**In search of biological substantiation through literature review and in silico analyses: the case of antipsychotic-associated pneumonia**

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**Background:** The safety profile of antipsychotic (AP) drugs has been widely investigated in the past decade. Several observational studies have specifically explored the association between AP use and pneumonia mostly in elderly people, with several studies producing seemingly convincing results in favor of such an association. However, these studies often limited themselves to investigating APs overall or by class. Nevertheless, there is a significant pharmacological difference among single APs, suggesting that their propensity to induce pneumonia can vary substantially. Despite the importance of evaluating the biological plausibility of the association between AP use and pneumonia, the mechanism underlying AP-associated pneumonia has not been studied in detail.

**Aim:** To investigate the known mechanisms of AP-associated pneumonia through a systematic literature review, confirm these mechanisms using an independent data source on drug targets and attempt to identify novel AP drug targets potentially linked to pneumonia.

**Methods**: A search was conducted in Medline and Web of Science to identify studies exploring the association between pneumonia and antipsychotic use, from which information on population, study design, exposure, outcome and, where available, hypothesized mechanism of action were tabulated. Public repositories of pharmacology and drug safety data were used to identify the receptor binding profile and safety events of the following APs commonly investigated in studies quantifying the risk of AP-associated pneumonia: amisulpride, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and zotepine. Cytoscape was then used to map biological pathways that could link AP targets and off-targets to pneumonia.

**Results:** The search in Medline and Web of Science yielded 200 articles, of which 41 were considered relevant. Thirty studies reported a hypothesized mechanism of action, most commonly activation/inhibition of cholinergic, histaminergic and dopaminergic receptors. Known pharmacology data confirmed the affinities of APs to receptors identified in the literature review, and graded these affinities by strength, while two targets, thromboxane A2 receptor (TBXA2R) and platelet activating factor receptor (PTAFR), were found to be novel AP target receptors associated with pneumonia. Biological pathways constructed using Cytoscape identified plausible biological links which could give rise to pneumonia downstream of the two novel targets found.

**Conclusion:** The literature review yielded plausible mechanisms of AP-related pneumonia ranging from sedation to excessive salivation. Available public sources of pharmacological data confirmed existing receptor-binding profiles for APs identified in the literature review. In addition, two novel targets that could explain the link between AP use and pneumonia were identified, TBXA2R and PTAFR.