Efficacy of atypical antipsychotic medication in the management of behaviour problems in children with intellectual disabilities and borderline intelligence: a systematic review

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CRD summary
This review concluded that risperidone significantly reduced problem behaviour compared with placebo in children with intellectual disabilities, with or without autism. Most trials found increased adverse events, mainly somnolence and weight gain, implying that risperidone should be used cautiously. Due to limitations in the review process, and few participants, the authors’ conclusions may not be reliable.

Authors’ objectives
To evaluate the effectiveness and safety of atypical antipsychotic medications for behaviour problems in children with intellectual disabilities.

Searching
PsycINFO, MEDLINE, EMBASE and CINAHL were searched for items from their inception to 28 May 2010. The search terms were adapted from those of a similar review by Brylewski and Duggan in 2004 (see Other Publications of Related Interest) and some were reported. Only publications with an abstract in English were included. The bibliographies of relevant reviews were handsearched.

Study selection
Double-blind, placebo, randomised controlled trials (RCTs) of the efficacy and safety of atypical (new generation) antipsychotic medications that were in use at the time were eligible for inclusion. They had to include at least 10 children or adolescents (as defined by the author or under 18 years old) who exhibited problem behaviour (as defined by the author) and had intellectual disabilities (as defined by the author or an intelligence quotient, IQ, below 70). Withdrawal trials were excluded. Target behaviours included: physical or verbal aggression; disruptive behaviour; property destruction; self-injury; tantrums; and stereotypical behaviour. Trials of children with Autism Spectrum Disorder were eligible if at least half of the participants had intellectual disabilities. Trials had to evaluate any outcome related to behaviour or change in behaviour measured by an objective assessment tool, including adverse events related to treatment.

All the included trials compared risperidone versus placebo; the average dose at the end of treatment ranged from 0.98 to 2.9mg per day. Half of the included trials had extensions recording the long-term response in open-label trials. Most of them targeted disruptive or aggressive behaviour and most were multicentre. The behavioural assessment tools were: the Clinical Global Impression (CGI) – Improvement Scale; the CGI – Severity Scale; the Aberrant Behavior Checklist (ABC) irritability subscale; the Nisonger Child Behavior Rating Form (NCBRF); Visual Analogue Scale (VAS); and other scales. Most trials assessed adverse events using the Extrapyramidal Symptoms Rating Scale (ESRS). Where reported, 59% of participants had intellectual disabilities, 5% had a normal IQ, and 36% had a borderline IQ; participants were aged between five and 17 years.

One reviewer screened the titles and two independent reviewers assessed the abstracts and full papers, with disagreements resolved by discussion.

Assessment of study quality
Methodological quality was assessed using the Jadad scale, with criteria for: randomisation, double-blinding (both present and methods described), and withdrawals and dropouts. Trials with a score of three or more out of a maximum of five were judged to be acceptable.

The authors did not report how many reviewers assessed quality.

Data extraction
Mean changes in behaviour score were extracted for each treatment group, for the various assessment tools.
Improvement in behaviour was calculated as the number or percentage rated as ‘much improved’ or ‘very much improved’. Statistical significance was reported for changes compared with the placebo group. Mean weight gain and the numbers or proportion of adverse events were extracted for each treatment group.

The authors did not report how many reviewers extracted the data.

**Methods of synthesis**

A narrative synthesis was provided for most outcomes. The numbers needed to treat (NNT) to achieve a rating of ‘much improved’ or ‘very much improved’ behaviour were calculated, with 95% confidence intervals, for each trial and pooled for the CGI scores across trials. Overall mean weight gain was determined for the treatment groups.

**Results of the review**

Six RCTs were identified, with 459 participants (range 13 to 118). One RCT scored five on the Jadad scale; three RCTs scored four; and two RCTs scored three. Follow-up ranged from four to eight weeks for the initial trials, and a further 16 to 48 weeks for the three extension trials. These three trials were completed by 47%, 78% and 81% of patients.

**Behaviour scores**: There was a significant reduction in the combined CGI improvement and severity scores for risperidone versus placebo for all six trials. With risperidone versus placebo, there were significant reductions in: ABC irritability scores in five out of six trials; VAS scores for the most troublesome behaviours in four out of four trials; and in all or most of the subscales of NCBRF scores for three out of three trials. The three longitudinal extension trials showed that the effect on behaviour was maintained. Five trials reported the number of patients rated as ‘much improved’ or ‘very much improved’, resulting in 54.5% of the risperidone group versus 11% of the placebo group. The pooled NNT to achieve a rating of ‘much or very much improved’ across the trials was three (range two to five) over a period of four to eight weeks.

**Adverse events**: Five trials found no significant differences in adverse events for risperidone versus placebo using the ESRS. One trial found a significant increase in Parkinsonism with risperidone versus placebo. Five of six trials found a significantly higher weight gain with risperidone versus placebo. The overall mean weight gain was 2.3kg with risperidone versus 0.7kg with placebo. The most commonly reported adverse events were: somnolence; tiredness, drowsiness or fatigue; weight gain (including increased appetite); and headache. The three longitudinal extensions found somnolence, headache and weight gain were the most common adverse events, with the mean weight gain with risperidone ranging from 5.1 to 7.1kg. The dropout rate due to adverse events ranged from 1.6% to 10.3%.

**Authors’ conclusions**

There was sufficient good quality evidence to show that risperidone was effective in treating problem behaviour in children with intellectual disabilities, with or without autism, but most trials found adverse events, mainly somnolence and weight gain, and it should be used with caution.

**CRD commentary**

The review question was well defined for participants, interventions, study design and relevant outcomes. Relevant databases were searched, but only trials with abstracts in English were included. It appears that unpublished trials were not considered and some relevant trials might have been missed. Publication bias was not assessed. Trial quality was assessed using suitable criteria and all trials were deemed to be of acceptable quality, with a score of three or more out of five on the Jadad scale). Part of the selection process was carried out in duplicate, but it was not clear whether efforts were made to reduce error and bias in other review processes. Relevant trial details were reported, but the gender of the children and the placebos used were not reported. The synthesis was mostly narrative, with little detail provided. There were relatively few participants in the trials.

The authors’ conclusions are supported by the data presented, but there were some potential limitations in the review process, and few participants in the trials. These conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice**: The authors suggested that adverse events should be monitored during treatment including its effect on cardiac rhythm. They stated that a detailed assessment of the causes and consequences of problem behaviours was necessary before an intervention was implemented. Non-drug management of problem behaviours should be considered before or
with medication if necessary. The smallest dose of medication should be used for as short a time as possible. At each follow-up medication should be reassessed and alternative treatment should be considered. If medication is withdrawn, a relapse programme should be in place and withdrawal symptoms should be considered. Children and their carers should be fully involved in the decision-making process as well as the multidisciplinary team. The aim of treatment should be to reduce symptoms and improve quality of life for both the child and their carer.

**Research** The authors identified a need for further studies of the impact on behaviour as well as adverse events, including the effect on the children’s cognition and learning. These studies should assess: the children’s quality of life including excessive drowsiness; the family carer’s burden; and cost-effectiveness. The planned follow-up should be defined at the onset of the study, including timing, methods and personnel involved.

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