Received: 19 November 2021 | Revised: 13 May 2022 | Accepted: 1 June 2022

DOI: 10.1111/cts.13358

ARTICLE

The effect of neuropsychiatric medication on pediatric nonalcoholic fatty liver disease

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Funding information
No funding was received for this work

Abstract

Obese and overweight children are at risk of developing nonalcoholic fatty liver disease (NAFLD), which can lead to steatohepatitis, cirrhosis, and liver transplantation. Neuropsychiatric conditions affect an increasing proportion of children and often require neuropsychiatric medications (NPMs) that are associated with weight gain and/or drug-induced liver injury. We sought to evaluate the role that the extended use of NPMs play in pediatric NAFLD. Medical chart review was conducted for 260 patients with NAFLD (NPM = 77, non-NPM = 183) seen in the Liver Care Center at Children's Mercy Hospital between 2000 and 2016. Outcome measures included body mass index (BMI) percentile, BMI *z*-score, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and gamma glutamyltransferase, and were collected at diagnosis, 6–18 month follow-up, and 18–36 months. Controlling for race and metformin, there was a significant increase over time in BMI *z*-score ($p < 0.01$) and total bilirubin ($p = 0.03$), with only initial decreases in ALT ($p < 0.01$) and AST ($p < 0.01$). Except for higher total bilirubin in the non-NPM group, no main effect of group or interaction effect was found. Similar patterns remained when subjects were analyzed by NPM drug class. Further study is needed to confirm these findings and to evaluate the effects of NPM dose and duration of exposure, by drug class, on pediatric NAFLD outcomes.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Nonalcoholic fatty liver disease (NAFLD) is affecting an increasing number of pediatric patients. Neuropsychiatric medications can be associated with weight gain and drug-induced liver injury. Drug-induced liver injury can worsen liver disease in those who already have NAFLD.

WHAT QUESTION DID THIS STUDY ADDRESS?

How do neuropsychiatric medications affect body mass index and common markers of hepatocellular inflammation over time in pediatric patients with NAFLD?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The use of neuropsychiatric medications among pediatric patients with NAFLD is not associated with significant increases in weight gain or transaminases over time.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Although further studies are needed, the use of neuropsychiatric medications in pediatric patients with NAFLD could potentially be continued to help prevent worsening of mental health issues.

INTRODUCTION

With the growing prevalence of obesity in the United States, nonalcoholic fatty liver disease (NAFLD) has become the most common pediatric chronic liver disease and affects more than one-third of overweight/obese youth compared to an estimated 10% of the general pediatric population.[1,2] NAFLD represents a disease continuum ranging from simple steatosis (i.e., fat deposits involving more than 5% of hepatocytes) to nonalcoholic steatohepatitis (NASH), cirrhosis, hepatocellular carcinoma, and end-stage liver disease requiring transplantation.[3] As the majority of patients are overweight or obese, NAFLD is also associated with complications of metabolic syndrome, including insulin resistance, hypertension, and dyslipidemia.[4,5]

In addition, neurodevelopmental and psychiatric conditions also affect an increasing proportion of youth, with one in six US children aged 2–17 years having at least one mental health disorder.[6,7] Although a combination of pharmacologic and non-pharmacologic therapies is commonly used to treat these conditions, medication management in the context of NAFLD presents specific challenges. Several neuropsychiatric medications (NPMs), each to varying degrees, are associated with weight gain, liver toxicity, or both, and the use of multiple NPMs further increases these risks.[8] The spectrum of liver disease resulting from drug-induced liver injury (DILI) is wide and includes asymptomatic mild elevation of liver function tests to rare severe idiosyncratic reactions, such as acute liver failure.[9,10] In a longitudinal study of 30 youths with suspected DILI, 40% of cases were associated with central nervous system (CNS) agents (i.e., anticonvulsants 20%, stimulants 13%, and antidepressants 7%).[11]

Although we know that NAFLD is an independent risk factor for DILI,[12] and that NPM can cause DILI, there is a paucity of published literature on the long-term effects of NPM use in pediatric patients with NAFLD. A recent literature review and case series highlighted the difficulties in caring for patients with both NAFLD and psychiatric disorders, suggesting that NPM use can worsen outcomes in the setting of NAFLD and called for more research in this area.[13] Mouzaki et al.[14] recently demonstrated slightly increased steatosis and increased likelihood of having a NASH activity score ≥5 (59% vs. 35%) on liver biopsy at a single timepoint in those taking psychotropic medications compared to those who did not. However, there is very little reported on the potential longitudinal effects of NPM on the NAFLD disease course. Thus, our study aimed to evaluate the role that NPM exposure might play in the disease course of NAFLD over time. It was hypothesized that patients exposed to NPM during treatment for NAFLD would have significantly higher body mass index (BMI) and biochemical evidence of increased liver injury compared with patients without NPM exposure.

METHODS

This retrospective cohort study included patients with NAFLD who were followed in the Liver Care Center at Children's Mercy Hospital (Kansas City, MO) between January 2000 and October 2016. Patients were identified via medical chart review using International Classification of Disease (ICD)–9/10 codes and Axis' Patient Analysis and Tracking System (Axis Clinical Software Inc.). Individuals with other liver diseases in addition to NAFLD (e.g., autoimmune hepatitis, hepatitis B or C, chronic viral hepatitis, Wilson's disease, and alpha-1-antitrypsin deficiency), history of neonatal cholestasis, or parenteral nutrition use in the previous 6 months were excluded from the study. The study was approved by the hospital's Institutional Review Board (#14030108).

All patients referred to our center with significantly elevated serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST; >50 U/L) and a BMI ≥95th percentile for age and sex complete an initial evaluation that includes screening lab work and abdominal imaging to demonstrate steatosis.[15] Laboratory tests

obtained per clinic protocol include antinuclear antibody, total IgG, anti-smooth muscle antibody, anti-liver kidney microsomal antibody, perinuclear antineutrophil cytoplasmic antibodies, serology for hepatitis B and C, ceruloplasmin, ferritin, total IgA, anti-tissue transglutaminase antibody IgA level, and alpha-1-antitrypsin phenotype, with other tests ordered as needed per patient and family history and clinical findings. Due to its invasive nature and unestablished role in pediatric NAFLD,[16] liver biopsy is typically reserved for cases where laboratory work is concerning for an alternative diagnosis, persistently elevated transaminases (>3× upper limit of normal over 6 months), or when elastography is concerning for worsening fibrosis. Available liver biopsy results were reviewed to confirm diagnosis. After the initial visit, patients are scheduled for follow-up every 3–6 months to monitor lifestyle changes, weight, and liver disease progression.

Data collection

Patient demographics, comorbid conditions, current medication regimen, radiology and histopathology reports, vital signs, and laboratory results were collected from the electronic medical records. Data were collected at the NAFLD diagnostic visit (T0), 6–18 month follow-up visit (T1), and at 18–36 months follow-up (T2). Follow-up periods were chosen due to variable clinic attendance in our patient population.

For purposes of the current study, patients with documented use of a medication in any of the following drug classes, either at T0 or T1, were included in the NPM group: antidepressants, CNS stimulants, attention-deficit/hyperactivity disorder (ADHD) non-stimulants, antipsychotics, anticonvulsants, and antimanic agents. Information on the prescribed dosage and/or exact duration of NPM use was not available in all cases, and, therefore, not collected as part of the current study.

Outcome measures

BMI percentile and BMI *z*-score were selected as outcome measures as weight stabilization/loss is the mainstay of treatment and associated with an improvement in disease.[16,17] BMI-for-age percentile (BMIpct) and BMI-for-age *z*-scores (BMIz) were calculated using the Centers for Disease Control and Prevention SAS program (CDC, Atlanta, GA). AST, ALT, total bilirubin, and gamma glutamyltransferase (GGT) were selected as secondary outcome measures as serum elevations broadly reflect hepatocellular inflammation.

Sample size

With conservative sample sizes of 55 and 125 for NPM and non-NPM groups, we have 86% power to detect a difference of 0.20 in BMIz in a design with three repeated measurements having a first-order autoregressive (AR[1]) covariance structure when the SD is 0.45, the correlation between observations on the same subject is 0.79 and the alpha level is 0.05. The AR(1) structure considers measurement correlations to be highest between adjacent times (i.e., T0 to T1 and T1 to T2), and to systematically decrease with increasing distance between timepoints (i.e., T0 to T2).[18]

Statistical analysis

Descriptive statistics were used to summarize the study sample. Continuous variables are presented as mean and SD or median and interquartile range (IQR), and categorical variables are expressed as frequencies and percentages. Patient demographic and medical characteristics were compared between the NPM and non-NPM groups using *t*-tests and Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Linear mixed effects models were used to evaluate main effects for group (NPM and non-NPM), time (T0, T1, and T2), and group × time interaction for each outcome measure (BMIpct, BMIz, AST, ALT, total bilirubin, and GGT). When a significant main effect was observed, Fisher's least significant difference test was used for post hoc comparisons. Separate models were tested across all NPMs and by drug class. Based on their significance in univariate analysis, models were specified to control for race (White vs. other) and metformin use (yes/no). Patients taking a stimulant drug only ($n = 13$) were not included in analyses examining a change in BMI over time given their association with weight loss (vs. weight gain).[19] The significance level was set at 0.05 and SAS version 9.4 (SAS Institute Inc.) was used for analyses. Patients with at least two clinic visits during the 36-month period, with documented height and weight or AST/ALT, were included in the analyses.

RESULTS

Patient characteristics

A flow diagram of the study population is depicted in Figure 1, with characteristics of the final sample summarized in Table 1. Of the 352 patients diagnosed with

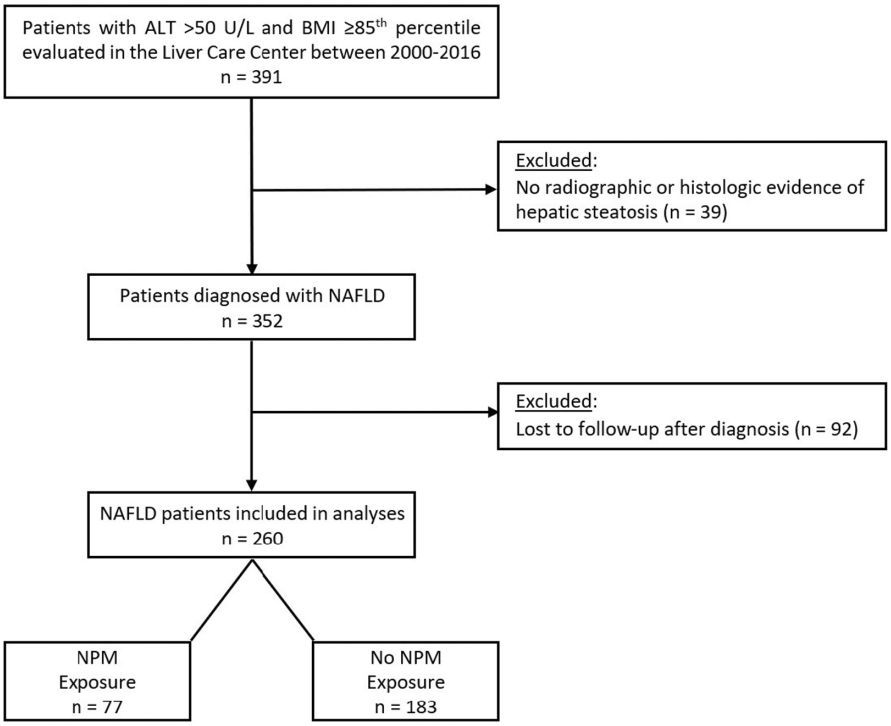

FIGURE 1 Flow chart of study population. ALT, alanine aminotransferase; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NPM, neuropsychiatric medication.

NAFLD between 2000 and 2016, 92 (26%) were lost to follow-up after the initial visit, resulting in a final sample of 260 patients. No significant differences were found between patients lost to follow-up and those included in the final analysis in baseline BMI ($p = 0.40$), BMI percentile ($p = 0.06$), AST ($p = 0.29$), ALT ($p = 0.43$), total bilirubin ($p = 0.34$), or GGT ($p = 0.06$). There was also no significant difference in the proportion of patients who had a liver biopsy performed at baseline (12% vs. 13%, $p = 0.71$), or the number of prescribed NPMs (1.65 vs. 1.47, $p = 0.57$).

The median baseline age of the sample was 13 years (IQR 11–15), and the majority were men (67%) and White (49%). Approximately one-third of patients ($n = 77$) were prescribed NPMs during the 36-month study period, with 65 (84%) patients taking NPMs at T0 ($n = 57$) or T1 ($n = 8$). The majority of patients were on more than one NPM concurrently (47% on 1 NPM, 25% on 2, and 28% on 3 or more). The most common medication class used was anti-depressants (56% of patients), followed by CNS stimulants (49%), atypical antipsychotics (32%), mood stabilizers (e.g., anticonvulsants and lithium; 32%), and ADHD non-stimulants (30%; Table S1).

In comparison with the non-NPM group, patients taking NPMs were significantly more likely to be White (73% vs. 39%, $p < 0.01$) and had a higher incidence of metformin use (38% vs. 22%, $p = 0.01$). There were no significant between-group differences with respect to any of the outcome measures at baseline, except for higher total bilirubin in the non-NPM group ($p = 0.04$; Table 1).

Clinical changes over time

Controlling for race and metformin use, analyses revealed a significant main effect of time on BMIz ($F[2393] = 5.89$, $p < 0.01$) and BMIpct ($F[2393] = 3.72$, $p = 0.02$). Post hoc comparisons showed a significant increase over time in BMIz (T0 to T2 $p < 0.01$), whereas BMIpct decreased from T0 to T1 ($p = 0.03$) but returned to baseline by T2 ($p = 0.02$). No significant differences were found between the NPM and non-NPM groups, nor was there a significant interaction effect (Table 2).

With respect to the included biochemical markers of liver injury, analyses also revealed a significant main effect of time on AST ($F[2358] = 5.37$, $p < 0.01$), ALT ($F[2360] = 9.89$, $p < 0.01$), and total bilirubin ($F[2333] = 3.57$, $p = 0.03$), but not GGT ($p = 0.60$; Table 2). Post hoc comparisons showed a significant decrease in liver transaminases from T0 to T1 (AST $p < 0.01$; ALT $p < 0.01$) but no further changes at T2 (AST $p = 0.31$; ALT $p = 0.49$), whereas total bilirubin significantly increased over time (T0 vs. T2 $p = 0.01$). There was no effect of group, except for total bilirubin ($F[1255] = 7.02$, $p = 0.01$), with significantly higher levels found in the non-NPM group compared to the NPM group. No interaction effect was found.

Findings were largely the same when examined by drug class (Table 3). Specifically, analyses revealed a main effect of time on BMIz for each of the five drug classes (i.e., antidepressants, stimulants, antipsychotics, mood stabilizers, and nonstimulants), with post hoc comparisons showing a significant increase over the study period,

TABLE 1 Patient characteristics

	Total ($n = 260$)	NPM ($n = 77$)	No NPM ($n = 183$)	p value
Median age in years (IQR)	13 (11–15)	13 (11–15)	12 (10–14)	0.08
Male (%)	175 (67)	50 (65)	125 (68)	0.60
Race (%)				<0.01
White	127 (49)	56 (73)	71 (39)	
Hispanic/Latino	99 (38)	12 (16)	87 (48)	
Other	34 (13)	9 (12)	25 (14)	
Biochemical parameters, mean (SD)				
ALT (U/L)	118.2 (82.7)	109.4 (77.8)	121.8 (84.6)	0.27
AST (U/L)	72.8 (64.4)	72.5 (74.1)	73.0 (60.1)	0.96
Total bilirubin (mg/dl)	0.5 (0.3)	0.4 (0.2)	0.5 (0.4)	0.04
GGT (U/L)	50.0 (30.2)	52.2 (27.1)	49.0 (31.5)	0.50
BMI, mean (SD)	32.8 (6.3)	33.4 (5.8)	32.5 (6.5)	0.28
BMI %, mean (SD)	98.6 (1.3)	98.6 (1.4)	98.6 (1.3)	0.79
Biopsy confirmed steatosis (%)	35 (13)	15 (19)	20 (11)	0.07
Fibrosis stage ≥2 ($n = 26$)	14 (54)	5 (42)	9 (64)	0.25
Comorbid condition—any point (%)				
Asthma/allergies	74 (28)	20 (26)	54 (30)	0.56
Chronic abdominal pain	5 (2)	2 (3)	3 (2)	0.63
Dyslipidemia	54 (21)	20 (26)	34 (19)	0.18
Diabetes mellitus, type 2	28 (11)	8 (10)	20 (11)	0.90
Gastroesophageal reflux disease	5 (2)	2 (3)	3 (2)	0.63
Epilepsy	7 (3)	4 (5)	3 (2)	0.20
Headache/migraine	11 (4)	6 (8)	5 (3)	0.09
Hypertension	34 (13)	12 (16)	22 (12)	0.44
Hypothyroidism	11 (4)	3 (4)	8 (4)	1.00
Insulin resistance	145 (56)	42 (55)	103 (56)	0.80
Obstructive sleep apnea	24 (9)	8 (10)	16 (9)	0.68
Polycystic ovarian syndrome	11 (4)	4 (5)	7 (4)	0.74
ADHD	50 (19)	45 (58)	5 (3)	<0.01
Anxiety disorder	26 (10)	21 (27)	5 (3)	<0.01
Bipolar disorder	17 (7)	16 (21)	1 (1)	<0.01
Depression	26 (10)	22 (29)	4 (2)	<0.01
Oppositional defiant disorder	6 (2)	6 (8)	0 (0)	<0.01
Pervasive developmental disorder	20 (8)	16 (21)	4 (2)	<0.01
Unspecified psychiatric disorder	3 (1)	1 (1)	2 (1)	1.00
Other medication—any point (%)				
Metformin	69 (27)	29 (38)	40 (22)	0.01
Ursodiol	15 (6)	3 (4)	12 (7)	0.56
Vitamin E	79 (30)	22 (29)	57 (31)	0.68

Note: Data collected at diagnosis unless otherwise specified.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; IQR, interquartile range; NPM, neuropsychiatric medication.

except for mood stabilizers where only an initial increase from T0 to T1 was found. For both BMIz and BMIpct, a significant group × time interaction effect was found for mood stabilizers. Patients in the NPM group who were taking a mood stabilizer showed an increase in BMIz and BMIpct from T0 to T1 and then a decrease at T2, whereas

TABLE 2 Results of linear mixed effects model across NPMs controlling for race and metformin

		Time periods			Main effects		Group × Time
		T0	T1	T2	Group	Time	
	Groups	LSM (SE)	LSM (SE)	LSM (SE)	*p*	*p*	*p*
BMIz	NPM	2.32 (0.06)	2.30 (0.06)	2.40 (0.06)	0.16	<0.01[b,c]	0.44
	Non-NPM	2.38 (0.04)	2.41 (0.04)	2.47 (0.04)			
BMI%	NPM	98.31 (0.52)	96.62 (0.55)	98.56 (0.60)	0.05	0.03[a,c]	0.06
	Non-NPM	98.63 (0.32)	98.56 (0.34)	98.73 (0.38)			
ALT	NPM	114.25 (9.82)	93.37 (10.47)	85.55 (11.39)	0.16	<0.01[a,b]	0.88
	Non-NPM	128.22 (6.71)	103.81 (7.03)	102.38 (7.89)			
AST	NPM	76.13 (7.53)	65.52 (8.00)	55.02 (8.68)	0.47	0.01[a,b]	0.54
	Non-NPM	78.96 (5.15)	66.84 (5.38)	67.20 (6.05)			
T BILI	NPM	0.42 (0.04)	0.45 (0.04)	0.51 (0.05)	0.01	0.03[b]	0.55
	Non-NPM	0.54 (0.03)	0.59 (0.03)	0.60 (0.03)			
GGT	NPM	54.37 (4.96)	52.86 (5.47)	48.29 (6.54)	0.55	0.60	0.55
	Non-NPM	49.53 (3.44)	46.70 (3.72)	49.38 (4.17)			

Note: Data are presented as least-squares means (standard error).

T0 = time of diagnosis, T1 = 6–18 month follow-up, T2 = 18–36 month follow-up.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMIz, body mass index *z*-score; GGT, gamma-glutamyltransferase; LSM, least-squares mean; NPM, neuropsychiatric medication; SE, standard error; T BILI, total bilirubin.

[a,b,c]Significant differences in post hoc analyses, with [a]T0 vs. T1, [b]T0 vs. T2, and [c]T1 vs. T2.

the non-NPM group showed an increase in BMIz over time and no change in BMIpct.

Simple main effects of time on our secondary outcome measures were also observed and varied by drug class. For antidepressants, antipsychotics, and stimulant medications, analyses revealed a significant decrease in ALT and AST (n.s. for stimulants) from T0 to T2, with an increase in total bilirubin for antidepressants only. A significant decrease in GGT was also found for nonstimulant medication. For mood stabilizers, the main effect of time showed a significant increase in ALT from T0 to T1, with a decrease at T2. There were no simple main effects of group except for antipsychotics where total bilirubin was lower in the NPM group compared to the non-NPM group. The only significant group × time effect was on total bilirubin for mood stabilizers, with those in the NPM group demonstrating a significant increase from T1 to T2, whereas no change was observed in the non-NPM group (Table 3).

DISCUSSION

We approached our study with the hypothesis that taking NPMs would be associated with elevations in transaminases and BMI over time as many NPM are associated with both DILI and weight gain.[14] This could lead healthcare providers to the conclusion that NPMs would worsen liver injury and should be discontinued in the setting of NAFLD.[12,13] Preliminary studies have not settled this concern. For example, Mouzaki et al. compared similar groups at a single timepoint with liver biopsy histology reports (these were available due to different clinic protocols in their management of NAFLD).[14] Their team included all NPM exposure into a single group similar to our study. That study did not find differences in BMI, transaminase elevation, or histologic fibrosis, but did find worsened steatosis and NAFLD Activity Scores on histology reports in those with NPM exposure again raising the concern of NPM exposure in pediatric NAFLD. However, their study did not follow patients longitudinally and did not break down analysis by drug class. Our study did not find statistically significant differences in BMI *z*-score or percentile and transaminases between patients who took NPM and those who did not, and, to our knowledge, is one of the first to report this longitudinally over time. Further analyzing by drug class, we demonstrated that these findings were consistent across multiple different treatments for neuropsychiatric conditions. Of note, because of the small number of patients with NAFLD with baseline liver biopsies, combined with a high degree of missingness (70–85% depending on the variable) and/or inconsistent reporting on relevant histologic findings (e.g., ballooning hepatocytes and Mallory bodies) across pathology reports, preliminary analysis was limited to fibrosis stage and not found to significantly differ between groups.

Our data suggests that children on NPMs have similar courses in BMI to those who do not take NPMs and

TABLE 3 Results of linear mixed effects model by NPM drug class controlling for race and metformin

		Time periods			Main effects		Group × Time	Group × Time post hoc test	
		T0	T1	T2	Group	Time			
	Groups	LSM (SE)	LSM (SE)	LSM (SE)	*p*	*p*	*p*	*F*	*p*
Antidepressants ($n = 43$)									
BMIz	NPM	2.30 (0.06)	2.35 (0.06)	2.43 (0.07)	0.44	<0.01[a,b]	0.48		
	Non-NPM	2.38 (0.03)	2.40 (0.03)	2.46 (0.04)					
BMI%	NPM	98.52 (0.29)	98.51 (0.30)	98.72 (0.32)	0.80	0.62	0.87		
	Non-NPM	98.67 (0.16)	98.60 (0.16)	98.69 (0.17)					
ALT	NPM	123.25 (13.32)	96.05 (14.38)	88.59 (15.43)	0.39	<0.01[a,b]	0.90		
	Non-NPM	130.14 (7.05)	105.66 (7.36)	103.93 (8.19)					
AST	NPM	85.14 (10.36)	69.84 (11.13)	60.56 (11.92)	0.92	0.01[a,b]	0.66		
	Non-NPM	80.88 (5.50)	68.68 (5.72)	68.76 (6.37)					
T BILI	NPM	0.42 (0.06)	0.50 (0.06)	0.52 (0.06)	0.07	0.02[a,b]	0.72		
	Non-NPM	0.55 (0.03)	0.60 (0.03)	0.61 (0.03)					
GGT	NPM	53.88 (5.94)	51.39 (7.06)	50.37 (7.87)	0.75	0.72	0.88		
	Non-NPM	50.70 (3.29)	48.00 (3.59)	51.03 (4.02)					
Stimulants ($n = 38$)									
BMIz	NPM	2.40 (0.08)	2.43 (0.08)	2.50 (0.08)	0.71	<0.01[b,c]	0.93		
	Non-NPM	2.38 (0.03)	2.40 (0.03)	2.46 (0.03)					
BMI%	NPM	98.97 (0.36)	98.84 (0.38)	99.08 (0.39)	0.42	0.64	0.92		
	Non-NPM	98.70 (0.15)	98.64 (0.16)	98.73 (0.17)					
ALT	NPM	113.30 (13.30)	97.40 (14.84)	96.76 (15.87)	0.33	0.02[a,b]	0.84		
	Non-NPM	131.05 (6.77)	106.68 (7.10)	105.51 (7.97)					
AST	NPM	70.36 (9.63)	65.36 (10.77)	58.45 (11.52)	0.31	0.21	0.77		
	Non-NPM	81.43 (4.90)	69.45 (5.14)	70.39 (5.81)					
T BILI	NPM	0.43 (0.06)	0.44 (0.07)	0.52 (0.07)	0.06	0.14	0.45		
	Non-NPM	0.55 (0.03)	0.59 (0.03)	0.60 (0.04)					
GGT	NPM	58.76 (7.21)	64.41 (7.78)	55.36 (9.51)	0.15	0.75	0.26		
	Non-NPM	49.83 (3.62)	47.10 (3.93)	49.85 (4.38)					
Antipsychotics ($n = 25$)									
BMIz	NPM	2.37 (0.08)	2.39 (0.08)	2.47 (0.08)	0.84	<0.01[b,c]	0.81		
	Non-NPM	2.39 (0.04)	2.41 (0.04)	2.47 (0.04)					
BMI%	NPM	98.69 (0.36)	98.59 (0.37)	98.78 (0.39)	0.98	0.70	0.96		
	Non-NPM	98.71 (0.15)	98.65 (0.16)	98.74 (0.17)					
ALT	NPM	115.42 (16.50)	76.18 (17.64)	75.08 (19.63)	0.08	<0.01[a,b]	0.70		
	Non-NPM	130.47 (6.80)	106.07 (7.11)	104.72 (7.94)					
AST	NPM	75.19 (12.05)	53.00 (12.89)	50.01 (14.36)	0.16	0.03[a,b]	0.67		
	Non-NPM	81.92 (4.96)	69.88 (5.19)	70.63 (5.83)					
T BILI	NPM	0.43 (0.06)	0.44 (0.07)	0.52 (0.07)	0.04	0.16	0.06		
	Non-NPM	0.55 (0.03)	0.59 (0.03)	0.60 (0.04)					
GGT	NPM	58.76 (7.21)	64.41 (7.78)	55.36 (9.51)	0.92	0.15	0.49		
	Non-NPM	49.83 (3.62)	47.10 (3.93)	49.85 (4.38)					
Mood stabilizers ($n = 25$)									
BMIz	NPM	2.35 (0.09)	2.21 (0.09)	2.37 (0.09)	0.24	<0.01	0.02	4.91	0.01[a,c]
	Non-NPM	2.37 (0.04)	2.40 (0.04)	2.46 (0.04)				3.83	0.02[b,c]

(Continues)

TABLE 3 (Continued)

		Time periods			Main effects		Group × Time	Group × Time post hoc test	
		T0	T1	T2	Group	Time			
	Groups	LSM (SE)	LSM (SE)	LSM (SE)	*p*	*p*	*p*	*F*	*p*
BMI%	NPM	98.46 (0.86)	94.36 (0.89)	98.58 (0.98)	0.02	<0.01	<0.01	8.10	<0.01[a,c]
	Non-NPM	98.58 (0.35)	98.52 (0.36)	98.70 (0.40)				0.07	0.93
ALT	NPM	105.63 (16.37)	72.43 (17.50)	79.46 (19.56)	0.05	0.01[a,b]	0.86		
	Non-NPM	130.88 (6.81)	106.49 (7.12)	105.18 (7.95)					
AST	NPM	67.75 (11.94)	50.32 (12.77)	54.60 (14.28)	0.11	0.09	0.92		
	Non-NPM	81.92 (4.96)	69.90 (5.19)	70.67 (5.83)					
T BILI	NPM	0.43 (0.06)	0.44 (0.07)	0.52 (0.07)	0.01	0.10	0.03	2.99	0.05[c]
	Non-NPM	0.55 (0.03)	0.59 (0.03)	0.60 (0.04)				2.31	0.10
GGT	NPM	58.76 (7.21)	64.41 (7.78)	55.36 (9.51)	0.48	0.23	0.54		
	Non-NPM	49.83 (3.62)	47.10 (3.93)	49.85 (4.38)					
Nonstimulants ($n = 23$)									
BMIz	NPM	2.29 (0.08)	2.32 (0.09)	2.45 (0.09)	0.53	<0.01[b,c]	0.30		
	Non-NPM	2.37 (0.04)	2.40 (0.04)	2.45 (0.04)					
BMI%	NPM	98.39 (0.40)	98.32 (0.41)	98.74 (0.44)	0.71	0.45	0.70		
	Non-NPM	98.64 (0.16)	98.57 (0.16)	98.66 (0.17)					
ALT	NPM	105.45 (17.12)	87.50 (19.06)	103.29 (20.75)	0.30	0.09	0.62		
	Non-NPM	131.30 (6.88)	106.89 (7.19)	105.49 (8.02)					
AST	NPM	67.42 (12.45)	54.48 (13.90)	62.84 (15.13)	0.25	0.21	0.90		
	Non-NPM	82.23 (5.00)	70.19 (5.23)	70.92 (5.87)					
T BILI	NPM	0.44 (0.08)	0.42 (0.09)	0.49 (0.09)	0.08	0.41	0.70		
	Non-NPM	0.55 (0.03)	0.59 (0.03)	0.60 (0.04)					
GGT	NPM	58.76 (7.21)	64.41 (7.78)	55.36 (9.51)	0.99	0.03[a]	0.18		
	Non-NPM	49.83 (3.62)	47.10 (3.93)	49.85 (4.38)					

Note: Data are presented as least-squares means (standard error).

T0 = time of diagnosis, T1 = 6–18 month follow-up, T2 = 18–36 month follow-up.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMIz, body mass index *z*-score; GGT, gamma-glutamyltransferase; LSM, least-squares mean; NPM, neuropsychiatric medication; SE, standard error; T BILI, total bilirubin.

[a,b,c]Significant differences in post hoc analyses, with [a]T0 vs. T1, [b]T0 vs. T2, and [c]T1 vs. T2.

did not support our initial hypothesis. This is important as weight management (either through healthy lifestyle, pharmacotherapy, or bariatric surgery) remains the mainstay of therapy in pediatric NAFLD.[3,16] There could be several explanations for these somewhat antithetical findings, ranging from diet modification and exercise to underlying genetic factors. Psychosocial changes (for example, the treatment of depression) resulting from NPMs could lead to greater participation in a healthy lifestyle. It is also possible that NPMs could benefit the liver through other pharmacologic mechanisms. One such pathway—autophagy—is a highly conserved cellular mechanism that maintains homeostasis through the clearance of aggregated and misfolded proteins as well as damaged organelles via sequestration degradation.[20] Enhancing autophagy using NPMs is under investigation in a number of liver diseases. Murine models that pharmacologically encourage autophagy alleviate steatosis and hepatic injury in mice with NAFLD.[21] Specifically, carbamazepine may have a role in the treatment of steatosis or conditions that result from the buildup of protein aggregates within hepatocytes, such as alpha-1-antitrypsin or fibrinogen storage diseases.[21–23] There are preliminary results suggesting that carbamazepine may be a radiation protector and mitigator through the mechanism of autophagy as well.[24] We note that other NPMs, including lithium and valproic acid, have been shown to induce autophagy or otherwise improve NAFLD, as in the case of amitriptyline.[25,26]

Currently, these mechanisms have limited demonstrated clinical utility, and unlike treating adults with obesity and NAFLD, there remains a paucity of data on pharmacologic options for pediatric NAFLD.[3,16] Adults have increasing

pharmacologic options for the treatment of both obesity and NAFLD which are often intertwined. Pediatric obesity has recent reports on pharmacotherapy, such as ADHD stimulant medications, that can aid in BMI normalization.[19] However, treatment of pediatric NAFLD specifically is often limited to lifestyle interventions and bariatric surgery. As a result, there have been calls to further clarify the role of pharmacology in pediatric NAFLD and medication usage in this setting has remained understudied, making treatment decisions more difficult for these patients.

These findings should be interpreted in the context of several limitations. First, because the study was performed at a single institution, the results may not be generalizable to other pediatric NAFLD cohorts. Second, given the retrospective nature of the study, data were limited to information available in the medical record that did not consistently include NPM dosage or the exact start date and duration of use, especially in cases where NPM was being prescribed by an outside provider. Many patients were also taking several different NPMs concurrently or at different timepoints, precluding us from analyzing the data by isolated exposure to a single NPM or drug class. Last, a quarter of the patients with NAFLD (NPM = 20, non-NPM = 72) were lost to follow-up after their diagnostic visit, although no significant differences were found between the two groups in baseline BMI, liver transaminase levels, or the number of NPMs prescribed. Taken together, a larger prospective, longitudinal, multicenter study incorporating more detailed NPM information is needed to confirm these findings, and to examine possible mechanisms and risk factors that may help explain individual differences in clinical outcomes. More attention to patient's adherence to the prescribed medication regimen, including NPMs, will also be important in future investigations, particularly given that weight gain is a common reason for nonadherence.[27,28] Last, whereas a sustained decrease in ALT is commonly used as a surrogate marker of improvement of NAFLD, it does not always reliably correlate with histologic disease.[14] These patients were seen in our clinic before the availability of noninvasive markers of steatosis and fibrosis, such as FibroScan, that would aid in the assessment process and could be used to monitor histological changes over time.

Our results suggest that pediatric patients with NAFLD who take NPMs may have similar changes in BMI and transaminases over time as those who do not take NPMs. This could indicate that NPMs can be safely tolerated in pediatric NAFLD; however, further study is needed to confirm these results and assess the effects of duration of therapy and dose of NPM on pediatric NAFLD. The use of NPM in pediatric patients with NAFLD should continue to be evaluated to help prevent worsening of mental health issues during treatment for NAFLD.

AUTHOR CONTRIBUTIONS

V.R.S., J.L.R., A.K.S., D.E.H., C.A.F., J.F.D., and R.T.F. wrote the manuscript. V.R.S. and R.T.F. designed and performed the research. V.R.S., J.L.R., and A.K.S. analyzed the data.

ACKNOWLEDGMENTS

The authors would like to thank Westin Hayes, Gayla Cheadle, RN, Kelly Hames, RN, and Shawna Ricks, RN, PhD, for their feedback on the study protocol, as well as their help identifying patients in the clinical database and with data entry.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ryan JL, Sherman AK, Heble DE, et al. The effect of neuropsychiatric medication on pediatric nonalcoholic fatty liver disease. *Clin Transl Sci*. 2022;15:2241-2250. doi: 10.1111/cts.13358