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Comparing Spontaneous Report Disproportionality Measures to Estimates of Adverse Events from Randomized Trials included in Cochrane Reviews

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Background

Although disproportionality measures are used by health authorities worldwide to identify adverse events signals in spontaneous report databases, update product labels and issue warnings, these measures are not commonly thought to be directly representative of the risk of adverse events occurrence. A recent study has found a strong correlation between disproportionality measures (Proportional Rate Ratios PRRs) from the European reporting system and the risk of 15 different adverse events recognized by the European Medicine agency commisions[1]. This study selected signals issued from expert consensus using several sources, summarized these risks and compared them with PRRs in the spontaneous report database. We further selected **medications at random** and compared their associated adverse events risks from randomized trials (RCTs) included in **the Cochrane database of systematic reviews** and corresponding signals in the **FDA's Adverse Event Reporting System (FAERS) database**[3] to examine this association.

Objectives

To compare disproporationality measures from the FAERS database to adverse event estimates from randomized trials included in **Cochrane reviews.**

Methods

100 medications were randomly selected from the list of medications included in the **FAERS database**. Drug combinations, vaccines, biologicals and herbal medicines were excluded. All Cochrane systematic reviews of the selected drugs found in the **Cochrane database systematic reviews** were reviewed. Selected systematic reviews were screened by two researchers to meet inclusion/exclusion criteria. Reviews comparing the medication of interest to another medication or intervention, comparing drugs as a group (not individually) and reviews missing relevant information on adverse events for the medication of interest were excluded. Odds ratios, hazard ratios or Risk Ratios referring to adverse events were extracted with corresponding confidence intervals from the reviews selected. Estimates were all appropriately converted into Odds ratios (ORs).

Access to the FAERS database was provided by **AdveraHealth** (www.adverahealth.com). Adverse events extracted from these reviews were then coded into appropriate PT (preferred term) in Meddra® (Medical Dictionary for Regulatory Activities) codelists by experienced coders and reviewed by clinical researchers and corresponding ROR (reporting Odds ratios) were calculated in the FAERS database for each medication-AE pair. RORs from the FAERS database and ORs from the systematic reviews were then reported graphically for each medication-AE pair, Pearson correlation and regression coefficients, were calculated.

Results

301 systematic reviews including information on the drugs selected were found in the Cochrane database of systematic reviews. Only 5 of these reviews responded to our inclusion/exclusion criteria and included relevant information on the risk of adverse events (OR, HR or RRs) for four drugs: bupropion, cycloserine, paliperidone and roflumilast. Two reviews included relevant adverse events information on paliperidone and were merged to give appropriate summary estimates for each medication-AE pair. A total of 81 AE-medication pairs were included in the analysis. Corresponding RORs and confidence intervals were calculated in the FAERS database (figure 1)

Overall, a poor correlation was found between the two sets of adverse events risk measures (Pearson coefficient=0.22). A poor correlation was also found when restricting to Cochrane estimates showing evidence of adverse events (pearson correlation coefficient=0.22 and P-value=0.4, n=16). When looking at the comparisons by drug of interest, Roflumilast showed a strong correlation (pearson correlation coefficient = 0.78 and regression p-value of 0.003) (Figure 2). Roflumilast review included the highest number of patients (12,654 vs. respectively 1,100, 48 and 4,782 for Bupropion, cycloserine and paliperidone).

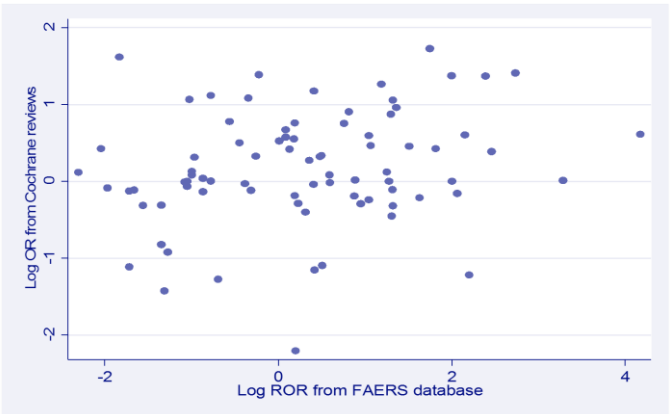

Figure 1. Comparison of ROR from FAERS database and ORs from Cochrane systematic reviews of RCTs (N=81) Pearson correlation coefficient=0.23

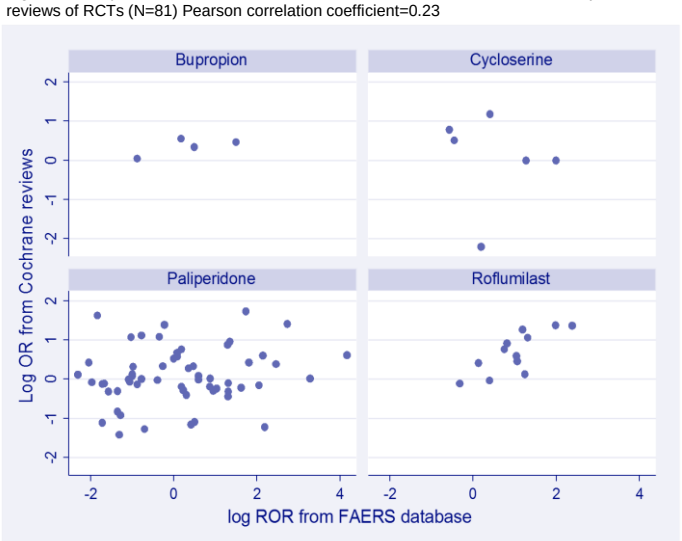

Figure 2. Comparison of ROR from FAERS database and ORs from Cochrane systematic reviews of RCTs by medication (N=81) Pearson correlation coefficient bupropion=0.71 (n=, cycloserine=-0.12, paliperidone=0.16 and roflumilast=0.78

Conclusion

Overall, adverse events risk estimates from **randomized trials** included in **Cochrane systematic reviews** were poorly correlated with corresponding disproportionality measures from the **FAERS database**. This suggests that adverse event risk estimates from voluntary report may not represent those obtained in clinical trials. However, a relatively strong correlation was found in the case of Roflumilast. This could be due to chance. It is interesting to note that the Roflumilast review included the highest number of patients (12,654 vs. respectively 1,100, 48 and 4,782 for Bupropion, cycloserine and paliperidone).

Contact

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References

[1] Macia-Martinez MA, de Abajo FJ, Roberts G, et al. An Empirical Approach to Explore the Relationship Between Measures of Disproportionate Reporting and Relative Risks from Analytical Studies. Drug Saf 2016;**39**(1):29-43.

[2] http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/index.html

[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm