Annals of Clinical Psychiatry, 17[3]:109–111, 2005

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230591001986

Guest Editorial: Celebrating the 50TH Anniversary of the Introduction of Chlorpromazine in North America and the Advent of the Psychopharmacology Revolution

VINOD S. BHATARA, MD, MS, MSHS

Professor, Departments of Psychiatry and Family Medicine, University of South Dakota School of Medicine, Sioux Falls, SD, USA

FRANCISCO LÓPEZ-MUÑOZ, MD, PHD

Department of Pharmacology, University of Alcalá, Madrid, Spain

SANJAY GUPTA, MD

Chairman, Department of Psychiatry, Olean General Hospital, Olean, NY, Clinical Professor, Departments of Psychiatry, SUNY at Buffalo, NY and Syracuse Medical, University, Syracuse, NY, USA

Chlorpromazine, the first antipsychotic drug, was introduced in the period from 1952 to 1955 (1,2). The discovery of the neuroleptic properties of chlorpromazine was an event fundamental to the practice of psychiatry, marking the advent of the so-called "psychopharmacology revolution," and is one that should be remembered. This Special Section on the history of antipsychotic drugs celebrates the 50th anniversary of the beginning of this revolution that still continues today (2,3).

This Special Section consists of four papers. The first paper, by López-Muñoz and colleagues, discusses the synthesis and usage of chlorpromazine for the target symptoms of psychosis (2). The success of chlorpromazine led to proliferation of similar drugs belonging to the antipsychotic class. Haloperidol was the most popular antipsychotic before the introduction of the second-generation antipsychotic drugs. An interesting article by Granger and Albu narrates the "story" of the synthesis and discovery of haloperidol (4). The availability of antipsychotic drugs has been highly beneficial to society, as it has substantially improved health outcomes, enabled deinstitutionalization and reduced the stigma associated with schizophrenia. There has also been a reduction in treatment costs, and improved quality of life for patients with schizophrenia. Providing a social context, Kirkby examines the health consequences of the revolution associated with the availability of antipsychotic drugs from a societal perspective (3). Finally, Aparasu et al. (5) examine the U.S. national trends in the outpatient use of antipsychotic agents. They report that the 1990s shift from first-generation antipsychotic drugs to second-generation drugs has persisted into the 21st century.

Address correspondence to Dr. Bhatara, 2601 W. Nicole Drive, Sioux Falls, SD 57105 USA. E-mail: Abhatara@aol.com

RECENT HISTORY: FIRST-TO-SECOND GENERATION SHIFT

To better understand the shift from the first-to-second generation agents, it is useful to set some historical perspective. Although the first-generation antipsychotic drugs had an unrivalled role as the cornerstone in the management of schizophrenia and other psychoses until the 1990s, their use was limited by a range of side effects, including extrapyramidal symptoms, problems in subjective tolerance, negative impact on the quality of life and daily functioning, and the development of tardive dyskinesia (6). There is an emerging expert consensus that the second-generation antipsychotic drugs (other than clozapine) may be preferred over first-generation drugs as first-line drugs (7). This is because the newer drugs are better tolerated, comparable in treating positive symptoms, and comparable or better in treating negative symptoms of schizophrenia. Further, the newer drugs are less likely to cause

tardive dyskinesia. There are also indications that the use of second-generation agents may be associated with improved treatment adherence and better quality of life (8). Despite the expert consensus, this growth in the use of second-generation agents is not unambiguously supported by the available safety and efficacy data (5–8). Hence, research studies (particularly those focusing on effectiveness and not on efficacy) on the second-generation agents are urgently needed to support burgeoning clinical use of these agents (5).

EXPANDING USE OF ANTIPSYCHOTIC DRUGS

Another recent trend to note is that nearly one-half of antipsychotic use is off-label now (5). Excellent reviews already exist on the off-label use of antipsychotics and we do not intend to duplicate previous efforts (8,9). From a historical perspective, there has always been considerable confusion about the possible multiple and varied uses of antipsychotic drugs. The discovery of chlorpromazine was a milestone because this drug proved to have hitherto unique pharmacological properties, including effectiveness in ameliorating the psychotic type of target symptoms. However, chlorpromazine was noted to have a broad spectrum of clinical effectiveness. In fact, its European commercial name, Largactil ("*large*" = broad; "*acti**" = activity), was intended to reflect its wide spectrum of activities; such as gangliolytic, adrenolytic, antifibrillatory, antiedema, antipyretic, anti-shock, anticonvulsant, and antiemetic properties. It is not surprising that the availability of more tolerable antipsychotic drugs has expanded the possible indications for their use (9). Although much off-label use of antipsychotic drugs (e.g., pervasive developmental disorder, bipolar disorder and Tourette's syndrome) is not supported by rigorous scientific data, expert consensuses based on limited evidence are available and are useful (8,9).

SECOND-GENERATION ANTIPSYCHOTIC DRUGS AND UNMET NEEDS IN CLINICAL PSYCHIATRY

The second-generation antipsychotic drugs have been available for a while now, some being used for about a decade. Following the development and success of clozapine in treating refractory patients, a host of other agents has been developed and approved for use in schizophrenia and some in bipolar disorder. The aim was to have drugs with the success of clozapine but without the same side-effect profile. More than a decade later we have a slew of second-generation agents. Yet, questions remain about their added value. First, second-generation agents are considerably more expensive than first-generation agents. Second, clinicians often prescribe drugs in chronic diseases, such as diabetes, with the expectation that the individual will be able to lead a productive life despite disease limitations. However, it appears that the newer drugs (with the exception of clozapine) are not clearly superior to older agents in efficacy. Despite the promises of improved cognition, it appears that the level of cognitive improvement is not sufficient for the majority of the patients to reach a productive level competitively.

Third, although second-generation antipsychotic agents are safer with regard to the risk of extrapyramidal symptoms and tardive dyskinesia, many carry the burden of metabolic side effects as well as related medical problems. It is now necessary for clinicians to assess the low risk of tardive dyskinesia on the one hand versus the metabolic side effects and their interrelated problems on the other. Finally, clinicians must consider the added cost to the exchequer (both the cost of the drug as well as treatment of problems such as diabetes, hypertension, dyslipidemias and related problems) and make an informed overall treatment decision to prescribe an antipsychotic agent to a patient with schizophrenia (10). Long-term controlled studies on the second-generation drugs are lacking. It is hoped that the future trials will provide practical data on the long-term safety and effectiveness of these newer drugs.

By Way of Reflection

The progress made in the psychopharmacology of schizophrenia in the last 50 years, which began with chlorpromazine and reserpine and continued with the atypical antipsychotics, while not definitive, has been of enormous importance. The psychoactive drugs that became available half a century ago allowed the treatment of the some of the most severe forms of mental disorders, improved the quality of scientific methodology in clinical research (e.g., objective measurement instruments), highlighted the need for a new nosology, and made possible the development, from neurobiochemical perspectives, of new etiopathogenic theories of psychiatric disorders, in general, and of schizophrenia, in particular. Moreover, the "psychopharmacology revolution" made possible new patterns of psychiatric attention, reducing the number of patients admitted to institutions and the length of hospital stays. Likewise, the introduction of these psychoactive drugs led to better use and acceptance of psychotherapeutic measures and of medication itself by patients, and this has facilitated the fulfilment of therapy, reducing the rate of relapses and helping to improve their quality of life.

Nevertheless, we are well aware that there are still problems associated with the treatment of these patients, and that future perspectives in the psychopharmacology of schizophrenia involve the development of more effective drugs that improve the clinical condition of a greater percentage of patients, that act on disorders resistant to therapy, that are more specific in their actions, and that are free of undesirable effects. Despite limitations, researchers have worked intensively to develop new chemical families (with extra-dopaminergic and extra-serotonergic mechanisms) for use in the treatment of schizophrenia, that may offer promising results (NMDA receptor agonists, glutamate release inhibitors, glycine uptake inhibitors,

muscarinic agonists, omega-3 fatty acids, proteinkinase C inhibitors, etc.) (11–13). So then, the great pharmacological contribution to the treatment of these patients is undoubtedly still to come.

REFERENCES

1. Wilkaitis J, Mulvihill T, Nasrallah H: Classic antipsychotic medications. In: Schatzberg A, Nemeroff C eds. *American Psychiatric Association Textbook of Psychopharmacology, 3rd edition.* Washington, DC: APA 2004:425–441
2. López-Muñoz F, Alamo C, Shen W.W, Clervoy P, Rubio G, Cuenca E: History of the discovery and clinical introduction of chlorpromazine. *Annals of Clinical Psychiatry* 17(3)
3. Kirkby KC: Social context and health consequences of the antipsychotics introduction. *Annals of Clinical Psychiatry* 17(3)
4. Granger B, Albu S: The haloperidol story. *Annals of Clinical Psychiatry* 17(3)
5. Aparasu RR, Bhatara VS, Gupta S: U.S. national trends in the use of antipsychotics during office visits. *Annals of Clinical Psychiatry* 1998–2002; 17(3)
6. Awad AG, Voruganti LN: New antipsychotics, compliance, quality of life, and subjective tolerability-are patients better off? *Can J Psychiatry* 2004; 49:297–302
7. Miller AL, Hall CS, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, Ereshefsky L, Essock SM, Finnerty M, Marder SR, Miller del D, McEvoy JP, Rush AJ, Saeed SA, Schooler NR, Shon SP, Stroup S, Tarin-Godoy B: The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry* 2004; 65:500–508
8. Fountoulakis KN, Nimatoudis I, Iacovides A, Kaprinis G: Off-label indications for atypical antipsychotics: A systematic review. *Ann Gen Hosp Psychiatry* 2004; 3:4–13
9. Alexopoulos G, Streim J, Carpenter D, Docherty J: The expert consensus panel for using antipsychotic agents in older patients—Introduction: methods, commentary, and summary. *J Clin Psychiatry* 2004; 65(suppl 2):1–105
10. Lehman A, Kreyenbuhl J, Buchanan R, Dickerson F, Dixon L, Goldberg R, Green-Paden L, Tenhula W, Boerescu D, Tek C, Sandson N, Steinwachs D: The schizophrenia outcomes research team (PORT): Updated treatment recommendations 2003. *Schizophrenia Bull* 2004; 30:193–217
11. Fleischhacker WW: New developments in the pharmacology of schizophrenia. *J Neural Transm Suppl* 2003; 64:105–117
12. Kane JM, Malhotra A: The future of pharmacotherapy for schizophrenia. *World Psychiatr* 2003; 2:81–86
13. Coyle JT: The demise of old certitudes and the birth of novel opportunities in neuropsychopharmacology. *Curr Opin Pharmacol* 2004; 4:1–3