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What "proof" is in the pudding? Integrating methodologies for adverse event signal detection

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Abstract

Background: Many methodologies exist to detect adverse drug event signals. Pharmacoepidemiological analyses have historically focused on understanding the association of medicines with adverse events at a population-level and primarily rely on utilisation of one methodology per study.

Aims: We apply an integrative multi-method approach to detect increased risk of Chronic Obstructive Pulmonary Disease with the use of commonly prescribed medicines.

Methods: In silico molecular modelling approaches were utilised to predict interactions that medicines have with a drug target, Glutathione Peroxidase 1, which is implicated in COPD development and progression. Subsequently, the FDA Adverse Event Reporting System (FAERS) was searched to uncover adverse event signals associated with COPD and a sequence symmetry analysis (SSA) was also conducted utilising the PBS 10% extract.

Results: FAERS and SSA analyses confirmed that selected medicines, that were predicted to inhibit Glutathione Peroxidase 1, were associated with increased risk of COPD progression or development in population-level analyses.

Conclusions: Integration of molecular modelling and pharmacoepidemiological analyses has the potential to improve medicine safety by providing an enhanced understanding of the mechanisms by which medicines cause adverse events.

Impact: Several peer-reviewed publications have highlighted the utility of combining and leveraging multiple methodologies to improve adverse event signal detection, however few studies have implemented such an approach. This study expands on the traditional approach to signal detection and demonstrates the value of integrating molecular modelling to understand the mechanisms by which adverse events occur to enhance adverse event signal detection. This study has generated new evidence of how registered medicines may cause adverse events related to development or progression of COPD.