

# Oppositional defiant disorder: a review of neurobiological and environmental correlates, comorbidities, treatment and prognosis

## Transtorno desafiador de oposição: uma revisão de correlatos neurobiológicos e ambientais, comorbidades, tratamento e prognóstico

Maria Antonia Serra-Pinheiro,<sup>a</sup> Marcelo Schmitz,<sup>b</sup> Paulo Mattos<sup>c</sup> and Isabella Souza<sup>d</sup>

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<sup>a</sup>Ph.D. undergraduate at the Institute of Psychiatry of the Federal University of Rio de Janeiro - UFRJ

<sup>b</sup>Ph.D. undergraduate in Medicine at the Federal University of Rio Grande do Sul

<sup>c</sup>Federal University of Rio de Janeiro and Group on Attention Disorder of the Institute of Psychiatry of the Federal University of Rio de Janeiro - UFRJ

<sup>d</sup>Ms.C. in psychiatry at the Institute of Psychiatry of the Federal University of Rio de Janeiro - UFRJ

### Abstract

*Oppositional defiant disorder (ODD) is an independent diagnostic entity but it is frequently studied in conjunction with Attention-Deficit Hyperactivity Disorder (ADHD) or Conduct Disorder (CD). The purpose of this paper is to review the extant evidence, through the PubMed database, on the neurobiological correlates of oppositional defiant disorder and also describe the familiar and school functioning, comorbidities, prognosis and therapeutic options for oppositional defiant disorder. Evidence of hormonal, genetic and neurofunctional findings in oppositional defiant disorder, correlation with the family, school relations and performance, and the association with mood and anxiety and disruptive disorders are described. The risk of an evolution to conduct disorder and of persistence of the oppositional defiant disorders symptoms is depicted. A review of the effect of Cognitive-Behavioral Therapy and medication is presented. Analysis of the available evidence shows that the impact of oppositional defiant disorders should not be ignored and it should be properly addressed. The effect of treatment for oppositional defiant disorder on the long-term outcome of patients still needs to be addressed.*

**Keywords:** Attention deficit and disruptive behavior disorder/therapy; Prognosis; Treatment outcome; Diagnosis, dual (Psychiatry).

### Resumo

*Transtorno desafiador de oposição (TDO) é uma entidade diagnóstica independente, mas é frequentemente estudada em conjunto com transtorno de déficit de atenção/hiperatividade (TDAH) ou com transtorno de conduta (TC). O objetivo deste artigo é o de fazer uma revisão das evidências existentes, obtidas por meio da base de dados PubMed, sobre achados neurobiológicos no transtorno desafiador de oposição, funcionamento familiar e escolar, comorbidades, prognóstico e opções terapêuticas para transtorno desafiador de oposição. A evidência de correlatos hormonais, genéticos e neurofuncionais de transtorno desafiador de oposição, a conexão com a família, as relações e desempenho escolares, a associação com transtornos do humor, ansiosos e disruptivos, o risco de evolução para transtorno de conduta e de persistência de sintomas de transtorno desafiador de oposição são descritos. Uma revisão do efeito da Terapia Cognitivo-Comportamental e tratamento farmacológico é apresentada. A análise das evidências disponíveis mostra que o impacto de transtorno desafiador de oposição não deve ser ignorado e que o transtorno desafiador de oposição deve ser devidamente abordado. O impacto do tratamento de transtorno desafiador de oposição no prognóstico de longo prazo dos pacientes ainda precisa ser determinado.*

**Descritores:** Transtornos de déficit da atenção e do comportamento disruptivo/terapia; Prognóstico; Resultado de tratamento; Diagnóstico duplo (Psiquiatria).

### Introduction

Oppositional Defiant Disorder (ODD) is a disruptive disorder, characterized by a pervasive pattern of disobedience, defiance and hostile behavior. Patients discuss excessively with adults, don't accept responsibility for their misbehavior, deliberately bother others and have difficulty accepting rules, easily losing temper if things don't go their way. DSM-IV, the most widely used diagnostic system, defines the diagnosis as a pattern of behavior fulfilling four (of eight) criteria for at least six months with social or occupational dysfunction. ODD's prevalence in community samples is around 6%.<sup>1</sup> Conduct Disorder (CD) is defined by more serious violations such as stealing, assaulting and cruelty to animals and people. Even though ODD is longitudinally strongly correlated to CD, a substantial sub-group of patients do not evolve

in this way. ODD is also highly comorbid with Attention-Deficit Hyperactivity Disorder (ADHD), being present in around 50% of these patients.<sup>2</sup> Bipolar disorder is associated with oppositional defiant symptoms as irritability is common in pediatric bipolarity. Grandiosity, diminished sleep, rapid thought course aid in the differential diagnosis.

Even though ODD is an independent diagnostic category, in most studies, ODD patients have comorbid ADHD or are grouped indistinctly with CD patients. This grouping might be leading to an overrepresentation of etiological factors, prognostic implications and therapeutic effects for ADHD and CD in our understanding of ODD. The object of this review is to analyze the existing evidence concerning ODD, as to its neurobiological correlates, familiar and school functioning, comorbidities, prognosis and

treatment and to attempt to differentiate them from ADHD and CD. We reviewed articles cited in the PubMed base containing terms such as oppositional defiant disorder and ODD, with no date restrictions.

## Neurobiological correlates

### 1. Hormones and neurotransmission

Van Goozen et al<sup>3</sup> have shown that adrenal androgens levels of patients with ODD are higher than that of normal controls or children with other diagnoses including ADHD. They have also demonstrated that ODD patients had lower baseline heart rates than normal controls,<sup>4</sup> but their heart rates were higher after provocation and frustration. Median cortisol levels were also lower in patients with ODD than controls.<sup>4</sup> Previously, they had demonstrated that patients with ODD have levels of 5-Hidroxyindoleacetic acid (5-HIAA) and Homovanillic acid (HVA) lower than controls.<sup>5</sup> Around 25% of their samples comprised patients who actually had CD. The lower heart rates, median cortisol level and HVA levels are congruent with underarousal of the autonomic nervous system, which has been demonstrated in patients with CD. Snoek et al<sup>6</sup> have shown that the postsynaptic serotonergic receptor of children with ODD might be oversensitive but of the 20 children with ODD in this study, 13 had comorbid ADHD

### 2. EEG

Clarke et al<sup>7</sup> compared EEGs of children with ADHD with and without ODD and normal controls. The comorbid group was closer to normality than the pure ADHD group leading to the assumption that the differences in the EEG of the comorbid group could be mostly attributed to ADHD. However, probably analysis of event-related potentials can find differences between ODD patients and controls, as was the case in a study with children with "conduct problems".<sup>8</sup> These procedures do not have utility in the clinical realm, though.

### 3. Genetics

Nadder et al<sup>9</sup> suggested, based on a twin study, that there was a genetic liability to the co-occurrence of ODD/CD with ADHD and also for persistence of ODD/CD symptomatology. They did not separate ODD from CD. Comings et al<sup>10</sup> demonstrated that in patients with Tourette's Disorder, genetic loading for markers of three different genes is associated with ODD. Previously, they studied 20 candidate genes for ADHD and found that ODD shared genes with ADHD, but different genotypes of the same genes were used.<sup>9</sup>

The androgen receptor gene,<sup>10</sup> DAT,<sup>11</sup> DRD2,<sup>12</sup> D-beta-H<sup>14</sup> have all been associated with ODD or oppositional-defiant symptoms. Some of these studies were conducted in sub-groups such as those with Tourette disorder. A recent finding associates oppositional-defiant symptoms with the DAT gene in patients whose mother has smoked during pregnancy, demonstrating a genetic-environmental interaction. The overall degree of genetic correlation with ODD is possibly dependent on the presence or not of comorbidities and environmental interactions.

### 4. Cognitive

Coy et al found that children with ODD were twice as likely as controls to generate aggressive solutions to problems.<sup>15</sup> VanGoozen et al testing executive functioning in children with ODD with and without ADHD and normal controls (NC) found that the ODD/ADHD group was worse than the NC in set shifting, and both ODD groups performed worse on a response perseveration task.<sup>16</sup> A motivational inhibition task correctly classified 77% of the children as ODD or NC. They concluded that ODD and ODD/ADHD children have problems in regulating their behavior under motivational inhibitory conditions. Once they are stimulated by the possibility of an award they become less sensible to the possibility of punishment.

## Familiar aspects, school functioning

In a study comparing patients with ADHD with and without ODD, Kadesjo et al found that having divorced parents and a mother with low socioeconomic level were more common in the comorbid group.<sup>13</sup> Frick et al demonstrated that children with ODD were distinguished from clinic controls in having higher prevalence of parental anti-social personality disorder and paternal substance abuse disorder.<sup>18</sup>

In a study comparing mothers of children at risk for ODD with mothers of children without elevated ODD symptoms, Cunningham et al reported that mothers of at risk for ODD children reported more family dysfunction, felt less competent as parents, suggested fewer solutions for child behavior problems, demonstrated a less assertive approach to management of child misbehavior and reported more internalizing disorders than did mothers of children without elevated ODD symptoms.<sup>19</sup> Fletcher et al<sup>20</sup> comparing the interaction between mothers and teenagers with ADHD or ADHD plus ODD and controls found that mothers of the comorbid group responded in a more similar negative way to their teens. Finally, Harada et al<sup>21</sup> found that children with ODD have more difficulties with their mothers than children with ADHD or even children with both diagnoses.

Greene et al<sup>22</sup> found that children with ODD have significantly greater family dysfunction than even psychiatric controls. ODD is clearly related to family distress and mal-functioning. Unfortunately, due to the cross-sectional nature of most of these studies, it is difficult to define the direction of the association between family disruption and ODD.

Gadow et al<sup>23</sup> compared patients with ODD, to patients with ADHD, to a comorbid group and to controls. They found that preschoolers with ODD and ADHD had the highest scores for difficulties with peers and developmental deficits. Carlson et al<sup>24</sup> demonstrated that children with ODD and ADHD fared worse in social functioning than kids with ADHD or ODD alone and than controls without these disorders. ODD children demonstrated fewer difficulties with learning than children with ADHD. Harada et al<sup>21</sup> found that children who had only ODD had more school refusal than children with ADHD and even the comorbid group. Greene et al<sup>22</sup> also found that ODD was correlated with social dysfunction compared to psychiatric controls.

## Present comorbidities

The estimated prevalence of ODD in clinical ADHD samples is around 50%, much higher than in the general population. Kadesjo et al<sup>17</sup> comparing children with ADHD with and without ODD found that ADHD combined sub-type and higher severity of ADHD symptoms were seen more often in the comorbid group. Burns et al<sup>25</sup> demonstrated that hyperactivity/impulsivity symptoms were a significant predictor of later development of ODD. ADHD seems to be a risk factor for the development of ODD.

Internalizing disorders are also more common in children with ODD.<sup>24</sup>

## Treatment

Parent Management Training, a modality of cognitive-behavioral therapy (CBT) intended to modify the child's behavior through alteration of the parent's way of dealing with the child, has proved effective for ODD. Studies define the amount of responders around 40-50%,<sup>26</sup> even in populations as culturally distinct as North-Americans and Chinese.<sup>27</sup> Cognitive therapies have recently come more into evidence,<sup>26</sup> with response rates as high as 74%. Probably the appropriate choice of therapy depends on psychological characteristics of the patient.<sup>26</sup> Kazdin et al<sup>28</sup> have demonstrated that CBT can even improve family functioning and marital satisfaction.

There are many reports of the effect of medication for

oppositiveness and for aggression, but mostly in patients who actually have CD or who have comorbid ADHD. In addition to the comorbidity issue, most studies focus on aggression or ODD symptoms not necessarily in patients with a diagnosis of ODD.

Kolko et al<sup>29</sup> demonstrated in children with ADHD and severe ODD or CD that methylphenidate diminished patient's oppositional symptoms. Serra-Pinheiro et al<sup>30</sup> found that methylphenidate was able to diminish 63% the fulfillment of ODD criteria in patients with ODD comorbid with ADHD. Clonidine<sup>31</sup> has also been found significantly effective for improvement in ODD symptoms in aggressive patients who had ADHD. There is no evidence that psychostimulants or clonidine is effective for ODD not comorbid with ADHD.

Anti-psychotics and mood stabilizers have been studied for severe disruptive disorders, grouping indistinguishably CD and ODD. Campbell et al<sup>32</sup> demonstrated the efficacy of haloperidol and lithium for aggression, noncompliance and temper outbursts in aggressive patients. Valproic acid was tested for patients with ODD or CD with explosive outbursts and mood lability.<sup>33</sup> Eighty percent of patients responded as compared to none on placebo. Risperidone<sup>34</sup> has been investigated for disruptive disorders especially in patients with low IQ and has been found significantly effective for the amelioration of "calmness or compliance". A case series reported improvement of 82% of patients with ADHD and ODD treated with buspirone<sup>35</sup> for ODD symptoms. However, to our knowledge, the effect of these drugs on a diagnosis of ODD has not been systematically tested.

### Prognosis

ODD is a risk factor for the development of CD, specifically in boys, with its occurrence ranging from 2.7% to 40%, as demonstrated in longitudinal studies.<sup>36-37</sup> ODD was not a risk factor for the development of CD in girls in a large epidemiologic study,<sup>38</sup> but the findings might not be generalizable to a clinical sample. Factors associated with the evolution from ODD to CD are family and environmental adversity, such as having an adolescent mother, frequent movings and having a step-parent.<sup>38</sup>

ODD is stable in a significant amount of patients. August et al<sup>36</sup> demonstrated that after 4 years 57% of their sample of children with ODD comorbid with ADHD, maintained an ODD diagnosis.<sup>39-40</sup>

ODD is also longitudinally associated with internalizing disorders and ADHD, even in preschoolers.<sup>38-39</sup>

Ford et al<sup>41</sup> have demonstrated that ODD, but not ADHD, is associated with an increased risk of victimization trauma.

### Conclusion

Certainly the field could gain with more precise definition of ODD samples in future studies. There are possibly many sub-types of ODD, for example, with and without ADHD; with and without physical aggression; ODD in boys and in girls. Refining our diagnostic classification would contribute to our better understanding of ODD. We did not search the ISI database, what might have brought some limitations to our study. Even so, it is possible to highlight some findings. There seems to be a genetic liability to ODD that interacts with environmental factors and is probably dependent on different ODD sub-types, such as with or without ADHD. Family and school dysfunction are definitely present in ODD. Therapeutic approach should probably vary according to the presence of comorbidity. Stimulants and clonidine seem effective for ODD symptoms comorbid with ADHD, with methylphenidate being able to induce remission in ODD in a large proportion of patients with ADHD comorbid with ODD. Valproic acid, haloperidol, risperidone and lithium are probably more effective when there is notable mood instability. Comorbid conditions and older age of the child probably have a negative effect on PMT. It is essential to see if therapeutic strategies are efficient in changing the long term

risks of ODD, specially its higher risk for CD. If they prove useful for improving prognosis they can be used as a secondary prevention measure for CD, a very hard to treat condition.

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**Correspondence**

Maria Antonia Serra-Pinheiro  
 Rua Souza Lima, 280/402 - Copacabana  
 22081-010 Rio de Janeiro, RJ, Brasil

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