FLUOXETINE AND SERTRALINE DOSAGES IN MAJOR DEPRESSION

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In a retrospective study, we sought to determine medication dosages usually prescribed to obtain euthymia in 59 outpatients with a diagnosis of major depression treated with fluoxetine or sertraline. Charts of veterans admitted to the outpatient mental health clinic at the West Los Angeles Veterans Hospital with a diagnosis of major depression and treated with either fluoxetine or sertraline were reviewed. Progress notes were analyzed for a 6-month time period after the initiation of the medication treatment, and improvement was rated by a physician blind to the drug used for treatment. No significant differences were found in overall response rates between the fluoxetine (81% responders) and sertraline (76% responders) groups. Eighty-one percent of the fluoxetine responders compared to 32% of sertraline responders were at the manufacturer's recommended starting dose (MRSD) at the time of clinical response. One-third of patients receiving sertraline were started on or rapidly titrated to more than 50 mg/day. When only those patients receiving an adequate trial of sertraline at 50 mg were considered, 47% required a dose increase to achieve a remission. These data suggest that 50 mg of sertraline may be inadequate for some patients to achieve a resolution of symptoms of major depression and that many clinicians currently prescribe in a manner suggesting that they believe the MRSD is a suboptimal dosage. Depression and Anxiety 9:78–82, 1999. *Published 1999 Wiley-Liss, Inc.*†

Key words*: sertraline; fluoxetine; depression*

INTRODUCTION

The treatment of major depressive illness represents a significant challenge to health care providers. Estimated lifetime prevalence of depression is 6–19% [Kessler et al., 1994]. The societal impact of depression both in terms of individual suffering and economic sequelae is great. In the United States, the costs of treatment, morbidity, and mortality has been estimated to cost 44 billion dollars annually [Greenberg et al., 1993].

In today's health care setting, both clinical and economic factors guide selection of a treatment strategy, including pharmacotherapy decisions. Pharmaceutical formularies are being revised with the objective of economic efficiency [Sclar et al., 1994]. Selective serotonin re-uptake inhibitors (SSRIs) have become a first line medication for the treatment of major depression, as studies have shown that SSRI antidepressants compare favorably to tricyclics in efficacy and are a cost-effective alternative to the tricyclic antidepressants when total cost of care to a provider network or institution is considered [Sclar et al., 1994; Song et al., 1993; Reimhan et al., 1990].

Sertraline and fluoxetine are two SSRIs that have been shown to be effective in the treatment of major depression. There have been relatively few double blind, placebo-controlled fixed dose studies of these two medications. A multicenter trial involving 356 subjects compared fixed doses of 20, 40, and 60 mg/day of fluoxetine and found that subjects on 20 and 40 mg doses differed from patients on placebo in several outcome measures, but that patients on 60 mg/day differed in only one outcome measurement [Wernicke et al., 1987]. Fabre et al. [1995] compared patients on placebo to patients on one of three doses of sertraline (50 mg./day, 100 mg/day, and 200 mg/day). They found no significant differences among the three doses and all three doses were more effective than placebo. Amin et al. [1989], in a fixed dose study, found no significant differences among three doses of sertraline.

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Several studies have been done, directly comparing the efficacy and dosage requirements of sertraline and fluoxetine. Aguglia et al. [1993], in a randomized, double blind prospective multicenter trial, compared the efficacy of sertraline and fluoxetine in outpatients with depression and found no significant differences between the treatment groups. The final mean daily dose for sertraline and fluoxetine was 72 and 28 mg, respectively. Two retrospective studies reported that patients receiving sertraline for the treatment of depression required greater upward dosage titration from the initial 50-mg dose compared to patients receiving 20 mg of fluoxetine for similar clinical improvement [Gregor et al., 1994; Navarro et al., 1995]. This observation has not always been seen. In a randomized double blind prospective study by Bennie et al.[1995], 76% of patients treated with fluoxetine and 76% of patients treated with sertraline responded to the initial starting dose of 20 mg and 50 mg, respectively.

In a retrospective chart review of patients treated with sertraline or fluoxetine for major depression, we sought to determine medication dosages usually prescribed to obtain euthymia in outpatients with a diagnosis of major depression. We also sought to assess whether adequate trials at manufacturer's recommended staring dosage (MRSD) were generally allowed prior to upward dosage titration. Hence, in this study, we examine both medication efficacy and physician prescribing patterns.

MATERIALS AND METHODS

A waiver was obtained through the Human Subjects Protection Committee (HSPC) to review the records of patients treated for unipolar depressive disorder at the outpatient mental health clinic at the West Los Angeles Veteran's hospital. Using the VA Integrated Decentralized Hospital Computer Program (IDHCP), a search was conducted of all veterans admitted to the Mental Health Clinic (MHC) between 1991 and 1996 with a diagnosis of unipolar depressive disorder. (Patients with bipolar depression, dysthymia, psychotic depression, etc. were excluded.) During this time period (1991–1996), the VA had no restrictions on the type of antidepressant that could be prescribed for depression. Charts of patients started on either fluoxetine or sertraline in the MHC were then selected. This was determined by looking in the order sheets for the medication and also by looking at the initial treatment plan and medication consent forms. If a patient was started on the medication on an inpatient ward at the VA within a month of enrolling in the MHC and progress notes from that hospitalization were available for review, the charts were also included. Charts were then reviewed to verify a DSM-IV diagnosis of major depressive disorder. This was done by reviewing the physician's initial intake evaluation and diagnosis. The initial diagnosis was further confirmed by reviewing sequential progress notes. Patients were excluded if, upon chart review, they did not meet criteria for major depressive disorder, they had previously failed an adequate trial of fluoxetine or sertraline, or if the trial to be reviewed was of inadequate length (less than 6 weeks). Additional DSM-IV diagnoses were recorded if they were present but not the primary focus of treatment. Substance dependence was defined as active, if use occurred within 90 days. Substance dependence in remission required greater than 90 days of sobriety at the time of the initial intake. If progress notes were illegible, missing, or did not contain information on the patient's mental status or target symptoms, the chart was not included.

Of the charts reviewed, 59 were suitable for analysis. Progress notes on each patient were analyzed for a 6-month time period after an antidepressant trial with fluoxetine or sertraline was initiated. In some instances, the medication was titrated toward increasing doses over 2 to 6 days to recommended starting doses. In these cases, the date that the medication was first administered was still considered the starting date. The date of the visit, dosage of medication at the time of the visit, interventions made during the visit (including change in dose, additional medications added, or discontinuation of the medication), were recorded. If any other psychoactive medication was being used at the time the SSRI was started or added during the treatment course, it was recorded.

Progress note data were abstracted, including information such as target symptoms, mental status exam, assessment, and plan. A physician, blind to the drug used for treatment, read the abstracted data and rated patient improvement on a scale of 1 to 4. Criteria for improvement were set a priori: (1) none to minimal improvement; (2) mild improvement (less than or equal to 50% better); (3) moderate improvement (less than 100% better); (4) full response. If the patient reached a rating of four and improvement was sustained for 1 month, or if a 6-month time period from the start of the antidepressant was reviewed in which less than a full response occurred, no further data were collected. If the medication was discontinued prior to 6 months, no further data were collected. A patient was considered a responder if an improvement score of 3 or 4 was reached and sustained over 1 month. A patient was considered a nonresponder if he or she were on medication for 6 weeks or greater, but did not achieve a score of greater than 2.

RESULTS

Of the charts reviewed, the clinical treatment of 26 patients on fluoxetine and 34 patients on sertraline was analyzed. Data are summarized in Table 1. Eighty-one percent of those on fluoxetine were responders (n = 21/26) and 19% (n = 5) were nonresponders. In the sertraline group, 76% were responders (n = 25/33), 24% were nonresponders (n = 8). The average dose that the fluoxetine nonresponders had received at the time of discontinuation was 24 ± 9 mg. In the patients receiving sertraline, the average dose nonresponders

TABLE 1. Dose and percent response for sertraline and fluoxetine

	N	N(%) responder	N(%) non-responder	Avg. dose of responder	Avg. dose of non-responders
Fluoxetine	26	21 (80.77)	5 (19.23)	23.81 mg ± 8.05	24 mg ± 8.94
Sertraline	33	25 (75.76)	8 (24.24)	89 mg ± 35.41	131.25 mg ± 53.03

had received at the time of discontinuation was 131 ± 53.03 mg. Of the fluoxetine responders, 81% (n = 17) were at a dose of 20 mg at the time of a positive response and 19% (n = 4) were at a dose of 40 mg at the time of a positive response. One of the four patients that responded to 40 mg of fluoxetine had his or her dose increased after less than 4 weeks on 20 mg. The average final dose of the fluoxetine responders was 24 ± 8 mg. Of the sertraline responders, 32% (n = 8) had a positive response while on 50 mg; 4% (n = 1) at 75 mg; 56% (n = 14) at 100 mg; 4% (n = 1) at 150 mg; and 4% (n = 1) at 200 mg. The average final dose of the sertraline responders was 89 ± 35 mg. Thus, over two-thrids (68%) of the sertraline responders were on more than 50 mg when a remission was achieved. Eighty-one percent of fluoxetine responders as compared to 32% of the sertraline responders were at the MRSD of 20 mg and 50 mg, respectively, at the time of clinical response (χ^2 = .06, P = 0.81). Of the 25 sertraline responders, 19 (76%) were started at 50 mg. While most of these were given 4 weeks or more on 50 mg before the dose was increased (n = 15), some were not (n = 4). Eight (53%) of those who had greater than a 4-week trial on 50 mg of sertraline responded at that dose. Seven (47%) who had greater than 4 weeks on the 50 mg daily dose required upward titration greater than 50 mg (average dose 111 ± 40 mg) before a positive response was achieved. In these subjects, the average time on 50 mg prior to dose increase was almost 6 weeks (41 ± 14.5 days).

Fifteen out of twenty-six patients on fluoxetine (57%) and eighteen of thirty-three on sertraline (55%) were receiving concurrent medications, usually for sleep. The type and number of concurrently prescribed medications is almost equally distributed between the fluoxetine and sertraline groups and is summarized in Table 2. Trazodone was the most common medication used (n = 19) followed by benzodiazepines (n = 8), antipsychotics (n = 5), and tricyclic antidepressants (n = 5).

Seven out of twenty-six patients had a comorbid condition in the fluoxetine group (27%) and seventeen out of thirty-three patients (52%) in the sertraline group (χ^2 = 3.6, P = 0.06). The incidence of comorbid conditions is summarized in Table 3. The most common secondary diagnosis in the depressed patients was substance dependence in remission (n = 9) followed by active substance dependence (n = 4) and personality disorder (n = 4).

TABLE 2. Other prescribed medications administered during acture antidepressant trial

Medications concurrently prescribed	Fluoxetine	Sertraline	Total
Trazodone	9	10	19
Benzodiazepines	4	3	7
Antipsychotics	2	3	5
Tricyclic Antidepressants	2	3	5
Lithium	1	2	3
Buspirone	2	0	2
Divalproex Sodium	0	1	1
Carbamazepine	0	1	1
Total prescriptions	20	23	43
Total patients	15/26 (57%)	18/33 (55%)	

DISCUSSION

In this retrospective study, we examined 59 VA records of outpatients treated with fluoxetine or sertraline for major depression. While groups treated with either medication showed a similar response rate overall, significant differences were noted both in terms of medication potency and clinician prescribing practices. Eighty-one percent of fluoxetine responders as compared to 32% of sertraline responders were at the MRSD of 20 mg and 50 mg, respectively, at the time of clinical response. Information published by the manufacturers of fluoxetine and sertraline suggests treatment should be instituted at 20 mg and 50 mg, respectively, of these medications. Our observations in this retrospective study suggest that either: (1) 50 mg of sertraline may be inadequate in many cases to achieve a moderate or full resolution of a major depressive episode, or (2) clinicians are not prescribing at the MRSD long enough to see a response. The factors explaining this rapid titration of sertraline are unknown, but could include physician (and patient) desire for rapid response, and a history of prior response or nonresponse to other antidepressants. The literature on dose titration for SSRIs is minimal and is thoroughly reviewed in this paper.

A recent study by Quitkin et al. [1996] indicates that patients whose depressive symptoms have not at least minimally improved after 4 weeks on an antidepressant should have their treatment regimen altered. We found that not all of the patients who were prescribed sertraline were started on 50 mg or received a 4-week trial at 50 mg prior to a dosage increase. However, when we examined the subset of patients who initially received 50 mg for 4 weeks or greater, only 53% responded at the 50 mg dose and 47% required a dose increase to achieve a remission. This suggests that some patients are not responding to 50 mg despite an adequate trial. The fact that some of the patients in this study were rapidly titrated to 100 mg of sertraline in the first 2 weeks of treatment suggests that clinicians who currently prescribe sertraline may believe

TABLE 3. Comorbid conditions

Secondary diagnosis	Fluoxetine (n=26)	Sertraline (n-33)	χ^2	*P*	Total (n=59)
Substance dependence in remission	2/26 = 7.7%	7/33 = 21.2%	2.06	0.15	9/59 = 15%
Substance dependence active	3/26 = 11.5%	1/33 = 3.0%	1.67	0.2	4/59 = 6.8%
Personality disorder	1/26 = 3.8%	3/33 = 9.1%	0.63	0.43	4/59 = 6.8%
PTSD[a]	0/26 = 0%	3/33 = 9.1%	2.5	0.12	3/59 = 5.1%
Panic disorder	0/26 = 0%	2/33 = 6.1%	1.6	0.2	2/59 = 3.4%
Dysthymia	0/26 = 0%	1/33 = 3.0%	0.8	0.4	1/59 = 1.7%
Anxiety disorder	1/26 = 0%	0/33 = 0.0%	1.3	0.26	1/59 = 1.7%
Schizoaffective disorder	0/26 = 0%	1/33 = 3.0%	0.8	0.4	1/59 = 1.7%
Total diagnoses	7	18[b]	3.6	0.06	25
Total patients	7/26 (27%)	17/33 (52%)			24/59 = 41%

[a]*PTSD, post-traumatic stress disorder.*
[b]*One patient had both personality disorder and substance dependence in remission.*

that the MRSD is a suboptimal dosage. In contrast, clinicians instituted fluoxetine treatment at 20 mg in 100% of cases, and in only two cases was the 20 mg dose increased before a 4-week trial. This suggests that physicians may have a greater confidence in the MRSD for fluoxetine.

Another possible explanation for our finding lies in the composition of the two medication groups. The sertraline group overall had a trend toward a greater proportion of patients with comorbidity. This comorbidity could have contributed to treatment refractoriness. The sertraline group had more patients diagnosed with substance abuse in remission (7/34) as opposed to patients in the fluoxetine group (2/26). In one study, a history of substance abuse contributed to rendering depression relatively treatment-refractory [Brown and Schuckit, 1988]. In a more recent study, however, depressed patients with comorbid alcohol dependence in remission had no difference in the rate of recovery when they were compared to those that were never alcoholic [Mueller et al., 1994]. In the current study, a greater percentage of the fluoxetine treatment group had patients with current active substance abuse but this was not significant. The sertraline group had higher percentages of other secondary diagnoses, in particular, post-traumatic stress disorder (PTSD), panic disorder, and personality disorder, but these differences were not significant.

This study is limited by the small sample size and retrospective design, which necessarily includes unknown factors that influence physicians in their selection of treatment and titration rate. Although the typicality of physician prescribing practices and patient typology as compared with other clinics is unknown and thus places in question the generalizability of these findings, the results are interesting and provide ideas for a well-designed prospective study. Further studies using prospective methods and larger sample sizes will need to be done to help clarify the comparative dosages of sertraline and fluoxetine needed for antidepressant efficacy. Such a prospective randomized blinded study is currently being conducted at our site. Our results, if replicated, may impact pharmacoeconomic decisions by large institutions, since fluoxetine and sertraline are comparably priced for a 1-month supply of 20 mg and 50 mg tablets (Veteran's Administration Medical Center wholesale acquisition cost) [Finley, 1994]. Medication cost, however, is just one aspect of the health care costs of treating depression. Two recent economic analyses of treatment of depressed patients have shown that the cost of a medication may be offset by a reduction in health resource utilization, thereby reducing total annual costs [Sclar et al., 1994, 1995]. Estimates of total cost of patient care to an institution requires consideration of all facets of care including hospitalization, therapists, frequency and duration of doctor visits, as well as cost of medications by the dosage required to achieve euthymia.

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REFERENCES

Aguglia E, Casacchia M, Cassano G. 1993. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 8:197–202.

Amin M, Lehmann H, Mirmiran J. 1989. A double blind placebo controlled dose finding study with sertraline. Psychopharacol Bull 25:164–167.

Bennie EH, Mullin JM, Martindale JJ. 1995. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 56:229–237.

Brown S, Schuckit M. 1988. Changes in depression among abstinent alcoholics. J Studies Alcohol 49:412–417.

Fabre L, Abuzzahab F, Amin M. 1995. Sertraline safety and efficacy in major depression: a double-blind fixed dose comparison with placebo. Biol Psychiatry 38:592–602.

Finley P. 1994. Selective serotonin reuptake inhibitors: pharmacologic profiles and potential therapeutic distinctions. Ann Pharmacother 28:1359–69.

Greenberg P, Stiglin L, Finkelstein S, Berndt E. 1993. The economic burden of depression in 1990. J Clin Psychiatry 54:405–418.

Gregor KJ, Overhage JM, Coons SJ, McDonald RC. 1994. Selective serotonin reuptake inhibitor dose titration in the naturalistic setting. Clin Therap 16:306–315.

Kessler R, McGonagle K, Zhao S, Nelson C. 1998. Lifetime and 12-month prevalence of DSM III R psychiatric disorder in the US: results from national comorbidity survey. Archives of General Psychiatry 51(1):8–19.

Mueller TI, Keller MB, Swartz A. 1994. Prognostic effect of the variable course of alcoholism on the 10-year course of depression. American Journal of Psychiatry 151(5):701–706.

Navarro R, Valler W, Spangler M. 1995. Antidepressant utilization of managed care: an evaluation of SSRI use in two HMO settings. Medical Interface 8(8):114–119.

Quitkin F, McGrath P, Stewart J. 1996. Chronological milestones to guide drug change: when should clinicians switch antidepressants? Arch Gen Psychatry 53:785–792.

Reimhan F, Chouinard G, Cohn C, Cole J. 1990. Antidepressant efficacy of sertraline and amitriptyline: a double blind placebo controlled and multicenter comparison study in outpatients with major depression. Journal of Clinical Psychiatry 51(suppl. B): 18–27.

Sclar D, Robison L, Skaer T, Legg R. 1994. Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. Clinical Therapeutics 16(4):715–30.

Sclar D, Robinson L, Skaer T, Gallin R. 1995. Antidepressant pharmacotherapy: economic evaluation of fluoxetine, paroxetine and sertralin in a health maintenance organization. Journal of International Medical Research 23(6):395–412.

Song F, Freemantle N, Sheldon T, House A. 1993. Selective serotonin reuptake inhibiters metaanalysis of efficacy and acceptability. British Medical Journal 306:683-7.

Wernicke J, Dunlop S, Dornseif B. 1987. Fixed-dose fluoxetine therapy for depression. Psychopharmacol Bulletin 23:164–168.