SOCIAL ADVERSE DRUG REACTIONS: A PHARMACOVIGILANCE-PHARMACODYNAMIC ASSESSMENT THROUGH THE FDA ADVERSE EVENT REPORTING SYSTEM

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Introduction: Despite the bio-psycho-social model (social component of diseases) is receiving increasing attention in contemporary medicine, data on social Adverse Drug Reactions (ADRs) are scarce in the literature. Social ADRs, like aggression, speech disorder, gambling, have an important impact on the patient's health, and spontaneous reporting systems represent a useful source to systemically describe direct social ADRs, also considering the increasing reporting by consumers. Therefore, we conducted a pharmacovigilance-pharmacodynamic study, both by quantifying the strength of association between drug and event, and investigating the putative relationship between pharmacological targets and reported direct social events.

Methods: The FDA Adverse Event Reporting System (FAERS) Public Dashboard was queried to select reports where at least one social event was recorded (updated at 31/12/18). A pre-specified list of 40 social ADRs was compiled meeting the definition of a direct social impact. Disproportionality analysis (cases/non-cases approach) was performed by calculating the Reporting Odds Ratio (ROR) with 95% confidence interval (CI). Potential signals were defined by statistically significant ROR (i.e., lower limit of the 95%CI>1), with at least 3cases reported, and were visualized through an heatmap. We assessed to what extent receptor binding properties could be associated to RORs, building linear regression models, using binding affinities (pKi; www.guidetopharmacology.org) of different targets (histamine, serotonin, dopamine and adrenoceptors) as independent variables (p-value <0.05for significance).

Results: We retrieved 173,184social ADRs over a 14-year period, analyzed 2157drugs and extracted pKi data for 93molecular targets. We found 43potential correlations between drugs and social adverse events, including different anti-parkinson, antidepressant and antipsychotic agents. Increased reporting for aggression emerged for first- and second-generation antipsychotics (e.g., risperidone: N=1489cases; ROR=3.5; 95%CI=3.3-3.8). Aripiprazole was significantly reported with 15direct social ADRs, including gambling (N=108; 99.9; 89.9-111.1), and shoplifting (105; 51.8; 39.3-68.3). Hypersexuality emerged for different pharmacological agents, including pramipexole (338, 1.7; 1.5-2.1), levodopa (173; 5.9; 4.3-8.0) and sertraline (14; 3.4; 1.4-8.5). Significant correlations between ROR strength and pKi were found for aggression with α1D-adrenoceptor antagonists (slope = -1.08, SE = 0.27) and D4receptor antagonists (slope = 1.99, SE = 0.49); speech disorder with 5HT1B receptor agonists (slope = 0.93, SE = 0.33), impaired work ability with 5HT1D receptor antagonists (slope = 0.54, SE = 0.23), compulsive shopping with D4receptor agonists.

Discussion and conclusion: This is the first systematic assessment of direct social ADRs, highlighting an increased reporting with different drugs acting at the nervous system level. This pharmacovigilance-pharmacodynamic approach underlines the potential role of dopamine receptors in the occurrence of these events and suggested the need to: (a) further explore the implication of the bio-psycho-social model; (b) establish actual event rates and identify risk factors that might lead to proper risk management. In the meantime, clinical monitoring is warranted to early intercept social ADRs.