do anticholinergics antagonize antipsychotic drug action?

The first point raised by Singh and Kay (1978) in their rejoinder to Meltzer and Stahl's (1976) criticisms of studies (Singh and Kay 1975a, 1975b, and 1975c and Singh and Smith 1973) purporting to demonstrate that anticholinergics antagonize the therapeutic effects of chlorpromazine more so than haloperidol is as follows. They maintain that the suggestion by Meltzer and Stahl of a repeated measures design "violate[s] the dictum against applying a treatment-by-subjects analysis where carry-over effects may be expected across different treatment conditions" (p. 3) and would test an inapplicable null hypothesis, i.e. that some change would take place over the three treatment periods: neuroleptics alone (period 1), neuroleptics plus anticholinergics (period 2), and neuroleptics alone (period 3). We would suggest their criticism missed the implicit but, to us, obvious point that we were proposing the use of post-hoc tests that would permit a comparison of period 1 vs. period 2, period 2 vs. period 3, and period 1 vs. period 3. The repeated measures design would be applicable to either a two-group or single-group study, but we will explain this approach by suggesting how it could have been used in the two-group study. First, it is necessary to briefly review the single-group research design of Singh and Kay (1975c). A crossover design was used in this study; subjects received 4 weeks of placebo, then 6 weeks on haloperidol or chlorpromazine, followed by 2 weeks of placebo with subsequent crossover to the other neuroleptic for 6 weeks, and finally 2 weeks of neuroleptic of choice. Three 2-week courses of benztropine were given—one in the last 2 weeks of the baseline placebo period and one each in the middle 2 weeks of the two 6-week neuroleptic periods. Combined pre- and postbenztropine periods vs. neuroleptic alone were used to test for therapeutic reversal by benztropine. Ratings from the first and fifth weeks of treatment with each neuroleptic were used to compare clinical effects of haloperidol and chlorpromazine alone. The clinical rating data were then analyzed by multiple correlated t tests.

We suggest that a split-plot, repeated measures ANOVA, as described by Kirk (1968, pp. 245-318) would have offered a more stringent test of the basic anticholinergic therapeutic reversal hypothesis as well as a number of their subsidiary conclusions, e.g., that haloperidol is superior to chlorpromazine. Table 1 outlines the two groups and study periods in our design and provides numbers for each group which will aid our discussion.

This split-plot ANOVA design incorporates two independent groups of subjects which differ only in one treatment—the neuroleptic they receive (chlorpromazine or haloperidol). The use of this design allows a test of the following effects simultaneously.

First, any differential effect due to chlorpromazine or haloperidol would be exhibited by a significant F ratio for an interaction effect or a main drug effect (chlorpromazine vs. haloperidol). If a significant F ratio for the interaction effect is obtained, then tests for simple main effects are conducted to determine if the anticholinergics, for instance, had a greater impact during the period of chlorpromazine administration than during haloperidol administration. A test for this effect is especially necessary since Singh and Kay (1975a) found a differential effect (chlorpromazine vs. haloperidol) on behavioral responses when anticholinergics were introduced. A significant interaction effect would allow a posteriori tests to be performed between the means (X1 vs. X2) or the neuroleptic plus benztropine condition (X3 vs. X4) with the appropriate nonbenztropine conditions (i.e., X3 vs. X4, X5 vs. X6). Secondly, this design would permit tests for main effects if an interaction F ratio was not significant, but main effect F ratios were. This would allow a posteriori comparisons to be made between the placebo plus benztropine condition (X1,2) or the neuroleptic plus benztropine condition (X3,4) with the appropriate nonbenztropine conditions (i.e., X1 vs. X3, X5). A posteriori tests such as Tukey's HSD test or Scheffe's ratio enable the researcher to make all planned comparisons among means and splits up the level of significance.
Table 1. Suggested split-plot ANOVA design for anticholinergic therapeutic reversal with haloperidol and chlorpromazine

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Anti-cholinergic plus placebo</th>
<th>Neuroleptic</th>
<th>Anti-cholinergic plus neuroleptic</th>
<th>Neuroleptic</th>
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<tr>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(chlorpromazine)</td>
<td>$\bar{X}_{11}$</td>
<td>$\bar{X}_{12}$</td>
<td>$\bar{X}_{13}$</td>
<td>$\bar{X}_{14}$</td>
<td>$\bar{X}_{15}$</td>
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<tr>
<td><strong>Group II</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>(haloperidol)</td>
<td>$\bar{X}_{21}$</td>
<td>$\bar{X}_{22}$</td>
<td>$\bar{X}_{23}$</td>
<td>$\bar{X}_{24}$</td>
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<td></td>
<td>$\bar{X}_1$</td>
<td>$\bar{X}_2$</td>
<td>$\bar{X}_3$</td>
<td>$\bar{X}_4$</td>
<td>$\bar{X}_5$</td>
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Note.—The means in table 1 represent the mean scores for a single behavioral parameter over the last week of the treatment period. This reduces the potential for confounding due to carryover effects from the previous treatment condition.

among the comparisons (Kirk 1968, p. 79).

Singh and Kay argue against a repeated measures ANOVA design since increasing clinical improvement with continued neuroleptic treatment can be expected, thereby resulting in a significant overall $F$ ratio. Their data, however, do not support their contention.

For instance, their graphs of anticholinergic-induced therapeutic reversal (figure 1, Singh and Kay 1975c) indicate a very slight change for such behavioral parameters as blunting of affect and thought disorganization over the 17-week period of study. Because of the high likelihood that in a small, randomly chosen group of schizophrenics there will be some nonresponders, as well as a great variation in response rate in the responders, we believe that the assumption of steadily increasing improvement over the period of study should be verified within the experimental design and not taken for granted, as Singh and Kay suggest, without proof, and without justification other than stating that such is their expectation. In any event, the averaging of the neuroleptic-alone periods before and after the neuroleptic plus benztropine period could only help test their hypothesis if they assume that the postulated benztropine-induced exacerbation of psychopathology rapidly clears. There is no evidence for or against such an assumption so it seems undesirable to introduce it into the design.

Meltzer and Stahl (1976) were next criticized by Singh and Kay for suggesting a multivariate analysis when investigating numerous dependent measures such as those employed by Singh and his colleagues in order to assess changes in psychopathology due to the introduction of anticholinergics. They argue that the various parameters of psychopathology, as measured by empirical indicators such as psychiatric ratings, do not conform to interval or ratio levels of measurement as required for the use of multivariate statistical techniques. Yet, these researchers employed correlated $t$ tests which also rest on the basic assumption of interval or ratio level data and a normally distributed sample (Wilson 1976).

Furthermore, the contention of Singh and Kay (1978) that psychiatric rating scales do not conform to, at least, interval level properties of measurement is a matter of opinion rather than fact. In general, psychiatric ratings of observed behavior must rest on the assumption that various degrees of behavior can be adequately observed (reliably and validly) and scaled along a continuum which is equidistant in psychological meaning.

Gainer and Creelman (1970, p. 61) state “... in psychological scaling, essentially all techniques are based on the acceptance of nominal ordinal properties with interval properties added by a further assumption about the statistical distribution of the scale value. And the common assumption is that psychological processes are distributed according to the normal distribution.” Therefore, one must assume that trained observers can use well-developed rating scales, such as the Brief Psychiatric Rating Scale (Overall and Gorham 1962),
and rate behaviors on an equal interval continuum, thereby yielding interval level data conformable for analysis using multivariate techniques. Thus, a choice must be made by the researcher to either assume only ordinal level properties for his rating scales and remain shackled by the use of nonparametric statistics, or he can make an inferential leap and assume interval level data from the ratings and use more fruitful multivariate statistics in the analyses of the data.

The sample sizes in the three studies in which Singh and colleagues investigated the effects of anticholinergics on behavioral response were extremely small. The first study in their series (Singh and Smith 1973) started with 10 patients and had only 8 patients available for their last treatment condition. The other two studies (Singh and Kay 1975a, 1975b, and 1975c) had N's of 18 and 20 (the latter study consisting of 2 groups of 10 each). Larger sample sizes are not impossible to obtain for psychopharmacologic research with psychiatric patients. With sample sizes as small as those employed by Singh and colleagues, the generalizability of study results is questionable. Furthermore, the investigation of a multitude of various clinical and physiological dependent measures within each of their studies, coupled with small sample sizes, brings to the forefront the problem that by chance alone, significant differences between anticholinergic conditions and neuroleptic conditions would be found for some of the dependent measures. The use of multiple correlated t tests to compare numerous means within a single experiment, without correcting the alpha level for error rate per comparison, results in a high probability of obtaining significantly different means due to chance alone (for a discussion of correction of alpha levels within an experiment, see Kirk 1968, pp. 82-86).

Thus, Singh and Smith (1973) investigated the effects of benztropine in 10 patients on various indices of psychopathology and life functions. The psychopathology measures included the Brief Psychiatric Rating Scale which contains 16 indicators of psychopathology, and a "much modified version" of the Periodic Evaluation Scale (Spitzer, Endicott, and Cohen 1969). The modifications they made are never described, but the scale as used by Singh and Smith certainly included the three scales they describe in their report. Also, "life functions" were rated in this study on over 17 separate subscales. This resulted in 10 patients being assessed on a minimum of 36 parameters within a single study.

Another study in the series (Singh and Kay 1975) assessed psychopathology on 32 dimensions along with 19 measures of neurological side effects. This resulted in 18 subjects being tested for clinical and neuroleptic change on 51 separate parameters. Singh and Kay (1975b) performed 18 correlated t tests to measure the antitherapeutic effects of benztropine against chlorpromazine or haloperidol (their table 1). Of the 18 tests, 6 tests were significant in the direction of their hypothesis. There were two measures of clinical states, however, which significantly improved with benztropine in the haloperidol-treatment phase. With such a multitude of dependent measures and small sample sizes in these studies, it would be extremely difficult not to find a statistically significant difference along some of the comparisons.

A multivariate statistic (specifically a multivariate analysis of variance [MANOVA]) is unequivocally the most appropriate model to employ when numerous behavioral parameters are assessed within a study (Tatsuoka 1971). Everitt (1975) recommends approximately 10 observations per dependent variable when performing a MANOVA. The only viable alternative which avoids the use of numerous correlated t tests would be to assess the effects of anticholinergics on one or two behavioral parameters and use the split-plot ANOVA design suggested earlier in this paper. However, we believe it would be far superior to employ a MANOVA model and use as many behavioral parameters as the sample size permits to assess the effects of anticholinergics. The large sample size would also increase the generalizability of the findings.

In further defense of their conclusions, Singh and Kay (1978) claim they combined the data from their three studies and carried out a series of chi-square tests of which 14 of 15 supposedly support the countertherapeutic claim. Here is yet another illustration of the casual way in which Singh and Kay use data to support their preconceived notions. Since the three studies differed markedly in design and execution (one open, two blind; two single groups, one double group) it would seem impossible to combine them into one analysis. We are never told how they used this mélange of data to determine if a significant countertherapeutic anticholinergic effect occurred. Further, in the analysis of their second study (Singh and Kay 1975c), they treat each measure of psychopathology as entirely independent, an absolute requirement for a chi-square analysis, whereas it is highly unlikely their measures meet this requirement since many of the measures are conceptually intercorrelated.
There are several other aspects of the research of Singh and colleagues that may have led to erroneous conclusions. Singh and Smith (1973, p. 52) state, “Suffice it to say that during the benztpine periods the ward staff attitudes deteriorated markedly and their anxiety level showed a corresponding increase.” This raises the possibility that the anxiety level and deterioration of staff attitudes, for reasons having nothing to do with benztpine, had an adverse effect on the patients’ behavior. It should be noted that this was not a blind study. In their supposed blind study (Singh and Kay 1975a and 1975c), the authors state (Singh and Kay 1975c, p. 260) that “the non-blind ward psychiatrist also participates in these (rating) interviews but his evaluations were excluded from statistical analyses.” This immediately raises the question whether the nonblind psychiatrist, the principal investigator who had organized this investigation to confirm or reject the results of his previous study, may somehow have transmitted clues to the other investigators or guided the interviews so that they produced desired results.

Meltzer and Stahl (1976) did not mention the numerous studies which have demonstrated that abrupt withdrawal of anticholinergic drugs had no salutary effect on the clinical state of schizophrenics (Ananth et al. 1970, Cahan and Parrish 1960, Ekdawi and Fowke 1966, Klett and Caffey 1972, Mandel, Claffey, and Margolis 1961, Mandel and Oliver 1961, McClelland et al. 1974, Orlov et al. 1971, St. Jean, Donald, and Bann 1964, and Stratas et al. 1963). Rather, in several of these studies, there was exacerbation of psychotic symptomatology in a few patients after withdrawal of antiparkinsonian drugs, the opposite of the prediction of the Singh and Kay studies (Mandel, Claffey, and Margolis 1961, Mandel and Oliver 1961, and Orlov et al. 1971). Mindham, Lamb, and Bradley (1977) recently found no adverse effects on psychopathology of the anticholinergic procyclidine, in comparison with placebo, in a double-blind crossover trial involving 16 chronic schizophrenics treated with fluphenazine decanoate. However, a dopamine agonist, piribidil, administered because of its supposed antiparkinsonian effects produced a variety of unpleasant effects. Gerlach et al. (1977) recently reported that a new anticholinergic, antiparkinsonian drug, G 31.406, resulted in improvement in anxiety and so-called schizophrenia score in a double-blind crossover study. They also cite several other investigations which report that antiparkinsonian drugs may enhance the antipsychotic effect of neuroleptics.

Singh and Kay (1978) suggest that we were misinformed that benztpine was the only anticholinergic they used in their studies. This is not the case. We correctly stated that benztpine was the anticholinergic employed in the Singh and Kay (1975a and 1975c) studies. Elsewhere we referred to their research with the group of anticholinergic drugs.

We are unable to detect any difference between our formulation of Singh and Kay’s theoretical position as summarized in the review by Meltzer and Stahl (1976) and Singh and Kay’s (1978) re-statement of it. Meltzer and Stahl (1976) stated that Singh and Kay believed that the basic deficit in schizophrenia may be a relative decrease in cholinergic activity and that the capacity of neuroleptics to promote cholinergic activity may be the basis of their therapeutic effect. In their rejoinder, Singh and Kay (1978) clearly state that they believe schizophrenia is due to excessive catecholamine-induced interference with cholinergic neurons whose function is to suppress “inappropriate or biologically insignificant behaviors” (p. 4) and that neuroleptics act by blocking these catecholamine neurons, and hence increasing cholinergic activity.

Singh and Kay (1978) also confuse the reader by citing evidence that benztpine does not increase dopamine turnover. Meltzer and Stahl (1976) made no comment about the effect of benztpine or other anticholinergics on dopamine turnover. Unequivocal evidence was cited that benztpine promotes dopamine release and blocks dopamine uptake and that this property is not shared by other anticholinergics. These facts do make it unwise to use benztpine in clinical studies of the type conducted by Singh and Kay since it is difficult to sort out the dopaminergic and anticholinergic effects of this drug.

McGeer and McGeer (1977) recently reported that choline acetyltransferase (CAT), the enzyme which synthesizes acetylcholine, was significantly increased in the caudate, putamen, nucleus accumbens, and hippocampus of 11 schizophrenic brains compared to 18 control brains. They rejected the possibility that this was due to postmortem changes or prior drug treatment and proposed it might be compensatory to a defect in cholinergic receptor sites. They proposed that schizophrenics might have a functional defect in cholinergic activity and that the function of neuroleptics is to reduce dopaminergic activity and restore the dopaminergic-cholinergic balance. This hypothesis is consistent with that of Singh and Kay. However, Domino, Krause, and
Bowers (1973) found normal CAT activity in the caudate, hippocampus, two cortical areas, posterior thalamus, hypothalamus, septal area, cerebellum, pons, medullary reticular formation, and cingulate gyrus of six chronic schizophrenics. They did find increased CAT activity in the medial amygdala, which McGeer and McGeer (1977) did not. Further, it is pure speculation by McGeer and McGeer (1977) that the increased CAT activity they found is compensatory to decreased cholinergic activity. If it is a valid finding, it might just as well be a primary abnormality and help explain why anticholinergics sometimes are therapeutically effective. It could also be compensatory to increased dopaminergic activity, an effort to restore a dopaminergic-cholinergic balance in the face of sustained increases in dopaminergic activity. As such, pharmacologic efforts to reduce cholinergic activity by anticholinergic drugs without reducing dopaminergic activity would be expected to have adverse consequences. There is evidence from recent reports of the use of anticholinergic drugs by schizophrenic patients in order to intensify psychotic symptoms, consistent with this proposal (MacVicar 1977). Simultaneous reduction of dopaminergic and cholinergic activity would also be expected to be useful in the treatment of schizophrenia in this view. We have cited some evidence for this previously. Given the presumptive heterogeneity of the schizophrenic syndrome and the likelihood of a multiplicity of relationships between dopaminergic and cholinergic balance based upon individual capacities for adaptive regulation, it is easy to see how a variety of outcomes might be expected from comparable manipulations of dopaminergic and cholinergic activity. This could contribute to the occasional schizophrenic who worsens with antipsychotic drug treatment. The McGeer and McGeer hypothesis is useful because it is testable. The number of cholinergic receptors in schizophrenic brains could be quantified as they have in Huntington's chorea (Enna, Bird, and Bennett 1976).

In the last section of their rejoinder, Singh and Kay (1978) provide their own hypothesis of the etiology of schizophrenia and, for us, an impossible-to-follow synthesis of the role of dopamine in schizophrenia or psychosis. Too little evidence for their hypothesis is cited for any meaningful response to be offered at this time. Suffice it to say we are in agreement with them that neurotransmitters other than dopamine may have an important influence on some types of schizophrenia and that dopamine may be more relevant to the psychotic state than to schizophrenia per se. However, we cannot accept their last comment that "the dopamine idea seems to be leading to a dead end in the study of schizophrenia" (p. 5). We believe the study of the role of dopamine in behavior in general and schizophrenia in particular is still in its early stages and that it remains a valuable guide to further careful clinical and basic research. We believe that Singh and Kay's therapeutic reversal hypothesis is worthy of further study and hope that they will heed our well-intentioned criticisms to design a study that can test their hypothesis, not confirm their prejudices.

Summary

The advantages of using a split-plot repeated measures analysis of variance to test the hypothesis that anticholinergics interfere with the therapeutic effects of chlorpromazine more so than haloperidol are presented. The need for large numbers of subjects and multivariate statistics in order to assess between-group differences on a large number of dependent variables and the problems associated with the use of correlated t tests without correction of the alpha level are discussed. The position that psychiatric rating scales can have ordinal properties is defended. Possible reasons why Singh and Kay appeared to find an antitherapeutic effect of anticholinergic drugs in chlorpromazine-treated patients include inadequate statistics, failure to use strictly double-blind raters, and concurrent staff problems that could have affected the patient's condition. Numerous studies reporting no change or worsening of schizophrenic patients after stopping anticholinergic drugs and clinical improvement after adding anticholinergic drugs are cited. The recent report of increased brain choline acetyltransferase activity in schizophrenics is discussed in relation to the theory of a dopaminergic cholinergic imbalance in schizophrenia.

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