JPPT | Single-Center Retrospective Study

Evaluation of the Use of Naltrexone for Cholestatic Pruritus

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OBJECTIVE Pruritus is a common symptom of liver disease, managed with various medications including opioid antagonists like naltrexone. Current literature surrounding the safety and efficacy of naltrexone for cholestatic pruritus is limited. Our objective was to describe naltrexone prescribing practices for cholestatic pruritus.

METHODS We conducted a single-center, retrospective review of inpatients who received naltrexone for cholestatic pruritus. We gathered information on naltrexone dosing, frequency, dose adjustments, duration, elevations in liver function tests (LFTs), and use of additional antipruritic agents.

RESULTS Thirty-nine patients and 122 dosing regimens were included for analysis. Most patients were male (56.4%) with a median age of 6.32 years (range, 0.63–18.89). The median weight-based doses of naltrexone were 1.45 mg/kg/dose (IQR, 0.84–2.81) and 1.86 mg/kg/day (IQR, 0.97–3.37). The median flat doses were 25 mg/dose (IQR, 12.25–50) and 50 mg/day (IQR, 25–50). The median number of additional antipruritic agents used before and after naltrexone initiation was 3 (IQR, 2–4) and 4 (IQR, 3–5), respectively ($p < 0.001$). The most common elevated LFTs were total bilirubin and alanine aminotransferase (ALT), occurring in 15% of patients.

CONCLUSIONS Naltrexone dosing ranged between 1 and 2 mg/kg/dose once or twice daily, with larger weight-based doses prescribed in younger and lower-weight patients. Naltrexone was commonly added as a fourth-line agent and did not lead to discontinuation of other antipruritic therapies. Larger, prospective, controlled studies are needed to assess the safety and efficacy of naltrexone for cholestatic pruritus.

ABBREVIATIONS AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; INR, international normalized ratio; LFT, liver function test; PT, prothrombin time; TBili, total bilirubin

KEYWORDS cholestatic pruritus; naltrexone; pediatrics

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Introduction

Cholestasis is a process defined by impairment of biliary flow or production that is associated with many liver disorders.[1] Patients may present clinically with fatigue, jaundice, and pruritus.[1] Severity of pruritus can range from mild, intermittent itching to debilitating symptoms that can severely affect quality of life. Notably, pruritus can be the sole indication for liver transplant in patients with severe, uncontrolled symptoms.[1] Liver conditions commonly associated with cholestatic pruritus include biliary atresia, primary biliary cholangitis, and primary sclerosing cholangitis.[2] Many different treatment options have been used for the management of cholestatic pruritus, including rifampin, cholestyramine, hydroxyzine, and ursodiol with variable success.[3] Cholestatic pruritus remains difficult to manage because the mechanism that induces itching is not fully understood. Accumulation of bile acid in skin tissues has been theorized to contribute to the pathogenesis of cholestatic pruritus.[4] Additionally, some studies suggest endogenous opioids in the central nervous system as the cause.[5–7] This hypothesis is supported by evidence of patients with cholestatic liver disease who had elevated endogenous opioid concentrations and experienced relief from opioid antagonists, like naltrexone.[8,9]

Notably, the 2018 American Association for the Study of Liver Diseases (AASLD) primary biliary cholangitis adult practice guidelines recommend naltrexone for refractory pruritus, starting at a dose of 12.5 mg by mouth once daily, increasing by 12.5 mg every 3 to 7 days, up to 50 mg once daily, until pruritus is ameliorated.[10] The dose should be gradually titrated owing to the risk of inducing an opioid withdrawal–like reaction in patients with high opioidergic tone.[10] The rationale for the guideline recommendations stem from a meta-analysis of 5 trials describing treatment of pruritus with opiate antagonists, including naltrexone, nalmefene, and naloxone.[11] To date, only a handful of case

reports have been published evaluating naltrexone for cholestatic pruritus in the pediatric population. These case reports have shown improvements in pruritic symptoms at naltrexone doses ranging from 0.25 to 5 mg/kg/day for durations ranging from 1 to 15 months.[12–14]

Naltrexone is an opioid antagonist that is US Food and Drug Administration approved for opioid and alcohol use disorder in adult patients. Availability includes a 50-mg oral tablet and a 380-mg intramuscular injection. When administered orally, naltrexone is almost completely absorbed, undergoes extensive first-pass metabolism, and is primarily excreted in the urine as metabolites with small amounts of unchanged drug.[15] Naltrexone is a well-tolerated medication with mild adverse effects consisting of nausea, abdominal pain, and headache. Mildly increased serum transaminases have been associated with naltrexone use, but these are more commonly seen in older patients and at larger doses.[16] Hepatotoxicity rarely occurs, but AASLD recommends routine monitoring.[10]

Although available literature suggests benefit in using naltrexone for cholestatic pruritus, this evidence is limited by small sample sizes and lack of randomized controlled trials. These limitations are especially true in the pediatric population. Naltrexone is used in patients on the hepatology service at our institution to treat patients with cholestatic pruritus. Because the optimal dose, frequency, and duration of use are unknown, naltrexone regimens prescribed are widely variable. The purpose of this study was to describe prescribing practices at a large pediatric institution for the use of naltrexone in pediatric and adolescent patients with cholestatic pruritus.

Table 1. Patient Demographics (N = 39)

Male, n (%)		22 (56.4)
Non-AA, n (%)		27 (69.2)
Age at naltrexone initiation, yr	Median (IQR)	6.32 (1.39–13.11)
	Min–Max	0.63–18.89
Age at time of liver disease diagnosis, median (IQR), yr		0.92 (0.28–9.26)
Liver transplant recipient, yes, n (%)		26 (66.7)
Etiology of liver disease, n (%)		Biliary atresia, 10 (25.6)
		Alagille syndrome, 8 (20.5)
		Other,* 21 (53.8)

Non-AA, non–African American

* Primary sclerosing cholangitis, cryptogenic cirrhosis, progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, Wilson disease, *MYO5B* mutations.

Materials and Methods

A single-center, retrospective chart review was performed at the Children's Hospital of Philadelphia. An Epic Business Objects report identified patients with orders for naltrexone between January 1, 2008, and July 31, 2021. Inclusion criteria consisted of inpatients who were diagnosed with liver disease and received at least 1 dose of naltrexone. Patients were excluded if naltrexone was used for indications other than cholestatic pruritus. The primary objective was to describe the prescribing practices for the use of naltrexone in cholestatic pruritus at our institution. The secondary objectives were to describe the changes in liver function tests after naltrexone initiation and dose adjustment(s), and to describe the use of antipruritic agents before and after naltrexone initiation.

Electronic medical records were reviewed for patient demographics including age, sex, race, etiology of liver disease, date of liver disease diagnosis, liver transplant status, and antipruritic medication history before and after naltrexone initiation. Dosing regimens defined as the dose of naltrexone, frequency of naltrexone administration, and the start and end date were recorded for each patient. In addition, each patient's weight was recorded for each dosing regimen collected. Patients were deemed to have multiple dosing regimens if the dose or frequency of administration was changed while on naltrexone. To assess naltrexone's place in therapy, additional antipruritic agents used at any time before and after naltrexone initiation were reviewed. Agents were collected on the basis of their ability to mitigate symptoms, even if they were not specifically indicated for itching. Additionally, the total duration of naltrexone treatment was collected for each patient. To evaluate safety, each dosing regimen was assessed for elevations in liver function tests (LFTs) 1 week after each dose adjustment, which were defined as an increase greater than 2 times the baseline value. LFTs collected included aspartate aminotransferase, alanine aminotransferase (ALT), total bilirubin (TBili), conjugated bilirubin, prothrombin time (PT), and international normalized ratio (INR). Finally, reason for discontinuation of naltrexone was collected to assess for safety as well.

Descriptive statistics were used to evaluate measures of central tendency, variability, and frequency. Nominal data were reported as numbers with percentage, and continuous, nonparametric data were reported as medians with IQR. Additionally, a Wilcoxon signed rank test was used to compare antipruritic agent use before and after naltrexone initiation with $p < 0.05$ defining statistical significance.

Results

A total of 68 patients had naltrexone ordered during the study period. One patient was excluded, because they never received a dose of naltrexone, and 28 others were excluded for receiving naltrexone for an

indication other than cholestatic pruritus. A total of 39 patients with 122 dosing regimens were included in data collection (see Supplemental Figure).

Most patients were male (22, 56.4%) and initiated naltrexone at 6.32 years of age (range 0.63–18.89). The median age at liver disease diagnosis was 0.92 years (IQR, 0.28–9.26) with biliary atresia (10, 25.6%) and Alagille syndrome (8, 20.5%) being the most common etiologies. Additionally, most patients were receiving 3 additional antipruritic agents prior to naltrexone initiation (IQR, 2–4) with ursodiol (36, 92.3%) and hydroxyzine (25, 64.1%) being the most prescribed agents. Further demographic information is listed in Tables 1 and 2.

Of the 122 dosing regimens evaluated, the median weight-based dose was 1.45 mg/kg/dose (IQR, 0.84–2.81) or 1.86 mg/kg/day (IQR, 0.97–3.37). The median flat-based dose of these evaluated dosing regimens was 25 mg/dose (IQR, 12.5–50) or 50 mg/day (IQR, 25–50). The total dosing ranges were 0.14 to 11.76 mg/kg/day for weight-based dosing and 5 to 400 mg/day for flat dosing. Dosing was additionally classified by patients' age and weight for weight-based doses (see Figures 1 and 2). Younger and lower-weight patients tended to receive larger weight-based doses of naltrexone than older and higher-weight patients. The outliers of this trend included the patients weighing at least 60 kg who received larger naltrexone doses, compared with the 15- to 29-kg and 30- to 59-kg patients. Flat doses were also classified by patients' age and weight (see Figures 3 and 4). The most common dosing frequency was once daily (61%), followed by twice daily (36%). Patients were on naltrexone for a median of 319 days (IQR, 97.5–777.5) and had a median of 2 dose adjustments (IQR, 1–3) during the duration of their therapy. Notably, patients weighing at least 60 kg required fewer dose adjustments on average (mean, 1.14 dose adjustments per patient) than the 30- to 59-kg (mean, 2.14 adjustments), 15- to 29-kg (mean, 2.38), and less than 15-kg (mean, 2.41) patients. A similar trend was seen in patients 12 years or older (mean, 1.5 dose adjustments per patient) when compared with the <1-year-old group (mean, 2.33), 1-year-old group (mean, 2.25), 2- to 5-year-old group (mean, 2.75), and 6- to 11-year-old group (mean, 2.5). A similar number of dose adjustments were seen in patients with biliary atresia (mean, 2.2) compared with the rest of the population.

The LFTs that most frequently increased greater than 2 times from baseline were ALT (15%) and TBili (15%). The PT and INR were elevated greater than 2 times from baseline in 8% of the dosing regimens evaluated. The most common reported reasons for naltrexone discontinuation included pruritus symptom resolution (26%), lack of efficacy (20%), and liver transplant (18%). Notably, 1 patient discontinued naltrexone owing to worsening pain symptoms.

The median number of additional antipruritic agents used at any time prior to naltrexone initiation was 3 (IQR, 2–4); after naltrexone initiation, a median of 4 additional agents (IQR, 3–5) was used at any time ($p < 0.001$) (Table 2). Of note, naltrexone was added to patients' existing antipruritic regimens as opposed to replacing previously trialed agents. Dose adjustments to patients' additional antipruritic agents was unable to be collected and assessed.

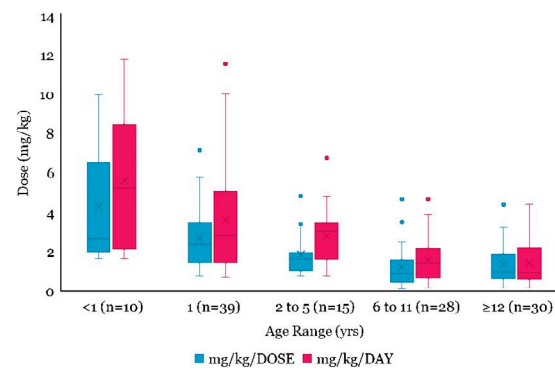
Discussion

This study describes a wide range in naltrexone dosing for cholestatic pruritus, ranging from 0.14 to 11.76 mg/kg/day and 5 to 400 mg/day. Younger and smaller patients received larger weight-based doses of naltrexone; however, this trend may be confounded by the dosage form limitations. Notably, enteral naltrexone is only available as a 50-mg tablet with poor solubility, which makes it unsuitable for crush and mix preparation, which was likely used for doses smaller

Table 2. Pre- and Post-Naltrexone Antipruritic Agent Use (N = 39)

Antipruritic agents prior to naltrexone initiation, n (%)	Ursodiol, 36 (92.3) Hydroxyzine, 25 (64.1) Diphenhydramine, 18 (46.2) Rifampin, 16 (41.0) Nalbuphine, 14 (35.9) Cholestyramine, 4 (10.3) Sertraline, 1 (2.6) Topical oatmeal, 0 (0)		
	Prior to Naltrexone Initiation	**After Naltrexone Initiation**	**p Value**
No. of antipruritic agents, median (IQR)	3 (2–4)	4 (3–5)	$p < 0.001$

Figure 1. Age breakdown of weight-based dosing (n = 122).



than 12.5 mg. This resulted in some of the younger and smaller patients receiving a minimum of 12.5 mg per dose, which may have contributed to patients receiving larger weight-based doses.

Interestingly, the younger and smaller patients did not require fewer dose adjustments than the older and larger patients, with the exception of the ≥12 years of age and ≥60-kg groups, even though they received larger weight-based doses. This may suggest that the younger and smaller patients appropriately received larger weight-based doses to manage their pruritus, rather than simply being a result of dosage form limitations. Although there was a slight increase in weight-based doses for patients weighing at least 60 kg, this may have been affected by 1 patient who received 400 mg/day (5.1 mg/kg/day) in that weight group. Additionally, patients with biliary atresia received a similar number of dose adjustments as the rest of the study group. This may indicate that larger weight-based dosing may not matter in this patient population and that naltrexone may not be efficacious for this indication.

Figure 2. Weight breakdown of weight-based dosing (n = 122).

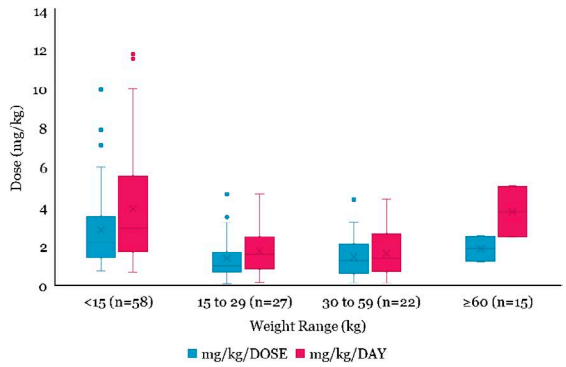


Figure 3. Age breakdown of flat-based dosing (n = 122).

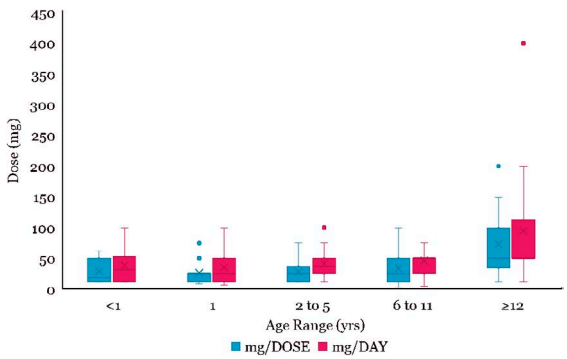
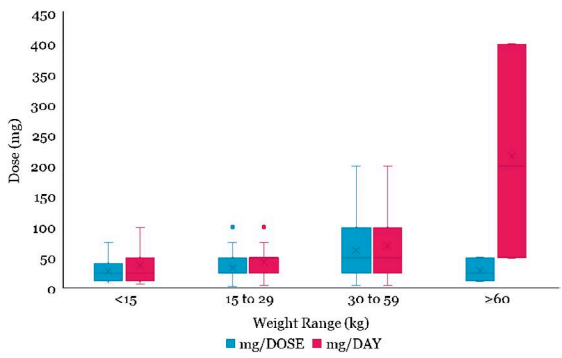


Figure 4. Weight breakdown of flat-based dosing (n = 122).



The dosing range described in this study is markedly larger than what has been published in adult and pediatric literature to date. In the meta-analysis cited in the AASLD guidelines, 2 trials evaluated naltrexone in adult patients with cholestatic pruritus.[17,18] These studies demonstrated a significant decrease in daytime and nighttime itching with naltrexone dosed 50 mg once daily at durations ranging from 2 weeks to several months.[17,18] Additionally, of the pediatric case reports published to date, naltrexone was used at doses ranging from 0.25 to 5 mg/kg/day with a duration of 1 to 15 months.[12–14] These dosing regimens are substantially smaller than what was described in this study. The results of this study may indicate that naltrexone is tolerated at these larger doses and that larger doses may be necessary to adequately treat cholestatic pruritus. A characteristic of the prescribing practices reported that was comparable to what has been described in the literature was the median duration of use (319 days).

Baseline liver dysfunction in this population likely confounds evaluation of LFTs in this study. However, our reported incidence of liver enzyme elevations suggests that naltrexone is well tolerated at the doses described. The highest incidences of liver enzyme elevations greater than 2 times from baseline were ALT and TBili, both seen in 15% of patients. To differentiate potential naltrexone-induced hepatotoxicity from liver disease progression, PT and INR elevations were assessed as well. This is because naltrexone-induced hepatotoxicity would likely not result in PT and INR elevations. However, PT and INR elevations may occur in the setting of liver disease progression. PT and INR were elevated greater than 2 times from baseline in 8% of patients, suggesting that these patients may have alternative causes of hepatotoxicity other than naltrexone.

Of the reported reasons for naltrexone discontinuation, worsening pain was the reported cause for 1 patient. The patient had been on naltrexone for a duration of 45 days at a dose of 50 mg once daily (1.21 mg/kg/day). A few potential causes for this worsening pain include naltrexone-induced opioid withdrawal, an adverse effect directly related to naltrexone, or pain induced by a different medical condition of the patient. Unfortunately, given the retrospective nature of this

study, the exact etiology of this patient's pain could not be determined. One of the more common reasons for naltrexone discontinuation was liver transplant (18%). This was an expected finding because liver transplant leads to resolution of the underlying disease and thus, all disease-related symptoms, including pruritus.

Our study also describes that patients received a median of 3 other antipruritic agents prior to naltrexone initiation. This suggests naltrexone is most often used as a fourth-line agent for cholestatic pruritus, which is consistent with the most recent AASLD guidelines.[10] Interestingly, addition of naltrexone to patients' pruritus regimens did not enable providers to discontinue prior therapies. In fact, the median number of additional antipruritic agents that patients were taking after naltrexone initiation was 4. This does not include naltrexone itself, meaning that patients were receiving a median of 5 antipruritic agents after starting naltrexone. We were unable to assess if the 4 antipruritic agents patients were taking after naltrexone initiation were used concomitantly with naltrexone or if they were replaced upon naltrexone initiation. While this may suggest limited efficacy associated with naltrexone, it is difficult to draw conclusions in the absence of an objective pruritus scoring system. This is especially true because agents considered to have any antipruritic effect were included in the patients' antipruritic list, even if they were being used for other indications.

This study has several limitations, including the retrospective study design and small sample size. The retrospective nature also limits the ability to fully assess concomitant medication use and adherence to naltrexone. Owing to our study design, we were only able to determine if patients had been prescribed concomitant antipruritic agents as scheduled or as needed. We were unable to determine the frequency at which patients received as-needed medications, simply we were able to evaluate the duration for which they were prescribed the medications. In addition, our study assessed the number of antipruritic agents patients were prescribed surrounding naltrexone use. We were unable to assess dose adjustments to these agents, which may have affected patients' pruritus management. Additionally, discontinuation information was limited to the most recent documentation of naltrexone in the patients' charts. Assessment of LFTs were confounded by patients' underlying liver disease. This is because liver disease progression would have led to LFT increases that would be difficult to differentiate from true naltrexone-induced hepatotoxicity. Concomitant antipruritic therapies may have also contributed to symptom improvement, which may have had an effect on naltrexone dosing decisions. However, these agents were collected on the basis of their ability to mitigate symptoms and not on whether their indication was for itching. Owing to the retrospective nature of this study, a pruritus assessment tool could not be used to assess patient's response to naltrexone, limiting our ability to assess efficacy of naltrexone. Finally, some patients included in this study were initiated on naltrexone prior to full integration of Epic in our institution's electronic health record, which may have limited accessible data.

Conclusion

Cholestatic pruritus can be a debilitating symptom in patients with liver disease. Naltrexone is sparsely described in the literature as a potential option for management of pruritus, particularly for pediatric patients. This study describes a wide range in naltrexone prescribing practices for cholestatic pruritus, with typical dosing ranging from 1 to 2 mg/kg/dose once or twice daily and a duration ranging from several months up to 2 years. Additionally, younger and smaller patients trended towards receiving larger weight-based doses. Naltrexone was commonly added after patients were treated with at least 3 other antipruritic agents without a subsequent reduction in the number of those agents after its addition. Naltrexone appeared to be well tolerated with a 15% incidence of live enzyme elevations, and only 1 patient discontinued therapy owing to adverse effects. Larger, prospective trials are needed to evaluate the safety and efficacy of naltrexone for the indication of cholestatic pruritus and how dosing may vary by etiology of liver disease. It would be beneficial to have a standardized scoring system for prospective studies to more accurately and objectively assess naltrexone's efficacy for cholestatic pruritus.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution.

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