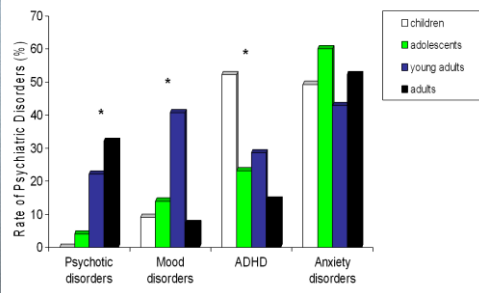


## Psychiatric Disorders in VCFS at Different Age Groups



Green, Gothelf, Eliez et al JAACAP 2009



## Psychiatric Disorders and Treatments in Children with VCFS

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## Risk Factors for ADHD in VCFS

- o Having a first degree relative with ADHD-
  - o Rate of ADHD in first degree relatives:
 

VCFS with ADHD	12%
VCFS without ADHD	2.2%

Gothelf et al Neuropsychiatric Genetics 2004

## Externalizing Disorders

- |                                 |        |
|---------------------------------|--------|
| o ADHD                          | 37.10% |
| o Oppositional defiant disorder | 14.25% |
| o Conduct disorder              | 0%     |

The Psychiatric Platform of the International 22q11.2DS Consortium

## Anxiety Disorders

- o Among patients with an anxiety disorders
  - o 69% with 1 anxiety disorder
  - o 22% with 2 anxiety disorders
  - o 9% with 3 or more anxiety disorders.

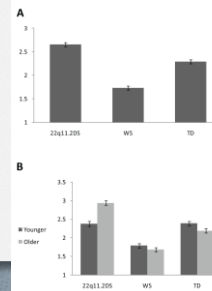
## Anxiety Disorders

- |                                 |        |
|---------------------------------|--------|
| o Any anxiety disorder          | 35.63% |
| o Specific phobia               | 21.94% |
| o Social phobia                 | 10.34% |
| o Generalized anxiety disorder  | 8.28%  |
| o Separation anxiety disorder   | 6.33%  |
| o Obsessive compulsive disorder | 5.52%  |
| o Panic disorder                | 1.20%  |
| o Posttraumatic stress disorder | 0.36%  |

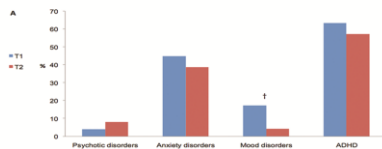
### Mood Disorders

- o Any mood disorder 3.29%
- o Major depressive disorders 2.19%
- o Dysthymia 1.10%

### Shyness in Children with VCFS, Williams syndrome (WS) and Typically Developing (TD) Controls



### Longitudinal Change in the Rate of Psychiatric Disorders During Childhood



Gothelf, Schneider, Green, Glaser, Elez, JAACAP, under revision

### Psychotic Disorders

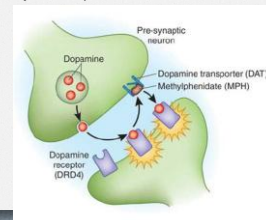
- o Any psychotic disorder 1.97%
- o Schizophrenia 0.22%
- o Psychotic disorder NOS 1.75%
- o Autism spectrum disorders 14%-45%

### Medications for ADHD

Medication	Duration (hours)	Dosage (mg/kg)
Ritalin		-
Ritalin SR		0.6-1.4
Ritalin LA		0.6-1.4
Concerta		
Adderall		- (total)
Strattera	continuous	

### Medications for ADHD: Mechanism of Action

- o Elevate brain catecholamines (dopamine & norepinephrine) levels



### Methylphenidate in VCFS- Why Yes?

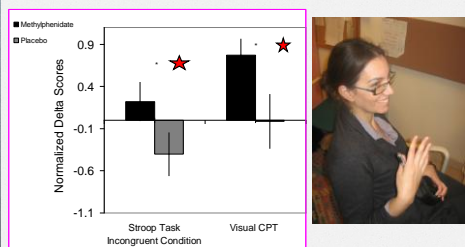
- o ADHD is a common and debilitating problem in ~half of children with VCFS
- o Methylphenidate has a robust clinical effect on symptoms of inattention and impulsivity which are common in VCFS
- o There are no good alternative treatments for ADHD

### Methylphenidate in VCFS- Why not?

#### Side effects

- o depressive symptoms
- o psychotic symptoms
- o Increased risk for sudden death in individuals with cardiac anomalies
- o Putatively high brain levels of catecholamines due to reduced dosage of COMT

### Ritalin Improved Prefrontal Cognitive Functioning and ADHD Symptoms in VCFS

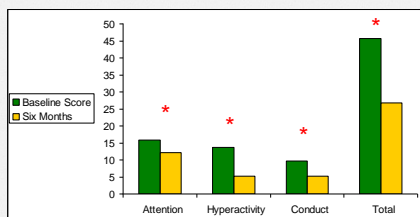


### Efficacy of Methylphenidate in VCFS

- o 34 children with VCFS aged 5 to 20 years (mean 11yrs; Males=20, Females=14)
- o Subjects were randomly assigned to receive ritalin (n=22) or placebo (n=12)
- o Ritalin dosage- 0.5 mg/kg
- o Outcome measures
  - o Prefrontal cognitive performance
    - o Directional Stroop Task
    - o Visual continuous performance test
  - o Side effects and measures of cardiac safety

Green et al., J Child Adolesc Psychopharmacol, 2011

### Improvement of ADHD Symptoms Following Six Months Treatment



- 40% reduction according to parent report using the Revised Conners' Rating Scale Total Scores

### Cardiac Safety

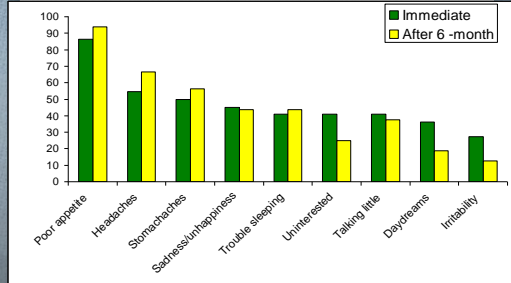
	Before Ritalin	On Ritalin	P value
Heart rate	82.4 13.5	87.9 17.8	<0.05
Diastolic BP	60.6 8.4	64.6 6.9	<0.05
Systolic BP*	108.1 11.2	108.7 7.9	NS
QTc	0.40 0.02	0.40 0.02	NS

\* An increase in systolic BP above 95<sup>th</sup> percentile occurred in 2 children

### Conclusions: Ritalin (Methylphenidate) in VCFS

- o Methylphenidate seems to be effective and well tolerated in children with VCFS and comorbid ADHD treated for 6 months.
- o Methylphenidate had a positive effect both on ADHD clinical symptoms and on some prefrontal cognitive functions.
- o Methylphenidate may increase heart rate and blood pressure which in a few cases is clinically significant.
- o A comprehensive cardiological evaluation is recommend for all children with VCFS prior and following initiation of methylphenidate treatment

### Rate (%) of Side Effects\*



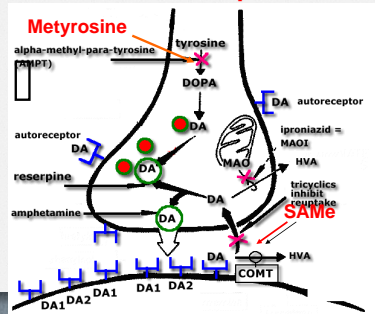
\* Barkley Side Effects Rating Scale

### SSRI Medications

Medication	Trade Names	Dose (mg)	Weight gain	Sex	Sleep	GI
Fluoxetine	prozac, fluotine, prizma	20-60	+	++	↑↓	
Citalopram	cipramil, recital	20-60	++	+	↑	
Escitalopram	cipralext, esto	10-30	++	+	↑	
Sertraline	lustral, serenada	50-200	+	+	↑	
Fluvoxamine	favoxil	100-300	+	++	↑	
Paroxetine	seroxat, paxxet	20-60	++	++	↑↑	

### Treatment of Anxiety Disorders and Depression

### Potential Pathophysiological Treatments in 22q11.2DS



### SSRI Efficacy and Suicidality in non-VCFS Children & Adolescents

	Response SSRIs	Response Placebo	NNT	Suicidality SSRIs	Suicidality Placebo
MDD	61%	50%	10	3%	2%
OCD	52%	32%	6	1%	0.3%
Other Anx. D.	69%	39%	3	1%	0.2%

Bridge et al JAMA 2007; 297:1683-96

### A Double-Blind Feasibility (Safety) Study of SAME in 22q11.2DS

- o 12 weeks
- o Randomized double-blind cross-over placebo control trial
- o Psychopathology:
  - o ADHD (n=7)
  - o Depression (n=5)
- o Patients were receiving additional psychiatric medications

Green et al 2012

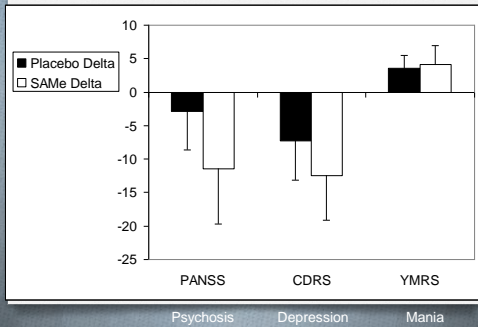
### S-Adenosyl-Methionine (SAME): A Potential Enhancer of COMT

- o SAME increases the activity of COMT enzyme
- o Slows down the degradation of COMT enzyme at body temperature

#### SAME clinical effects

- o Osteoarthritis
- o Liver diseases
- o Depression (Papakostas, 2009)
- o Schizophrenia (Strous et al., 2009)
- o Memory (Levkovitz et al., 2011)
- o Might induce switch into mania and exacerbation of psychotic symptoms

### Results -Treatment Effect



### SAME in 22q11.2DS - Side Effects

	SAME	Placebo	P value
<b>Gastrointestinal</b>			
Gastrointestinal upset	41.6% (5)	8.6% (1)	NS
Nausea	8.6% (1)	8.6% (1)	NS
Diarrhea/gas	8.6% (1)	25% (3)	NS
Increased appetite	8.6% (1)	0	NS
<b>Other side effects</b>			
Restlessness	8.6% (1)	16.6% (2)	NS
Nervousness	0	16.6% (2)	NS
Sleep disturbance	8.6% (1)	0	NS
Flu-like symptoms	8.6% (1)	8.6% (1)	NS

### SAME: Conclusions

- o SAME is safe in 22q11.2DS
- o Is not effective for ADHD and enhancing cognition
- o Possibly effective for depressive and psychotic symptoms