confounding factors other than the intervention. However, several confounding factors that may influence pain in CP were not adequately controlled in this study, namely, analgesic use, psychological comorbid conditions, alcohol use, and duration of CP.

For ethical considerations, analgesics were allowed during follow-up. Yet, the study did not disclose detailed information about the use of analgesics, including dose, frequency of previous use, and type of analgesics during follow-up. This may interfere greatly with the outcome.

Patients with CP who had anxiety or depression had higher pain prevalence, pain severity, and pain interference scores (2). In this study, there was no adequate enrollment control or baseline disclosure of psychological comorbid conditions or the use of antidepressants and antianxiety drugs.

The study excluded patients with "active alcohol" (as stated in the exclusion criteria); however, the detailed definition or quantitative thresholds of active alcohol (for example, the criteria of drinking and alcohol intake scores) were not provided. Furthermore, although more than half of the patients in this study had alcohol-related CP, the details of alcohol use (such as abstinence and alcohol burden) were unclear at baseline.

According to the "burnout" hypothesis of CP, patients will have relief of pain symptoms with CP progression. A study found that approximately 50% of patients with alcohol-related CP and 30% of those with idiopathic CP had a pain-free period within 6 years (3). However, this study did not reveal the CP courses.

We suggest that these confounding factors should be carefully considered in the design stage. Additional research strategies include CP-specific pain assessment tools, subgroup analysis, and sensitivity analysis that could be used to control confounding factors in order to better clarify the efficacy of endoscopic therapy in patients with CP who have chronic pain.

In addition, the visual analogue scale—a 10-cm straight line representing a score between 0 and 100 (4)—is a simple and effective tool for patients' self-assessment. In this study, patients recorded scores ranging from 0 to 10, which is an inaccurate way to apply the scale. We also note that patients in this study performed quantitative sensory testing, which helps to assess hyperalgesia. We expect that the data will be made available to the public.

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Disclosures: Disclosure forms are available with the article online.

doi:10.7326/ANNALS-25-00441

Extracorporeal Shock-Wave Lithotripsy and Endoscopy for the Treatment of Pain in Chronic Pancreatitis

TO THE EDITOR: We read with great interest the study by Talukdar and colleagues (1), which to our knowledge is the first randomized controlled trial to investigate the pain-relieving effect of extracorporeal shock-wave lithotripsy and endoscopic retrograde pancreatography versus sham procedures in patients with chronic pancreatitis (CP). This study is meaningful and valuable, but some points might need further discussion.

Pain scores decreased significantly in both groups, indicating the possible influence of placebo response and

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TO THE EDITOR: This study by Talukdar and colleagues investigates a promising approach to pain management in CP (1). Pain in CP is notoriously difficult to treat, often requiring a combined approach of medications and interventions. Current treatments include antioxidants, nonsteroidal anti-inflammatory drugs, and pancreatic enzyme supplements. Endoscopic intervention, aimed at relieving pain by decompressing the pancreatic duct through stone removal and stricture dilation, is a common initial treatment. However, its effectiveness and long-term benefits are often inferior to surgery, particularly for complex strictures and strictures that are located distally (2, 3).

This study focused on patients with CP and pancreatic stones, excluding those with strictures. The authors do note that a small subgroup (8%) still had strictures despite meeting exclusion criteria, suggesting potential misclassification. In addition, although the study achieved an impressive 88% stone clearance rate, 12% of patients had incomplete stone removal. As the authors acknowledge, only one third of their patients had alcohol-related pancreatitis; more had tropical CP (3), which may explain why the prevalence of strictures was lower than that in other regions (4). Investigating outcomes within the alcohol-related subgroup, which represents a larger global population, could be highly informative.

Although the study's limited sample size is a constraint, whether patients with multiple strictures, incomplete stone clearance, or both had the least pain relief is worth exploring. The authors' previous clinical experience with a larger patient cohort could provide valuable insights if they could share relevant data on pain management outcomes in this specific subgroup. I believe that endoscopic treatment may be a viable option for tropical pancreatitis with single or no strictures and pancreas divisum, whereas surgery might be more suitable for complex strictures and multiple stones associated with CP pain (2). Nevertheless, optimal pain management requires a comprehensive approach that includes analgesics and optimized medical therapy.

Of note, the sham group in this study still received medications, which may have contributed to the observed pain relief. This additional analysis may stimulate the need for further research on the efficacy of endoscopic interventions in patients with complex strictures, a more prevalent population in many areas.

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Disclosures: Disclosure forms are available with the article online.

doi:10.7326/ANNALS-25-00442

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TO THE EDITOR: I read with interest Talukdar and colleagues' well-designed randomized controlled trial of pain relief with combined extracorporeal shock-wave lithotripsy and endoscopic retrograde pancreatography versus sham therapy in chronic calcific pancreatitis (CCP) (1). The trial excluded patients with CCP who had local complications and those with only ductal strictures. Although international consensus guidelines by pancreatologists recommend endoscopic therapy as the initial therapy for pain in CCP, this has never been compared with sham therapy. Such a comparison should have been the ideal before recommending such interventions in chronic diseases like CCP, especially when these interventions are associated with substantial capital and recurrent costs as well as morbidity and, rarely, mortality (2).

I congratulate the authors for undertaking this trial using well-validated outcome measures of chronic pain in a center known for above-average competence in performing extracorporeal shock-wave lithotripsy and endoscopic retrograde pancreatography in CCP. Of note, of all of the primary end points and many of the secondary end points that the authors assessed, they found only a statistically significant reduction in mean weekly pain scores on a visual analogue scale of −0.7 (95% CI, −1.3 to 0) at the end of 3 months; the clinical significance of this according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations is "minimal" or "little change" (3). Furthermore, even this improvement disappears on longer follow-up of 6 months. Although the authors acknowledge this doubtful advantage in pain relief with active intervention, they also claim that there is notable improvement in depression, psychological well-being, and frequency of opioid (low-potency tramadol) use. However, the text and tables in the article do not show any statistically significant differences between active and sham procedures with respect to these variables.

As such, this trial shows that in patients receiving optimal medical care and on-demand analgesics, additional endoscopic therapy is no better than sham procedures in most patients with CCP. We therefore need to

revise the present guidelines accordingly. The authors also do not present data on the enrolled patients' disease duration or quantitative sensory testing. Previous reports have suggested that surgical interventions are less effective for pain relief in CCP if done late after disease onset (4). In addition, data on quantitative sensory testing would have revealed whether the patients enrolled in the trial had abnormal pain processing, sensitization, or both; this would have made active and sham procedures equivalent.

In conclusion, considering the socioeconomic burden of CCP (5), this trial shows that costly endoscopic interventions must be used sparingly.

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Disclosures: Disclosure forms are available with the article online.

doi:10.7326/ANNALS-25-00444

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TO THE EDITOR: We read with interest the randomized sham-controlled trial by Talukdar and colleagues (1) and congratulate them for presenting an exemplary study to evaluate extracorporeal shock-wave lithotripsy versus sham procedures in patients with CP and intraductal stones. We would like to bring attention to some observations.

Sham trials are known to have the limitation of the placebo effect, which requires further discussion in this context. Studies reporting subjective outcomes (such as pain) often exhibit a higher placebo response than those reporting objective outcomes (such as gastrointestinal bleeding) (2). This study reported a statistically significant sham effect, with the visual analogue scale score for pain declining from 5.7 to 1.5 even in the sham group. This could represent a true or perceived placebo effect. Therefore, in an ideal scenario, a 3-group study composed of an extracorporeal shock-wave lithotripsy, a sham, and a nonintervention nonsham group would quantify the amount of the placebo effect. The perceived placebo effect may be higher because of the natural course of the disease, regression toward the mean effect, other time effects, and unidentified parallel interventions (3).

Moreover, clarity is lacking on whether all patients enrolled in the study were receiving optimized medical therapy at the time of recruitment and, if so, for how long and what type of analgesia was being given. Of note, one half of the patients had mild to moderate pain. If a portion of the cohort was already benefiting from medical management, the decision to subject them to potentially invasive procedures like extracorporeal shock-wave lithotripsy raises valid concerns.

Another notable aspect of this trial is the development of postprocedure pancreatitis in the sham group. The Methods section mentions that there was no contact with the papilla in the sham group. What could be the cause of such postprocedure pancreatitis? Were these events truly related to the sham procedure? In addition, there is a discrepancy in the protocol and article about whether the sham procedure was a gastroscopy or gastroduodenoscopy.

Finally, pain in CP can also be secondary to ischemia, neural entrapment, and central hypersensitivity. These causes can explain the persistence of pain in some patients despite the complete clearance of the main pancreatic duct (4). Therefore, focusing solely on pain relief may not be the most appropriate treatment end point for these patients.

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Disclosures: Disclosure forms are available with the article online.

doi:10.7326/ANNALS-25-00446

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IN RESPONSE: We do not agree with Dr. Zhou and colleagues' comment on confounding variables. Because this was a randomized controlled study, both measured

and unmeasured confounding variables would be expected to be equally distributed between groups (1). Groups were well-balanced for all variables at baseline, including analgesic use and an alcohol-related cause of CP. The median duration of CP was 3 years (interquartile range, 1 to 7 years) in the extracorporeal shock-wave lithotripsy/endoscopic retrograde pancreatography group and 2 years (interquartile range, 1 to 6 years) in the sham group. We did not collect baseline information on psychiatric comorbid conditions. We reported the use of analgesics (opioids) during the trial as a key secondary end point. As such, a change in consumption of opioids (or other analgesics) should not be considered a confounder of our study but an outcome, as specified in the study protocol (2). We also disagree that our study's visual analogue scale of 0 to 10 is inferior because this is considered a standard outcome measure and has been used in many previous studies (3). Data on pancreatic quantitative sensory testing will be published separately later.

We agree with Dr. Rerknimitr that a subanalysis of patients by cause of CP would be useful to gain further insight into patients most likely to respond to endoscopic therapy. Yet, the relatively limited sample size does not allow for a subanalysis with sufficient statistical power. A pancreatic duct stricture was discovered in a small proportion of patients after randomization during the endoscopic procedure. Therefore, these patients were included in the intention-to-treat analysis.

Dr. Das mentioned that only pain intensity scores significantly differed between groups after 12 weeks. This is not correct; as reported in our article, we also observed a decrease in the use of opioid-based analgesics, lower levels of depression, and overall better-perceived health status after 12-week follow-up in the active group. However, these were all secondary end points. Therefore, 95% CIs accompanied these estimates, reserving the reporting of a *P* value to the primary end point according to journal guidelines.

We agree with Dr. Bhateja and associates that a noninterventional (control) group would have been useful for investigating the sham response. Before or at enrollment, all patients were prescribed optimal medical therapy, including antioxidants and analgesics. Gastroduodenoscopy was performed in the sham group. We have no explanation for the postprocedure pancreatitis flare observed in the sham group; this may have been a coincident event.

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Disclosures: Disclosure forms are available with the article online.

doi:10.7326/ANNALS-25-00447

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