Atypical Psychotropic Agents

Trazodone and Buspirone

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1. Introduction: Identifying Atypical Agents

The discovery and development of truly atypical psychotropic agents are by far more challenging endeavors than synthesizing an additional member of a prototypical class of compounds and demonstrating that it retains a desired pharmacological profile. The identification of novel molecules with potential for clinical application is often hampered by the preconceived notions of structure-activity requirements, desired neurochemical effects, and empirically validated behavioral predictors of clinical success that comfort those seeking to develop second generations of an existing class of drug. Despite dramatic progress in the neurosciences, we still do not understand the biological bases of psychopathology enough to design drugs that will selectively reverse those aberrant states of neural activity that are associated with many disorders. Rather, in order to rationally conceptualize future avenues of pharmacotherapy, we must rely upon imperfect, evolving knowledge about disease states and inferences we may make based upon a similarly incomplete appreciation of the mechanism of action of drugs known to be effective against clinical targets.

When structurally novel molecules are synthesized, perhaps the products of medicinal chemistry theories of what is required to achieve the therapeutic action sought, animal and biochemical models help identify those that are safe and believed to be effective in humans. However, the criteria against which we gage the
probability of success in humans are often derived from assumptions based upon the activity of known, standard agents. Thus the preclinical models relied upon to predict the utility of new and potentially atypical psychotropic agents may be uniquely sensitive to the pharmacological actions of the prototypical classes of molecules that, by virtue of their clinical success, validated the use of particular screening tests. The development of atypical psychotropics is a high-risk venture because the empirical relationships between preclinical pharmacology and clinical efficacy have not yet been established for unique structural series. Should a new class of molecule prove to be inactive or only weakly active in the screening tests routinely used to characterize the actions of classical agents, then either the compound has little potential for success or the tests are not appropriate to the type of compound under investigation.

The clinic is the final arbiter of this dilemma; only after clinical trials have supported or disproven preclinical predictions of therapeutic activity can the distinction between inactive compound and inappropriate test be made. However, broad clinical screening of compounds would be both impractical and inappropriate. The combination of rational design, targeted biochemical and behavioral screening, and appropriately planned pharmacological studies that has contributed to the development of atypical antidepressants and anxiolytics is described in the case histories to follow.

2. Antidepressants

2.1. An Atypical Antidepressant: Trazodone

Trazodone (Desyrel®) was the first nontricyclic antidepressant to be registered for use in the United States. The complete story of trazodone’s discovery has been reviewed previously (Silvestrini et al., 1981). Clinical trials have consistently shown trazodone to be an effective antidepressant when compared to placebo and at least as effective as the tricyclic antidepressants (TCA) in treating a variety of depressive disorders (for a review, see Bryant and Ereshefsky, 1982). Moreover, clinical reports suggested it might possess a rapid onset of action (3–7 d; Kellems et al., 1979) in a wide range of subtypes of depression (for a review, see Georgotas et al., 1982). In contrast to the TCAs, trazodone represents a major therapeutic step forward in its elimination of anticholinergic side