Psychiatric Hospital Utilization in Patients Treated With Clozapine for up to 4.5 Years in a State Mental Health Care System

William H. Reid, M.D., M.P.H.; and Mark Mason, M.S.

Objective: We wished to study long-term psychiatric hospital utilization in a large sample of patients with schizophrenia and/or schizoaffective disorders who were treated with clozapine for up to 4.5 years, and to determine whether or not the reduction in hospital utilization we previously observed in smaller groups for up to 2.5 years was sustained with larger groups and in the longer term.

Method: Patients in Texas state hospitals who had schizophrenia and/or schizoaffective disorder took either clozapine or traditional antipsychotics for 1.5 to 4.5 years. The number of patients in the clozapine group ranged from 383 (1.5 years of treatment) to 29 (4.5 years). The group of patients who took traditional antipsychotics was made up of all patients (N = 233) with similar diagnoses, symptom severity, and duration of illness present in Texas state hospitals on an index day.

Results: The clozapine group showed a rapid and continuing decrease in hospital bed-days compared with controls who took traditional antipsychotics. The number of clozapine-treated patients who required little or no hospitalization during successive 6-month periods became significant ($p < .0001$) within 1.5 years, and continued to increase. Conversely, the number of patients taking clozapine who required virtually continuous state hospitalization decreased markedly compared with those taking traditional antipsychotics.

Conclusion: Potential hospital cost savings are substantial, even though overall group results are diluted by clozapine nonresponders. Most treatment costs for clozapine nonresponders were related to hospital care; most or all of such costs would have been present in any event had these patients remained on traditional antipsychotic therapy. We believe a trial of clozapine therapy provides a low-cost opportunity for a highly effective and highly cost-saving outcome in those patients who will favorably respond to this therapy. We discuss clinical, social, and economic advantages of modern pharmaceutical treatments over traditional drugs.

(J Clin Psychiatry 1998;59:189–194)

Received June 25, 1997; accepted Feb. 13, 1998. From the University of Texas Health Science Center, San Antonio (Dr. Reid), and the Texas Department of Mental Health and Mental Retardation (Mr. Mason).

Although this paper relies upon data collated by the Texas Department of Mental Health and Mental Retardation, the views expressed herein do not necessarily reflect those of the Department or the State of Texas.

The authors gratefully acknowledge the assistance and support provided by Thomas J. Hogan, M.B.A., Novartis Pharma AG, Basel, Switzerland.

Reprint requests to: William H. Reid, M.D., P.O. Box 4015, Horseshoe Bay, TX 78657 (e-mail: reidpsychiatry@compuserve.com).

Schizophrenia is arguably society's most expensive psychiatric illness.[1] Total 1990 costs of schizophrenia in the United States alone were about $32.5 billion.[2] Lost productivity due to morbidity and mortality account for $12 billion of this total, and $17.3 billion represents direct medical costs of patient care.[2] Notably, costs of hospitalization represent 83% of total direct medical costs of care of schizophrenia patients, whereas drug costs make up only 2.3%.[2]

In spite of rising pharmaceutical costs, many health economists and mental health system managers believe that providing the best available treatments for schizophrenia and schizoaffective illness is far less expensive than relying on older and less expensive—but less effective—drug interventions.[3,4] Expenditures for traditional neuroleptics account for well under 1% of the total cost of inpatient care, and roughly 2% of total outpatient costs. Drug and monitoring costs for clozapine and other atypical neuroleptics are under $15 per day, representing less than 6% of total average hospital costs in the Texas State system.

In 1994, we reported substantial inpatient bed-day reductions and estimated cost savings associated with clozapine therapy based on review of 172 patients treated for 1.5 years and 53 patients treated for up to 2.5 years.[5] Potential dollar savings were estimated at about $33,000 per patient per year after 1.5 years, and over $50,000 per patient per year at 2.5 years.[1]

Many other authors have reported on clozapine's clinical effectiveness,[6–13] reduction of schizophrenia-related morbidity and mortality,[14,15] safety,[16] and cost-effectiveness.[17–19] Findings in favor of clozapine's cost-effectiveness have been reported consistently in published studies undertaken in 4 countries, in 11 different settings,

and using an array of dissimilar study designs and patient groups—they suggest a relatively robust effect.[20] However, many of these reports are based on observation periods of no longer than 2 years; it would be informative to examine effects over longer periods. Are the reductions in hospital utilization seen in short-term treatment sustainable in long-term treatment? What is the magnitude of the reduction in long-term hospital utilization (and the estimated cost saving) for patients on clozapine therapy?

The purpose of this article is to report findings of a study of patients with schizophrenia and schizoaffective disorder treated with clozapine for periods of between 1.5 years and 4.5 years in a state mental health care system. Our results reflect the longest observation period reported to date for clozapine-treated patients. The data may be of value to health care decision makers. These results extend earlier work and represent data on more than twice as many subjects.

METHOD

The subjects of this report (the clozapine group) were all of the Texas Department of Mental Health and Mental Retardation (TDMHMR) patients who began clozapine therapy in a state hospital during the study period and who continued treatment for 1.5 to 4.5 years. The controls (traditional antipsychotics group; N = 223) included all TDMHMR patients who (1) had the same diagnoses as, and symptom severity similar to, clozapine patients; (2) were hospitalized in a state hospital on a specific date; and (3) either received no clozapine during the study period or started and stopped clozapine within 12 months. No attempt was made to match the 2 groups in terms of age or gender, although we believe there are no imbalances that would skew analytical results.

Clozapine patients were identified and followed using a TDMHMR clozapine database. State facility bed-days were monitored by another central information system and referred to all days during which a patient was on the rolls of a state-funded inpatient facility. Hospitalizations outside the TDMHMR system were not addressed for either group.

Inpatient bed-days were tallied for two 180-day periods beginning 1 year before administration of clozapine. These periods are designated as M2, referring to the period 360–181 days before clozapine, and M1, referring to the 6 months immediately prior to clozapine initiation. For clozapine patients, consecutive 180-day periods beginning 90 days after initiation of clozapine treatment (to allow for titration) are referred to as P1, P2, P3, etc. For patients taking traditional antipsychotics (controls), M2 and M1 represent 180-day periods prior to an arbitrary starting date, and P1, P2, etc., denote consecutive 180-day periods beginning 90 days after the designated starting date (to mimic the clozapine titration period). Pre-clozapine bed-days were calculated using M2 alone to avoid bias arising from inclusion of any patients admitted specifically for clozapine treatment.

Patients who discontinued clozapine after the first year were included in the analyses only for those entire periods in which they received the drug. For example, if they stopped clozapine between 2.5 and 3 years (P5 and P6, respectively), they would be part of analysis through P5 but not thereafter.

For the purposes of this article, inpatient costs were estimated at $250 per bed-day. This figure includes the costs of physician care, special care such as one-to-one monitoring or treatment in psychiatric intensive care units (PICUs), and all prescriptions apart from antipsychotic medications. No effort was made to separate PICU and acute care costs (more than $250/day) from those for extended care units ($175–$200/day).

All clozapine data refer to patients who took clozapine for the period reported: 1.5 years (P3), N = 383; 2.5 years (P5), N = 299; 3.5 years (P7), N = 101; 4.0 years (P8), N = 54; 4.5 years (P9), N = 29. Differences in clozapine group size for each period are due primarily to lower numbers of patients initiating clozapine therapy in the early 1990s than in subsequent years and, to a lesser extent, to patients discontinuing therapy. About 81% of patients who completed the 90-day clozapine trial before the P1 period remained on the drug for another 18 months (through P3) and thus were included in the P3 group. About 75% of those who started clozapine in late 1990, almost 5 years before completion of the study, remained on clozapine for 54 months (through P9). Note that only 29 patients are in the P9 group (4.5 years on clozapine therapy) because few patients started clozapine therapy early enough to amass 4.5 years of therapy, not because of a high patient dropout rate.

Statistical Analysis

Inpatient days for the M2 time period (181–360 days prior to initiation of clozapine) were compared with inpatient days over subsequent 180-day intervals (P1, P2, etc.) after the 90-day clozapine titration/adjustment period using Student t test.

RESULTS

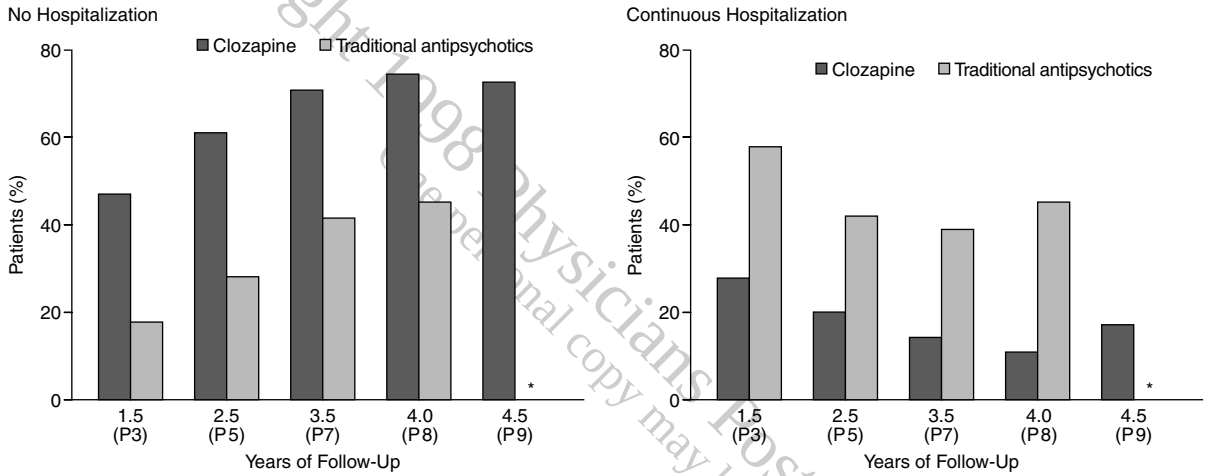
During the pre-clozapine period, virtually all patients were heavy users of inpatient care: 44% to 61% of all clozapine patients and 73% of controls had been continuously hospitalized for at least 6 months, and fewer than 3% of either the clozapine or the traditional antipsychotics group had been out of the hospital continuously during the previous 6 months. After starting clozapine, the clozapine group showed impressive decreases in hospital bed-days (Table 1).

Table 1. Distribution of Hospital Bed-Day Utilization Over Various Observation Periods for the Cohort of Clozapine-Treated Patients

Days of Hospitalization/ 6-Month Period	Percentage of Patients Requiring Hospitalization in Given Observation Period (no. of patients)[a]					
	M2 (N = 383)	M1 (N = 383)	P3 (N = 383)	P5 (N = 299)	P7 (N = 101)	P9 (N = 29)
0	19.3	1.7	46.8	60.5	70.3	72.4
1–30	4.7	7.4	4.3	2.7	1.0	3.4
31–60	2.7	4.0	1.7	2.3	2.0	3.4
61–90	3.0	6.7	2.0	0.7	1.0	3.4
91–120	5.7	5.7	2.3	2.0	1.0	0
121–150	4.7	7.0	4.0	3.3	3.0	0
151–180	59.9	67.6	38.8	28.4	21.8	17.2

[a]M2 = period 360–181 days before clozapine, M1 = 180 days immediately prior to clozapine initiation, P = consecutive 180-day periods beginning 90 days after initiation of clozapine.

Figure 1. Percentage of Patients in the Clozapine and Traditional Antipsychotics Groups During Various 6-Month Periods (P) Prior to and During Treatment



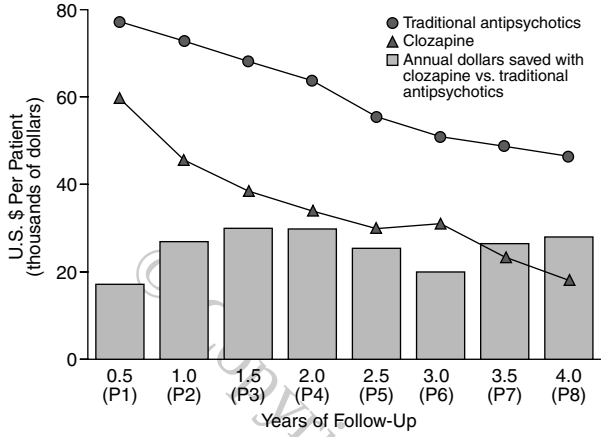
*Data not available.

The within-group difference between pre-clozapine and clozapine bed-days is striking, becoming statistically significant by the end of the first year ($t = -4.1$ to -12.5; $p < .0001$ for all clozapine groups). Most clozapine patients either remained out of hospital altogether or were hospitalized for most of the 180-day period (a highly bimodal distribution). For many, administrative aspects of clozapine use (e.g., the requirement for weekly blood monitoring) made discharge into community care more difficult.

By the middle of the second year of treatment (P3), the level of hospitalization was still declining rapidly among clozapine-treated patients, with 47% requiring no inpatient care at all during the third 180-day period. At 2.5 years (P5), the number of clozapine patients with no hospital days had risen to over 60% (versus 28.3% of controls), and those requiring a full 180 days of inpatient care had declined to 19.7% (versus 42.2% of controls). At 4.0 years (P8), 74.1% were continuously out of hospital for 180 days (versus 44.8% of controls), and only 11.1% were continuously in the hospital during the same period (versus 45.7% of controls) (Figure 1).

Patients taking traditional antipsychotics also showed some decrease in hospital bed-days. Whether this represents regression toward the mean or a real underlying trend is unclear from the data. Nevertheless, the decrease in the group who took traditional antipsychotics was less marked and slower than that in the clozapine group. Differences favoring clozapine in patients who had very high hospital use (those hospitalized for > 160 days per 180-day period) were especially pronounced. Controls required almost 4 years to attain the same rate of "no hospitalization" that the clozapine group attained in 1.5 years. In addition, the proportion of patients requiring continuous hospitalization declined more slowly in the group who took traditional antipsychotics, leveling off at approximately 40% after 2.5 years. In contrast, the proportion of clozapine patients requiring continuous hospitalization declined by approximately 40% in the first 1.5 years, falling to only 11.1% by the end of 4.0 years of treatment (Figure 1).

Figure 2. Potential Annual Hospital Costs and Savings in U.S. Dollars (Costs of Clozapine Are Excluded)



Compared with the M1 pre-clozapine period, clozapine-treated patients showed a mean decrease in hospital bed-days of 128.4 days/patient/year during the first 1.5 years (P1 + P2 + P3) of treatment (versus 69.2 days/patient/year for M2 controls; $p < .0001$). Hospital use by clozapine patients continued to decrease throughout the study.

After 1.5 years (P3), the annualized difference between all clozapine-treated patients and controls was 119.8 bed-days/patient/year, representing potential savings of $29,950/patient/year over traditionally medicated patients (at $250/day), less costs of clozapine and outpatient care (which were not examined in this study). Total potential hospital cost savings calculated for these 383 clozapine patients during 1.5 years of treatment (following the titration period), compared with an identical number of traditionally medicated controls, were $17,206,275, representing $11,470,850 per year (Figure 2). The annualized per-patient hospital bed-day savings in subsequent monitoring periods was 102.4 days (at 2.5 years; P5), 103.2 days (at 3.5 years; P7), and 111.4 days (at 4 years; P8).

DISCUSSION

Hospital Bed-Days

We conclude that clozapine therapy decreases state hospital bed-day usage among patients with a history of frequent hospitalization for schizophrenia or schizoaffective disorder, particularly in clozapine patients who may be described as "responders." In our experience, the decrease in hospital bed-day usage reflects improved patient health status, which allows patients to remain discharged from hospital care. When health improvements are considered with respect to cost consequences of reduced hospitalization, clozapine therapy appears to be highly cost-effective in responding patients, mitigated somewhat by clozapine therapy or therapeutic trial costs in nonresponding and discontinuing patients.

The bimodal distribution of hospital bed-days among clozapine responders appears to suggest an all-or-none response to clozapine therapy, with patients improving either dramatically or not at all. However, this is an oversimplification. Many patients remain hospitalized despite improvements in their clinical condition, while others are able to remain out of the hospital despite continuing psychotic symptoms. Hospital bed-days per se do not reflect all aspects of the clinical response.

Several potential sources of error should be considered in interpreting the present findings. Difficulty arranging suitable community care kept many clozapine patients, and some patients who were taking traditional antipsychotics, in hospital long after they satisfied clinical criteria for discharge. We believe that the resulting inflation of hospital bed-days is a source of error that tended to penalize clozapine patients more than controls who took traditional antipsychotics. Conversely, once discharged, clozapine-treated patients and patients treated with traditional antipsychotics may have tended to remain in the community simply because they did not exhibit severe symptoms or behaviors (e.g., violence, public disruption) that triggered rehospitalization. Since virtually all Texas state hospital admissions are involuntary, our study of hospital bed-day savings does not distinguish between patients who are doing very well and those who may merely avoid precipitating rehospitalization episodes. We believe this limitation would falsely skew results for the clozapine group in a negative direction as well.

The initial difference in bed-days between clozapine-treated patients and patients treated with traditional antipsychotics may cast some doubt on the magnitude of later savings, suggesting that control patients had to overcome a greater initial hospital occupancy in order to match the success of clozapine-treated patients. While this should be taken into consideration, the rapid reduction in hospital days in the clozapine group suggests a pronounced drug effect, regardless of the initial magnitude or subsequent rate of reduction of bed-days in the group that took traditional antipsychotics. In addition, it is worth noting that we chose period M2 as the baseline clozapine reference period for hospital costs, not M1 (which had higher hospital costs), to avoid any possible artifact arising from patients being hospitalized expressly to gain access to clozapine. It is possible that M1 hospital costs for the clozapine group simply reflect costs arising from normal exacerbations or relapses of disease, following which many patients begin clozapine therapy. Lastly, this article highlights group analysis in a therapeutic environment that does not routinely discontinue clozapine therapy in individual patients whose response may be small. Our group results therefore reflect the net effect of the dramatic results attributed to clozapine "responders," aver-

aged with moderate or smaller impact in other clozapine patients.

The hospital inpatient cost of $250/day employed in these calculations is an estimate used in the TDMHMR budget process. We did not differentiate between time spent in intensive, acute, and extended inpatient care. We believe that the estimate of $250/day is conservative, since it includes all physician, other clinician, procedural, and laboratory costs. It is likely that calculating actual time spent in PICU versus less expensive units would reveal even more clozapine benefit. Other authors have noted that clozapine is associated with a decreased need for intensive inpatient services.[8,14,21]

Clozapine treatment involves more than medication. Clozapine patients were seen by a health care worker (often only for venipuncture) on a weekly basis. This may favorably influence health and rehospitalization outcomes. On the other hand, at least 1 study indicates that close monitoring of schizophrenic and schizoaffective patients tends to increase their hospital bed-days, because severe symptoms are more likely to be observed by a clinician.[22]

Some additional direct monetary cost savings related to clozapine use can be inferred through reduced need for acute care staff, one-to-one patient monitoring, patient restraint and seclusion, as well as through reduced injury to staff and patients.[13,14,18] TDMHMR experience indicates that, after starting clozapine, many severely ill patients can be transferred to lower-staffed, less expensive units while awaiting appropriate community placement. Such cost savings are not considered in this study.

Cost-Effectiveness vs. Realized Savings

Decreased hospital usage by these patients does not necessarily translate into immediate dollar savings.[4,5] Although patients may have fewer hospital bed-days, which means that more people may be treated with the same hospital budget, state hospitals themselves (as cost centers) do not realize occupancy-related savings unless they can decrease staffing or permanently reduce or close entire units. Payers, especially state legislatures, prefer to see actual decreases in dollars spent rather than productivity gains attained by treating more patients within the same budget. Be that as it may, achieving economic efficiency by treating more patients within constrained budgets is a worthwhile public (as well as economic) goal, and one that maximizes the health of needy citizens within the context of public budget constraints. In addition, possible longer-term savings achievable from reduced staffing needs represent an important public policy issue and should not be ignored.

Cost-shifting between state and local mental health administrative units may also come into play. For example, interventions such as clozapine treatment, which may benefit patients and state hospitals alike, may not be accompanied by changes in community administrative and funding behavior (or attitudes) needed to support their ultimate success. Even health benefits to patients and savings for the state and its taxpayers may not encourage cities or counties to readily accept patients ready to return to the community, especially if they require more burdensome monitoring or more expensive (outpatient) care than other patients. As a separate issue, nontroublesome yet symptomatic patients who are suboptimally controlled with older, less expensive drugs in the community may be seen as a low priority for expensive medications, even when clinically indicated. Policy research into such issues would be informative.

Other Potential Benefits and Cost Consequences

There are other health and cost benefits of clozapine therapy that are not considered in this study, but that merit consideration by clinical decision makers. Meltzer and Okayli[15] report that clozapine is associated with significantly reduced suicidality compared with traditional antipsychotics, and Walker et al.[23] report a dramatically lower suicide rate in clozapine patients than in those who discontinue clozapine. These reports are further supported by our own data suggesting a favorable effect of clozapine therapy on suicide rates (manuscript submitted).

The cost of adverse drug effects should also be considered in long-term clinical and administrative decision making. It is likely that the costs associated with adverse effects of clozapine are lower than those of traditional antipsychotics. In the course of treating some 1400 patients with clozapine within the TDMHMR system, we are aware of only 3 confirmed cases of leukopenia or agranulocytosis severe enough to require hospitalization (0.21% of all clozapine-treated patients); all recovered completely after brief, uncomplicated treatment. Our experience with conventional antipsychotics and their associated adverse effects (e.g., tardive dyskinesia, neuroleptic malignant syndrome, severe dystonia, intractable akathisia) has been much more problematic in terms of clinical outcome, cost of care, and risk of malpractice litigation.

The number of severely and chronically mentally ill patients who can benefit from interventions such as psychological and social therapies and vocational rehabilitation—not merely support and case management—increases as more effective drug treatment becomes available. The array of services that the clozapine-responsive patient often requires to optimize his or her improvement goes beyond the relatively minor cost of blood monitoring. Community focus on basic psychosocial management, still needed for many, must shift to more sophisticated programs for those who can benefit from them. Community mental health staff invested in a socially supportive, largely nonbiological, view of treatment will need to reevaluate their priorities and allegiances to allow trials of new treatments that, for many, offer clinical improvement previously unavailable.

CONCLUSION

Our analysis focused on the single greatest component of the direct cost of care of patients with severe schizophrenia: hospitalization. We report favorable long-term results with respect to hospital bed-day utilization associated with clozapine versus traditional neuroleptic therapy in a state mental health system. Significant ($p < .0001$) hospital bed-day reductions of over 100 days per year were noted from 1.5 years (P3) through 4.0 years (P8), representing economic savings of over $25,000 per patient per year (based on an estimated cost of $250 per bed-day).

The most important goals of medical care of severely and chronically mentally ill patients are the alleviation of personal misery and improvement of personal function. We believe there is intrinsic value to helping severely ill patients live outside the hospital setting through provision of good psychiatric care. To achieve our professional and public sector mandate of improving clinical status, health functioning, and quality of life, psychiatrists and other mental health providers must "reset the drug cost thermostat." We must stop thinking of psychiatric treatment in terms of inexpensive but poorly effective conventional antipsychotics, and instead focus on the most effective agents available for our patients.[24] Although it may seem counterintuitive, a higher-priced but more effective drug may be a very good value.

Drug name: clozapine (Clozaril).

REFERENCES

1. Martin P. Medical economic impact of schizophrenia. Encephale 1995;21(special section 3):67–73
2. Rice DP, Miller LS. The economic burden of schizophrenia: conceptual and methodological issues, and cost estimates. In: Moscarelli M, Rupp A, Sartorius N, eds. Handbook of Mental Health Economics, vol 1: Schizophrenia. Chichester, England: John Wiley & Sons Ltd; 1996
3. Revicki DA, Luce BR, Wechsler JM, et al. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. Hosp Community Psychiatry 1990;41:850–854
4. Reid WH. Schizophrenia, modern treatment, and the economics of care. Rev Contemp Pharmacother 1995;6:209–215
5. Reid WH, Mason M, Toprac M. Savings in hospital bed-days related to treatment with clozapine. Hosp Community Psychiatry 1994;45:261–264
6. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151:20–26
7. Chow EW, Collins EJ, Nuttall SE, et al. Clinical use of clozapine in a major urban setting: one year experience. J Psychiatry Neurosci 1995;20: 133–140
8. Ebrahim GU, Gibler B, Gacono CB, et al. Patient response to clozapine in a forensic psychiatric hospital. Hosp Community Psychiatry 1994;45: 271–273
9. Kane JM. Clinical efficacy of clozapine in treatment-refractory schizophrenia: an overview. Br J Psychiatry 1992;17(5, suppl):41–45
10. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994;151:1744–1752
11. Meltzer HY, Cola PA. The pharmacoeconomics of clozapine: a review. J Clin Psychiatry 1994;55(9, suppl B):161–165
12. Neuhalfen EA, Kaplan A. Are you missing anything? recent psychotropics available in Europe, but not in the United States. Psychiatric Times, March 1994:34
13. Wilson WH, Claussen AM. 18-month outcome of clozapine treatment for 100 patients in a state psychiatric hospital. Psychiatr Serv 1995;46: 386–389
14. Chiles JA, Davidson P, McBride D. Effects of clozapine on the use of seclusion and restraint at a state hospital. Hosp Community Psychiatry 1994; 45:269–271
15. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
16. Gury C, Dechelette N, Gayral P. Leponex: experience of the hospital pharmacist. Encephale 1995;21(special section 3):61–65
17. Davies LM, Drummond MF. Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. Br J Psychiatry 1993;162:38–42
18. Jonsson D, Walinder J. Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia. Acta Psychiatr Scand 1995;92:199–201
19. Meltzer HY, Cola P, Way L, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. Am J Psychiatry 1993;150:1630–1638
20. Morris S, Hogan T, McGuire A. The cost-effectiveness of clozapine: a survey of the literature. Clin Drug Invest. In press
21. Essock SM, Hargreaves WA, Dohm FA, et al. Clozapine eligibility among state hospital patients. Schizophr Bull 1996;22:15–25
22. Tyrer P, Morgan J, Van Horn E, et al. A randomised controlled study of close monitoring of vulnerable psychiatric patients. Lancet 1995;345: 756–759
23. Walker AM, Lanza LL, Arellano A, et al. Mortality in current and former users of clozapine. Epidemiology 1997;8:671–677
24. Reid WH. The treatment of psychosis: resetting the drug cost "thermostat." J Clin Psychiatry 1994;55(9, suppl B):166–168