



# Gallbladder and Sphincter of Oddi Disorders

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The concept that motor disorders of the gallbladder, cystic duct, and sphincter of Oddi can cause painful syndromes is attractive and popular, at least in the United States. However, the results of commonly performed ablative treatments (eg, cholecystectomy and sphincterotomy) are not uniformly good. The predictive value of tests that are often used to diagnose dysfunction (eg, dynamic gallbladder scintigraphy and sphincter manometry) is controversial. Evaluation and management of these patients is made difficult by the fluctuating symptoms and the placebo effect of invasive interventions. A recent stringent study has shown that sphincterotomy is no better than sham treatment in patients with post-cholecystectomy pain and little or no objective abnormalities on investigation, so that the old concept of sphincter of Oddi dysfunction type III is discarded. Endoscopic retrograde cholangiopancreatography approaches are no longer appropriate in that context. There is a pressing need for similar prospective studies to provide better guidance for clinicians dealing with these patients. We need to clarify the indications for cholecystectomy in patients with functional gallbladder disorder and the relevance of sphincter dysfunction in patients with some evidence for biliary obstruction (previously sphincter of Oddi dysfunction type II, now called “functional biliary sphincter disorder”) and with idiopathic acute recurrent pancreatitis.

**Keywords:** Cholecystectomy; Biliary Pain; Post-Cholecystectomy Pain; Sphincter Manometry; Sphincterotomy; Idiopathic Pancreatitis; Endoscopic Retrograde Cholangiogram; Cholangiography.

Functional disorders of the gallbladder (GB) and the sphincter of Oddi (SO) are controversial topics. They have gone by a variety of names, including acalculous biliary pain, biliary dyskinesia, GB dysmotility, and SO (or ampullary) stenosis. This article builds on the Rome III consensus,<sup>1</sup> recognizing that the evidence base is slim. This article does not cover the anatomy and physiology, which are well described elsewhere.

## Biliary Pain

The concept that disordered function of the GB and SO can cause pain is based mainly on the fact that many patients have biliary-type pain in the absence of recognized organic causes, and that some apparently are cured by removal of the GB or ablation of the sphincter.

### E1. Diagnostic Criteria for Biliary Pain

Pain located in the epigastrium and/or right upper quadrant and all of the following:

1. Builds up to a steady level and lasting 30 minutes or longer
2. Occurring at different intervals (not daily)
3. Severe enough to interrupt daily activities or lead to an emergency department visit
4. Not significantly (<20%) related to bowel movements
5. Not significantly (<20%) relieved by postural change or acid suppression

### Supportive Criteria

The pain may be associated with:

1. Nausea and vomiting
2. Radiation to the back and/or right infra-subscapular region
3. Waking from sleep

This definition for biliary pain differs from Rome III only in quantitating “not significantly” to mean <20%. We included the Rome III criterion that pains should be “not daily” although this is not evidence-based. Further studies are needed.

## Functional Gallbladder Disorder

### Definition

In conformity with the Rome consensus that defines functional gastrointestinal disorders as symptom complexes

**Abbreviations used in this paper:** CCK-CS, cholecystokinin-stimulated cholescintigraphy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FGBD, functional gallbladder disorder; GB, gallbladder; GBEF, gallbladder ejection fraction; MRCP, magnetic resonance cholangiopancreatography; SO, sphincter of Oddi; SOD, sphincter of Oddi dysfunction.

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not explained by a clearly identified mechanism or by a structural alteration, we use the term *functional gallbladder disorder* (FGBD) to describe patients with biliary pain and an intact GB without stones or sludge.

<p>E1a. Diagnostic Criteria for Functional Gallbladder Disorder</p> <ol style="list-style-type: none"> <li>1. Biliary pain</li> <li>2. Absence of gallstones or other structural pathology</li> </ol> <p><i>Supportive Criteria</i></p> <ol style="list-style-type: none"> <li>1. Low ejection fraction on gallbladder scintigraphy</li> <li>2. Normal liver enzymes, conjugated bilirubin, and amylase/lipase</li> </ol>
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Since the diagnosis is primarily one of exclusion, the prevalence depends on the rigor of investigation. Ultrasonography is the usual primary investigation, but endoscopic ultrasound (EUS) is more sensitive for detecting small stones and biliary sludge, and can also detect small tumors, and subtle changes of chronic pancreatitis.

The only change from Rome III is that normal liver and pancreatic enzymes have been moved to the supportive category. There can be other reasons for elevated liver enzymes, like fatty liver disease, that do not rule out GB dysfunction. We have also added a low ejection fraction on GB scintigraphy as supportive. It is not required for the diagnosis, nor is it specific for the diagnosis when abnormal.<sup>2</sup>

**Epidemiology**

Biliary pain is a common clinical problem, and cholecystectomy is a frequent operation. The number and proportion done for FGBD seems to be increasing in the United States, where case series now list it as the indication for cholecystectomy in 10%–20% of adults<sup>2,3</sup> and in 10%–50%

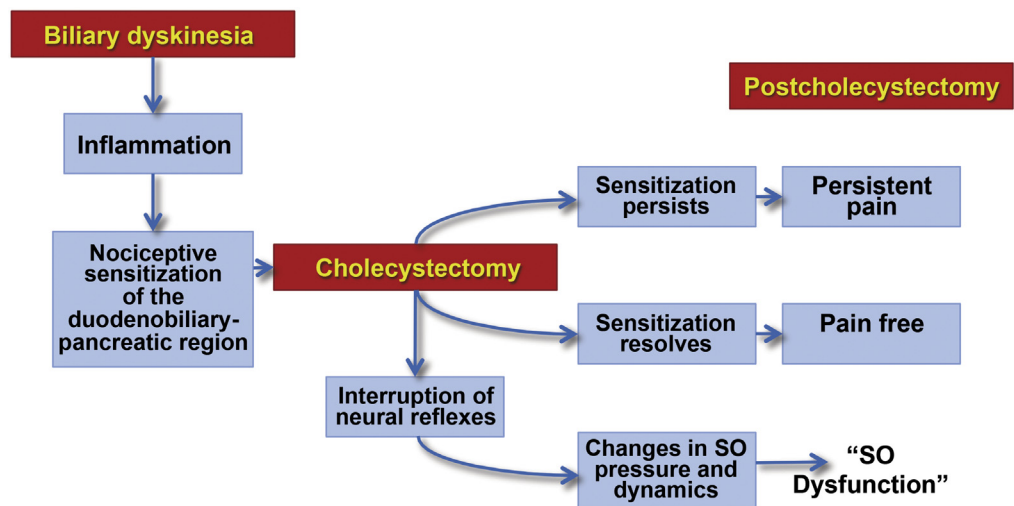
of children.<sup>4</sup> FGBD is rarely diagnosed outside the United States.<sup>5</sup>

**Pathophysiology**

FGBD is often diagnosed by a low gallbladder ejection fraction (GBEF) at cholecystokinin-stimulated cholescintigraphy (CCK-CS). Although the relationship between GBEF and clinical outcome remains unclear, gallbladder dysmotility may still play a role in the pathogenesis of symptoms, by promoting gallbladder inflammation, which is commonly found. Microlithiasis is associated with a delayed ejection fraction on scintigraphy.<sup>6</sup> Investigators have found multiple defects in gallbladder contractility, including spontaneous activity and abnormal responses to both CCK and neural stimulation.<sup>7</sup> A vicious cycle of stasis and inflammation exists in the GB. Some patients may have intrinsic defects in contractility, and subtle defects in bile composition may also play a role. Studies have shown elevated sphincter of Oddi (SO) pressures in patients with GB dyskinesia, but without correlation between GBEF and SO pressure.<sup>8</sup> GB dysfunction may represent a more generalized dysmotility, as in irritable bowel syndrome and chronic constipation, and perhaps gastroparesis.<sup>9</sup> Experimental evidence has implicated several molecules that can link inflammation to motility, the most important of which may be prostaglandin E2 (PGE2).<sup>10,11</sup> Possible etiological mechanisms and outcomes in patients with “biliary dyskinesia” are illustrated in Figure 1.

**Clinical Evaluation**

GB stones should be excluded by ultrasound scanning (repeated if necessary), and complemented with EUS. Other tests may be needed to rule out peptic ulcer disease, subtle chronic pancreatitis, fatty liver disease, or musculoskeletal syndromes. Esophageal manometry, gastric emptying tests, and transit studies may be required if symptoms suggest alternative dysfunctional syndromes. Further management depends on the level of clinical suspicion. The diagnosis of FGBD may be made by exclusion if the pains are typical and



**Figure 1.** Potential etiological pathways and clinical outcomes in patients with “biliary dyskinesia”

severe. A key issue is whether current methods for assessing GB muscular function are useful.

### Assessment of Gallbladder Emptying

CCK-CS is a popular diagnostic test, but its value is controversial. The test involves the intravenous administration of technetium 99m (Tc 99m)-labeled hepatobiliary iminodiacetic acid analogs. These compounds are readily excreted into the biliary tract, and are concentrated in the GB. The net activity-time curve for the GB is derived from serial observations, and GB emptying is expressed as the GBEF, which is the percentage change of net GB counts.<sup>12</sup>

An interdisciplinary panel proposed a standardized test and emphasized that proper patient selection is a critical step when considering whether to perform CCK-CS, because delayed emptying is seen in many other conditions, including asymptomatic individuals and patients with other functional gastrointestinal disorders. The injection of CCK can cause biliary-like pain, but using this observation to determine patient-care decisions was discouraged by the panel, because CCK also increases bowel motility, which can cause symptoms. In some countries, CCK preparations have not been approved for human use.

**Other imaging methods.** GB emptying can be assessed with ultrasound scanning after CCK or fatty meal stimulation, but these methods have not become popular. Attempts are being made to study emptying patterns during magnetic resonance cholangiopancreatography (MRCP)<sup>13</sup> and computed tomography (CT) scanning<sup>14</sup> with results that appear to mimic those of cholescintigraphy.

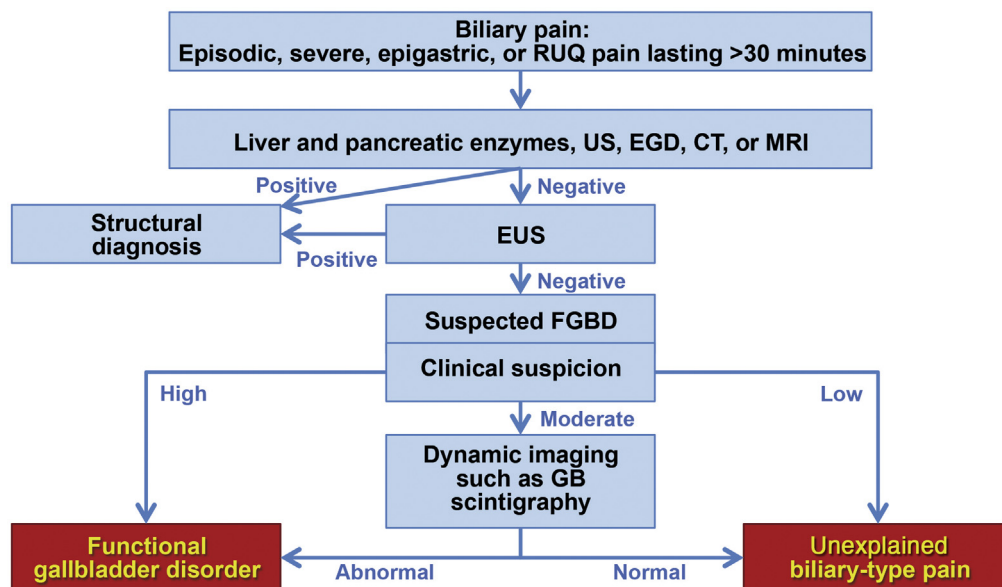
### Treatment of Functional Gallbladder Disorder

Symptoms suggestive of FGBD often resolve spontaneously,<sup>3</sup> so that early intervention is unwarranted. Patients may respond to reassurance and medical treatments such as antispasmodics, neuromodulators, or ursodeoxycholic acid,

although their value has not been evaluated formally. Cholecystectomy is considered when these methods fail, and symptoms are severe. The reported results of surgery vary widely.<sup>2,3,15</sup> Many claim benefit in >80% of patients, but most studies are of poor quality with several potential biases; none have limited intervention to patients with negative EUS exams. There has been only one small randomized trial, favoring cholecystectomy.<sup>16</sup> Several authorities have called for more definitive studies.<sup>3,17</sup>

The predictive value of the CCK-CS test is in question. Two systematic reviews have concluded that there is insufficient evidence to recommend its use.<sup>18,19</sup> The review by DiBaise and Oleynikov<sup>19</sup> found that 19 of 23 papers suggested that the GBEF was useful in selecting patients for cholecystectomy. However, cholecystectomy is claimed to benefit most patients with “typical biliary” symptoms, raising the question as to what additional utility is afforded by CCK-CS.<sup>20</sup> One study reported symptomatic relief after cholecystectomy in 94% of patients with a low GBEF, but also in 85% of those with a normal GBEF.<sup>19</sup> The degree of dysfunction (ie, GBEF <20% vs <35%) did not improve the predictive value.<sup>21</sup> Similarly, in a study of patients with reduced GBEF (<35%), CCK-CS was of minimal clinical utility in predicting symptomatic relief in patients with atypical symptoms, 30% resolving spontaneously, and of those with persistent symptoms, only 57% benefitted from cholecystectomy.<sup>20</sup> A “blind” cholecystectomy based on symptoms without CCK-CS evidence has been reported with a >90% satisfaction rate. That many patients with suspected FGBD are not helped by cholecystectomy is shown by the significant number who present afterward with “post-cholecystectomy pain,” and are considered for another contentious diagnosis, sphincter of Oddi dysfunction (SOD).

**Conclusion.** Current evidence indicates that cholecystectomy can provide symptom relief in many patients with acalculous biliary pain, and GBEF is often low in these patients. However, more stringent studies are needed to



**Figure 2.** Evaluation of biliary pain in patients with intact GB. In patients with biliary pain and negative investigations (including EUS), the decision to proceed to cholecystectomy or dynamic imaging of the gallbladder will depend on the strength of the clinical suspicion. CT, computed tomography; EGD, esophagogastroduodenoscopy; MRI, magnetic resonance imaging; RUQ, right upper quadrant; US, ultrasound.

establish which patients are likely to benefit (or not), and to clarify the predictive value of the CCK-CS test.

One approach to managing these patients is shown in Figure 2, but the need for more research is obvious.

**Future Research.** We need to know more about the etiology of FGBD, better methods for making and excluding the diagnosis, the natural history, and the role of different treatments. More stringent prospective studies of cholecystectomy, with independent outcome assessments, are required to provide a more evidence-based approach.

## Functional Biliary Sphincter Disorder

Dysfunction of the biliary sphincter is commonly considered in patients with biliary-type pains after cholecystectomy, when stones and other pathology are excluded.<sup>1,22</sup>

### Epidemiology

Many patients have persistent or recurrent pain after cholecystectomy.<sup>23,24</sup> The proportion is higher in patients who have had elective rather than emergency surgery, in patients without GB stones, and in those with less typical symptoms.<sup>25</sup>

### Diagnostic Criteria

The longstanding popular classification of 3 clinical types of SOD<sup>1,22,26</sup> seemed validated by the fact that the likelihood of abnormal sphincter manometry, and relief by sphincterotomy, appeared to correlate with the types. However, most data came from cohort studies of poor quality,<sup>27,28</sup> and one showed no such correlation.<sup>29</sup> Earlier recommendations were that type I patients (with a dilated bile duct and elevated liver enzymes) should undergo biliary sphincterotomy without manometry, and that type II (dilated duct or elevated liver enzymes) patients and type III (no abnormalities) patients should be considered for manometry-directed sphincterotomy.<sup>1</sup>

This classification is now outdated and should be abandoned. Most patients with prior SOD type I have organic stenosis rather than functional pathology; they benefit from biliary sphincterotomy. The EPISOD (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction) trial<sup>30</sup> showed that patients with SOD type III do not respond to sphincter ablation better than sham intervention. We therefore now recommend using the term *suspected functional biliary sphincter disorder* (suspected FBSD) for patients with post-cholecystectomy pain and some objective findings (the prior SOD type II). Further research is needed to establish more precisely which clinical features and investigations can best identify those who are likely to respond (or not) to sphincter treatments.

#### E1b. Diagnostic Criteria for Functional Biliary Sphincter of Oddi Disorder

1. Criteria for biliary pain
2. Elevated liver enzymes or dilated bile duct, but not both

3. Absence of bile duct stones or other structural abnormalities

#### Supportive Criteria

1. Normal amylase/lipase
2. Abnormal sphincter of Oddi manometry
3. Hepatobiliary scintigraphy

**Changes Since Rome III.** Elevated liver enzymes or a dilated bile duct (but not both) are now required, rather than supportive, criteria. Normal amylase and/or lipase have been moved to supportive criteria because they may occur in some episodes of pain. We have added abnormal biliary manometry as supportive because randomized trials showed that it is predictive of response to biliary sphincterotomy.<sup>31,32</sup> Hepatobiliary scintigraphy is also included, although its value is disputed.

### Pathophysiology

Classical teaching is that aberrant sphincter physiology leads to biliary pain by increased resistance to bile outflow and subsequent rise in intrabiliary pressure. This concept is intuitively appealing, leading to widespread acceptance, especially by biliary endoscopists. However, both theoretical and experimental evidence indicate a more complex pathophysiology.

There is evidence that sphincter dynamics are altered after cholecystectomy.<sup>33</sup> Animal studies have shown a cholecystosphincteric reflex with distention of the GB that results in sphincter relaxation.<sup>34</sup> Interruption of this reflex could affect sphincter behavior by an altered response to CCK, or because the loss of innervation unmasks the direct contractile effects of CCK on smooth muscle. Abnormalities in both basal pressure and responsiveness to CCK have also been described in humans.<sup>35</sup>

The simple concept of SOD leading to obstruction and biliary pain is now being challenged, as the EPISOD trial has shown.<sup>30</sup> One explanation for this syndrome stems from the concept of nociceptive sensitization.<sup>36</sup> Significant tissue inflammation, such as cholecystitis, will activate nociceptive neurons acutely and, if it persists, will also result in sensitization and the gain in the entire pain pathway is increased. In most patients with GB disease, cholecystectomy removes the ongoing stimulus and the system reverts back to its normal state. However, in a subset of patients, the “gain” stays at a high level (Figure 1). In such patients, even minor increases in biliary pressure (within the physiological range) can trigger nociceptive activity and the sensation of pain (allodynia).

A relevant related phenomenon is cross-sensitization. Many viscera share sensory innervation. For example, nearly half of the sensory neurons in the pancreas also innervate the duodenum.<sup>37</sup> Therefore, it is difficult to distinguish pain resulting in one organ from that in another. Persistent sensitization in one organ can lead to



sensitization of the nociceptive pathway from an adjacent organ. Thus, an entire region can be sensitized with innocuous stimuli (such as duodenal contraction after a meal) leading to pain that was indistinguishable from that associated with the initial insult. Evidence for this was provided by a study in which patients with post-cholecystectomy pain were found to have duodenal, but not rectal, hyperalgesia.<sup>38</sup> A strong case can be made for nociceptive sensitization to be the principal cause of pain. Motor phenomena, such as sphincter hypertension, might still be relevant, but more as a marker for the syndrome rather than the cause.

### Exclusion of Organic Disease

The first task in patients with post-cholecystectomy pain is to exclude organic causes. Possibilities include retained stones or partial GB; postoperative complications (such as a bile leak or duct stricture); other intra-abdominal disorders, such as pancreatitis, fatty liver disease, peptic ulceration, functional dyspepsia and irritable bowel syndrome; musculoskeletal disorders; and other rare conditions. Non-biliary findings are more likely when the symptoms are atypical and longstanding, similar to those suffered preoperatively and without a period of relief postoperatively, and when the GB did not contain stones.<sup>1,25,39</sup>

The initial diagnostic approach should consist of a careful history and physical examination, followed by standard liver and pancreas blood tests, upper endoscopy, and abdominal imaging. Although ultrasound or computed tomography scanning may be used initially, MRCP or EUS provide more complete information. The report of a "dilated bile duct" on any of these studies is difficult to interpret. It is widely believed that the bile duct enlarges after cholecystectomy. However, some studies have shown no change, others only a slight increase in size; there is a gradual increase with age.<sup>40-43</sup> Regular narcotic use can cause biliary dilation, although usually associated with normal liver enzymes.<sup>44</sup> EUS is the best way to rule out duct stones and pathology of the papilla.<sup>45,46</sup>

### Noninvasive Testing

A major problem with assessing diagnostic tools in this context is the lack of a gold standard. One could argue that the only proof that the sphincter is (or was) the cause of the pain is if patients are satisfied by the results of sphincter ablation, albeit recognizing the often prolonged placebo effect of endoscopic retrograde cholangiopancreatography (ERCP) intervention.<sup>30</sup> There are very few studies with objective blinded assessments and even fewer randomized trials. Many tests are assessed by comparison with the results of manometry, whose validity is also uncertain. Thus, arguments are often circular, and our comments on the value of these various tests are not based on solid evidence. Liver enzymes, which peak with attacks of pain, might be a good sign of obstruction by spasm (or passage of stones),<sup>47</sup> but confirmation is lacking. Another problem is that most patients have intermittent pains, so that measurements taken when pain-free are open to question.

The drainage dynamics of the bile duct have been tested after stimulation with a fatty meal or injection of CCK and measuring any dilatation of the duct with abdominal or endoscopic ultrasound. These techniques deserve further evaluation, and there is potential for studying dynamic parameters with contrast agents during MRCP<sup>13</sup> and computed tomography scanning.<sup>14</sup>

**Hepatobiliary scintigraphy.** Hepatobiliary scintigraphy involves intravenous injection of a radionuclide and deriving time-activity curves for its excretion throughout the hepatobiliary system. This technique has been used to assess the rate of bile flow into the duodenum and to look for any evidence of obstruction. Interpretation of the literature is difficult due to the use of different test protocols, diagnostic criteria, and categories of patients, and whether the results are compared with manometry (usually) or the outcome of sphincterotomy. Various parameters are used: time to peak activity, slope values, and hepatic clearance at predefined time intervals, disappearance time from the bile duct, duodenal appearance time, and the hepatic hilum–duodenum transit time.<sup>48-51</sup> One study in asymptomatic post-cholecystectomy subjects showed significant false-positive findings and intra-observer variability.<sup>52</sup> The reported specificity of hepatobiliary scintigraphy was at least 90% when manometry was used as the reference standard, but the level of sensitivity is more variable.<sup>53</sup> Although hepatobiliary scintigraphy with hepatic hilum–duodenum transit time was shown to be predictive of the results of sphincterotomy in type I and II patients,<sup>54</sup> it is not widely used currently; further studies are needed.

**Endoscopic retrograde cholangiopancreatography and sphincter of Oddi manometry.** ERCP should be reserved for patients who need sphincter manometry or endoscopic therapy, such as those with strong objective evidence for biliary obstruction.

**Manometry technique.** ERCP allows measurement of both the biliary and pancreatic sphincters, but the method is imperfect. Recording periods are short and subject to movement artifact. The effects of medications commonly used for sedation and anesthesia have not been studied sufficiently. Furthermore, reproducibility is in question.<sup>55</sup>

The assessable variables at SO manometry include the basal sphincter pressure and the phasic wave amplitude, duration, frequency, and propagation pattern. However, only basal pressure has so far been shown to have clinical significance.<sup>31,32</sup> The standard upper limit of normal for baseline biliary sphincter pressure is 35–40 mm Hg. Normal pancreatic sphincter pressures are accepted as similar to those of the bile duct, although reference data are more limited.

In normal volunteers, pressures obtained from the bile duct and pancreatic duct are similar.<sup>56</sup> However, abnormalities may be confined to one side of the sphincter in up to 50% of patients.<sup>57-59</sup> For patients in whom the indication for SO manometry is biliary pain and not idiopathic pancreatitis, some authorities avoid pancreatic cannulation entirely to reduce the frequency of pancreatitis. The value of studying the pancreatic sphincter has been questioned, given 2 recent studies that failed to show superiority for

dual sphincterotomy over biliary alone in suspected biliary sphincter dysfunction and in idiopathic recurrent pancreatitis.<sup>30,60</sup>

Solid-state manometry catheters have also been used, with results identical to those of the water-perfused system.<sup>61</sup> A technique using a sleeve device also showed similar results, with the advantage of reducing movement artifacts, but is not commercially available.<sup>62</sup>

**Indications for manometry.** Sphincter manometry has been recommended in patients with suspected biliary type II SOD because 3 randomized trials showed that biliary manometry predicted the response to biliary sphincterotomy.<sup>31,32,63</sup> However, in clinical practice, biliary sphincterotomy is often performed empirically in those patients. Because of the EPISOD trial findings, manometry is no longer recommended in patients without objective findings (prior type III SOD).<sup>30</sup>

*Non-Manometric Endoscopic Retrograde Cholangiopancreatography Diagnostic Approaches*

Trial placement of a pancreatic or biliary stent to predict response to subsequent sphincterotomy has been proposed as an alternative method for diagnosing SOD, but should be avoided due to the very high risk of inducing pancreatitis. Injection of Botulinum toxin has been shown to relax the sphincter complex temporarily<sup>64,65</sup> and no complications have been reported. It is claimed to predict which patients would benefit from sphincterotomy,<sup>65,66</sup> but more data are needed.

Figure 3 suggests diagnostic pathways, based on current limited evidence.

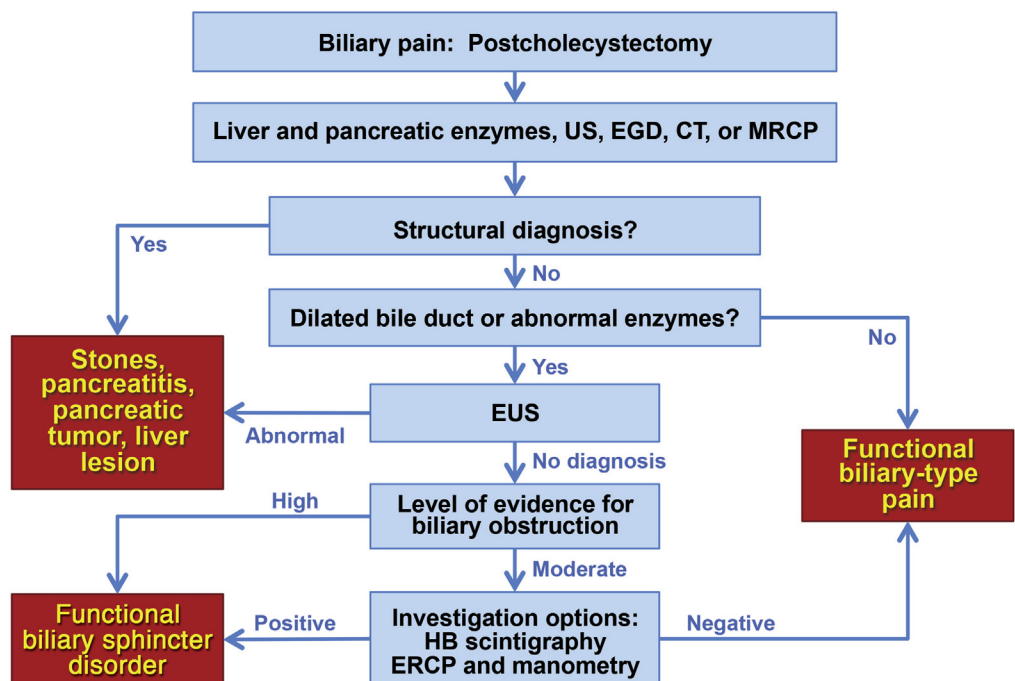
*Treatment*

Current recommendations for management of patients with suspected functional biliary sphincter disorder are based on expert consensus, with inadequate evidence. Many patients are disabled with pain and desperate for assistance. The placebo effect of intervention is strong, with about one-third of sham-treated patients claiming long-term benefit in blinded randomized studies.<sup>30,31,32,63</sup>

**Medical therapy.** Because of the risks and uncertainties involved in invasive approaches, it is important to explore conservative management initially. Nifedipine, phosphodiesterase type-5 inhibitors, trimebutine, hyoscine butylbromide, octreotide, and nitric oxide have been shown to reduce basal sphincter pressures in SOD and asymptomatic volunteers during acute manometry.<sup>67,68</sup> H2 antagonists, gabexate mesilate, ulinastatin, and gastrokinetic agents also showed inhibitory effects on sphincter motility. Amitriptyline, as a neuromodulator, also has been used along with simple analgesics. A trial of duloxetine had encouraging results.<sup>69</sup> A French group was able to avoid sphincterotomy in 77% of patients with suspected SOD using treatment with trimebutine and nitrates.<sup>70</sup> None of these drugs are specific to the SO and therefore may also have positive effects in patients with nonbiliary dysfunctional syndromes. Transcutaneous electrical nerve stimulation<sup>71</sup> and acupuncture<sup>72</sup> also have been shown to reduce SO pressures, but their long-term efficacy has not been evaluated.

**Endoscopic therapy: sphincterotomy.** Consensus opinion remains that patients with definite evidence for SO obstruction (former biliary SOD type I) should be treated with endoscopic sphincterotomy without manometry.<sup>1</sup> The

**Figure 3.** Post-cholecystectomy biliary pain. Patients with clear evidence for biliary obstruction should have a biliary sphincterotomy; if the evidence is less convincing, further testing with manometry or scintigraphy may be helpful. CT, computed tomography; HB is hepatobiliary; US, ultrasound.



evidence base for biliary sphincterotomy in patients with less objective clinical evidence (prior SOD type II) is not strong; many studies have been retrospective, unblinded, and have not used objective assessments.<sup>27,28</sup> One large study claimed success in about three-quarters of patients simply because they did not return to the treatment site for further intervention.<sup>73</sup> The most convincing data come from 3 small randomized studies of suspected type II patients, which showed that sphincterotomy was more effective than a sham procedure in patients with elevated basal biliary sphincter pressures.<sup>31,32,63</sup> The EPISOD trial showed that there is no justification to perform manometry or sphincterotomy in patients with normal labs and imaging (prior SOD type III patients).<sup>30</sup> Outcomes were also poor in a parallel observational study (EPISOD 2) of 72 similar patients who did not agree to randomization and underwent manometry-directed sphincterotomies (Table 1). ERCP in this context is clinically dangerous and has medicolegal consequences when complications arise.

Better predictors of outcomes of sphincterotomy in patients with “suspected functional biliary sphincter disorder” (prior SOD II) are needed. Freeman and colleagues<sup>29</sup> showed that normal pancreatic manometry, delayed gastric emptying, daily opioid use, and age younger than 40 years predicted poor outcomes. It has been reported that patients are more likely to respond if their pain was not continuous, if it was accompanied by nausea and vomiting, and if there had been a pain-free interval of at least 1 year after cholecystectomy.<sup>74</sup> Future studies should re-examine these items and a range of possible predictors, including laboratory findings (fluctuating or not), the actual size of the bile duct, and whether it is known to have enlarged since surgery, the severity and pattern of the pain, the presence of other functional disorders, psychosocial factors, the reason for the cholecystectomy and response to it, as well as any potential diagnostic methods as described here.

**Endoscopic retrograde cholangiopancreatography adverse events.** ERCP in patients with SOD (with or without manometry) is associated with a high risk of pancreatitis. The rate is 10%–15%, even in expert hands using pancreatic stent placement and/or rectal nonsteroidal anti-inflammatory drugs.<sup>75,76</sup> Sphincterotomy adds the risks

of bleeding and retroduodenal perforation, which both occur in about 1% of cases, and also a significant risk for late restenosis, especially after pancreatic sphincterotomy.

**Surgical therapy.** Surgical sphincteroplasty can be performed primarily or after failed endoscopic therapy. Case series and one small randomized study (published in abstract) suggest good outcomes in most patients,<sup>63,77–80</sup> but endoscopic intervention is currently preferred for primary treatment.

### Functional Biliary Sphincter Disorder in Patients With an Intact Gallbladder

Very few studies have addressed the role of sphincter dysfunction in patients with biliary-type pain in the presence of the GB. Two small retrospective case series showed a lower chance of clinical response to biliary sphincterotomy in patients with an intact GB than in those with prior cholecystectomy.<sup>81,82</sup> Response was more likely if the bile duct was dilated. A third study reported that 43% had long-term pain relief.<sup>83</sup> More information is needed on how to manage these patients. At this time, it is not appropriate for patients with intact GBs (without stones) to undergo ERCP, manometry, or sphincterotomy unless they are enrolled in a clinical trial.

### Summary of Functional Biliary Sphincter Disorder

Post-cholecystectomy pain is a common complaint, the cause of which often remains obscure after standard investigations. This is a clinical minefield, which patients and physicians should enter only with extreme caution, especially when considering the use of ERCP and sphincterotomy, with or without sphincter manometry. The EPISOD trial again showed the strength of the placebo effect of intervention, which bedevils the assessment of all types of treatment. Further stringent trials are needed.

## Functional Pancreatic Sphincter Dysfunction

The idea that dysfunction of the pancreatic sphincter can cause pancreatic pain and pancreatitis is popular. It seems a logical extension to the consensus that sphincter hypertension can cause biliary pain. Obstruction at the sphincter causes pancreatitis in animal experiments, and in several clinical situations, including tumors of the papilla, duct stones, and by mucus plugs in intrapancreatic mucinous neoplasm. In addition, opiates increase sphincter pressure and have been implicated in attacks of pancreatitis.<sup>84</sup> Finally, patients with unexplained attacks of pancreatitis are often found to have elevated pancreatic sphincter pressures.<sup>28,85–87</sup>

Proof that elevated sphincter pressures actually cause pancreatitis would require demonstration of abnormal sphincter activity, and resolution of the attacks after sphincter ablation. Earlier small cohort studies suggested benefit after endoscopic or surgical sphincterotomy with recurrence in less than one-third of patients.<sup>28</sup> More recent studies suggest that pancreatitis recurs in about 50% of patients with longer follow-up.<sup>88,89</sup> A recent prospective

**Table 1.** Results of the EPISOD Randomized Trial and the EPISOD 2 Observational Study

Study	Sphincter treatment	n	Pain relief,
			n (%)
EPISOD	None (sham)	73	27 (37)
	Any sphincterotomy	141	32 (23)
	Biliary sphincterotomy without PSH	43	8 (19)
	Biliary sphincterotomy with PSH	51	10 (20)
	Dual sphincterotomy with PSH	47	14 (30)
EPISOD 2	Biliary sphincterotomy	21	5 (24)
	Dual sphincterotomy	39	12 (31)
	None	12	2 (17)

EPISOD, Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction; PSH, pancreatic sphincter hypertension.

study showed a 50% recurrence rate in 2 years after sphincterotomy in patients with raised pressures.<sup>60</sup> This did show a 3.5 times greater likelihood of recurrent attacks in patients with elevated pressures without treatment. However, there was no additional benefit of dual (pancreatic and biliary) sphincterotomy over biliary sphincterotomy alone. Whether these reports mean that sphincterotomy is beneficial is difficult to interpret in the absence of controls.

It remains possible that the finding of sphincter abnormality in these patients is an epiphenomenon, the result of previous attacks, or due to an unexplained cause. The fact that many patients eventually develop features of chronic pancreatitis suggests that the underlying pathogenesis of the disease is not altered.

### Can Pancreatic Sphincter Dysfunction Cause Pain Without Pancreatitis?

Historically, it was proposed that SOD can cause pancreatic pain without definite evidence of pancreatitis and, indeed, a categorization of pancreatic SOD types similar to that used in suspected biliary SOD was suggested.<sup>28</sup> Pancreatic pressures higher than the accepted norm are found in many patients with unexplained pain (including those in the EPISOD study). Many such patients have undergone sphincterotomies, but proof of benefit is lacking.<sup>85</sup>

### Diagnosis and Criteria for Functional Pancreatic Sphincter Disorder

Given the uncertainty about the role of pancreatic SOD, efforts to provide useful guides to investigation and treatment are currently speculative. Pancreatic SOD may be considered in patients with documented acute recurrent pancreatitis, after a comprehensive review of known etiologies and search for structural abnormalities, and with elevated pancreatic pressures on manometry.

#### E2. Diagnostic Criteria for Pancreatic Sphincter of Oddi Disorder All of the following:

1. Documented recurrent episodes of pancreatitis (typical pain with amylase or lipase >3 times normal and/or imaging evidence of acute pancreatitis)
2. Other etiologies of pancreatitis excluded
3. Negative endoscopic ultrasound
4. Abnormal sphincter manometry

**Alternative diagnostic tests.** Measuring the size of the pancreatic duct by MRCP or EUS before and after an intravenous injection of secretin has been used to demonstrate sphincter dysfunction. One report suggests that the results do not correlate with sphincter manometry, but may predict the outcome of sphincterotomy in patients with otherwise unexplained pancreatitis.<sup>90</sup> This test deserves further assessment. Injection of Botulinum toxin into the

sphincter and temporary stenting have been used in this context, but have not been validated.<sup>91</sup>

### Treatment

Patients with recurrent acute pancreatitis that remains unexplained after detailed investigation should be reassured that the attacks may stop spontaneously and if they recur, they usually follow the same course and are rarely life threatening. They should be counseled to avoid factors that may precipitate attacks (eg, alcohol, opiates). While certain medications (such as antispasmodics and calcium channel blockers) are known to relax the sphincter, there have been no trials of their use.

In earlier days, cholecystectomy was often recommended after 2 unexplained attacks of pancreatitis, assuming that small stones or microlithiasis were responsible.<sup>92</sup> That approach seems less acceptable now that these are easier to exclude with modern imaging. Others have approached the problem of microlithiasis with biliary sphincterotomy, or treatment with ursodeoxycholic acid, but current data are unconvincing.

Pancreatic sphincterotomy would be the logical treatment if the sphincter dysfunction is indeed causative. Historically, complete division of the both sphincters was done by an open transduodenal approach. Case series of patients who have undergone this procedure have claimed resolution of episodic pancreatitis in the majority of patients.<sup>93,94</sup> The pancreatic sphincterotomies performed endoscopically are much smaller, and repeat manometry studies in patients with recurrent problems often show them to be incomplete.<sup>60,89</sup> Manometry has not been repeated in patients without recurrent symptoms, so it is not clear whether treatment has failed because of inadequacy of the sphincterotomy, or an incorrect diagnosis. Stenosis of the pancreatic orifice is not uncommon after pancreatic sphincterotomy, and repeat ERCP treatment rarely resolves the problem. Endoscopic biliary sphincterotomy is known to reduce pancreatic sphincter pressures in many cases, and the recent prospective trial showed no benefit of adding pancreatic sphincterotomy.<sup>60</sup>

At the present time, practitioners and patients should approach invasive treatments in this context with considerable caution, recognizing the short and long-term risks, and the marginal evidence for benefit. Additional stringent trials are required.

### Functional Pancreatic Sphincter Dysfunction and Chronic Pancreatitis

Elevated pancreatic sphincter pressure has been described in 50%–87% of patients with chronic pancreatitis of many etiologies.<sup>94,95</sup> Whether it plays a role in the pathogenesis or progression of chronic pancreatitis is not known. Endoscopic pancreatic sphincterotomy was reported to improve pain scores in short-term uncontrolled studies in 60%–65% of chronic pancreatitis patients with pancreatic SOD,<sup>95</sup> but long-term data are not available. The role of endoscopic treatment (in the absence of stones or strictures) remains unclear.



## Summary of Functional Pancreatic Sphincter Dysfunction

There is no proven role for ERCP with manometry in patients with suspected pancreatic pain without evidence for pancreatitis. Patients with a single episode of unexplained acute pancreatitis should not undertake the risks of ERCP because a second episode may never happen, or may be long delayed. Similarly, there is currently no clear role for treating SOD in patients with chronic pancreatitis. The optimal approach for patients with unexplained recurrent acute pancreatitis needs clarification by stringent studies with long follow-up. Currently, it appears reasonable to consider ERCP with sphincterotomy when manometry is abnormal. Biliary sphincterotomy alone appears as effective as dual sphincterotomy, and likely lowers the short and long-term risks. Patients should understand the significant risks and uncertain benefits.

## Conclusions

Our understanding of functional gall bladder and sphincter disorders is far from complete, and our current treatment recommendations are not firmly evidence-based. The need for more stringent prospective research is obvious.

## Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <http://dx.doi.org/10.1053/j.gastro.2016.02.033>.

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**Conflicts of interest**

The authors disclose no conflicts.

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