CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Chronic Pancreatitis

Santhi Swaroop Vege, M.D., and Suresh T. Chari, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 52-year-old man reports having had two to three episodes of acute pancreatitis each year for the past 6 years. During the past 6 months, debilitating, continuous upper abdominal pain has gradually developed despite escalating treatment with meloxicam, tramadol, and, recently, oxycodone. He has three to four bulky, foul-smelling stools daily; he reports no weight loss. He has a 20-year history of alcohol use and a 25 pack-year smoking history. He has left his position at a company owing to frequent absences. Computed tomography of the abdomen reveals scattered pancreatic ductal calcifications, a dilated pancreatic duct, and an atrophic pancreas. How would you manage this case?

From the Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN (S.S.V.); and the Department of Gastroenterology, Hepatology, and Nutrition, Division of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston (S.T.C.). Dr. Chari can be contacted at stchari@mdanderson.org or at the Department of Gastroenterology, Hepatology and Nutrition, Division of Internal Medicine, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

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THE CLINICAL PROBLEM

Chronic pancreatitis is a progressive fibroinflammatory disease. Classic chronic pancreatitis, usually associated with alcohol use, smoking, or certain gene mutations,[1] typically begins with recurrent painful bouts of pancreatitis, followed by the insidious development of chronic, debilitating pain during the next 3 to 5 years after an initial episode. Classic imaging findings of one or more of the triad of pancreatic ductal calcifications, ductal dilatation, and parenchymal atrophy indicate progression to chronic pancreatitis. A substantive subgroup of patients also classified as having chronic pancreatitis have neither pain (nearly 30%)[2] nor a previous diagnosis of acute pancreatitis (approximately 50%).[3] The primary form without pain or previous acute pancreatitis may be a different disease with a distinct pathogenesis.[3] In practice, chronic pancreatitis is often used with a qualifier to describe other chronic inflammatory diseases of the pancreas (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), which share some, but not all, of the characteristic features of classic chronic pancreatitis.[4] This general overview is focused only on classic chronic pancreatitis in adults.

The annual incidence of chronic pancreatitis in the United States ranges from 5 to 8 per 100,000 adults, and the prevalence ranges from 42 to 73 per 100,000 adults.[5] Risk factors include alcohol use (in 42 to 77% of patients), smoking (in >60%), and genetic mutations (in 10%); the disease is considered to be idiopathic in 28% of patients.[5] Alcohol use (>80 g per day for 6 to 12 years[1]) and smoking (a smoking history of >35 pack-years increases the risk of chronic pancreatitis by a factor of 5[1,5]) have synergistic effects.[1,5] Two thirds of patients with chronic pancreatitis are men, and risk is higher among Black persons than among White persons.[5] Genetic mutations most commonly involve cystic fibrosis transmembrane conductance regulator (*CFTR*), serine protease inhibitor Kazal type1 (*SPINK1*),

KEY CLINICAL POINTS

CHRONIC PANCREATITIS

Chronic pancreatitis, which is commonly associated with alcohol use, smoking, or genetic risk factors, often manifests as recurrent bouts of abdominal pain or pancreatitis. Characteristic imaging findings include pancreatic stones, dilated ducts, and atrophy.

Complications of chronic pancreatitis include pseudocysts, biliary strictures, exocrine and endocrine pancreatic insufficiency, bone loss, and pancreatic cancer; there is currently no effective early detection strategy for pancreatic cancer.

Exocrine insufficiency causing steatorrhea leads to weight loss, sarcopenia, and deficiencies of fat-soluble vitamins and other micronutrients and is mitigated by treatment with pancreatic-enzyme replacement.

Strategies for managing chronic abdominal pain include medical therapies (analgesic agents, limited use of narcotics, antioxidants, and neuromodulators), endoscopic treatment (pancreatic stenting with or without extracorporeal shockwave lithotripsy), and surgical interventions (duct drainage and resection procedures), as well as behavioral interventions for centrally mediated pain.

or chymotrypsin C (*CTRC*); more than 90% of these cases manifest as apparently sporadic early-onset (<35 years of age) pancreatitis.[4] Hereditary pancreatitis, a rare autosomal dominant disease caused by cationic trypsinogen (*PRSS1*) gene mutation, accounts for approximately 1% of all cases.[5] Regardless of the cause, chronic pancreatitis confers a predisposition to pancreatic cancer. The cumulative risk is 1.8% at 10 years and 4% at 20 years of follow-up among patients with sporadic chronic pancreatitis and 7.2% by 70 years of age among those with hereditary pancreatitis.[5,6]

Approximately 70% of patients present with episodic upper abdominal pain, nausea, and vomiting. Pain patterns include intermittent severe attacks with or without pancreatitis that occur early in the course of disease (type A), persistent chronic pain between intermittent severe attacks (type B), and chronic severe pain without severe attacks (type C), which is the most debilitating pain pattern (Table 1). Chronic pain is attributed to peripheral and central neural sensitization[7-9] that results in visceral sensitivity, allodynia (pain elicited by a stimulus that normally does not produce pain), and hyperalgesia. Severe disabling pain that warrants narcotic use disrupts patients' lives, with consequences often compounded by alcohol use and psychosocial factors, such as poor resilience and inadequate social support.

Complications of chronic pancreatitis include pseudocysts, bile-duct stricture, duodenal stricture, splanchnic venous thromboses, and pancreatic cancer. Loss of islet mass and insulin causes glucose intolerance and eventually diabetes (type 3c)[10]; loss of counterregulatory hormones can cause wide swings in blood glucose levels. Exocrine pancreatic dysfunction can progress from a "pancreas sufficient" phase (stage I or II) to pancreatic exocrine insufficiency characterized by steatorrhea (stage III or IV)[11]; pancreatic exocrine insufficiency occurs with near total (>90%) loss of pancreatic exocrine function. Prolonged steatorrhea leads to weight loss, sarcopenia (decreased muscle mass), and deficiencies of fat-soluble vitamins (A, D, E, and K), vitamin B_{12}, and other micronutrients (zinc and magnesium)[1,12] (stage IV[11]). The chronic inflammatory state and deficiency of vitamin D and possibly vitamin K often result in osteopenia or osteoporosis, with bone pain and low-impact fractures.[13,14] Chronic pancreatitis is associated with increased mortality from any cause.[15]

STRATEGIES AND EVIDENCE

EVALUATION AND DIAGNOSIS

Evaluation for chronic pancreatitis and its complications includes a careful clinical history taking, laboratory testing, and imaging. Histologic analysis (Fig. S1) is not needed for diagnosis and is often not available; definitive diagnosis rests heavily on imaging findings. Laboratory testing includes assessment of pancreatic endocrine function (screening for diabetes mellitus) and exocrine function (described below).

Imaging

Imaging methods include computed tomography (CT) (Fig. 1), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonog-

Table 1. Suggested Assessments for Impairments in Biophysical Domains.

Domain and Assessment	Categorization
Pain: duration since onset, intermittent or continuous, frequency of flares, severity during and between flares on visual analogue scale, documentation of pancreatitis during flares (serum lipase or imaging evidence), relationship of pain to activities such as eating and exercise, response to treatments, and use and frequency of narcotics and side effects (constipation, bloating, and increased pain)	Pain patterns: type A is intermittent attacks of pain or pancreatitis without intervening pain; type B is intermittent attacks of pain or pancreatitis with intervening pain for which narcotics are not used (type B1), for which narcotics are used for ≤6 mo (type B2), or for which narcotics are used for >6 mo (type B3) (centrally mediated abdominal pain syndrome[7]); and type C is continuous narcotic-treated pain for >6 mo without intermittent attacks of pain or acute pancreatitis or complications (centrally mediated abdominal pain syndrome[7])
Imaging: evidence on CT, MRI, or endoscopic ultrasonography of amenability to endoscopic intervention or surgical drainage	Examples: strictures, stones, pseudocyst, or dilated pancreatic duct
Pancreatic exocrine function*	
Symptoms of steatorrhea	Classic symptoms, suggestive but not diagnostic symptoms, or no symptoms
Fecal elastase level	Generally <50 μg per gram of stool in stage III or IV
Fecal fat test over period of 48 or 72 hr	>7 g per day in stage III or IV
Serum fat-soluble vitamins (A and E) and other micronutrients (zinc, magnesium, and vitamin B_{12})	Vitamin and micronutrient deficiency: present or absent
Malnutrition: hand grip, body-mass index, unplanned weight loss, and bone density	Muscle wasting (none, mild, moderate, or severe), muscle strength (normal or impaired), and osteoporosis or osteopenia: present or absent

* Treatment with pancreatic-enzyme replacement is appropriate if one or more of the following is present: classic symptoms of steatorrhea (bulky, foul-smelling, difficult-to-flush stools with weight loss); suggestive symptoms plus a fecal elastase level of less than 50 μg per gram of stool or low micronutrient levels; or a fecal fat level of 15 g or more per day. The Malnutrition Universal Screening Tool calculator can be used to establish nutritional risk with the use of either objective measurements of height and weight to obtain a score and a risk category or subjective criteria to estimate a risk category but not a score. The Timed Up and Go (TUG) instrument can be used for assessing fall risk (https://www.cdc.gov/steadi/pdf/TUG_test-print.pdf).
Interventions include strength training and nutritional supplementation.

raphy (EUS); endoscopic retrograde cholangiopancreatography (ERCP) is no longer recommended owing to complications and the availability of noninvasive imaging.[1] Of these, CT is the most readily available and widely used. In a large meta-analysis, the sensitivity and specificity of CT, magnetic resonance imaging (MRI), and EUS did not differ significantly,[16] but EUS is invasive, observer-dependent, and prone to false positive results.

MRCP, especially after secretin stimulation, has the advantages of better delineation of the pancreatic and bile ducts, the absence of radiation, and safety in patients with allergy to contrast media or with renal insufficiency with the use of noncontrast T2-weighted sequences. However, MRCP takes longer and is more expensive than CT or MRI, is unsuitable for patients with claustrophobia, and can miss calcification.[17]

Other Evaluations

Assessment of multiple domains (Tables 1 and 2) is warranted, including the nature and severity of upper abdominal pain, imaging findings, nutritional status, substance abuse, disability due to disease, resilience and motivation for behavioral change, and effect of the disease on psychosocial function. Pancreatic exocrine function is evaluated by history taking and laboratory testing. Individual symptoms (abdominal pain, diarrhea, and bulky, foul-smelling, difficult-to-flush, pale, or oily stools) are neither sensitive nor specific for steatorrhea; however, a reduction in symptoms with pancreatic-enzyme replacement strongly supports steatorrhea.[23] Persistent steatorrhea is associated with weight loss and micronutrient deficiencies. In the absence of a classic symptom complex, exocrine function should be assessed by fecal elastase-1 measured in a single stool sample and, when indicated,

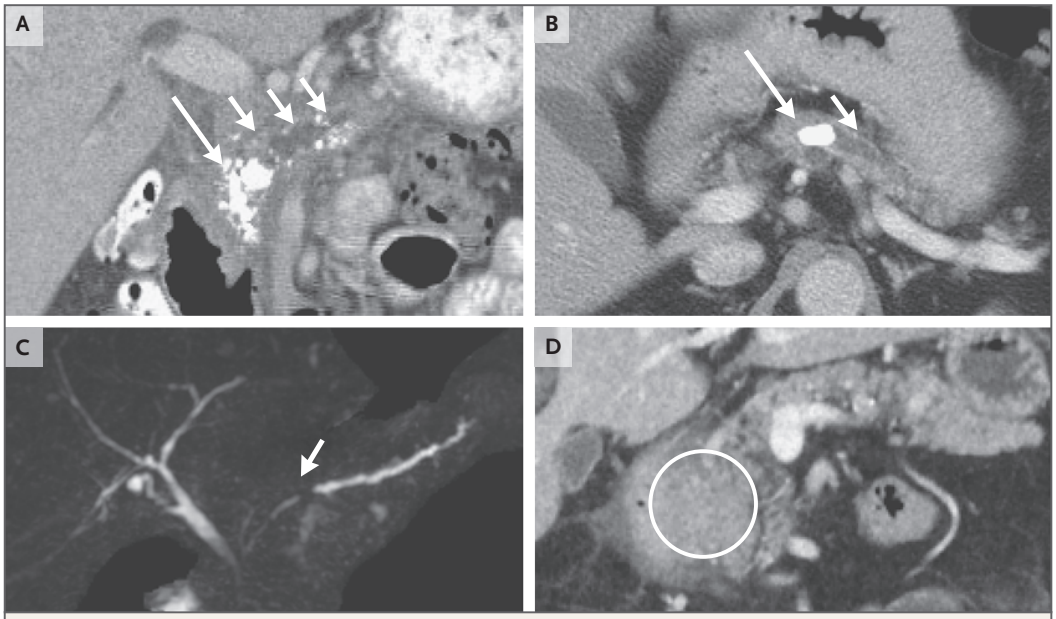

Figure 1. Examples of Imaging Findings and Suggested Interventions in Painful Chronic Pancreatitis.

In Panel A, CT shows multiple calcifications (long arrow) with a dilated pancreatic duct (short arrows). Possible interventions include duodenum-preserving resection of the head of the pancreas (Beger procedure), coring of the pancreatic head with pancreaticojejunostomy (Frey procedure), or pancreaticojejunostomy (Partington Rochelle procedure). In Panel B, CT shows a single 1-cm stone in a pancreatic duct (long arrow) and upstream dilatation of the duct (short arrow). Possible interventions include extracorporeal shockwave lithotripsy with clearance of the pancreatic duct by means of endoscopic retrograde cholangiopancreatography or pancreaticojejunostomy (Partington Rochelle procedure). In Panel C, magnetic resonance cholangiopancreatography shows a stricture of the main pancreatic duct (arrow). A possible intervention is endoscopic stenting with intermittent exchanges for 1 year. In Panel D, CT shows a mass in the head of the pancreas (within circle). Possible interventions include duodenum-preserving resection of the head of the pancreas (Beger procedure), pancreaticoduodenectomy (Whipple procedure), or coring of the pancreatic head with pancreaticojejunostomy (Frey procedure).

quantitative fecal fat measured in stool collected over a period of 48 to 72 hours while the patient follows a diet containing 100 g of fat daily.

Measurement of the fecal elastase level is simple, inexpensive, and widely available. Levels below 200 μg per gram of stool are considered to be abnormal, but only very low values (≤50 μg per gram or even <15 μg per gram, according to one report[24]) are reasonably predictive of steatorrhea.[25,26] Abnormal levels above 50 μg per gram occur in many other conditions, including diabetes, old age, irritable bowel syndrome, inflammatory bowel disease, renal failure, functional dyspepsia, and any watery diarrhea[26] and have poor specificity for steatorrhea. The frequent mischaracterization of any abnormality in fecal elastase levels as pancreatic insufficiency has led to overdiagnosis and overtreatment.

Quantitative fecal fat testing is available through many academic centers and major reference laboratories in the United States. Challenges to its routine use include patient adherence to the recommended diet, complete stool collection, and cumbersome manual laboratory testing and analysis. With proper instructions and adherence to the 100-g fat diet for 2 days before and throughout the stool-collection period, fecal fat testing provides the best estimate of digestive capacity. A normal value for the coefficient of fat absorption is at least 93%, and a normal amount of fat in stool is less than 7 g per 24 hours; elevated values occur in disorders of absorption and digestion.

In routine clinical practice, a fecal elastase test can be performed annually as a screening test for pancreatic exocrine insufficiency. A fecal fat test should be performed to confirm pancreatic insufficiency if fecal elastase levels or vitamin

Table 2. Suggested Assessments and Interventions for Impairments in Psychosocial Domains.

Domain	Assessment*	Categorization	Intervention
Disability due to disease	Functional impairment at home, work, school, or in other social areas[18]	Disability: none, mild, moderate, severe, or extreme	Options include cognitive behavioral therapy, resilience training, and formal pain rehabilitation programs
Substance use disorders	Use of tobacco, alcohol, prescription medication, and other substances[19]	Addictions: present or absent; if present, to which substances	Encourage patient to seek help from addiction clinics
Resilience	Ability to bounce back from setbacks[20]	Resilience: low, normal, or high	If resilience is impaired, recommend referral to stress management and resilience training program
Motivation	Motivation to initiate or maintain behavior changes[21]	Motivation: low (not interested), moderate (skeptical but willing to engage), or high (believes in and wants help)	For type B or C pain patterns, introduce patients to and encourage participation in nonstructural interventions
Social support	Quality of social relationships[22]	Social support: low, moderate, or high	If social support is low, refer patient to social worker

* Assessments can be performed at bedside in all patients, especially those with pain patterns type B and C. Validated questionnaires include the World Health Organization Disability Assessment Schedule 2.0[18]; Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool[19]; Brief Resilience Scale[20]; Motivation and Attitudes toward Changing Health (MATCH) scale[21]; and Multidimensional Scale of Perceived Social Support.[22]
The integrated (holistic) management of patients with impairments in multiple biophysical and psychosocial domains may require referral to tertiary care centers.

A or E levels are very low in the absence of the classic complex of symptoms of steatorrhea.

MANAGEMENT

Indications for treatment in patients with chronic pancreatitis are pain, complications, and functional (endocrine and exocrine) insufficiency. Treatment options are described below.

Pain

Management of pain in patients with chronic pancreatitis has traditionally relied on the biophysical model of health and disease, which posits that all symptoms have a structural basis. However, recognition of central sensitization and the role of psychological and social factors associated with chronic pain support expansion of management approaches to include attention to nonstructural behavioral interventions.[27,28]

Management of pain starts with developing a strong patientñphysician rapport and acknowledging patients pain and disability. Patients should be educated about both structural and nonstructural interventions (Fig. 2). The latter are particularly important for patients with centrally mediated abdominal pain syndrome and impairments in nonstructural domains; this is supported by evidence of a high incidence of ongoing long-term narcotic use (>40%) for abdominal pain among patents who have undergone total pancreatectomy,[29] particularly among those with prolonged preoperative narcotic use and alcoholic and nonhereditary pancreatitis.

There is no effective medical treatment to stop the recurrence of acute pancreatitis. For acute and chronic pain, medical therapies include analgesic agents, antioxidants, and neuromodulators (e.g., gabapentinoids and tricyclic antidepressants)[1,5,9,30-32] (Table 3). Regular use of opioids should be avoided owing to risks of tolerance, addiction, narcotic bowel syndrome, and a paradoxical increase in pain due to opioid-induced hyperalgesia. Two meta-analyses of randomized trials of various commercially available antioxidant combinations (vitamins A, C, and E and S-adenosyl-methionine) have shown significant reductions in the number of days with pain and in narcotic use.[33,34] However, the trials included small numbers of patients, and one trial showed no benefit; the recommendation to use these is based on potential benefits and the absence of adverse effects. Short-term placebo-controlled trials have shown reductions in pain among patients with chronic pancreatitis with pregabalin alone[31] or in combination with antioxidants.[35] Other neuromodulators, such as gabapentin, tricyclic antidepressants, and serotoninñ norepinephrine reuptake inhibitors, have also been suggested as possible treatments, but randomized trials of their use specifically for pan-

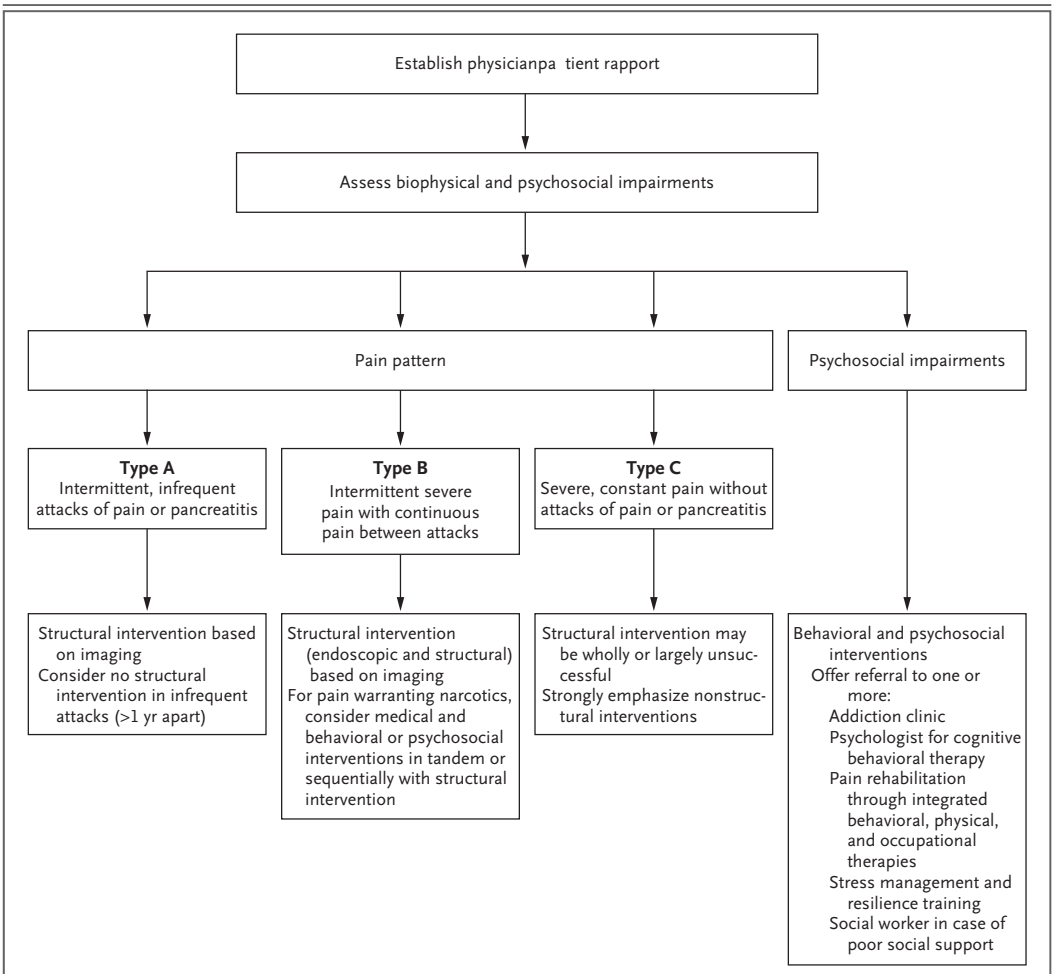

Figure 2. An Integrated Approach to Biophysical and Psychosocial Impairments.

creatitis-associated pain are lacking.[42] Although pancreatic enzymes can alleviate symptoms of maldigestion, a systematic review and meta-analysis showed no evidence of benefit for pancreatic pain.[36]

Endoscopic Therapy

Endoscopic therapy, predominantly involving the removal of stones in a pancreatic duct, dilatation of strictures, or both, is often the first intervention[43] for moderate-to-severe pain (types A, B1, and B2) that does not respond to medical therapy. Extracorporeal shockwave lithotripsy is used for breaking up stones, either as a stand-alone therapy (for stones <5 mm in diameter) or as an adjunct to ERCP[44] (Fig. 1). For strictures in a pancreatic duct, prolonged dilatation (of approximately 1 year) with the use of 10 French plastic stents, with intermittent stent exchanges, is generally warranted; pain relief is reported in more than 70% of patients.[43] Endoscopic management is also indicated for some complications of chronic pancreatitis (e.g., pseudocysts and pancreatic ascites).

Surgery

Options for surgery for pain relief include pancreatic resection for persistent focal inflammation (standard pancreaticoduodenectomy and its variants or distal pancreatectomy), drainage of an obstructed duct (longitudinal pancreaticojejunostomy and its variants), or a combination of both (Frey procedure)[45-47] or, in the most refractory cases, total pancreatectomy with or without

Table 3. Interventions for Pain in Chronic Pancreatitis.*

Intervention	Indications	Comments
Analgesics: NSAIDs, tramadol, and opioids	Initial treatment	Use WHO pain ladder (for mild pain, nonopioid analgesics; for moderate pain, weak opioids; and for severe pain, potent opioids with nonsteroidal agents, the adjuvants listed below, or both); consider alternate interventions if opioids are used continuously
Neuromodulators	Within months after narcotic use, neuropathic pain	Can be used along with structural therapies; pregabalin superior to placebo in randomized, controlled trial[31]; gabapentin and selective epinephrine or norepinephrine reuptake inhibitors also recommended by experts
Antioxidants: vitamins A, C, and E, selenium, and methionine	At any stage to reduce painful attacks as well as days with pain	Reduced pain in meta-analyses of randomized trials of supplements[33,34] (although trials were small, and one showed no benefit); randomized trial showed benefit in combination with neuromodulators[35]; can be combined with any intervention; generally given as fixed-dose combination; increased intake from dietary sources may be encouraged but has not been formally studied
Treatment with pancreatic-enzyme replacement	Reduce bloating, cramping, and borborygmi	Meta-analyses show no benefit for pain relief[36]
Pain procedures: celiac plexus block, spinal cord stimulation, and acupuncture	Neuropathic pain, usually after endoscopic and surgical interventions, if no relief	Evidence limited for acupuncture,[37] spinal cord stimulation,[38] and celiac plexus block[9]
Addiction treatment, counseling, and psychosocial interventions (cognitive behavioral therapy, stress management and resilience training, and pain rehabilitation)	Neuropathic pain, along with or after endoscopic or surgical interventions	Abstinence from alcohol may protect against recurrence of attacks, slow deterioration of pancreatic function, and reduce mortality[39]; randomized, controlled trial showed benefit of Internet-based cognitive behavioral therapy[40]; psychosocial or behavioral therapy effective for chronic pain[41] and useful for motivated patients, especially those with clinically significant disability from disease, addictions, or poor resilience

* NSAIDs denotes nonsteroidal antiinflammatory drugs, and WHO World Health Organization.

autologous islet-cell transplantation[45,48] (Fig. 1). Complications of chronic pancreatitis, such as biliary entrapment or pancreatic cancer, are additional indications for surgery. For best results, it is important to consider surgery before the development of opioid dependence and neuropathic pain.[8,42,47]

Three randomized trials have compared surgery with endoscopic therapy for painful chronic pancreatitis[46,49,50]; all showed higher percentages of patients having pain relief with surgery than with endoscopy (34 to 78% vs. 15 to 39%), with similar complication rates and mortality and a greater use of reinterventions in the endoscopy group. Because endoscopic intervention is less invasive and does not preclude subsequent surgery, it is typically preferred as the initial option. However, patients with persistence of pain despite endoscopic therapy should be reevaluated for surgery and nonstructural interventions (Fig. 1).

Nonstructural Interventions

Important adjuvants to structural interventions include cognitive behavioral therapy (to help change the way patients think about and cope with pain); stress management and resilience training (to reduce anxiety and improve coping skills); dedicated pain rehabilitation programs that incorporate behavioral, physical, and occupational therapies; and treatment of addictions (nicotine, alcohol, and narcotics) (Table 2). On the basis of studies of the management of chronic pain in other contexts[51] and of clinical experience with patients with chronic pancreatitis, these interventions improve functional status and psychosocial well-being. A recent randomized, controlled trial showed efficacy of Internet-based cognitive behavioral therapy for pain in patients with chronic pancreatitis.[40]

Exocrine Pancreatic Insufficiency

Treatment with pancreatic-enzyme replacement mitigates the effects of steatorrhea.[12] It is indicated if a patient has one or more of the following: classic symptoms of steatorrhea; suggestive but not diagnostic symptoms plus a fecal elastase level of less than 50 μg per gram of stool or low micronutrient levels; or a fecal fat level of 15 g

or more per day. All Food and Drug Administrationñapproved enzyme products are of porcine origin, and most are coated to delay degradation by gastric acid.[52] Although enzyme therapy (usual starting dose, 20,000 to 50,000 U.S. Pharmacopeia units of lipase activity) generally does not abolish steatorrhea (mean coefficient of fat absorption during enzyme therapy, approximately 85%),[52] it reduces symptoms and ameliorates nutritional deficiencies. Many factors influence the efficacy of enzymes, including the caloric and fat content of the diet, secretion of gastric acid, gastric emptying, altered anatomy, variable increase in extrapancreatic lipolysis, and bacterial overgrowth in the small bowel. The effectiveness of enzyme therapy may be increased by taking the enzymes with meals (distributed throughout the meal), distributing dietary calories across four or five meals per day, using acid-reducing agents, and testing and treating for bacterial overgrowth in the small bowel. Dietary fat restriction should be avoided to prevent weight loss and deficiency of fat-soluble vitamins and essential fatty acids.[53]

PANCREATIC CANCER

There is no effective screening strategy for early detection of pancreatic cancer in patients with chronic pancreatitis. In patients with hereditary chronic pancreatitis, alternating MRI and EUS have been recommended for screening without evidence of effectiveness or improved outcomes.[6] Carbohydrate antigen 19-9, the best known serologic marker of pancreatic cancer, may be falsely elevated in patients with chronic pancreatitis and is not helpful for screening.

AREAS OF UNCERTAINTY

Further study is needed of strategies for early detection of chronic pancreatitis,[54] prevention of recurrent pancreatitis and its progression, identification and assessment of centrally mediated chronic neuropathic pain, identification of pancreatitis-related diabetes (type 3c) as compared with other causes of diabetes, and early detection of pancreatic cancer. The natural history of chronic pancreatitis is not well understood but is currently being studied in a prospective cohort study in the United States (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies [PROCEED]).[55] The relationship between exocrine and endocrine dysfunction (type 3c diabetes) in chronic pancreatitis and the role of newer diabetes therapies in treating type 3c diabetes are uncertain. Larger and longer-term trials are needed to better assess pharmacologic, behavioral, and structural interventions for chronic pain (particularly neuropathic type) associated with chronic pancreatitis.

GUIDELINES

Several guidelines have been published in the past 5 years (Table S2), some involving overall evaluation and management and others focused on one specific aspect of the disease. The recommendations in this article are generally consistent with these guidelines, except that guidelines have not addressed the evaluation and management of psychosocial domains contributing to chronic pain.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has chronic pancreatitis associated with alcohol and smoking, with both centrally mediated and pancreatitis-related pain (type B2). His history also suggests exocrine pancreatic insufficiency; confirmation with fecal elastase or fecal fat testing is recommended. We would assess levels of fat-soluble vitamins, zinc, magnesium, vitamin B_{12}, and glycated hemoglobin and consider baseline dual-energy x-ray absorptiometry. If pancreatic insufficiency is confirmed, we would treat with pancreatic-enzyme replacement and a balanced diet supplemented with fat-soluble vitamins and micronutrients and with normal fat content. For his chronic pain, structural as well as nonstructural interventions will probably be necessary. Given the presence of stones of more than 5 mm in diameter, extracorporeal shockwave lithotripsy would be appropriate, with or without ERCP (if a stricture in a pancreatic duct is present) to clear the fragments, with a plan for surgical intervention if pain persists. For further management of ongoing pain, we would recommend pregabalin along with referral to a pain rehabilitation program, where available, including cognitive behavioral therapy. Counseling regarding alcohol, nicotine, and narcotic use; stress management; and resil-

ience training are important. Periodic follow-up, initially at intervals of 6 months or 1 year, will be needed to evaluate the effectiveness of treatment and disease progression.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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