Time Course of Antipsychotic Effects of Neuroleptic Drugs

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The authors reviewed relevant studies in an attempt to define the onset and time course of antipsychotic effects of neuroleptic drugs. After excluding open trials, studies of chronically psychotic patients, and studies not using a placebo or nonneuroleptic sedative as a control, they found only five reports suitable for analysis. Among these, the degree of patients' improvement during neuroleptic treatment was similar regardless of the duration of the study. Also, in studies comparing neuroleptics with sedatives, similar improvement was observed with both treatments. Although neuroleptic drugs have been used clinically for 35 years, the timing of their specific therapeutic effects remains unclear.
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The introduction in the early 1950s of medicines with antipsychotic properties revolutionized the practice and theory of psychiatry (1). The efficacy of neuroleptics in the treatment of psychoses, both functional and organic, has been established beyond doubt (1, 2). However, after more than 35 years of use of these drugs and research into their action, many basic issues concerning their clinical pharmacologic properties remain obscure (3). Among these uncertainties is the time course of patients' response to these agents (3).

Although there are many reports describing relationships between neuroleptic dose, route of administration, and the onset of antipsychotic effects, relatively few of these studies have been controlled (3). Since the symptoms of psychosis are variable, may respond to environmental factors, or may decrease or remit spontaneously (4), only controlled studies can provide interpretable data on the specific antipsychotic effects of neuroleptic drugs.

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We reviewed controlled studies in an attempt to determine the onset and time course of the antipsychotic effects of neuroleptics. Knowledge of the course of such effects would be of potential value not only in establishing rational guidelines for clinical treatment but also in designing and interpreting studies on the pharmacologic actions of these drugs.

METHOD

We examined published studies of the efficacy of antipsychotic agents in controlled trials. Access to this large body of literature was facilitated by the use of two extensive bibliographies on the subject (5, 6) augmented by a computer-assisted literature search of the National Library of Medicine's MEDLINE file through 1986. This process yielded more than 1,300 citations.

We selected for further review reports in which patients with acute psychotic episodes or acute exacerbation of chronic psychosis were randomly assigned to treatment with a neuroleptic and either an inactive placebo or a nonneuroleptic sedative. Most studies were open trials and therefore were excluded from analysis. We excluded 18 studies in which antipsychotic agents were administered to stable, chronically ill patients, because there are inherent difficulties in rating the degree of improvement of such patients and because many such patients respond only minimally to treatment (1). Also, we excluded studies comparing the efficacy of two or more different neuroleptic regimens unless a placebo or a sedative was used as a control, because such designs do not allow the separation of nonspecific (e.g., spontaneous, placebo, or sedative) and specific (antipsychotic) effects. By applying these criteria, we excluded a number of important studies from our analysis. For example, three National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group reports (7–9), which were designed to assess the efficacy of antipsychotic drugs (7), identify predictors of response (9), and compare treatment with high and low doses (8), were not included because of the absence of time course data. These important studies did, however, document the superiority of antipsychotic drugs over sedatives and placebo after 6 weeks of treatment (7, 9). Other important studies by Casey et al. (10, 11) were excluded

TABLE 1. Data From Five Controlled Studies of Time Course of Neuroleptic Effects in Acutely Psychotic Patients

Study	N	Diagnosis	Treatment	Mean Neuroleptic Dose (mg/day)	Outcome Measure	Length of Treatment (days)
Abse et al. (16)	30	Acute psychosis	Chlorpromazine, opium, or placebo	Chlorpromazine, 329 p.o.	Nurses' ratings of ward behavior	21
Reschke (17)	50	Acute psychosis	Haloperidol, chlorpromazine, or placebo	Haloperidol, 8.7 i.m.; chlorpromazine, 100 i.m.	Target symptom severity scale	0.08
Schooler et al. (18)	24	Acute schizophrenia (RDC)	Chlorpromazine or placebo	Chlorpromazine, 900 p.o.	Psychiatrist's global severity rating	21
Johnstone et al. (19)	45	Acute schizophrenia (Present State Examination)	α-flupenthixol, β-flupenthixol, or placebo (and chlorpromazine as needed)	α-flupenthixol, 8 p.o.; β-flupenthixol, 8 p.o.	Rating scale for schizophrenia	28
Lerner et al. (20)	40	Acute psychosis	Haloperidol or diazepam	Haloperidol, 27.5 i.v. and p.o.	Brief Psychiatric Rating Scale	1

because chronically psychotic patients constituted the majority of the study samples. Finally, the important long-term, multimodality treatment outcome studies of May et al. (12, 13) and Hogarty et al. (14, 15) were excluded because of the lack of time course data and because a majority of the patients studied were chronically psychotic. This exclusion process left only five reports (16–20) that provided sufficient information regarding time course of antipsychotic effect to permit analysis.

Although several studies had used similar psychometric scales for rating symptomatic improvement and outcome, time course data had been assessed by different instruments in each study. Therefore, to permit standardized comparisons, we converted measures of response to percentage reductions in symptom severity, with the severity scores recorded immediately before initiation of treatment uniformly set at 100%.

RESULTS

The five controlled studies (16–20) describing the time course of antipsychotic effects in acutely psychotic patients spanned an interval from 1960 (16) to 1979 (20). They were heterogeneous in subject samples, cohort sizes, specification of diagnostic criteria, study intervals, and neuroleptic and control agents studied. Abse et al. (16) studied 30 patients exhibiting acute "excessive tension, anxiety or emotional disturbance causing severe personal discomfort or difficulties in word management." Patients were randomly assigned to treatment with chlorpromazine, 600 mg/day for 2 days, then 300 mg/day (N=7), powdered opium (N=7), or placebo (N=10)—dropouts were not accounted for—for a 21-day trial. Ratings were made on the MMPI, an anxiety checklist, and a scale for nurses' ratings of ward behavior. Reschke (17) studied 50 "severely agitated schizophrenic patients" (further criteria not specified) randomly assigned to treatment with haloperidol, 1, 2, or 5 mg i.m. every 30 minutes (N=29), chlorpromazine, 25 mg i.m. over 30 minutes (N=10), or placebo (N=11) over a 2-hour interval. A target symptom scale and the Brief Psychiatric Rating Scale (BPRS) were used to rate response. Schooler et al. (18) reported on 24 patients meeting the Research Diagnostic Criteria (RDC) for schizophrenia who were "at least 'moderately ill' on a 7-point scale of severity after a 1-week placebo washout period." Subjects were randomly assigned to chlorpromazine, increased to 1000 mg/day after 7 days (N=24), or placebo (N=9) for a total treatment period of 28 days. Clinical assessment included the Inpatient Multidimensional Psychiatric Scale, the Clinical Global Impression (CGI), the Nurses' Observation Scale for Inpatient Evaluation, and global severity ratings. In the fourth study, Johnstone et al. (19) studied the response of 45 patients with acute schizophrenia, defined by the Present State Examination (PSE), to α-flupenthixol, up to 9 mg/day (N=15), β-flupenthixol, up to 9 mg/day (N=15), or placebo (N=15). Response was measured over a period of 4 weeks by the Krawiecka rating scale for schizophrenia. Finally, Lerner et al. (20) studied 40 newly admitted, acutely psychotic patients (heterogeneous diagnoses) randomly assigned to treatment with haloperidol, 20–35 mg i.v. or p.o. (N=20), or diazepam, 30–40 mg i.v. (N=20), received over a period of 24 hours. Ratings were done using the BPRS and the CGI.

One study (17) examined improvement during the first 2 hours of acute treatment, one (20) measured improvement after 1 day, and three studies followed improvement at 3-day intervals (16) or weekly (18, 19) over 3–4 weeks (table 1).

The reported time courses of improvement are shown in figures 1 and 2. Figure 1 represents a compilation of the studies of neuroleptic versus placebo; figure 2 represents the studies of neuroleptic versus an active control drug.

The same overall degree of improvement was observed during treatment with all the agents tested within each of the markedly different time intervals studied. Furthermore, when a neuroleptic was com-

FIGURE 1. Time Course of Symptom Reduction in Acutely Psychotic Patients in Four Studies Who Were Given Neuroleptics or Placebo

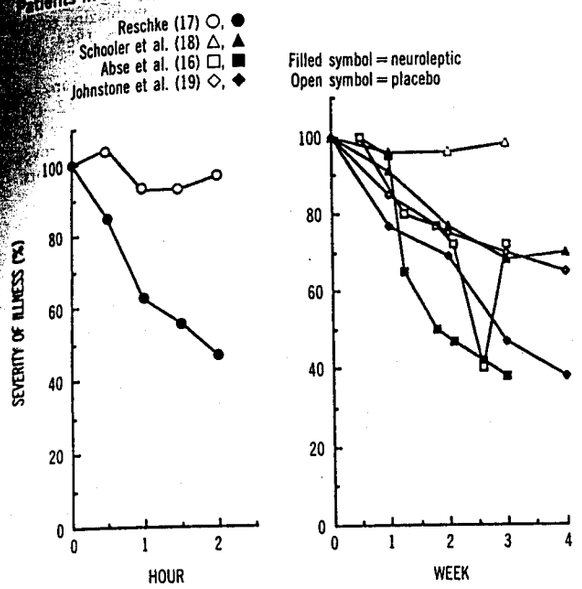
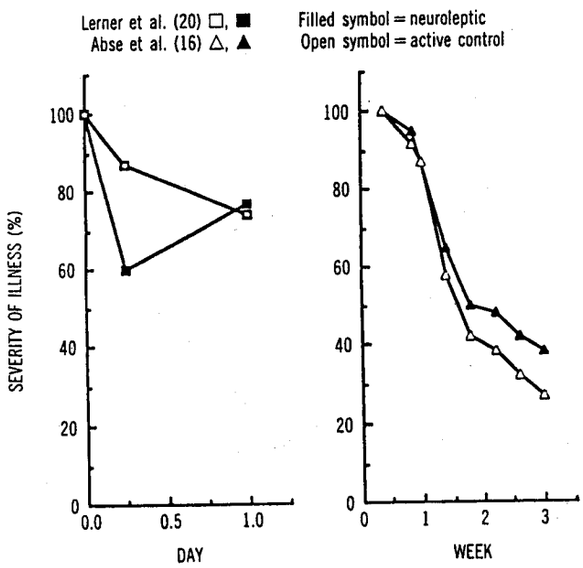


FIGURE 2. Time Course of Symptom Reduction in Acutely Psychotic Patients in Two Studies Who Were Given Neuroleptics or Active Control Drugs



pared to a sedative—diazepam (2) or opium powder (16)—the sedative demonstrated efficacy similar to that of the neuroleptic during the first day (16, 20) and through 4 weeks (20) of treatment.

DISCUSSION

It is striking that in an extensive literature search, we found only five controlled studies which yielded informative data on the onset of the antipsychotic effects of neuroleptic drugs in patients suffering acute episodes or acute exacerbation of psychosis. It is also interesting that in studies ranging in length from hours (17) to weeks (16, 18, 19), the degrees of overall response observed in the patients were quite similar. That is, short studies observed moderate improvement within hours or days, but longer studies observed little improvement in the first few days and marked improvement only over weeks of treatment. Finally, it is notable that in studies in which neuroleptics were compared to active nonneuroleptic sedative agents (16, 20), both treatments produced similar symptomatic improvement in the first days, and perhaps weeks, of treatment.

The proper interpretation of these findings is not clear. Perhaps the early effects of antipsychotic drugs are nonspecific and are largely the same as those of sedative agents. The success of placebo treatment suggests that early improvement may be largely due to the nonspecific effects of hospitalization or other clinical interventions apart from the specific therapeutic effects of prescribed pharmacologic agents (3, 20). Alternatively, it is possible that standard ratings of psychosis do not provide a reliable measure of specific antipsychotic responses. In particular, they may be heavily influenced by expectations of both observers and patients about the course of response, as suggested by the correlation we observed between the predetermined length of the studies cited and the rate at which patients were reported to improve. In that case, little can be gained by studies, such as those reviewed here, not designed to be blind with respect to time.

There are, of course, other limitations to the comparability and interpretation of the studies we examined. First, since each study used a different psychometric rating scale, it is possible that the similarity in improvement observed over widely dissimilar time intervals was an artifact of the variability in rating methods or of a tendency for ratings to regress to lower mean values in repeated assessment, regardless of the duration of a study (21). However, it seems unlikely that the substantial apparent improvement recorded on one scale within hours of treatment would not be observable on other scales if ratings reliably reflect clinical state.

Second, these findings might be attributable to differences between studies in neuroleptic dosage or route of administration. However, neuroleptics were administered at doses widely considered to be within the range for producing maximal therapeutic effects (22).

Finally, the wide variability in time course of response that we found in these studies might reflect differences in the composition of the subject samples. Since diagnostic criteria were specified in only two studies (18, 19), this possibility could not be assessed.

Whatever the limitations of the available studies, one striking conclusion remains: there appears to be no body of controlled studies with replicable results that provides convincing documentation of the onset

and characteristic time course of the antipsychotic effects of neuroleptic drugs given to patients with acute exacerbations or acute onset of psychosis. Rather, available studies are few and yield conflicting data on this subject. It is interesting that little is known about this same variable in stable, chronically psychotic patients as well (1). Thus, the main conclusion from the limited data available is that the timing and rate of development of the specific therapeutic effects of neuroleptics remain uncertain. Since this information has considerable importance in planning clinically optimal and cost-effective treatment of psychotic patients, new, well-controlled studies—especially studies with ratings performed blind to or controlling for the duration of treatment—would be worthwhile.

These findings also suggest the need for further studies designed to compare the acute response to treatment with neuroleptics and the response to treatment with nonneuroleptic sedative agents. Such studies would be particularly valuable if comparable short-term results are achieved, suggesting that lower doses of neuroleptic agents augmented by sedative agents may effectively manage acute psychosis while reducing the risk of neuroleptic-related side effects. Finally, further controlled studies designed to assess the time course and onset of antipsychotic effects would be well-suited to address the relationship between rapidity of response and long-term outcome (23).

REFERENCES

1. Baldessarini RJ: Chemotherapy in Psychiatry: Principles and Practice. Cambridge, Harvard University Press, 1985
2. Cole JO, Davis JM: Antipsychotic drugs, in The Schizophrenic Syndrome. Edited by Bellak L, Loeb L. New York, Grune & Stratton, 1969
3. Cohen BM: Neuroleptic drugs in the treatment of acute psychosis, in Psychopharmacology: Current Trends. Edited by Casey DE, Christensen AV. New York, Springer-Verlag, 1988
4. Gottschalk LA: A preliminary approach to the problems of relating the pharmacokinetics of phenothiazines to clinical response with schizophrenic patients, in Pharmacokinetics of Psychoactive Drugs: Further Studies. Edited by Gottschalk LA. New York, Spectrum, 1979
5. Klein DF, Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams & Wilkins, 1969
6. Appleton WS, Davis JM: Practical Clinical Psychopharmacology, 2nd ed. Baltimore, Williams & Wilkins, 1980
7. National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group: Phenothiazine treatment of acute schizophrenia. Arch Gen Psychiatry 1964; 10: 246–260
8. Prien RF, Cole JO: High dose chlorpromazine therapy in chronic schizophrenia. Arch Gen Psychiatry 1968; 18:482–495
9. National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group: Short-term improvement in schizophrenia: the contribution of background factors. Am J Psychiatry 1968; 124:900–909
10. Casey JF, Bennett IF, Lindley CJ, et al: Drug therapy in schizophrenia. Arch Gen Psychiatry 1960; 2:210–220
11. Casey JF, Hollister LE, Klett CJ, et al: Combined drug therapy of chronic schizophrenics. Am J Psychiatry 1961; 117:997–1003
12. May PRA, Tuma AH: Treatment of schizophrenia: an experimental study of five treatment methods. Br J Psychiatry 1965; 111:503–510
13. May PRA, Tuma AH, Yale C, et al: Schizophrenia—a follow-up study of results of treatment. Arch Gen Psychiatry 1976; 33: 481–486
14. Hogarty GE, Goldberg SC, Schooler NR: Drug and sociotherapy in the aftercare of schizophrenic patients, III: adjustment of nonrelapsed patients. Arch Gen Psychiatry 1974; 31:609–618
15. Hogarty GE, Goldberg SC, Schooler NR, et al: Drug and sociotherapy in the aftercare of schizophrenic patients, II: two-year relapse rates. Arch Gen Psychiatry 1974; 31:603–608
16. Abse DW, Dahlstrom WG, Tolley AG: Evaluation of tranquilizing drugs in the management of acute mental disturbance. Am J Psychiatry 1960; 116:973–980
17. Reschke RW: Parenteral haloperidol for rapid control of severe, disruptive symptoms of acute schizophrenia. Dis Nerv Syst 1974; 35:112–115
18. Schooler NR, Sakalis G, Chan TL, et al: Chlorpromazine metabolism and clinical response in acute schizophrenia: a preliminary report, in Pharmacokinetics of Psychoactive Drugs: Blood Levels and Clinical Response. Edited by Gottschalk LA, Merlis S. New York, Spectrum, 1976
19. Johnstone EC, Crow TJ, Frith CD, et al: Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. Lancet 1978; 1:848–851
20. Lerner Y, Lwow E, Levitin A, et al: Acute high-dose parenteral haloperidol treatment of psychosis. Am J Psychiatry 1979; 136: 1061–1064
21. Gibbons RD, Hedeker D, Davis JM: Regression toward the mean: more on the price of beer and the salaries of priests. Psychoneuroendocrinology 1987; 12:185–192
22. Baldessarini RJ, Cohen BM, Teicher MH: Significance of neuroleptic dose and plasma level in the pharmacologic treatment of psychoses. Arch Gen Psychiatry 1988; 45:79–91
23. Sakurai Y, Takahashi R, Nakahara T, et al: Prediction of response to and actual outcome of chlorpromazine treatment in schizophrenic patients. Arch Gen Psychiatry 1980; 37:1057–1062