

Toxicology and Clinical Pharmacology

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Mechanisms underlying adverse endocrine and metabolic side effects of Atypical Antipsychotic (AA) medications: Central vs. direct effects

A typical antipsychotic medications (AA) are FDA approved for psychosis associated with schizophrenia, bipolar disorder and irritability associated with autism. AA display complex pharmacology, antagonizing multiple G-protein coupled receptor families. Antagonism of dopamine receptors is thought to be a pivotal component of clinical efficacy. Despite FDA warning labels for metabolic side effects, these are among the most highly prescribed drugs world-wide due to prescribing for non-approved indications. Common clinical side effects include obesity, dyslipidemia, hyperglycemia, sudden cardiac death and increased fractures. Despite the severity of these side effects, there is a paucity of literature examining the underlying pharmacology. We and others have shown that central/indirect side effects of AA include increased appetite and obesity, hyperprolactinemia and hypothalamic insulin resistance, which underlies hepatic insulin resistance. The mechanisms underlying AA-induced dyslipidemia and increased fractures have not been elucidated. Our laboratory is focusing on the emerging side effects of AA medications on bone. Clinical data show that fracture risk is elevated in schizophrenic patients treated with AA vs. the general population, and limited studies show that patients treated with risperidone (RIS) have reduced bone mineral density. We hypothesize that AA impact bone biology by both indirect and direct mechanisms. Our approach includes evaluating effects of clinically relevant doses of AA in pre-clinical models as well as direct effects on bone cells *in vitro*. We explored the role of hypogonadism in RIS-induced bone loss and developed bioanalytical methods to quantify dynamic concentrations of dopamine and RIS in bone marrow to evaluate possible direct drug effects *in vivo*. Our overarching goal is to elucidate the pharmacology associated with undesirable health effects of AA medications to better inform prescribing practices and drug discovery efforts. With such a large patient population taking these medications, these data are of special concern for vulnerable populations including children and the elderly.

Biography

Karen L Houseknecht is currently Professor of Pharmacology, College of Osteopathic Medicine, and Interim Dean of the College of Pharmacy at the University of New England (Portland, Maine USA). She received her PhD from Cornell University and has held multiple leadership positions in academic and corporate research organizations. She is the author of over 50 peer-reviewed publications and her NIH-funded research program focuses on new therapeutic discovery (including drug metabolism) and the pharmacology underlying adverse metabolic effects of psychiatric medications.

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