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Adjunctive imipramine for a broader group of post-psychotic depressions in schizophrenia ☆

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Abstract

As an expansion of work examining the usefulness of adjunctive imipramine added to fluphenazine decanoate and benztropine in the treatment of post-psychotic depression, a previously successful and informative protocol was extended to a larger and more heterogeneous cohort of clinic and day-treatment patients. Although the benefit of the adjunctive antidepressant strategy was still observable in the total sample, as calculated by the prospectively intended data analysis, the findings were weaker than those obtained for the initial cohort. Owing to the possibility that differences between the later and earlier cohorts might account for the muted nature of the benefit, a post-hoc analysis was undertaken. This revealed that the later cohort was sicker in general and more psychotic in particular. The later cohort was also treated with lower doses of neuroleptic medication while remaining out of hospital longer, consistent with more recent treatment trends. It was also possible that the later cohort was subtly selected for more refractoriness of depression, since treatment of post-psychotic depression with adjunctive antidepressants had become more commonplace, and patients responding to this in general practice would not have gone on to be referred to the study. Thus a benefit from adjunctive antidepressant medication persists, but more remains to be learned about its character and likelihood in specific situations.

Keywords: Adjunctive medication strategy; Antidepressant medication; Neuroleptic medication; Post-psychotic depression; Schizophrenia

1. Introduction

Adjunctive antidepressant medication, added to a continuing dose of neuroleptic medication, has often been described as being useful in the treatment of depressive syndromes occurring in the course of schizophrenia (Siris, 1991, 1995). In particular, in our own previous work, the addition of adjunctive imipramine to a continuing regimen of fluphenazine decanoate and benztropine was found to be beneficial in a randomized double-blind trial versus adjunctive placebo in schizophrenic and schizoaffective patients with syndromally defined post-psychotic depressions (Siris et al., 1987). The use of combinations of antidepressants and antipsychotic agents, however, has not been universally found to be helpful for depres-

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sion occurring in the course of schizophrenia (Siris, 1991, 1995; Kramer et al., 1989; Plasky, 1991). Because our pre-existing protocol had been so informative, we expanded our initial double-blind trial of adjunctive imipramine in patients with post-psychotic depression to include a larger and more heterogeneous group of clinic and day-treatment patients who nevertheless met the same fundamental inclusion criteria. We did this to test the generalizability of our original observations of the utility of that medication combination (Siris et al., 1987, 1994), and to explore the potential boundaries of those effects.

2. Methods

As previously described (Siris et al., 1987), patients were identified who (a) met Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for schizophrenia (S) or schizoaffective disorder (SA) for their most recent episode of flagrant psychosis, (b) were currently either non-psychotic or only residually psychotic according to the RDC, and (c) concomitantly manifest a depressive syndrome consistent with the definition of post-psychotic depression (PPD) in the Appendix of DSM-IV (American Psychiatric Association, 1994). After giving informed consent following a full explanation of the study, patients were stabilized on their individually best-adjusted weekly doses of fluphenazine decanoate (FD), and received a clinical trial of benztropine (BZT), building up to a final dose of 2 mg p.o. TID which was administered for a minimum of 1 week (for most patients it was at least 3 weeks) prior to study entry. Also prior to study entry, patients were required to have a Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score of at least 12, and were required to maintain that score for at least three consecutive weekly ratings. The last HDRS rating could not be the lowest of the three for the patient to be allowed to be randomized at baseline.

Under double-blind randomized conditions, either imipramine (IMI) or placebo (PBO) was added to the patients' continuing regimens of FD and BZT. IMI was begun at 50 mg/day p.o., and raised 50 mg/day p.o. per week, until a final dose of 200 mg/day. Assessments were made at baseline, 3, and 6 weeks with selected items from the Scale for the Assessment of Depression and Schizophrenia (SADS) (Endicott and Spitzer, 1978), the Clinical Global Impression (CGI) (Guy, 1976), and Global Assessment Scale (GAS) (Endicott et al., 1976) instruments. Statistical comparisons were made by the *F*-test for interaction between treatment group and time in a repeated measures ANOVA.

3. Results

Seventy out of a combined total of 72 patients completed the trial. Two patients receiving adjunctive PBO were lost to the study, with little clinical change prior to the 6 week time point. The data involving these two patients were not included in further analyses. The demographic features of the completing population ($N=70$) are shown in Table 1. Although the mean 6 week CGI Global Improvement score for the group receiving adjunctive IMI was superior to the group receiving adjunctive PBO (3.09 ± 1.16 vs 3.31 ± 1.02), this result was not statistically significant ($p=0.366$). Fourteen out of the 38 patients (36.8%) receiving IMI were rated as substantially improved at week six (a rating of 'much improved' or 'very much improved') on the CGI Global Improvement Scale, vs only 7 out of 32 (21.8%) for the patients who received adjunctive PBO ($p=0.178$). Comparative results, between groups over time, involving items included in the RDC definition of the depressive syndrome and the GAS are shown in Table 2. A sign test of these variables favors the adjunctive IMI group with statistical significance (12 vs 2, $p=0.0129$). Table 3 describes the results for the four SADS-derived scales for depression (Endicott and Spitzer, 1978; Endicott et al., 1981), with a highly significant result favoring adjunctive IMI in the endogenous depression scale and a trend-level result favoring IMI in the depressive-associated features scale. Table 4 presents the results for SADS psychosis items involving hallucinations, delusions, and thought disorder. None of the psychosis items showed a difference between the adjunctive IMI and adjunctive PBO groups.