

Interventions for Pancreatitis—New Approaches, Knowledge Gaps, and Research Opportunities

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

Anna Evans Phillips, MD, MS,* Steven J. Hughes, MD,† Dana K. Andersen, MD,‡ Adam Bell, PhD,§ Randall Brand, MD,* Gregory A. Coté, MD, MS,|| Adriana Cowdin, BS,¶ Nancy Diazgranados, MD, MS,# Vikas Dudeja, MD,** Sinead N. Duggan, PhD, RD,†† Evan Fogel, MD, MSc,‡‡ Chris E. Forsmark, MD,§§ A. Jay Freeman, MD, MSc,|||| George Gittes, MD,¶¶ Phil A. Hart, MD,### Christie Jeon, DSc, MS,**** William Nealon, MD,††† John Neoptolemos, MD, PhD,‡‡‡§§§ Tonya M. Palermo, PhD,||||| Stephen Pandol, MD,¶¶¶ Kristen M. Roberts, PhD, MS, RD,#### Martin Rosenthal, MD,***** Vikesh K. Singh, MD, MSc,†††† Dhiraj Yadav, MD, MPH,* David C. Whitcomb, MD, PhD,‡‡‡‡§§§§ and Nicholas Zyromski, MD,|||||||

Abstract: There exists no cure for acute, recurrent acute or chronic pancreatitis and treatments to date have been focused on managing symptoms. A recent workshop held by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) focused on interventions that might disrupt or perhaps even reverse the natural course of this heterogeneous disease, aiming to identify knowledge gaps and research opportunities that might inform future funding initiatives for NIDDK. The breadth and variety of identified active or planned clinical trials traverses the spectrum of the disease and was conceptually grouped for the workshop into behavioral, nutritional, pharmacologic and biologic, and mechanical interventions. Cognitive and other behavioral therapies are proven interventions for pain and addiction, but barriers exist to their use. Whilst a disease specific instrument

quantifying pain is now validated, an equivalent is lacking for nutrition - and both face challenges in ease and frequency of administration. Multiple pharmacologic agents hold promise. Ongoing development of Patient Reported Outcome (PRO) measurements can satisfy Investigative New Drug (IND) regulatory assessments. Despite multiple randomized clinical trials demonstrating benefit, great uncertainty remains regarding patient selection, timing of intervention, and type of mechanical intervention (endoscopic versus surgery). Challenges and opportunities to establish beneficial interventions for patients were identified.

Key Words: chronic pancreatitis, recurrent acute pancreatitis, clinical trial, intervention, patient-reported outcomes, health outcomes

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From the *Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA; †Division of Surgical Oncology, Department of Surgery, University of Florida College of Medicine, Gainesville, FL; ‡Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; §Translational Medicine and Regulatory Affairs, Theraly Fibrosis, Gaithersburg, MD; ||Division of Gastroenterology and Hepatology, School of Medicine, Oregon Health and Science University, Portland, OR; ¶The National Pancreas Foundation, Bethesda, MD; #National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD; **Division of Surgical Oncology, Department of Surgery, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL; ††Department of Surgery, School of Medicine, Trinity College Dublin, Dublin, Ireland; ‡‡Digestive and Liver Disorders, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN; §§Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL; |||Gastroenterology, Hepatology, and Nutrition, Nationwide Children's Hospital, The Ohio State College of Medicine, Columbus, OH; ¶¶Pediatric General and Thoracic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA; ###Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH; ****Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA; †††Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, Hempstead, NY; ‡‡‡Department of Surgery, University of Heidelberg, Heidelberg, Germany; §§§Botton-Champalimaud Pancreatic Cancer Center, Lisbon, Portugal; ||||Department of Anesthesiology and Pain Medicine, University of Washington, Seattle Children's Research Institute, Seattle, WA; ¶¶¶Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA; ####School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH; *****Department of Surgery, University of Florida, Gainesville, FL; ††††Division of Gastroenterology, Johns Hopkins University School of Medicine, Baltimore, MD; ‡‡‡‡Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; §§§§Ariel Precision Medicine, Pittsburgh, PA; and |||||Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.

Address correspondence to: Steven J. Hughes, MD, Division of Surgical Oncology, Department of Surgery, University of Florida College of Medicine, 1600 SW Archer Rd, PO Box 100109, Gainesville, FL 32610 (e-mail: steven.hughes@surgery.ufl.edu).

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There currently exists no cure or drug therapy for acute pancreatitis (AP), recurrent acute pancreatitis (RAP), or chronic pancreatitis (CP), and to date, treatments are focused on the management of symptoms alone. A recent workshop held by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) focused on interventions that have the potential to disrupt progression or even reverse the natural course of this heterogeneous disease, aiming to identify knowledge gaps and research opportunities that might inform possible future funding initiatives for NIDDK. The breadth and variety of identified active or planned clinical trials traverse the spectrum of the disease and were conceptually grouped for the workshop into behavioral, nutritional, pharmacologic and biologic, and mechanical (endoscopic, surgical, and bioengineering) interventions.

BEHAVIORAL INTERVENTIONS

Behavioral, social, psychological, and environmental factors contribute significantly to the disease burden associated with RAP and CP, and furthermore, health outcomes in these individuals. Specific health behaviors such as smoking and alcohol use place individuals at risk for progression of RAP to end-stage CP with higher associated risks of diabetes and exocrine insufficiency. More constant and more severe pain is also often seen in individuals with ongoing alcohol and smoking. Pain is the most common symptom experienced in RAP and CP; is the main driver of disease morbidity,¹ and is the highest priority symptom identified by patients.² Pain is associated with comorbidities affecting quality of life (QOL) such as low physical activity, sleep problems, and symptoms of anxiety and depression, all of which are targets for treatment.³ Many of the comorbid symptoms are modifiable with behavioral interventions; however, these have been sparsely used to date, and access to adequate behavioral health treatment has remained a common issue in this patient population. Both baseline assessment of disease symptoms—most commonly pain and related comorbid conditions—and the impact of interventions have remained a challenge to quantify and characterize in the absence of disease-specific tools that acknowledge both the complexity and the specific needs of this patient population. Disease-specific pain assessment with a dedicated instrument may offer more precision in measuring both pain in CP and response to interventions. Widely disseminated systematic approaches are needed to screen RAP and CP patients for a range of comorbidities (eg, nicotine, alcohol use, depression), and to deliver interventions that can be accessed equitably by all individuals with RAP and CP.

Whole-Person Approach: Connections Across Biological, Behavioral, Social, and Environmental Domains

For many patients, RAP and CP exist in a disease continuum where they may progress in a single direction toward the latter with repeated episodes of acute inflammation, or persistent toxic or metabolic factors that cause progressive fibrosis or scarring of the pancreas.⁴ In the absence of a cure for either disease, cessation of risky health behaviors (alcohol or tobacco use), correction of metabolic factors (triglyceride or calcium levels), or removal of an impetus for the disease (gallstones) represents the lone interventions that can be performed to stop this progression. A whole-person health approach involves considering multiple factors that promote either health or disease across interconnected biological, behavioral, social, and environmental domains. This approach may be especially useful given that, for many patients, RAP and CP may result from multiple factors, creating opportunities to intervene in multiple domains. Using the concept of whole-person health, the interventions pursued for each individual

will be different according to their needs but allow for the acknowledgment of areas not commonly addressed in conventional interactions surrounding pancreatic health. In addition to this, whole-person health allows for the acknowledgment of multiple consequences of the disease and the treatment of those resultant comorbidities. Some of these additional domains were addressed at length, including mental health, addiction behaviors, and racial factors that may influence outcomes.

Of specific relevance to CP, multicomponent cognitive behavioral therapies (CBTs) are available for chronic pain management and have a strong evidence base for reducing pain, disability, and distress in other chronic pain conditions. Behavioral interventions are underutilized in patients with pancreatitis, but early studies show promise.^{5,6} Barriers in implementation of CBT include shortage of interdisciplinary clinics that address pain and gastrointestinal disorders, geographic distance to trained specialists, insurance limitations, and stigma. A pilot feasibility study of Internet CBT for painful CP⁷ demonstrated that a series of skill-building lessons, including thought challenging, relaxation, and activity pacing, substantially reduced pain and pain interference in patients with RAP and CP compared with a control condition. Cognitive behavioral therapy approaches are also used to treat other comorbidities. Insomnia is an important yet underappreciated comorbidity affecting over 50% of people with chronic pain, is related to worse pain and disability, and potentially reduces effectiveness of pain interventions. Interventions that collectively address insomnia and pain are being evaluated in ongoing trials.⁸

It is unclear how the effectiveness of interventions for CP differs across groups that vary by their cultural and social experiences (eg, poverty, access to care), and this area requires more study. Disparities in mortality rates have been documented for CP in Black males compared with White males,⁹ and disparities in pain management and quality of pain care have been documented across racial minority groups.^{10,11} Racial minorities are underrepresented in pain intervention RCTs. In fact, race distribution is underreported in clinical trials of pain, making the disparity difficult to enumerate. Inclusive practices for the conduct of clinical trials are critical to developing equitable interventions in CP.

In the future, the implementation of screening tools to identify patients who would benefit from whole-person interventions and implementing multicomponent behavioral interventions are likely to improve the management and QOL in CP.¹² Longitudinal data collection in prospective studies using multiple biomarkers such as brain imaging, quantitative sensory testing, assessment of psychosocial factors, and blood markers may predict progression of CP and aid in identifying patients suitable for whole-person interventions. Specific research methodologies and clinical trial designs to study interconnected systems (eg, machine learning methods, latent class/profile analysis, adaptive interventions) may be particularly pertinent in CP clinical trials.

Alcohol Use Disorder in Patients With RAP and CP: Context and Treatment Strategies

Alcohol is identified as an etiology in 25% of patients with AP and at least 30% of CP patients, and is associated with more than 200 health conditions.¹³ Alcohol is the third leading cause of cancer and causes 1 in 10 deaths among adults 20–64 years in the United States.¹⁴ High recidivism to drinking even after disease occurrence warrants intervention beyond mere recommendation, although this is rarely pursued, often due to reluctance on the part of patient or provider, or lack of knowledge or resources regarding how to proceed.

Problematic alcohol use, however, is easily identifiable and measurable. Criteria for alcohol use disorder (AUD) include cravings, loss of control, interruption in life activities due to alcohol,

tolerance, and withdrawal symptoms.¹⁵ The Alcohol Use Disorder Identification Test–C is a 3-question version of a longer questionnaire specifically developed by the World Health Organization to identify problematic alcohol use and can be implemented as a screening tool in clinical settings.¹⁶ Heavy drinking, another measure of degree of use, is defined by the National Institute on Alcohol Abuse and Alcoholism as ≥ 4 drinks per day or ≥ 14 drinks per week for men, and ≥ 3 drinks per day or ≥ 7 drinks per week for women.¹⁷

Appreciation for the neurobiology of AUD may help to tailor treatments for alcohol-associated pancreatitis. More than half of AUD are heritable, and patients who tout tolerance are at higher risk for AUD.¹⁸ The euphoric rewards of alcohol diminish with continued use, and with prolonged history of dependence, a state of “relief craving” sets in, when low mood, elevated anxiety and increased sensitivity to stress become dominant.¹⁹ Recognizing the stages of addiction will also enhance and inform treatment strategies (Fig. 1).

Both pharmacological and nonpharmacological treatments are available to address AUD, including CBT in individual or group settings.²⁰ Among pharmacological options, naltrexone and acamprosate have demonstrated decreases in number of drinking days and frequency of heavy drinking.²¹ Family, community, and vocational interventions may also play an important role.

Disease-Specific Assessment of Pain in CP

Pain assessment instruments used in clinical trials and studies of CP to date have frequently lacked a multidimensional

approach limiting their use and interpretation, especially in areas such as total duration of pain and impact of food intake on pain, both disease-specific features important in CP.²² Because pain is such a salient feature of CP (>80% over the course of disease, ~60% in the past week, 50% managed with chronic opioids), a standardized disease-specific pain assessment tool is needed to accurately identify pain profiles and also measure effectiveness of treatments.³ Although pain remains a predominant feature of CP among all age groups, the pattern and impact on daily activities may differ.^{23,24} An ideal pain assessment tool would have developmentally relevant versions applicable to children and adults to maintain consistency throughout trials across the lifespan.

As described in a previous workshop held by the NIDDK,²⁴ the Comprehensive Pain Assessment Tool for Chronic Pancreatitis (COMPAT), a self-administered research instrument specific to CP consisting of 6 pain dimensions,²⁵ has been made more useful through distillation into a short-form (COMPAT-SF) that can be completed in under 10 minutes at bedside. The COMPAT-SF includes 6 questions total that evaluate (a) pain severity, (b) pain pattern, (c) factors provoking pain, (d) widespread pain, and (e) qualitative pain descriptors.²⁶ Criterion validity has been demonstrated by the association of higher COMPAT-SF scores with more frequent hospitalizations and with higher levels of pain as measured by the Izibicki and Brief Pain Inventory. In patients with CP disease, COMPAT-SF also demonstrated high test-retest reliability. The COMPAT-SF is an important patient-reported outcome (PRO) measurement that holds promise for wide dissemination and use in interventional studies to chart patient progress. Ongoing efforts to translate the current version into multiple languages for use in centers around the world will open pathways to assess CP symptoms across multiple populations (potentially helping to identify disparities), making it affordable for patients and clinicians, and accessible on mobile platforms.

NUTRITIONAL INTERVENTIONS

Overview of Nutrition Research Priorities in Pancreatitis

The effect of nutritional disorders experienced by patients with AP, RAP, and CP is broad considering the dual endocrine and exocrine functions of the pancreas. The spectrum of complications includes malnutrition, micronutrient deficiencies, sarcopenia, diabetes, and metabolic bone disease.^{27–29} Input from patients and patient advocates has indicated that nutrition, diet, and the ability to eat are important issues.² In fact, these concerns rank second only to abdominal pain, which, in turn, has a central role in feeding and nutrition. Unfortunately, data on directly recorded dietary patterns and nutrition-focused interventions in AP, RAP, and CP remain sparse.³⁰ More of both are needed to inform better management of pancreatitis.

Several important considerations must be accounted for when approaching study design for nutrition studies in pancreatitis. As with all clinical trials in pancreatitis, the development and implementation of a core outcome set are desirable to reduce heterogeneity and produce higher-quality evidence.³¹ In the absence of such guidance, investigators are encouraged to adopt standard definitions from nutrition societies. For example, the Global Leadership Initiative on Malnutrition criteria were developed by an international consortium and represent a consensus for the diagnosis of malnutrition.³² This model can be followed in the future by other groups to develop consensus agreements as a foundation for future studies.

Considering the multifactorial contributions to nutritional compromise, multimodal interventions represent the preferred

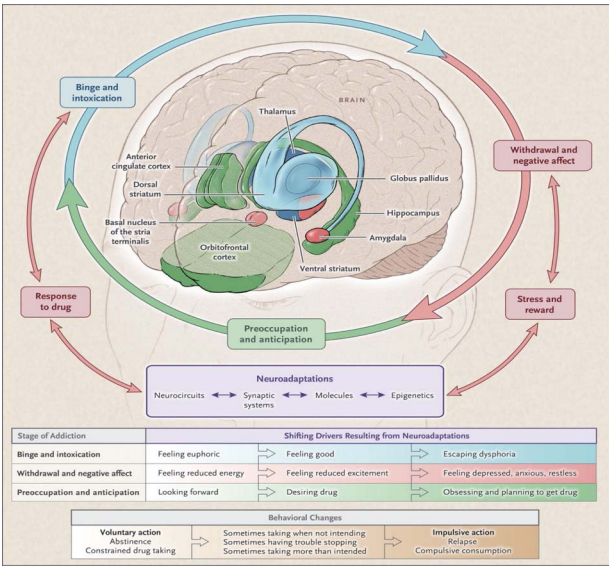


FIGURE 1. Stages of the addiction cycle. During intoxication, drug-induced activation of the brain's reward regions (blue) is enhanced by conditioned cues in areas of increased sensitization (green). During withdrawal, the activation of brain regions involved in emotions (pink) results in negative mood and enhanced sensitivity to stress. During preoccupation, the decreased function of the prefrontal cortex leads to an inability to balance the strong desire for the drug with the will to abstain, which triggers relapse and reinitiates the cycle of addiction. The compromised neurocircuitry reflects the disruption of the dopamine and glutamate systems and the stress-control systems of the brain, which are affected by corticotropin-releasing factor and dynorphin. The behaviors during the 3 stages of addiction change as a person transitions from drug experimentation to addiction as a function of the progressive neuroadaptations that occur in the brain.

approach for successful application of findings to clinical practice. Types of interventions include dietary modifications, micronutrient supplementation, pancreatic enzyme replacement therapy (PERT), prescriptive physical activity, and nutrition support (ie, oral nutrient supplementation, enteral nutrition, or parenteral nutrition). As an example from other pancreatic diseases, a group has recently completed a feasibility study in pancreatic cancer with an intervention composed of a fish oil–based supplement (eicosapentaenoic acid–enriched), PERT, a prescriptive exercise regime, and registered dietician-led dietary counseling.³³

Dietary Patterns

The role of medical nutrition therapy for prevention and treatment of AP, RAP, and CP remains in their infancy. Before identifying candidate approaches to investigate in nutrition-based clinical trials, it is necessary to understand differences in baseline dietary patterns in patients with pancreatitis compared with control populations and define the degree of variability within groups. In addition to potential heterogeneity of dietary intake, other modifiable (eg, gut microbiota, adiposity, smoking, and alcohol status) and nonmodifiable factors (eg, age, race, sex) should be considered in the design of nutrition-based trials. Because of these complexities, careful assessment of dietary intake before and during the intervention is necessary. In addition, disease-related factors, such as the etiology of pancreatitis, may be associated with differences in dietary patterns and should be accounted for in the trial design and analysis plan.²⁷ Also, food security remains an important consideration in all nutrition researches, and given suspected disparities within the population of patients across the pancreatitis disease spectrum, this needs to be taken into account.³⁴

Quantitative estimation of dietary intake for the purpose of nutrition research can be performed in several ways, and there is no universal standard. Dietary records, often identified as the gold standard dietary assessment tool, require high participant literacy and can be resource intensive. Larger population studies often rely on food frequency questionnaires, which provide a less costly approach to categorizing habitual dietary intake but lack the precision of dietary records. Ultimately, the selection of the most appropriate dietary assessment tool and the frequency of assessment should be determined based on the scientific question being addressed.

Qualitative assessments of dietary patterns—measurements of dietary patterns and behaviors for optimal health—have recently evolved with the introduction and dissemination of dietary inflammatory scores. Previously, the Healthy Eating Index or Mediterranean diet scores were used by nutrition scientists to estimate the quality of the diet of a group compared with normative population values. In recent years, dietary inflammatory scores have been introduced that study dietary patterns associated with proinflammatory biomarkers.³⁵ This approach has been used in the investigation of other gastrointestinal disorders: higher dietary inflammatory scores have even previously been associated with higher risk of developing Crohn disease.³⁶ The empirical dietary inflammatory index, empirical dietary inflammatory pattern, and the dietary inflammation score and lifestyle inflammation score have been of interest in chronic inflammatory conditions, whereas other tools, such as polyphenol or phytochemical assessments, are rarely reported in AP or CP, but may also be reflective of the inflammatory potential of the diet. Recent pilot studies have shown more inflammatory diet characteristics in CP patients compared with controls on the Healthy Eating Index, alternative Mediterranean diet score, empirical dietary inflammatory pattern, and polyphenol intake, findings that merit further study moving forward.^{34,37}

Enteral Nutrition in Pancreatitis

In pancreatitis, it has long been recognized that, when both are feasible, enteral nutrition remains the preferred route over parenteral route for caloric delivery as well as the noncaloric benefits of maintaining gut integrity, modulating disease burden, and enhancing the immune system in severe medical illnesses. Enteral nutrition supplementation as a gold standard is supported by data from randomized controlled trials, observational studies, expert consensus, and society recommendations.^{38–41} Additional studies are needed to better ascertain discernible outcome differences between proximal and distal feeding in AP and RAP, as well as clear benefits of distal feeding to provide “pancreatic rest” in these disorders.

There is growing interest in the pancreatitis field to use nutrition as a therapy to provide nutrients to promote enhanced recovery, decrease inflammation, restore immunity, combat catabolism, maintain gut function, and ultimately improve patient outcomes.⁴² Borrowing from concepts and tools used in critical care and pancreatic cancer nutrition research, adaptive nutrition for AP, RAP, and CP also includes immune-enhancing formulas, novel nutraceuticals, and disease-specific treatment. Nutritional candidates with emerging preliminary data that warrant further investigation include omega 3 fatty acids, arginine, leucine, and specialized proresolving mediators.^{43–45} These supplements may be considered in combination with other behavioral and/or nutritional interventions.

Pancreatic Enzyme Replacement Therapy

The role of exogenous PERT for the management of exocrine pancreatic insufficiency (EPI) is a cornerstone in the nutritional management of patients with CP.⁴⁶ Exocrine pancreatic insufficiency is also an increasingly recognized phenomenon in AP: it is estimated that approximately two thirds of AP patients may be affected with EPI during their AP admission, and one third of AP patients have EPI during follow-up.⁴⁷ There is a physiological basis to hypothesize that PERT may be useful to improve other clinical outcomes in pancreatitis by reducing nutrient-stimulated secretion of cholecystokinin. Studies to date investigating the use of PERT for management of abdominal pain have been challenging to interpret due to heterogeneity in study designs, including the dose and formulation of PERT.⁴⁸ Of note, there are observational retrospective data from a pediatric pancreatitis study population demonstrating that use of PERT was associated with a reduction in the incidence rate of recurrent AP (although no change in pain pattern) after PERT initiation (unpublished data). These preliminary data also warrant careful design and conduct of a clinical trial to understand the potential role of PERT for preventing AP in high-risk populations. Lastly, there is an ongoing need for additional research to identify effective alternatives to provide exogenous pancreas enzyme supplementation for patients who have either allergies to active or inactive ingredients of current PERT formulations or personal objections to consumption of animal-derived products.

PHARMACOLOGIC AND BIOLOGIC INTERVENTIONS

There exists no current disease-modifying drug or biologic therapy for treatment of AP, RAP, or CP. Approved pharmacologic or biologic therapies are currently lacking, and few agents are in development.⁴⁹ Ongoing experimental efforts focus on several known agents that are being repurposed to target pathologic processes in both AP and CP, such as inflammation and fibrosis. Consensus is lacking at present on optimal targets for drug development, or acceptable outcome measures to assess efficacy. Several ongoing trials were highlighted to serve as examples for discussion in how to best move forward the field of pharmacologic or biologic interventions in pancreatic disease.

Antifibrotic Agents

Pirfenidone, an antifibrosis agent approved by the Food and Drug Administration (FDA) for treatment of idiopathic pulmonary fibrosis,⁵⁰ has been repurposed in an effort to test its use as a disease-modifying therapy for predicted moderately severe and severe AP.⁵⁰ Preclinical mouse models of AP demonstrate that pirfenidone reduces the severity of inflammation through an increase in levels of the anti-inflammatory cytokine IL-10.⁵¹ Pirfenidone has previously been used safely in humans (as treatment for idiopathic pulmonary fibrosis)⁵² but has never been used in acutely ill patients with AP. A clinical trial has been initiated to test the safety and tolerability in patients with predicted moderately severe and severe AP (NCT05350371). This trial will also measure multiple clinical endpoints to assess for a signal of efficacy. Future studies on prevention of CP are also being considered.

Another antifibrotic agent, TLY012, a soluble trimeric form of human tumor necrosis factor–related apoptosis-inducing ligand, has been developed with the help of animal models in which it has shown potent antifibrotic activity in CP and models of other fibrotic diseases such as scleroderma and NASH.^{53–55} TLY012 acts on activated myofibroblast and pancreatic stellate cells, but not quiescent pancreatic stellate cells, driving apoptosis and resulting in rapid reductions in fibrosis, reducing pancreatic injury in animal models of CP compared with controls. It is also thought to limit fibrosis-associated pain: in rat models of CP, TLY012 treatment reduced somatic-referred hyperalgesia and direct visceral pain sensitivity in the pancreas. Although the concept of an antifibrotic agent is well established, development of a stable trimer with a long half-life and good solubility provides the first opportunity to evaluate potential efficacy in humans. The FDA has granted orphan drug designation for this agent in both CP and scleroderma and authorized initiation of a phase 1 trial in healthy volunteers. This safety study will open the door for proof-of-concept trials in patients with painful CP and other fibrotic diseases.

Neuroleptic Agents

Lacosamide, an antiepileptic agent that dampens voltage-gated sodium (NaV1.7) ion channel excitability, has previously been observed in preclinical studies in combination with opioid analgesics to diminish sodium channel activity and improve pain control.⁵⁶ Previous human studies with lacosamide for chronic pain conditions including fibromyalgia and diabetic peripheral neuropathy have failed to demonstrate significant pain reduction, but patients on opioids were excluded.⁵⁷ The working hypothesis of the present study (extrapolated from an understanding of the mechanism for opioid-induced hyperalgesia) is that opioids activate the nonclassical opioid receptor, toll-like receptor 4, and elicit greater pain in individuals due to the opening of the voltage-gated sodium channel NaV1.7. Lacosamide dampens NaV1.7 ion channel excitability and therefore would allow for an improvement in pain in response to opioids at potentially lower doses. Given the key role of opioid analgesics in this mechanism, previous work excluding patients on opioids eliminated participants most likely to respond to treatment.⁵⁷ The aim of the ongoing phase 1 study (NCT05603702) is to evaluate the effect of adding lacosamide to opioid therapy on the safety and tolerability in treating CP pain. The results of this pilot study may support a subsequent phase 2 trial assessing the efficacy of lacosamide added to opioid therapy to alleviate abdominal pain in CP.

Human Autologous Stem Cell Therapies

The use of human autologous stem cells represents a potential nondrug biologic therapy that may serve as a disease-modifying intervention to reduce inflammation AP and has previously been eval-

uated in preclinical studies on necrotizing disease. In severe AP, inflammation is exacerbated by resident macrophage activation potentiating the immune response leading to acinar cell death that further amplifies the early inflammatory cascade locally and systemically. Previous clinical attempts to target specific inflammatory modulators to ameliorate the inflammatory response in AP have failed. In contrast, systemic delivery of mesenchymal stem/stromal cells (MSCs) has reproducibly shown marked anti-inflammatory effects in rat models of severe AP, even after inflammation was well established.^{58,59} Although autologous bone marrow MSCs require prolonged processing, adipose-derived MSCs, adipose stem/stromal cells (ASCs), are readily available by liposuction and require no ex vivo expansion. Preclinical studies with human ASCs have confirmed that systemic provision of human ASCs, such as MSCs, significantly reduces local tissue injury and systemic inflammation in a murine model of AP.⁶⁰ The breadth of evidence of the ability of ASCs to ameliorate inflammation, in conjunction with their safety profile in several clinical studies, provides a strong rationale to consider a clinical trial of ASCs in severe AP.⁶¹

ENDOSCOPIC, SURGICAL, AND BIOENGINEERING APPROACHES

In the early stages of CP, medical management of exocrine and endocrine functions and mild to moderate pain can be effective in many cases.^{62,63} With progression of disease, long-term pain relief can often only be achieved using additional invasive interventions such as endoscopy and surgery in conjunction with adjunctive therapies for comorbid conditions.^{64,65} Although technical aspects of endoscopic and surgical interventions have changed little in recent years, the debate is ongoing about optimal patient selection, timing, and modality of treatment.⁶⁶ A multimodal and multidisciplinary approach is often required to determine the best treatment plan, frequently multifaceted to manage all treatable aspects of painful CP.

Advances in Pancreatic Endoscopy

Imaging

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound are the 2 endoscopic modalities that are commonly used in the management of patients with pancreatitis. Endoscopic retrograde cholangiopancreatography is no longer used in the diagnostic setting, but rather only in settings of a therapeutic intervention. Endoscopic ultrasound, a commonly used imaging modality for the pancreas, can visualize the entire pancreas and offers the potential for simultaneous tissue sampling when appropriate. It has excellent sensitivity and specificity for features of late disease (main pancreatic dilation and irregularity or calcifications), but current criteria for diagnosing early CP remain suboptimal due to lack of specificity, poor interobserver reliability, and inconsistent histopathologic correlation.^{67–69} There is a critical need to leverage ongoing innovation in artificial intelligence to address these diagnostic limitations, likely in conjunction with imaging enhancements such as strain or shear wave elastography. Importantly, there are no tests to confirm the presence of pancreatic hypertension within a dilated (“obstructed”) pancreatic duct.

Therapy for Pain

Because endoscopic therapy is predicated on decompression of a dilated pancreatic duct, a biomarker for pressure-mediated pancreatic pain may be useful in predicting which patients will derive the greatest benefit from endoscopic drainage. Pancreatic duct dilation is considered a phenotypic manifestation of increased pancreatic

duct pressure, which is hypothesized to represent 1 mechanism for pain in CP.^{70,71} However, small studies suggest poor correlation between findings at ERCP, pain scores, and intraductal pressure.^{72,73} It is widely recognized that the etiology of pain is multifactorial, with pancreatic duct obstruction representing 1 of several mechanisms that include pancreatic ischemia, intrapancreatic nerve damage (manifested by inflammation, enlargement, fibrosis, or some combination), and impaired central nervous system modulation.⁷⁴ Given the complex pathogenesis of CP pain and variability in pain phenotypes,⁷⁵ treatment of pancreatic duct obstruction (and thus pancreatic duct hypertension) is logical but not unequivocally beneficial—randomized trials comparing endoscopy with surgery or extracorporeal shock wave lithotripsy reported favorable outcomes in <50% of the endoscopy population.^{76–79}

Approaches to endoscopic transpapillary pancreatic duct drainage have continued to focus on the basic principles: (1) traverse the segment of dominant obstruction using a guidewire; (2) remove main duct calculi, perhaps first by debulking them via lithotripsy before or after; (3) dilating the obstruction using graduated catheters or hydrostatic balloon catheters; and (4) maintain duct patency through placement of 1 or more plastic pancreatic duct stents in parallel. A complete treatment course usually requires at least 3–4 procedures over approximately 1 year. There are 2 approaches to pancreatic lithotripsy: intraductal (electrohydraulic or laser mediated) and through extracorporeal shock waves. Preliminary studies suggest that extracorporeal shock wave lithotripsy alone may have comparable efficacy to the same technique accompanied by ERCP with stone fragment extraction and stenting. It is also possible that neither are superior to medical therapy and the placebo effect; there are 2 ongoing sham-controlled trials (SCHOKE NCT03966781 and PERCePT NCT04232670) and several other longitudinal cohort or clinical trials comparing endoscopic techniques.⁸⁰ Pancreatic stents have not changed in decades. Recent development of a removal, self-expandable metallic stent has been halted by a study which failed to meet its pain endpoint.⁸¹

Advances in intraductal pancreatoscopy allow for a more sophisticated—and probably more efficient—approach to removing

main duct calculi during the first endoscopic session when the anatomy is favorable. Innovation in interventional endoscopic ultrasound is expected to expand the role of endoscopy in treating pancreatic pain, ideally with more objective imaging and prognostic tests to optimize patient selection.

Therapy for Local Complications of Acute Pancreatitis

Endoscopy now represents the first-line modality for treating most local complications of pancreatitis—leaks, cysts, and necrotic collections.⁸² Natural orifice transluminal endoscopic surgery was merely a concept until the endoscopic treatment of walled off pancreatic necrosis evolved to become the preferred strategy for debriding necrotic collections with favorable anatomic boundaries. Initially, these drainage and debridement procedures were performed using tools developed for tissue sampling and biliary drainage. The advent of lumen apposing metal stents preloaded onto an electrocautery enhanced cystotome (Axios; Boston Scientific Corp, Marlborough, Mass) reduces procedure times, technical complexity to gain access, and facilitates repeated intubations of the necrotic cavity. Internal drainage procedures spare the patient the consequences of external drains and eliminate the likelihood of cutaneous fistulae. However, endoscopic treatment of pancreatic necrosis remains imperfect. Each debridement requires anesthesia, is time-consuming, and not without risk of hemorrhage, perforation, and infection. Cases that require 3–4 debridements—each 60–90 minutes—are resource intense and inconvenient for patients who may have to travel from a distance.

Surgery in Pancreatitis

Endoscopy Versus Surgery

There lacks consensus agreement in the field regarding the optimal timing and order of invasive interventions to treat painful CP.^{83,84} Despite well-conducted randomized studies showing superiority of pain outcomes with surgical drainage compared with endoscopic drainage and early surgery to be favored over later

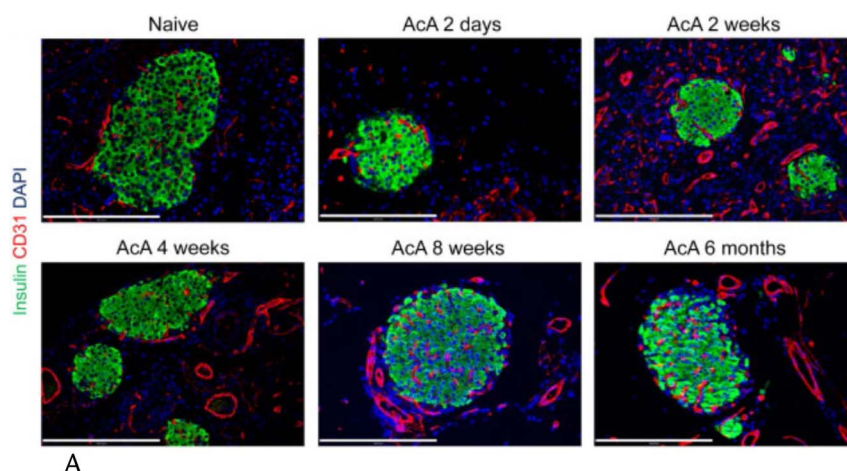


FIGURE 2. Morphological and histological changes in mouse pancreas specimens after chemical pancreatectomy. A, After AcA infusion, gross morphology of the pancreas was abnormally white and edematous at 2 days, translucent with visible islets (arrow) at 2 weeks, and replaced by fatty tissue with visible islets (arrow) at 8 weeks. B and C, Normal pancreas histology is seen at 2 days after saline infusion (B). Two days after AcA infusion, exocrine tissue necrosis (asterisks) is seen with intact islets (i). Magnification (inset) of the apparently preserved acinar cells revealed cell swelling and cytoplasmic vacuolization (arrows) (C). D, Histology of the pancreas after AcA infusion. Intact islets are denoted by i. Arrows denote fat cells at 4 weeks. E, Immunostaining after AcA infusion showed negative amylase staining (arrows denote amylase remnants at 2 days), with normal insulin and glucagon staining. Illustrative histology results from 5 animals per time point are shown. Scale bars: 200 μ m.

surgery, many clinicians persist with multiple endoscopic procedures before surgical referral. The reasons for this are many and include patient preference and reluctance to undergo surgical intervention, regional differences in practice patterns, lack of adequate surgical experts to perform these interventions as training for these surgeries has declined, and lack of consensus definition on identification of an early stage of CP during which intervention is theoretically optimized to prevent progression to end-stage disease.^{85,86}

A nuanced surgical approach is necessary to adequately address the individual pathological pattern of each candidate for intervention. Several randomized controlled trials have compared classical pancreatoduodenectomies with Beger-type procedures but have not adequately addressed the fact that more advanced cases with venous compression are able to undergo a Beger-type procedure but not a classical resection of the head of the pancreas. What has additionally not been addressed in the literature is the type of patient with advanced symptoms and total parenchymal and vascular involvement with a nondilated main pancreatic duct. Although a formal total pancreatectomy is often not possible in this situation, a subtotal in situ resection often achieves good clinical outcomes.⁸⁷ Contrary to widely held perceptions, both the Frey procedure and the Beger procedure can be applied in patients who have a small main pancreatic duct; previous work has established the success of drainage procedures in these patients despite small duct disease.⁸⁸ There has been a recent rise in the application and ongoing study of outcomes related to total pancreatectomy and islet auto transplantation.⁸⁹ In patients with small duct disease or patients with hereditary pancreatitis, this can result in significant improvements in QOL for patients who typically

require frequent hospitalizations for pain, and theoretically, it eliminates the risk of malignant degeneration in those patients with a genetic basis for disease.

Although a conceptual mechanism for progression to end-stage CP has been published and widely discussed, a universally accepted definition for each of the individual stages of CP remains a barrier to forward progress.⁴ Wider agreement on this would provide a foundation on which to build future randomized clinical trials of appropriate interventions at each stage.

Chemical Pancreatectomy: An Experimental Nonoperative Treatment for Chronic Pancreatitis

A serendipitous observation in mice that an infusion of 100% ethanol into the pancreatic duct led to total ablation of the ducts and acini, with complete preservation of the endocrine islets, may lead to the development of a nonoperative approach for RAP and CP, having potential to serve as a nonoperative alternative to total pancreatectomy and islet auto transplantation. Subsequent investigation in this area found that a simple dilute 1% solution of acetic acid achieved the same effects with much less toxicity and a simultaneous improvement in glucose tolerance.⁹⁰ Subsequently, a cerulein and diet-induced murine model of CP showed improved pain signaling and avoidance of pancreatitis-induced dysglycemia. It was found that the islet innervation and vascularization were maintained (Fig. 2). Fenestrations adjacent to islet endocrine cells seen in normal islet cell architecture that facilitate glucose sensing and hormone release were also preserved on electron microscopy. Evaluation in nonhuman primates found that 2% acetic acid was more effective than 1%, but supranormal glucose tolerance and enhanced

TABLE 1. Selected Gaps and Opportunities for the Advancement of Development of Interventions for AP, RAP, and CP

Behavioral interventions	-Understand and overcome access limitations to behavioral health resources (ie, shortage of interdisciplinary gastrointestinal and pain clinics, geographic distance to trained specialists, insurance limitations, stigma) -Development of study designs to evaluate integrated multimodal interventions -Assessment of and intervention to reduce healthcare disparities across the spectrum of pancreatic disease -Further development of psychological interventions including CBT for pain and behavioral contributors to pancreatic disease -Development of novel treatment strategies for alcohol and tobacco addiction in patients with RAP and CP -Expansion of the use of digital technologies for data measurement and delivery of interventions including disease-specific tools
Nutritional interventions	-Consensus development for key definitions of nutritional problems (ie, malnutrition, sarcopenia, dynamic frailty) in patients with AP, RAP, and CP -Development of a disease-specific standardized PRO tool for nutritional endpoints in AP, RAP, and CP -Clinical trial assessment of frequently used or promising dietary supplements in the treatment of AP, RAP, and CP -Development of collaborative intervention trials assessing the efficacy of multimodal nutrition-centered interventions on QOL and PROs for CP -Further assess the role and effects of PERT in AP, RAP, and CP
Pharmacologic and biologic interventions	-Development of an FDA-approved PRO tool that can be used in standardized fashion to measure efficacy -Collaboration between basic scientists and clinical trial specialists to harmonize the experimental pipeline: animal models to resemble the human experience of disease (ie, etiology, disease course, fibrosis) -Further study of existing pharmacologic agents that can be repurposed, and experimental therapies such as stem cell therapy for intervention in AP, RAP, and CP -Development of large-scale collaborative networks for the execution of clinical trials of pharmacologic/biologic agents
Bioengineering, surgical, and endoscopic interventions	-Consensus definition for the understanding of stages of RAP and CP (to include multimodal clinical metrics, etiologic contributors, and additional endpoints) -Guideline creation by consensus agreement on the interventional management of painful CP (incorporating known data on prediction of success, timing of procedure, and modality of procedure) -Further exploration of safety and efficacy of experimental techniques for painful CP (ie, chemical pancreatectomy and others)

insulin release were again observed.⁹¹ Follow-up in some nonhuman primates for up to 20 months revealed no evidence of exocrine regeneration. Currently, there is ongoing work with the FDA to begin a human trial.

CONCLUSIONS

In summary, there remain many challenges to establishing a set of beneficial interventions that will achieve meaningful improvement in clinical outcomes for patients with AP, RAP, and CP. Opportunities for advancement in the field were identified during the course of workshop discussions and outlined to target future developments that will specifically benefit patients (Table 1). This summary report represents the opinions and expertise of the invited speakers, and does not include a systematic review of all available treatments for RAP or CP nor does exclusion of a treatment suggest that it has less value than those discussed here. The items discussed in Table 1 include many efforts that will require cooperation of large consortia and consensus agreements in the field to establish foundational definitions on which future advancements can be built. Through these efforts, we anticipate iterative progress toward the ultimate goal of addressing the unmet needs of patients with AP, RAP, and CP, and improvement in clinical care and overall outcomes.

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