



Review Article

Update on Sphincter of Oddi Dysfunction: A Review



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Abstract

Sphincter of Oddi dysfunction (SOD) encompasses a spectrum of clinical syndromes that are not fully understood, and various diagnostic and therapeutic methods have had varying results depending on the type of dysfunction. This review explored various mechanisms that might play a role in SOD and methods of diagnosis and management. It is important to rule out other causes of abdominal pain with laboratory testing, imaging studies, and endoscopic procedures. Medications that affect sphincter motility should be identified as well. Manometry is the gold standard for diagnosis but it is not always required. For example, patients with type I SOD may have symptomatic improvement with sphincterotomy without need for a diagnostic manometry. Hepatobiliary scintigraphy and fatty meal sonography may also have diagnostic utility. Sphincterotomy is not always effective for symptomatic improvement in type II and III SOD. Alternate therapies with calcium channel blockers and botulinum toxin have been studied and might be considered as options after discussing the risks and benefits with the patients.

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Introduction

The pathophysiology of sphincter of Oddi dysfunction (SOD) is not fully understood, but has been categorized into different types, which helps guide clinicians on the most appropriate management. The purpose of this review was to explore the mechanisms that might play a role in SOD and the methods used for diagnosis and management.

SOD

SOD encompasses a spectrum of clinical syndromes involv-

ing an abnormality of the sphincter that causes an intermittent or fixed acalculous obstruction that impedes the free flow of bile or pancreatic juice. It is also referred to as biliary dyskinesia, but that only denotes a motility disorder and not an anatomical obstruction.¹ It presents with symptoms and signs of biliary and/or pancreatic disorder, typically including biliary-type pain.² Other signs and symptoms include elevated liver or pancreatic enzymes, common bile duct (CBD) or pancreatic duct dilatations, and recurrent pancreatitis.

The Milwaukee classification of SOD is based on symptoms, biochemical abnormalities and radiographic results, and is the widely adopted (Table 1).¹ Type I SOD is characterized by both abnormal chemistries and dilated biliary or pancreatic duct on imaging. Type II SOD has either abnormal biochemical markers or abnormal imaging, while type III SOD has neither. Up to 35% of patients with type I SOD have normal manometry. Manometry shows sphincter hypertension in 55–65% of patients. Type III patients have no objective findings of obstruction,¹ and pain is usually experienced by patients with all three types.

Epidemiology

The prevalence of SOD in the general population is around 1.5%,³ but in patients with idiopathic recurrent pancreatitis it is thought to be as high as 72%.⁴ SOD occurs in 1% of patients after cholecystectomy and in up to 23% of patients with post-cholecystectomy syndrome with elevated liver enzymes and biliary pain. This might be because of exposure of SOD after cholecystectomy, or because of the symptoms that led to cholecystectomy.³ It presents most commonly in women between 20 and 50 years of age.^{3,4} Around 10–20% of patients with cholecystectomy experience biliary colic, of which 9–51% meet the diagnostic criteria of SOD. The gallbladder acts as a backflow reservoir for bile and dampens sudden increases in SOD pressure. Patients with cholecystectomy have elevated basal sphincter of Oddi (SO) pressure, increased frequency of contractions, and retrograde phasic contractions.⁴ Risk factors for SOD include agenesis of gallbladder, preoperative cholelithiasis, lithotripsy, liver transplant, alcohol use, hypothyroidism, and irritable bowel syndrome (IBS).⁴

Clinical features

SOD commonly presents with intermittent or episodic epigastric or right upper quadrant pain that lasts from 30 m to several hours as per the ROME III criteria (Table 2).⁴ The pain is not necessarily postprandial, and may be accompanied by nausea and vomiting. Pancreatic SOD usually presents with more prolonged pain that may radiate

Keywords: Sphincter of Oddi; Sphincter of Oddi dysfunction; Common bile duct; Manometry; Sphincterotomy.

Abbreviations: BTX, botulinum toxin; CCK, cholecystokinin; ERCP, endoscopic retrograde cholangiopancreatography; FMS, fatty meal sonography; GTN, glyceryl trinitrate; HBS, hepatobiliary scintigraphy; MRCP, magnetic resonance cholangiopancreatography; SO, sphincter of Oddi; SOD, sphincter of Oddi dysfunction.

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Table 1. Milwaukee classification

SOD	Biliary pain	Biochemical abnormality and/or dilated biliary or pancreatic duct on imaging
Type I	Present	Both
Type II	Present	Either
Type III	Present	Neither

SOD, sphincter of Oddi dysfunction. Adapted from Wilcox *et al.*¹

to the back and be associated with recurrent episodes of pancreatitis.^{2,5} Unlike biliary SOD, pain commonly appears after meals. SOD can present with intermittent biliary colic, recurrent pancreatitis, abnormal liver function tests, and/or ductal dilatation.¹ It has also been implicated as a cause of post-cholecystectomy syndrome.

Pathogenesis

The underlying mechanism of SOD is not fully understood. The proposed causes include trauma from persisting passage of microlithiasis or crystals, increased pressure caused by a congenital hypertrophic sphincter, or increased/paradoxical response of smooth muscle to neuronal or hormonal stimuli that cause contraction. In other words, a dyskinetic or stenosed sphincter can cause the clinical syndrome because of functional or mechanical obstruction.⁵ Other proposed mechanisms include rapid contraction frequency, or excess retrograde contractions.⁶

Ponchon *et al.*⁷ studied patients in whom SOD was suspected after ruling out choledocholithiasis and bile duct strictures by endoscopic retrograde cholangiopancreatography (ERCP). They performed ampulla biopsies at least 10 days after endoscopic sphincterotomy in 69 of 75 patients. The remaining six patients were found to have gallstones. Biopsies of the ampullary region showed inflammation or fibrosis in 43% of the patients, and ampullary adenocarcinoma in 4.3%. The investigators mentioned that sampling bias was likely, as many patients had prior histories of difficulty in performing ERCP and were elderly. The study included many patients with mechanical obstruction, which means that the patients with presumed SOD were misdiagnosed and had underlying SO structural abnormalities because of fibrosis or carcinoma, causing manifestations similar to SOD. Even though they performed biopsies at a later time to allow tissue healing, they did not specify whether the symptoms resolved after sphincterotomy, or if there was a correlation with patients found to have abnormal biopsies. The presence of microlithiasis that could have caused inflammation of the ampulla in some patients was not ruled out. Furthermore, use of manometry would have been helpful to diagnose the patients with SOD.⁷

Rashdan *et al.*⁸ looked for crystals in the bile of 85 patients (81 with gallbladders) with type II and III SOD who

had no evidence of cholelithiasis on ultrasound. The patients had manometry with collection of bile for crystal analysis. Only 3.5% had bile microlithiasis, regardless of whether manometry found SOD or normal sphincter function. This study was overall well executed. The presence of crystals in the bile is a strong predictor of small stones in the gallbladder, but it has higher yield when obtained directly from gallbladder rather than the bile duct, which was possible in 23 out of the 81 patients.⁸ Quallich *et al.*⁹ found bile crystals in 5% of 68 patients who had prior cholecystectomy and biliary pain; two had normal SO pressure and one had elevated pressure. Both studies showed that regardless of whether patients had cholecystectomy, bile duct crystals or microlithiasis were seldom found in those with type II and III SOD.⁹ Those studies had larger samples than others in which the incidence of microlithiasis was higher, but the exclusion of SOD type I patients may have caused differing results.

Cholecystokinin (CCK) stimulates nonadrenergic and noncholinergic inhibitory nerves that act on SO to decrease resistance to flow. However, there is also a direct stimulatory effect of CCK on SO smooth muscle. An imbalance between CCK inhibition on SO and direct stimulation of smooth muscle may lead to inappropriate spasm of the SO.¹⁰ Luman *et al.*¹¹ performed manometry studies in five women 2–3 weeks before and 6 months after cholecystectomy to determine if there was a difference in SO function. The women were undergoing cholecystectomy for cholelithiasis, were not taking drugs affecting gastrointestinal motility, and choledocholithiasis was ruled out by ultrasound. They were sedated with midazolam, and the same operator performed all manometry studies. CCK injection pre-cholecystectomy consistently suppressed SO phasic activity. Even though mean basal pressures decreased, the changes were not statistically significant. Post-cholecystectomy, decrease in basal SO pressure was not significant, but there was a small effect on phasic contractions that was statistically significant.¹¹ The study suggested that there was a relationship between cholecystectomy and SO motility and a small depressive effect on SO phasic contractions after cholecystectomy. The study limitations included a small patient sample and that the pharmacological dose of CCK that was used might not accurately reflect the physiological activity of CCK. Rolny *et al.*¹² studied 62 patients with suspected biliary dyskinesia, performing manometry before and after injection of intravenous CCK or ceruletide. The patients were divided into three groups depending on baseline SO

Table 2. Rome III criteria

Biliary pain and any of the following:
Duration of 30 m or more
Recurrent episodes occurring at variable intervals, not daily
At least one episode in the past year
Pain that builds up to a steady level
Pain significant enough to affect daily life activity
No structural abnormality

Adapted from Afghani *et al.*⁴

pressure (i.e., whether normal or elevated) and response to hormonal injection. Group III included 10 patients with elevated baseline pressure who had a paradoxical increase in SO pressure after hormone injection. Group II included nine patients with elevated baseline pressure who experienced a decrease in SO pressure in response to hormone injection, although pressure only normalized in three patients. It is noteworthy that in all groups, the majority of patients had had cholecystectomy, raising the possibility of cholecystectomy being related to biliary dyskinesia. The investigators performed a workup that included biochemical tests, endoscopy and ERCP in all patients without an identifiable cause of right upper quadrant pain. However, because the study groups had different responses to hormone injection, other factors that were unaccounted for might have had a role in biliary dyskinesia. The time since cholecystectomy, use of medications affecting SO motility, and the dose of CCK or ceruletide could have been some of the factors.¹²

Evans *et al.*¹³ performed manometry with CCK provocation in 42 patients with post-cholecystectomy syndrome in whom blood work, imaging, colonoscopy, and ERCP had ruled out other causes of pain. Patients were classified as SOD type I, II, or III by objective findings. The investigators measured SO pressure, contractile frequency, direction of propagation, and response to CCK with manometry. Subsequent small bowel manometry found that disturbances of duodeno-jejunal motor activity were more pronounced in SOD I/II compared with SOD type III patients. Differences in small bowel motility in patients with normal SO manometry and in healthy controls were not significant. The investigators were blinded to clinical and manometry criteria. Drugs known to affect gastrointestinal motility were stopped at least 48 h prior to small bowel manometry, making the results credible. The authors showed that there was an association between small bowel dysmotility and SOD type I/II, but a causal relationship is difficult to prove.¹³ Evans *et al.*¹⁴ did not find differences in SO basal pressure between patients with post-cholecystectomy syndrome with and those without IBS. However, abnormal responses to CCK infusion with failure of complete inhibition of phasic contractions were more frequent ($p=0.01$) in IBS patients. The study suggested that SOD type I/II was associated with intestinal dysmotility. As with other previous studies, it was well executed, but the nature of the relationship between IBS and abnormal responses of SO to CCK remained unexplained. The fact that the patients had cholecystectomies raises the question of whether it had caused changes in the neural and hormonal reflexes in the gut and gallbladder. Nonetheless, it remains unclear why some patients developed SOD and some did not. Knowing the interval between cholecystectomy and the start of IBS symptoms would be useful to determine whether bowel and SO dysmotility were present before cholecystectomy. A study performing manometry in patients with IBS and intact gallbladder compared with IBS with cholecystectomy would be valuable to determine whether there is an independent association between IBS and SOD.¹⁴ Normally, intraductal pressure is normal with contraction of the SO because the biliary system decompresses by draining bile into the gallbladder.¹⁵ Theoretically, decompression is no longer present following cholecystectomy, and was thought to be the cause of SOD in post-cholecystectomy patients. However, SOD also occurs in patients with intact gallbladders indicating that another mechanism must be involved.¹⁶

Diagnostic evaluation

If SOD is suspected, structural abnormalities and malignancies must be ruled out by imaging such as endoscopic

ultrasound, abdominal ultrasound, computed tomography or magnetic resonance cholangiopancreatography (MRCP). Biopsy of the ampulla should be considered as well to rule out ampullary tumors.³ The diagnosis is usually confirmed by manometry of sphincter.²

Manometry

Manometry is the gold standard for the diagnosis of SOD, although results vary with patient and operator experience. Medications such as hyoscyamine, midazolam, calcium channel blockers, anticholinergics, cholinergics, nitrates, and opioids can also affect the results, and should not be used prior to procedures. Elevated sphincter pressures can confirm a presumptive diagnosis of SOD.¹⁵ SOD is defined by manometry as a basal biliary or pancreatic sphincter pressure of >40 mmHg, which is greater than three standard deviations above average pressure.¹ Other criteria that have been used are increased phasic wave frequency, or tachyoddia >8/min, an increase of >50% in the number of retrograde propagations of SO phasic contractions, and a paradoxical response to CCK.¹⁷ Manometry is not without risk, as post-procedure pancreatitis has been reported. Also, the test is nonconfirmatory in 13–40% of patients with SOD type I.⁴ Other noninvasive tests such as provocation with cholecystokinin or secretin in combination with an imaging study have been reported to provide information regarding dilated bile or pancreatic ducts.⁵

Hepatobiliary scintigraphy

Hepatobiliary scintigraphy (HBS) uses a radionuclide tracer to quantify biliary flow with aid of CCK intravenous infusion and measuring duodenal appearance time (DAT), and hepatic hilum to duodenum transit time (HDTT). It is a viable option in patients with prior cholecystectomy. Sostre *et al.*¹⁵ studied 26 patients with cholecystectomy, comparing manometry and ERCP with scintigraphy using CCK injection (interpreted visually). Two independent observers interpreted and scored the images based on six parameters. The scores indicated that 12 patients had SOD, seven of whom had elevated basal pressure, three had normal pressure and a paradoxical response to CCK, and two had CBD dilatation and delayed contrast emptying on ERCP. Fourteen had no radiologic evidence of SOD, and all had normal SO pressure during manometry. There was no overlap between SOD patients and controls, and sensitivity and specificity were found to be 100%.¹⁵ The finding seems reliable because the observers were blinded to clinical findings, and patients had manometry performed within 48h of scintigraphy study for comparison. In addition, patients received CCK infusion to stimulate bile flow in order to reduce false positives because of low flow rates. However, these results have not been replicated in other studies, which might be due to use of their subjective scoring system and low disease prevalence. Even though there was no inter-observer variability among their two interpreters, this does not exclude the possibility of variability among others.

Craig *et al.*¹⁸ studied 32 post-cholecystectomy patients with biliary pain. They compared scintigraphy with CCK infusion by the Sostre score, which includes six parameters, HDTT, and DAT. Eight of 29 patients had elevated basal pressure on manometry and five had evidence of dyskinesia. The Sostre score, HDTT and DAT were higher in patients with elevated basal pressure but the difference was not statistically significant and there was no correlation between basal pressure and HDTT or DAT. There was also no association between SOD types II and III and Sostre score

or DAT. Ultimately, the study revealed poor sensitivity and specificity of scintigraphy.¹⁸ The divergent results compared with the Sostre report could have been caused by different protocols for CCK infusion, scintigraphy imaging methods, and observer variability.

A study by Thomas *et al.*¹⁹ compared scintigraphy with and without morphine provocation in patients with SOD. Eighteen of 34 patients had elevated basal pressures. Initial scintigraphy without morphine showed no significant difference in time to maximal activity or percentage excretion at 45–60 m between patients with normal and elevated basal pressure. However, after morphine administration, the median percentage excretion at 60 m was 4.8% in those with elevated pressure and 28.2% in those with normal pressure.¹⁹ Morphine use increased the sensitivity and specificity for detecting elevated SO pressure. The use of morphine provocation in scintigraphy might help with diagnosis and guidance in regards to therapy.

Fatty meal sonography

Fatty meal sonography (FMS) depends on increased bile flow induced by CCK after a fatty meal. With obstruction of bile flow, there should be an increase in the diameter of the CBD compared with baseline. Rosenblatt *et al.*²⁰ compared manometry with FMS and HBS for diagnosis of SOD in 304 patients post-cholecystectomy. FMS was considered positive if there was an increase in the diameter of the CBD of >2 mm 45 m after fatty meal ingestion. All patients underwent HBS with a radiologist and FMS with a different radiologist, followed by manometry by a gastroenterologist who was blinded to the imaging results. Of the 304 patients, 73 had basal pressures ≥ 40 mmHg by manometry and were diagnosed with SOD. Eighty-six had abnormal HBS and only 22 had abnormal FMS, which means that 58 patients had false negative results with FMS. The sensitivity and specificity of FMS were 21% and 97%, respectively. Even with the combination of HBS and FMS, the sensitivity and specificity for diagnosis of SOD were 53% and 77%, respectively.²⁰ Having one radiologist read the FMS images, another interpret the HBS results, and the gastroenterologist who performed manometry blinded to the radiology results, made the study convincing. It showed that FMS, HBS or a combination of both was less sensitive and specific for the diagnosis of SOD compared with manometry. Patients with both abnormal FMS and HBS might be predictive of response to sphincterotomy, but further information is needed regarding which patients had both abnormal HBS and FMS in order to determine the clinical utility or need for future studies. SOD type I patients are known to respond well to sphincterotomy, and further investigation with FMS or HBS may not add significant information. FMS also has limited use in SOD type II and III patients. Type I patients have objective findings of biliary obstruction, making them less of a diagnostic problem than the other types. FMS is also operator dependent, which may cause variable results.³

Therapeutic measures

Medical treatment

Calcium channel blockers such as nifedipine and nicardipine have been used to cause smooth muscle relaxation. In a study by Khuroo *et al.*,²¹ 28 patients with elevated SO basal pressure without abnormal phasic wave contractions or tachyoddia on manometry were given nifedipine or placebo over 12 weeks. They were later switched to the other

therapy for the next 12 weeks. Patients kept diaries of pain levels, and visits to the emergency department because of biliary pain were monitored. Compared with patients on placebo, patients on nifedipine had significant decrease in the number of pain episodes, emergency visits, and the use of analgesics. Twenty-one patients had improved pain and seven did not. There were no significant between-group differences in the tolerated nifedipine dose, but patients who improved had predominantly antegrade propagation of phasic contractions, whereas patients who did not improve had predominantly retrograde contractions. Laboratory tests, FMS, SO pressure, and CBD pressure were not predictive of responsiveness to treatment. Eight patients had repeat ERCP and manometry after completion. Nifedipine decreased basal and phasic pressures, but did not have an effect on the sequence of phasic contractions.²¹ Even though the results suggested that nifedipine was effective, they were based on perception and tolerance toward pain intensity, and were highly subjective.

A short-term double-blind cross-over study by Sand *et al.*²² followed 13 SOD type II patients with cholecystectomy for 16 weeks. The patients kept logs of pain and need for analgesics or antispasmodics. They took nifedipine or placebo for 8 weeks and then switched to the other study treatment. There was a significant reduction in days with pain while taking nifedipine 10 mg three times a day compared with placebo, as well as a decrease in use of pain medications. Liver function tests performed every 4 weeks did not change in patients with abnormal values.²² The results seem convincing as other causes of pain had been excluded by endoscopy, ERCP, abdominal ultrasound, oral lactose tolerance test, duodenal biopsy and biochemical tests. Even though the study lasted 16 weeks, the patients were given the option of continuing the medication. At a median of 22 months of follow-up, eight patients were still taking the medication satisfactorily. However, there was no mention of whether pain had improved or resolved and how much pain medication was being used at that time. Interestingly, patients with rapid clearance of isotope in ≤ 15 m on quantitative cholescintigrams had a significantly greater decrease in days with pain and use of pain medication. Therefore, cholescintigraphy may be useful in predicting response to nifedipine. Given the lack of significant differences in blood pressure or headaches, nifedipine seemed to reduce pain effectively and safely in the patients.

A pilot study by Craig *et al.*²³ randomized patients with SOD type II or III in a double-blind fashion to either nifedipine 30–60 mg daily or placebo for 6 months. They found no benefit compared with placebo, and in addition reported significant side effects requiring discontinuation of medication. A downside of the study was the small sample of five patients, with one withdrawal after 5 days because of unilateral calf swelling and another withdrawal at 1 month because of nonadherence. The authors mentioned that there was no long-term benefit of nifedipine because of side effects, but the time of appearance of the side effects was not reported. Therefore, conclusions on whether the side effects were associated with prolonged use of the medication cannot be reliably drawn. Furthermore, they did not specify the doses the patients were taking and whether increased doses were associated with more side effects. The findings may have differed from previous studies because of the use of higher doses of medication and the inclusion of type III SOD patients.

The efficacy of nitrates has been proven in small studies. Staritz *et al.*²⁴ studied 17 patients who underwent ERCP and manometry. Nine received 1–2 mg sublingual glyceryl trinitrate (GTN) with manometry performed before and after administration, and the patients were compared with eight controls. There was no between-group difference in baseline SO pressure. In the group that received therapy, there

was no difference in frequency of contractions but, there was a significant difference in amplitude of contractions. In the control group, there were no differences in the frequency or amplitude of contractions.²⁴ The study showed that SO pressure did decrease with use of GTN. However, there was no mention of whether the patients were symptomatic with biliary pain and whether GTN had long-term effects in symptom management. Clinical trials in patients with SOD would be needed to assess the side effects and long-term efficacy of nitrates. Other drugs such as octreotide, E1 analogues like alprostadil, and protease inhibitors like gabexate mesilate have been shown to have an effect on SO pressure, but their clinical utility is yet to be explored.

Endoscopic therapy

Patients with SOD type I generally respond well to endoscopic intervention. Around 60–94% of SOD type II patients have had improvement following a biliary sphincterotomy. However, the clinical response ranged from 8–62% in type III SOB.¹ Rolny *et al.*²⁵ studied 17 patients with type I SOD and previous cholecystectomies who underwent surgical or endoscopic sphincterotomy because of biliary pain. Only six had normal SO pressure, but all had relief of symptoms with sphincterotomy. Microlithiasis and ampullary tumors were ruled out in all patients by analysis of bile and biopsies. LFTs improved in all but one patient who had diabetes. Two patients experienced restenosis with reappearance of symptoms, and repeat sphincterotomy improved symptoms again.²⁵ The study showed that type I SOD responded to sphincterotomy regardless of SO pressure. However, the authors did not determine whether there were other abnormalities in patients with normal pressure, such as retrograde contractions or tachyoddia, that could have improved with sphincterotomy. Similarly, Sugawa *et al.*²⁶ performed a study in eight patients with type I SOD, all of whom had improvement of symptoms with sphincterotomy. None were evaluated by manometry. Even though the study was small, the results seem convincing because choledocholithiasis, ampullary tumors, and other causes of obstruction were ruled out by ERCP. Furthermore, patients were followed for a median of 26 months, and all were asymptomatic, except for one who required re-intervention for restenosis and remained asymptomatic at the 5-month follow-up. There is a possibility of placebo effect in the study.

Geenen *et al.*²⁷ assigned 47 post-cholecystectomy patients with type II SOD to either endoscopic sphincterotomy or a sham procedure in a double-blind randomized study. They excluded patients with type I or III SOD and those who had an identifiable cause of biliary pain on prior ERCP. Twenty-three patients with abnormal basal SO pressures were compared with 24 patients with normal pressures. In patients with normal pressure, four of 12 had improvement of symptoms after the sham procedure and four of 12 had improvement after sphincterotomy. In other words, in patients with normal SO basal pressure, pain scores were similar regardless of treatment. Of those with elevated SO basal pressure, three of 12 improved after the sham procedure, and 10 of 11 improved after sphincterotomy and remained asymptomatic at the 1-year follow-up. Seven of nine patients with an elevated SO pressure that did not improve with the sham procedure underwent sphincterotomy at 1-year and had symptomatic improvement at the 4-year follow-up. Similarly, five of eight patients with normal SO pressures and sham procedures had sphincterotomy after 1 year, and only two experienced symptomatic improvement at their 4-year follow-up. Objective findings such as CBD diameter, positive morphine-prostigmin provocation or biochemical tests, were not predictive of responsiveness to the

procedure.²⁷ Overall findings are credible given the methodology used, exclusion of patients who were found to have a specific cause of biliary pain (including papillary tumor, bile duct obstruction, and choledocholithiasis), and the long follow-up period of 4 years. Additionally, at the 1-year follow-up, repeat measurement of pressures in patients who had sham procedure were reproducible. This strengthens the belief that those with initial normal SO pressures had accurate measurements, and as shown in the study, were less likely to improve after sphincterotomy.

In the EPISOD trial, Cotton *et al.*²⁸ studied SOD type II and III patients to determine whether endoscopic sphincterotomy reduced pain and whether pressures assessed by manometry were predictive of pain relief. This sham-controlled, randomized, double-blind clinical trial studied 214 patients with post-cholecystectomy pain not responsive to acid-suppressing agents or antispasmodics. The subjects had normal upper endoscopy, normal abdominal imaging with a CBD ≤ 9 mm, and normal or slightly elevated liver function tests for the previous 6 months, without prior history of sphincter intervention or anatomical variations. They were randomized in a 2:1 ratio to sphincterotomy or a sham procedure. From the procedure group, they were then randomized to obtain either biliary sphincterotomy alone or combined biliary and pancreatic sphincterotomy.²⁸ A successful primary outcome was based upon days of lost productivity for pain measured by a score obtained by a health survey (RAPID). Many patients from the different groups reported decreased disability as a result of pain, and sphincterotomy was not more effective than the sham procedure.²⁸ The study was well executed and excluded patients with other identifiable sources of pain including psychiatric and functional gastrointestinal disorders. The authors included specific cutoffs for biochemical values, and likely included type II and III SOD patients, but there was no indication of whether one group predominated. Contrary to the prior studies, sphincterotomy was not more effective compared with the sham procedure, but that could have been caused by more patients with SOD type III than included previously. The percentages of patients with abnormal manometry in patients with sphincterotomy and with the sham procedure were similar, it was therefore not predictive of improvement in the pain score.

Toouli *et al.*²⁹ studied 81 patients with biliary-type pain after cholecystectomy with dilated CBD and/or biochemical abnormalities. They all underwent SO manometry and were then assigned to sphincterotomy or a sham procedure. Eleven of 13 patients with SO stenosis had symptomatic improvement after sphincterotomy compared with five of 13 with the sham procedure. However, in patients with SO dyskinesia, there were no differences between patients who had sphincterotomy versus the sham procedure.²⁹ The findings seem reliable as they excluded patients with structural abnormalities or symptoms of recurrent pancreatitis, and patients were followed regularly for 2 years with a clinician who was blind to their procedure. Evaluation of symptoms was subjective and variation could have affected the results, but patients who improved after 6 months continued to show improvement at 24 months and the opposite occurred with patients who did not show improvement, which made the results more convincing. They also measured SO pressure, frequency of phasic contractions, incidence of retrograde contractions, and paradoxical response to CCK-octapeptide to differentiate SO stenosis and dyskinesia. One of the downsides was that there was no mention of whether patients could have been taking medications that affect SO motility.

Botulinum toxin injection

Wehrmann *et al.*³⁰ studied 21 patients with cholecystecto-

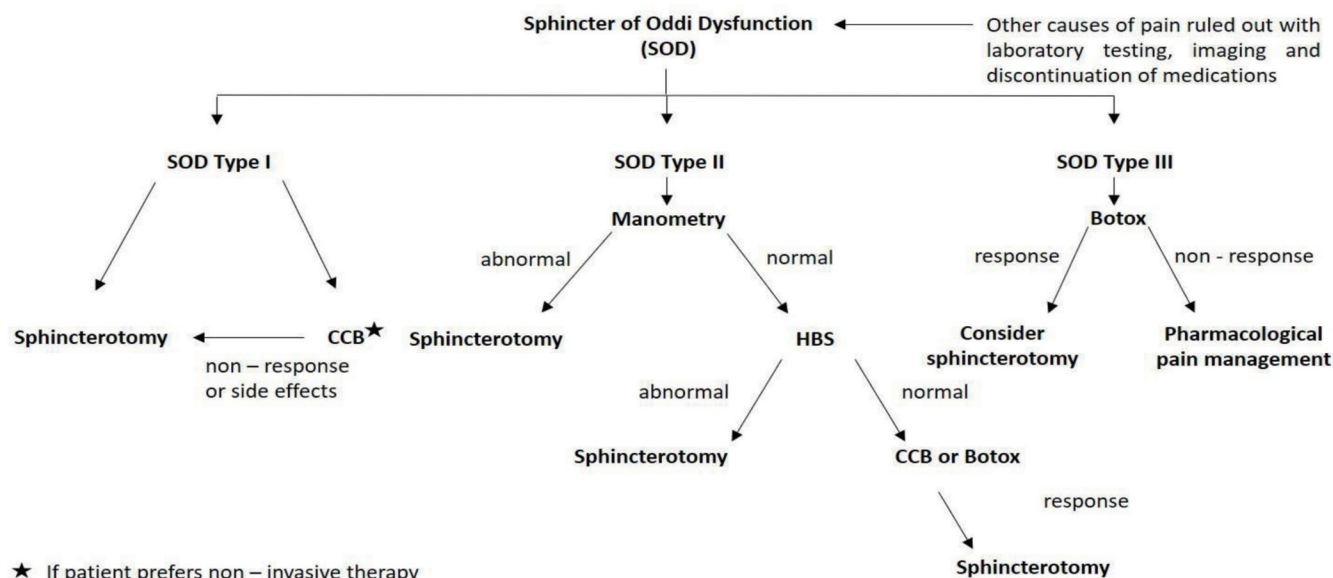


Fig. 1. Proposed algorithm for SOD management. Botox, botulinum toxin; CCB, calcium channel blocker; HBS, hepatobiliary scintigraphy. Adapted from Bistriz et al.³

my and type III SOD confirmed by manometry (SO pressure >40 mmHg) who received a single injection of 100 mouse units of botulinum toxin (BTX) in the papilla of Vater. Symptomatic response was evaluated 6 weeks later. Twelve patients (11 of whom had elevated SO basal pressure) were asymptomatic after BTX injection, and ten remained symptomatic. Of 10 symptomatic patients, five with normal baseline SO pressures did not benefit from subsequent sphincterotomy, and two with elevated SO pressures had symptomatic relief following the procedure. Eleven of 12 patients who improved after BTX injection had a recurrence of symptoms after a median period of 6 months and further benefited from sphincterotomy. All of them had elevated SO pressures.³⁰ The study showed that BTX injection had short-term symptomatic benefits in patients with elevated SO pressure, as seen with its other uses as well. Findings are convincing as they ruled out organic or functional gastrointestinal disorders with ultrasonography, endoscopic studies, esophageal manometry, pH measurement, lactose intolerance test, and others. Of the 10 patients who did not respond to injection, five still had elevated basal SO pressure as seen before. It is hard to determine whether they failed to therapy or there was operator variability, as there was no mention of whether more than one person performed the procedure. They found that BTX had no effect on amplitude, duration or frequency of contractions, which could have explained why some patients with elevated SO pressure failed to improve with injection and sphincterotomy, assuming they might have had SO dyskinesia as well.

Conclusions

Patients with suspected SOD should have other causes of abdominal pain ruled out by laboratory testing, imaging studies such as MRCP and ultrasound, and endoscopic procedure. Ampullary biopsy to rule out tumors and testing bile for microlithiasis should be considered, even though prior studies indicate that the incidence is not high.

Manometry remains the gold standard, at least for diagnosing SOD type I. In addition, measuring the frequency and direction of phasic contractions, together with the re-

sponse to CCK injection might increase the sensitivity of diagnosis. All medications should be carefully reviewed to identify those that could alter SO motility. HBS is a viable option in patients with prior cholecystectomy, depending on availability at the center. Its usefulness in diagnosing type II and III SOD still remains in question, and it might not be superior to manometry. However, combination with morphine provocation might increase its sensitivity and specificity. The value of FMS for diagnosis of type II and II SOD is also uncertain, and its low sensitivity remains one of its greatest limitations.

It seems that management is highly dependent on the type of SOD and whether the sphincter is stenosed or dyskinetic (Fig. 1).³ Nifedipine can be useful in patients with elevated SO pressure, but its usefulness for patients with tachyoddia or retrograde phasic contractions has not been proven. It might be an option for patients who do not wish to subject themselves to invasive procedures, but close monitoring for side effects would be judicious. Patients with SOD type I can have symptomatic improvement with sphincterotomy without the need for manometry. However, the effectiveness of sphincterotomy in SOD type II is not fully understood, and might be successful if there is proven elevated basal SO pressure.

Some authors do not accept SOD type III as a definitive entity, but rather a functional disorder that may or may not be associated with the SO.³¹ The approach to management of these patients is variable and dependent on the clinician. Response to BTX injection might be predictive of responsiveness to sphincterotomy. It may be associated with risk comparable to sphincterotomy, such as acute pancreatitis, but given that sphincterotomy has had inconsistent results in SOD type III, it might be worthwhile as an initial treatment. Drugs that target visceral pain pathways such as serotonin norepinephrine reuptake inhibitors (SSRIs), might have potential for managing these patients in the future.^{31,32}

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Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. JVK has no conflict of interest related to this publication.

Author contributions

JVK wrote the manuscript and prepared the figure, GYW proposed writing the review and critically revised the manuscript.

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