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Utilization of Informatics Tools to Mechanistically Analyze Drugs Associated with Serotonin Syndrome

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Background: Serotonin syndrome (SS) is often a drug-drug interaction that results in enhanced serotonin neurotransmission by acting through different drug protein targets/pathways.

Research Question: Second generation antipsychotics (SGAs) and concomitant drugs highly associated with SS and their molecular protein targets were evaluated to explore molecular protein targets and mechanisms for developing SS.

Methods: SGAs were data mined in FAERS to identify the concomitant drugs taken with SGAs and disproportionally associated with SS. Bioinformatics and cheminformatics tools were used to further mechanistically evaluate disproportionality of four classes of drugs. A bioinformatics tool data mines public FAERS for individual drugs, drug combinations and drug targets for disproportionality using Proportional Reporting Ratio (PRR) scores. A cheminformatics tool evaluates potential unknown off-target binding. Literature searches and case analyses followed to further analyze signals, associations, and mechanisms.

Results: SGAs are disproportionally associated with SS (N: 1075, PRR: 4.59). Many serotonergic receptors were associated with SS; 5-HT_{2A} (N: 916, PRR: 7.90), 5-HT_{1A} agonism (N: 600, PRR: 8.73), and 5-HT_{2C} antagonism (N: 186, PRR: 15.07). Benzodiazepines were highly associated with SS (N: 1188, PRR: 4.83). Alprazolam and clonazepam were 2 of the top 20 concomitant medications with SGAs in 1075 SS cases (alprazolam concomitant N: 66, PRR: 4.28; clonazepam concomitant N: 133, PRR: 10.75). Cholinesterase inhibition (N: 120, PRR: 3.56) was found to be significantly associated with SS. N-methyl-D-aspartate (NMDA) antagonism was associated with SS (N: 219, PRR: 5.07). Pregabalin was predicted to bind to the NMDA receptor.

Discussion: Strong evidence exists for an association of SGAs and SS likely via two potential mechanisms of action found in literature: 5-HT_{1A} upregulation via 5-HT_{2A} antagonism and partial agonism at 5-HT_{1A}. Some benzodiazepines may enhance serotonin activity via several mechanisms, including decreasing serotonin metabolism and increasing 5HT receptor reactivity, causing concern over their use for SS treatment. By increasing acetylcholine, cholinesterase inhibitors may have opposing serotonergic action through the muscarinic (decrease serotonin) and nicotinic (increase serotonin) receptors, while predicted pregabalin NMDA binding may increase serotonin neurotransmission.

Conclusions: SGAs, benzodiazepines (alprazolam and clonazepam), cholinesterase inhibitors, and pregabalin were found to be disproportionately associated with SS via various mechanistic pathways/targets.