

# Evidence based administration of risperidone and paliperidone for the treating conduct disorder

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**Background:** This study evaluates the evidence-based administration of risperidone and paliperidone for the treating children and adolescents with conduct disorder (CD). **Materials and Methods:** A review of the current literature from clinical trials that investigated the efficacy of risperidone and paliperidone on CD considering the inclusion criteria and search strategies was performed by a search of PubMed and Google Scholar databases. **Results:** Out of 53 titles, 31 were irrelevant. The abstract of 22 potentially related articles were studied. Only six articles reported the results of clinical trial. However, one of them reported the effect of risperidone on conduct behaviors in autistic disorders. One study was a re-analysis of two previous studies, one study reported the effects of maintenance versus withdrawal of risperidone treatment and two studies included children with sub-average intelligence. Headache, somnolence and increased appetite are among the most common reported adverse effects. No study examined the effect of paliperidone on CD was found. **Conclusion:** Current literature suggests that risperidone could be effective for treating some conduct behaviors in children and adolescents. The effect of risperidone on CD is not a well-researched area. There is no well-controlled evidence based reports about the safety and efficacy of risperidone for the treatment of CD. Further trials should examine the efficacy of these medications on CD rather than conduct behaviors or disruptive behavior disorders.

**Key words:** Conduct disorder, paliperidone therapeutic, risperidone

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## INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition defines that the cluster of disruptive behavior disorders (DBDs) includes oppositional defiant disorder (ODD), conduct disorder (CD) and DBDs not otherwise specified.<sup>[1]</sup> ODD is a pattern of negativistic, hostile and defiant behaviors. Although, CD includes "a repetitive and persistent pattern of behaviors in which the basic rights of others or major age-appropriate societal norms or rules are violated". Children with CD may have antisocial behaviors such as lying, stealing, running away, physical violence, sexually coercive behaviors, bullying, threatening, or intimidating others. There are two subtypes of CD including childhood and adolescent-onset forms of CD. In addition, the symptoms of CD are categorized to: Aggression to people and animals, destruction of property, deceitfulness or theft and serious violations of rules. There is a discussion whether ODD and CD disorder are two different distinct disorders (42-44).

The prevalence of CD is 3.2%.<sup>[2]</sup> Its prevalence in detained male adolescents is very high up to 46.4% (95% confidence interval [CI] 45.6-47.3%).<sup>[3]</sup> The rate

of CD in incarcerated adolescents in Iran is 55%.<sup>[4]</sup> At least in clinical samples, CD is more common in boys than girls.<sup>[5]</sup> The comparison of data from 25 countries showed that the prevalence of CD does not differ among different cultures and geographic locations.<sup>[2]</sup>

CD (relative risk [RR] = 2.0, 95% CI = 1.2-3.4) and hyperkinetic CD (RR = 2.7, 95% CI = 1.6-4.4) increase the risk of criminal behaviors in adulthood.<sup>[6]</sup> CD is associated with negative communication between parents.<sup>[7]</sup> Furthermore, CD is associated with substance use disorder. The severity of CD in adolescents is associated with the level of nicotine dependence.<sup>[8]</sup> Moreover, it is a significant predictor of substance use disorder.<sup>[9]</sup> These findings emphasize the necessity for treatment of CD.

A combination of non-pharmacological and pharmacological interventions is suggested. A combination of lithium plus antipsychotics or lithium alone is effective for treatment of aggression in CD.<sup>[10,11]</sup> However, the adverse effects are very common. Moreover, its serum level needs to be carefully monitored. Other mood stabilizers such as carbamazepine is effective

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for treatment of aggressive behaviors in children with CD.<sup>[12]</sup> Clonidine in combination with psycho-stimulant medication reduces conduct behaviors, but it can cause bradycardia and severe sedation.<sup>[13]</sup>

Typical antipsychotics are associated with the increased risk of extrapyramidal side-effects especially considering that CD is a long term problem and it needs long term treatments. It is reported that the newer generation of antipsychotics, atypical antipsychotics, are associated with lesser extrapyramidal side-effects than that of typical antipsychotics in children and adolescents.<sup>[14]</sup> Therefore, atypical antipsychotics can be a more favorable option for pharmacotherapy of children and adolescents with CD.<sup>[15]</sup> Olanzapine, an atypical antipsychotic, reduces aggression in CD.<sup>[16]</sup> Olanzapine and risperidone cause adverse glycemic changes, hyperlipidosis and metabolic effects.<sup>[17]</sup> However, the risk for olanzapine is more than risperidone.<sup>[18]</sup> This is a possible explanation that the efficacy of risperidone on conduct behaviors is studied more than that of olanzapine. Meanwhile, olanzapine earlier than risperidone had been introduced in markets.

Risperidone is a benzisoxazole atypical antipsychotic. Paliperidone (9-hydroxyrisperidone) is a metabolite of risperidone. Actually, paliperidone should not be considered as a novel medication. Its affinity for D2 receptors is more than risperidone. Moreover, risperidone more potently blocks alpha2 receptors than paliperidone. Therefore, it is suggested that paliperidone less than risperidone induces orthostatic hypotension. In addition, the titration of paliperidone can be faster than risperidone.<sup>[19]</sup> Furthermore, the affinity of paliperidone to block 5-hydroxytryptamine 2C (5-HT<sub>2C</sub>) receptors is less than risperidone. This receptor blockage is associated with the increased appetite.

Orally taken risperidone is absorbed well and it is not affected by food. Its bioavailability is about 66%.<sup>[20]</sup> Its half-life is about 3 h while the half-life of paliperidone is about 21 h. Therefore, it is expected that the clinical efficacy of risperidone is due to both risperidone and its metabolite, paliperidone.<sup>[20]</sup> Some medications have interactions with risperidone. Carbamazepine decreases the serum level of risperidone. However, many SSRIs increase its serum level.

The aim of this study is to review the evidence on the efficacy and safety of treatment with risperidone or paliperidone in children and adolescents with CD.

## METHODS

### Inclusion criteria

All controlled clinical trials, evaluated the efficacy and/or safety of treatment with risperidone or paliperidone in

children and adolescents with a diagnosis of CD, assessed main outcome results using a valid and reliable instrument were included.

Trials examined the effect of other pharmacological treatments and did not investigate the efficacy of risperidone were excluded.

### Search strategies

Electronic searches were conducted in the two databases of PubMed/Medline and Google Scholar. The terms of "CD and risperidone" and "CD and paliperidone" were searched. Time of publication, gender, and language were not considered as limitations. The searches were conducted in August 2011, updated on July 2013. All the abstracts were carefully screened to decide that which studies include current inclusive criteria. The reference lists of retrieved articles were searched to find more possible related articles.

### Outcomes selected

The studies used reliable and validated instruments were included.

### Data extraction and evaluation of methodological quality of the studies

At first, the main methodological issues of articles were extracted. The following items were considered to evaluate the quality of reported clinical trials including the risk of bias, randomization, allocation, blinding, diagnosis, persons who evaluated the patients, outcome measurements, outcome data, complete and non-selective reported of findings.<sup>[21]</sup>

### Statistical analysis

It was decided to run a statistical analysis to integrate the results of studies. However, it was not practical due to lack of enough well-controlled double-blind clinical trials and data.

## RESULTS

### Literature search

The electronic literature searches retrieved of 53 titles. 31 titles were irrelevant (Figure 1). The abstracts were carefully studied and screened that 22 articles reported the effect of risperidone on CD.

One study investigated the effect of risperidone on CD in preschool children in an open-label case series,<sup>[22]</sup> two study was retrospective,<sup>[23,24]</sup> six articles were not experimental studies,<sup>[25-28]</sup> one study was *post hoc* analysis of data reporting the effect of risperidone on affective symptoms in DBDs,<sup>[29]</sup> three studies followed the efficacy, safety and tolerability of risperidone in patients of an open label study with DBDs,<sup>[30-32]</sup> and two studies were a pooled analysis of risperidone effects in children with low intelligence.<sup>[33,34]</sup>

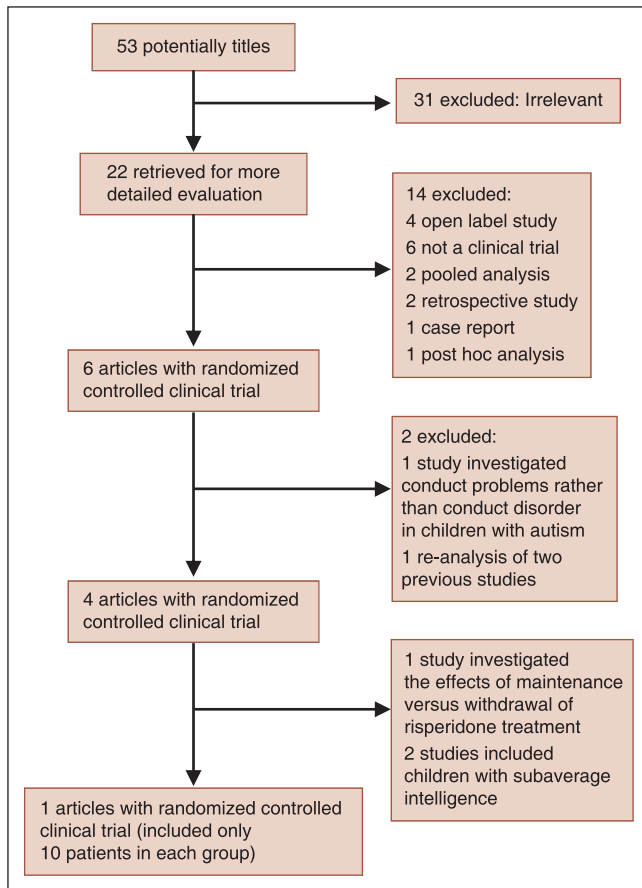


Figure 1: Flowchart of trial selection process

Six studies were randomized, double-blind, placebo-controlled (Table 1).<sup>[35-40]</sup> However, one of them reported the effect of conduct problems rather than CD in children with autistic and other pervasive developmental disorders,<sup>[37]</sup> one study reported re-analysis of two previous studies,<sup>[36]</sup> one study reported the effects of maintenance versus withdrawal of risperidone treatment,<sup>[35]</sup> two studies included children with sub-average intelligence.<sup>[38,39]</sup>

## DISCUSSION

All the published clinical trials supported the efficacy and safety of risperidone for treatment of children and adolescents with conduct problems such as aggression. However, its efficacy on CD is not a well-researched area. In fact, no published well-controlled randomized clinical trial targeted CD with a wide age range of children and an adolescent was found.

Meanwhile, there are many concerns about the methodological issues and interpretation of current literature. Impairment is a required criterion for making diagnoses of CD. Meanwhile, the presence of conduct problems is not equal to CD. Nearly, all studies reported the effect of risperidone on conduct problems rather than CD.

Another limitation in the current literature is the lack of any research directly investigated the efficacy of risperidone on the subgroups of children with CD. The subcategories of symptoms of CD including aggression to people and animals, destruction of property, deceitfulness or theft and serious violations of rules should be considered in future studies.

Moreover, most of these studies have been conducted in the US or Canada. The generalization of results to other cultures and countries cannot be guaranteed. This is important because specific thresholds for what is considered pathological or impairing can be different across cultures. This can impact in order to make a diagnosis and treatment approach.

In addition, most of the published studies included children with age range of 5-12 years. Only one study included children younger than 5 years that it was a case series study.<sup>[22]</sup> Literature regarding children older than 12 years is very scanty.<sup>[35]</sup> Therefore, the results of the current literature cannot be generalized to younger or older children.

Another limitation is that current literature investigated the efficacy and safety of risperidone in children with sub-average intelligence. As a result, for generalization of these results to all children with conduct problems, further trials should be performed on children without intellectual problems.

Nearly all the trials reported that sedation or somnolence is one of the most common adverse effects of risperidone. This question is not answered whether we are sedating these children rather than treating their conduct problems. If their sedation takes their opportunity to express aggression and conduct problems, we can induce sedation with safer profile medications. No study was found investigated whether conduct problems reduction is associated with sedation.

Moreover, weight gain is reported in many studies after taking risperidone. There is a long-lasting course for CD extending from childhood to adolescents and adulthood. These patients may need to take risperidone for long-terms. Hence, cost-benefit analysis should be conducted to investigate the risk of metabolic adverse effects. Paliperidone is a metabolite of risperidone with less affinity to 5-HT<sub>2C</sub> receptors. Therefore, paliperidone can be a better choice than risperidone for treatment of conduct problems.

Most of the controlled clinical trial investigated short term efficacy and adverse effects of risperidone. A few studies followed children for 48 weeks.<sup>[31,41]</sup> On the other hand, many

**Table 1: Double blind randomized controlled clinical trials of risperidone for children and adolescents with conduct disorder**

Reference	Patients condition	Design	Sample size	Intervention	Main outcome measures	Main results	Main adverse effects
[39]	Severely disruptive behaviors with sub-average intelligence (IQ between 36 and 84)	Multicenter, double-blind, parallel-group	118 children (aged 5-12 years)	Risperidone: 0.02-0.06 mg/kg/day or placebo	Nisonger child behavior rating form-conduct problem subscale	Risperidone significantly decreased conduct problems more than did the placebo	Adverse in risperidone group: 98%, placebo group: 70%. Somnolence, headache, vomiting, dyspepsia, increased appetite, weight gain. Serious adverse effects: None
[35]	Disruptive behavior disorders (IQ more than 54)	Randomized, double-blind, placebo-controlled, 6 months (possible bias in recruitment)	335 patients (5-17 years)	Risperidone (patients <50 kg: 0.25-0.75 mg/day; patients ≥50 kg: 0.5-1.5 mg/day) or placebo	Nisonger child behavior rating form	Recurrence of conduct symptoms in 25% of Risperidone group: After 119 days, placebo group: After 37 days with placebo	Adverse in risperidone group: 54.8%, placebo group: 34.9%. Headache, somnolence, fatigue, increased appetite
[38]	A disruptive behavior disorder with sub-average intelligence (IQ between 36 and 84)	1 week, single-blind, placebo run-in period followed by a 6 weeks, double-blind, placebo-controlled period	110 children (aged 5-12 years)	Risperidone (0.02-0.06 mg/kg/day) or placebo	Nisonger child behavior rating form	Risperidone decreased 47% in the conduct problem subscale score, placebo: 20.9%. The effect of risperidone is independent of: Presence/absence of ADHD, psychostimulant use, and IQ status	Somnolence, headache, appetite increase, and dyspepsia. No more extrapyramidal side effects than the placebo group. No cognitive side effects measured by continues performance test
[40]	Conduct disorder	randomized, double-blind, placebo-controlled pilot study with 2 parallel arms	10 patients in each group	Risperidone (weight <50 kg: A maximum total daily dose of 1.5 mg. weight >49 kg: Maximum total daily dose of 3.0 mg) or placebo	Rating of aggression against people and/or property scale	Risperidone significantly decreased aggression more than did the placebo	No more extrapyramidal side effects. Risperidone was well tolerated
[41]	Disruptive behavior disorder (including ADHD: 79.3%) with borderline intellectual function or mild or moderate mental retardation	48 weeks open-label extension study	77 children 5-12 years	Risperidone, at a mean dose of 1.38 mg/day (range: 0.02-0.06 mg/kg/d)	Nisonger-child behavior rating form	The efficacy of risperidone was independent of disorder type, intelligence level, presence/absence of somnolence or ADHD, or use of psychostimulants	76 out of 77 patients experienced adverse effects. Serious adverse effect: 0.0%. The most common: Somnolence (52%), headache (38%), and weight gain (36%). Lack of deterioration of cognitive function
[31]	Severe disruptive behavior disorders (including ADHD: 61.6%) with sub-average intelligence (IQ 36-84)	48 weeks, open-label extension study	107 children ages 5-12 years	Risperidone up to 0.06 mg/kg/day	Nisonger child behavior rating form	Risperidone more than placebo reduced conduct problem subscale score. This efficacy is maintained during long-term treatment	The most common: Somnolence (33%), headache (33%), rhinitis (28%), and weight gain (21%). No clinically relevant changes in ECGs or vital signs

(continued)



**Table 1: (continued)**

Reference	Patients condition	Design	Sample size	Intervention	Main outcome measures	Main results	Main adverse effects
[22]	Conduct disorder with ADHD and intellectual disability	An 8 weeks open-label case series	10 boys and 2 girls with a mean age: 42.4 months	Risperidone: 0.125 mg/day or 0.25 mg/day	Turgay DSM-IV based disruptive behavior disorders child and adolescent rating and screening scale	Risperidone is effective to reduce conduct problems in pre-school children	Risperidone is well tolerated. Adverse effects: Sedation, increased prolactin level

IQ=Intelligence quotient; ADHD=Attention deficit hyperactivity disorder; DSM-IV=Diagnostic and statistical manual of mental disorders, fourth edition; ECGs=Electrocardiograms

of these studies reported that the rate of extra-pyramidal effects was very low or it was not statistically different with control groups. This should not be interpreted that risperidone is safe in this regards. Some extra-pyramidal effects can be appeared very late.

## CONCLUSION:

Current literature supports the efficacy and safety of risperidone for the treatment of conduct problems in children older than 5 years. However, considering above-mentioned limitations, well-controlled long-term trials need to be performed to test these preliminary findings. Until that, psychotherapeutic intervention may be another choice for treatment.

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