Psychopharmacology (Medication Treatments) for Behavior in Fragile X Syndrome

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Psychopharmacology in Fragile X Syndrome

- Targets behavior to improve functioning
- Supportive, does not target underlying cognitive problem
- Only one prior controlled trial in FXS (N=15) shows Ritalin effective in 2/3 of boys
- Therapeutic decisions based on target largest problem symptom complex(es) – trial and error
- May need to treat multiple behavioral domains

Decision to Use Behavioral Medication

- Individual engaging in dangerous behaviors
- Individual is dysfunctional from behavior
- Individual could accomplish more or be higher functioning if specific behavior is managed
  - Increase ability to participate
  - Able to be in more inclusive setting
- Not necessarily “when all else fails”
- ALWAYS an adjunct to behavioral, environmental measures

Medication Choice Based on Clinical Assessment

- Identify most problematic class of symptoms
  - hyperactivity/distractibility
  - anxiety/OCD/perseveration
  - depression/mood
  - Hypersensitivity/overarousal
  - aggression/agitation/self-abusive behavior
- Often overlap in FXS
- Target problem areas with appropriate class(es) of meds

Management of Medications in Developmental Disabilities

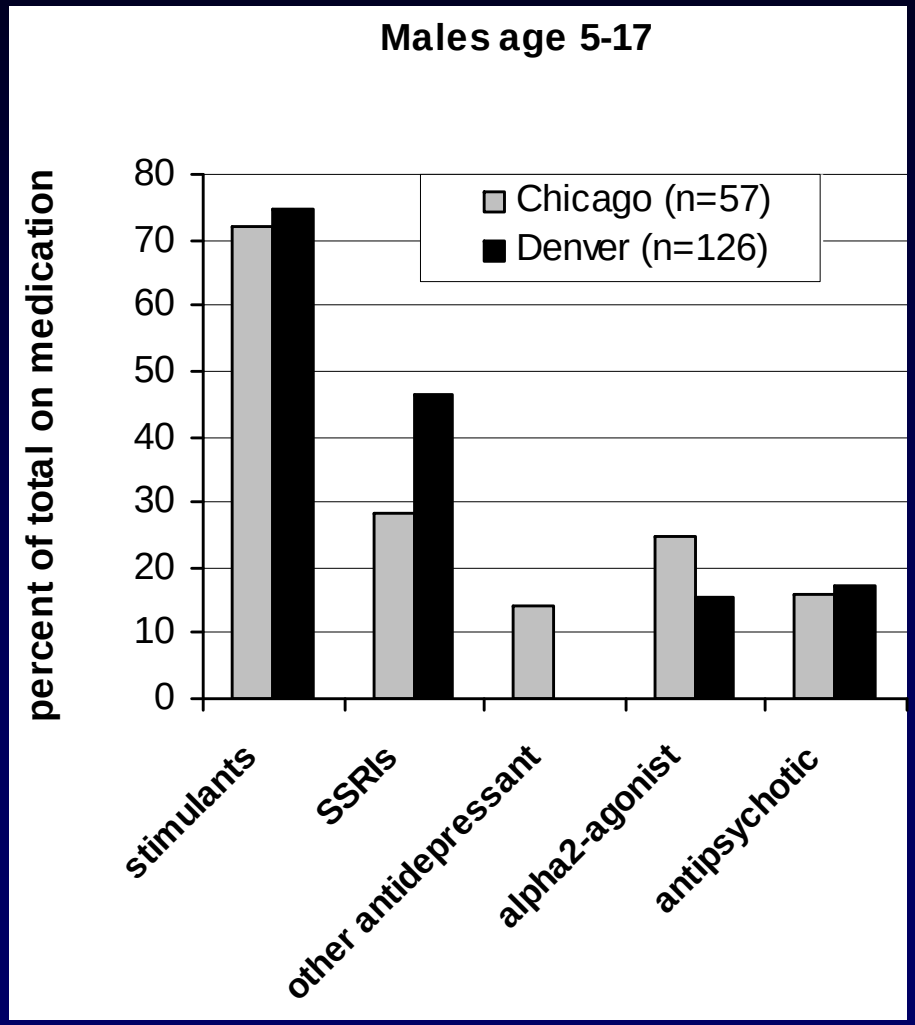
- Start with low dose
- Titrate up every week or two until at maximum dose, side effects, or effectiveness for target behavior
- Focused systematic “trial and error” method
- May need two meds to target different symptom classes
- Never start two meds at once
- Never change two meds at once unless emergency situation

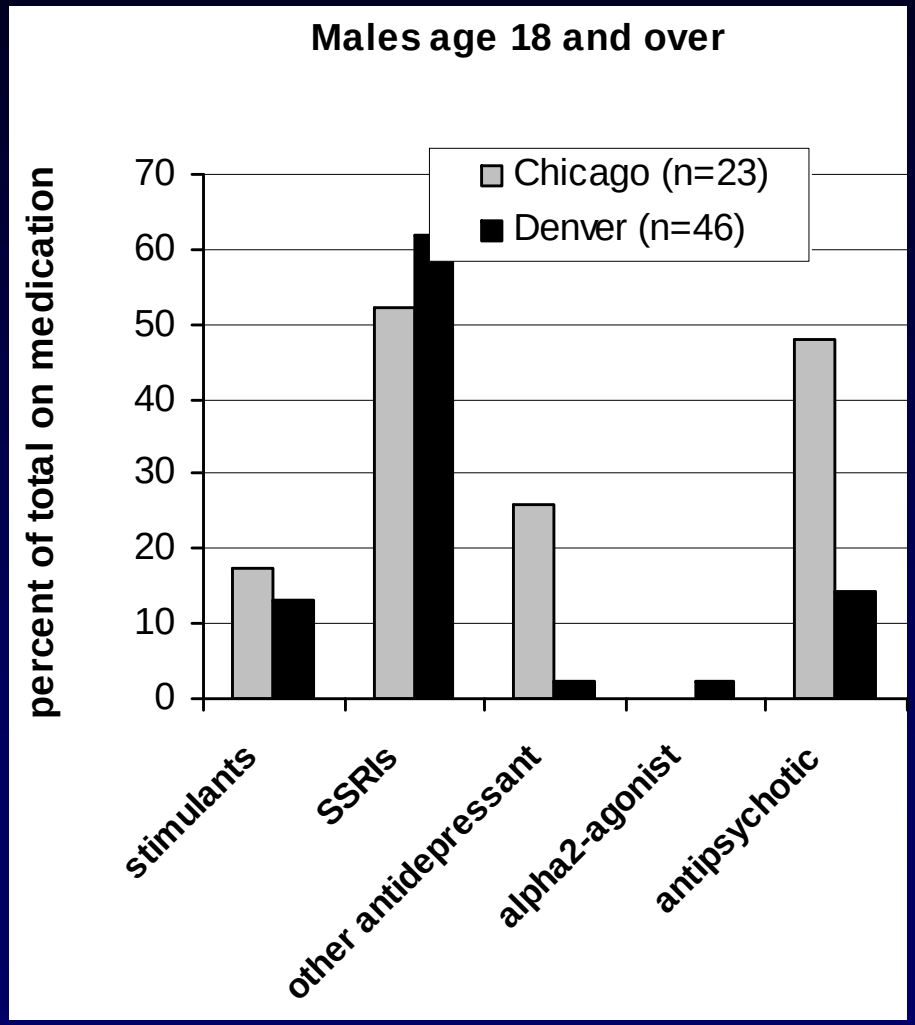
FXS - Types of Medications and Indications*

*meds may be targeting several clusters

Problem Behavior Cluster	Medication Class	Medications
Distractibility/ Hyperactivity	Stimulants	Methylphenidate, Adderall, Provigil
Overarousal/ Hypersensitivity	Alpha-agonists	Clonidine, Tenex
Anxiety/OCD/ Perseverative	SSRIs	Prosac, Zoloft, Celexa, Lexapro
Mood Lability	Antidepressants, AEDs, Lithium	Tricyclics, Effexor, Li, SSRIs, VPA, TPX, CBZ
Aggression/Self abusive	Atypical Antipsychotics,	Risperdal, Abilify, Seroquel, Geodon

Medication Use in FXS





Berry-Kravis and Potanos, 2004

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

Distractibility/Hyperactivity/ Impulsiveness

Stimulants

Methylphenidate -Ritalin, Concerta, Metadate, Focalin, Daytrana

Dextroamphetamine - Adderall, Vyvanse, Dexedrine

- Best for managing short attention span – benefits increased focus, decreased hyperactivity
- Raise dopamine levels in frontal lobe
- Don’t necessarily work prior to 5-6 years and side effects may be worse
- Dosing variable - individualize to max effect, min side effects

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, tics, anxiety, OCD, perseveration
- Occasionally may see stuttering, decreased talking, increased seizures
- No major organ side effects – can’t use with heart condition

Stimulants - Medicines Available

- Ritalin (methylphenidate)
  - short acting (3-4 hours)
  - may get peak/trough effects
    - post-dose lethargy, “drugged” look
    - wild, moody or aggressive behavior as wearing off
- Focalin - purified active form of methylphenidate – slightly longer lasting, sometimes less side effects
  - SR forms may help with ups and downs - either alone or with superimposed regular doses

Stimulants - Medicines Available – slow release (SR)

- SR forms may help with ups and downs - alone or with regular doses
- Old SR methylphenidate (Ritalin SR, Metadate, Methylin), 8-10 hr, little peak effect
- New long-acting methylphenidate (Concerta, Metadate CD, Ritalin LA, Focalin XR)
  - formulated for release early, then late
  - 8-10 hours
  - Concerta more release in afternoon
  - Ritalin LA, Focalin XR more release in AM

Stimulants - Medicines Available

- **Daytrana – methylphenidate patch**
  - **Put patch on once daily for 9 hours**
  - **Treat for 12 hours**
  - **10, 15, 20, 30 mg patches**
  - **10 mg – 1.1 mg/hour for 9 hours then tapers when patch comes off**
  - **Can wear patch in pool/shower without affecting med delivery**
  - **Good for patients with rebound or agitation when stimulant wearing off**
  - **Can individualize dosing time by varying time patch is on (patch will keep releasing past 9 hours)**
  - **May be hard to get FXS patients to keep patch on**

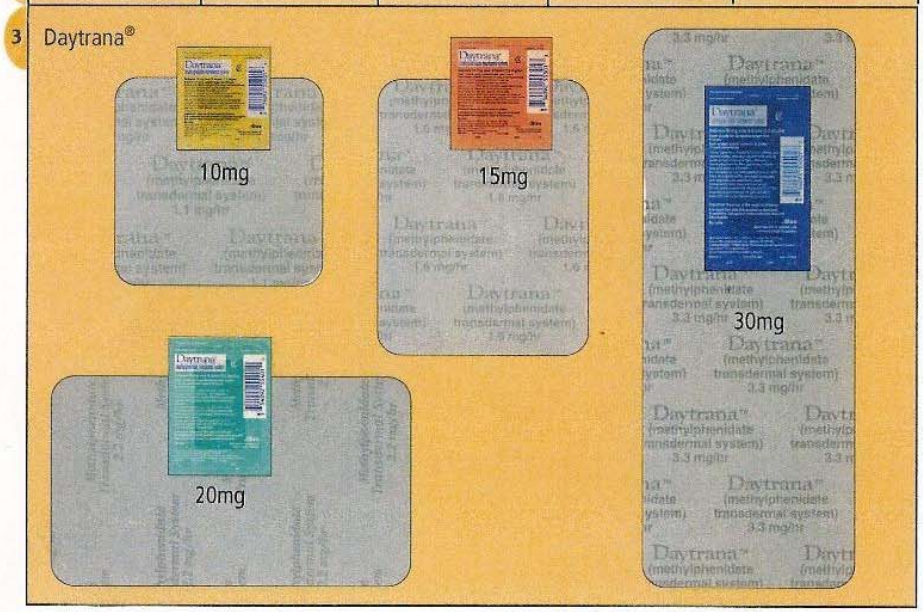
ADHD Medication Guide*

Revised: 9/27/11

Methylphenidate Derivatives – Long Acting/Extended Release

	Concerta® †	18 mg G 5	27 mg G 5	36 mg G 5	54 mg G 5	72mg + G 6				
	Focalin XR® ‡ (dexmethylphenidate)	5 mg 5		10 mg 5	15 mg 5	20 mg 5	25 mg 5	30 mg 5	35 mg 9	40 mg 9
2	Ritalin® LA ‡	10mg		20mg	30mg	40mg				
3	Metadate® CD ‡	10mg		20mg	30mg	40mg	50mg	60mg		
2	Methylin® ER	10mg		20mg						
4	Ritalin® SR			20mg G						

3 Daytrana®



Methylphenidate Derivatives – Short Acting/Immediate Release

3	Focalin® (dexmethylphenidate)		2.5mg G	5mg G	10mg G
4	Ritalin®		5mg G	10mg G	20mg G
2	Methylin®		5mg	10mg	20mg
2	Methylin® Chewable § (Grape Flavor)	2.5 mg	5mg	10mg	
2	Methylin® Solution (Grape Flavor)		5mg/5ml	10mg/5ml	

G indicates a generic formulation is available; generic products are not shown.

*Disclaimer: The ADHD Medication Guide was created by Dr. Andrew Adesman of the North Shore-LIJ Health System. The North Shore-Long Island Jewish Health System is not affiliated with the owner of any of the brands referenced in this Guide.

This Guide should not be used as an exclusive basis for decision-making. The user understands and accepts that if the health system were to accept the risk of harm to the user from use of this Guide, it would not be able to make the Guide available because the cost to cover the risk of harm to all users would be too great. Thus, use of this ADHD Medication Guide is strictly voluntary and at the user's sole risk.

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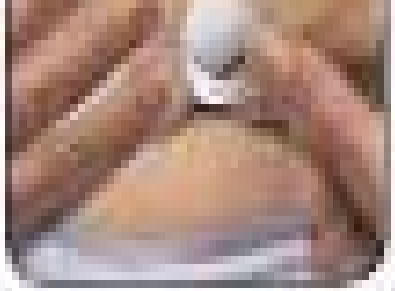

Stimulants - Medicines Available

- Adderall (mix of amphetamines)
  - mix of 4 stimulants - 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 and norepinephrine activity than methylphenidate
- Adderall XR - 2-dose slow release, 10-12 hrs

Stimulants - Medicines Available

- **Vyvanse – NEW – long acting d-amphetamine**
  - **Long acting due to has to go through metabolic step before active – no addictive potential**
  - **Steady levels through day – may last longer than Adderall XR (at least 10 hours)**
  - **Has been good in some FXS patients having trouble with agitation or mood when Adderall dose wearing off**
  - **Some complain that this medication takes longer to start working.**

ADHD Medication Guide*

Revised: 9/27/11

Amphetamine Derivatives – Long Acting/Extended Release

5	Vyvanse® ¥ (lisdexamfetamine)	20mg	30mg	40mg	50mg	60mg	70mg
	Adderall XR® ‡ (mixed amphetamine salts)	5mg G	10mg G	15 mg G	20mg G	25mg G	30 mg G
7	Dexedrine Spansule® (d-amphetamine)	5mg G	10mg G	15mg G			

Amphetamine Derivatives – Short Acting/Immediate Release

1	Adderall® (mixed amphetamine salts)	5mg G	7.5mg G	10mg G	12.5mg G	15mg G	20mg G	30mg G
8	Dextroamphetamine	5mg G		10mg G				
8	ProCentra® (Bubblegum Flavor)	5mg/5ml						

Non-Stimulants

3	Intuniv® † (guanfacine, extended release)	1mg	2mg	3mg	4mg			
3	Kapvay™ † (clonidine, extended release)	0.1mg						
5	Strattera® † (atomoxetine)	10 mg	18mg	25mg	40mg	60mg	80mg	100mg

Medication Administration Key

† Must be swallowed whole
¥ Can be dissolved in liquid
§ Chewable
‡ Capsule can be opened and medication sprinkled on applesauce

AGES FOR WHICH MEDICATIONS HAVE AN FDA INDICATION FOR TREATMENT OF ADHD.

Tab #	3-5 Year	6-12 Year	13-16 Year	17 Year	Adults
1	✔	✔			
2		✔			
3		✔	✔	✔	
4		✔			✔
5		✔	✔	✔	✔
6			✔	✔	✔
7		✔	✔		
8	✔	✔	✔		
9					✔

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The ADHD Medication Guide is a visual aid for professionals caring for individuals with ADHD. The Guide includes only medications indicated for the treatment of ADHD by the FDA. In clinical practice, this guide may be used to assist patients in identifying medications previously tried, and may allow clinicians to identify ADHD medication options for the future. Medications have been arranged on the card for ease of display and comparison, but dosing equivalence cannot be assumed. Practitioners should refer to the FDA-approved product information to learn more about each medication. Although every effort has been made to depict each medication in its actual size and color, we cannot guarantee that there are not minor distortions in the final image. This guide is accurate as of September 27, 2011. For updates, visit www.ADHDMedicationGuide.com.

- Future revisions of the **ADHD Medication Guide** can be viewed at **www.ADHDMedicationGuide.com**
- Laminated copies of the **ADHD Medication Guide** can be obtained at: **www.ADDWarehouse.com**
- For questions or comments, contact Dr. Andrew Adesman at **ADHDMedGuide@NSHS.edu**

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Atomoxetine (Strattera)

- New non-stimulant medicine for ADHD symptoms
- SNRI - selective norepinephrine reuptake inhibitor – increase brain NE
- Less aggravation of picking, anxiety, irritability
- ? Subgroups of patients with ADHD sx who do better on either stimulants or atomoxetine
- Mixed results in FXS – problems with agitation response

Provigil (modafanil)

- Narcolepsy med
- Increases dopamine in brain (like stimulants)
- Successful in some adults with behavior, attention problems in whom stimulants are no longer working or are aggravating aggression
- No major side effects

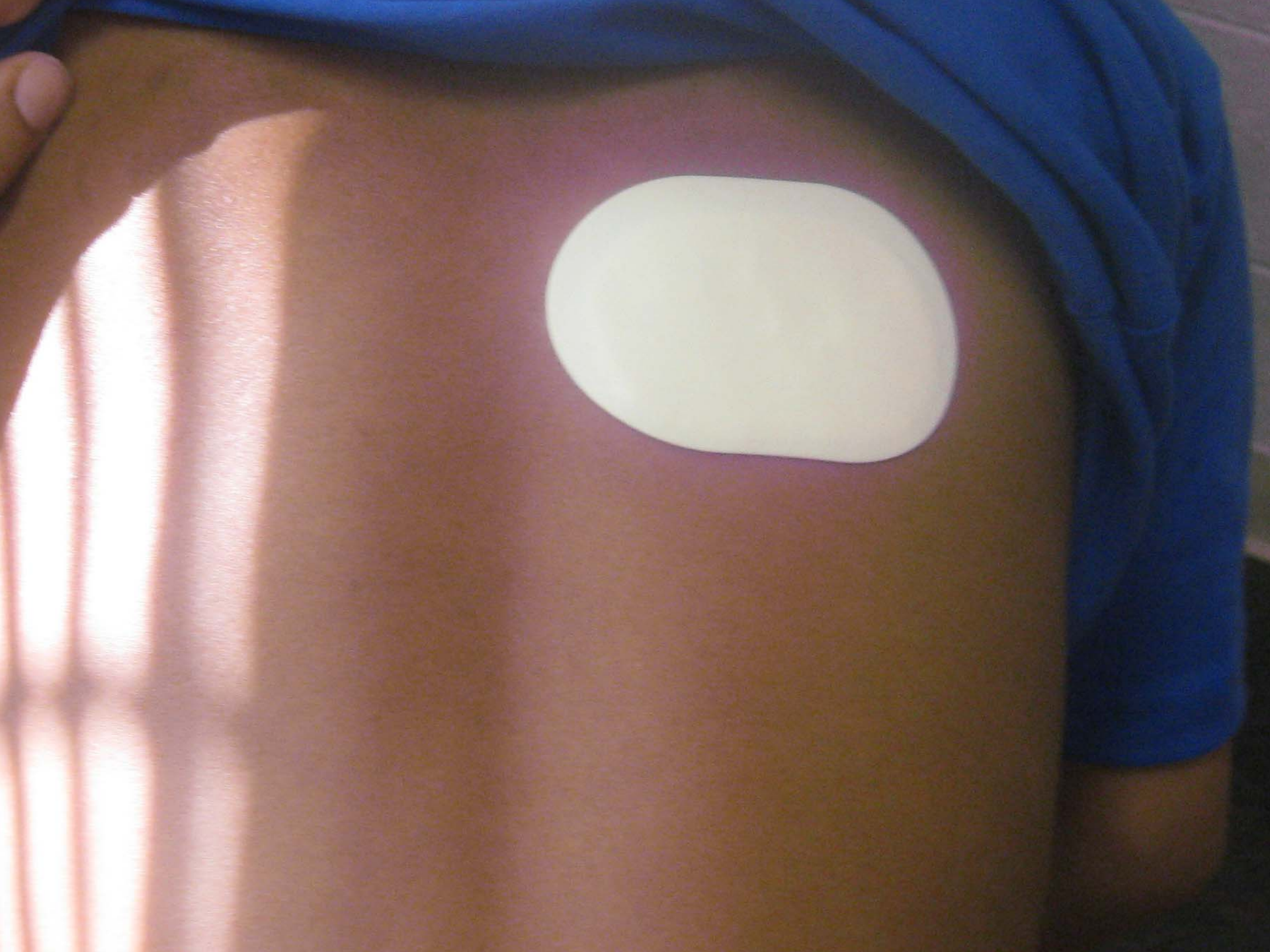
Hyperactivity/ Hypersensitivity/Agitation-Aggression

Clonidine/Tenex(guanfacine)

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

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, daily to BID dosing
- clonidine patch gives even dosing but annoys patients
- Long acting forms less sedation – Kapvay, Intuniv



Anxiety/OCD/Perseveration/ Mood Swings and Depressive Symptoms

SSRIs

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

Prosac, Zoloft, Paxil, Celexa, Lexopro

SSRIs - Benefits

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

SSRIs - Side Effects

- activation/hyperactivity/disinhibition - wild/odd behaviors – about 10-15%
- appetite changes
- insomnia - usually wears off
- nausea - not common
- decreased sexual drive/impotence - rarely an issue

SSRIs - Medicines Available

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

SSRIs - Medicines Available

- Zoloft (sertraline) - less activating, good for patients with ADHD and OCD/anxiety symptoms, good in young FXS patients
- Paxil (paroxetine) - fastest acting
- Luvox - (fluvoxamine) used for children for OCD symptoms, potency like Zoloft
- Celexa (citalopram) and Lexapro (s-citalopram) - newest ones, most selective, Lexapro most potent, minimal drug interactions, work fast 1-2 weeks, ? Less side effects

Other Antidepressants

- work on 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 (bupropion)
  - more dopamine effect
  - may work for focusing and mood/anxiety
  - not usually activating
  - not use if active seizures

Other Antidepressants/Anxiolytics

- Effexor (venlafexine)
  - NE and 5HT reuptake blocker
  - good anti-anxiety effects
  - not as activating as SSRIs
  - may have some effects on distractibility
- Trazodone
  - helps a lot with sleep
  - not activating
  - good anti-anxiety effects
- MAO inhibitors (St. John's wort)
- Buspar (buspirone) – not an antidepressant – generally weak but can work for anxiety in some individuals with FXS

Aggression/Outbursts/ Agitation/Anxiety/ Perseveration

Older Antipsychotics

- Haloperidol (Haldol)
- Thioridazine (Mellaril)
- When compared to newer antipsychotics
  - more sedating
  - more motor reactions
  - ? more tardive dyskinesia
  - Mellaril - watch for eye pigment

Newer Antipsychotics

- Risperdal (risperidone)
- Zyprexa (olanzapine)
- Seroquel (quetiapine)
- Geodon, Zeldox (ziprasidone)
- Abilify (aripiprazole)
- Saphris (asenapine)
- Latuda (lurasidone)

Antipsychotics

Risperdal, Abilify, Seroquel, Zyprexa, Geodon

- 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

Antipsychotics - Benefits

- Work on anxiety, agitation, aggression
- Can be helpful for aggressive behavior with puberty
- Can help with sleep
- High response rate but also highest side effect rate

Antipsychotics - Side Effects

- Can be oversedating
- Nausea, constipation
- Increased prolactin and gynecomastia
- Dystonic and parkinsonian (extrapyramidal) reactions
- Can have BIG problems with weight gain

Risperdal (risperidone)

- 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
- High use in developmental disabilities

Zyprexa (olanzapine)

- Similar to Risperdal mechanism - generally similar response and side effect profile
- Less studies in developmental disorders
- Can give impaired glucose tolerance (more so than others)
- May aggravate weight gain more than others in some patients

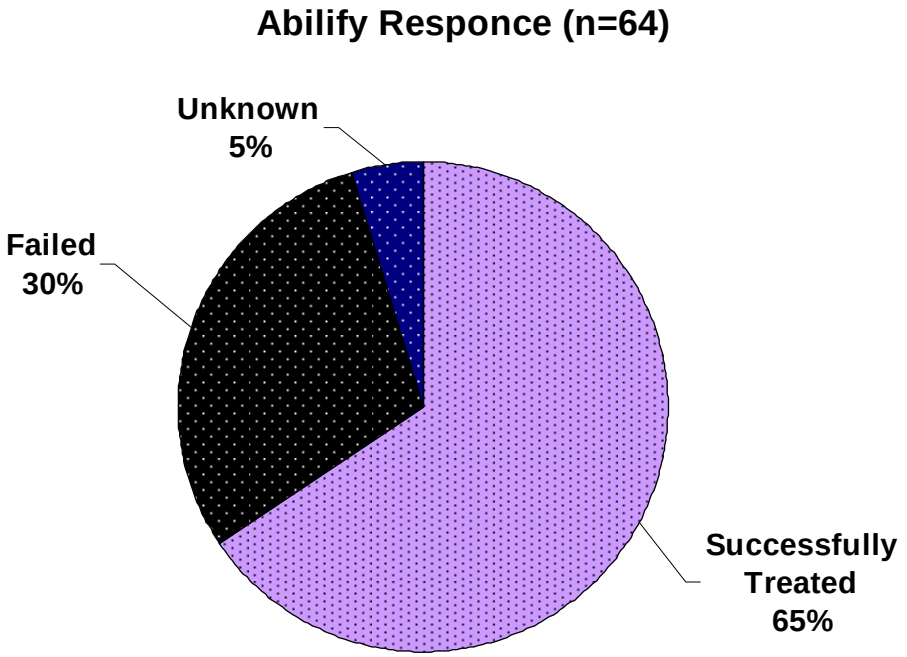
Seroquel (quetiapine)

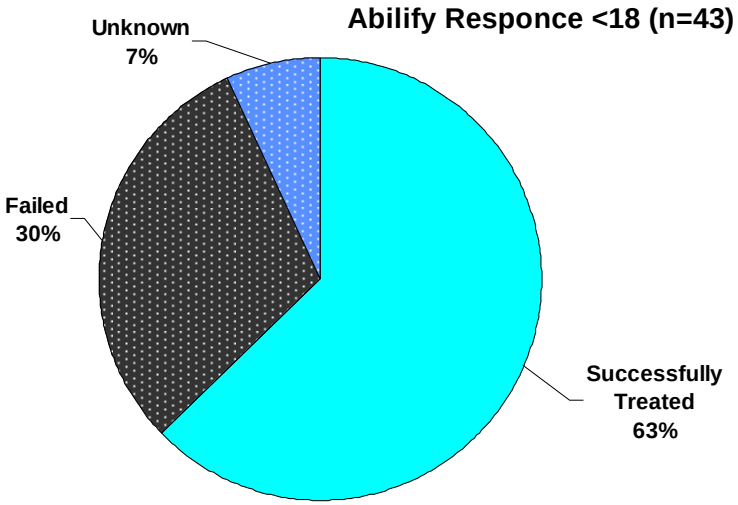
- Blocks 5HT2 more than D2
- Very little or no motor side effects
- Less weight gain
- Some antidepressant effects
- Good in Parkinson’s patients
- May not be as effective in developmental disabilities - no studies

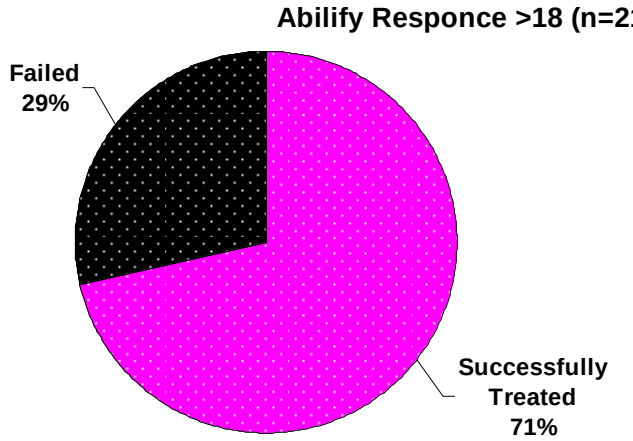
Abilify (aripiprazole) – New Mechanism

- Partial agonist (activator) at dopamine D2 and serotonin 5HT1a receptors, antagonist at 5HT2a
- May be particularly good in FXS because may help with ADHD symptoms (dopamine effect) as well as anxiety/irritability
- Likewise can get aggravation of irritability, perseveration, agitation due to dopamine effect in subgroup
- Social behaviors better in animal models compared to other antipsychotics
- Thus far best antipsychotic response rate for FXS – can give dramatic social improvements

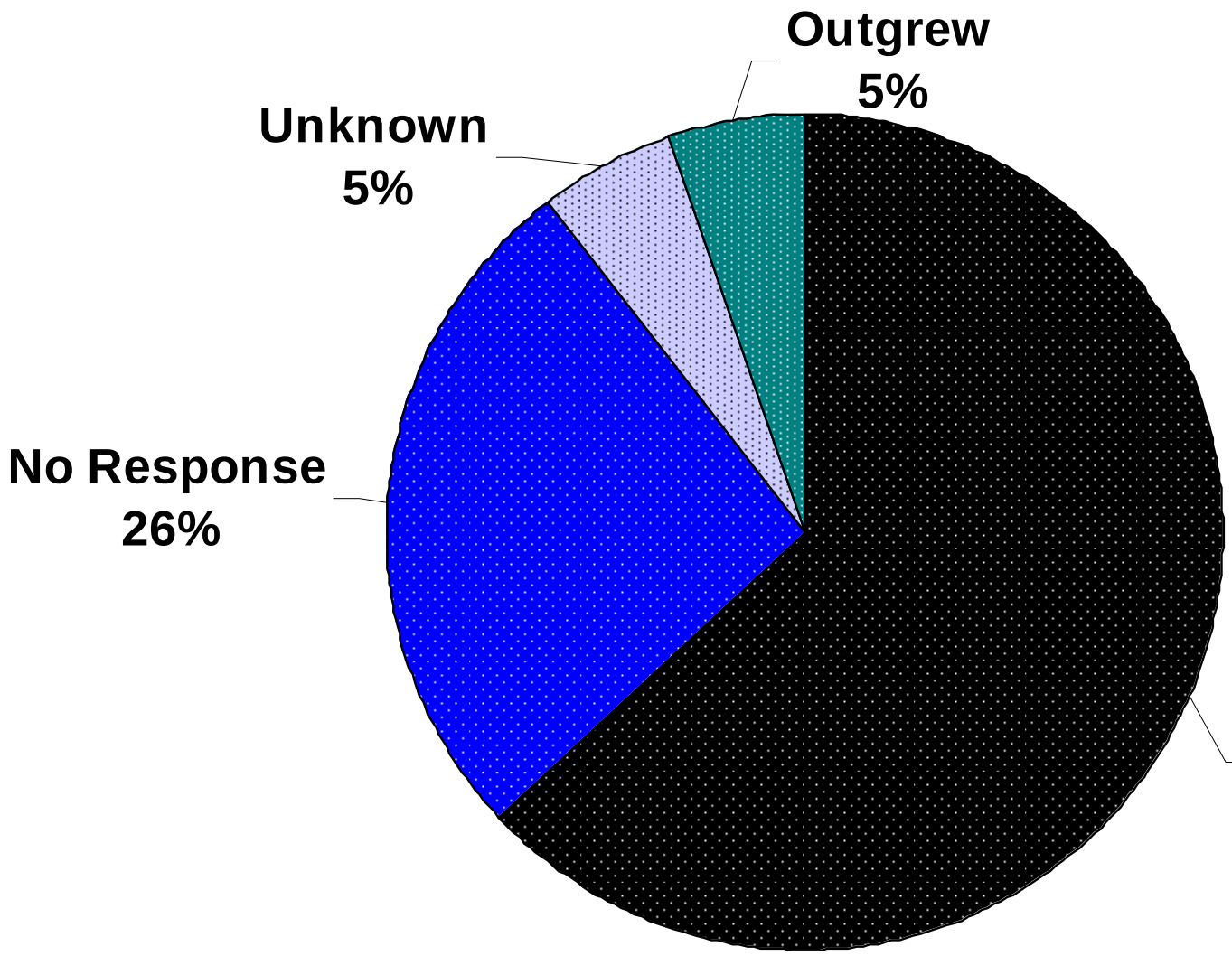
Abilify – High Response Rate in FXS (2004-2007)







Reason for Ablify Failure (n=19)



Side effect is almost always excessive agitation, increased aggression, occasionally weight or other

Newest Atypical Antipsychotics

- Little FXS experience
- Saphris (asenapine)
  - Works on many receptors – dopamine, serotonin, norepinephrine, histamine
  - Have to leave in mouth until it disolves, 5-10 mg twice a day, monitor EKGs
- Latuda (lurasidone)
  - Similar mechanism as risperidone
  - Blocks dopamine (D2) and serotonin (5HT2) receptors, also 5HT7 and has extra effects on norepinephrine receptors, activates 5HT1 receptors
  - 20-120 mg/day – take with food

Mood Stabilizers - Anticonvulsants

Anticonvulsants

- may be needed to treat seizures
- also may improve behavior in some patients
- anticonvulsants that work on mood
  - Depakote (valproic acid)
  - Tegretol (carbamazepine)/Trileptal (oxcarbazine)
  - Lamictal (lamotrigine)
  - Topamax (topiramate)

Anticonvulsant side effects

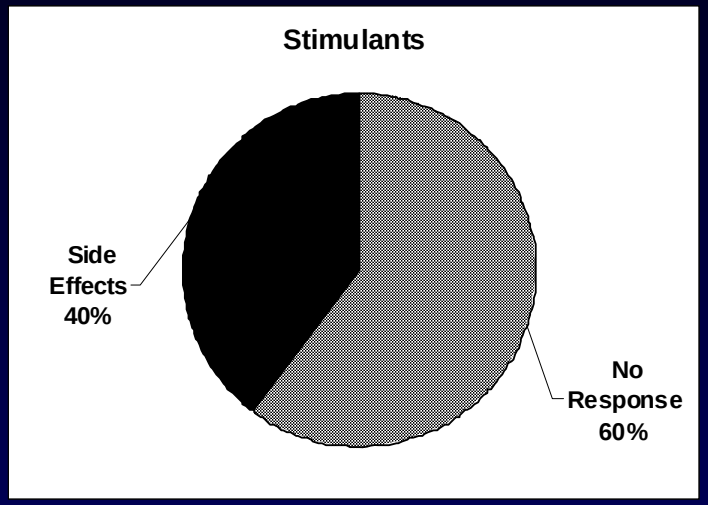
- sedation
- cognitive slowing
- aggravate hypotonia
- some need bloodwork to monitor liver and blood counts (carbamazepine, valproic acid)
- least cognitive side effects - Lamictal, Keppra

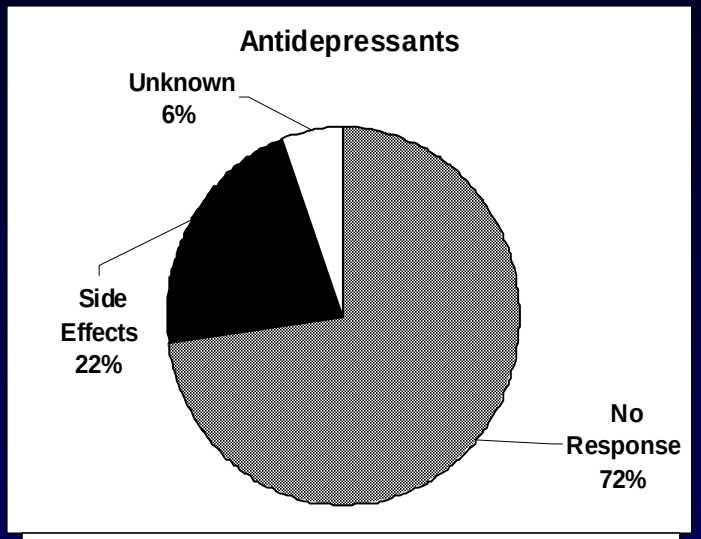
Self-Abusive Behavior

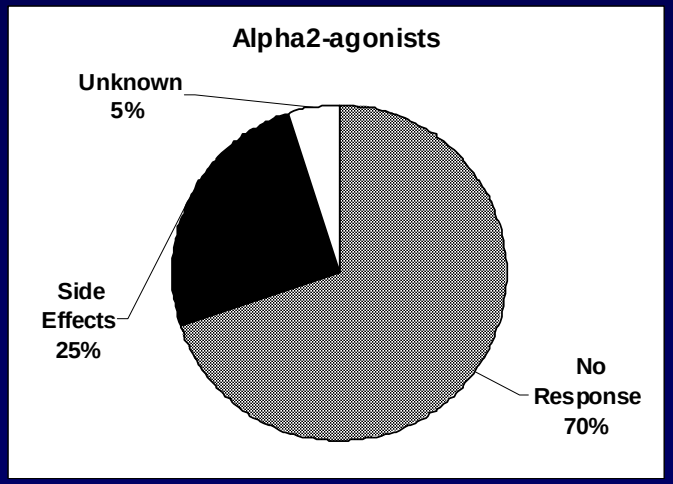
Naltrexone

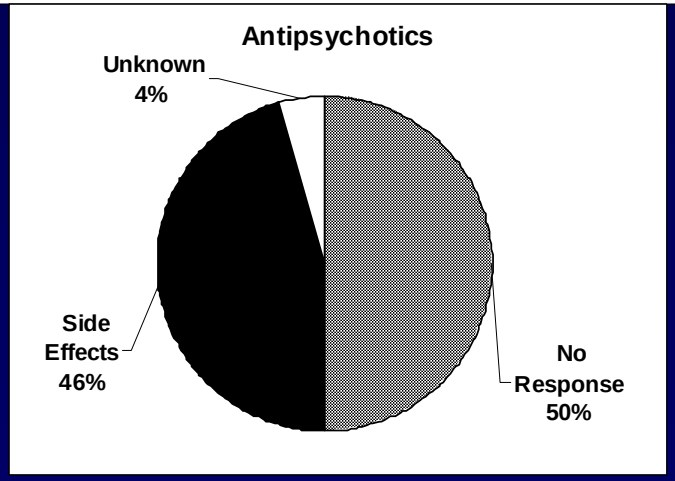
- Trexan, Revia
- mixed opiate agonist/antagonist
- works on pain perception
- blocks self-abusive behavior in some cases
- ? decrease in other aggressive/dysfunctional behaviors
- main side effect sleepiness

Reasons for Medication Failure in FXS



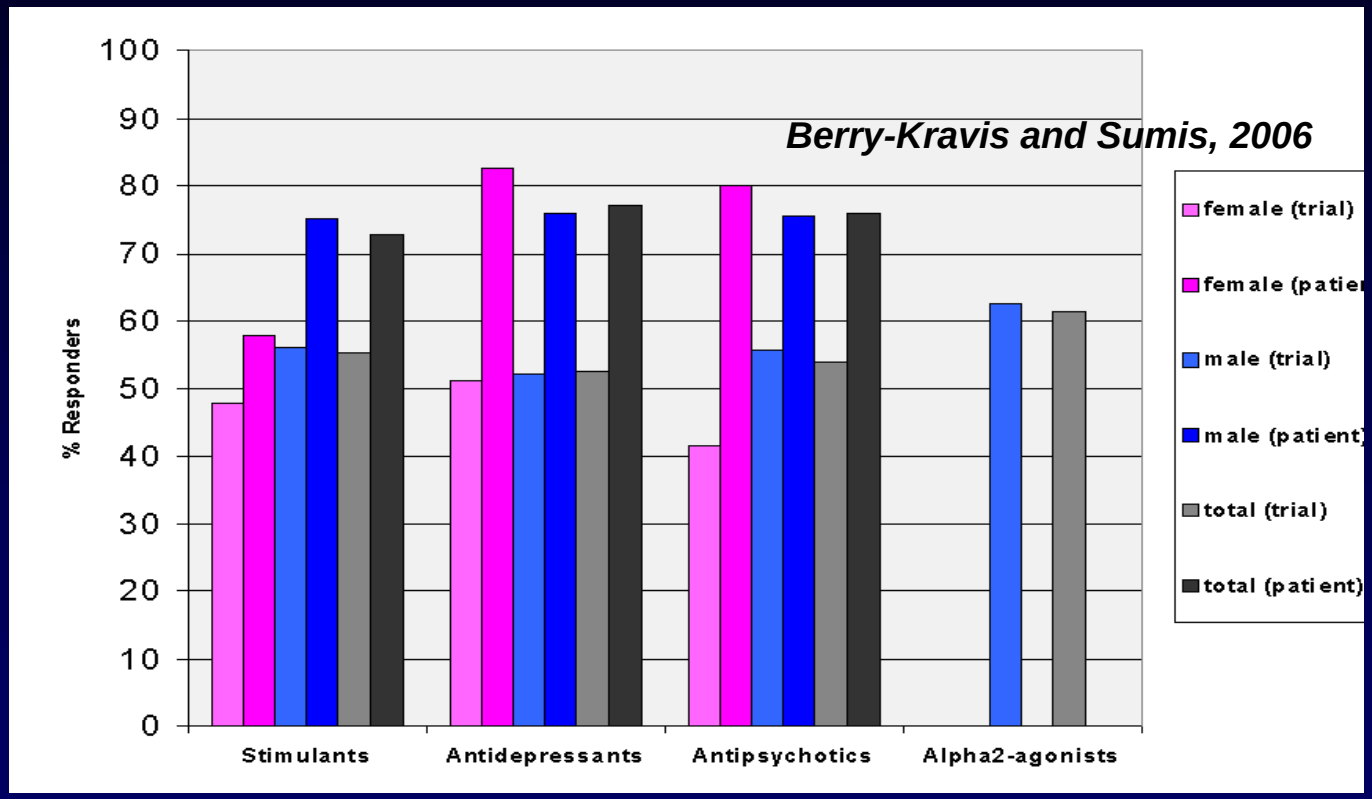






Rush Fragile X Clinic:

Supportive Psychopharmacology is Helpful in FXS…



208 trials
136 patients

231 trials
123 patients

100 trials
58 patients

52 trials
52 patients

Attention Hyperactivity	Anxiety Mood	Aggression Irritability	Hyperarousal Oversensitivity

…but treating the underlying disorder would be better

Seizures: Basic Principles of Seizure Management in FXS

1. start medicines after 2 or more clinical seizures, do not need to treat abnormal EEG
2. stop 2 years after last seizure
3. single drug regimen, lowest effective dose best
4. dose guide is effectiveness and toxicity
5. Match drug to seizure type, patient characteristics
6. Use drugs with less effect on cognition and behavior
7. EEG is adjunct for deciding which drug, how much, and how long
8. more drug is not necessarily more effective

Seizure Medication Selection

- Define the seizure type
- Select medicine for type
- Match medicine to patient characteristics
- Good seizure medicines in FXS have less cognitive suppression: Keppra, Trileptal, Lamictal best; Tegretol, Depakote not bad
- Side effects common for AEDs
  - Keppra – behavior worse – aggression (~15%)
    Lamictal – rash
  - Depakote – liver, pancreatitis, need blood monitoring
  - Topomax – speech regression

Sleep Problems (Aggravate Behavior)

Sleep Problems - Melatonin

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