Psychopharmacotherapy in Individuals with 22q11.2 Deletion Syndrome with Comorbid Psychiatric Disorders

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Background

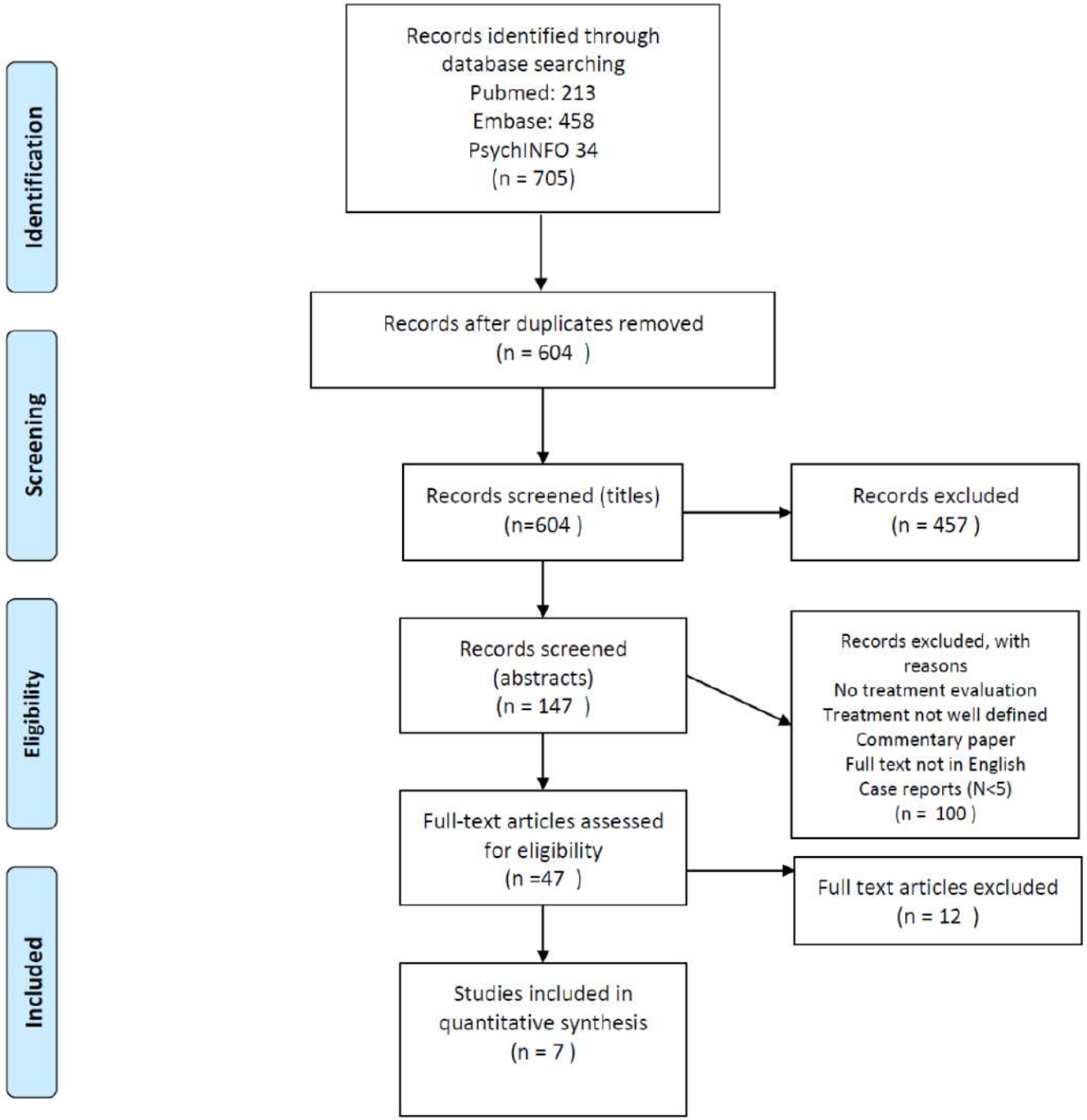
- 60-80% of individuals with 22q11.2DS cope with at least one lifetime psychiatric disorder
- Psychiatric disorders are of major concern in individuals with 22q11.2DS.
- Practical guidelines for the psychiatric management and side effect monitoring are highly important

AIMS

- To identify all studies reporting on pharmacological treatments for psychiatric disorders in 22q11.2DS
- We focused on pharmacotherapy directed towards the major psychiatric comorbidities in 22q112DS:
  - ADHD
  - Mood and anxiety disorders
  - Psychotic spectrum disorders

Systematic Review (PRIZMA) of Psychiatric Treatments in 22q11.2DS

Figure 1 flow diagram, depicting the systematic review



Antipsychotics in 22q11DS

- 3 original retrospective papers consisting of 67 individuals and 7 medications
  - 3 typical antipsychotics (amisulpride, clotiapine, fluphenazine)
  - 4 atypicals (clozapine, olanzapine, quetiapine, risperidone)
- The studies were conducted largely on adult population (age ≥18 years), and only one included adolescents (age range 23.5±7.8) (Dori et al. 2017)
- Long-term follow up (mean duration of treatment: 2.9 years to more than 6 years)

Butcher et al. *Brit J Psychiatry,* 2015; Verhoeven et al. *Pharmacopsychiatry,* 2015; Dori et al. *J Child Adolesc Psychopharm,* 2017

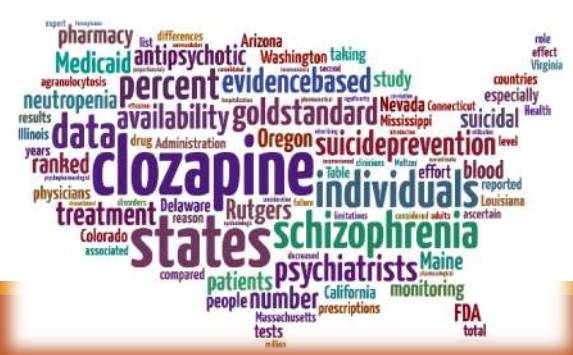
Side effects- antipsychotics

- Rate of 60% rates
- the majority were considered mild (59%)
  - extrapyramidal including akathisia and parkinsonism (26%)
  - weight gain (14%)
  - QT prolongation (3%)

Butcher et al. 2015

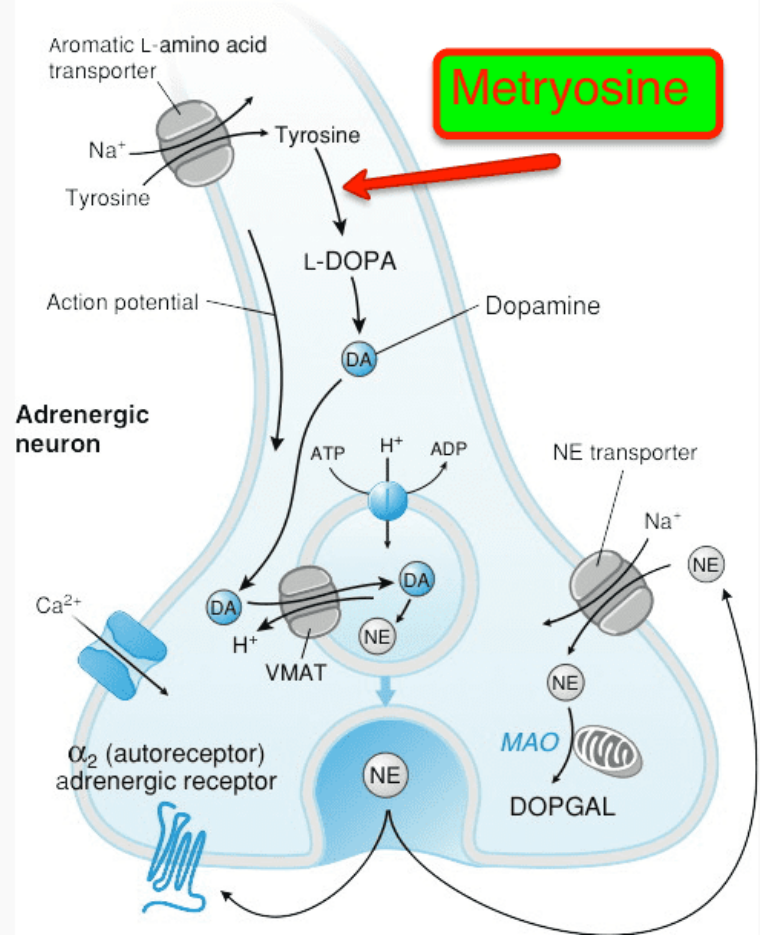
Clozapine

- Most common side effects: drowsiness/sedation (75%), weight gain (50%), hypersalivation (50%)
- half of 22q11.2DS group treated with clozapine presented with serious side effects: seizures (44%), severe neutropenia (15%) and myocarditis (5%)
- Rates of these clozapine induced side effects were higher in the 22q11.2DS patients compared to the non-22q11.2DS group



Metyrosine

- Tyrosine hydroxylase inhibitor that reduces the synthesis of dopamine.
- A case series of effectiveness and side effects of metyrosine in five individuals with 22q11.2DS
- Improvement in neuropsychiatric symptoms in 4/5 patients (enhancing interpersonal interactions, decreasing anxiety and irritability, and decrease in psychotic symptoms (2/5 patients).
- Only mild side effects: moderate weight gain, mild weight loss and decreased appetite (16%), headache (16%).



Stimulants in 22q11DS

- The only medication studied for the treatment of ADHD in 22q11.2DS is short-acting methylphenidate
- 1 randomized placebo-controlled trial consisting of 34 individuals (22 treatment / 12 placebo); treated with methylphenidate (mean dose 15.7±5.6 mg)

(Green T et al. *Biological psychiatry.* 2009)

- 1 open label study consisting of 40 individuals; treated with methylphenidate (mean dose 9.4±5.2 mg)

(Gothelf D et al.*The Journal of clinical psychiatry.* 2003)

Side effects

- Poor appetite (92-94%)
- Stomachache (42-50%)
- Headaches (25-67%)
- Depressive symptoms (40%)

Antidepressants in 22q11DS

- 1 original retrospective papers consisting of 21 individuals and 5 medications (Fluoxetine 20-60 mg/day, Escitalopram 10-30 mg/day, Sertraline 50-150 mg/day, Paroxetine 10-60 mg/day, Venlafaxine 300 mg/day)

(Dori et al. *J Child Adolesc Psychopharm,* 2017)

- 1 case series consisting of 3 individuals

(Stachon AC et al. *J of the Canadian Academy of Child and Adolescent Psychiatry,* 2011)

Recommendations- Stimulants

Potential side effects	Monitoring (at baseline and follow up)
Cardiac [Tachycardia Hypertension Arrhythmia (QTc prolongation)]	a comprehensive clinical evaluation by a pediatric cardiologist at baseline including: • Physical examination • Family history • echocardiogram • electrocardiogram • heart rate • blood pressure Once every three or six months • electrocardiogram • heart rate • blood pressure

Recommendations- Stimulants

Potential side effects	Monitoring (at baseline and follow up)	Comment
Depressive symptoms	Psychiatric evaluation every 3 months	Consider switching to atomoxetine
Psychotic symptoms	Psychiatric evaluation every 3 months	Discontinue MPH, psychiatric evaluation is required
Decreased appetite/Weight loss Growth retardation	Weight and height measurement at baseline and every 6 months	If there is a decline in percentile of the growth curve, consider switching to another drug with less effect on appetite or growth such as clonidine
Sleep problems	For children with sleep-onset problems and/or possible delayed sleep phase syndrome: Sleep hygiene behavior therapy techniques based on stimulus control bedtime scheduling	Consider adding melatonin A switch of medication should be considered when sleep problems persist after careful dose adjustment and dose scheduling; for instance, patients taking a stimulant medication might switch to atomoxetine

Recommendations- SSRIs

Potential side effects	Monitoring (at baseline and follow up)	Comment
Gastrointestinal symptoms		Gastrointestinal symptoms are usually transient and respond quickly to dosage lowering or taking the medication with meals.

Recommendations- Antipsychotics

Potential side effects	Monitoring (at baseline and follow up)
Cardiac [QTc prolongation]	Electrocardiogram for QTc monitoring at baseline and during dose escalation and then once a year.
Seizures	If antipsychotics associated with high risk of seizures (e.g., clozapine) consider prophylactic addition of anticonvulsant (e.g valproic acid) Consider supplementation of calcium and vitamin D low doses and slow titration
Movement disorders	Monitor calcium concentrations because hypocalcemia may induce or aggravate existing tremors (Fung et al., 2015) Functional imaging, where available, to distinguish Parkinson disease from extrapyramidal side effects of antipsychotics (Boot et al., 2015; Fung et al., 2015)
Weight gain and metabolic syndrome	At baseline: • Weight, height • Metabolic measures (fasting glucose, triglycerides and cholesterol) • blood pressure

Conclusions

- Individuals with 22q11.2DS and comorbid psychiatric disorders are treated in a manner comparable to non-22q11.2DS individuals.
- However, distinctive medical comorbidities typical to individuals with 22q11.2DS may complicate the administration of pharmacotherapy
- Polypharmacy- several antipsychotics and mood-stabilizers prescribe concomitantly
- There is a challenge in studying standard psychiatric treatments in 22q11DS as most centers evaluate patients infrequently, during study visits and are not managing their psychiatric treatment

Conclusions

- To pool data on the effectiveness and safety of psychiatric treatments in 22q11DS we should all use the same clinical tools:
  - Clinical Global Impression Scale (CGI)
  - PANSS
  - The ADHD Rating Scale
  - decide on measures for patients treated with anti-depressants
  - Standardize how we measure side effects
- Further trials with RCT design, larger sample sizes and more syndrome specific pharmacological agents are needed to improve evidence-based psychiatric care of 22q11.2DS individuals with comorbid mental disorders

THANK YOU!!

Prof. Doron Gothelf

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Prof. Avi Weitzman