Adjunctive Treatments in Schizophrenia: Pharmacotherapies and Electroconvulsive Therapy

by Celeste A. Johns and James W. Thompson

Abstract

Substantial proportions of patients with schizophrenia do not achieve acceptable levels of response with antipsychotic therapy alone, which commonly leads clinicians to use additional somatic interventions. This article reviews the literature on the use of adjunctive pharmacological treatments and electroconvulsive therapy (ECT) in schizophrenia. The authors find that, despite a large volume of literature, it is difficult to draw conclusions or treatment recommendations from available data because of small sample sizes and widely divergent study designs. At present, there is little firm evidence that adding adjunctive agents to standard neuroleptics will dramatically change the somatic treatment of schizophrenia. The most promising adjunctive agents are benzodiazepines, lithium, and carbamazepine, as well as antidepressants and ECT for affective symptoms. Future inpatient research on adjunctive treatments should be multicenter studies, followed by long-term outpatient trials that assess quality-of-life issues as well as symptom relief.


Antipsychotic drugs have been the mainstay of treatment for schizophrenia for more than 40 years, and they continue to represent the primary agents of choice for most patients with schizophrenia. However, in substantial proportions of patients, symptoms persist when treated with antipsychotic therapy alone, even when that therapy involves the newer antipsychotic agents, clozapine and risperidone. Hence, clinicians commonly use additional somatic interventions, either to augment antipsychotic response or to address symptoms not typically helped by the antipsychotic agents.

This article reviews the literature on the use of adjunctive pharmacological treatments and electroconvulsive therapy (ECT) in schizophrenia. A treatment trial of an adjunctive agent is defined as an investigation of a drug or ECT administered in conjunction with a standard neuroleptic, either to diminish the core symptoms of schizophrenia or to relieve the commonly encountered ancillary symptom complexes—specifically anxiety, depression, and aggression and hostility. In addition, we also examine the efficacy of some of these therapies alone in reducing the symptoms of schizophrenia, although the use of these agents as the sole somatic intervention is not an "adjunctive" use, per se.

The review addresses these questions:

1. What is the efficacy of adjunctive somatic therapies in producing overall improvement and reducing the positive and negative symptoms of schizophrenia?
2. What is the efficacy of adjunctive somatic therapies in alleviating ancillary symptom complexes, specifically depression, anxiety, and aggression and hostility?
3. What patient characteristics predict response to adjunctive somatic therapies?

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Methods

Many hundreds of articles address adjunctive somatic treatments in schizophrenia. Computerized searches of the PSYCLIT and MEDLINE bibliographic data bases for 1966 through mid-1993 were undertaken. Key words signifying individual categories of pharmacological agents and ECT were used in conjunction with the key word “schizophrenia.” The bibliographic searches were restricted to English-language articles (with one exception) and to studies done on humans (i.e., animal model studies were excluded). In addition, an ECT data base maintained by R.D. Weiner at Duke University was searched. Key words included all reviews of ECT and ECT in combination with schizophrenia.

These searches yielded 2,394 pharmacologic and 684 ECT citations. This overwhelming volume of literature and the availability of reviews for almost every subheading led to the decision to conduct primarily a review of reviews. The quality of reviews was assessed using criteria adapted from Beaman (1991). These criteria are stringent, however, and few reviews satisfied them; in general, reviews were included if they met most criteria.

When several reviews were available on a given agent, the more recent ones were selectively chosen if they satisfactorily subsumed the earlier ones. Most reviews are confined to a single agent or class of agents. The ones we include are those by Wolkowitz and Pickar (1991) on benzodiazepines; Simhandl and Meszaros (1992) on carbamazepine; Schulz et al. (1990) on carbamazepine and lithium; McElroy et al. (1989) on valproate; Atre-Vaidya and Taylor (1989) on lithium; and Siris et al. (1978), Plasky (1991), and Siris (1991) on antidepressants. Included reviews of ECT are those by Grinspoon and Greenblatt (1963), Riddell (1963), Turek and Hanlon (1977), Erwin and Thompson (1978), Fink (1978), Weiner (1979), and Salzman (1980). ECT reviews by Taylor (1981), Small (1985), Varghese and Singh (1985), Martin (1986), and Weiner and Coffey (1988) are mentioned briefly. A few reviews are included that provide an overview of adjunctive medications for patients with schizophrenia (Donaldson et al. 1983; Christison et al. 1991; Meltzer 1992; Siris 1993). Christison and Meltzer also include ECT.

Because of space limitations, we discuss only a small number of the studies contained in each review. These were chosen because they illustrate a conclusion drawn by the reviewer. Unless otherwise noted, we discuss only prospective, controlled studies. Where the reviewer has been silent about the degree of scientific rigor used in a primary study, the study is usually not reported. Where the reviewer has drawn conclusions based in part on studies that were not methodologically sound (e.g., those that contained no control group), we noted it.

Primary studies were consulted if they were needed to clarify points raised in reviews or were published after the reviews cited here were written. Primary studies are reported if they were double-blind controlled studies of an agent used adjunctively with a neuroleptic in a population of patients with schizophrenia or schizoaffective illness. Single-blind studies, open studies, and case reports were excluded except on rare occasions when such a study offered a unique insight. The design of such studies is noted.

Although the literature on a large number of adjunctive treatments was searched, the scientific data base on only a few such treatments was judged sufficient to include here. Among the agents searched but not included because of inadequate information were beta adrenergic receptor blockers, apomorphine, calcium channel blockers, clonidine, naltrexone, amphetamine, reserpine, bromocriptine, caerulein, cholecystokinin, levodopa, methylphenidate, and peptides. The agents that were reviewed include benzodiazepines, anticonvulsants, lithium, antidepressants, and ECT; however, even for these agents there was not enough in the literature to speak to some review questions.

This review is organized according to the review questions rather than the specific adjunctive interventions. For the first review question, overall improvement is separated from improvement in positive and negative symptoms although this is not a clean distinction. This was done because many studies use overall outcome measures (e.g., total score on the Brief Psychiatric Rating Scale [BPRS; Overall and Gorham 1962]), preventing easy classification into positive and negative symptom outcomes. Also, some studies and reviews of studies that report on global outcome and on positive, negative, and ancillary symptom changes are reported in the overall improvement section.

Findings

Efficacy of Adjunctive Somatic Therapies.
Overall improvement. Benzo- diazepines. In the most satisfactory and thorough review of benzo-
diazepines, Wolkowitz and Pickar (1991) note that in nearly all stud-
ies, some individual patients re-
responded well and some responded
poorly. Nearly two-thirds of the
studies published in or after 1975
report positive results, although
outcome measures on which these
were judged vary widely, ranging
from improvement in positive
symptoms to improvement in
tension/ anxiety, to overall (non-
specific) improvement as measured
by the Clinical Global Impressions
(CGI; Guy 1976) or the total BPRS
score. Overall, approximately 30
to 50 percent of individual patients
showed favorable responses, the
magnitude of which was often
modest. In certain patients, how-
ever, the response was striking.

Further conclusions can be
drawn only with caution, as many
of the secondary analyses and nar-
rative summations in Wolkowitz
and Pickar (1991) were done on
the total body of primary studies
reviewed (30 studies) rather than
on the 16 adjunctive studies. Thus,
while a secondary data analysis re-
veals a mean response rate of 48.7
percent (range = 12%-83%) among
patients in the 15 studies that re-
ported response rates, 7 of those
studies evaluated the nonadjunc-
tive use of benzodiazepines rather
than their adjunctive use. Although
the authors do not cite specific
data, they comment that benzo-
diazepines are more effective when
added to neuroleptics than when
used alone.

Christison et al. (1991) assessed
double-blind studies of benzo-
diazepines and conclude that a (pro-
bably small) subgroup of patients
with chronic schizophrenia received
significant benefit from an adjunc-
tive benzodiazepine. For example,
Barbee et al. (1992) gave alprazo-
lam or placebo as an adjunct to
either haloperidol to 28 acutely psychotic
schizophrenia patients recruited
from a hospital emergency room.
They found no significant dif-
ferences between the two groups
variant multiple rating scales, although
the haloperidol-alprazolam group
required significantly less halo-
peridol to achieve similar results.
Wolkowitz et al. (1992) report pre-
liminary results on a group of 48
treatment-resistant patients with
schizophrenia, finding that about
half of the alprazolam-treated pa-
tients demonstrated clinically signifi-
cant improvements in both positive
and negative symptoms.

Carbamazepine. Simhandl and
Meszaros (1992) indicate that of
nine double-blind studies of car-
bamazepine, seven showed some
degree of positive outcome over
placebo and two demonstrated no
significant difference. (In one of
these two studies, carbamazepine
was compared with lithium.) They
conclude that the administration of
carbamazepine, either adjunctively
or as a monotherapeutic agent, is
often associated with the improve-
ment of positive and negative
symptoms in schizophrenia and
schizoaffective disorders. However,
they include several caveats to this
conclusion and point out various
methodological problems that make
it difficult to draw conclusions
from the literature reviewed.

Christison et al. (1991) conclude,
based on five studies, that any an-
tipsychotic action of carbamazepine
is quite modest and perhaps more
likely to be seen in patients with
psychomotor overactivity or con-
comitant manic symptoms. The au-
thors feel that the most impressive
clinical benefit noted seemed to re-
late mainly to a reduction of ex-
citement, impulsivity, and ag-
gression rather than of actual
psychotic symptoms. Schulz et al.
(1990) found the results of re-
viewed primary studies to be rela-
tively weak and conclude that
added carbamazepine may be of
mild help for the selected neuro-
leptic nonresponder. They state
that there is continued promise for
the use of carbamazepine in se-
lected schizophrenia patients, hy-
oposing that such patients
might be violent, aggressive, or
excited.

Valproate. McElroy et al. (1989)
grouped five open and three
double-blind studies of valproate
in the treatment of schizophrenia
and conclude that the results are
less than encouraging. We ex-
amined these three double-blind
studies (Linnola et al. 1976; Ko et
al. 1985; Fisk and York 1987) in
somewhat more detail. The study
by Linnola and colleagues (1976)
adds little to the question of val-
proate's utility in treating patients
with schizophrenia, as only 7 of
the 31 study participants were di-
agnosed with "chronic schizophre-
nia" and diagnostic criteria were
not specified. Neither of two
double-blind adjunctive studies of
valproate in which most patients
studied had schizophrenia (Ko et
al. 1985; Fisk and York 1987) re-
port any beneficial effects of val-
proate when compared with
placebo.

Lithium. Christison et al. (1991)
report that lithium may be useful
as an adjunct to neuroleptics in
some patients with schizophrenia
or schizoaffective illness. These re-
viewers believe that the three
studies in neuroleptic-resistant pa-
tients (Small et al. 1975; Growe et
al. 1979; Carmen et al. 1981) were all well designed, with placebo-controlled multiple crossover treatment trials, each of 4-weeks duration, in a well-diagnosed group of patients with either schizophrenia or schizoaffective illness. The Small et al. (1975) and Carmen et al. (1981) studies both report clear clinical improvement in one-third to one-half of their patients in multiple spheres ranging from positive symptoms to social competence. The Growe et al. (1979) study of eight patients demonstrated improvement only in psychotic excitement. Neither the study by Biederman et al. (1979) nor that by Lerner et al. (1988) is as promising; both examined acutely admitted patients and found significant improvement mainly in symptoms or patient subgroups that might be construed as more affective than schizophrenic.

The Schulz et al. (1990) review is somewhat more positive, although the Lerner et al. (1988) article is not included. They summarize the four other studies as being all in the positive direction, although two are only mildly so. Schulz and his colleagues urge an adjunctive lithium trial in patients who do not satisfactorily respond to neuroleptics alone.

Atre-Vaidya and Taylor (1989) reviewed only double-blind lithium trials done in schizophrenia populations. Because most of these studies included patients with schizoaffective illness, the reviewers attempted to break down study results to isolate the findings in the subgroup with schizophrenia but no affective symptoms. Having reclassified several patients, the reviewers conclude that the Small et al. (1975) study provided a likely sample of six schizophrenic patients, three of whom responded to lithium. Similarly, they analyzed the results of the Carmen et al. (1981) study and point out that although the total study population was 18, only 11 of these had Research Diagnostic Criteria (RDC; Spitzer et al. 1978) schizophrenia, of whom 2 responded to lithium. Atre-Vaidya and Taylor's (1989) overall conclusion is that the number of chronic schizophrenic patients responding in the positive trials is too small to be conclusive, which leaves unanswered the question regarding the efficacy of lithium to treat schizophrenia. In a primary study not included above, Johnstone et al. (1988) found no additional benefit when lithium is added to pimozide.

ECT. In a review of the therapeutic efficacy of ECT in schizophrenia, Riddell (1963) found only seven clinical reports that are methodologically acceptable. All of these reports were done before neuroleptics were widely used. Miller et al. (1953) and Naidoo (1956) found no difference between ECT and controls on psychotic symptoms. In a similar study by Brill et al. (1957), all groups improved but were not different from one another. Ulett et al. (1956), however, found that the ECT group achieved significantly greater benefit than the other groups. Riddell concludes that the results are mixed but that no studies show a clear advantage to ECT.

Fink (1978) reviewed the pre-neuroleptic era studies but also included several early studies comparing neuroleptics and ECT. He concludes that ECT is an effective treatment for schizophrenia, although many of the studies he included used questionable methods. Among those with sound methods, Fink quotes a report by Childers (1964), which found no difference in symptom ratings between ECT and chlorpromazine with ECT, although both of these groups showed more improvement than groups treated with chlorpromazine or fluphenazine alone.

Childers concludes that the combination of ECT and drug increases the percentage of patients who attain a moderate or better improvement. Smith et al. (1967) found greater short-term improvement (within 1–3 weeks) with chlorpromazine versus ECT alone, but at 6 weeks, 6 months, and 1 year, the treatments are equal in effectiveness. Heath et al. (1964) found little difference between ECT and anesthesia simulated ECT groups. In a classic study, May and Tuma (1965) showed that drugs are superior to ECT in the short term but that patients with ECT and drugs have shorter lengths of stay and shorter rehospitalization periods after initial release.

Erwin and Thompson (1978) also review the May and Tuma (1965; May 1968) study, noting that it was the first to compare ECT and drugs, each under its own ideal conditions, that is, with clinicians who were free to adjust ECT frequency or drug dosage as the clinical situation dictated. Erwin and Thompson conclude that the advantage of drugs in the first year is clear but that the lack of control groups on followup makes the followup data impossible to interpret. They indicate that the literature does not support the benefit of ECT in schizophrenia.

A brief review by the Royal College of Psychiatrists (1977) con-
cludes that ECT may be effective but offers no advantages over drugs. Turek and Hanlon (1977) found the data so ambiguous that no conclusions could be drawn. Weiner (1979) concludes that the effect of ECT is comparable to that of drugs and that some evidence shows that the combination of ECT and drugs may potentiate the therapeutic benefit of ECT.

Salzman (1980) indicates that only seven studies are prospective, have a control or comparison group, and compare ECT with other treatment modalities. Several of these are mentioned above (e.g., May and Tuma 1965; Smith et al. 1967). Murillo and Exner (1973) used regressive ECT, finding that the ECT group showed more improvement on ratings of psychopathology, self-reports of symptom distress, family reports of patient behavior, indices of social adjustment, and hospital discharge rates. Salzman criticizes this study methodologically and indicates that regressive ECT is drastic and experimental. He also reviews Gambrill and Wilson (1966), who report that ECT alone and prochloperazine alone are superior to the combination of ECT and drugs, which is only slightly better than placebo. However, Rahman (1968) indicates that the combination of drugs and ECT is better than either one alone. Salzman concludes that ECT reduces acute schizophrenic symptoms and in some cases produces a complete remission. This conclusion is based on very limited data, however. With regard to the potentiation of neuroleptics, he indicates that the results are equivocal.

In other reviews, Taylor (1981) indicates that no studies clearly show the efficacy or nonefficacy of ECT for schizophrenia. Small (1985) evaluated six studies comparing ECT and neuroleptics, finding that the short-term results are equivalent. Varghese and Singh (1985) and Martin (1986) conclude that ECT is an effective treatment for schizophrenia. Weiner and Coffey (1988) agree that ECT is effective in acute or subacute illness but that it is not the treatment of choice. They also conclude that ECT and drugs do appear to potentiate each other. Christison et al. (1991), in reviewing the management of treatment-resistant patients, conclude that ECT is most likely to benefit those with catatonia, affective symptoms, or a very short duration of illness. They indicate that in chronic illness, ECT alone rarely produces significant lasting benefits.

Positive symptoms. Benzodiazepines. According to the reviews previously referenced, the core positive symptoms (e.g., hallucinations, delusions, thought disorder) appear to be significantly reduced by benzodiazepines in some but not all studies (Guz et al. 1972; Kellner et al. 1975; Lingjaerde et al. 1979; Lingjaerde 1982; Wolko- witz et al. 1988; Pato et al. 1989). Many studies provide contradictory results: Six found no significant effect on psychotic symptoms (Holden et al. 1968; Marneros 1979; Ruskin et al. 1979; Karson et al. 1982; Altamura et al. 1987; Csernansky et al. 1988), and several describe detrimental effects in at least a subset of patients studied (Michaux et al. 1966; Hanlon et al. 1969, 1970; Pato et al. 1989). Carbamazepine and antidepressants. Simhandl and Meszaros (1992) report that positive symptoms improved in only a fraction of the nine double-blind studies with carbamazepine. It is fairly well accepted clinically that adjunctive antidepressants have no role in the treatment of positive symptoms of psychosis, and studies published in the 1970s and earlier adequately substantiate this impression (Siris et al. 1978).

Negative symptoms. Benzodiazepines. The reviews referenced above found that few studies of benzodiazepines have measured change in negative symptoms. Three found adjunctive benzodiazepines to have beneficial effects (Holden et al. 1968; Csernansky et al. 1988; Wolkowitz et al. 1988), although one of these studies (Csernansky et al. 1988) notes that this effect dissipated by weeks 4 to 5. One study (Karson et al. 1982) specifies that clonazepam has no significant effects on the symptom “withdrawal.” No studies identify a worsening of negative symptoms by benzodiazepine addition, but the small number of studies that address this symptom complex makes conclusions difficult to draw.

Carbamazepine. Simhandl and Meszaros (1992) found that negative symptoms improved in two studies with carbamazepine (Kunovac et al. 1991; Meszaros et al. 1991). Earlier open studies had also suggested that carbamazepine might be useful in treating certain negative symptoms such as anhedonia and social isolation.

Antidepressants. Based on limited data, the review by Plasky (1991) found little evidence of any efficacy of tricyclic antidepressants for the negative symptoms of schizophrenia. For example, Waehrens and Gerlach (1980) found the symptoms of anergy, social withdrawal, and blunted affect to be unchanged after antidepressant therapy, and Becker (1983)
found no improvement in an energy in his adjunctive imipramine group. In contrast, Siris et al. (1991) compared adjunctive imipramine with placebo in 27 stable outpatients with schizophrenia or schizoaffective disorder. Using the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) ratings, they found statistically significant improvements in negative symptoms, specifically loss of interest and improvements in negative symptoms, and Spitzer 1978) ratings, they found that most patients in a bupropion adjunctive group dropped out and did poorly. Nevertheless, Siris (1991) concluded that the most methodologically sound studies demonstrate that adjunctive antidepressants provide significant benefit for some patients with schizophrenia if they are depressed but otherwise stable.

Lerner et al. (1988) found that the presence of affective symptoms, especially mild depressive symptoms, predicts a greater likelihood of response to adjunctive lithium. Four of the five double-blind studies reviewed demonstrated a specific therapeutic effect of adjunctive lithium on affective symptoms. Antidepressants. Siris et al. (1978) found that when depression is present in schizophrenia, the literature hints at benefits gained from treatment with an antidepressant-neuroleptic combination. Prusoff et al. (1979) found that adjunctive amitriptyline significantly reduced depression scores on the Hamilton Rating Scale-Depression (HAM-D; Hamilton 1960). Siris et al. (1987b) found that depression significantly improved on several rating scales after 6 weeks. Four studies report no significant antidepressant effect on measures of depression (Waehrens and Gerlach 1980; Johnson 1981; Becker 1983; Kramer et al. 1989), although some of these studies were complicated by the use of the BPRS energy scale instead of a depression scale (Waehrens and Gerlach 1980), the presence of anergic patients in the sample (Becker 1983), and the inclusion of actively psychotic patients (Kramer et al. 1989). Plasky (1991) interprets these results as indicating that adjunctive tricyclic antidepressants are useful in treating depression in patients who are not currently acutely psychotic.

In his 1991 review, Siris agreed that the primary role for adjunctive antidepressants in patients with schizophrenia appears to be for the treatment of a depressive syndrome. He notes, for example, that Singh et al. (1978) found significant improvement in CGI and HAM-D ratings in the adjunctive trazodone group. However, Kurland and Nagaraju (1981) found no added benefit of vilotrazine, and Dufresne et al. (1988) report that most patients in a bupropion adjunctive group dropped out and did poorly. Nevertheless, Siris (1991) concluded that the most methodologically sound studies demonstrate that adjunctive antidepressants provide significant benefit for some patients with schizophrenia if they are depressed but otherwise stable.

Plasky (1991) points out a common methodological problem—proper diagnosis. Some studies (e.g., Siris et al. 1987a, 1987b) included schizoaffective patients; others (e.g., Waehrens and Gerlach 1980; Johnson 1981) provided unclear criteria to distinguish schizophrenia from schizoaffective or psychotic mood disorders. It has been pointed out that the lack of diagnostic clarity is also a problem in the ECT literature (Erwin and
ECT. Most reviewers conclude that the presence of depression is a factor predicting a positive effect of ECT in schizophrenia. Some conclude that the relief of depression is the only therapeutic effect. Weiner (1979) and Weiner and Coffey (1988) indicate that ECT is effective, especially when affective or catatonic symptoms are present; Christison et al. (1991) agree. Erwin and Thompson (1978) believe that ECT does not treat the schizophrenic process but rather treats secondary mood disorders in schizophrenia. Taylor (1981) agrees, and a retrospective chart review by Folstein et al. (1973) supports this view: Being hopeless, feeling worthless or guilty, or having a family history of affective disorder will better predict ECT response than will a diagnosis of schizophrenia. Folstein et al. (1973) also found that having Schneiderian first-rank symptoms (in the absence of affective symptoms) does not predict response to ECT. Wells (1973) examined records in a university hospital over 10 years and found that 76 percent of schizophrenia patients given ECT for the first time had moderate to severe depression and 54 percent had depression as the most prominent symptom. Patients with schizoaffective disorder and catatonia had the best response rate (85% and 82%, respectively).

Anxiety. Benzodiazepines. Few studies have examined the role of adjunctive benzodiazepines in the treatment of anxiety in persons with schizophrenia. Of the reviews summarized here, only Wolkowitz and Pickar (1991) address the utility of adjunctive benzodiazepines for specific symptom complexes in their narrative, and this discussion is incomplete because the authors cite only positive treatment responses. Five reported studies indicate that adjunctive benzodiazepines ameliorate anxiety, tension, hostility, and irritability (Guz et al. 1972; Kellner et al. 1975; Marneros 1979; Altamura et al. 1987; Pato et al. 1989). However, anxiety is noted to increase in high-dose alprazolam nonresponders and to increase rapidly in a separate small sample of schizophrenia outpatients given alprazolam (Pato et al. 1989). Karson et al. (1982) specify that clonazepam has no significant effect on anxiety, and two studies observed an antianxiety effect at week 2 that was not sustained by week 4 (Kellner et al. 1975; Altamura et al. 1987).

Aggression and hostility. Benzodiazepines. None of the double-blind studies discussed in the cited reviews address the utility of benzodiazepines to modify disruptive and dangerous behaviors. They do, however, note that several open-label or retrospective studies have suggested an important role for benzodiazepines combined with neuroleptics in the acute management of such behavior.

Carbamazepine. The only double-blind study of the effectiveness of carbamazepine on aggressiveness (Neppe 1983) found decreases in overt aggression and increases in self-control in interpersonal situations. Reduction of affective symptoms and aggression was highlighted as the most impressive clinical benefit noted in the reports reviewed by Christison et al. (1991). These reviewers summarize Okuma et al. (1989), indicating that patients with prominent violence, aggression, or paranoia are more likely to respond. Schulz et al. (1990) draw similar conclusions.

Lithium. Reviewers agree that any impacts of lithium on aggression and hostility among patients with schizophrenia may be mediated through reductions in manic-like symptoms (Schulz et al. 1990; Christison et al. 1991). Christison and colleagues conclude that affective symptoms need not be present for patients with schizophrenia to respond to lithium.

Antidepressants. Agitation as a presenting characteristic is a contraindication to antidepressant administration, according to Siris and colleagues (1978). They indicate that antidepressants may worsen agitation in persons with schizophrenia.

Summary. If they are not administered in the active, psychotic exacerbation phase of illness, antidepressants appear to benefit patients who have episodic signs and symptoms of depressive illness in addition to schizophrenia. Antidepressants can be efficacious without exacerbating psychotic symptoms when used adjunctively with neuroleptics. There appears to be a specific therapeutic effect of adjunctive lithium on affective symptoms. ECT also is an effective treatment for affective symptoms, whether or not the patient is acutely psychotic. Anxiety may respond to treatment with adjunctive benzodiazepines; however, a few studies report a waning effect of these agents, perhaps due to tolerance, after a few weeks of treatment. Aggression and hostility may be modified by the addition of benzodiazepines or carbamazepine.

Patient Characteristics. Benzodiazepines. Most reviewers remark upon the high degree of interindividual variability in benzodiazepine trials in schizophrenia. Rather than producing a.
consistent effect across an entire study population, adjunctive benzodiazepine treatment appears to benefit some patients but not others. Unfortunately, characteristics that differentiate responders from nonresponders remain elusive. Wolkowitz and Pickar (1991) report little that seems predictive of an individual’s response to adjunctive benzodiazepine treatment. No predictive value for age or sex has been identified in those studies that specifically assessed these factors (Michaux et al. 1966; Lingjaerde 1982; Wolkowitz et al. 1988). The only finding that is relatively consistent across several studies is that patients respond more favorably to adjunctive benzodiazepines when they have more prominent initial psychotic and/or anxiety or panic symptoms, or high levels of motor tension, agitation, or retardation (Michaux et al. 1966; Kellner et al. 1975; Ruskin et al. 1979; Wolkowitz et al. 1988). Only one study (Hanlon et al. 1969) fails to show such a relationship. Christison et al. (1991) reiterate the possible relationship between degree of initial symptomaticity and adjunctive benzodiazepine responses, but offer nothing further on this subject.

Christison et al. (1991) also comment on the subset of reviewed studies (n = 4) that specifically investigate patients with neuroleptic-resistant schizophrenia. They point out that two of the four studies describe significant improvement when adjunctive benzodiazepines were added (Ruskin et al. 1979; Wolkowitz et al. 1986). They conclude, based on this very limited data set, that patients who respond poorly to traditional neuroleptics appear to be among the potential responders to adjunctive benzodiazepine treatment.

Meltzer (1992) provides a brief narrative review of benzodiazepine augmentation in treatment-resistant schizophrenia. He concludes that there is minimal evidence supporting the efficacy of benzodiazepine augmentation in this patient population.

**Carbamazepine.** Simhandl and Meszaros (1992) define patient characteristics that might predict a therapeutic benefit of adjunctive carbamazepine; these include violent outbursts; overactivity or poor impulse control; excitement; neuroleptic therapy resistance; affective or anxiety symptoms; positive symptoms combined with affective symptoms; negative symptoms; electroencephalogram (temporal lobe) abnormalities or symptoms suggesting epileptic aura; a history of organic brain disorder, central nervous system trauma, or neurological soft signs; and a history of alcohol or drug abuse.

**Lithium.** Biederman et al. (1979) found adjunctive lithium to be superior to neuroleptics alone in patients with good functioning between episodes, noting a less robust response in patients with interepisode psychotic symptoms. This finding is repeated by Atre-Vaidya and Taylor (1989), who further conclude that patient characteristics most suggestive of a positive response to lithium are a family history of affective disorder, active affective symptoms, and previous affective episodes. This conclusion, however, appears to be based largely on studies done using lithium as a sole rather than an adjunctive treatment.

**Antidepressants.** No review provides data on demographic or other subgroups of patients who might benefit from adjunctive antidepressant treatment. In an individual study, Siris et al. (1978) explore whether paranoia influences outcome in adjunctive antidepressant use; finding conflicting evidence, they came to no conclusion.

**ECT.** Christison et al. (1991) conclude that the usefulness of ECT in chronic, neuroleptic-resistant patients is debatable, although in fact there have been no controlled studies of ECT in such patients. Using noncontrolled studies, Meltzer (1992) quotes several of the reviews noted above, as well as a study of his own in which five of six neuroleptic-resistant patients had a moderate-to-good response with significant improvement in positive and negative symptoms. With monthly maintenance treatments, two of four patients had a sustained improvement, and two relapsed. Meltzer concludes that there is modest evidence to support the use of ECT in treatment-resistant patients. Despite this endorsement, however, he indicates that ECT is a last resort, to be used after all pharmacological approaches have been systematically considered. Both Christison and Meltzer agree that ECT may be especially useful for treatment-resistant patients with affective symptoms.

**Summary.** No clear patient characteristics consistently predict response to adjunctive agents. Other than the presence of the symptom complexes mentioned above, which may be responsive to particular adjunctive somatic therapies, it seems clear that none of these treatments is superior to antipsychotic medications, and the benefits of their adjunctive use with neuroleptics is marginal at best. The use of adjunctive treatments may have a larger role in...
the treatment of neuroleptic-nonresponsive patients, although this has not been fully studied. ECT, for example, can be used when response to antipsychotic therapy is less than satisfactory or when, for other reasons, antipsychotic medications cannot be used or are not accepted by the patient.

**Discussion and Conclusions**

A vast body of literature pertains to the utility of adjunctive pharmacological treatments and ECT for patients with schizophrenia. Most of the literature published to date focuses on the relief of positive symptoms or on the improvement of global behaviors as central measures of the utility of adjunctive agents. More recently, investigators have included changes in negative symptoms as outcome measures. Specific syndromes such as depression are also being targeted in treatment trials with symptom-specific agents. It is rare for non-symptom-specific outcome measures—interpersonal or vocational functional status, quality of life, family well-being, patient satisfaction—to be addressed in adjunctive pharmacological or ECT treatment trials or review articles.

Most double-blind studies have been performed with chronic, often treatment-resistant inpatients. Less often, studies are done with acutely psychotic or recently admitted inpatients. Outpatient studies and studies of adjunctive agents for maintenance of stable or remitted phases of illness are uncommon. Additionally, with the exception of ECT, virtually no studies focus on the use of adjunctive agents in first-episode schizophrenia, although several groups (including those led by E. Johnstone and J. Lieberman) are currently working with this patient population.

Despite the volume of publications on the use of adjunctive somatic treatments for patients with schizophrenia, it is surprisingly difficult to draw conclusions or treatment recommendations from the available data. Most treatment studies, regardless of the stringency of entry criteria and methodology, enroll a relatively small number of patients. Over the past 20 years, studies with fewer than 30 patients have been the norm, and samples of 10 to 15 are not uncommon. Such small sample sizes make broad extrapolations to the entire patient population difficult. Studies also differ widely in terms of study design, patient population characteristics, and outcome measures. Thus, the task of identifying several reasonably similar studies that confirm hypothetical treatment results can be formidable.

It should also be made clear that no adjunctive agent has been clearly demonstrated to be markedly efficacious for the treatment of a specific dimension of schizophrenia. Instead, to draw conclusions from the available data, it is usually necessary to weigh the clinical significance of statistically significant yet small changes, or of changes that are noted in only a small percentage of subjects entered.

Specifically with regard to ECT, reviewers of the literature uniformly indicate that the literature is poor. There are several scientifically sound studies, but even these suffer from methodological problems. More recent studies have used standard diagnostic criteria to identify persons with schizophrenia, and have been more careful about standardizing the treatment procedure and developing adequate outcome measures. However, studies that provide definitive conclusions concerning the place of ECT in schizophrenia have yet to be done.

**Recommendations for Future Research**

1. Instead of studying overall improvement in schizophrenia, future research should focus on a subgroup of patients or on specific symptom complexes related to this illness, recognizing that the efficacy and effectiveness of adjunctive agents are likely to be partial at best.

2. Future inpatient studies of adjunctive treatments should be multicenter studies, entering a large number of carefully diagnosed and characterized patients (>100) and measuring outcome on a variety of assessment scales.

3. Dangerous behaviors and assaultiveness are clinically very significant but understudied problems. Double-blind prospective studies of the utility of adjunctive benzodiazepines and anticonvulsants to reduce such behaviors should be carried out.

4. Promising inpatient adjunctive treatment trials should be followed by long-term outpatient trials that assess quality-of-life issues as well as symptom relief.

5. The most promising adjunctive agents (benzodiazepines, lithium, carbamazepine, and antidepressants) should be studied in conjunction with new and atypical antipsychotics, such as clozapine.

6. Future ECT research is needed to clearly delineate its selective role in the treatment of
schizophrenia, including whether ECT potentiates the effects of neuroleptics. Patient groups that could be targeted include those with affective symptoms and those who are refractory to both the conventional and the newer anti-psychotics.

References


Guy, W., ed. *ECDEU Assessment Manual for Psychopharmacology*, revised. Rockville, MD: National In-


Siris, S.G.; Morgan, V.; Fagerstrom, R.; Rifkin, A.; and Cooper, T.B.


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