included clonidine and guaneficine (Tenex). Tricyclic antidepressants included imipramine and amitryptyline. SSRIs included fluoxitine (Prosac), sertraline (Zoloft), fluvoxamine (Luvox), and citralopram (Celexa). Response rates are given as a fraction of the total possible respondents for males (m), females (f) and the total group treated with each medication class (t). Number of individuals treated is indicated for males, females and the total group underneath the figure label for the drug category.

References

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(4) Li J, Pelletier MR, Perez Velazquez JL, Carlen PL. Reduced cortical synaptic plasticity and GluR1 expression associated with fragile X mental retardation protein deficiency. Mol Cell Neurosci 2002;19:138-151.
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1 # *Medications in Fragile X Syndrome*

- Target behavior to improve functioning

2 ## *Behavior in Neurodevelopmental Disorders with Cognitive Impairment*

- major problem behaviors in >50% of patients with cognitive disability
- behaviors stem from cognitive/executive dysfunction
- problems from language deficits and difficulty communicating
- problems with immature reactions, inability to regulate emotional state, and misinterpretation of environment

3 ## *Decision to Use Behavioral Medication*

- child engaging in dangerous behaviors
- child is dysfunctional from behavior
- child could accomplish more or be higher functioning if specific behavior is managed

4 ## *Medication for Attention/Behavior Problems*

- Not necessarily "when all else fails"
- An adjunct to behavioral measures
- May substantially increase ability to attend/participate

5 ## *Behavior Types Causing Problems in Fragile X Syndrome*

- Hyperactivity/distractibility/overarousal
- Anxiety/OCD/perseverative
- Mood swings
- Aggressive behaviors
- Behavior in fragile X often out-of-proportion to cognitive level

6 ## *Controlled Studies of Psychopharmacology in Fragile X Syndrome*

- Hagerman, 1988 methylphenidate and dextroamphetamine in 15 children
  - double blind placebo-controlled crossover design
  - methylphenidate -better attention/social on checklists
  - 10 children were responders
- Hagerman, 2000 Adderall vs Ritalin, double blind crossover
- Hagerman, 1980s high dose folate; Strom, 1992, high dose folinic acid
- This meeting: Roberts - behavior and arousal measures on and off stimulants (not blinded)

7 ## *Medication Choice*

- identify most problematic class of symptoms
  - hyperactivity/distractibility
  - anxiety/OCD
  - depression/mood
  - self-abusive behavior
  - hypersensitivity
  - aggression/agitation
- often overlap
- target problem areas with appropriate class(es) of meds

8 ## *Types of Medications/Indications*

1 Problem

Attention/distractibility
Hyperactivity
Hypersensitivity
Anxiety/perseveration

Mood swings/Outbursts
Aggression

Psychosis

2 Medications

Adderall
Ritalin/Dexedrine
Clonidine
Prozac/Zoloft
Buspar
Tricyclics
Prozac/SSRIs
Lithium/Tegretol
Clonidine
Inderal, Risperdal
Antipsychotics
Risperdal

9 ## *Management of Medications in Developmental Disabilities*

- start with low dose
- titrate up every week or two until at maximum dose, side effects, or effectiveness for target behavior
- focused systematic "trial and error" method
- may need two meds to target different symptom classes
- never start two meds at once
- never change two meds at once unless emergency situation

10 ## *Medication Tolerance*

- a medication may work well for a while then stops working
- dose increase may result in effectiveness again
- brain chemistry adapts to medication
- not the same as addiction - no physical dependence
- if going up and up on dose may need to switch medications
- sometimes can alternate two successful medication regimens each time tolerance develops

11 ## *Distractibility/Hyperactivity/ Impulsiveness*

12 ## *Stimulants*

- best for managing short attention span
- raise dopamine levels in frontal lobe
- don't necessarily work prior to 5-6 years
- side effects may be worse in very young children

- dosing variable - individualize to max effect, min side effects

13 *Stimulants - Benefits*

- longer attention span
- decrease fidgeting and motor overactivity
- decrease impulsive behaviors

14 *Stimulants - Side Effects*

- appetite suppression
- insomnia (less if no late day dose)
- lethargic "drugged" appearance
- moodiness as dose wears off, crying
- increased general aggressiveness
- picking behaviors, tics, anxiety, OCD, perseveration
- occasionally may see stuttering, decreased talking, increased seizures
- no major organ side effects

15 *Stimulants - Medicines Available*

- Ritalin (methylphenidate), Focalin
  - short acting
  - may get peak/trough effects
    - post-dose lethargy, "drugged" look
    - wild, moody or aggressive behavior as wearing off
  - SR form may help with ups and downs - either alone or with superimposed regular doses

16 *Stimulants - Medicines Available*

- Long-acting methylphenidate
  - Ritalin SR, Metidate, Methylin
  - 8-10 hour duration
  - no peak effects
- Concerta, Metidate CD
  - specially formulated for release early, then late
  - 8-10 hours
  - Concerta targets especially afternoon behaviors

17 *Stimulants - Medicines Available*

- Adderall (mix of amphetamines)
  - mix of 4 different stimulants with different timing of action
  - 1.7 times potency of Ritalin
  - longer lasting (6-8 hr) and more effective for ADHD in some studies
  - less peak/trough and wearing off effects
  - more serotonin activity than methylphenidate
- Adderall XR - new 2-dose slow release, 10-12 hrs

18 *Stimulants - Medicines Available*

- Dexedrine (d-amphetamine)
  - same potency as Adderall
  - only one medicine
  - regular and SR forms with similar duration of action to comparable Ritalin forms
  - ? more side effects because is not a mix of d- and l- forms

- Cylert (pemoline)
  - long half life - takes a while to "kick in"
  - not as potent as others
  - in system all the time ? more side effects
  - need to do blood tests to monitor liver function

19 ☐ ***Hyperactivity/Hypersensitivity/Agitation-Aggression***

20 ☐ ***Clonidine/Tenex(guaneficine)***

- block a-adrenergic receptors to decrease amount of sensory input perceived by brain
- decrease hypersensitivity/overeaction to environment, transition problems
- may decrease overstimulation, hyperactivity, impulsivity, aggressiveness due to overarousal
- helpful in young children who may not respond well to stimulants or antidepressants
- worth a try for hyperactivity if stimulants not helpful or give side effects
- work less well in teenagers and adults

21 ☐ ***Clonidine/Tenex***

- main side effect is sleepiness
- can have middle night awakening, especially with tolerance
- at higher doses monitor blood pressure/EKG
- clonidine may need up to QID dosing
- Tenex longer lasting, less peak sleepiness
- clonidine patch gives even dosing but annoys patients

22 ☐ ***Anxiety/OCD/Perseveration/Mood Swings and Depressive Symptoms***

23 ☐ ***SSRIs***

- best for managing OCD symptoms, anxiety, moodiness/depression
  - major transition problems
  - shyness/withdrawal
  - fixations and perseverations
- increase serotonin throughout brain

24 ☐ ***SSRIs - Benefits***

- less fixations and compulsive behaviors
- able to transition more easily
- less irritability, happier
- less pacing/picking
- able to tolerate things in environment better
- able to be more comfortable socializing
- some show increased speech

25 ☐ ***SSRIs - Side Effects***

- activation/hyperactivity/disinhibition - wild/odd behaviors
- appetite changes
- insomnia - usually wears off
- nausea - not common
- decreased sexual drive/impotence - rarely an issue

26 ☐ *SSRIs - Medicines Available*

- Prozac
  - most potent, most activating
  - good for non-hyperactive patients with shyness and social anxiety or withdrawal
  - works for selective mutism

27 ☐ *SSRIs - Medicines Available*

- Zoloft - less activating, good for patients with ADHD and OCD/anxiety symptoms
- Paxil - fastest acting
- Luvox - approved for children for OCD symptoms, potency like Zoloft
- Celexa - new in 1999

28 ☐ *Celexa*

- as potent as Prosac
- very serotonin selective -tolerance more frequent
- thought to have less side effects
  - less disinhibition/activation
  - less sleep problems
  - less nausea
- less drug interactions
- works relatively fast - one to two weeks

29 ☐ *Other Antidepressants*

- work on mix of dopamine, serotonin, norepinphrine
- tricyclics
  - eg. imipramine (Tofranil), amitryptiline (Elavil)
  - can help attention some and anxiety/mood issues
  - can help with bedwetting and sleep dysregulation
  - monitor EKGs
- Wellbutrin
  - more dopamine effect
  - may work for focusing and mood/anxiety
  - not usually activating

30 ☐ *Other Antidepressants*

- Effexor
  - good anti-anxiety effects
  - not as activating as SSRIs
- Trazodone/Serzone
  - helps a lot with sleep
  - not activating
  - good anti-anxiety effects
- MAO inhibitors (St. John's wort)

31 ☐ *Mood Swings (Seizures)*

32 ☐ *Anticonvulsants*

- may be needed to treat seizures
- also may improve behavior in some patients
- anticonvulsants that work on mood

- Depakote (valproic acid)
- Tegretol (carbamazepine)
- Neurontin (gabapentin)
- Topamax (topiramate)

33 ☐ *Anticonvulsant side effects*

- sedation
- cognitive slowing
- aggravate hypotonia
- some need bloodwork to monitor liver and blood counts (carbamazepine, valproic acid)
- least cognitive side effects - Lamictal, Keppra

34 ☐ ***Self-Abusive Behavior***

35 ☐ *Naltrexone*

- Trexan, Revia
- mixed opiate agonist/antagonist
- works on pain perception
- blocks self-abusive behavior in some cases
- ? decrease in other aggressive/dysfunctional behaviors
- main side effect sleepiness

36 ☐ ***Outbursts/Over-reaction***

37 ☐ *Beta-Blockers/Inderal*

- decreases adrenalin rush when anxious or overstimulated
- sometimes works for outbursts/over-reaction
- can try for aggressive and self-abusive behavior also
- relatively low response rate in fragile X although can work

38 ☐ ***Aggression/Outbursts/Agitation/Anxiety/ Perseveration***

39 ☐ *Antipsychotics*

- most "heavy duty" type of medicine
- also known as neuroleptics or "tranquilizers"
- often used as a last resort due to risk of long term side effect of tardive dyskinesia
- dopamine (D2) receptor blockers

40 ☐ *Antipsychotics - Benefits*

- work on anxiety, agitation, aggression
- can be helpful for aggressive behavior with puberty
- can help with sleep
- high response rate

41 ☐ *Antipsychotics - Side Effects*

- can be oversedating
- nausea, constipation

- dystonic and Parkinsonian (extrapyramidal) reactions
- can have BIG problems with weight gain

42 ☐ *Older Antipsychotics*

- haloperidol (Haldol)
- thioridazine (Mellaril)
- when compared to newer antipsychotics
  - more sedating
  - more motor reactions
  - ? more tardive dyskinesia
  - Mellaril - watch for eye pigment

43 ☐ *Newer Antipsychotics*

- Risperdal (risperidone)
- Zyprexa (olanzapine)
- Seroquel (quetiapine)
- Geodon, Zeldox (ziprasidone)

44 ☐ *Risperdal*

- blocks dopamine (D2) and serotonin (5HT2) receptors
- good anti-anxiety effect, works on agitation/aggression
- documented effectiveness and safety in populations with developmental disorders
  - mental retardation
  - autistic disorders
  - fragile X syndrome
- not too much sedation
- current high use in developmental disabilities

45 ☐ *Zyprexa*

- similar to Risperdal mechanism - generally similar response and side effect profile
- less studies in developmental disorders
- can have impaired glucose tolerance
- may aggravate weight gain more than others in some patients

46 ☐ *Seroquel*

- blocks 5HT2 more than D2
- very little or no motor side effects
- less weight gain
- some antidepressant effects
- good in Parkinson's patients
- may not be as effective in developmental disabilities - no studies

47 ☐ *Geodon*

- like Risperdal, 5HT2 and D2
- NO weight gain
- less motor side effects and sedation
- studies in children with tics suggest it is safe
- promising but NEW - no good data on effectiveness in developmental disabilities though works for tics

- may need to monitor EKG

48 *Response to Psychopharmacology in Fragile X Patients*

49 ## *Sleep Problems (Aggravate Behavior)*

50 ### *Melatonin*

- hormone normally made mostly at night
- may be dysregulation (less at night, more in day) in developmental disabilities
- sleep problems may respond to melatonin
- over-the-counter, start at 1 mg, work to 3 mg
- if no benefit after 1 month on full dose, not likely to help

51 ## *The Future of Psychopharmacology in Fragile X Syndrome- Treatment of the Underlying Problem: Cognitive Dysfunction*

52 ### *FMRP and Regulation of Synaptic Strength*

- LTP strengthening, LTD selective weakening
- fragile X knockout mouse - LTD very exaggerated
- exaggerated LTD occurs through increased activity of mGluR5 receptors which down regulate AMPA receptors
- impaired LTP in cortex but not hippocampus
- weakening and strengthening defects associated with too few AMPA receptors

53 ### *AMPA Receptors*

- mediate rapid excitatory synaptic transmission
- required for LTP
- NMDA receptor activation, synaptic stimulation cause AMPA receptors to move to the synapse to give LTP
- phosphorylated and further activated in Ca-dependent fashion by CaMKII during LTP

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55 ### *FMRP and AMPA Receptors*

- AMPA receptor subunit GluR1 specifically decreased in cortex of knockout mouse
- reduced GluR1 due to absence of proper transcriptional regulation by FMRP leads to depressed cortical synaptic plasticity
- suggests hyperactivation of AMPA receptors or partial block of mGluR5 receptors might be therapeutic for cognitive disability

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57 ### *Ampakines*

- AMPA receptors determine strength of brain connections
- AMPA receptors are deficient at brain connections in fragile X syndrome