Conventional Antipsychotic Medications for Schizophrenia

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Abstract

This article reviews the existing evidence for the efficacy and effectiveness of conventional antipsychotic medications in the treatment of schizophrenia. Among the issues reviewed are their efficacy for acute symptom episodes and for long-term maintenance therapy, differential efficacy among medications, the gap between research-based efficacy rates and effectiveness rates in practice, dosing strategies, and the treatment of first-episode cases. Evidence for efficacy is overwhelming for reduction of positive symptoms but quite limited for other outcomes. Effectiveness in practice may be substantially less than efficacy in clinical trials, perhaps owing to patient heterogeneity, prescribing practices, and noncompliance. First-episode patients should be treated with antipsychotic medication, but perhaps at lower dosages, with consideration of a gradual decrease or discontinuation at 6 months to 1 year.

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Conventional antipsychotic medications refer to those widely used and available in the United States before 1990, including the phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, and dihydroindolones. Their common mode of action is to block dopamine D_2 receptors throughout the brain, and their therapeutic activity is presumably related to such blockade in the mesolimbic system. Their widespread use, as well as the anticipated future availability of nonconventional antipsychotic agents, underlines the importance of examining research that supports use of conventional agents. This article reviews evidence for the efficacy and effectiveness of these conventional antipsychotic medications during both the acute and long-term phases of treatment for schizophrenia.

The acute phase refers to the periods during which the patient experiences an acute episode of positive symptoms, with either the onset of symptoms after an asymptomatic period or a marked increase in symptoms over a baseline of less severe symptoms. Operationally, we define this phase as the first 6 to 8 weeks after onset of an episode of positive symptoms. Symptom remission is the central goal in the acute phase.

The phase of long-term maintenance treatment refers to the periods during which the patient is not experiencing an acute episode as defined above. The nature of this phase varies tremendously across individuals. Some individuals are asymptomatic and relatively free of any disability; others experience persistent psychotic symptoms in addition to considerable impairment in their ability to live independently, work, and relate to others. The central goals of antipsychotic drug treatment in the long-term treatment phase are continued suppression of the acute symptoms (continuation therapy) or prevention of the occurrence of another episode of acute symptoms (maintenance or prophylactic therapy).

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Review Questions

1. What is the efficacy of conventional antipsychotics for—
   a. relief of acute positive symptoms of schizophrenia?
   b. prevention of relapse and recurrence of positive symptoms?
   c. reduction of cognitive impairments and negative symptoms?
2. What is the effectiveness of the conventional antipsychotics for—
   a. relief of acute positive symptoms of schizophrenia?
   b. prevention of relapse and recurrence of positive symptoms?
   c. reduction of cognitive impairments and negative symptoms?
3. Is there differential efficacy and effectiveness among the alternative conventional antipsychotics, including depot forms?
4. What effects do conventional antipsychotics have on functional status and other nonclinical outcomes?
5. What strategies can be recommended in the pharmacological treatment of individuals suffering their first acute episode of schizophrenia?

Methods

The literature on conventional antipsychotic medications is extensive and sometimes lengthy. This literature review began with searches of PSYCLIT and MEDLINE covering the years 1966 to 1993 using key words. All references related to the following key words were requested with the "explode" command: *schizophrenia* "and" *tranquilizing agents; schizophrenia* "and" *tranquilizing agents, major* "or" *tranquilizing agents; schizophrenia* "and" *clinical trials* "or" *comparative study* "or" *followup studies; schizophrenia* "and" *neuroleptic drugs-effective* "or" *efficacy drug therapy.* Additional discussions with experts in the field and other key informants provided additional unpublished manuscripts and articles not obtained from the literature search. Our total search yielded 956 citations.

Given the volume of literature, we largely reviewed existing reviews. Because subsequent reviews tend to update prior reviews by the same authors, and because the research questions changed over time, we decided to focus only on reviews published since 1984. Although most of the reviews we considered do not meet the minimum criteria for high quality according to Beaman (1991)—for example, they typically lack specification of procedures used to identify and select the studies covered—we selected a group of higher quality reviews that we judged to provide ample information about the review questions. Kane et al. (1985, 1986), Kane and Lieberman (1987), Baldessarini et al. (1988, 1990), Davis et al. (1989, 1993), Kane (1989), Schooler (1991), Kane and Marder (1993), and Bollini et al. (1994) authored these reviews.

This review is organized according to the review questions. For each question, the findings and conclusions from each review are summarized. Subquestions related to the main review question are also addressed. When other reviews offer new information or present divergent findings or conclusions, they are mentioned. Citations of primary studies are reserved for questions not addressed in reviews or for the most recent studies that have not been covered by prior reviews.

Efficacy of Conventional Antipsychotics: Acute Phase

What Is the *Efficacy* of Conventional Antipsychotics for Relief of Acute Positive Symptoms of Schizophrenia? Davis et al. (1989) summarize the approximately 100 double-blind studies comparing a conventional antipsychotic drug and placebo in the acute treatment of schizophrenia. They conclude that the vast majority of studies found the drug to be more effective than placebo. Overall, 75 percent of patients treated with phenothiazines were much improved after 6 weeks compared with less than 25 percent of placebo-treated patients. Studies with adequate dosage levels, duration of treatment, design, and clinical improvement measures indicate unequivocally that phenothiazines have a therapeutic effect on schizophrenia (Cole and Davis 1969). The greatest drug–placebo differences were seen at both ends of the prognosis spectrum (Davis et al. 1989). On the good prognosis end, 16 percent of drug-treated versus 1 percent of placebo-treated patients were in complete symptom remission. Among poor prognosis patients, 33 percent of placebo-treated versus 2 percent of drug-treated patients remained moderately ill or worse after 6 weeks. Reviews by Baldessarini and colleagues (1990) and Kane and Marder (1993) concur with these conclusions.

What Is the Expected *Time Course* of the Improvement Brought About by Antipsychotic

Medications? Davis and colleagues (1989) conclude that most of the therapeutic gains from antipsychotic drugs occur in the first 6 weeks of treatment, with further treatment gains made during the subsequent 12 or 18 weeks. Baldessarini and colleagues (1990) pooled data from several studies and found an initial rapid reduction of symptoms over the first 5 to 10 weeks, with slower and more subtle symptom reduction continuing for as long as 30 weeks in chronically ill patients.

Does *Rapid Neuroleptization* Produce a Faster or Greater Treatment Response Than the Standard Pace of Increasing Medication Dosage? Rapid neuroleptization refers to the practice of using a massive loading dose of antipsychotic medication with the assumption that a more rapid and vigorous antipsychotic effect will be achieved. All key reviews generally agree, however, that there is no evidence supporting this assumption (Davis et al. 1989; Baldessarini et al. 1990; Kane and Marder 1993).

What *Dosage Range* Has Been Shown To Be Most Effective in Achieving Symptom Reduction in the Acute Phase of Illness? There is general agreement that between 300 and about 750 mg of chlorpromazine (CPZ) equivalents per day is probably the optimal dosage range for the average patient. Davis and colleagues (1989) summarize all studies in which patients were randomly assigned to a higher or lower dosage, and they note that doses in the range of 300 mg CPZ or less were inadequate for optimal treatment. High doses (>940 mg CPZ equivalents) produced no better responses than doses in the range of 540 to 940 mg CPZ equivalents. Baldessarini et al. (1990) reviewed 65 short-term trials of CPZ and found that in all trials that used daily doses of CPZ 500 mg or more, CPZ had a statistically superior effect compared with placebo. However, doses of 300 mg per day or less yielded results significantly better than placebo in only two-thirds of trials.

Baldessarini and colleagues (1990) found that a dose–effect relationship with optimal moderate doses is strongly supported by three studies using haloperidol (HPL). There was an apparent sigmoid dose–effect relationship between the equivalent of 2 and 10 mg of HPL. Kane and Marder (1993) cite studies (Levinson et al. 1990; Van Putten et al. 1990; Rifkin et al. 1991) comparing acute patients receiving different fixed dosages of HPL and fluphenazine (FLU) as well as a study of the neuroleptic threshold dose (McEvoy et al. 1991). They conclude that these studies show a considerable degree of consistency despite differences in patient populations and methodology. They find no significant advantages to using dosages of HPL greater than 10 to 20 mg per day for acute treatment, and even dosages of 20 mg per day could be associated with a substantial number of adverse neurological effects.

A relevant double-blind study, not previously reviewed, tested the efficacy of physician-prescribed "individually adapted" dosages of HPL compared with two fixed dosages (10 and 20 mg per day) (Klieser and Lehmann 1987). Patients in the individually adapted cell received 19 mg (standard deviation [SD] = 15.8 mg) per day of HPL by day 14, with a range of 1 to 80 mg. Patients in all three treatment groups experienced a statistically significant improvement in almost all symptoms, and no group differences were found on most measures. The investigators suggest that it was not possible to demonstrate an advantage of clinical judgment over standard dosing.

Efficacy of Conventional Antipsychotics: Maintenance Therapy

What Is the *Efficacy* of Conventional Antipsychotics for Prevention of Relapse and Recurrence of Positive Symptoms? The Baldessarini et al. (1990) and Davis et al. (1993) reviews find overwhelming evidence that conventional antipsychotic agents reduce the risk of relapse of the positive symptoms of schizophrenia. Based on 44 placebo-controlled studies of antipsychotics with a total of 3,939 subjects and an average followup period of 9.8 months, Baldessarini et al. (1990) found that the rate of symptom exacerbation on placebo was 55 percent versus 14 percent on active medication (mean daily dose = 397 CPZ equivalents), a 3.9-fold overall sparing of relapse attributable to medication. Davis and colleagues (1993) evaluated 35 randomized double-blind studies with 3,720 patients and a minimum of 6 weeks of followup (most in the 4- to 6-month range) and estimated relapse rates to be 55 percent on placebo versus 21 percent on active medication, a highly significant difference.

In interpreting this substantial impact, both reviewers point out several limitations to their research: (1) selection design for

these studies probably favored treatment-responsive patients; (2) most of these studies used one of three agents—CPZ, thioridazine, or FLU—and none used HPL; (3) the two studies with followup periods exceeding 1 year both suggest that the rates of relapse on placebo and active agent become much more similar after about 18 months; (4) most studies were conducted during the 1960s and 1970s, when the diagnostic criteria for schizophrenia differed substantially from those used today; and (5) the difference in relapse rates between placebo and drug varies from 15 to 100 percent across sites. The reviewers attribute this variation to different lengths of followup and different definitions of relapse.

What Dosing Strategy Is Needed to Achieve This Efficacy?

Dosage level. Bollini and colleagues (1994) conducted a meta-analysis to assess the relationship between dosage and efficacy. They extracted data from 22 randomized clinical trials that assigned patients to low- versus high-dose therapy. Converting dosages to CPZ equivalents, they divided patients into four groups based on the observed quartiles of dosage levels: less than 166, 166 to 375, 376 to 830, and more than 830 mg CPZ equivalents. They then computed a linear regression model to predict the proportion of patients improved. They determined that incremental clinical improvement was not found at doses above 375 mg CPZ equivalents.

To examine the lower end of the dose spectrum, Baldessarini et al. (1988) cite results from a subset of four studies that explored these lower ranges. In one nonrandomized study (Lehmann et al. 1983), patients with chronic schizophrenia had their usual daily dose of medication lowered from an average of 452 mg CPZ equivalents to 50 to 100 mg. By the end of 1 year, the relapse rates were 28 percent among those kept on the higher dose versus 42 to 45 percent among those on the lower doses. In a second study, in which patients' daily dosage was progressively reduced over several months from an average starting dose of 700 CPZ equivalents (Branchey et al. 1981), the rate of symptom exacerbation did not exceed the baseline rate on the standard dose until the dose was lowered to 13 percent of the starting dose, at which point the exacerbation rate rose by a dramatic 71 percent. In another study (Kane et al. 1983, 1985), in which patients were randomly assigned for 1 year to either standard dosage (500–600 CPZ equivalents) or one of two low doses (100–200 or 50–60 CPZ equivalents), the relapse rates were 5, 22, and 42 percent, respectively. Finally, Baldessarini et al. (1988) reanalyzed data from a Japanese study (Nishikawa et al. 1984) and found evidence for a dose-dependent antipsychotic effect only below a daily dose of 200 mg CPZ equivalents. Based on these studies, the researchers conclude that there is evidence that the minimal effective daily dose to protect 50 percent of patients against relapse of chronic psychosis is in the range of 50 to 150 mg CPZ. While they acknowledge that clinicians are interested in a higher response rate than 50 percent, they cite this as evidence that a substantial number of patients with schizophrenia may be maintained at doses lower than those conventionally prescribed.

Continuous low-dose strategies. Schooler (1991) reviews six studies of the continuous low-dose strategy. These studies used random assignment to standard versus at least one fixed low dose, included a total of 474 patients, and used either depot FLU (five studies) or depot flupenthixol (one study). The duration of followup was at least 12 months for all but one study. Low doses ranged from 1.25 to 12.5 mg FLU decanoate equivalents every 2 weeks, and the standard doses ranged from 12.5 to 50 mg every 2 weeks. The ratio of relapse on low versus standard dose ranged from 1.1:1 to 8:1 (mean = 3.3:1). Schooler (1991) concludes that medication can be reduced for some schizophrenia outpatients who are stable. Large dosage reductions can lead to fewer adverse effects and improvement in some measures of well-being. However, Schooler (1991) points out that the risk of psychotic exacerbation increases with very low dosage (Kane et al. 1986) or less stable patients (Goldstein et al. 1978) and, in the second year, even with moderately low dosage (Marder et al. 1987; Hogarty et al. 1988).

Targeted-dose strategies. The intermittent- or targeted-dose strategy provides medication on a fixed intermittent schedule or, more typically, only when prodromal signs of relapse occur. This strategy requires prodromal signs that accurately predict relapse in a timely manner, a patient support network to detect these signs, and a patient who is willing to take the medication when the signs occur. Schooler (1991) reviews four randomized studies of this approach. These studies include a total of 636 patients who were fol-

lowed for 2 years. The patients in the targeted conditions received substantially less medication compared with those in the standard, continuous-dose conditions; the ratio of standard versus intermittent dosages ranged from 1.7:1 to 5.4:1 (sample size–weighted mean = 2.4:1). The 12-month relapse rates ranged from 9 to 33 percent (sample size–weighted mean = 17.0%) for continuous-dose patients versus 22 to 55 percent (36.6%) for the targeted-dose groups. Similarly, the 2-year relapse rates for the continuous-dose group ranged from 14 to 39 percent (sample size–weighted mean = 24.2%) compared with 36 to 62 percent (sample size–weighted mean = 49.9%) for the targeted-dose groups. Schooler (1991) concludes that although the targeted-dose strategy may reduce the risk of side effects, it clearly increases the risk of relapse.

Davis et al. (1993) conducted a more formal meta-analysis on the four studies of targeted-dose strategies reviewed by Schooler (1991). They computed an overall relapse rate of 25 percent among the continuous-dose patients versus 50 percent in the targeted group, which is a highly statistically significant difference. Similarly, in three of the studies that explicitly report on rehospitalization, they found that 23 percent of the continuous-dose group versus 38 percent of the targeted-dose group required rehospitalization, also a statistically significant difference. They conclude that the results on the efficacy of the targeted approach are "poor."

Finally, the as-yet unpublished National Institute of Mental Health multicenter Treatment Strategies in Schizophrenia (TSS) Study provides the most definitive data to date on the relative efficacy of standard, continuous low-dose, and targeted intermittent maintenance antipsychotic therapy because it compares these three approaches in a single study (Schooler et al. 1989). The overall conclusions from the TSS with regard to maintenance therapies are consistent with those drawn from previous studies. Targeted dose clearly carries high risk and is not recommended. Low dose also carries additional risk of relapse but may offer some advantages with regard to reduced side effects.

What Is the *Efficacy* of Conventional Antipsychotics for Reduction of Cognitive Impairments and Negative Symptoms? Most of the literature on the efficacy of antipsychotic medication focuses on positive symptoms. Even when ratings of negative symptoms are given, primary and secondary negative symptoms are not distinguished. It is therefore difficult to determine the efficacy of conventional antipsychotics for relief of negative symptoms of schizophrenia. The key reviews identified for this article are notably silent about this topic.

Cassens et al. (1990) published a comprehensive and high-quality review of the effects of antipsychotic agents on neuropsychological functioning among patients with chronic schizophrenia. The authors state that their review represents an improvement over prior reviews in that it evaluates effects on specific areas of neuropsychological functioning and attempts to control for drug type, dose, and duration of administration. However, their efforts were substantially hindered by the state of the literature. Their overall conclusions are that antipsychotic medications produce some short-term impairments in attention and vigilance, but that administration of these drugs for more than 8 weeks produces variable results depending on the neuropsychological function being assessed. Maintenance antipsychotic therapy may enhance vigilance and attention, problem solving, and ability to organize, but it detracts from fine motor task performance.

Summary of Acute and Long-Term Efficacy Findings. The major points of consensus from these reviews on the efficacy of acute and long-term antipsychotic therapy are as follows:

1. Antipsychotic medications for persons with schizophrenia in the acute phase of illness are efficacious at inducing remission of positive symptoms in roughly 70 percent of patients.
2. The vast majority of patients who are medication-responsive and experience remission will achieve this benefit in the range of 300 to 750 mg CPZ equivalents.
3. There is no evidence that large loading doses of neuroleptics speed or enhance treatment response.
4. At least during the first 12 months following an acute symptom episode, maintenance antipsychotic therapy substantially reduces the risk of relapse.
5. The vast majority of patients who are medication responsive and experience this reduction in relapse will achieve this benefit in the range of 300 to 600 mg CPZ equivalents, although a substantial percentage of these patients (up to 50%) also may be successfully

maintained at dosages below 300 mg.

6. There is no evidence that, on average, high maintenance doses (> 600 mg CPZ equivalents) are more efficacious in preventing relapse than are lower, standard doses.

7. Daily dosages below 150 to 165 mg CPZ equivalents carry a particularly high risk of relapse.

8. Continuous low-dose strategies that follow the above guidelines carry some additional risk of relapse but also may have reduced adverse side effects.

9. Targeted, intermittent-dose strategies carry substantial increased risk of relapse. However, for patients who refuse to take medication continuously, this strategy may be a useful alternative.

10. The above conclusions pertain primarily to the first year after the acute episode. Data on efficacy beyond 1 year of maintenance therapy are insufficient; however, those that do exist suggest that continued therapy is advantageous.

11. Antipsychotic medications produce some short-term impairments in attention and vigilance, but administration of these drugs for more than 8 weeks produces variable results depending on the neuropsychological function being assessed. Maintenance antipsychotic therapy may enhance vigilance and attention, problem solving, and ability to organize, but it detracts from fine motor task performance.

Effectiveness of Conventional Antipsychotics

What Is the *Effectiveness* of the Conventional Antipsychotics for Relief of Acute Positive Symptoms, Prevention of Relapse and Recurrence of Positive Symptoms, and Reduction of Cognitive Impairments and Negative Symptoms? There is a great paucity of research on the effectiveness of conventional antipsychotic medications among typical patients with schizophrenia in typical practice settings. In theory, the effectiveness of any treatment lies between the efficacy of the treatment and the natural course of the disorder without the treatment. The benchmarks for the two ends of this range can be estimated from the controlled clinical trials reviewed earlier and from followup studies from the era before antipsychotics. Davis and Andriukaitis (1986) summarize the results from eight followup studies of patients with schizophrenia before the era of antipsychotic medications. They do not present 1-year relapse rates per se, but report on the proportion of patients who remained psychotic after an acute symptom episode or whose condition worsened. The sample size–weighted mean rate of continued severe symptoms from these studies with a total of 2,029 patients was 67.8 percent. From 44 randomized clinical trials of antipsychotics versus placebo, Baldessarini et al. (1990) estimate the relapse rate on placebo to be 55.2 percent over an average 10-month period. Using data from three large, long-term, followup studies, these same reviewers project a 12-month relapse rate of about 72 percent. Kissling (1992) summarizes relapse rates on placebo from six placebo-controlled studies with 1-year followup rates and reports a mean 1-year relapse rate of 74 percent. Based on these figures, a 72-percent relapse rate during the year after an acute symptom episode may be a reasonable upper estimate in untreated patients.

The lower boundary of 1-year relapse on optimal antipsychotic therapy in controlled trials is estimated by Kissling (1992), who computes a rate of 16 percent from the six trials with 1-year followups. Baldessarini et al. (1990) compute an average relapse rate of 14.3 percent over 10 months from the 44 placebo-controlled trials, and project a 12-month rate of about 30 percent from the three longer term trials. An estimate of a 23-percent relapse rate on medication over 1 year therefore seems reasonable.

These estimates yield efficacy benchmarks (annual relapse rates) ranging from 23 percent on medications to 70 percent off medications. Data on the actual relapse rates among typical groups of patients with schizophrenia treated in typical settings are scarce, but estimates put them in the range of 50 percent (Kissling 1992), about midway in the 23- to 72-percent benchmark range.

The reasons for the discrepancy between relapse rates on medications in clinical trials and those in clinical practice are several and have been discussed in various reviews (Kane 1989; Kissling 1992). The major reasons cited include patient noncompliance with prescribed medications, failure of some practitioners to prescribe adequate doses of medication for those patients who would benefit from it, and greater patient heterogeneity (prognosis, comorbid conditions, etc.) in clinical practice than in clinical trials.

Summary of Effectiveness Findings. With the limited information available, it appears that anti-

psychotic medications improve relapse rates in clinical practice compared with no antipsychotic medication treatment, but effectiveness in practice is substantially less than efficacy in clinical trials for reasons that are yet to be determined fully.

Differential Efficacy and Effectiveness Among Conventional Antipsychotics

Is There Differential Efficacy and Effectiveness Among the Alternative Conventional Antipsychotics, Including Depot Forms? In the acute phase, reviewers agree that there are no substantive differences in efficacy among the conventional antipsychotics. Davis and colleagues' (1989) review of studies in which the efficacy of different antipsychotics was compared reported that mepazine and promazine are less effective than CPZ but found no other differential efficacy between CPZ and other antipsychotics. Studies comparing thioridazine and trifluoperazine with other antipsychotics showed no differential efficacy. Little is known about the differential effectiveness of different antipsychotics in the acute phase. Kane and Marder (1993) caution that for an individual patient, prior drug response, tolerance of side effects, and long-term treatment plan should be considered in selecting an antipsychotic medication.

The absence of differential efficacy of conventional antipsychotic agents in the long-term treatment phase cannot be asserted with any certainty because, as Baldessarini et al. (1990) point out, the available controlled trials of maintenance treatment have primarily focused on only three medications—CPZ, thioridazine, and FLU. None, for example, has used HPL.

Oral vs. depot. The major issue that has been examined in some detail regarding different antipsychotic agents in the maintenance phase is the use of long-acting depot agents, primarily depot FLU, in comparison with oral forms. Davis et al. (1993) reviewed six controlled studies comparing oral versus depot antipsychotic medications. All studies followed patients for at least 1 year, except for one that had a 40-week followup. These studies involved 522 patients, and the differences in percentage of relapse on oral versus depot ranged from 48 percent (favoring depot) to 16 percent (favoring oral). Five of the six studies favored the depot form, and the average difference in relapse on oral versus depot, weighted for sample size, was 16.5 percent, a significant finding (Davis et al. 1989, 1993).

However, Davis et al. (1993) interprets the results from these six studies as mixed. In three of the studies, the advantage in percentage of patients who did not relapse on depot versus oral is appreciable: 48 percent (del Guidice et al. 1975), 27 percent (Crawford and Forrest 1974), and 25 percent (Hogarty et al. 1979). In two studies, there is little difference although depot is favored by 9 percent (Schooler et al. 1979) and 2 percent (Rifkin et al. 1977). Falloon et al. 1978) found a relative 16-percent relapse advantage for oral pimozide over depot FLU decanoate. Davis et al. (1989) point out that the hypothesized advantage of depot forms in improving compliance may be attenuated in the standard controlled clinical trial. This is because such trials typically tend to exclude noncompliant patients and provide better clinical management (more enthusiastic prescribers and better informed patients) than is found in typical clinic settings. In essence, these observations by Davis and colleagues suggest that the relative advantage of the depot form may be in its effectiveness rather than its efficacy, and standard clinical trials designed primarily to evaluate efficacy may not adequately test differential effectiveness. Kane and Lieberman (1987) further note that the existing controlled trials of depot versus oral may have insufficient followup periods and sample sizes for the differential effects of these modalities to be detected.

Summary of Relative Efficacy and Effectiveness Findings

1. Given the lack of differential efficacy of conventional antipsychotic medication in the acute phase as well as the lack of evidence on differential effectiveness, the choice of medication should be made individually on clinical grounds.

2. Because few conventional antipsychotics have been studied in the long-term treatment phase, their relative efficacy and effectiveness in this phase are not known. It can be stated that, to date, there has been no evidence that different classes of antipsychotic agents have differential impacts during long-term treatment.

3. On balance, there is evidence that depot medication reduces the risk of relapse in the maintenance phase. However, the design limitations of existing controlled clinical trials limit this conclusion. Generally these limitations would sug-

gest that the impact of depot is underestimated by existing controlled trials; however, other patient factors (e.g., patient acceptance of depot forms) may work against differential effects in typical practice settings.

Impacts on Functional Status and Other Outcomes

What Effects Do Conventional Antipsychotics Have on Functional Status and Other Nonclinical Outcomes? There is relatively scant information about the impact of conventional antipsychotic medications on nonclinical outcomes. Among the key reviews, the only discussion of other outcomes arises in the context of alternative dosing strategy studies. From the very limited number of studies and results, Schooler (1991) concludes that low continuous-dose regimens seem to lend some advantage over standard doses on such outcomes as subjective well-being (Kane et al. 1983, 1985), relatives' anxiety (Johnson et al. 1987), family relations (Hogarty et al. 1988), and employment (Kane et al. 1986; Hogarty et al. 1988), but her discussion of these results is too cursory to be evaluated. Schooler (1991) found no evidence favoring the targeted, intermittent approach on these other outcomes. In fact, she describes one study (Carpenter et al. 1990*a*, 1990*b*) in which patients on the targeted approach fared less well on employment outcomes than patients on continuous standard-dose therapy. In sum, there is insufficient evidence to draw conclusions regarding the impact of maintenance antipsychotic therapy on nonclinical outcomes.

Antipsychotic Therapy for First-Episode Patients

What Strategies Can Be Recommended in the Pharmacological Treatment of Individuals Suffering Their First Acute Episode of Schizophrenia? Should the treatment of persons suffering from their first episode of schizophrenia differ from that of patients who have had previous acute episodes? Whereas the current literature cites a 70-percent rate of response to antipsychotics in the acute episodes of chronic patients (Kane 1989), it appears that the rate of antipsychotic response in first-episode patients and patients with nonchronic disease may be somewhat higher (Cole et al. 1964, 1966). Lieberman et al. (1993) found that 83 percent of 70 first-episode patients treated with antipsychotic medication had remitted by 1 year postinpatient admission, with a mean and median time to remission of 35.7 and 11 weeks, respectively. It could be argued that the increased rate of response suggests that some of these patients might have remitted spontaneously without medication. However, patients in this study were judged to have exhibited formal psychotic symptoms for an average of 52 weeks before treatment, which suggests that they did *not* remit spontaneously.

McEvoy et al. (1991) found that the neuroleptic threshold dose of HPL was significantly lower in patients not previously exposed to neuroleptics than in individuals who had been exposed. This suggests that first-episode patients can be treated with lower doses of antipsychotics than chronic patients.

Davis et al. (1989, 1993) argue that long-term maintenance should not be instituted for first-episode cases who experience a full remission of symptoms. They recommend continuation treatment for 6 months, and then a trial discontinuation if the patient does not experience any symptom recurrence during those 6 months. However, they also recommend, based primarily on clinical judgment and a very limited number of studies, that patients who have suffered recurrences, regardless of other prognostic features, should receive maintenance therapy. Somewhat in contrast, the European Consensus Conference (Kissling 1992) recommends 1 to 2 years of continuation therapy for first-episode cases, pointing out that there are no prospective studies of this issue. With regard to multiepisode patients, they recommend a minimum of 5 years of treatment, again based primarily on clinical opinion.

The research to date thus indicates that first-episode patients should be treated with antipsychotic agents rapidly but may require lower dosages. Also, it is appropriate to taper or discontinue medication within 6 months to 1 year.

Discussion

Almost four decades of research has provided strong evidence that the use of conventional antipsychotic medications, which is routine in the treatment of schizophrenia, is helpful in controlling the positive symptoms of the syndrome, has immeasurably reduced its morbidity and mortality, and thus should be continued. Generally speaking, this research has very much penetrated clinical practice. Less clear, however, is the ex-

tent to which optimal dosing strategies have penetrated clinical practice. It is likely that physicians often prescribe dosages in excess of required levels.

Given what we have learned from the body of research on conventional antipsychotics, the gaps of knowledge in the literature are most striking. Studies of effectiveness are scarce. Little can be said about the efficacy and effectiveness of conventional antipsychotics on nonclinical outcomes. Well-designed long-term studies are virtually nonexistent, so the longitudinal impact of treatment with conventional antipsychotics is unclear. Although not covered in this review, the impact of patient factors such as race, ethnicity, sex, and age on efficacy and effectiveness has also been understudied.

These deficits in the literature define a research agenda that must also be modified in concert with the emerging literature on new antipsychotic agents. Studies of the efficacy of acute and maintenance antipsychotic therapy for enhancing outcomes other than positive symptom relapse should be given high priority. Of particular interest are the impacts of standard-dose maintenance therapy, as well as the relative efficacy of low- versus standard-dose strategies, vis-à-vis functional status and quality of life.

The interactions of maintenance antipsychotic therapies (the impact of standard-dose therapy as well as the relative impacts of alternative dosing strategies) with psychosocial rehabilitation interventions for improving nonsymptom outcomes should be studied. Finally, high priority should be given to studies of the effectiveness of maintenance antipsychotic therapies in various practice settings. What patient and practice setting factors account for variations in effectiveness? What can be done to improve the effectiveness of maintenance antipsychotic therapy in terms of enhanced patient compliance and appropriate provider prescription and monitoring practices? Interventions that may be studied include alternative dose strategies, depot versus oral administration, frequency of visits, and integration of pharmacotherapy with other services.

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