Implementation of Oral and Extended-Release Naltrexone for the Treatment of Emergency Department Patients With Moderate to Severe Alcohol Use Disorder: Feasibility and Initial Outcomes

Erik S. Anderson, MD*; Mac Chamberlin, MD; Marisa Zuluaga, MD; Monish Ullal, MD; Kathryn Hawk, MD; Ryan McCormack, MD; Gail D'Onofrio, MD; Andrew A. Herring, MD

*Corresponding Author. E-mail: esanderson@alamedahealthsystem.org.

Study objective: Despite evidence supporting naltrexone as an effective treatment for alcohol use disorder, its use in emergency department (ED) patients has not been described. We implemented a protocol that combined substance use navigation with either oral naltrexone or extended-release intramuscular naltrexone for patients with alcohol use disorder as a strategy to improve follow-up in addiction treatment after ED discharge.

Methods: In this descriptive study, we analyzed the results from adult patients discharged from the ED with moderate to severe alcohol use disorder who received either oral naltrexone or extended-release intramuscular naltrexone between May 1, 2020, and October 31, 2020, and assessed their engagement in formal addiction treatment within 30 days after discharge from the ED.

Results: Among 59 patients with moderate to severe alcohol use disorder who accepted naltrexone treatment, 41 received oral naltrexone and 18 received extended-release intramuscular naltrexone. The mean (SD) age of the patients was 45.2 (13.4) years; 22 patients (37.3%) were Latinx, 18 (30.5%) were Black, and 16 (27.1%) were White. Among all patients, 9 (15.3%) attended follow-up formal addiction treatment within 30 days after discharge; 5 patients (27.8%) who received extended-release intramuscular naltrexone and 4 patients (9.8%) who received oral naltrexone attended follow-up treatment within 30 days.

Conclusion: We implemented a clinical protocol for ED patients with moderate to severe alcohol use disorder using oral naltrexone and extended-release intramuscular naltrexone together with substance use navigation. Identification of alcohol use disorder, a brief intervention, and initiation of naltrexone resulted in a 15% follow-up rate in formal addiction treatment. Future work should prospectively examine the effectiveness of naltrexone as well as the effect of substance use navigation for ED patients with alcohol use disorder. [Ann Emerg Med. 2021;78:752-758.]

Please see page 753 for the Editor's Capsule Summary of this article.

A **podcast** for this article is available at www.annemergmed.com.

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INTRODUCTION

Background

Alcohol use disorder is a significant public health burden in the United States. Between 2006 and 2010, alcohol use was associated with 9.8% of all deaths in the United States and cost the US health care system US$45.3 billion related to emergency department (ED) visits and hospitalizations alone.[1,2] Recently, the COVID-19 pandemic has been associated with a rapid increase in the consequences of alcohol consumption.[3]

The treatment of moderate to severe alcohol use disorder in primary care settings consists of a combination of a psychosocial intervention, including a brief intervention, motivating patients to reduce drinking and/or accept a referral, along with medical pharmacotherapy for cravings and relapse prevention.[4] Unfortunately, fewer than 10% of patients with alcohol use disorder in the United States receive either specialty alcohol treatment or medical management.[1] Naltrexone is 1 of 3 FDA-approved medications for alcohol use disorder and is available in 2 formulations: oral daily naltrexone and extended-release naltrexone administered monthly as an intramuscular injection. Naltrexone is a potent nonselective opioid receptor antagonist that reduces the rewarding effects of

Editor's Capsule Summary

What is already known on this topic

Naltrexone is an effective treatment for alcohol use disorder. Its use in emergency department patients has not been reported.

What question this study addressed

The authors describe the implementation of a naltrexone program combined with a brief intervention and substance use navigation for emergency department patients with moderate to severe alcohol use disorder.

What this study adds to our knowledge

Naltrexone treatment was accepted by 59 eligible patients. Oral naltrexone was used in 41 patients; 4 (9.8%) returned for follow-up visit within 30 days. Injectable extended-release naltrexone was administered in 18 patients; 5 (27.8%) attended follow-up.

How this is relevant to clinical practice

Naltrexone therapy was successfully instituted. The external validity of the study is unclear because there was an existing system to support patients and guide them to further treatment.

alcohol consumption and the conditioned anticipation of these rewarding effects by inhibiting the activity of endogenous opioids in the mesolimbic system. A meta-analysis found that the number needed to treat with oral naltrexone to prevent return to heavy drinking was 12, and extended-release intramuscular naltrexone treatment was associated with a decreased number of heavy drinking days.[1]

Previous ED studies have focused on brief interventions for patients with unhealthy alcohol use.[5] To our knowledge, no studies have been published describing the implementation of treatment protocols using alcohol use disorder medications for ED patients, and pragmatic experience with implementation of oral naltrexone and extended-release intramuscular naltrexone for ED patients with alcohol use disorder has not yet been described.

Importance

ED patients with alcohol use disorder have high morbidity and mortality and frequently use the ED as an access point for acute care needs. The effectiveness of brief interventions alone for ED patients is low, and the addition of pharmacotherapy, such as ED-initiated naltrexone, to alcohol use disorder treatment protocols could improve outcomes.[5]

Goals of This Investigation

This investigation aimed to describe the implementation of a protocol for ED patients with moderate to severe alcohol use disorder using oral naltrexone or extended-release intramuscular naltrexone combined with a brief intervention and substance use navigation, and to examine rates of engagement in formal addiction treatment within 30 days after ED discharge.

MATERIALS AND METHODS

Study and Program Design

We describe a pilot program for adult ED patients with moderate to severe alcohol use disorder who accepted treatment with oral naltrexone or extended-release intramuscular naltrexone. ED providers were trained to identify alcohol use disorder, consult substance use navigators and perform a brief intervention, and evaluate the appropriateness of initiation of naltrexone for alcohol use disorder (Figure 1). Substance use navigators were available during business hours (8 AM to 5 PM) to provide motivation interviewing and care navigation assistance after discharge. A hospital-based Bridge Clinic was available to accept patients for follow-up addiction treatment. Extended-release intramuscular naltrexone was stored in the ED automated medication dispensing system and was available without prior authorization or cost to the patient through the manufacturer's free trial program. Program implementation began on May 1, 2020, and we report the results of the first 6 months of treatment with oral naltrexone or extended-release intramuscular naltrexone, ending on October 31, 2020. The study was approved by the Highland Hospital–Alameda Health System institutional review board with a waiver of written informed consent.

Outcomes

Our primary outcome of interest was the rate of follow-up engagement in formal addiction treatment within 1 month after ED discharge for patients who selected either oral naltrexone or extended-release intramuscular naltrexone. The secondary outcomes were documented adverse events, including injection-site reactions, precipitated opioid withdrawal, and hepatitis due to naltrexone. We followed the Strengthening the Reporting in Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

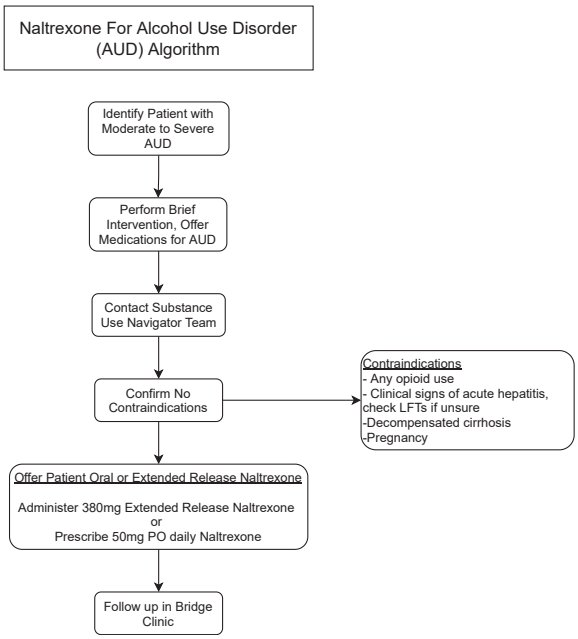

Figure 1. Algorithm for emergency department treatment of patients with alcohol use disorder. Opioid use is an absolute contradiction. Naltrexone does not treat alcohol withdrawal; treat withdrawal before initiating treatment. Naltrexone is an opioid receptor blocker and will produce a severe withdrawal syndrome in anyone using opioids. If a patient has acute hepatitis with liver function tests greater than 5 times the upper limit of normal, do not use naltrexone. Naltrexone can be used together with medications for protracted alcohol withdrawal symptoms on emergency department discharge. All patients should be followed up in the Bridge Clinic, regardless of whether or not they accept pharmacotherapy for alcohol use disorder. *AUD,* alcohol use disorder; *LFT,* liver function test.

Study Setting and Population

Highland Hospital is an urban, safety-net teaching hospital in Oakland, California. Formal addiction treatment for patients with alcohol use disorder is provided by the Alameda Health System Bridge Program, a low-barrier, multidisciplinary, addiction medicine clinic.

Selection of Participants

We included patients aged 18 years or older who presented to the ED during the study period who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria for moderate to severe alcohol use disorder and who were referred to the Alameda Health System Bridge Program substance use navigator team for alcohol use disorder treatment and linkage to care. Patients were excluded from the clinical protocol if they had used any opioids (by self-report) within the previous 7 days, had liver transaminase levels greater than 5 times the upper limit of normal (baseline liver transaminase levels were not required before treatment), had decompensated cirrhosis, or if naltrexone was prescribed for opioid use disorder.[6] A naloxone challenge was not required before treatment with either oral naltrexone or extended-release intramuscular naltrexone; we excluded patients with opioid use in the previous 7 days and used clinical history to assess physical dependence on opioids. Patients with detectable blood alcohol levels were eligible if they were deemed clinically capable of understanding the risks and benefits of naltrexone. The clinical eligibility criteria were the same for oral naltrexone and extended-release intramuscular naltrexone formulations, and the choice of treatment was made by shared decisionmaking between the treating clinician and the patient. Providers were trained to counsel patients that the 2 medications have similar effectiveness, but that one requires a daily pill and the other a monthly injection.

Data Collection and Abstraction

All data were collected from the electronic health record (Epic Systems Corporation). Administration of naltrexone was verified by electronic health record query of the ED medication administration record and chart review. We used a standardized electronic abstraction form (Appendix E1, available at http://www.annemergmed.com/) to collect data for all patients 1 month after ED discharge. Follow-up attendance was identified from the electronic health record or by continued contact with the substance use navigator team, who attempted to maintain contact with all patients referred to the Bridge Clinic in accordance with standard clinical protocols. We analyzed unique patient encounters; patients who received naltrexone on a subsequent encounter were not included in the analysis. To isolate the ED-based intervention, we excluded patients who were admitted to the hospital and received naltrexone, as well as patients who had been receiving formal addiction treatment in the 2 months preceding the index ED visit.

The abstractors received training from the principal investigator (E.S.A.), which included piloting and refining the abstraction process on the first 10 charts of the cohort. Adverse events that were not documented were considered to be absent; specifically, naltrexone-induced hepatitis was determined by chart review documentation of a clinical diagnosis, since monitoring of liver transaminases in the referral clinic is not standard practice.[6] Two investigators (M.C. and M.Z.) who were not blinded to the study hypothesis conducted independent chart reviews with

discrepancies adjudicated by a committee of 2 senior authors (E.S.A. and A.A.A.). One reviewer (E.S.A.), who was a nonblinded investigator, reviewed 3 data elements (naltrexone-induced hepatitis, precipitated withdrawal, and route of administration of naltrexone) in 10 charts to generate a value for interrater reliability.

Data Analysis

Descriptive statistics were generated for all variables. Cohen's κ statistic for interrater reliability was found to be 1.0 ($P<.001$) for primary (M.C.) and secondary reviewers (E.S.A.) based on a total of 60 observations. All analyses were performed with Stata version 13.1 (Statacorp).

RESULTS

The final cohort consisted of 59 unique patients who agreed to take naltrexone for alcohol use disorder; 18 patients (30.5%) received extended-release intramuscular naltrexone, and 41 (69.5%) received oral naltrexone (Figure 2). The mean (SD) age of patients in the combined cohort was 45.2 (13.4) years; 22 patients (37.3%) were Latinx, 18 (30.5%) were Black, and 16 (27.1%) were White; 13 patients (22.0%) were homeless; 35 patients (59.3%) were insured by MediCal (California state Medicaid) or the county health plan. The median number of ED visits and hospitalizations in the previous 12 months was 2 (interquartile range, 1-6; range, 0-43) and zero (interquartile range, 0-0; range, 0-9), respectively. Baseline characteristics and process measures associated with

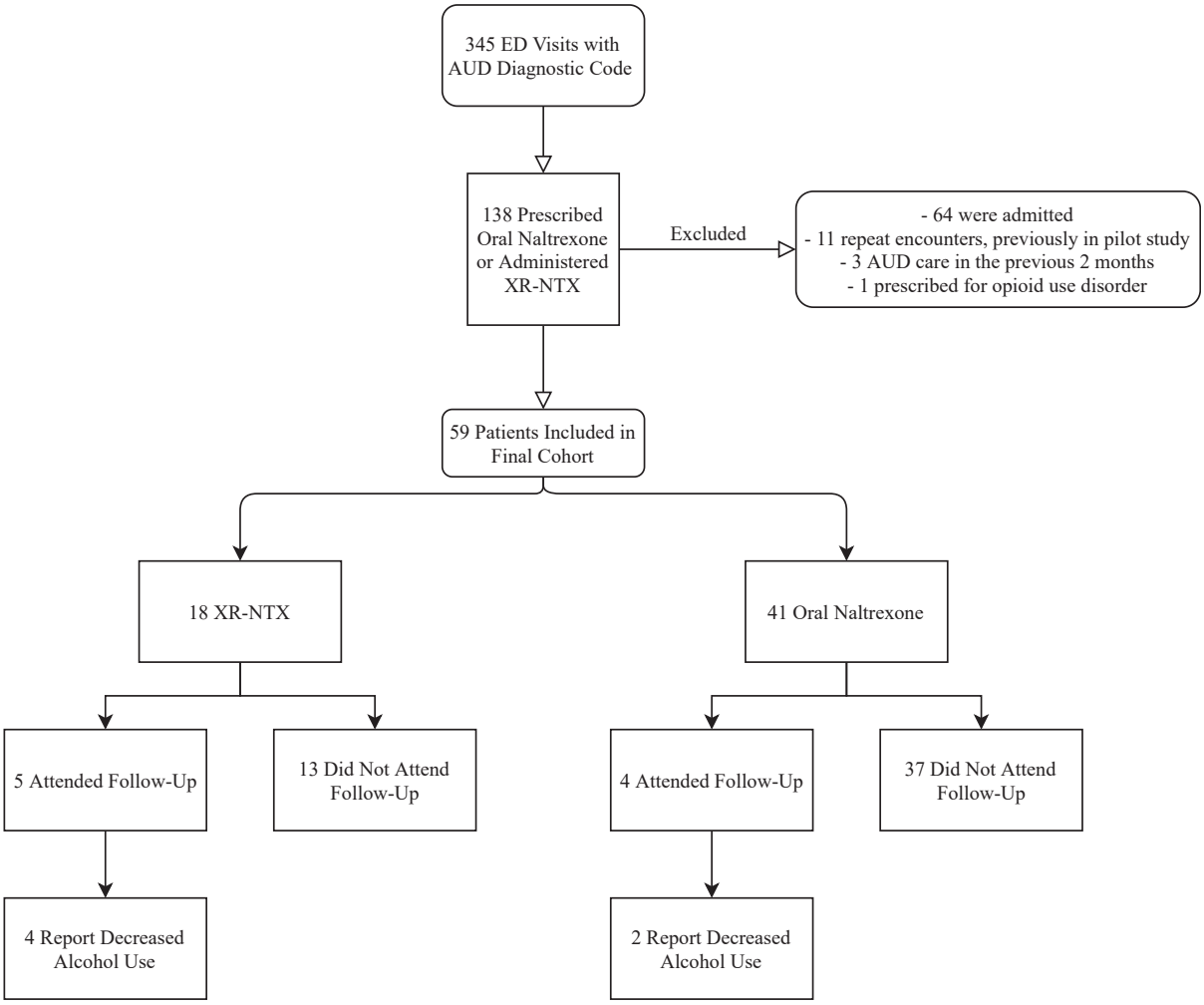

Figure 2. CONSORT diagram for pilot study of naltrexone for alcohol use disorder at Highland Hospital, April 1 through October 31, 2020. Diagnostic codes included those for severe alcohol use disorder, alcoholism, and alcohol abuse with dependence. Patients admitted to the hospital were excluded from the analysis; they received naltrexone at hospital discharge as part of a parallel inpatient alcohol use disorder treatment protocol. Follow-up outcome was within 30 days after emergency department discharge. *AUD,* alcohol use disorder; *XR-NTX*, extended-release intramuscular naltrexone.

Table. Characteristics of ED patients who received oral naltrexone or extended-release intramuscular naltrexone for alcohol use disorder.

Characteristic	Oral Naltrexone (N=41)	Extended-Release Intramuscular Naltrexone (N=18)
Age, mean (SD), y	44.8 (13.7)	46.3 (13.0)
Sex, no. (%)		
Male	32 (78.0)	14 (77.8)
Female	9 (22.0)	4 (22.2)
Race or ethnicity, no. (%)		
Black	14 (34.1)	4 (22.2)
Latinx	15 (36.6)	7 (38.9)
Asian	1 (2.4)	0
White	10 (24.4)	6 (33.3)
Other or unknown	1 (2.4)	0
Insurance, no. (%)		
Medicare	2 (4.9)	2 (11.1)
MediCal/County health plan	25 (61.0)	10 (55.5)
Private	7 (17.1)	3 (16.7)
Uninsured or self-paying	7 (17.1)	3 (16.7)
Homeless, no. (%)	9 (22.0)	4 (22.2)
Index laboratory findings, mean (SD)		
AST, IU/L*	77.0 (50.8)	86.7 (58.1)
ALT, IU/L*	57.6 (40.4)	74.9 (44.0)
Blood alcohol level, mg/dL†	282 (97)	297 (52)
Adjunctive alcohol use disorder or withdrawal medications prescribed at discharge, no. (%)		
Gabapentin	14 (34.1)	2 (11.1)
Acamprosate	1 (2.4)	0
Benzodiazepines	0	0
ED visits in previous year, median (IQR)	2 (1-9)	4 (1-5)
Hospital admissions in previous year, median (range)	0 (0-9)	0 (0-3)

ALT, Alanine transaminase; *AST*, aspartate aminotransferase; *IQR*, interquartile range.
*Liver enzyme tests were ordered for 29 of 41 patients in the oral naltrexone cohort and 14 of 18 patients in the extended-release intramuscular naltrexone cohort.
†Blood alcohol tests were ordered for 14 of 41 patients in the oral naltrexone cohort and 6 of 18 patients in the extended-release intramuscular naltrexone cohort.

encounters are shown in the Table for patients who received oral naltrexone or extended-release intramuscular naltrexone.

Overall, 9 of 59 patients (15.3%) attended follow-up formal addiction treatment within 30 days after ED discharge. Four patients (9.8%) in the oral naltrexone cohort attended follow-up treatment, 2 of whom reported decreased alcohol use at their initial clinic visit; 5 patients (27.8%) in the extended-release intramuscular naltrexone cohort attended follow-up treatment, 4 of whom reported decreased alcohol use at their initial clinic visit. There were no documented incidents of precipitated opioid withdrawal among patients who received naltrexone in the ED; chart review revealed no cases of naltrexone-induced hepatitis, and one patient reported an injection-site reaction with mild pain at the injection site.

LIMITATIONS

Our study was not designed to test the comparative effectiveness of oral naltrexone versus extended-release intramuscular naltrexone or to assess adverse events. In addition, we were unable to determine whether engagement in formal addiction treatment occurred outside the Alameda Health System. In this retrospective study of pragmatic implementation, data from patients who were offered treatment with naltrexone but declined were not available for analysis. In addition, we were unable to report standardized assessments of alcohol use for patients in the ED or in follow-up. No patients received benzodiazepines for alcohol withdrawal symptoms after discharge, and the use of gabapentin was common for alcohol withdrawal and alcohol use disorder treatment, a practice that is supported

by the American Society of Addiction Medicine but may not be generalizable to many EDs.[7] Our hospital has a robust multidisciplinary substance use disorder treatment program and a low-barrier hospital-based Bridge Clinic, services that may not be widely available at other hospitals.

DISCUSSION

To our knowledge, this is the first report of a program designed to identify ED patients with moderate to severe alcohol use disorder, initiate either oral or extended-release naltrexone, and refer the patients to ongoing formal addiction treatment. We found that 15.3% of patients attended follow-up treatment within 30 days after discharge from the ED, and we observed a substantially higher rate of follow-up (27.8%) among patients treated with extended-release intramuscular naltrexone. Our preliminary results suggest that implementation of a program aimed at initiating treatment of patients with alcohol use disorder in the ED is possible and that extended-release intramuscular naltrexone is a promising intervention.

Previous ED studies evaluated brief interventions and motivational interviewing alone and suggested a small effect size for reducing at-risk drinking among patients with low or moderate alcohol intake.[5] It is important to note, however, that for patients with moderate to severe alcohol use disorder, brief interventions alone are ineffective. Pharmacotherapy, in addition to psychosocial interventions that motivate individuals to accept treatment and referral, is the most evidence-based treatment strategy.[4] There is a growing consensus that medications for substance use disorders should be implemented on demand in any health care setting where patients seek care. We present the first description of a pragmatic approach to treatment initiation for ED patients that includes medications for alcohol use disorder.

Although multiple medications are available for alcohol use disorder, including several promising off-label medications, we chose to offer naltrexone in 2 formulations because of the ease of dosing and the extended-release option—a promising choice for our safety-net population who often face substantial barriers to care. In addition, naltrexone has been shown to be effective when combined with simple brief interventions—a model of care that translates well to the ED, as well as for patients who may follow up in primary care settings.[8] Medication costs and local approval processes for use in the ED may pose barriers to widespread implementation. However, a meta-analysis found similar or lower overall health care costs of extended-release intramuscular naltrexone compared with other alcohol use disorder medications or no alcohol use disorder medications, and a smaller study in Australia found lower overall health care costs for patients receiving implantable naltrexone attributable to reduced ED and hospital admissions.[9,10]

Future studies should emphasize combining brief psychosocial interventions and ED-initiated medications for alcohol use disorder, along with optimized medical treatment for alcohol withdrawal symptoms after discharge from the ED, as well as the effect of substance use navigation.[7] Future work should also examine formal assessments of reduced alcohol use, changes in ED utilization and hospitalization rates after the initiation of medications for alcohol use disorder, and the cost-effectiveness of extended-release intramuscular naltrexone for alcohol use disorder. Although our program relied on free extended-release intramuscular naltrexone, future studies should consider potential patient-level costs in addition to system-level costs.

In conclusion, identification of alcohol use disorder, brief interventions performed by substance use navigators, and initiation of treatment with oral naltrexone or extended-release intramuscular naltrexone in the ED is possible and resulted in a 15% follow-up rate in formal addiction treatment in our clinical setting.

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Author affiliations: From the Department of Emergency Medicine (Anderson, Chamberlin, Zuluaga, Herring), the Department of Medicine, Substance Use Disorder Program (Anderson, Ullal, Herring), and the Division of Primary Care, Department of Medicine (Ullal), Highland Hospital–Alameda Health System, Oakland, CA; the Department of Emergency Medicine (Hawk, D'Onofrio), Yale University School of Medicine, New Haven, CT; the Ronald O. Perelman Department of Emergency Medicine (McCormack), New York University Grossman School of Medicine, New York, NY; and the Department of Emergency Medicine (Herring), University of California–San Francisco, San Francisco, CA.

Author contributions: ESA, MC, and AAH conceived and designed the study; ESA, MC, and MZ acquired the dataset; and ESA conducted the analysis. ESA, MC, and MZ drafted the manuscript, and all authors contributed meaningfully to its revisions. ESA takes responsibility for the paper as a whole.

All authors attest to meeting the 4 ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the

work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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IMAGES IN EMERGENCY MEDICINE

(continued from p. 724)

DIAGNOSIS:

Retrobulbar mass with hemorrhage. Ocular ultrasonography revealed a heterogeneous mass in the retro-ocular region (Figure 1). Orbital magnetic resonance imaging confirmed a 19×10×19-mm retrobulbar mass with acute hemorrhage (Figure 2). He was treated medically for increased intraocular pressure with carteolol ophthalmic solution, and the parent refused additional interventions. At 8 months, he was symptom-free.

Retrobulbar hemorrhage is a rare, rapidly progressive, sight-threatening emergency characterized by acute increased pressure due to the accumulation of blood in the retrobulbar space.[1] The most common symptoms include proptosis, eye pain, eye swelling, loss of vision, headache, diplopia, nausea, and vomiting.[2] The treatment aims at lowering intraocular pressure to protect the optic nerve from damage.[3] The diagnosis is clinical, and diagnostic imaging must be prompt.[4]

Author affiliations: From the Department of Emergency Medicine, Chi Mei Medical Center, Tainan, Taiwan.

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