More innovation needed

Dr. Henry Nasrallah's editorial on polypharmacy ("Innovative polypharmacy: When dopamine blockade is not enough." From the Editor, Current Psychiatry, November 2007, p. 17-18) was thought provoking. The available medication databases are very good at detecting pharmacokinetic drug-drug interactions but poor at informing clinicians about pharmacodynamic drug-drug interactions. The receptor profile of a drug is its unique signature. One can argue that combining 2 drugs with 2 different receptor specificity and potency profiles is akin to creating a designer drug with a unique receptor profile that is different from the sum of its parts.

Neurotransmitter receptor selectivity is an in vitro myth. Due to the well-known interactions among serotonergic, dopaminergic, adrenergic, cholinergic, and many other pathways, it is almost impossible to expect a selective drug to affect 1 pathway without affecting others. The so-called selective serotonin reuptake inhibitors may bind selectively to receptors in vitro, but other pathways will be affected in the dynamic, interactive brain. A change in 1 neurotransmitter pathway will lead to changes in many—if not all—others.

The complexity of interactions among the different neurotransmitter systems makes oversimplification the rule, not the exception. Given that the human mind is capable of manipulating very limited variables concomitantly, artificial intelligence will be needed to try to predict the pharmacodynamic interactions of multiple agents through neurochemical network modeling, similar to programs used to predict the weather.

Last, I offer a defense of speculation and prescribing based on good theoretical proposals, such as the ones made by Dr. Nasrallah. Good research starts with a good hypothesis. Clinical studies in humans and research using animal brains will lag years—maybe decades—behind theory because of the complexity of pharmacodynamic interactions.

The obsession with double-blind, randomized, controlled studies in psychopharmacologic literature has resulted in a false dichotomy between the theoretical and experimental, with respect heaped on the experimental and contempt for the theoretical. Drug-drug pharmacodynamic interactions are more suited for theory-based computer modeling programs, which may drive innovative polypharmacotherapy research as much as—if not more than—clinical studies.

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