True and Apparent Side Effects
in a Controlled Trial of Chlorpromazine and Imipramine
in Depression

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Received September 10, 1971; Final Version March 20, 1974

Abstract. Five hundred and fifty-five acutely depressed patients receiving chlorpromazine and imipramine, were studied to determine the incidence and severity of drug-related side effects. The ability of clinicians to distinguish between drug-related side effects and symptoms considered natural to the depressive illnesses was also investigated. The results indicated that side effects were minimal for both active drug groups and that among the dropouts for serious side effects (31 cases) the majority were receiving chlorpromazine. Skin rash and hypotension were the most frequent reasons cited for side effect terminations from the study.

It appeared that clinicians were generally able to distinguish drug-related side effects from symptoms usually associated with depression. There was some indication, however, that they tended to rate as non-medication related, certain symptoms which were actually drug-induced. The latter included muscle rigidity, edema, and dry mouth on chlorpromazine and tremulousness on imipramine.

Key words: Depression — Chlorpromazine — Imipramine — Side effects.

One of the major problems in evaluating side effects is that of distinguishing between drug-produced side effects and symptoms commonly associated with the illness being treated. This is a particular problem in the depressive illnesses where symptoms such as dry mouth and constipation often occur as natural accompaniments of depression and are also prominent side effects of some of the antidepressant drugs. Busfield, Schneller, and Capra (1962) have suggested that one way to minimize the error of overincluding symptoms native to the illness as though they were side effects is to distinguish between “true” and “apparent” side effects. According to Busfield, et al. (1962) an “apparent” side-effect is any somatic complaint or clinical sign that was present prior to treatment and persisted during treatment. A “true” side-effect, on the other hand, is a symptom not present prior to treatment but one that appeared after treatment was instigated. These authors concluded that true side effects are found much less frequently than is usually reported in the literature.

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There is also a reverse problem these authors did not address. This is the clinician's astuteness in identifying "true" side effects when they appear and of accurately tying them to the drugs being administered.

This study is part of a larger National Institute of Mental Health (NIMH) collaborative study that compared the efficacy of chlorpromazine, imipramine and a placebo in hospitalized depressed patients. (Raskin, Schulerbrandt, Reatig, McKeon, 1970). The present study had three major aims. First, to document the incidence and severity of drug-induced side effects; second, to extend Busfield's findings by establishing the frequency of true and apparent effects for the reported symptoms or observed signs on our side effects checklist; third, to see how well clinicians were able to distinguish drug-induced side effects from other somatic complaints which are generally considered symptoms of a depressive illness.

Methods

Patients. The study sample consisted of 555 newly hospitalized patients drawn from the psychiatric populations of two large metropolitan receiving hospitals¹, four state hospitals² and four private institutions³. There were 395 females and 160 males. Forty-one percent of the sample were diagnosed as psychotic depressions (mainly psychotic depressive reaction) and 45% were diagnosed as neurotic depressions (mainly depressive reaction). The remaining patients were diagnosed as schizophrenics (mainly schizo-affective type). The median age was 42 years and the typical patient had attended but did not complete high school. Eighty-five percent of the males and 89% of the females were, or had been married.

A diagnosis of depression was not a requirement for inclusion in the study. Patients being considered for the study were rated by clinicians on three, five-point intensity scales which measured depression in verbal report, behaviour and historical or secondary symptoms of depression. To be accepted into the study, a patient had to obtain a total score of at least nine on the three scales which was equivalent to a moderate amount of depression.

Medication Schedule. At the end of three to four days in the hospital, during which no drugs were administered except chloral hydrate for sleep when necessary, patients were randomly assigned to one of three treatment groups. One hundred and seventy-five patients received chlorpromazine, 201 imipramine and 179 an inert placebo. Chlorpromazine and imipramine were increased in daily step increments to a dosage level of 600 mg/day of chlorpromazine and 300 mg/day of imipramine by the patient's sixth day in the study. Patients were maintained on these dosage levels until the thirtieth day in the study. Between the seventh and thirtieth day the physician had the option of raising the daily dosage level of chlorpromazine

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