Management of psychiatric disorders in 22q11.2 deletion syndrome

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Agenda

- Prevalence of Psychiatric disorders in 22q11.2DS
- ADHD
- ASD
- Anxiety
- Mood disorders
- Psychosis
- Challenges/future directions

> 40% prevalence of any schizophreniform disorder in adults > 26 years old

TABLE 2. Prevalence of DSM-IV-TR Psychiatric Disorders in Five Age Groups of Subjects With 22q11.2 Deletion Syndrome

Diagnosis	Children and Adolescents				Adults					
Any anxiety disorder	155/435	35.63	97/286	33.92	71/295	24.07	37/149	24.83	35/127	27.56
Separation anxiety disorder[c]	25/395	6.33	4/259	1.54	2/113	1.77	0/28	0.00	0/20	0.00
Specific phobia[d]	95/433	21.94	48/282	17.02	19/263	7.22	5/131	3.82	3/106	2.83
Social phobia[e]	45/435	10.34	28/286	9.79	14/295	4.75	4/149	2.68	1/127	0.79
Panic disorder[f]	4/333	1.20	2/231	0.87	17/270	6.30	12/137	8.76	17/118	14.41
Posttraumatic stress disorder	1/274	0.36	3/222	1.35	2/240	0.83	0/109	0.00	2/73	2.74
Obsessive-compulsive disorder	24/435	5.52	17/286	5.94	15/295	5.08	8/149	5.37	8/127	6.30
Generalized anxiety disorder	36/435	8.28	30/286	10.49	29/295	9.83	18/148	12.16	14/127	11.02
Anxiety disorder not otherwise specified	1/435	0.23	1/286	0.34	2/295	0.68	1/149	0.67	0/127	0.00
Any mood disorder	15/456	3.29	41/346	11.85	59/323	18.27	22/150	14.67	26/127	20.47
Major depressive disorder[g]	10/456	2.19	31/346	8.96	35/323	10.84	18/150	12.00	20/127	15.75
Dysthymia[h]	5/456	1.10	8/346	2.31	16/320	5.00	2/145	1.38	1/110	0.91
Bipolar disorder or (hypo)manic episode in children	0/318	0.00	2/317	0.32	6/320	1.88	3/150	2.00	5/127	3.94
Mood disorder not otherwise specified	0/456	0.00	4/346	1.16	7/323	2.17	0/150	0.00	2/127	1.57
Substance-related disorder (substance abuse and dependence)	0/300	0.00	1/221	0.45	7/278	2.52	9/142	6.34	5/110	4.55
	Children (6–12 Years)		Adolescents (13–17 Years)		Adults (≥18 years)					
	N	%	N	%	N	%				
ADHD[i]	161/434	37.10	63/264	23.86	29/186	15.59				
Autism spectrum disorders[j]	12/94	12.77	43/162	26.54	47/292	16.10				
Any disruptive disorder[k]	57/400	14.25	25/229	10.92	9/127	7.09				
Oppositional defiant disorder	57/400	14.25	25/229	14.79	7/115	6.09				
Conduct disorder	0/316	0.00	0/180	0.00	2/138	1.45				

Schneider et al,
Am J Psych, 2014

ADHD in 22q11.2 DS

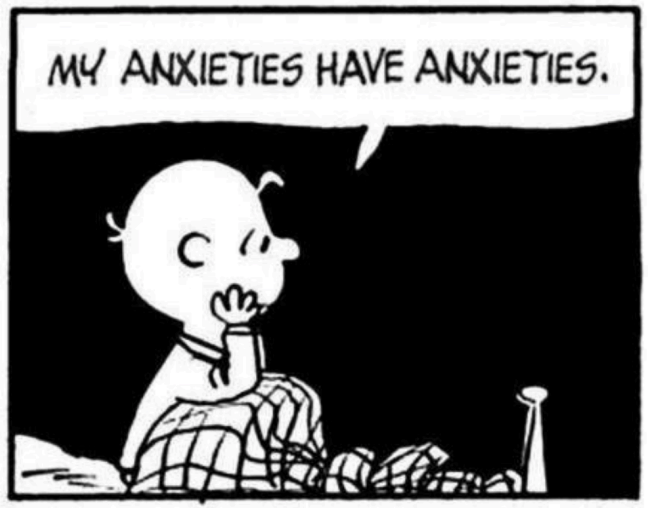
(Niarchou et al, 2014)

- Higher rates of inattentive type in 22q11.2DS
- Lower rates of conduct disorder in 22q11.2DS
- Higher rates of anxiety disorder in 22q11.2DS
- Future research will need to assess long-term benefits versus risks of stimulant medication given the elevated rate of psychosis in this group.

ASD in 22q11.2DS

- The prevalence of autism spectrum disorder differed among age groups and was highest among adolescents (Schneider et al, 2014)
- Autism Spectrum Disorder or a Different Endophenotype?
- Social impairment?

Anxiety disorders in 22q11.2 DS (Schneider et al, 2014)



- Common at all age groups (30.57% of the total group), but more frequent in children and adolescents than in the adult groups.
- More frequent in females in adults, but not in children and adolescents
- 69.11% met the criteria for one anxiety disorder, 22.03% for two, and 9.11% for three or more disorders.
- obsessive compulsive disorder and generalized anxiety disorder were similar across age groups.
- Specific phobia, social phobia, and separation anxiety disorder decreased with age.
- Panic disorder significantly increased with age.
- Posttraumatic stress disorder was rarely diagnosed

Mood disorders in 22q11.2 DS

(Schneider et al, 2014)

- The frequency of major depressive disorder significantly increases with age
- More frequent in females in adults but not in children and adolescents
- Low rates of bipolar affective disorder

Comorbidity (Schneider et al, 2014)

- The presence of an anxiety disorder increased the likelihood of a mood disorder
- Having an anxiety disorder increased the likelihood of having comorbid diagnoses of both a mood disorder and a schizophrenia spectrum disorder
- Being diagnosed with a mood disorder significantly increased the risk of having both an anxiety disorder and a schizophrenia spectrum disorder

Management of psychiatric conditions in 22q11.2 DS

As per clinical guidance for individuals with mental health conditions without 22q11.2 deletion.

Recommended assessments for 22q11.2 DS

Assessment	At diagnosis	Infancy (0–12 months)	Preschool age (1–5 years)	School age (6–11 years)	Adolescence (12–18 years)	Adulthood (>18 years)
Ionized calcium, parathyroid hormone†	✓	✓	✓	✓	✓	✓
Thyrotropin (thyroid-stimulating hormone)†	✓		✓	✓	✓	✓
Complete blood cell count and differential (annual)	✓	✓	✓	✓	✓	✓
Immunologic evaluation‡	✓	✓§	✓§			
Ophthalmology	✓		✓			
Evaluate palate¶	✓	✓	✓			
Audiology	✓	✓	✓			✓
Cervical spine (>age 4 years)			//			
Scoliosis examination	✓				✓	
Dental evaluation				✓	✓	✓
Renal ultrasound	✓					
Electrocardiogram	✓					✓
Echocardiogram	✓					
Development**	✓	✓	✓			
School performance				✓	✓	
Socialization/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioral††	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counseling‡‡	✓				✓	✓
Gynecologic and contraceptive services					✓	✓

Bassett et al, 2011, J Paed

Table 2 Signs and symptoms representing a change from baseline that may suggest a treatable psychiatric illness

New onset or exacerbation of problems

Thinking	**Emotions**
• Impaired memory, concentration, or attention	• Increased anxiety, worry, nervousness, fear
• Preoccupations	• Irritability, anger, hostility, resentment
• Increased irrational statements or repetitive ideas	• Increased sadness, crying
• Misinterpretation of people's motives, situations	• Increased apathy, not as interested in or enjoying life
• Suspiciousness	• Smiling or laughing for no apparent reason
• Threatening suicide	• Rapidly changing mood—from happy to sad to angry for no apparent reason
• Delusions and hallucinations (changed perception of reality, e.g., believe phone is tapped, hearing voices, new onset of imaginary friends)	• Hypersensitivity to perceived criticisms/insults (hurt feelings)
Behavior	**Physical/somatic**
• Avoidance of people, social withdrawal (even from family)	• Changes in amount of sleep (much less or much more)
• Increased impulsive behaviors and/or emotional outbursts	• Disruption of sleep patterns
• Agitation (e.g., screaming, pacing, aggression)	• Changes in energy level (e.g., increased fatigue)
• Unusual/odd or self-injurious behavior	• Changes in appetite and/or weight
• Neglect in self-care (e.g., hygiene, clothing, appearance)	• Increased motor disturbances (e.g., tremors, tics)
• Deterioration in functioning at home, in social situations, at school or work	• Increase in physical complaints (e.g., gastrointestinal symptoms)

Differential diagnosis/potential confounding or exacerbating factors

- Endocrine (e.g., thyroid dysregulation, hypocalcemia) or other processes (e.g., infection, sleep apnea, drinking excess water/carbonated beverages, Parkinson disease, emerging dementia) causing, e.g., metabolic disturbance or hypoxia
- Substance use (e.g., caffeine, alcohol, street drugs such as marijuana)
- Treatment related (medication side effects or undertreatment, e.g., secondary to poor/improper compliance)
- Changes in physical environment (e.g., caregivers, co-residents, living space)
- Hearing or other sensory deficits

Fung et al, 2015

Management of depression/anxiety in 22q11.2DS

- Psychological therapies as per standard clinical guidance
- Pharmacological management- similar efficacy and side effect profile with individuals without the deletion

Anxiety disorder

Cognitive decline

Low IQ at baseline

Lower baseline functioning

Predictors for psychosis

Management of schizophrenia and other psychotic disorders

- Standard management is recommended, including antipsychotic medication.

- Patients may benefit from a “start low, go slow” approach to antipsychotic dosing and prophylactic (e.g., anticonvulsant) management strategies to help reduce the risk of associated side effects, particularly with respect to seizures during clozapine treatment

Recommendations for prescribing and monitoring antipsychotic medication (De Boer et al, 2019)

A motor assessment should be part of standard clinical practice due to increased risk for movement disorders
Molecular imaging may be helpful to distinguish Parkinson's disease from antipsychotic medication-induced parkinsonism.
As most antipsychotic medications lower seizure threshold and 22q11.2DS is associated with hypocalcemic seizures, frequent monitoring of calcium levels is warranted.
To reduce seizure risk, consider the addition of low-dose anticonvulsant when clozapine is initiated.
Consider to consult a neurologist in case of, nonhypocalcemic seizures.
Promote daily exercise and a healthy diet to prevent weight gain during antipsychotic treatment.
In general, it is recommended to monitor calcium levels, thyroid function and platelets on a regular basis, and to follow general management recommendations for adults with 22q11.2DS

Main challenges in management of psychiatric conditions in 22q11.2 DS

- Comorbidity-physical and neuropsychiatric
- Variability in presentation
- Individuals not meeting diagnostic criteria for psychiatric condition
- Adaptive functioning in 22q11.2 DS
- Transition to adulthood and adult services

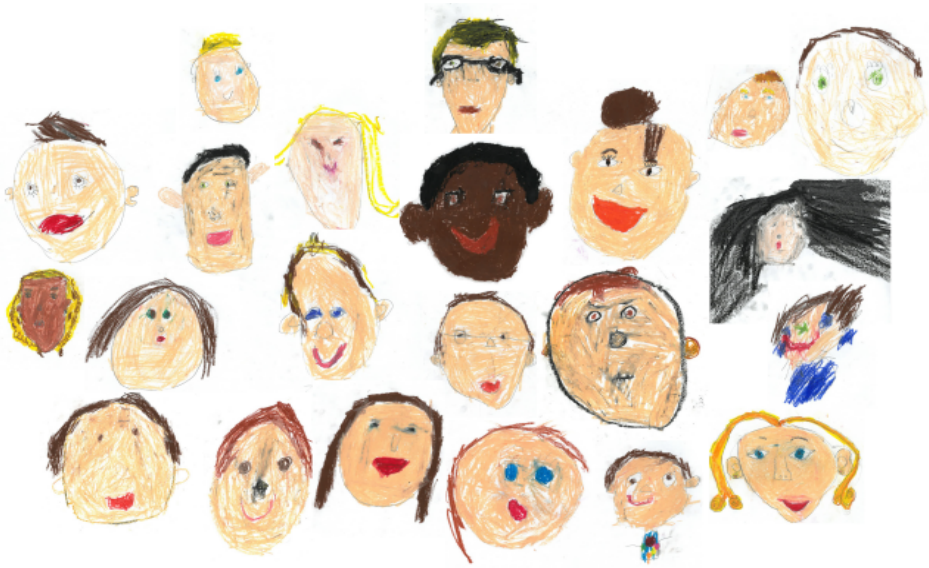
Main challenges in management of psychiatric conditions in 22q11.2 DS

- Limited availability of integrated care pathway/ named key worker
- Limited awareness of 22q11.2DS in local services, starting with GPs and continuing with mental health services
- Peak of psychosis risk in 22q11.2 DS coincides with transition to adult mental health services
- Specialist clinics for adults in the UK are limited- https://www.slam.nhs.uk/our-services/service-finder-details?CODE=SU0295

Future Directions

- Increase awareness about 22q11.2DS in primary care and mental health services.

- Development of a general care pathway for neuropsychiatric disorders related to chromosomal abnormalities, to which genotype-specific recommendations can be added as needed.



Thank you!

SLEEP

- **Physical environment & sleeping space**
- •Relaxing/Unexciting: colour, textures, bed location, electronic devices...
- •Quiet: no sounds or smells, earplugs, white noise machines...
- •Dark/dim light (melatonin/anxiety)
- •Comfortable temperature: better cool and use blanket
- •Safe: organisation of furniture, obstacles...
- •Use bed only for sleep

- **Sleep position**
- •Very important, specially: physical disabilities, mechanical contraptions
- •Back or side

- **Bedding**
- •Mattress (mobility problems, sensory integration difficulties,...)
- •Pillows (breathing, hyperhidrosis/impaired sweating...)
- •Blankets (sensory integration difficulties, temperature dysregulation...)

Sleep hygiene

- Get into a sleeping and waking up routine:
- No more than 1 hour difference week/weekends/holidays.
- Engage in routine relaxing activities before bedtime

Bath, scents, hot drinks, meditation, deep breathing...

- Avoid exciting activities before bedtime.
- Day time: •Avoid naps, exercise,

•Implement routine & Structure

- If you have a bad night, continue with your normal activities

•Avoid coffee or stimulants 6-8 hours before bedtime.

•Avoid large meals and alcohol before bedtime.

•Decrease fluid intake.

•Don’t go hungry or thirsty, light, carbohydrate rich, meal

•Need to be sleepy, don´t stay awake in bed

Melatonin

- Regulatory hormone, produced by the Pineal gland.
- Controlled by changes in light, high levels secreted at night and low levels during the day, and suprachiasmatic nucleus
- 1-10mg given 30-60 minutes before going to sleep.
- May also have additive hypnotic effects and effects on anxiety.
- Useful in insomnia, sleep-related breathing disorders, hypersomnolence, circadian rhythm, sleep–wake disorders and parasomnias.
- SE: headache, dizziness, nausea, drowsiness.
- Immediate-release and controlled-release

Non pharmacological interventions

- **Relaxation techniques**-Teaches to systematically tense and relax muscles in different areas of the body. This helps to calm the body and induce sleep.
- **Breathing exercises**, mindfulness, meditation techniques, guided imagery. help you fall asleep and also return to sleep in the middle of the night.
- **Stimulus control** builds an association between the bedroom and sleep by limiting the type of activities allowed in the bedroom, going to bed only when you are sleepy, and getting out of bed if you've been awake for 20 minutes or more.
- **Sleep restriction** involves a strict schedule of bedtimes and wake times and limits time in bed to only when a person is sleeping.
- **Cognitive behavioural therapy (CBT)**-Sleep hygiene with cognitive or "thinking" component. Challenge unhealthy beliefs and fears around sleep and teach rational, positive thinking.