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IN VITRO RECEPTOR-BINDING PROFILE OF LURASIDONE AND OTHER COMMONLY-USED ANTIPSYCHOTICS

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Introduction: Atypical antipsychotics bind to multiple receptor types and subtypes. Improved outcomes in schizophrenia are linked to activity at D_2 and serotonin receptors 5-HT_7, 5-HT_{2A} and 5-HT_{1A}.
Objectives: To characterize the receptor-binding profile of lurasidone and other antipsychotics.
Aims: To compare receptor-binding profiles of antipsychotics.
Methods: Replicated, side-by-side receptor-binding assays used human recombinant receptors (for 5-HT_7, α_2A, and α_2C) or membrane-fractions of animal CNS tissue. Affinities were determined via Hill plot analysis for IC_{50} values; Ki values were determined using $Ki=IC_{50}/(1+ S/Kd)$ (S=concentration of competing radioligand, Kd=dissociation constant).
Results: Lurasidone displayed potent binding and full antagonism at dopamine D_2
(Ki, 1.68nM) and serotonin 5-HT_{2A} (Ki, 2.03nM) receptors (the highest D_2 affinity of all tested agents). Lurasidone's dopamine binding was selective for D_2 receptors. Unlike other antipsychotics tested, lurasidone had very high affinity and full antagonism at serotonin 5-HT_7 (Ki, 0.49nM), and nanomolar affinity (Ki=6.75nM) with weak-moderate partial agonism at serotonin 5-HT_{1A} receptors., Lurasidone showed higher affinity for 5-HT_7, 5-HT_{2A}, and 5-HT_{1A} receptors relative to D_2 receptor-binding than other agents. Lurasidone displayed moderate affinity for α_2C adrenoceptors (Ki, 10.8nM); moderate-weak affinity for α_1 adrenoceptors (Ki, 48nM); and minimal or unappreciable affinity for receptors associated with undesirable effects (5-HT_2C [Ki, 415nM], histamine H_1
[IC_{50} >1000nM] and muscarinic [cholinergic] M_1 [IC_{50} >1000nM] receptors).
Conclusions: The unique pharmacological profile of lurasidone is consistent with observed antipsychotic efficacy, low-to-moderate likelihood of EPS, low weight-gain potential, and possible mood, anxiety, and cognitive benefits.

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