

## ARIPIRAZOLE AND RISPERIDONE IN PEDIATRIC POPULATION, AN UPDATE OF SAFETY ISSUES AND FOCUS ON OFF-LABEL USE: AN ANALYSIS OF THE EUROPEAN PHARMACOVIGILANCE DATABASE (EUDRAVIGILANCE) FROM 2016 TO 2018

Simona Brusco<sup>1</sup>, Michele Bertini<sup>1</sup>, Cristina Scavone<sup>1</sup>, Carmen Ferrajolo<sup>1</sup>, Liberata Sportiello<sup>1</sup>, Maria Giuseppa Sullo<sup>1</sup>, Eleonora Landolfi<sup>1</sup>, Pasquale Maria Berrino<sup>2</sup>, Annalisa Capuano<sup>1</sup>, Concetta Rafaniello<sup>1</sup>

<sup>1</sup>Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Department of Experimental Medicine, Section of Pharmacology L. Donatelli, University of Campania Luigi Vanvitelli, Naples - Italy, <sup>2</sup>University of Campania Luigi Vanvitelli, Naples - Italy

**Introduction:** During the last decades, there has been an increasing use of second generation of antipsychotic (SGA) drugs in children and adolescents. SGAs are used effectively for several psychiatric conditions, but only few of them have regulatory approval in youths. Although effective, these drugs could potentially determine several adverse events of which cardio-metabolic ones are still of special concern. Thus, in this study, we analyzed the European pharmacovigilance database (EudraVigilance) to take stock of the situation in terms of the safety profile associated with aripiprazole and risperidone.

**Materials and methods:** We performed a descriptive analysis of suspected adverse reactions related to aripiprazole and risperidone collected from EudraVigilance database from 2016 to 2018.

**Results:** From 2016 to 2018 have been reported 1069 Individual Case Safety Reports (ICSRs) associated to risperidone and 564 to aripiprazole. Most of these were related to male patients (77.8% for risperidone and 57.4% for aripiprazole) and the median age was 15 years for both drugs. Attention deficit and hyperactivity disorder, Disruptive, impulse-control and conduct disorders and Schizophrenia spectrum and other psychotic disorders were the more frequent therapeutic clinical indication of risperidone use; Schizophrenia spectrum and other psychotic disorders, Bipolar and related disorders and Disruptive, impulse-control and conduct disorders resulted the three most common clinical indications of use associated to aripiprazole. Overall, a total of 4146 preferred terms (PT) were reported for risperidone and 1949 for aripiprazole; the majority of PT was serious either for risperidone (93.8%) and for aripiprazole (78.4%); Other Medically important condition (risperidone 64.9%; 43.6% aripiprazole) and caused/prolonged hospitalisation (risperidone 14.9%; 22.4% aripiprazole) were the more common reported seriousness criteria. Risperidone showed the highest percentage of PT in the following System Organ Class (SOC): "reproductive system and breast disorders" (16.4%), "psychiatric disorders" (16.3%) and "Injury, poisoning and procedural complications" (14.8%). "Psychiatric disorders", "Nervous system disorders" and "Injury, poisoning and procedural complications" were the most reported SOC for aripiprazole (21.3%, 15.3% and 15.1% respectively). 91 (16.1%) out of 564 ICSRs related to aripiprazole and 170 (15.9%) out of 1069 ICSRs associated to risperidone reported a dose modification; among this ICSRs subpopulation, comparing SOC distribution among ICSRs in which increasing dosage has been reported to those in which instead the dosage was unchanged, we observed an increased rate of "Psychiatric disorders" (25.2% vs 20.3%;  $p < 0.05$ ) and "Renal and urinary disorders" (2.9% vs 1.0%;  $p < 0.05$ ) for aripiprazole while "Injury, poisoning and procedural complications" (17.6% vs 14.2%;  $p < 0.05$ ), "Reproductive system and breast disorders" (20.8% vs 15.4%;  $p < 0.05$ ) and "Investigations" (11.5% vs 9.1%;  $p < 0.05$ ) for risperidone. Basing on the posology recommended for the pediatric population, as reported in the Summary of Product Characteristics (SmPC), we found that the dosage reported for aripiprazole and risperidone was consistent for 53.1% and 51.07% respectively, higher in 3.1% and 44.7% respectively and lower in 43.7% and 4.16% of the analysed ICSRs. The "off-label", as PT, was reported in 258 ICSRs (24.1%) with risperidone, reported as suspected drug, and in 100 ICSRs (17.7%) associated to aripiprazole. Finally, out of 552 reported clinical indications use of aripiprazole and 1375 for risperidone, 37% and 16% were in-label and 63% and 84% off-label respectively.

**Discussion and conclusion:** These data confirm the widespread off-label use of antipsychotics and suggest that to date there is still no valid therapeutic alternative for mental illness in pediatric population.