INTRODUCTION

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Advancing the Treatment of Mood and Anxiety Disorders: The First 10 Years' Experience with Paroxetine

By Charles B. Nemeroff, MD, PhD

The last half of the 20th century witnessed remarkable advances in the field of psychiatry that began with serendipity and were realized through the combined efforts of astute clinical observation, scientific investigation, and patient advocacy. The modern era of psychopharmacology of mood disorders began in the late 1940s with John Cade's discovery of the mood-stabilizing properties of lithium.[1] Less than 5 years later came the unexpected observation of elevated mood and activation among patients on a tuberculosis ward who were treated with the antitubercular agent, iproniazid. Subsequent clinical trials led to the widespread, but short-lived, use of iproniazid for treatment of depression in 1957 and demonstration of its monoamine oxidase inhibitor properties.[2]

At about the same time that iproniazid was first used in the clinic, Robert Kuhn tested the tricyclic compound, imipramine, for effectiveness as an antipsychotic agent. Although imipramine failed as an antipsychotic, it did exert marked mood-elevating effects in patients with depression.[3] Later studies demonstrated that imipramine and related compounds blocked neuronal reuptake of norepinephrine and serotonin, resulting in increased concentrations of these neurotransmitters in the synapse. The work of Arvid Carlsson and others in the 1960s gave credence to the notion that serotonin was a pivotal neurotransmitter in the physiology of mood[4] and prompted drug-discovery programs to search for compounds with potent and selective inhibition of serotonin reuptake.

These milestones mark the birth nearly 50 years ago of the monoamine theory of depression and sowed the seeds for the eventual use of evidence-based psychopharmacologic treatment approaches for mood disorders. Coincident with the burgeoning field of psychopharmacology were 2 major advances: one in the domain of patient advocacy, the other in neuroscience. The medical community and general public were made aware of the problem of depression in the early 1990s with the "Decade of the Brain" campaign of the National Institute of Mental Health, which sought to educate about major depression and reduce the stigma associated

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with mental illness.[5] The remarkable advances in the field of neuroscience were rapidly applied to psychiatry and psychopharmacology.

As a result of concerted drug-discovery efforts by the pharmaceutical industry that began in the 1970s, the first SSRI (selective serotonin reuptake inhibitor), fluoxetine, was identified[6] and brought to market in the late 1980s. Paroxetine was identified as a compound with serotonin (5-HT) reuptake activity in the late 1970s,[7] and after extensive preclinical and clinical study, was approved in the United States in 1993 for the treatment of major depression. Paroxetine subsequently was approved for use in the treatment of obsessive-compulsive disorder and panic disorder in 1996, for social anxiety disorder in 1999, and for generalized anxiety disorder and posttraumatic stress disorder in 2001.

Soon after they became available for clinical use, the SSRIs gained notoriety for a variety of reasons and became household words for patients and physicians alike. Because of their efficacy, tolerability, and safety in overdose, the SSRIs were soon firmly established as first-line agents replacing the tricyclic antidepressants in the treatment of depression. By 1994, the SSRIs were the most widely prescribed class of drugs in the United States. Interest in the SSRIs, including paroxetine, from the clinical and research communities was intense, and a large number of controlled clinical trials with paroxetine were conducted, generating a large and comprehensive body of published literature. Contributions to the literature and to patient care include the use of radiolabeled paroxetine in the laboratory as a ligand for the serotonin transporter and in the clinic as treatment for a wide range of mood and anxiety disorders. Recently, paroxetine has been reformulated into a controlled-release formulation, which preserves the efficacy of the original compound and improves its tolerability profile. In this supplement to *Psychopharmacology Bulletin*, leading experts in the fields of psychiatry, pharmacokinetics, and neuropsychopharmacology comprehensively review the first 10 years of experience with paroxetine and paroxetine CR. Their contributions summarize a vast literature and suggest future directions. Preparation of these contributions was supported by an unrestricted educational grant from GlaxoSmithKline.

REFERENCES

1. Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Austr*. 1949;2:349-352.
2. Kline NS. Clinical experience with iproniazid (Marsilid). *J Clin Exp Psychopathol*. 1958;19(suppl 1):72-78.
3. Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). *Am J Psychiatry*. 1958;115:459-464.
4. Carlsson A. Transport of biological amines as an element of drug action. *Protoplasma*. 1967;63:123-125.
5. Judd LL. The decade of the brain: prospects and challenges for NIMH. *Neuropsychopharmacology*. 1990;3:309-310.
6. Wong DT, Horng JS, Bymaster KL, Hauser KL, Molloy BB. A selective inhibition of serotonin uptake: Lilly 110140, 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropanolamine. *Life Sci*. 1974;15:471-479.
7. Petersen EN, Bechgaard E, Sortwell RJ, Wetterberg L. Potent depletion of 5HT from monkey whole blood by a new 5HT uptake inhibitor, paroxetine (FG 7051). *Eur J Pharmacol*. 1978;52:115-119.