

Psychiatric Treatments in 22q11DS

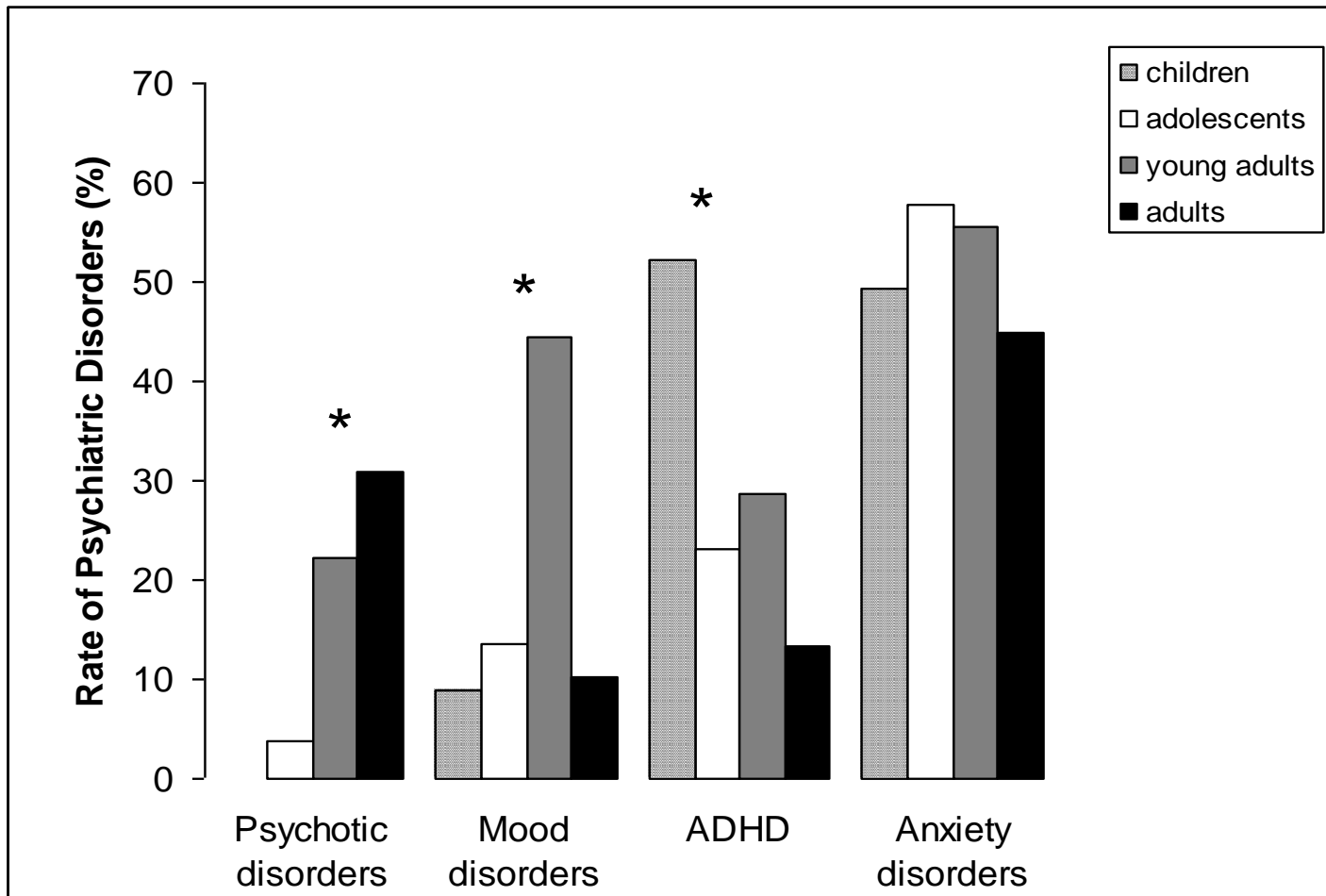
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In A Nutshell

- About two-thirds of individuals with 22q11DS cope with at least one psychiatric disorder
- There are effective treatments for psychiatric disorders
- These treatments have been recently studied and proven to be effective and safe also in 22q11DS

Distribution of Psychiatric Disorders in 22q11DS Across Development



ADHD in 22q11DS

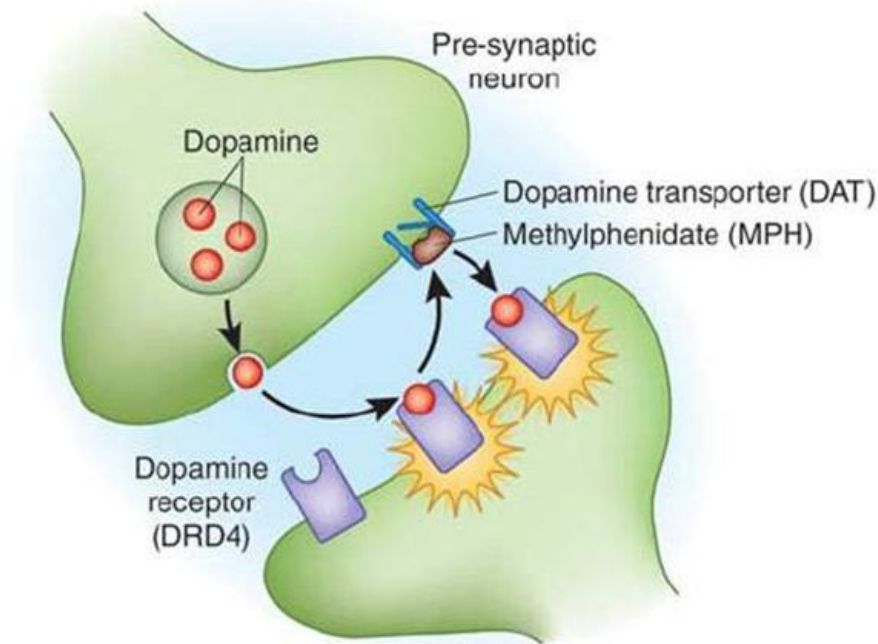
- Diagnosed in about half of children with 22q11DS and in only 13% of older adults.

Subtypes of ADHD

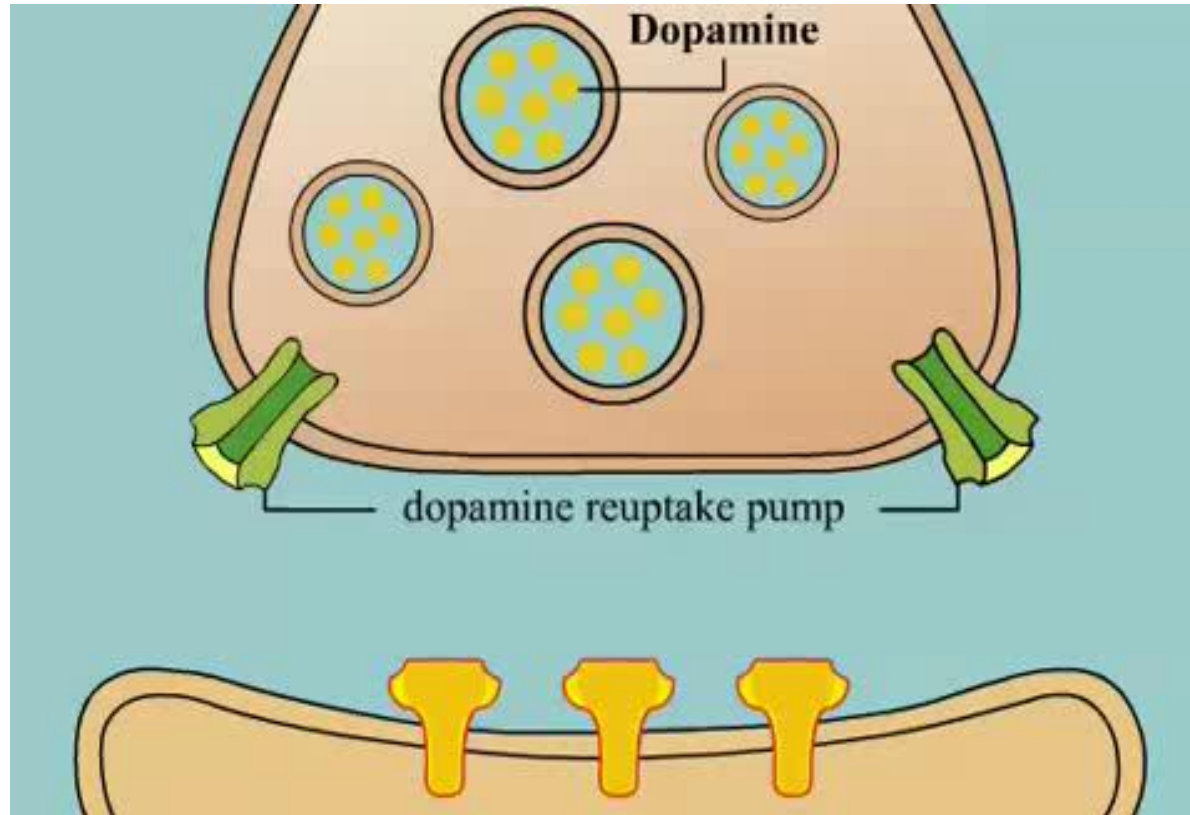
- Inattentive type: at least 6 of 9 symptoms of inattention (very common)
- Hyperactive-Impulsive type: at least 6 of 9 symptoms of hyperactivity and impulsivity (not-common)
- Combined type (common)

Treatment of ADHD: Ritalin

- Elevates brain catecholamines (dopamine, norepinephrine) levels



Ritalin: Mechanism of Action



Ritalin in 22q11DS: Study 1

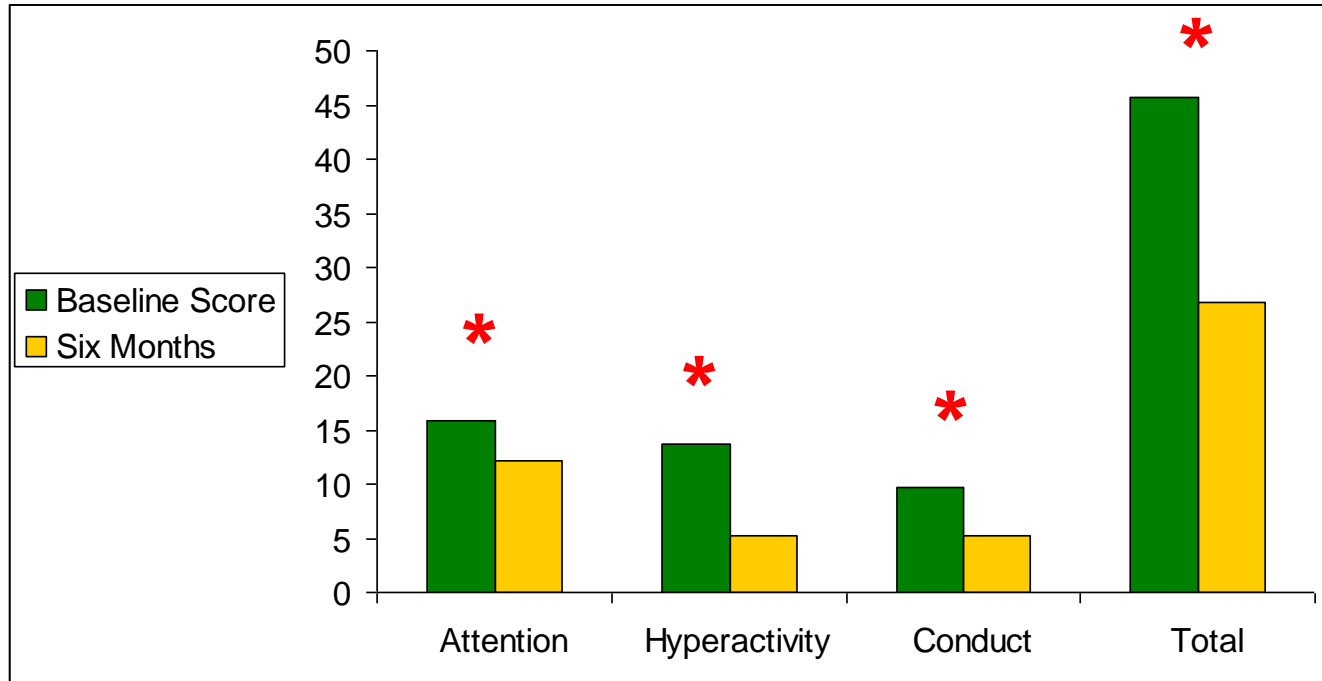
An Open-Label Study

- One open label 4 weeks study showed effectiveness and safety of ritalin 0.3 mg/kg in 22q11DS:
 - 9 of 12 children with VCFS (75%) significantly improved.
 - Duration of clinical effect was 3.2 ± 1.4 hours.
- None of the children
 - Experienced psychotic or manic exacerbations
 - discontinued ritalin

Ritalin in 22q11DS: Study 2

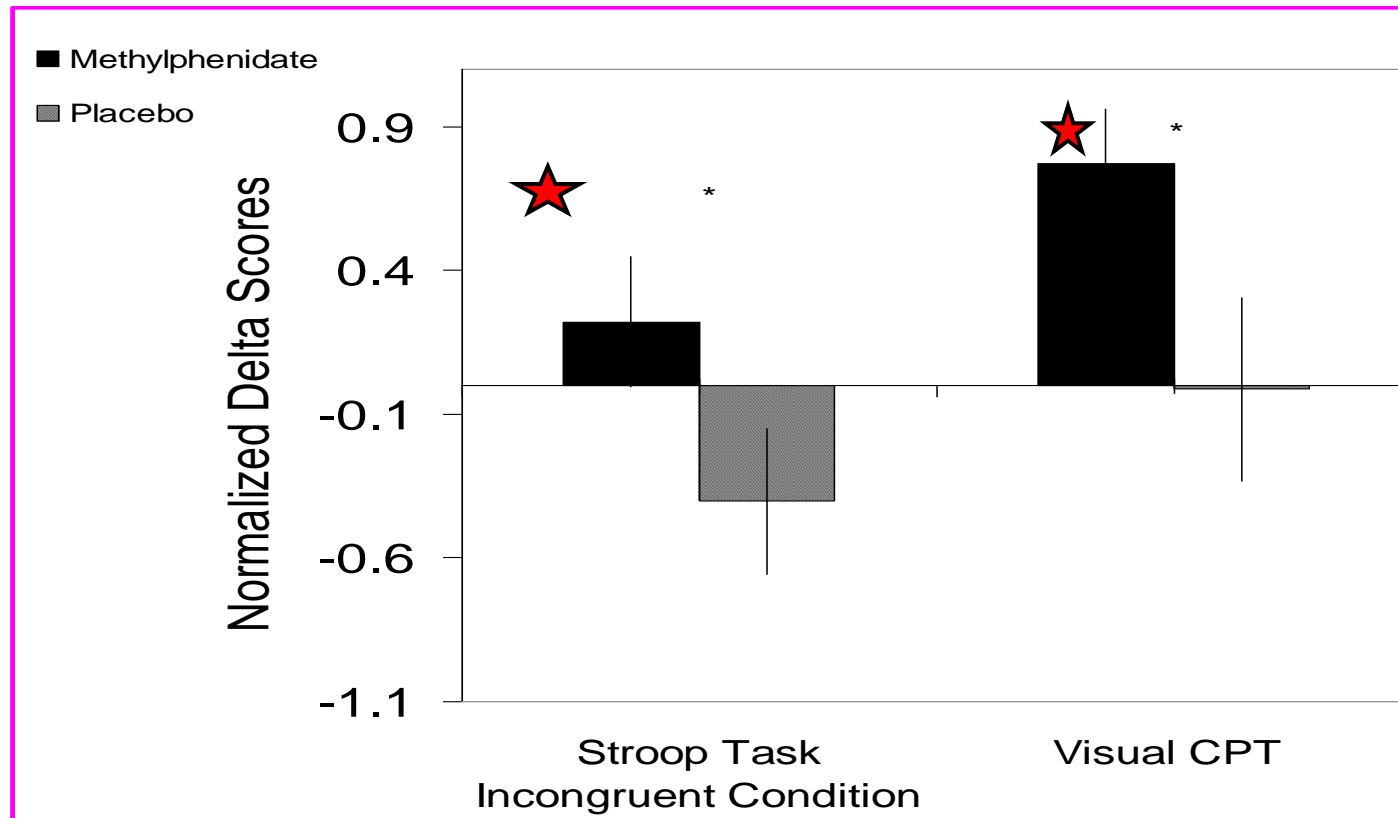
- 34 children with VCFS aged 5 to 20 years (mean 11yrs; Males=20, Females=14)
- Subjects were randomly assigned to receive ritalin (n=22) or placebo (n=12)
- Ritalin dosage- 0.5 mg/kg

Improvement of ADHD Symptoms Following 6 Months of Ritalin Treatment

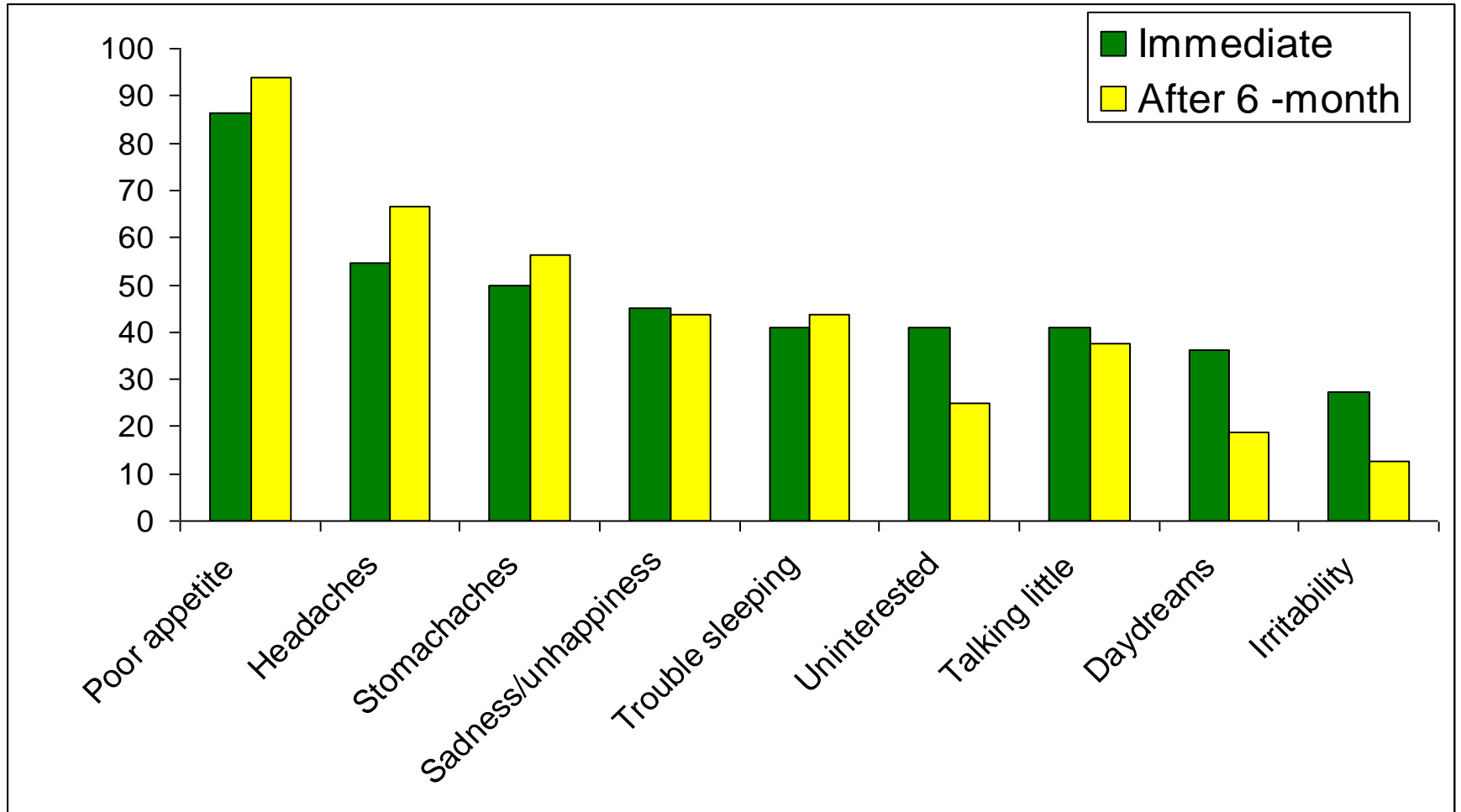


- 40% reduction in severity of ADHD symptoms

Ritalin Also Improved Prefrontal Cognitive Functioning Compared to Placebo



Rate (%) of Ritalin's Side Effects in 22q11DS



Ritalin's Side Effects in 22q11DS

- At least one side effect reported in all subjects
- No psychotic symptoms
- No manic or hypomanic exacerbation
- ~40% of depressive-like symptoms

Ritalin in 22q11DS: 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 95th percentile occurred in 2 children

Other Medications for ADHD

Name	Duration of Effect	Starting Dose
Stimulants		
Ritalin	3-4 hours	0.3mg/kg
Ritalin-LA	8 hours	0.6mg/kg
Concerta	10-12 hours	1.0mg/kg
Adderall		5-20 mg
Stratera		1.0 mg/kg



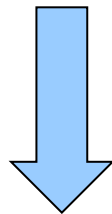
**Take
home message*

- The only medication studied for the treatment of ADHD in 22q11DS is the short-acting Ritalin
- Ritalin is effective and safe in 22q11DS
- Before initiation of ritalin treatment evaluation by a cardiologist is recommended-
 - Echocardiogram
 - EKG
 - Heart rate and blood pressure

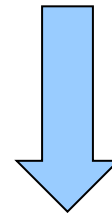
Treatment of Anxiety Disorders and Depression

SSRI Medication

**Cognitive-
Behavioral
Therapy**



1 retrospective study
In 22q11DS



No data in 22q11DS

Common Anxiety Disorders in VCFS

1. Specific Phobias
2. Separation-anxiety disorder
3. Social anxiety disorder/Selective mutism
4. Obsessive-compulsive disorder

Social Anxiety Disorder/Selective Mutism

- Marked and persistent fear of social and/or performance situations such as:
 - Speaking in front of colleagues classmates
 - talking with teacher or other adults unless he/she knows them very well
 - Shy with peers

Separation Anxiety Disorder

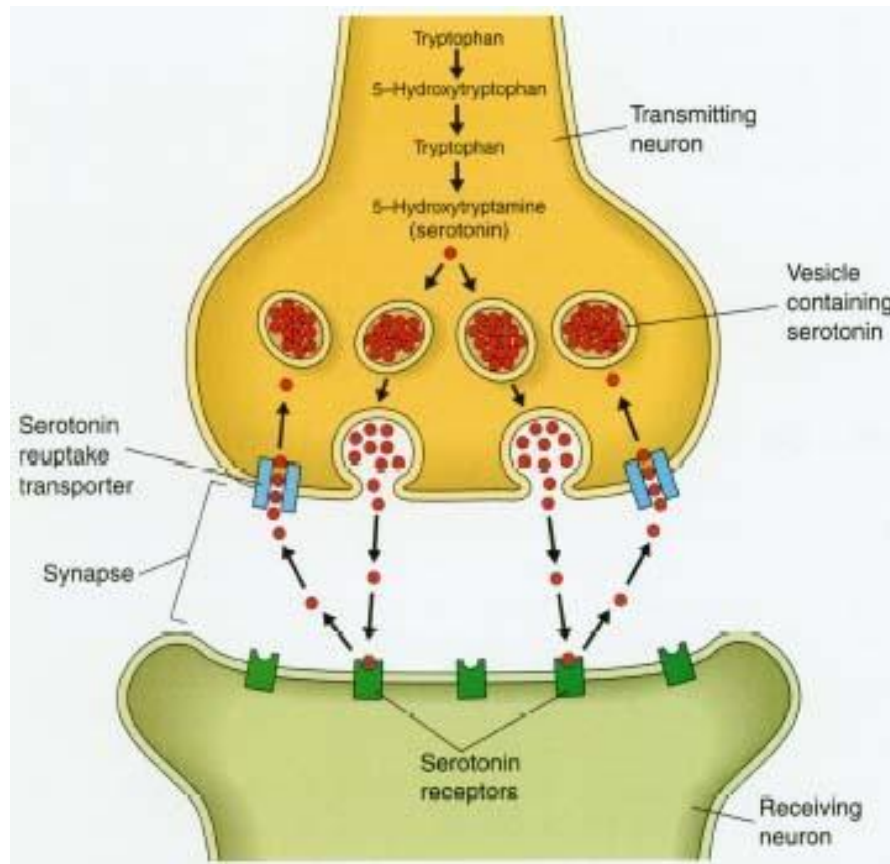
- Excessive anxiety concerning separation from parents accompanied by-
 - Fear of possible illness or harm befalling the parents or himself when without the parents
 - Insisting to sleep in the parents' bed
 - Refusal to go to school

Obsessive-Compulsive Disorder

Common OCD themes

- Disgust of dirt, fear of contamination accompanied by compulsions of washing
- Doubt and checking
- Aggressive obsessions
- Hoarding
- Repetitive questions

Selective Serotonin-Reuptake Inhibitors (SSRIs): Mechanism of Action



SSRIs & Antipsychotics in Individuals with 22q11DS: A Retrospective Study

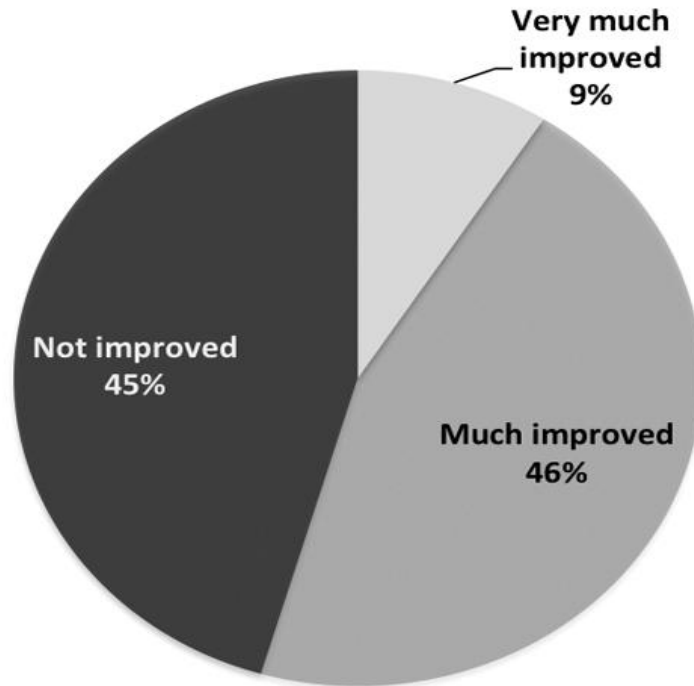
- Age range 11 to 41 years
- Mean duration of treatment 41.3 months (range 1.5-233 months)
- 21 subjects treated with an SSRI medication (13 with Fluoxetine (prozac) 20-60mg/day)
- 10 for depressive disorders
- 6 for anxiety disorders
- 5 for OCD

SSRIs in Individuals with 22q11DS

- 21 subjects treated with an SSRI medication (13 with Fluoxetine (prozac) 20-60mg/day)
- 10 for depressive disorders
- 6 for anxiety disorders
- 5 for OCD

Response to Treatment with SSRIs in 22q11DS

Improvement Rates of the Antidepressants Cohort



SSRI Medications: Adverse Events in the 22q11DS Sample

Adverse event	Number of patients
Fatigue	2 (7.6%)
Irritability	1 (3.8%)
Hypomania	1 (3.8%)
GI	1 (3.8%)
Dry mouth	1 (3.8%)

Treatment of Psychotic Disorders in 22q11DS

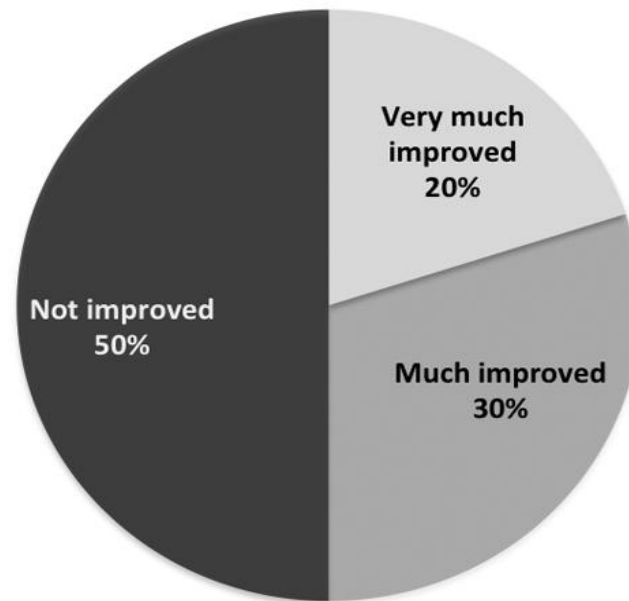
- 3 recently published studies:
 - The effectiveness and safety of antipsychotic and antidepressant medications in individuals with 22q11DS.
Dori et al. Journal of Child & Adolescent Psychopharmacology, 2015
 - Atypical antipsychotics and relapsing psychoses in 22q11.2DS: a long-term evaluation of 28 patients.
Verhoeven & Egger Pharmacopsychiatry 2015
 - Response to clozapine in a clinically identifiable subtype of schizophrenia.
Butcher et al. British Journal of Psychiatry 2015

Treatment with Antipsychotics: The Israeli Trial

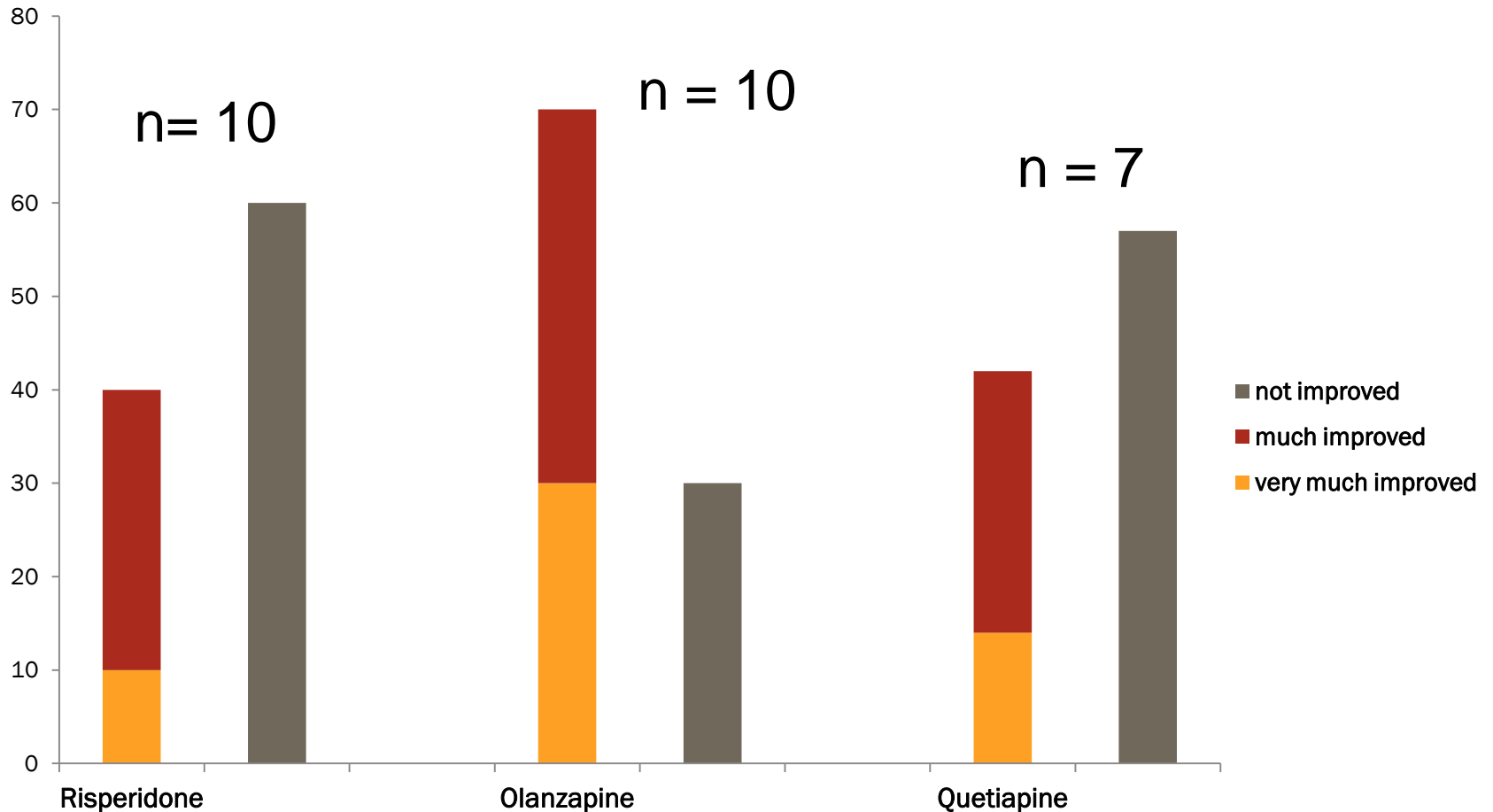
Medication	Trade Name	Number of Subjects Treated	Mean Dosage mg/day (range)
Risperidone	Risperidal	10	3.1 (1-5)
Olanzapine	Zyprexa	10	14.8 (10-20)
Quetiapine	Seroquel	7	485 (75-800)
Fluphenazine	Modecate	2	
Clothiapine	Etumine	2	
Amisulpiride	Solian	1	
Consta	Risperidal long acting	1	

Response to Treatment with Antipsychotics in 22q11DS: the Israeli Trial

Improvement Rates of the Antipsychotic Cohort



Antipsychotics: Improvement per Medication in 22q11DS

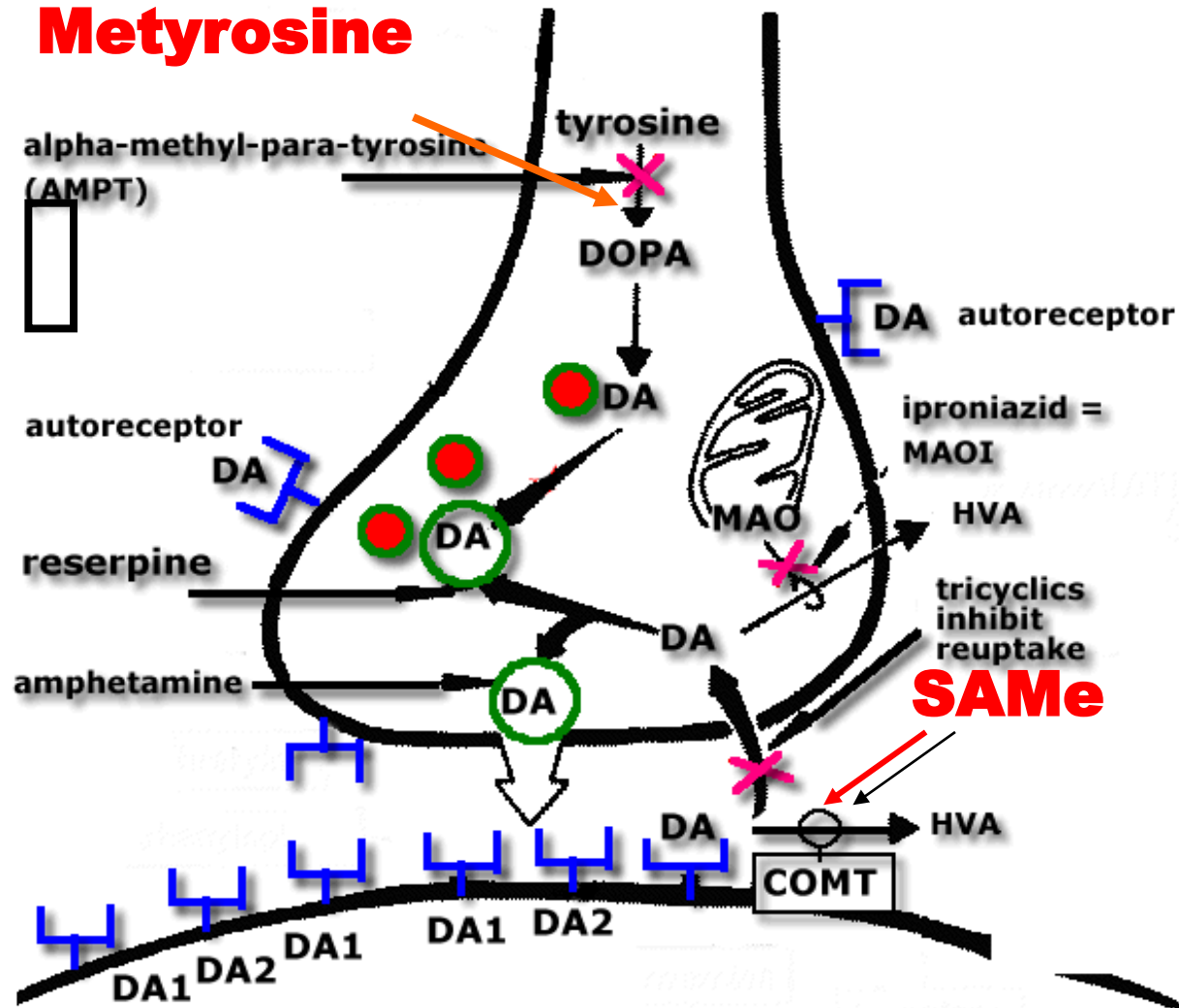


Antipsychotics Medications: Adverse Events in the 22q11DS Israeli Sample

Adverse Event	Number of Patients
Akathisia	6 (17.1%)
Weight gain	5 (14.2%)
Drowsiness	3 (8.5%)
Parkinsonism	3 (8.5%)
Decreased appetite	3 (8.5%)
QT prolongation	2 (5.7%)
Seizures	2 (5.7%)

Potential Novel-Specific Treatments in 22q11.2DS

Metyrosine



Metyrosine (Demser)

- Reduces the synthesis of dopamine
 - Improvement in neuropsychiatric symptoms in 4 of 5 treated patients
- Potential side effects: drowsiness, hypotension, extrapyramidal symptoms
- A potential treatment for 22q11DS refractory psychosis

Conclusions

- It is important to diagnose and treat psychiatric disorders in 22q11DS because they have a negative effect on the quality of life, development and risk for the later evolution of psychosis
- Evaluation by a child psychiatrist skilled in developmental disabilities is recommended for all individuals with 22q11DS
- The critical periods for evaluation are-
 - During transition to elementary school
 - Transition to adolescence
 - Frequent evaluations during adolescence and up to age 25 years

Conclusions

Psychiatric treatments in 22q11DS :

- ADHD
 - stimulants (e.g., ritalin, concerta)
- Anxiety disorders and depression
 - Cognitive-behavioral therapy
 - SSRI medications (e.g., prozac)
- Psychotic disorders
 - Antipsychotics
 - If 2 antipsychotics fail clozapine should be initiated