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lithium

CONTROVERSIES AND UNRESOLVED ISSUES

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INTRODUCTION

Nathan S. Kline

Director of Research, Rockland Research Institute, Orangeburg, New York, and Clinical Professor, Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, U.S.A.

In the summer of 1978, almost 30 years after lithium was first introduced into psychiatric treatment, a large scale international meeting was held to review the subject in depth. The full five days had to be scheduled to include both the relevant topics and the 60 relevant investigators. Concern was expressed that a five-day meeting held in the center of New York City would be subject to seepage and erosion since the customary time was two and one-half days. The organizers were adamant in their insistence that a shorter time would be unacceptable.

The participants were invited with the clear understanding that they would be present for the entire five days. The exceptions granted were to the nephrologists for whom most of the sessions were not relevant and to Dr. Tosteson who, as Dean of the Harvard Medical School, was permitted to go back to Boston for graduation ceremonies. With very few other exceptions, all the participants were present for all the sessions.

The meeting was closed not only to the general public but to the medical and psychiatric "public" as well. The purpose of this was to keep the group small and intimate enough to encourage as much communication as possible between those having expertise in different aspects of the problem. No publicity was given to the meeting and reporters from two medical publications who heard about the event were firmly but politely refused admission. Among other reasons for so doing was that we felt reporters might inhibit the discussions. One of them was quite indignant and threatened to "take action" because a few of the participants from the National Institute of Mental Health were "being paid with his tax dollars."

The present volume more than adequately justifies the time and effort of the participants. Incidentally, all of the discussion was recorded. We have reviewed it and included those parts which are not covered in the formal papers.

Those who worked with lithium -- and, for that matter, other psychopharmaceuticals -- some quarter of a century ago were quite hardy and independent-minded investigators and clinicians. They were tough enough to

buck the psychodynamic tide which in some countries threatened to inundate psychiatry. Their fortitude and resilience is evidenced by their ability to change psychiatry -- and by their high survival rate.

Gershon, Kline and Schou were responsible for the selection of the participants. Heinz Lehmann served as general consultant. Tom Cooper competently carried the heavy burden of secretary and general director. In addition to reporting our own research (lithium in the management of alcoholism), I served as overall organizer and "producer." Excerpta Medica arranged the practical aspects of the meeting which, in turn, was underwritten by SmithKline Corporation. The meeting was officially sponsored by the National Institute of Mental Health, New York University College of Medicine and the Rockland Research Institute of the New York State Office of Mental Health.

Most of us respond up to the level of our audience. And here was an audience of most of the world's best informed psychopharmacologists and clinicians in the area of lithium research. They dealt not only with the conventional and accepted, but with the unresolved issues and controversies. Because the group was knowledgeable, critical and curious, the presentations were unusually concise, clearly stated and often provocative. The free-ranging discussions led at times to a clash of opinion and information. Some problems that might have dragged on in the literature for years were resolved. Insights sparked by the unfamiliar and original led to the recognition of new and more relevant questions to be answered.

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CLINICAL USES OF LITHIUM - PART I: INTRODUCTION

Robert F. Prien

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This session will critically evaluate the clinical use of lithium in primary affective disorders, schizophrenia, and schizoaffective illness; mood and behavior disorders in children and adolescents; drug abuse; and psychosomatic disorders. The following session will focus on the use of lithium in other psychiatric disorders.

This paper will present an overview of the session topics. The topics will be discussed in more detail by the panelists Dr. Gershon, Dr. Lena, Dr. Mendels, Dr. Rifkin, and Dr. vanKammen.

USE IN PRIMARY AFFECTIVE DISORDERS

Long-Term Maintenance Therapy

It is appropriate to initiate the session on clinical use of lithium with a discussion of the effectiveness of long-term maintenance therapy with lithium for recurrent affective illness. The use of lithium maintenance treatment to prevent or attenuate recurrences of mania and depression has been described as one of the most important advances in psychiatric therapeutics (1). It has also been one of the most controversial. The "prophylatic" use of lithium had its origin in the late 1950s and early 1960s when several investigators reported that maintenance doses of lithium were effective in preventing recurrence of both depressive and manic episodes in patients with a history of frequent attacks (2-5). However, it was not until 1967 that long-term maintenance treatment with lithium attracted widespread attention. Baastrup and Schou conducted a large scale study comparing course of illness before lithium therapy against course of illness during lithium therapy and concluded that "lithium is the first drug demonstrated as a clear-cut prophylactic agent against one of the major psychoses" (6). This report prompted well-publicized rebuttals (7,8) and generated questions and controversies that have not been completely resolved.

Two diagnostic classifications have assumed prominent roles in the evaluation of long-term maintenance lithium treatment. These are the primary versus secondary classification and bipolar versus unipolar classification. Most of the studies on maintenance lithium

therapy are limited to patients with primary affective illness. As described by Robins and Guze (9), a primary affective illness is an affective disorder occurring in a patient who has no preexisting nonaffective psychiatric illness. Secondary affective illness is defined as a disorder occurring in a patient who has a preexisting psychiatric illness other than depression or mania.

The majority of maintenance lithium trials are analyzed in terms of the bipolar-unipolar dichotomy. This classification separates depressed patients with a history of mania (bipolar) from those with a history of only recurrent depression (unipolar). Occasionally, patients with recurrent mania and no history of depression are characterized as unipolar manic (10), although this usage is rarely employed in lithium studies. The bipolar classification has been further refined to included a second group, labeled bipolar II, consisting of patients who have a history of hypomanic episodes and depression but no history of mania.

The literature on long-term maintenance lithium therapy has been independently reviewed by two important committees in the United States - the Neuropsychopharmacology Advisory Committee to the Food and Drug Administration (FDA) and the American Psychiatric Association (APA) Task Force on Lithium Therapy. Both concluded that lithium has demonstrated superior efficacy over placebo in the treatment of bipolar recurrent affective illness. The FDA Advisory Committee's conclusion was made part of the revised Lithium Carbonate Package Insert (11), issued in 1974, which approved the use of lithium for the long-term maintenance treatment of bipolar affective illness. The insert states that maintenance therapy with lithium carbonate "prevents or diminished the intensity of subsequent episodes in those manic-depressive patients with a history of mania" (i.e., bipolar patients). The APA Task Force Report on Lithium Therapy (12), published in 1975, concurs with the FDA's position that lithium is effective in preventing or attenuating recurrences in bipolar illness.

There is no provision in the package insert for the long-term maintenance treatment of unipolar affective illness. Both the FDA Advisory Committee and the APA Task Force concluded that, although there is evidence that lithium is effective in unipolar recurrent affective illness, there is need for further evaluation of the drug's use in this disorder. In 1976, the FDA Advisory Committee reexamined the issue of lithium's effectiveness in unipolar illness and concluded that there was still insufficient evidence to warrant change in the approved indications for lithium therapy (13).

The FDA Advisory Committee and APA Task Force cited two reasons for failing to recommend use of lithium for the long-term maintenance treatment of unipolar illness. First, evidence for lithium's effectiveness in the dis-