Antidepressant Medication Change in a Clinical Treatment Setting: A Comparison of the Effectiveness of Selective Serotonin Reuptake Inhibitors

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Background: This investigation focuses on the 3 most frequently used selective serotonin reuptake inhibitors (SSRIs) (paroxetine, fluoxetine, sertraline) and examines the rate of medication switches as a measure of effectiveness. We answer 2 questions: (1) What is the likelihood that a patient starting treatment with an SSRI will complete treatment with the same agent? and (2) Depending on the initial SSRI agent used, do patients switch at different frequencies?

Method: A retrospective chart review was performed on 2779 patients treated in a university outpatient clinic from March 1995 to January 1997. Of these, 263 patients given antidepressants were randomly selected: 214 were prescribed SSRIs; 24, novel antidepressants; and 25, tricyclic antidepressants.

Results: There was no significant difference in rate of switching between the different classes of antidepressant ($p = .1$) nor between drugs within the SSRI class ($p = .513$). When medication change was the independent factor, significant differences between the groups were total time in treatment and number of visits ($p < .001$ and $p = .011$, respectively). Age, education, and Clinical Global Impressions-Severity of Illness scale scores (admission, discharge, and change) were not significantly different between the groups.

Conclusion: Approximately 25% of patients started with an SSRI will switch to another antidepressant in the course of their treatment. The SSRIs appear to be equivalent in effectiveness. They are not interchangeable, because patients who discontinue one SSRI for lack of tolerability or response can generally be treated effectively with another.

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Although the efficacy of antidepressant agents has been demonstrated extensively, their effectiveness is less understood and researched. *Efficacy* refers to the performance of the agent under point-to-point trial conditions; it is distinguished from the broader construct *effectiveness*, which refers to the performance of the agent under routine clinical circumstances.[1] This conceptual difference is illustrated by findings that 70% to 80% of subjects with major depression respond to antidepressants in trials,[2] but 40% or more of patients discontinue antidepressant treatment during the first 3 months of treatment in clinical settings.[3] While the former figure may be of primary importance to the clinical investigator or pharmaceutical company seeking U.S. Food and Drug Administration (FDA) approval, the latter becomes the primary consideration for the practicing clinician. In addition, with the growing emphasis on economic factors in the management of care, and because the acquisition of selective serotonin reuptake inhibitor (SSRI) agents represents a substantial component of hospital and health plan pharmacy expenditures, focus on antidepressant effectiveness has taken on increased importance. However, a paucity of independent data on antidepressant effectiveness is currently available to allow clinicians and others responsible for institutional acquisition to make the best informed decisions on which agents to select for patients.

The SSRIs significantly advanced the treatment of depression and anxiety disorders with improved tolerability and more efficient dosing, but they have no better efficacy than the traditional tricyclic antidepressants (TCAs). Most comparative studies suggest an advantage of SSRIs as a group over TCAs for various effectiveness parameters, particularly in outpatients. These studies emphasize less discontinuation, easier titration, and pharmacoeconomic advantage in overall cost of treatment for the SSRIs, i.e., lower medical utilization and decreased hospitalization as acquisition price offsets.[4] However, another interesting trend in the literature emerges; for example, among 6 influential published studies, 5 identify support by the pharmaceutical company that manufactures the SSRI recommended as superior to or equally cost-effective as the comparison TCA.[5–10]

Comparative studies between the various SSRIs are more limited in number and tend to claim an often confusing array of effectiveness advantages in terms of titration, discontinuation, total dosages, adverse effects, concomitant drug treatment, and economics of one SSRI over another. For example, studies by Sclar et al.,[11] DeWilde et al.,[12] Gregor et al.,[13] Hylan et al.,[14] and Thompson et al.[15] report, respectively, advantage for fluoxetine over paroxetine and sertraline for economics, paroxetine over fluoxetine for onset and adverse events, fluoxetine over sertraline for titration and dose increases, fluoxetine over paroxetine for adjunctive anxiolytic or hypnotic use, and greater rate of switching and augmentation for sertraline compared with fluoxetine. Again, the reported advantage, usually in head-to-head SSRI comparisons on a select efficiency variable, generally finds the preferred agent to be that of the industry sponsor. Besides questions of potential bias that can be raised by such funding support,[16] differences in treatment designs, control groups, illness severity, methods of analysis, and other methodological conditions make such SSRI studies difficult to compare and further confound decision making on SSRI selection. Independent, prospective, randomized, blinded studies of comparative SSRI effectiveness in systematically assessed subjects would be helpful for more informed decision making in antidepressant drug selection. However, naturalistic studies of prescribing and utilization patterns are also needed to bridge research and clinical practice, since clinicians and patients do not perfectly mirror the controlled conditions of researchers and research subjects.

Medication switching is a useful measure of antidepressant clinical efficiency because it incorporates several measures of effectiveness (i.e., adverse effects, compliance, titration, and discontinuation) and is quite relevant for clinician decision making. The purpose of this investigation is to focus on the 3 most frequently used SSRIs (paroxetine, fluoxetine, and sertraline) and examine medication switching in a naturalistic clinical setting with the following questions: (1) What is the likelihood that a patient starting treatment with an SSRI will complete treatment with the same agent? and (2) Depending on the initial SSRI agent used, do patients switch at different frequencies? The hypothesis is that there is no significant difference in the rate of switching between paroxetine, fluoxetine, and sertraline in the general psychiatric outpatient clinical setting.

METHOD

Subjects and Setting

A retrospective chart review was performed on patients randomly selected from the caseload of the General Clinic at the University of New Mexico (UNM) Mental Health Center in Albuquerque, New Mexico. The General Clinic is an outpatient psychiatry teaching clinic that serves as the initial intake clinic to the UNM system, and it serves a primarily lower socioeconomic public sector population. It is an innovative model teaching clinic that has been presented and reported on in various formats.[17] The aims of the clinic are to provide a comprehensive diagnostic assessment with psychosocial and medication management. Patients are followed in the clinic for up to 6 months, with the endpoint target either remission or stabilization of their primary disorder. When discharged, they are referred within the UNM system either to a primary care physician for remitted or resolved conditions or to the Center's Continuing Care Clinic for stabilized patients with chronic psychiatric conditions that will require ongoing team management under the direction of a psychiatrist (e.g., schizophrenia, chronic bipolar affective disorder, serious mental disorders with substance abuse).

As part of the initial assessment, patients first have a complete nursing assessment and fill out a Symptom Checklist-90 (SCL-90). Demographic information on every patient is recorded as follows: age, sex, race, marital status, employment, health insurance status, and years of education. The clinical database includes primary DSM-IV Axis I through III clinical diagnosis, total days in the clinic, number of visits, medications prescribed, Clinical Global Impressions-Severity of Illness scale (CGI-S) score on admission and discharge, and discharge disposition. All patients are treated by a postgraduate year 2 psychiatric resident under direct on-site supervision by a full-time faculty attending. In accordance with federal regulations, the attending is present with the patient and trainee for the diagnostic evaluation and essential follow-up visits. At every visit, the resident or a medical student under the direct supervision of the chief resident completes a CGI-S. Regular daily formal case teaching presentations with patient interview occur for difficult diagnostic and management questions. This procedure allows for the development of a "best estimate" clinical diagnosis. The clinic sees up to 30 new patients and 120 follow-up patients per week with an active caseload of approximately 500.

Statistical Analysis

Independent variables chosen to determine variance in switch rates were age, years of education, number of visits, total days in clinic, CGI-S score on admission, CGI-S score on discharge, and change in CGI-S score. A secondary analysis included antidepressant drug dosages. Continuous distribution data was analyzed using the Student t test and analysis of variance (ANOVA). Categorical variables were tested by the chi-square test.

RESULTS

From March 1995, when the General Clinic program became fully operational, to January 1997, 2779 patients

Table 1. Primary Clinical Diagnosis of Subjects Prescribed Selective Serotonin Reuptake Inhibitors (SSRIs) (N = 214)

Diagnosis	Percentage of Subjects
Mood disorders	69
Bipolar disorder	9
Major depression	55
Single	16
Recurrent	39
Dysthymia	5
Anxiety disorders	19
Panic disorder	12
Without agoraphobia	4
With agoraphobia	8
Generalized anxiety disorder	< 2
Posttraumatic stress disorder	2
Social phobia	< 2
Obsessive-compulsive disorder	< 2
Schizophrenia/schizoaffective disorder	2
Other	10
Bulimia	1
Adjustment disorder	< 1
Dissociative disorders	< 1
Attention-deficit/hyperactivity disorder	< 1
Impulse-control disorder	1
Borderline personality disorder	2
Dementia	< 1
Brief reactive psychosis	2
Substance-induced disorder	2

Table 2. Rates of Change in Antidepressant According to Class of Medication (N = 263)[a]

Antidepressant Class	N	Rate of Change, %	95% Confidence Interval
SSRI	214	22.0	16.6% to 28.1%
Novel antidepressant	24	41.7	22.1% to 63.4%
Tricyclic antidepressant	25	24.0	9.4% to 45.1%

[a]No significant difference in change between the different classes of antidepressants ($\chi^2 = 4.6$, p = .1).

Table 3. Demographic and Clinical Characteristics of SSRI Subjects (N = 214)[a]

Characteristic	Switch	Nonswitch	Total
Age (y)	34.8 ± 9.5	35.4 ± 10.4	35.3 ± 10.2
Education level (y)	12.6 ± 3.1	12.9 ± 3.3	12.8 ± 3.3
Total days in clinic	114.2 ± 85.0	73.7 ± 87.1	82.6 ± 87.6[b]
Number of visits	9.6 ± 5.7	6.8 ± 5.1	7.6 ± 5.4[b]
CGI-S score on admission	3.7 ± 1.0	3.4 ± 1.0	3.5 ± 1.0
CGI-S score on discharge	2.7 ± 1.5	2.5 ± 1.4	2.5 ± 1.4
CGI-S score change	1.0 ± 1.3	0.9 ± 1.5	0.9 ± 1.4

[a]All values given in mean ± SD format. Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.
[b]Significant differences are found with "days" (N = 214; F = 7.9, p = .005) and number of visits (N = 214; F = 6.5, p = .011).

were admitted to the clinic. From these patients, a group of 342 patients for whom complete demographic information was available was randomly selected. Antidepressants were prescribed for 263 of these patients. The demographics of the group prescribed antidepressants were as follows: age, 18 to 67 years (mean ± SD = 35.8 ± 10.3 years); 67% female; and 36% Hispanic, 61% white, 2% African American, 0.5% Native American, and 1% other racial groups. This was representative of the racial demographics of Bernalillo county, which was 36.2% Hispanic, 56% white, 2.7% African American, and 3.4% Native American by 1994 selected health statistics. Mean ± SD level of education was 12.9 ± 3.8 years. Reflecting the public sector setting, approximately 50% of patients were covered by Medicare or Medicaid, 45% were indigent or self-pay (working poor), and fewer than 5% had commercial insurance.

With the primary focus on selective serotonin reuptake inhibitors, the objective of this study was to determine if patients prescribed antidepressants require switches in medication at different rates depending on which antidepressant they are taking. Of the 263 patients treated with an antidepressant, 214 were prescribed SSRIs; 24, novel antidepressants; and 25, TCAs. This became the study sample on which the data analysis was performed. Table 1 presents the distribution of primary diagnoses of the patients treated with SSRIs. The most common primary diagnoses were mood disorders (in 69% of SSRI-treated patients) and anxiety disorders (in 19% of SSRI-treated patients). A substantial number of these patients had a comorbid condition.

Table 2 shows the rate of change for the antidepressants grouped by class. There was no significant difference in rate of antidepressant change between the different classes of antidepressants ($\chi^2 = 4.6$, p = .1), nor between drugs within the SSRI class ($\chi^2 = 1.3$, p = .513). There was only a small yet statistically significant difference in switch rates if the TCA group was excluded (Fisher exact p = .043); then the SSRI class switched less than the novel antidepressant class.

Table 3 shows the age, education level, total days in clinic, number of visits, CGI-S score on admission, CGI-S score on discharge, and change in CGI-S score for the SSRI subjects who switched and those who did not switch medications over the course of their treatment. When medication change was the independent factor, significant differences were found with total days in clinic (N = 214; F = 7.9, p = .005) and number of visits (N = 214; F = 6.523, p = .011). Age, sex, CGI-S score on admission, CGI-S score on discharge, difference in CGI-S score, and education level were not significantly different.

Of the 214 patients prescribed SSRIs (Table 4), 60 were given fluoxetine, 39 received paroxetine, and 115 received sertraline. There were no significant differences in medication change rates when paroxetine was compared with all other antidepressants (N = 263; $\chi^2 = 1.71$, p = .19), when fluoxetine was compared with all other antidepressant medications (N = 263; $\chi^2 = 0.079$, p = .779), and when sertraline was compared with all other antidepressants (N = 263; $\chi^2 = 0.116$, p = .734).

Table 5 presents the medication dosages prescribed for each of the 3 SSRIs. The mean doses with 95% confidence intervals (CI) were fluoxetine, 26 mg/day (95%

Table 4. Rates of Change in Antidepressant According to SSRI Medication (N = 214)

Antidepressant	N	Rate of Change, %	95% Confidence Interval	χ^2	p Value
Fluoxetine	60	25.0	14.7% to 37.9%	0.079	.779
Paroxetine	39	15.4	5.9% to 30.5%	1.71	.19
Sertraline	115	22.6	15.3% to 31.3%	0.116	.734

Table 5. Selective Serotonin Reuptake Inhibitors: Frequency of Use and Mean Dose

SSRI	N	Daily Dose, mg (mean ± SD)	95% Confidence Interval
Fluoxetine	60	26 ± 21.0	23 to 33 mg
Paroxetine	39	24 ± 8.1	21 to 26 mg
Sertraline	115	84 ± 44.2	76 to 92 mg

CI = 23 to 33 mg); paroxetine, 24 mg/day (95% CI = 21 to 26 mg); and sertraline, 84 mg/day (95% CI = 76 to 92 mg). For final doses, 74% of fluoxetine-treated patients completed with 20 mg/day, 82% of paroxetine patients with 20 mg/day, and 87% of sertraline patients with 100 mg/day or less (52% at 50 mg/day).

Caveats

The naturalistic aspects of an effectiveness study introduce confounds that are generally controlled for by a randomized, controlled efficacy study. For example, patients may differ over various domains and conditions that affect outcome, e.g., motivation, concurrent psychiatric and medical conditions, concurrent medications, medication adjustments, clinical assessment, management of side effects, provider personality practices, assignment to treatment modality. Specifically, included in this study were patients in different and frequently multiple diagnostic groups who were taking other prescribed and nonprescribed medications (i.e., trazodone for sleep [17%], benzodiazepines for anxiety [3%]). It must be recognized that these additional variables could make patients more or less vulnerable to therapeutic or adverse effects of the drugs they are taking, and could affect switching. Factors such as polypharmacy and comorbidity would be controlled for in a randomized, controlled efficacy study because these factors are operative in influencing primary outcome measures. However, these factors also need to be considered in the effort to bridge research results derived from specific diagnostic categories to the often confounded or complex diagnostic boundary situations found in the clinical community.

DISCUSSION

Using antidepressant medication switching in a naturalistic clinical setting as a measure of effectiveness, the SSRIs appear to be equivalent in terms of which is the optimal drug of first choice. Regardless of the initial SSRI chosen and absent specific individual case considerations, approximately one quarter (17% to 28%) of patients started with an SSRI will switch to another antidepressant agent in the course of their treatment. There were no overall differences in rates of changing medications between drugs within the SSRI class, nor between different classes of antidepressant drugs over the course of treatment. Age, sex, education, severity, outcome, and clinical improvement did not distinguish patients that switched SSRI or completed treatment with the initial agent. However, in patients whose SSRI was changed, the duration of their treatment increased substantially (54%) and they utilized more clinical visits (40%) compared with patients who completed treatment with their initial agent. These findings are consistent with those of other studies[16,18] that found medication change rates not significantly different when either paroxetine, fluoxetine, or sertraline was compared individually with other antidepressant medications over the course of treatment. The results also extend previous findings[19–21] that the SSRIs are not interchangeable, because patients who discontinue one SSRI for lack of tolerability or response can generally be treated effectively with another.

There are limitations to the generalizability of this report that need mention. Obviously, its naturalistic retrospective methodology cannot substitute for a prospective controlled study with appropriate blinds. Patients were not systematically assessed or treated in terms of specific diagnosis, outcome measures, initial choice of SSRI, or dosage titration, but instead a best estimate clinical judgment approach was used. To be consistent with general clinical practice guidelines, patients with recurrent conditions would be assigned to an agent with which they had previously been effectively treated. For patients referred by a primary care physician, the presenting dose of antidepressant would be considered, adjusted, and recorded as the initial agent for the switching analysis. The proportionately higher use of sertraline over the other SSRIs was due to the fact that patients are often referred back to the primary care setting, in which sertraline was the primary or preferential institutional formulary SSRI. An ascertainment bias must also be considered as operative because the psychiatric clinic is in an academic tertiary care center that serves a lower socioeconomic population with generally higher illness severity and comorbidity. Given these limitations, the independent effort to determine medication switching across the spectrum of conditions for which they are used in general clinical practice can provide a practical estimate of what percentage of response a clinician in practice can expect when prescribing an SSRI. Clearly, further investigation of this important parameter of antidepressant drug treatment is indicated and should explore, for example, the percentage of switching due to adverse effects compared with lack of efficacy.

Competitive market forces and the emphasis on pharmacoeconomics have placed medical practitioners and others involved with drug acquisition in the position of facing an array of apparently efficacious agents from which they must choose when prescribing an antidepressant for patients. Given the equal efficacy between antidepressants established in randomized placebo-controlled trials, the parameters to guide the choice present a bewildering variety of comparative clinical effectiveness measures (i.e., tolerability, select adverse effects profile, dose titration, safety in overdose, discontinuation, concomitant medication use, and direct/indirect monetary costs). However, the literature on these various measures is derived to a large extent from uncontrolled naturalistic data or industry-supported studies and is often contradictory when different efficiency measures are compared. The reported advantages of SSRIs over TCAs with respect to tolerability, medical utilization, and discontinuation are most notable early in treatment and diminish after 3 to 6 months.[5,18] The pharmacoeconomic cost equality claims of SSRIs with TCAs rely on the inclusion of medical intensive care costs for drug overdoses.

In SSRI (or SSRI/novel antidepressant) comparisons, every agent has a report of advantage over another on some effectiveness parameter. An additional finding of the present study can serve to illustrate the highly contended issue of cost efficiency in drug dosage titration. A review of titration studies[4] shows some with an advantage to paroxetine over fluoxetine, others show fluoxetine over paroxetine, and still others recommend sertraline over fluoxetine. The various methodologies used rate of dose increases, endpoint mean doses, differences between start and endpoint, and splitting 100-mg sertraline tablets in half as the preferred dose. In this study, mean dose with 95% confidence interval were fluoxetine, 26 mg/day (95% CI = 23 to 33 mg), paroxetine, 24 mg/day (95% CI = 21 to 26 mg), and sertraline, 84 mg/day (95% CI = 76 to 92 mg). Methodologies based on mean doses may not be accurate because individual patients take tablets, not mean doses. The salient questions are, What is the clinical relevance of such varied reports of advantage? and Are these reports substantial enough to guide agent choice?

The data from this investigation of SSRI medication switching would suggest that, in the absence of a specific indication for a particular patient, the differences are not substantial enough to singularly determine choice of agent. However, the results also indicate that any trend to selection of an exclusive SSRI for a hospital or managed care plan formulary is ill advised because a significant number of patients, approximately 25%, will not respond to the first antidepressant agent prescribed. They will need, and in most cases respond to, a second agent. The lack of ready availability of a second SSRI, particularly in the primary care setting, can compromise effective patient care, prolong morbidity, and increase the costs of care by inefficiently diverting patients that could have been treated in the primary care setting into the psychiatric specialty sector. In the worst case scenario, patients will drop out of treatment and not be treated at all, thus placing them at increased risk for suicide. Further studies, independently funded (e.g., by the National Institute of Mental Health) and prospectively designed, that compare agents with established efficacy and are conducted in large health systems according to more structured clinical pathways and along various parameters of effectiveness can further identify the variables influential for optimal antidepressant selection and treatment compliance.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others).

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