Sertraline as a First-Line Treatment for Cholestatic Pruritus

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Pruritus is frequently the most debilitating symptom of cholestatic liver diseases. Moreover, existing therapies are often ineffective. Recent small, retrospective case series reports suggest that serotonin reuptake inhibitors can improve pruritus. This study was undertaken to establish the dose of sertraline and to evaluate its efficacy for cholestatic pruritus. Twenty one subjects with chronic pruritus due to liver disease (including primary biliary cirrhosis, primary sclerosing cholangitis, chronic hepatitis C, and postnecrotic cirrhosis) initially underwent an open-label, dose escalation to determine the dose with optimal efficacy and tolerability. After a washout period, 12 of the subjects entered a randomized, double-blind, placebo-controlled trial. Participants quantified their pruritus using a 0-10 visual analog scale, and pruritus was assessed for distribution, timing, degree of disability, and physical evidence of scratching. The optimum sertraline dose (75-100 mg/day) was well tolerated. In the controlled portion of the study, itch scores improved in patients taking sertraline, but worsened in patients taking placebo ($P = 0.009$). Changes in itch distribution, duration, direction, and physical evidence of scratching paralleled changes in the visual analog pruritus score. *Conclusion:* Sertraline seems to be an effective, well-tolerated treatment for pruritus due to chronic liver disease. These results suggest that serotonergic pathways are important in the perception of itch. (HEPATOLOGY 2007;45:666-674.)

Therapies for cholestatic pruritus are often unsatisfactory for both patient and physician. There is no FDA-approved therapy for cholestatic pruritus, and many patients report persistent pruritus even with current therapies. Bile acid–binding resins, which are partially effective in up to 85% of patients,[1] are unpalatable, and they bind to and prevent absorption of almost all other medications. Rifampicin is modestly effective, but may cause increases in serum bilirubin or, rarely, severe hepatotoxic reactions.[2] Opioid receptor blockers are also effective but may result in an opioid withdrawal syndrome or chronic pain.[3] Other therapies include antihistamines, phenobarbital, and propofol, which are heavily sedating; *S*-adenosyl methionine (marketed as the dietary supplement SAMe); phototherapy; gabapentin; ondansetron; and albumin dialysis or plasmapheresis. Despite these therapeutic options, chronic pruritus remains one of the most prominent and vexing symptoms of cholestatic liver diseases.

In a retrospective study of 32 patients with pruritus due to primary biliary cirrhosis (PBC),[4] 6 of 7 subjects who had been given sertraline for another indication improved considerably, and pruritus completely disappeared in 3 of those individuals. This pilot study was undertaken to find the optimal dose and to evaluate the safety and feasibility of sertraline as a possible first-line treatment of cholestatic pruritus.

Patients and Methods

Subjects

All subjects provided written informed consent prior to study entry. This study was approved and overseen by the Institutional Review Board at UT Southwestern Medical Center. Subjects were recruited from outpatients seen at UT Southwestern Medical Center outpatient liver specialty clinics and were eligible for the study if they had chronic pruritus for at least 3 months due to stable or gradually progressive cholestatic liver disease. Subjects

Abbreviations: IDS-SR$_{30}$, Inventory of Depressive Symptomatology, 30-Item Self-Report; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; VAS, visual analog scale.

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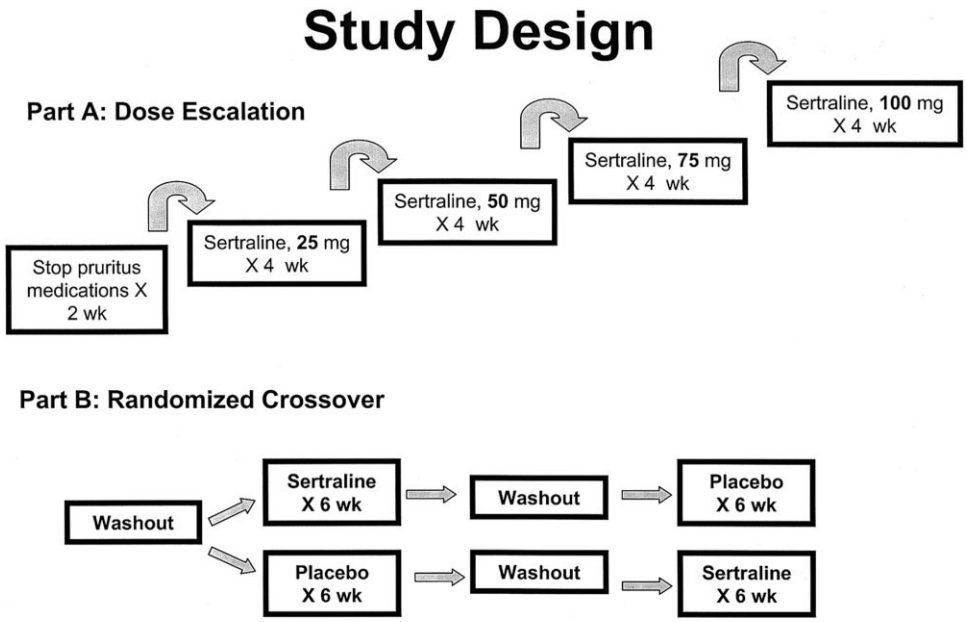

Fig. 1. Study design.

were excluded if they were already taking another antidepressant, opioid-containing medication, ondansetron, corticosteroids, phenothiazines, octreotide, or antiviral medication for viral hepatitis. Concomitant ursodiol treatment was allowed only if subjects were on a stable dose for at least 6 months before and throughout the study. Subjects who were taking other medications for pruritus (e.g., antihistamines, rifampicin, bile acid–binding resins) were allowed entry if they stopped these medication(s) at least 2 weeks before beginning the protocol. Subjects were examined by a dermatologist and excluded if they had evidence of a primary skin disorder.

Treatment Protocol

The treatment protocol was divided into Part A (dose finding) and Part B (efficacy) (Fig. 1). After 2 weeks of observation after going off all antipruritus medications, subjects began an open-label dose titration (part A) with 25 mg of sertraline once daily. The dose was increased in 25 mg increments at 4-week intervals until subjects reported that (1) pruritus was resolved, (2) side effects were intolerable, or (3) they expected no further benefit with additional dose increases. Once the optimal sertraline dose for an individual was identified, it was continued for a total of 6 weeks. Then sertraline was stopped and allowed to wash out until serum sertraline and metabolite levels were undetectable. Then, Part B of the study consisted of subjects randomized to double-blind treatment with either sertraline or placebo. The dose in Part B was the same dose previously determined to be optimal for that individual in Part A. Subjects were treated for 6 weeks, then washed out again for 4 weeks, and crossed over to the other therapy for 6 weeks. Office evaluations occurred before each change in medication.

Outcome Measures

Subjects completed a daily itch diary in which they graded the severity of their pruritus on a continuous scale from 0 (no pruritus) to 10 (the worst pruritus imaginable) using a visual analog scale (VAS) with points anchored with facial expressions to guide their selection (Fig. 2). This pruritus score was the primary outcome measure.

Dermatologic exams were conducted at each visit. Secondary scratching lesions were noted and graded as worsened, stable, improved, or resolved. A detailed pruritus history was obtained at each visit to assess pruritus duration, quality, course, worsening factors, distribution, and disability. Subjects also completed the self-report version

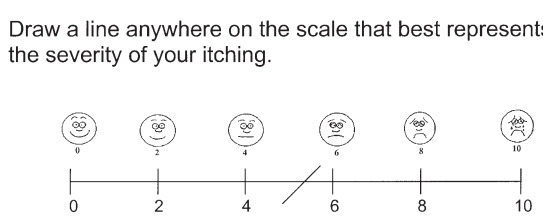

Fig. 2. Visual analog tool. The primary outcome was this visual analog scale with facial expression and number anchors. This scale was reproduced in the subject diaries so that each line was exactly 100 mm in length.

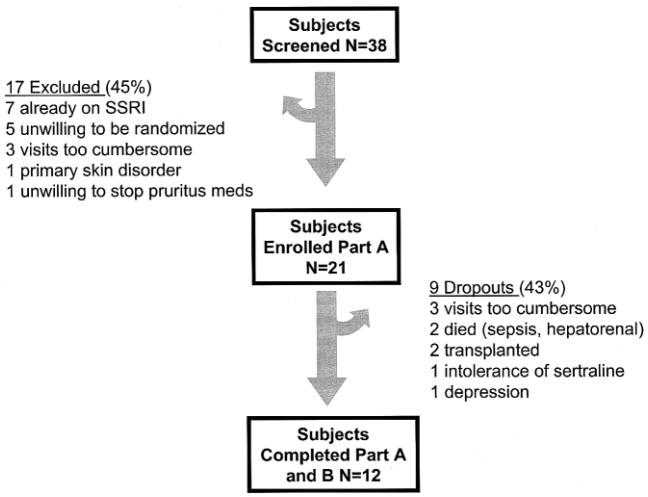

Fig. 3. The flow of subjects through the study.

Table 1. Clinical and Demographic Features

Feature	Open-Label Dose Escalation (n = 21)	Randomized Crossover (n = 12)
Sex		
Male	14%	17%
Female	86%	83%
Race/Ethnicity		
White, not Hispanic	71%	50%
African American	14%	25%
Hispanic White	14%	17%
Mixed*	5%	8%
Disease		
Primary Biliary Cirrhosis	57%	75%
Hepatitis C Cirrhosis	24%	0%
Primary Sclerosing Cholangitis	9.5%	17%
Drug Induced Liver Injury†	9.5%	8%

*50% American Indian, 50% White.
†Postnecrotic cirrhosis from previous submassive acute liver injury.

of the 30-item Inventory of Depressive Symptomatology[5-7] at each visit to evaluate the effect of sertraline on depressive symptoms. Sertraline and desmethylsertaline levels obtained at each visit were measured by mass spectroscopy at Med Tox Scientific Inc.(St. Paul, MN).

Statistical Analysis

Daily VAS scores over the entire period of treatment with each dose of sertraline were averaged to determine the net VAS score for each treatment dose. Change in raw VAS scores in the open-label dose escalation were compared with a repeated measures ANOVA, and the pairwise comparisons between each dose and baseline was made using the Holm-Sidek method. In the crossover study, repeated measures ANOVA was used to assess treatment differences and evaluate treatment order. A sample size of 13 subjects receiving each treatment was estimated to provide a 90% power to detect a clinically significant (2.0 point) difference in VAS score, assuming a standard deviation of 2.0 points and a Type 1 error of 0.05.

Results

Subjects

Thirty eight subjects with cholestatic pruritus were screened for the study. Seventeen (45%) were excluded for the reasons outlined in Fig. 3. The most common reason for exclusion was current use of another serotonin reuptake inhibitor. Nine subjects (43%) dropped out before completing both parts of the study (Fig. 3), though 17 (81%) completed Part A. The most common reason for dropout was liver-related death or transplant in a patient with advanced cirrhosis.

The subject population (Table 1) was enriched in white females with PBC, but also contained subjects with sclerosing cholangitis, hepatitis C, and postnecrotic cirrhosis. The mean Model for End-Stage Liver Disease (MELD)[8] score of the population (Fig. 4) was 11, with a range of 6-24. Thus, many subjects had advanced cirrhosis, particularly those with pruritus due to HCV.

Dose Finding

Results of the dose escalation (Fig. 5) showed there was no overall change from baseline VAS scores with the 25 mg dose ($P = 0.11$). All but 2 subjects experienced significant improvement in their pruritus when given the 50 mg dose (50 mg versus baseline, $P = 0.002$). Increasing the dose further to 75 mg/day resulted in greater decreases in pruritus scores (75 mg versus baseline $P < 0.0001$), particularly in subjects who had not responded well to the 50 mg dose. Increasing the dose even further to 100 mg was useful in many subjects (100 mg versus baseline, $P < 0.0001$), primarily those who had not yet achieved a 50% improvement in their pruritus with the 75 mg dose. Fur-

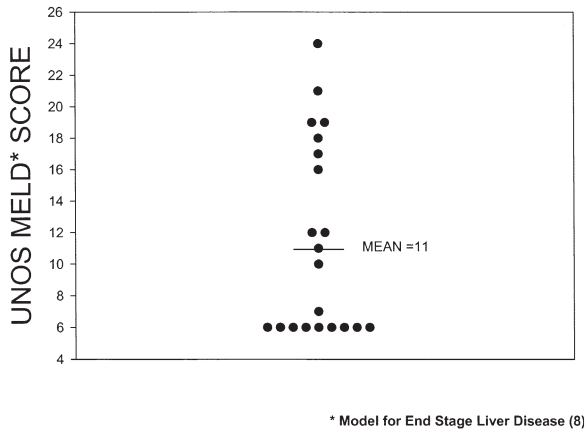

Fig. 4. The severity of liver disease assessed by MELD.

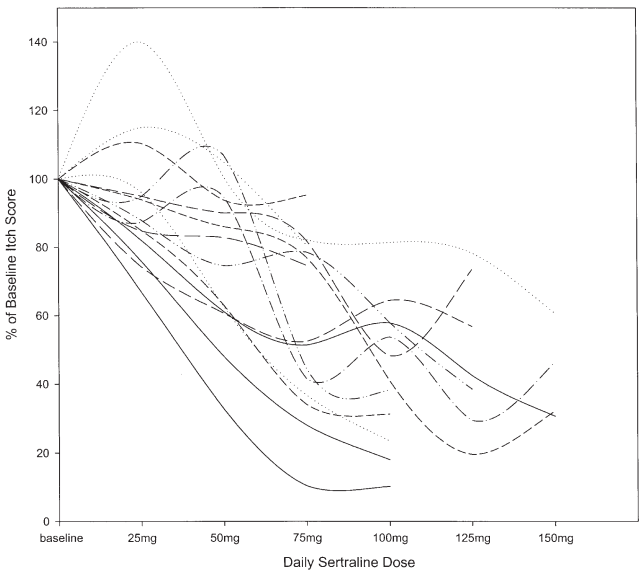

Fig. 5. Response of pruritis to sertraline open label dose escalation.

ther dose increases to 125 or 150 mg did not necessarily result in improved pruritus scores. Furthermore, these doses were usually not considered worthwhile by the subjects due to increasing frequency of side effects such as insomnia, fatigue, and increasing bowel frequency.

After the optimum clinically effective dose for each subject was determined, the data were analyzed to see if either weight-based dosing, sertraline, or desmethylsertraline (the major metabolite of sertraline) level-based dosing was more predictive of ultimate benefit than using a standard dose. The median optimum dose was 1.52 mg/kg, with the lowest value of 0.81 mg/kg and highest value of 2.38 mg/kg. However, weight-based dosing did not approximate the best dose any better than simply using 100 mg/day for every patient.

Sertraline and desmethylsertraline levels were also monitored throughout the open-label dose escalation. Although there was a positive correlation between dose and both drug and metabolite levels, the optimal clinically effective dose in each subject was associated with a wide distribution of study drug and metabolite levels.

Placebo-Controlled, Double Blind Crossover

Visual Analog Score. The results of the double-blind crossover are illustrated in Fig. 6. Pruritus in subjects taking sertraline improved a mean of 1.86 raw points on the visual analog scale, whereas pruritus in subjects taking placebo actually worsened 0.38 points. The difference between the two (net beneficial effect of 2.24 points) was statistically significant ($P = 0.009$). Prior to the start of the study, a clinically significant improvement was defined as a 20% reduction in pruritus from baseline. The mean improvement of pruritus on sertraline was actually 33% in the randomized portion of the study and was 53% in the open-label portion of the study. Although the degree of individual response was variable in the double-blind phase, 8 of the 12 subjects met the predefined treatment success endpoint of a 20% or greater improvement in pruritus while taking sertraline, whereas there were no (0 of 12) treatment successes on placebo (z-test, $P = 0.0.002$).

Scratching Lesions. The most common secondary scratching lesions noted were excoriations, red crusted nodules, and hyperpigmented prurigo nodules. The course of skin lesions is shown in Fig. 7. All 12 subjects who completed the entire double-blind, randomized portion of the study had excoriations. Excoriations improved in subjects taking sertraline (10 of 12, 83%) more commonly than in subjects taking placebo (0 of 12, $P < 0.001$). Red crusted nodules were the second most common lesion, found in 8 of the 12 subjects who completed the controlled portion of the study. Red crusted nodules tended to improve in subjects taking sertraline (7 of 8, 88%) more often than in subjects taking placebo (1 of 8, 13%). Improvement in hyperpigmented prurigo nodules was a rare event, occurring in only 1 subject (1 of

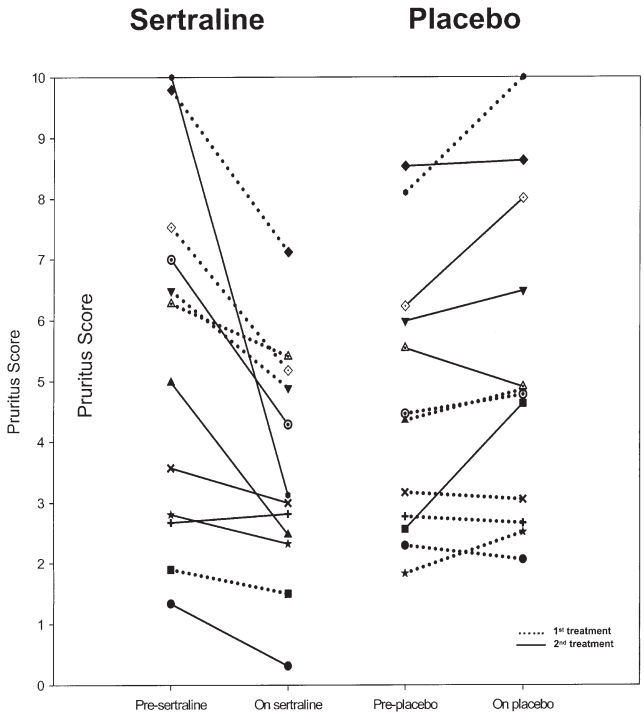

Fig. 6. Change in pruritus during double-blind treatment. Visual analog scores improved a mean of 33% from baseline (1.84 raw score points) in subjects taking sertraline, as compared to a net worsening of pruritus of 0.38 points in subjects taking placebo ($P = 0.009$). Improvement of pruritus during sertraline therapy was consistently seen, whereas responses to placebo were variable

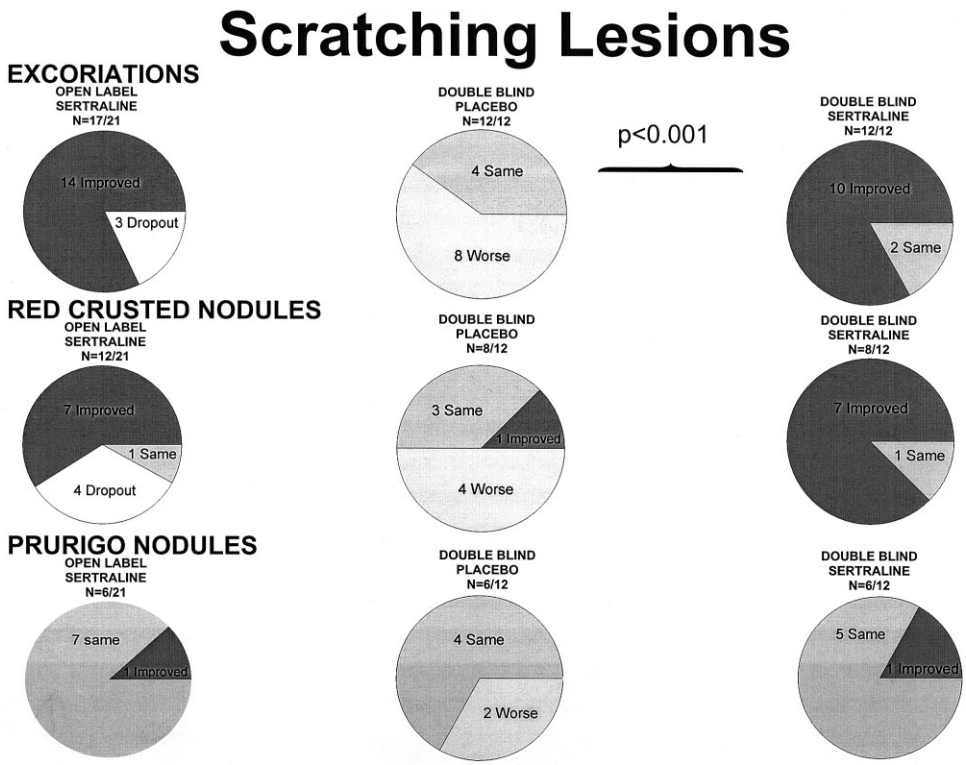

Fig. 7. Change in scratching lesions during treatment.

6, 17%) taking sertraline and none of the subjects taking placebo.

Pruritus Course. Subjects reported whether they felt their pruritus was progressive, static, fluctuating, improved, or resolved at each visit. After open-label sertraline, one subject reported complete resolution, and the remainder all reported improvement in their pruritus. When sertraline was given in a double-blind fashion, however, subjects were less confident in their willingness to report improvement (8 of 12, 67%), and many reported "fluctuating" (4 of 12, 33%). However, the majority of subjects (7 of 12, 58%) classified their pruritus as "progressive" both before and after taking double-blind placebo therapy.

Pruritus Duration. Subjects estimated the duration of itching using 5 categories: constant, >18 but ≤24 hours daily, >12 but ≤18 hours daily, >6 but ≤12 hours daily, or <6 hours daily. At study entry, most subjects felt their itching was either constant or lasted 12-18 hours per day. After open-label treatment with sertraline, all subjects reported that their itching lasted ≤6 hours per day. After double-blind placebo treatment, 2 subjects downgraded their pruritus to <6 hours per day, but there was little overall change in the duration of pruritus with placebo treatment. In contrast, after double-blind sertraline treatment, all subjects categorized the duration of their pruritus as <6 hours per day, except 1 who reported between 6 and 12 hours per day.

Pruritus Distribution. A checklist of body areas was surveyed at each visit, and subjects reported whether they had experienced any itching in those areas during the 2 weeks before their visit. Overall, the most common areas affected by cholestatic pruritus were the back, lower legs, upper arms, and thighs. The number of itchy body areas

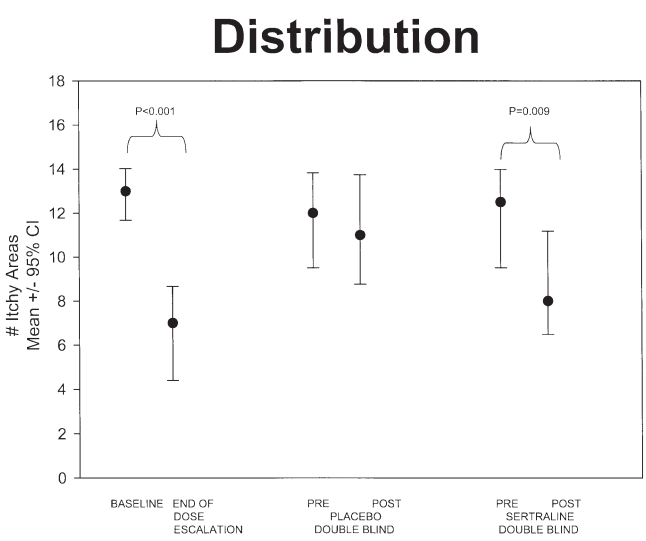

Fig. 8. Change in the distribution of pruritus with treatment.

Table 2. Tolerability (n = 21)

Event	Sertraline	Placebo	No Drug*
Improved Mood Stability	8	1	0
Increase in bowel frequency	2	0	0
Visual hallucinations	2	0	0
Increase in fatigue	2	1	1
Insomnia	3	6	14
Dizziness	1	0	0
Nausea	1	1	1
Death	0	0	2
Transplant	2	0	0

*During baseline and washout phases.

decreased from 13 to 7 after open-label sertraline ($P < 0.001$, Wilcoxon) and from 12.5 to 8 ($P = 0.009$) after double-blind sertraline. The distribution decreased from 12 to 11 areas ($P = 0.69$) with double-blind placebo treatment (Fig. 8).

Pruritus Insomnia. The disabling effect of pruritus was measured by asking individuals whether their pruritus interfered partially, completely, or not at all with certain daily activities. Sleep was the most common activity disturbed by pruritus. At baseline, 8 (38%) subjects said their pruritus was partially interfering with their sleep, and 4 (19%) subjects felt it was totally interfering with their sleep. Four of these subjects (3 in the "partially" group and one in the "totally" group) subsequently dropped out of the study. However, 7 of 8 of the remaining individuals with pruritus-related insomnia reported improvement after open-label sertraline. Interestingly, sertraline was not clearly better than placebo at improving disturbed sleep. After double-blind sertraline treatment, only 2 subjects reported improvement in their sleep, 1 said it was worse, and the remainder (9 subjects) said it was unchanged. After placebo treatment, 3 subjects reported improvement, 3 said it was worse, and 5 reported pruritus was unchanged.

Tolerability. Overall, sertraline was well tolerated by patients with cholestatic pruritus. One subject discontinued sertraline due to side effects. She had intolerable dizziness that occurred within minutes following each ingestion of sertraline. This dizziness even occurred at half of the starting dose (12.5 mg/day). The side effects of all subjects are reported in Table 2. The most frequently reported "side effect" was actually a beneficial effect of increased mood stability, described as feeling less emotionally labile, less likely to enter into conflicts with other individuals, better able to cope with negative events in their lives, or in some instances, less depressed. In other previous treatment trials examining sertraline as an antidepressant, the most common side effects reported have been headache, diarrhea/loose stools, nausea, and insomnia. In this small study, headache and nausea were not associated with sertraline treatment, but looser stools were reported by 2 individuals. In 1 subject, this influenced their decision to cut back to 75 mg from 100 mg. Three subjects on sertraline reported insomnia as an adverse event, but this was actually less frequent than subjects who were not taking any medication at all. Four subjects dropped out of the study because of liver-related death (overwhelming sepsis and hepatorenal syndrome) or successful transplantation. None of these events were felt to be related to administration of sertraline, but rather related to the fact that patients with advanced liver disease, some of whom were already listed for liver transplantation, were admitted to the study. These 4 subjects had the highest MELD scores of the group at study entry, and the 2 deaths occurred during washout periods. Two subjects reported interesting visual hallucinations, a side effect not previously recognized as common in persons taking sertraline. One subject taking 75 mg sertraline witnessed extra people roaming her house, and another subject taking 50 mg sertraline thought she saw a snake and a cat in her house. Both subjects felt these were hallucinations and were evaluated by a psychiatrist. In the latter case, Animal Control confirmed the absence of evidence for these animals in the house.

Depression. At each visit, subjects completed the 30-item Inventory of Depressive Symptomatology–Self-report (IDS-SR_{30}), a measure of depression that has been validated in diverse cohorts of patients and shown to be quite sensitive at detecting mild depressive symptoms and changes over time. The number of subjects with no, mild, moderate, or severe depressive symptoms before and after each treatment are shown in Table 3. All 4 subjects with moderate or severe depression improved with sertraline. One of these subjects also improved with placebo. Sub-

Table 3. Inventory of Depressive Symptoms with Treatment

Depressive Symptoms	Baseline	End of Dose Escalation	Pre-Placebo	Post-Placebo	Pre-Sertraline	Post-Sertraline
None (0-14)	8	10	7	7	9	10
Mild (15-30)	9	5	3	4	1	2
Moderate (31-45)	2	1	1	1	1	0
Severe (>45)	2	0	1	0	1	0
Total No. of Subjects	21	16	12	12	12	12

jects with mild depressive symptoms, however, did not reliably improve their IDS-SR_{30} score with sertraline. Two of 9 subjects improved on open-label sertraline, but no subject in the crossover study with mild depressive symptoms improved. In order to determine how much of the improvement in pruritus may have been related to improvement in depressive symptoms, an analysis of covariance was performed on the serial IDS-SR_{30} and VAS scores obtained in the open-label dose titration. The improvement in VAS after adjusting for IDS-SR_{30} was still highly significant ($P < 0.0002$). The IDS-SR_{30} effect was also significant ($P = 0.0011$). Thus, both VAS and IDS-SR_{30} improved with increasing doses of sertraline, but the change in IDS-SR_{30} did not explain all of the change in VAS.

Study Drug Preference. At the end of the double-blind treatment, subjects were asked (1) which treatment (first or second) they thought was the sertraline, (2) why they thought so, and (3) which treatment they preferred. Eleven of 12 subjects correctly identified sertraline versus placebo. Ten subjects said they based that decision upon the improvement in their pruritus, and 1 said the active drug tasted more bitter than the placebo. All 12 subjects stated a preference for sertraline and chose to participate in an optional 2-year open-label sertraline long-term follow-up study.

Discussion

This prospective study extends and validates our previous observation that sertraline use is associated with an improvement in cholestatic pruritus. The optimal dose of sertraline for this indication was identified as 75-100 mg. Subjects who experienced a greater than 50% reduction in pruritus with 75 mg experienced only a small improvement with a dose increase to 100 mg. Dosing according to weight or sertraline or desmethylsertraline levels was not more accurate than using a standard dose of 100 mg daily. Note that sertraline was gradually titrated up to the therapeutic dose, a strategy which has been associated previously with reduced gastrointestinal side effects.

The overall number of side effects was lower than expected. Only 1 subject could not tolerate the drug due to dizziness, and 1 subject decreased the dose from 100 mg to 75 mg because of loose stools. Because sertraline is metabolized in the liver, one might have expected a higher frequency of side effects in a population with liver dysfunction. One-third of subjects had advanced cirrhosis, with a MELD score of >15. Sertraline had not been previously tested in a population of patients with advanced cirrhosis; only 1 study examined pharmacokinetics in 9 patients with Childs' A cirrhosis.[9] The reason for the low rate of side effects in our study is not certain. However, side effects have been associated specifically with desmethylsertraline levels, and slower formation of this metabolite may be responsible. Interestingly, 2 subjects reported visual hallucinations, a side effect not previously associated with sertraline. These hallucinations occurred in depressed individuals with advanced cirrhosis and disappeared with further dose increases. Thus, the hallucinations might have been a manifestation of their depression, although hallucinations in depression are rare and are typically auditory.

Sertraline treatment was clearly associated with improvement in pruritus in both the open-label and randomized portions of the study. The magnitude of the response to sertraline, as with other treatments for cholestatic pruritus, was variable. Etiology of the pruritus did not predict the extent of the response, although the number of subjects with any individual disease was small. The biggest improvement was seen in one of the individuals with postnecrotic cirrhosis and the smallest was seen in one of the patients with PBC. Pruritus appeared to be a late feature of HCV cirrhosis, as these subjects were selectively lost to death or transplant. However, in the open-label study, responses in HCV subjects were similar to other cholestatic diseases.

No subject reported complete disappearance of pruritus; thus, sertraline may be quite effective as a single agent, but not a cure for pruritus. Overall, there was a 33% improvement in pruritus scores in subjects taking double-blind sertraline, which was above the preset clinically significant threshold of 20% improvement and similar in magnitude to other previously tested pruritus treatments such as rifampicin. The raw score difference between the sertraline and placebo groups was 2.24 points, which was also statistically significant ($P = 0.009$).

In addition to the daily visual analog pruritus scores, subjects were interviewed and examined at each visit (approximately monthly) during the study to assess change in secondary scratching lesions, course, duration, distribution, and disability of pruritus. Other studies have used piezoelectric finger monitors to measure scratching activity, but this was felt to be too cumbersome for the long duration of this study. Excorations improved significantly in sertraline-treated as compared to placebo-treated subjects. Red crusted nodules trended toward improvement, but this was not statistically significant. Hyperpigmented prurigo nodules did not improve appreciably. However, all these subjects elected to participate in a long-term 2-year follow-up study, and some are now experiencing fading and flattening of these lesions. Thus, the study duration was probably too short to allow resolution of hyperpigmented prurigo nodules. The mean number of itchy body areas also decreased from 12.5 to 8 ($P =$

0.009) with sertraline treatment as opposed to 12 to 11 with placebo; this indicates that as pruritus improves with treatment, it becomes more localized. The data also indicate that as the severity of pruritus improves with treatment, it becomes less frequent. After double-blind sertraline treatment, all subjects except 1 reported itching less than 6 hours per day. Most subjects also graded their pruritus as "improving" after sertraline treatment, whereas they chose "progressive" after placebo treatment. Collectively, these data demonstrate that sertraline improves the severity, distribution, duration, course, and skin manifestations of cholestatic pruritus. Patients with chronic pruritus often complain that their itching disturbs their sleep, so sertraline's effect on sleep was evaluated. Although patients slept better on sertraline, they slept just as well on placebo. Perhaps the known side effect of insomnia counterbalances the improvement in pruritus seen with sertraline treatment.

The mechanism by which sertraline improves pruritus is fascinating to speculate, but in fact cannot be determined from this study. The hypothesis that sertraline would improve pruritus as compared to placebo was not based on physiologic evidence, but rather the previous clinical experience that some patients with PBC reported dramatic improvement in pruritus with sertraline. The fact that pruritus from various liver diseases (PBC, primary sclerosing cholangitis, HCV, etc.) responded to sertraline in this trial illustrates that the effect is not exclusive to patients with PBC. Other smaller case series have reported improvements in pruritus with serotonin reuptake inhibitors in other pruritic disease states such as renal failure, psychogenic pruritus, and malignancy.[10-12] Thus, the effect of sertraline is probably generalizable to other serotonin reuptake inhibitors and disease states. However, no other report has carefully determined the appropriate dose and effect size in a prospective study. Several subjects with ongoing pruritus were excluded from the study because they were already taking another serotonin reuptake inhibitor. None were taking sertraline, but both dose and differences in serotonin and norepinephrine receptor specificity of the different serotonin reuptake inhibitors may be important. We propose that sertraline mediates its effect through serotonergic signals in the central nervous system that provide inhibitory signals to the itch pathways. The perception of itch involves both a physical sensation and an emotional response, culminating in the desire to scratch. Sertraline may affect 1, 2, or all 3 of these steps. Itch-specific neuronal pathways have been identified that project from the lamina I of the spinal cord to the ventrocaudal part of the nucleus medialis, and then to the anterior cingulate and dorsal insular cortex. These same pathways are involved in pain perception; thus, it is easy to reconcile the known antagonism of pain and itch. However, the specific role of serotonergic fibers in these pathways is not well known, even though serotonin and its receptors are important in pain control.[13] It is also well recognized that psychological stress can worsen pruritus, and sertraline may work solely as a neuropharmacologic inhibitor of stress. One of the questions at the start of this study was whether only depressed individuals would experience improvement in their pruritus with sertraline, implying that the pruritus response was intimately tied to the antidepressant response. However, this did not turn out to be true. Most subjects had either no or mild depressive symptoms which did not change with therapy, yet these subjects experienced similar improvement in their pruritus. The depression measure we used (IDS-SR_{30}) is a very sensitive measure of even mild depressive symptoms. Thus, these data demonstrate that the antiitch effect is not merely a manifestation of the antidepressant effect. However, several subjects who were not at all depressed, as measured by the IDS-SR_{30}, reported that they felt more even-tempered, supporting the theory that sertraline may reprogram the stress response and inhibit the emotional response arm of itch perception.

It is important to remember that this study was designed as a dose-finding, tolerability, and feasibility study. As a pilot study, there are certain limitations in the interpretation of the results. Perhaps the most significant is that a small number of subjects was used for maximal purpose. Although the differences in pruritus between the sertraline and placebo treatments were both statistically and clinically significant, the absolute number of treated patients is small and limited to a single center. Further validation of these findings in larger populations is needed. Several of the outcomes evaluated in this study, such as pruritus course and duration trended toward a beneficial effect of sertraline, but did not meet statistical significance, perhaps due to the limited sample size. The high dropout rate was mostly due to the attrition of patients with very advanced cirrhosis, but one cannot exclude a selective dropout of treatment failures. In addition, subjects randomized to sertraline or its matching placebo were not naïve to sertraline; they had previously been treated with sertraline in the open-label dose escalating phase of the study. Thus, even though the subjects were treated in a double-blind fashion, they potentially might have been able to recognize the feeling of sertraline treatment. In fact, 11 of 12 subjects correctly identified which study drug (first or second) was the sertraline. Only 1 of these subjects admitted to recognizing a bitter taste of real drug; the others said their decision was based on a change in pruritus. However, these statements

may not reflect an unconscious perception of which drug made them feel different.

Not surprisingly, a greater improvement in pruritus was seen in the open-label part (53%) as compared to the randomized part (33%). In fact, all of the self-reported pruritus symptoms (course, duration, distribution) improved more in the open-label part than in the randomized part. At face value, this would seem to be due to the additive placebo effect and study drug effect in the open-label study. Placebo effects in controlled pruritus studies are notoriously high. However, it is interesting to note that the starting 25 mg dose in the open-label study had no effect on pruritus, which argues against a significant placebo effect. Also, when the open-label drug was stopped and washed out completely, pruritus scores increased, but did not rebound to levels at study entry. Thus, lower starting pruritus scores at the beginning of the randomized treatment allowed less room for improvement with treatment. This might have been due to a carry-over effect of the open-label treatment. Even though the serum sertraline and metabolite levels were undetectable, central nervous system levels and serotonin receptor expression levels could not be measured. Even subjects randomized to placebo as the first treatment did not reach their baseline pruritus scores at the end of the 6-week placebo treatment, suggesting that if there is a carry-over effect, it is very long lasting. Another possibility is that subjects rarely rebounded to their original level of pruritus because they felt better simply by virtue of participating in a study addressing their problem. Prior exposure to sertraline probably also explains the lack of a big placebo effect seen in the randomized portion of the study. Pruritus scores actually worsened slightly in the placebo group. Subjects who have just experienced relief of their pruritus (on open-label sertraline) are more likely to recognize true relief when they feel it. All of these findings may shed light on the mechanisms of effect of both sertraline and placebo, but also show that randomized trials of sertraline-naïve subjects are needed to accurately quantify its therapeutic effect.

In summary, despite these limitations, this study provides sufficient data to justify adding sertraline to the armamentarium of drugs for the treatment of cholestatic pruritus. This study tested sertraline as a first-line agent and demonstrated both statistical and clinically significant improvements in pruritus via multiple different outcome measurements. These findings deserve to be confirmed in a larger efficacy study. Because of its excellent tolerability and infrequent drug-drug interactions, sertraline would be an excellent choice for first-line therapy, particularly in depressed subjects who may also benefit from its known antidepressant effect.

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