Sertraline is an effective management option for cholestatic pruritus

Rudy W. Wenner
Wayne State University School of Medicine, rwenner@med.wayne.edu

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RUDY W. WENNER, Wayne State University School of Medicine, rwenner@med.wayne.edu

ABSTRACT

Keywords: cholestatic pruritus, treatment, SSRI, clinical trial

Clinical Context
A 74 year-old Caucasian female with history significant for renal cell carcinoma status post right nephrectomy presented as a transfer from an outside hospital with three weeks of pruritus, jaundice, elevated liver function tests (LFTs), and elevated bilirubin (total and direct). Two months prior, results from a routine surveillance CT abdomen/pelvis revealed a pancreatic head mass as well as a severely distended gallbladder with multiple stones and intrahepatic biliary dilation. Under our care she underwent endoscopic retrograde cholangiopancreatography (ERCP) and an endoscopic ultrasound (EUS), revealing compression of the major papilla from a mass found in the distal common bile duct and pancreatic head. Cannulation could not be performed and she was admitted for percutaneous transhepatic cholangiography (PTC) drain placement with Interventional Radiology. Patient remained stable with no signs of cholangitis, and the drain was placed two days later. Bilirubin and liver function tests trended down following drain placement. Biopsy results were consistent with metastatic renal cell carcinoma, clear cell type. The patient preferred to follow up with oncology closer to home and was discharged with the drain to be removed in six to eight weeks. Throughout her hospitalization, the patient was asymptomatic besides unbearable pruritus and jaundice. She received treatment with the PTC drain and anti-histamines, however the pruritus persisted to discharge. Her main concern was always, “Doctor, what can I take to stop this itching?”

Addressing the patient’s concern began with understanding the standards of care for cholestatic pruritus. An UpToDate article titled Pruritus associated with cholestasis outlined multiple medication options. For moderate to severe pruritus, trials of cholestyramine, rifampin, naltrexone, or sertraline were recommended. Of the options serotonin was of particular interest because in addition to pruritus, the patient also described multiple weeks of depressive symptoms and worsening mood with her recent diagnosis. Since sertraline has known effective anti-depressive properties, the team wanted to investigate the efficacy of the medication’s anti-pruritic effects in order to reduce pill burden.

Clinical Question
Do selective serotonin-reuptake inhibitors provide a clinically significant reduction in symptoms for patients with cholestatic pruritus?

RUDY W. WENNER, B.S., is a 3rd year student in the Wayne State University School of Medicine.
Research Article


Related Literature

A PubMed search with keywords “cholestatic pruritus” and “treatment” and “SSRI” sorted by the most recent feature yielded 17 results. Of those results, six were relevant to the clinical question. The Cochrane Review evaluated the evidence on multiple pharmacological interventions for pruritus in palliative care patients and concluded that SSRI’s are a viable option for reduction of pruritus symptoms.\(^1\) This and the second systematic review were utilized to evaluate for further relevant citations.\(^2\) Of the remaining four citations, Mayo proved to be the strongest and most applicable trial to the patient clinical scenario discussed.

The Zyclizc study\(^3\) was excluded due to poor clinical fit and study duration. Zycliz included palliative care patients with pruritus of varying natures, including both non-malignant and malignancies of multiple origins. Of the 26 patients, only three had pruritus of cholestatic origin. Additionally, the Zycliz study was of shorter duration compared to Mayo: one week per each arm of the randomized crossover versus six weeks in Mayo. Mayo’s study also analyzed a secondary outcome measure and discussion about depression with SSRI use, while Zycliz did not.\(^4\) The Browning trial was excluded for two reasons: inadequate patient demographics and retrospective nature of study.\(^1\) Only primary biliary cholangitis (PBC) was included in Browning’s study, while PBC, primary sclerosing cholangitis (PSC), and Hepatitis C Virus (HCV) cirrhosis were included in Mayo’s study. Therefore, Mayo’s study better reflects the breadth of cholestatic disease. Mayo’s study was also selected because a placebo-controlled double blind crossover study provides more strength than a retrospective analysis of patients who used sertraline “at some point.”\(^1,4\) Finally, Unotoro was excluded due to the low number of patients included in analysis.\(^6\)

Critical Appraisal

This research is a two part clinical trial, including an initial dose escalation (Part A) followed by a placebo-controlled double blind crossover study (Part B). Part A was designed to determine the optimal sertraline dose for participation in part B and to identify tolerability. Part B was designed to determine the efficacy of sertraline as a first-line treatment for cholestatic pruritus. Prior to Part A, patients received a two-week washout of all anti-pruritic medications. In Part A, all participants were evaluated with a starting dose of 25 mg sertraline daily. Every four weeks the dose was titrated by 25 mg to one of three endpoints: resolution of pruritus, intolerable side effects, or no further experienced benefits from increased dose. Once reached, the optimal dose was continued for a total of six weeks. Prior to Part B, all patients underwent a two-week washout period. In Part B patients were randomly assigned to double blind treatment with either placebo or sertraline. All patients underwent six weeks of treatment with either placebo or optimal dose sertraline as determined in Part A. Treatment was followed by a four week washout period and cross over to other therapy for an additional six weeks. Primary endpoints in treatment were improvements in subjective itching in terms of course, duration, and distribution. Secondary endpoints included tolerability and depression.

Patients were recruited from UT Southwestern Medical Center and included in the study if they had stable or slowly progressive liver disease and at least three months of pruritus. Exclusion criteria included subjects currently taking another antidepressant, opioid-containing medication, ondansetron, corticosteroids, octreotide, phenothiazine, or anti-retroviral for viral hepatitis. Current use of another anti-pruritic medication was not an exclusion criterion as long as subjects underwent a two-week washout period. The described patient met both inclusion and exclusion criteria. Additionally, the patient reflects demographics features of the trial subjects: (83% female and 50% white in the randomized crossover). However, while all subjects included in the study have pruritus of cholestatic origin, none had the similar mechanism of obstructive cholestasis secondary to malignancy.

Significant improvements in pruritic symptoms were found in both the open-label (53%) and randomized crossover (33%), while no treatment successes were found in the placebo group. In fact, the placebo group experienced worsening of symptoms. Clinically significant improvement in pruritus was determined prior to start of the study as at least a 20% reduction in pruritus from baseline based on the visual analog scale. Additional outcomes included improvement in scratching lesions (83%) and symptoms of patients...

with moderate to severe depression. Depressive symptoms were analyzed at each visit with the 30-item Inventory of Depressive Symptomatology Self-Report.

Despite clinically significant improvement in symptoms, the trial had some limitations. The most significant limitation is the small subject size. Of the 38 subjects screened, 17 were excluded (most commonly for previous SSRI use), and of the 21 enrolled in Part A only 12 subjects completed Part B. High dropout rates were most commonly due to advancement of disease course or transplant. These high rates may have masked potential failures of treatment, influencing positive results. Any study with low number of participants raises the question of whether the study reflects and can be applied to the population at large. Additionally, the participants were recruited from one center, which may also limit the generalizability of the study to the population as a whole.

Another weakness of the study was the subjective nature in which the data was collected. Pruritic symptoms were subjectively reported in daily itch journals using a visual analog scale with facial expressions as a guide. Use of a reporting with a 0-10 scale becomes problematic with a crossover study design. For example, a patient who was initially assigned to the sertraline group and received relief may report higher scores of pruritic symptoms while in the placebo group after washout. This subjective reporting may inflate the effect of sertraline. Similar assumptions can be made of the reporting and effect of depressive symptoms.

One strength of the study includes the placebo-controlled double blind nature of Part B. However, the authors identified the inclusion of part A to have limited the effectiveness of the placebo group. Participants already underwent optimal treatment with sertraline prior to being randomized. Patients were familiar with their expected response to sertraline, defeating the purpose of randomization. The nature of the trial also allowed for establishment of multiple markers for evaluating improvement of pruritic symptoms. This offers strength over retrospective cohort studies, which would be unable to find multiple consistent markers of itching status. Lastly, one must consider the possible bias of the study as Dr. Rush disclaims that he has stock in the company Pfizer which is a producer of Zoloft (sertraline hydrochloride).

This placebo-controlled double blind study meets criteria for level 2 evidence using the SORT criteria.4

**Clinical Application**

Clinicians will face patients similar to the clinical scenarios described above with the question of “What are my options for long term control of my itching symptoms?” Multiple management options exist for pruritus with different physiologic targets of action: histamine, bile acid, serotonin, etc. Serotonin reuptake inhibitors were selected for analysis due to desire for management of the above patient’s concomitant depression. Based on multiple different outcome measurements, this paper has shown sertraline to have some effectiveness as an option for cholestatic pruritus therapy, in addition to improvement in moderate to severe depressive symptoms.4 This paper is valuable to patients and physicians because it additionally measured and acknowledged the use of sertraline for its antidepressant effects. As physicians it is our due diligence to reduce pill burden and search for opportunity to take advantage of medication side effect profiles. Therefore, sertraline can be considered as a treatment option for patients with cholestatic pruritus, particularly those with concomitant depression. The above patient was offered the option of sertraline for her pruritus and concomitant depression, due to the low risk profile of the medication. However, the patient elected to not begin any new medications on discharge, desiring to wait until she spoke with her oncologist outpatient.

Take Home points:

1. Multiple pharmacologic options exist for the management of cholestatic pruritus, including: anti-histamines, sertraline, cholestyramine, rifampin, and naltrexone. Sertraline can be considered with caution in patients with cholestatic pruritus and concomitant depression.

2. While sertraline has been shown to have some effect as an option for cholestatic pruritus, the current data should be used with caution. Further, larger studies are required before definitive recommendations can be made.
3. Clinicians should always take into consideration the entire clinical picture and consider when patients may benefit from medication side effect profiles.

4. While blinded placebo crossover studies have many strengths, the design itself creates a bias in results when patients are able to recognize differences in feeling or clinical results and figure out which group to which they were randomized.

References


