ANTIPSYCHOTIC MAINTENANCE TREATMENT IN PAEDIATRIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF FUNCTIONAL IMPROVEMENTS AND TOLERABILITY ACROSS MENTAL HEALTH AND NEURODEVELOPMENTAL CONDITIONS

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INTRODUCTION

- Limited data on long-term use of antipsychotic medication on the safety and efficacy across mental health /neurodevelopmental conditions in paediatric populations

OBJECTIVES

- To evaluate the efficacy in terms of functional improvements, and tolerability of antipsychotic medication in children and adolescents with mental health or neurodevelopmental conditions

AIMS

- To evaluate the long term benefit and risk of antipsychotic use compared to placebo in paediatric population

METHODS

- A systematic review of RCT literature from 1974 to present, on antipsychotics use in paediatric population for 12 weeks or over, < 18 year old subjects, in any setting
- Diagnosis of any mental health or neurodevelopmental conditions - ICD 10, or DSM III, DSM III-R, DSM IV, DSM IV-TR, DSM V classifications
- Any comorbid diagnoses included
- Electronic databases: MEDLINE - Cochrane Highly Sensitive Search Strategy for RCTs. Modified for 8 other electronic databases/trial registers
- Reference lists and citations of the relevant systematic reviews were searched
- Primary outcome - Improvement in daily functioning
- Adverse events - Meta-analysis performed

HYPOTHESIS

- Antipsychotic medication would be more efficacious than placebo at or beyond 12 weeks of treatment, but would be associated with significant side effects in paediatric subjects with mental health and neurodevelopmental conditions

QUALITATIVE RESULTS OF THE NARRATIVE REVIEW

- Six studies with inclusion criteria, a total of 939, < 18 years of age
- Diagnoses - Autism, Conduct Disorders, Disruptive Behaviour, Bipolar Disorders, ADHD, Schizophrenia
- Multi-centre studies - in Belgium, Germany, Great Britain, Israel, Poland, South Africa, Spain, Netherlands, India, Malaysia, Philippines, Romania, Russian Federation, Taiwan and the United States
- Risperidone and aripiprazole - only antipsychotics.
- Antipsychotics vs Placebo:
 - Improvement of global functioning (Exception one study (Findling 2017: CGI-I, p = 0.054)
 - Significant symptomatic improvement or significantly more time before discontinuation

QUANTITATIVE RESUTS OF THE META-ANALYSIS

- 48 adverse symptoms
- Abdominal pain/discomfort (p = 0.009), Respiratory tract infections (p = 0.003) and Cough (p = 0.05) with aripiprazole (Figure 4 and 5) compared to placebo
- Actual numbers low and symptoms were mild and tolerable
- Extrapyramidal events in risperidone/aripiprazole groups compared to placebo - p = 0.46
- Meta-analysis of two studies (Finding 2012, Reyes 2006 - Figure 6) - mean difference weight gain - 2.29kg, p = 0.00001
- Meta-analysis of two studies (Finding 2013, Correll 2017 - Figure 7) - mean difference fasting Cholesterol 3.34 mg/dl, p = 0.13) – with aripiprazole
- No clear evidence to support higher metabolic risk other than increased weight gain (Baselines at the point of randomization)
- Higher serum prolactin levels - with risperidone compared to placebo
- Cognitive functions – No significant difference in short term memory and concentration – with risperidone beyond 12 weeks (Reyes 2006)
- No serious adverse effects or deaths

Figure 4 : Forest plots: Significantly more subjects with abdominal pain/discomfort with aripiprazole (p = 0.009) compared to placebo.

Figure 5 : Forest plots : Significantly more subjects with respiratory tract infections with aripiprazole (p = 0.003) compared to placebo.

Figure 1: PRISMA Flow Diagram

Figure 2: Risk of bias summary

Study	SAMPLE n (I:C)	COMPLETED THE STUDY: n (%)
Findling 2014	85 (41 : 44)	I – 22/41(53.7%) C – 19/44 (43.2%)
Reyes 2006	335 (172: 163)	I – 100/172 (58.1%) C – 62/163 (38.0%)
Findling 2017	103 (54:49)	I – 47/54 (87%) C – 41/49 (83.7%)
Findling 2012	60 (30:30)	I – 6/30 (20.0%) C – 0/30 (0.0%)
Findling 2013	210 (75:71:64)	I – 34/75 (45.33%) C – 12/64 (18.8%)
Correll 2017	146 (98: 48)	I – 15/98 (15.3%) C – 6/48 (12.5%)

Figure 3: Incomplete outcome data
I- Intervention; C- Control

Figure 6 : Forest plots (Findling 2012 and Reyes 2006): Significant mean difference weight gain(2.29kg, p = 0.00001) with risperidone/aripiprazole compared to placebo. Baseline at the point of randomization.

Figure 7 : Forest plots (Findling 2013 and Correll 2017): No significant mean difference in serum cholesterol (mean difference 3.34 mg/dl, p = 0.13) with aripiprazole compared to placebo.

CONCUSIONS

- Favour overall efficacy of aripiprazole/risperidone maintenance therapy for 12 weeks or beyond, in children and adolescents, with an acceptable safety and tolerability profile.
- This conclusion is based on a small number of moderate-quality trials, and the findings needs to be interpreted cautiously.
- The choice of long term use of risperidone or aripiprazole in children or adolescents for 12 weeks or beyond needs careful consideration of the benefits and potential risks of these medication for each individual.
- Further RCTs on long-term effects of antipsychotic medication in children and young people are needed.