Relationship Between Costs and Symptoms in Schizophrenia Patients Treated With Antipsychotic Medication: A Review

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Background: The purpose of this review is to understand how changes in costs of illness are related to the effects of antipsychotic medications on symptoms in schizophrenia patients.

Method: A search of the MEDLINE database was performed using the keywords *costs*, *symptoms*, and *schizophrenia*. Studies published between 1965 and 2003 in English, French, German, or Spanish that assessed costs, symptoms, and relationships between costs and symptoms were reviewed.

Results: Twenty studies were identified. Most of the reviewed clinical trials of antipsychotic medications reported a decrease in mean costs of illness and an improvement in symptoms. However, many of the studies did not examine the relationship between changes in costs and symptoms.

Conclusion: There is little evidence that changes in costs of illness are directly related to the effects of antipsychotic medications on symptoms. This review emphasizes the need for standardizing the assessment of costs and clinical outcomes, looking more specifically at the relationship between types of costs and specific aspects of psychopathology and developing new statistical models relating changes in costs and clinical outcomes.

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In the past several years, there has been an increased concern with the ability of antipsychotic medications to reduce costs of schizophrenia. Confronted with rising treatment costs and pressure from third-party payers to be more "cost-effective," clinicians treating schizophrenia patients with antipsychotic medications have to deal with the following questions: Are costs related to some aspects of psychopathology? Is there a cost impact of treating symptoms with antipsychotic medications?

Health care providers who have to allocate limited resources for specific programs may also be interested in estimating and projecting costs for the treatment of a particular patient mix. It has been usually assumed that an improvement in psychopathology results in a decreased use of health care services, improved productivity, and enhanced quality of life. However, schizophrenia is a heterogeneous illness, and the effects of antipsychotic medications on costs of illness may vary among individuals depending on their symptom profile. Thus, the purpose of this review is to examine how changes in costs of illness are related to the effects of antipsychotic medications on symptoms in schizophrenia patients.

METHOD

A MEDLINE database search for the years 1965 to 2003 was performed using the keywords *costs*, *symptoms*, and *schizophrenia*. Criteria for selecting and evaluating studies were (1) publication in English, French, German, or Spanish; (2) treatment intervention with an antipsychotic medication; (3) inclusion of cost estimates; and (4) inclusion of symptom measurements. Relevant references cited in selected papers were also examined.

Studies are classified into 2 broad categories: nonrandomized and randomized controlled studies. Nonrandomized studies compare costs and clinical variables for periods before and after the initiation of an antipsychotic medication. Most nonrandomized studies do not include a control group. These studies use retrospective databases for the period preceding the treatment intervention and sometimes collect cost data for the period after the initiation of antipsychotic medication. In randomized con-

trolled studies, patients are randomized into groups with different treatment interventions, and a control group is included. These studies are specifically designed to collect cost and clinical outcome data.

Nonrandomized and randomized studies are reported in separate tables (Tables 1 and 2, respectively). This review only includes costs studies that reported symptom assessment. Since the purpose of this review is to look at the association between changes in costs and clinical outcomes, each table has a column indicating whether the study includes the analysis of this association.

RESULTS

Nonrandomized Studies

Table 1 shows 11 studies that have considered changes in costs and clinical outcomes in patients treated with an antipsychotic medication. Honigfeld and Patin[1] reviewed the records of 105 patients who received clozapine for at least 2 years and found lower Brief Psychiatric Rating Scale (BPRS)[2,3] total scores compared with the 2 years prior to initiation of clozapine. Honigfeld and Patin[1] compared direct mental health care costs for 86 of these patients with a group of treatment-resistant patients and found lower mean hospitalization costs at years 1 and 2. The study did not include costs related to clozapine treatment itself and did not analyze the association between costs and clinical outcomes. There is no information regarding the comparison group and no comparison of clinical outcomes between the clozapine and control groups. The relationship between costs and compliance (clozapine patients may have more outpatient services associated with blood monitoring, and, therefore, better compliance) is not addressed.

Revicki et al.[4] compared 87 clozapine-responder schizophrenia patients with 46 clozapine-dropout patients and 51 patients taking conventional antipsychotics. Direct costs were assessed 1 year prior and up to 2 years after the initiation of clozapine. Clozapine patients had a decrease in BPRS scores. The clozapine patients had lower hospitalization costs and lower direct costs than patients taking conventional antipsychotics after 2 years of treatment. The drawbacks of this study are small sample size, no analysis of the association between costs and clinical outcomes, and selection bias (clozapine patients had higher initial hospitalization costs and BPRS scores than patients taking conventional antipsychotics). In response to some criticisms,[5,6] the authors included in a reanalysis the costs of 46 patients who dropped out of the study and found that clozapine resulted in a cost increase after 2 years of treatment.[7]

Meltzer et al.[8] compared 37 treatment-refractory patients who received clozapine for 2 years with 10 patients who dropped out of clozapine treatment for the 2-year period before and after starting clozapine. Compared with dropout patients, those patients who received clozapine for 2 years had lower total BPRS scores, an improvement in Quality of Life Scale (QLS)[9] scores, and higher outpatient costs but lower hospitalization costs, resulting in a decrease in total costs. There were no changes in indirect costs (housing, family burden, loss of income). Compared with baseline, patients taking clozapine for 2 years had lower positive- and negative-symptom BPRS scores, a nonsignificant decrease in Clinical Global Impressions-Severity of Illness scale (CGI-S) scores,[10] improved QLS scores, and decreased hospital days. Although this study tried to address the limitations of the Revicki et al.[4] study and includes direct and indirect costs, it has its own shortcomings, which include small sample size, no control group of patients not treated with clozapine, no analysis of the association between costs and clinical outcomes, use of clozapine dropouts as a control group and no blind ratings,[11] and restrictive eligibility criteria.[12]

Lindström et al.[13] looked at 59 schizophrenia patients who were enrolled in a long-term follow-up study of risperidone. Thirty-two patients received risperidone for at least 1 year, and 19 of the 32 patients received risperidone for at least 2 years. Patients had decreased scores on the positive, negative, excited, anxious/depressive, and cognitive symptom factors derived from the Positive and Negative Syndrome Scale (PANSS),[14] and improved CGI-S, Social Functioning Scale,[15] and Extrapyramidal Symptom Rating Scale (ESRS)[16] scores after being treated with risperidone for 1 or 2 years. Compared with a 2-year period before the initiation of risperidone, those patients treated with risperidone had decreased inpatient days and increased days spent in treatment homes, suggesting lower direct costs related to risperidone. Limitations of this study are the small sample size, lack of a control group, no monetary estimates of direct costs, no cost information on patients who dropped out after 1 year (46%) and 2 years (68%) of risperidone treatment, and no analysis of the association between costs and clinical outcomes.

Guest et al.[17] collected direct cost (accommodation and medication) data retrospectively for 31 patients 1 year before and up to 2 years after the initiation of risperidone. Clinical outcomes were PANSS, CGI-S, and ESRS scores. Treatment with risperidone decreased hospitalization costs and increased residential costs. On balance, total accommodation costs were decreased, and PANSS, CGI-S, and ESRS scores were also decreased. Limitations of this study are small sample size, no control group, no inclusion of outpatient service costs in direct costs, no statistical analysis of cost data, and no analysis of the association between costs and clinical outcomes.

A British study[18] compared costs 3 years before and a minimum of 1 year after initiating clozapine treatment in 26 treatment-refractory patients with schizophrenia or schizoaffective disorder. There was no significant differ-

Table 1. Nonrandomized Studies of Costs and Clinical Outcomes in Patients Treated With Antipsychotic Medication

Study	N	Method	Length of Study (mo)	Direct Costs	Indirect Costs	Clinical Outcomes Assessment	Limitations	Analysis of the Association Between Costs and Clinical Outcomes
Honigfeld and Patin, 1990[1]	86	Comparison of costs between clozapine and conventional psychotropics	24	Yes	No	BPRS, side effects	No detailed information on direct costs Costs of clozapine not included No information on comparison group No comparison of clinical outcomes between clozapine and control drugs	No
Revicki et al, 1990[4]	184	Comparison of clozapine responders, clozapine-dropout patients, and patients taking conventional psychotropics	Up to 36	Yes	No	BPRS, CGI-S	Small sample size No statistical analysis of changes in costs and clinical outcomes Cost and clinical selection biases No intent-to-treat analysis	No
Revicki et al, 1991[7]	133		Same as Revicki et al,[4] with intent-to-treat analysis					
Meltzer et al, 1993[8]	47	Comparison of pre- and post-clozapine initiation periods between clozapine responders and clozapine-dropout patients	48	Yes	Yes	BPRS, CGI-S, GAS, QLS	Small sample size No control group of patients not treated with clozapine No blind ratings Eligibility criteria more restrictive than common practice	No
Lindström et al, 1995[13]	32	Comparison of pre- and post-risperidone initiation periods	Up to 48	Yes	No	PANSS, CGI-S, SFS, ESRS,	Small sample size No control group No cost information for patients who dropped out	No
Guest et al, 1996[17]	31	Comparison of pre- and post-risperidone initiation periods	Up to 36	Yes	No	PANSS, CGI-S, ESRS	Small sample size No control group No inclusion of outpatient service costs in direct costs No statistical analysis of costs data	No
Aitchison and Kerwin, 1997[18]	26	Comparison of pre- and post-clozapine initiation periods	At least 48	Yes	Yes	BPRS, GAS, QLS, AIMS	Small sample size No control group Improvement in QLS may be related to more intensive outpatient treatment No monetary estimates of indirect costs	No
Blieden et al, 1998[20]	33	Comparison of pre- and post-initiation periods between clozapine and dropout patients	12	Yes	No	BPRS, NSAS, HAM-D, QLS	Small sample size No control group Short follow-up period High dropout rates for clozapine	No
Lewis et al, 2001[23]	91	Comparison of patients taking risperidone, olanzapine, or clozapine	10	Yes	No	PANSS, QLS	Small sample size No randomization	Yes
Lynch et al, 2001[24]	21	Comparison of pre- and post-quetiapine initiation periods	24	Yes	No	BPRS, CGI-S, AIMS, Simpson-Angus	Small sample size No control group Costs limited to hospital days Assumptions about costs of medications (data on use and dose not collected)	No

continued

Table 1. Nonrandomized Studies of Costs and Clinical Outcomes in Patients Treated With Antipsychotic Medication (cont.)

Study	N	Method	Length of Study (mo)	Direct Costs	Indirect Costs	Clinical Outcomes Assessment	Limitations	Analysis of the Association Between Costs and Clinical Outcomes
Killian et al, 2001[26]	258	Multivariate regression analysis	12	Yes	No	24-item BPRS, GAF, CAN, LQLP, VSSS	Cost estimates based only on information provided by patients No information on antipsychotic medications Symptoms assessed only at beginning and end of study Regression model only explaining 38% of variance	Yes
Killian et al, 2003[32]	307	Multivariate regression analysis	30	Yes	No	PANSS, CDSS, GAF, SOFAS, SF-36	Cost estimates based only on information provided by patients No information on antipsychotic medications Regression models explain only a small percentage of variance	Yes

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CAN = Camberwell Assessment of Need, CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, ESRS = Extrapyramidal Symptom Rating Scale, GAF = Global Assessment of Functioning, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, LQLP = Lancashire Quality of Life Profile, NSAS = Negative Symptoms Assessment Scale, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale, SF-36 = Medical Outcomes Short Form 36-item health survey, SFS = Social Functioning Scale, Simpson-Angus = Simpson Angus Scale, SOFAS = Social and Occupational Functioning Assessment Scale, VSSS = Verona Service Satisfaction Scale.

ence between pre- and post-clozapine total costs, but there was a significant improvement in total BPRS, QLS, Global Assessment Scale (GAS),[19] and Abnormal Involuntary Movement Scale (AIMS; a scale assessing tardive dyskinesia)[10] scores and employment status. Compared with the pre-clozapine period, despite an increase in prescription and accommodation costs, there was a decrease in total costs due to a decrease in hospitalization costs in the post-clozapine period, however, not significant. Since the study did not include a comparison group, changes in clinical outcomes may have been related to more intensive outpatient treatment or other uncontrolled factors. The study did not include monetary estimates of indirect costs or an analysis of the association between costs and clinical outcomes.

Blieden et al.[20] assessed 33 treatment-refractory schizophrenia patients within a week of starting clozapine and 6 months later. Symptoms were assessed with the BPRS, the Negative Symptom Assessment Scale,[21] the Hamilton Rating Scale for Depression (HAM-D),[22] and the QLS. At 6 months, 17 patients were still taking clozapine. These patients had lower BPRS scores and direct health care costs compared with the 16 patients who discontinued clozapine. Drawbacks of this study are small sample size, lack of a control group, short follow-up period, high dropout rates for clozapine, and no analysis of the association between costs and clinical outcomes.

In a naturalistic study, Lewis et al.[23] compared 19 patients taking risperidone, 41 patients taking olanzapine, and 31 patients taking clozapine for direct costs assessed from their records and by their nurses. Costs were collected for a 10-month period. The number of patients who agreed to be interviewed for symptoms and quality of life was 8 in the risperidone group, 21 in the olanzapine group, and 22 in the clozapine group. PANSS and QLS scores were assessed at 6-month intervals. Total mean costs per month were highest for the clozapine group and lowest for the risperidone group. There were no differences between groups for total PANSS and QLS scores. The authors used regression analysis to calculate that an increase of 1 point on the PANSS scale leads to an increase of $61 in costs (1998 value). They found a positive effect of symptom ratings and number of inpatient days and a negative effect of having a partner and being employed on direct costs. After controlling for those factors, the cost difference between the risperidone and clozapine groups was only related to price difference between the acquisition costs for drugs. The main limitations of this study are small sample size and lack of randomization. Patients in the clozapine group were more chronically ill and sicker, which may explain higher costs for the clozapine group. To control for patient characteristics, the authors used a regression analysis model.

Lynch et al.[24] collected data on hospitalization, symptoms (BPRS, CGI-S), the AIMS, and the Simpson-Angus Scale (Simpson-Angus; scale assessing extrapyramidal symptoms)[25] in 21 schizophrenia patients retrospectively for 12 months before and after initiating quetiapine treatment. Although data on medication costs were not collected, the authors included the cost of 1 year of treatment with a conventional antipsychotic medication for the year before the initiation of quetiapine treatment and the cost of 1 year of treatment with quetiapine for the year following the initiation of quetiapine treatment. They found a decrease in BPRS, CGI-S, AIMS, and Simpson-Angus scores and hospitalization costs following the initiation of quetiapine. Limitations of this study include a small sample size, lack of a control group, restriction to patients who had responded to quetiapine during an initial 6-week treatment period, cost assessment limited to hospital days and antipsychotic medications, data on use and doses of medication not collected, medication costs based on recommended daily dosage rather than on actual dose received, and no analysis of the association between costs and clinical outcomes.

In a German study, Killian et al.[26] assessed 258 patients at 6-month intervals for symptoms (BPRS 24-item version[27] and Global Assessment of Functioning [GAF][28]), needs of care (Camberwell Assessment of Need),[29] quality of life (Lancashire Quality of Life Profile),[30] and satisfaction with treatment (Verona Service Satisfaction Scale).[31] They estimated direct costs (hospital, ambulatory, medication, etc.) for a 12-month period on the basis of interviews with patients. A multiple linear regression analysis was used to determine which factors were associated with direct costs. Significant factors included (starting with the strongest predictor): number of previous hospitalizations, BPRS total score, and living with other people. The authors estimated that an increase of 1 point in the 24-item BPRS total score would lead to an increase of 12-month costs by DM 14,112.60 (approximately U.S. $7000). Limitations of this study are cost estimates based only on information provided by patients, no information on antipsychotic medications, symptoms assessed only at the beginning and end of the study period, and a regression model that accounted for only 38% of the cost variance.

Killian et al.[32] extended their study to assess 307 patients up to 5 times over a 2½-year period. Clinical assessments included PANSS, Calgary Depression Scale for Schizophrenia,[33] GAF, Social and Occupational Functioning Assessment, and Medical Outcomes Study Short-Form 36-item health survey (SF-36)[34] scores. Killian et al.[32] found a significant effect of PANSS total score on direct costs using different regression models. Similar to the previous study, cost estimates were based only on information provided by patients. There is no information on antipsychotic medications, the random-effect model accounted for only 10% of the within-cost variance and 32% of the between-cost variance, and no analysis of the effects of PANSS subscale scores on costs is included.

Randomized Controlled Studies

Table 2 presents 9 studies that have compared costs and clinical outcomes in patients randomized between 2 or more treatment interventions. In a randomized controlled study,[35] 228 first-admission patients with schizophrenia were assigned to 5 treatment groups: (1) individual psychotherapy alone, (2) trifluoperazine alone, (3) individual psychotherapy plus trifluoperazine, (4) electroshock, and (5) milieu treatment for 6 to 12 months. Estimated costs were treatment services (medication, therapies, nursing care) and overhead costs during hospital stay from admission to release or termination of treatment. The clinical outcome was assessed with the Menninger Health-Sickness Rating Scale.[36] After 1 year, total direct costs were lower and clinical improvement higher for the groups that received trifluoperazine alone or in addition to individual psychotherapy compared with the other groups. The main limitation of this study is that costs were limited to the index hospitalization. The authors did not analyze the association between costs and clinical outcomes.

In a randomized, 1-year, double-blind study, Rosenheck et al.[37] compared treatment-refractory patients treated with either clozapine (N = 205) or haloperidol (N = 218). Clinical outcomes were assessed with the following: PANSS, QLS, Barnes Akathisia Scale (BAS)[38] for restlessness, AIMS, Simpson-Angus, and a checklist for adverse reactions. Compared with the haloperidol group, the clozapine group had lower positive and negative symptom levels, no significant change in total costs, lower inpatient costs, and higher costs for medication and outpatient services. The study did not include an assessment of baseline costs.

Rosenheck et al.,[39] using the same sample,[37] compared 141 patients who were high hospital users (116 or more days per year) with 282 low hospital users (less than 116 days per year). In high hospital users, clozapine lowered hospitalization costs and total health care costs (which included hospitalization, other health care services, and costs of medication). In low hospital users (i.e., inpatient costs less than $60,000 per year), despite a decrease in hospitalization costs, there was an increase in total health care costs due to medication costs. However, the authors argued that clozapine may be worth prescribing in these patients if clinical benefits outweigh the additional cost. The study did not include an analysis of the association between costs and symptoms.

A multicenter, international, randomized, double-blind study compared patients treated with either olanzapine or haloperidol during an acute phase (6 weeks) and a maintenance phase (46 weeks).[40] In the U.S. sample, there were 551 patients taking olanzapine and 266 patients

Table 2. Randomized Controlled Studies of Costs and Clinical Outcomes in Schizophrenia Patients Treated With Antipsychotic Medication

Study	N	Method	Length of Study (mo)	Direct Costs	Indirect Costs	Clinical Outcomes Assessment	Limitations	Analysis of the Association Between Costs and Clinical Outcomes
May, 1971[35]	228	Randomization to 4 treatment conditions and 1 nontreatment condition	6–12	Yes	No	Menninger Health-Sickness Rating Scale	Costs limited to the index hospitalization	No
Rosenheck et al, 1997[37]	423	Randomization to haloperidol or clozapine	12	Yes	Yes	PANSS, QLS, BAS, AIMS, Simpson-Angus, adverse effects checklist	No assessment of baseline costs	No
Rosenheck et al, 1999[39]	423[a]	Comparison of patients with high and low levels of hospital use	12	Yes	No	PANSS, QLS, Simpson-Angus, QALY	No assessment of baseline costs	No
Hamilton et al, 1999[41,b]	817	Double-blind randomization to haloperidol or olanzapine	12	Yes	No	BPRS (extracted from PANSS), QLS	Inclusion of patients who cannot tolerate conventional antipsychotic medication in the haloperidol group No analysis of PANSS subscale scores Lack of patient data after withdrawal	No
Le Pen et al, 1999[42,b]	275	Double-blind randomization to haloperidol or olanzapine	12	Yes	No	BPRS	Inclusion of patients who cannot tolerate conventional antipsychotic medication in the haloperidol group No data on direct costs prior to the randomization No analysis of PANSS subscale scores Lack of patient data following withdrawal	No
Tunis et al, 1999[43,b]	812	Double-blind randomization to haloperidol or olanzapine	12	Yes	No	SF-36: physical and mental health factors	No inclusion of nonresponders in acute phase No report of dropouts No inclusion of medication and outpatient costs Limited range of symptoms included in the mental health factor	Yes
Essock et al, 2000[44]	227	Open-label randomization to conventional antipsychotics or clozapine	24	Yes	Yes	BPRS, QOLI, AIMS	No inclusion of baseline costs	Yes
Edgell et al, 2000[46]	150	Double-blind randomization to risperidone or olanzapine	28	Yes	No	PANSS, CGI-S, Simpson-Angus, BAS, AIMS	Exclusion of nonresponders after 8 weeks of treatment	No
Jerrell, 2002[47]	108	Open-label randomization to risperidone, olanzapine, or conventional antipsychotics	12	Yes	No	PANSS, BPRS, DIS-III-R, RFS, SAS, DISCUSS, Simpson-Angus, BAS, QLS, SF-36, CUAD	High refusal rates Small sample size	No
Gureye et al, 2003[54]	65	Double-blind randomization to risperidone or olanzapine	6 ½	Yes	Yes	PANSS, BPRS, Simpson-Angus, BAS, QLS, SF-36, CGI-S	Small sample size No monetary cost estimates High dropout rates Possible bias in cost data	No

[a]Same sample as Rosenheck et al.[37]
[b]Same trial as Tollefson et al.[40]
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CUAD = Chemical Use, Abuse, and Dependence Scale, DIS-III-R = Diagnostic Interview Schedule III-R, DISCUSS = Dyskinesia Identification System Condensed User Scale, PANSS = Positive and Negative Syndrome Scale, QALY = Quality Adjusted Life Year, QLS = Quality of Life Scale, QOLI = Quality of Life Inventory, RFS = Role Functioning Scale, SAS = Social Adjustment Scale-Severely Mentally Ill, Simpson-Angus = Simpson Angus Scale, SF-36 = Medical Outcomes Short Form 36-item health survey.

taking haloperidol during an acute phase, and 270 patients taking olanzapine and 74 patients taking haloperidol during a maintenance phase.[41] Compared with patients taking haloperidol, patients receiving olanzapine had greater improvement in BPRS and QLS scores and lower inpatient and outpatient costs. During the maintenance phase, there was no difference between groups for BPRS and QLS scores, but the olanzapine group had lower mean inpatient/outpatient costs and lower total costs (despite higher mean medication costs) than the haloperidol group. Limitations of this study are lack of costs for dropout patients, no analysis of PANSS data, and no analysis of the association between costs and clinical outcomes.

In the French sample, Le Pen et al.[42] looked at the BPRS scores and mean medical direct costs per day in patients treated with either haloperidol (N = 90) or olanzapine (N = 185) for 1 year. In agreement with the analysis of the U.S. sample,[40] the olanzapine group had a higher proportion of patients with BPRS score improvement and lower mean hospitalization costs per day than did the haloperidol group. There was no difference between groups for other service costs. The study did not include information on patients who withdrew from the study and did not compare patient groups for direct costs prior to the study. Direct costs prior to the study may have been higher for patients in the haloperidol group, which may have resulted in higher direct costs during the study despite a similar or higher drop in direct costs. Higher BPRS response rates in the olanzapine group compared with the haloperidol group may be related to higher dropout rates and shorter observation periods in the haloperidol group. Higher dropout rates were to be expected since patients who did not tolerate conventional antipsychotic medications were included in this study. The study did not include an analysis of the association between costs and clinical outcomes.

Tunis et al.[43] looked at a subsample of patients from English-speaking countries. They compared 772 patients treated with olanzapine and 383 patients treated with haloperidol for physical and mental health factors on the SF-36 over a 1-year period. Hospitalization costs were assessed for 812 patients, but the authors did not specify how many patients in each group had cost data. Compared with patients treated with haloperidol, patients treated with olanzapine had lower hospitalization costs and an improvement in SF-36 physical and mental health factor scores. The authors calculated that a change of 1 point in the SF-36 mental health factor score results in savings of $5655. The study has several limitations. It did not include dropout rates and other direct costs such as outpatient and medication costs. In view of much higher acquisition costs for olanzapine compared with haloperidol, the inclusion of medication costs may have resulted in nonsignificant cost differences between groups. Furthermore, as discussed by the authors, the exclusion of nonresponder patients during the initial 6 weeks of double-blind therapy is "problematic for an effectiveness or intent-to-treat analysis."[(p40)] The SF-36 mental health factor only includes some mood, anxiety, and fatigue-related items and does not include questions about psychotic symptoms. Finally, the authors did not report changes for specific SF-36 items.

In a randomized open-label study, Essock et al.[44] compared treatment-resistant schizophrenia patients treated with either conventional antipsychotics (N = 89) or clozapine (N = 138). Effectiveness was assessed with the BPRS, Quality of Life Inventory,[45] and AIMS every 4 months for 2 years. Chart reviews provided information on problematic behavior such as disruptiveness and assaultiveness. Cost measurement included direct (inpatient and outpatient services, medications) and indirect (state supplement to supplemental security income, administrative costs of state-funded transfer payments, loss of earned income) costs. Compared with patients receiving conventional antipsychotics, clozapine patients had fewer extrapyramidal symptoms, less disruptiveness, and lower hospital readmission rates. However, there was no difference between groups for changes in BPRS scores and total costs over the 2-year period. The study did not include baseline costs (i.e., total costs for a period preceding study entry). The study did include a sophisticated statistical analysis (bootstrap techniques) showing that clozapine is more cost-effective than usual care with a probability of at least 80%.

Edgell et al.[46] assessed patients randomized to either olanzapine (N = 75) or risperidone (N = 75) treatment for a maximum of 28 weeks. They compared direct costs and scores for total PANSS, CGI-S, Simpson-Angus, BAS, and AIMS scales. The authors found lower inpatient/outpatient service costs in the olanzapine-treated group compared with the risperidone-treated group. There were no significant differences between groups for clinical scores, but the olanzapine-treated patients were more likely to maintain response. The study did not include the costs of nonresponders and did not look at the association between costs and clinical outcomes.

In an open-label study, Jerrell[47] randomly assigned 108 patients with schizophrenia or schizoaffective disorder to treatment with risperidone (N = 36), olanzapine (N = 30), or conventional antipsychotics (N = 42). Clinical outcomes were assessed with the PANSS, the BPRS, the Diagnostic Interview Schedule III-R–Depression and Mania Modules,[48] the Role Functioning Scale,[49] the Social Adjustment Scale-Severely Mentally Ill,[50] the Dyskinesia Identification System Condensed User Scale,[51] the Simpson-Angus, the BAS, the Chemical Use, Abuse and Dependence Scale,[52] and the Client Satisfaction Questionaire-8.[53] There was a significant decrease over time of PANSS negative and positive subscale scores, BPRS total scores, substance abuse symptoms, and side

effects. There was a significant increase over time of depression/mania symptoms, role functioning, and client satisfaction. Medication costs and total mental health costs were higher for the risperidone and olanzapine groups compared with the conventional antipsychotic group. Limitations of this study are small sample size, possible selection biases (e.g., high refusal rates; compared to risperidone and conventional antipsychotic groups, the olanzapine group had more acute inpatient days prior to the study), and no analysis of the association between costs and clinical outcomes.

In a double-blind randomized study of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, Gureye et al.[54] found greater improvement in PANSS total and subscale scores, BPRS scores, and quality-of-life assessment (QLS and SF-36) scores in 32 patients treated with olanzapine compared with 33 patients treated with risperidone. In both groups, PANSS and BPRS scores improved over time. Both groups had a decrease in hospital days and use of community crisis teams but an increase in home visits. There were no differences in costs between groups. In the olanzapine group but not in the risperidone group, there was an increase in productive hours per month. Limitations of this study are small sample size, no monetary cost estimates, a short study period ($6^1/_2$ months), high dropout rates, possible bias in cost data in favor of the olanzapine group, and no analysis of the association between costs and clinical outcomes.

DISCUSSION

The first study looking at the relationship between change in costs and symptoms was published by May[35] in 1971. This prospective study demonstrated that conventional antipsychotic medications reduce costs by decreasing the length of the index hospitalization and improving clinical outcomes. Despite these remarkable results, it took almost 20 years to generate further interest in the association between changes in costs and symptoms. The advent of atypical antipsychotic medications seems to have triggered this renewed interest. Because of higher acquisition costs of the atypical antipsychotics compared with conventional antipsychotics, most of the recent prospective studies have compared atypical and conventional antipsychotics for costs and clinical outcomes. Most of the reviewed studies analyzed costs and clinical outcomes separately, and only 5 studies looked more specifically at the relationship between costs and clinical outcomes.[23,26,32,43,44]

As shown in Table 1, about half of the studies were not randomized. Such studies have an advantage over controlled studies in reflecting clinicians' daily practices more closely. Unfortunately, these studies have limitations that may compromise their conclusions. Limitations include the absence of randomization, selection bias, the absence of control for variations in the natural course of illness and changes in the health care system,[12] and bias in cost estimates related to the exclusion of dropouts from analysis.[55,56] The remaining studies (Table 2) were randomized and controlled. These studies address most of the limitations of nonrandomized studies but are long, expensive, more difficult to perform than nonrandomized studies, and have their own biases. These studies are biased by the exclusion of individuals who will not accept randomization to treatment and also by premature dropout from treatment following randomization.

This review also examines other methodological issues that are relevant in studying the relationship between changes in costs and psychopathology following antipsychotic treatments. The study of this relationship requires (1) the assessment of costs at baseline and during treatment, (2) the assessment of clinical outcomes that are sensitive to the effects of antipsychotics, and (3) the application of statistical methods to relate changes in costs (dependent variable) to changes in clinical outcomes (independent variables).

Assessment of Costs

Health care costs are usually described as direct (i.e., costs of providing services), indirect (i.e., costs resulting from loss of productivity), and intangible (monetary value assigned to pain, suffering, and family burden). Costs of interest vary depending on the economic perspective of the investigator. A study conducted from the perspective of a health care system will be concerned with direct costs. A study conducted with a macroeconomic perspective (i.e., the society as a whole) will collect data on both direct and indirect costs. Finally, a study conducted with a microeconomic perspective (i.e., the individual) will include direct, indirect, and intangible costs. Unfortunately, most of the studies were conducted from the perspective of health care systems and included only direct costs. A few studies had a macroeconomic perspective and assessed direct and indirect costs. Regrettably, none of the reviewed studies attempted to assess the monetary value of intangible costs. The assessment of intangible costs in schizophrenia has been limited. In a previous study,[57] we assessed the intangible costs of side effects associated with antipsychotics using the willingness-to-pay method and found an association between the severity of side effects and the amount of available income that patients were willing to pay to get rid of their side effects. However, these findings need to be replicated, and methods for the assessment of intangible costs in schizophrenia should be developed further.

Assessment of Clinical Outcomes

Clinical outcomes have been assessed along 3 main dimensions: symptoms, social skills, and behavior. Most of

the studies have looked at the association between costs and general measures of psychopathology (e.g., BPRS or PANSS total scores, CGI-S), but not between specific costs and specific factors of the BPRS or PANSS (e.g., BPRS anxiety, depression, thought disorder, anergia).[10,58] For instance, one could hypothesize that direct costs may be more associated with thought disorder, anxiety, or depression factors, and indirect costs with the anergia factor. A patient who is delusional or severely depressed may require inpatient care (direct cost). In contrast, limited social skills, lack of motivation, or impaired executive functioning may result in poor or no productivity (indirect cost).[59] Most of the studies have used similar rating instruments for assessing psychopathology (generally the BPRS or PANSS). However, there is little consensus about the assessment of social skills and behavior or cognitive functioning.

Statistical Methods

In regard to statistical methods, this review has identified 2 main approaches. In the first approach, costs are assessed for periods before (6 to 12 months) and after (up to 24 months) the initiation of the antipsychotic medication of interest. Clinical outcomes are assessed at baseline and during the treatment period. The quality of studies varies greatly from nonrandomized (Table 1) to prospective, randomized, controlled (Table 2) studies. The second approach was used by only 2 studies[23,32] in which changes in direct costs are related to changes in clinical outcomes using multivariate statistical methods. These studies assessed multiple marginal effects (including symptoms) on costs using regression models.[60] Randomized, controlled studies that evaluate possible sources of interindividual cost or outcome variation are a powerful model for looking at the effects of a single treatment variable on costs but may be of limited use in providing guidance for clinical practice. Multivariate statistical methods may provide more relevant information to improve services.[61] In contrast to randomized controlled studies, multivariate statistical analyses of naturalistic costs and outcome data can examine the association between costs and multiple aspects of clinical outcomes.[32] Variation in costs associated with treatment can be related to unexplained errors (accounting/measurement errors), interindividual differences (sociodemographic variables), or variables that change over time (e.g., changes in symptoms).

Thus, this review of the literature shows that the relationship between changes in costs and clinical outcomes in patients treated with antipsychotics has rarely been addressed. No study looked at costs from a microeconomic perspective. The scope of clinical assessments has been too narrow, and multivariate statistical methods relating changes in costs and clinical outcomes have been used only in 2 studies. From this review, we can conclude that psychotropic medications can decrease costs (mostly direct costs) and the severity of psychotic symptoms. However, we know very little about (1) the effects of antipsychotic treatment on indirect and intangible costs and (2) the relationship between changes in costs and symptoms.

In summary, we still have a poor understanding of the relationship between changes in costs and clinical outcomes resulting from treatment with antipsychotic medications. Because of the lack of data regarding the relationship between costs and clinical outcomes, cost-effectiveness studies have been of limited utility in enabling health care providers to integrate costs into their treatment plans for schizophrenia patients. Future studies will have to address the relationship between costs and clinical outcomes in schizophrenia by expanding the assessment of costs to indirect and intangible costs, considering a wider range of clinical outcomes, and developing new statistical models relating changes in costs to changes in clinical outcomes. The development of such studies will require several preliminary steps such as development of methods for assessing intangible costs, standardization of cost and clinical outcome assessments, and the identification of variables that will explain a high proportion of cost variation in multivariate analyses.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trifluoperazine (Stelazine).

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