

## Sphincter of Oddi dysfunction Type III: New studies suggest new approaches are needed

C Mel Wilcox

C Mel Wilcox, Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, Basil I Hirschowitz Endoscopic Center of Excellence, Birmingham, AL 35294-0113, United States

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**Correspondence to:** C Mel Wilcox, MD, MSPH, Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, Basil I Hirschowitz Endoscopic Center of Excellence, 1720 2<sup>nd</sup> Ave., South BDB 380, Birmingham, AL 35294-0113, United States. [melw@uab.edu](mailto:melw@uab.edu)

Telephone: +1-205-9754958

Fax: +1-205-9348493

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any these objective findings. Many prior studies have shown that the clinical response to endoscopic therapy is higher based upon the presence of these objective criteria. However, there has been variable correlation of the manometry findings to outcome after endoscopic therapy. Nevertheless, manometry and sphincterotomy has been recommended for Type III patients given the overall response rate of 33%, although the reported response rates are highly variable. However, all of the prior data was non-blinded and non-randomized with variable follow-up. The evaluating predictors in SOD study - a prospective randomized blinded sham controlled one year outcome study showed no correlation between manometric findings and outcome after sphincterotomy. Furthermore, patients receiving sham therapy had a statistically significantly better outcome than those undergoing biliary or dual sphincterotomy. This study calls into question the whole concept of SOD Type III and, based upon prior physiologic studies, one can suggest that SOD Type III likely represents a right upper quadrant functional abdominal pain syndrome and should be treated as such.

**Key words:** Abdominal pain; Sphincter of Oddi dysfunction; Manometry; Sphincterotomy

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**Core tip:** Prior observations suggest that biliary sphincterotomy may be of benefit in patients with sphincter of Oddi dysfunction (SOD) Type III who have biliary type pain but no objective findings of bile duct obstruction. The prospective randomized blinded sham controlled trial termed evaluating predictors in SOD demonstrated no correlation between manometry and outcome and furthermore showed that patients receiving sham therapy had a better outcome than those receiving either biliary or dual sphincterotomy. Until other studies are available, patients with biliary type pain in the absence of objective findings

### Abstract

Sphincter of Oddi dysfunction (SOD) has been classified into three types based upon the presence or absence of objective findings including liver test abnormalities and bile duct dilatation. Type III is the most controversial and is classified as biliary type pain in the absence of

should not routinely undergo endoscopic retrograde cholangiopancreatography and do not benefit from sphincterotomy.

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## INTRODUCTION

It has been almost 130 years since the muscular structure at the terminal end of the biliary and pancreatic ducts was first described by a young anatomist and physiologist Rugero Oddi<sup>[1]</sup>. His subsequent studies demonstrated that this sphincter muscle was under physiologic regulation. While bile duct pressures had been previously reported, it was not until 1980 that Geenen *et al*<sup>[2]</sup> described the use of a small catheter placed through the biliary sphincter into the bile duct at the time of endoscopic retrograde cholangiopancreatography (ERCP) whereby sphincter activity could be identified, measured and where its physiologic regulation was confirmed. At that time, they<sup>[2]</sup> and others<sup>[3]</sup> had postulated that perhaps disorders of the sphincter could result in clinical syndromes such as post-cholecystectomy abdominal pain.

## DEFINITION

Sphincter of Oddi dysfunction (SOD) has been defined as an abnormality of either the biliary and/or pancreatic sphincter causing intermittent or fixed obstruction to flow of bile or pancreatic juice, respectively, associated with episodic biliary-type pain, recurrent pancreatitis, abnormal liver chemistry tests, or ductal dilatation. The ROME III criteria defined biliary SOD as epigastric or right upper quadrant pain which included all of the following: episodes of pain lasting at least 30 min, symptoms occurring at different intervals but not on a daily basis; the pain was constant in nature and was of severity enough to alter or interrupt the patient's daily activities or lead to an emergency department visit; the pain was not relieved by postural changes, bowel movements, or antacid therapy; and finally that the exclusion of other structural pancreaticobiliary diseases were excluded<sup>[4]</sup>. In contrast to the prior criteria, noninvasive methods were used to measure common bile duct diameter and contrast drainage times were not required. Manometrically, SOD is defined as a basal biliary or pancreatic sphincter pressure of > 40 mmHg which is greater than 3 standard deviations above normal<sup>[5]</sup>. Since the seminal observations of Geenen *et al*<sup>[2]</sup>, many studies worldwide have reported

on the use of both biliary and pancreatic manometry in symptomatic patients. In addition, a positive outcome of endoscopic therapy (sphincterotomy) has been reported for the treatment of abdominal pain or idiopathic pancreatitis of patients identified with SOD<sup>[6-11]</sup>. Indeed, SOD became a common place diagnosis for referral of patients to selected centers with biliary-type pain or idiopathic pancreatitis for sphincter manometry in the hopes of making the diagnosis and providing effective therapy. The results of the EPISOD (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction) study<sup>[12]</sup> have now challenged the diagnosis of the most complex of these sphincter "disorders", SOD Type III.

## SOD TYPES

In 1987, these clinical syndromes all of which have in common biliary-type pain were classified into one of three types, often termed the Milwaukee classification<sup>[13]</sup>. Such a classification scheme takes into account the presence of objective findings (abnormal liver chemistry tests, ductal dilation) and based upon subsequent studies, such a classification system could help determine the likelihood of a positive manometric study thereby guiding therapy. As shown in Table 1, biliary Type I SOD is defined as a dilated bile duct and abnormal liver tests. It was considered that these patients either have small stones, sludge, or true stenosis of the biliary sphincter leading to obstruction; some data suggests crystals are rare<sup>[14]</sup>. Nevertheless, even with these objective findings, biliary manometry can be normal in up to 35% of these Type I patients<sup>[15]</sup>. Type II patients have abnormal liver tests or biliary dilatation but not both potentially suggesting a sphincter disorder. In these patients manometric findings of sphincter hypertension can be found in up to 55%-65%<sup>[16-18]</sup>. Silverman *et al*<sup>[19]</sup> suggested a hybrid classification for type II patients where these patients had pain and marginal (< 1.5 × ULN) elevation of liver enzymes with normal duct diameter<sup>[1]</sup>. They found no difference in prevalence of elevated sphincter pressures between the hybrid group and standard classification. Type III patients have no objective findings of biliary obstruction and manometric findings of sphincter hypertension are less frequent, but were reported to be 59% in one study<sup>[17]</sup>. A similar classification scheme has also been proposed for those with pancreatic abnormalities<sup>[18]</sup>.

## ROLE OF MANOMETRY

While considered the gold standard, manometry is an imprecise technique and it is important that the number of normal patients evaluated has been small<sup>[5,20]</sup>. Manometric findings can be influenced by a number of both patient and technical factors<sup>[6,21,22]</sup>. Use of a guidewire through the catheter may alter pressure recordings. Likewise, if the catheter is up against the

**Table 1 Classification of sphincter of Oddi dysfunction**

	Abnormal liver or pancreatic chemistries	Biliary or pancreatic duct dilation on imaging
Type I	Both	Both
Type II	Either	Either
Type III	Neither	Neither

**Table 2 Randomised controlled trials of Type II sphincter of Oddi dysfunction n (%)**

	Geenen ('89)	Toouli (2000)
Rome type 3	-	-
Concealed assignment	?	+
Blinded f/u	Yes	Yes
Type I	0	0
Type II	47 (100)	81 (100)
Type III	0	0
Sham EBS	Yes	Yes
Mano Directed	No	Yes
Response		
+ mano (EBS vs S)	91%, 25%	85%, 38%
- Mano (EBS vs S)	33%, 42%	62%, 42%

F/U: Follow-up; EBS: Endoscopic biliary sphincterotomy; mano: Manometry; S: Sham.

bile duct wall, readings may be artificially elevated. The readings can also be influenced by where the baseline sphincter zone is interpreted to be located. Other factors include medications taken as well as those administered at the time of ERCP. One cannot use anti-motility agents such as hyoscyamine as the pressure may be reduced. Chronic opioid use can increase basal sphincter pressure; midazolam has been found to alter sphincter pressure whereas diazepam does not. Lastly, reproducibility may be an important issue. For example, in one study of over 5000 patients<sup>[23]</sup> a small group of patients ( $n = 30$ ) in whom manometry was initially normal underwent repeat manometry. In these patients, 60% now had an abnormal tracing. From the original cohort, 80% were found to be positive on the initial study. If one then adds the number of patients in whom the study was positive initially, and then assumes 60% of all patients with an initially negative study would be positive, then this would suggest that up to 93% of patients from this cohort could have an initially positive manometry study. Such a high percentage is incredibly hard to believe.

## OUTCOME AFTER SPHINCTEROTOMY

The correlation between SOD classification and clinical outcome after biliary sphincterotomy has been widely studied. Overall, a wealth of literature has suggested the efficacy of biliary sphincterotomy for sphincter of Oddi dysfunction<sup>[7]</sup>. For patients with types II and III SOD, there is a variable correlation between manometry findings and clinical outcomes after sphincterotomy<sup>[22,24]</sup>. Patients with SOD Type II have

shown improvement following biliary sphincterotomy in approximately 69% of patients, ranging from 60%-94%<sup>[7]</sup>. In contrast, for patients with biliary Type III SOD, the clinical response is less ranging from 8%-62%<sup>[7]</sup>. The Indiana group has suggested that sphincterotomy of both the biliary and pancreatic sphincters (dual sphincterotomy) may further increase response<sup>[25]</sup>.

It should be cautioned, however, that these positive studies were from selected centers, retrospective and non-blinded. We know from the pain literature that when pain is the primary outcome measure, non-blinding is a significant shortcoming<sup>[26,27]</sup>. We also appreciate that the placebo effect is strong in patients with pain and are well documented after interventions including endoscopic therapies<sup>[28]</sup>. For example, there have been numerous interventional trials in many disciplines where uncontrolled studies suggested efficacy, but when randomized blinded sham procedure trials were performed, no differences were found<sup>[29]</sup>.

Prior to EPISOD, there were two prospective randomized studies which evaluated the role of biliary manometry and outcome after sphincterotomy, but these were limited to patients with SOD Type II (see Table 2).

## PROSPECTIVE STUDIES IN TYPE II SOD

Geenen *et al*<sup>[30]</sup> randomized 47 patients with post-cholecystectomy abdominal pain and meeting criteria for sphincter of Oddi Type II to either biliary sphincterotomy or sham biliary sphincterotomy. Prior to sphincterotomy, biliary manometry was performed in all patients although the results of manometry were not used to decide on therapy. Sphincterotomy resulted in improvement in pain scores at the one year follow-up in 10 of 11 patients in whom elevated biliary sphincter pressures were found. Conversely, only 3 of 12 patients with elevated basal sphincter pressure undergoing a sham procedure had improvement. In patients with normal sphincter pressure, no difference in outcome was observed whether sphincterotomy was performed. Thus, overall 17 of 18 patients with SOD documented manometrically benefitted clinically from biliary sphincterotomy.

Toouli *et al*<sup>[31]</sup> performed biliary manometry in 81 patients with SOD Type II. The manometric findings were categorized as either sphincter of Oddi stenosis (elevated basal sphincter pressure > 40 mmHg), dyskinesia or normal. Following manometry, in contrast to the Geenen study<sup>[30]</sup>, patients were randomized based upon the manometric findings to either biliary sphincterotomy or sham. Patients were followed up to 24 mo by an independent observer and manometry was repeated to assess the effect of sphincterotomy. Of the cohort, 32% had evidence of sphincter hypertension. Of these, 85% improved after sphincterotomy as compared to 38% after sham which was statistically significant. In contrast, patients

in whom dyskinesia was diagnosed, approximately 50% in the sham group as compared to 36% in the sphincterotomy group had symptomatic improvement. For those with normal biliary manometry, 42% in the sham group compared to 61% in the sphincterotomy group had improvement but both of these were statistically not significant. Several observations can be made from this study. Firstly, overall, the number of patients with SOD in Type II patients was relatively low. Secondly, it appeared that patients in whom SOD was confirmed had a better symptomatic improvement compared to sham, but this was not seen in those with normal manometry or with dyskinesia. Of note, there was a high response rate in those with a normal manometry approaching 50%.

Given the high rates of documented abnormal manometry, favorable clinical outcomes and the fact that manometry is not widely available, several groups have studied empiric biliary sphincterotomy and outcome<sup>[11,32]</sup>. Such a practice was also adopted in a number of community settings. Results similar to the larger studies have been reported. These studies suggest that perhaps manometry may not be needed given the high response rate and as shown in some studies the lack of correlation between manometric findings and outcome after endoscopic therapy.

## EPISOD

With that as a background, the EPISOD trial was conducted<sup>[12]</sup>. From initial planning to execution took approximately a decade<sup>[33]</sup>. Patients enrolled were ages 18-65 years who had significant post-cholecystectomy biliary type pain without evidence of prior pancreatitis or prior intervention of the biliary and/or pancreatic sphincter. Patients with a bile duct larger than 9 mm or were on daily narcotics were excluded as were those with significant psychological comorbidity. A number of questionnaires were also administered evaluating the burden of pain as well as psychological parameters. Overall, 214 patients underwent ERCP with manometry of both the biliary and pancreatic sphincter. Patients were then randomized in a 2 to 1 fashion irrespective of the results of manometry to sphincterotomy or to sham. Those in whom sphincterotomy was planned and who also had elevated pancreatic sphincter pressures were also randomized again to either biliary sphincterotomy alone or dual sphincterotomy. All patients received temporary pancreatic stents including the sham patients. The primary outcome measure was defined as a reduction in their pain score at 9 and 12 mo using the recurrent abdominal pain intensity and disability (RAPID) scale, without any sphincter reintervention and also without any additional use of narcotics. The RAPID scale assesses recurrent abdominal pain intensity and its effect on disability. It is a 90 d summary evaluation of the number of days where various daily activities were reduced because of episodes of abdominal pain. The instrument itself is

quite similar to one used for headache related disability from migraines. The RAPID score was validated by study in two distinct groups of patients totaling over 100 patients<sup>[34]</sup>.

The results were remarkable. The success rate for the sham-treated patients was in fact higher than those receiving endoscopic therapy. Thirty-seven percent of the sham treated patients were reported as a success as compared to only 23% in those receiving biliary sphincterotomy. Overall, 30% of those who received dual sphincterotomy responded clinically as compared to 19% for those undergoing biliary sphincterotomy alone which was not statistically significant. Overall, reinterventions occurred in 26% of treated and 34% of the control patients. As in many other studies, there was no correlation with the results of sphincter manometry and outcome. Likewise, 31% receiving dual sphincterotomy improved compared to 27% for biliary and 17% for sham had no improvement; these findings were not statistically significant. A group of patients who declined the randomization were also observed following sphincterotomy directed by the findings at manometry and the final results were similar. The data was analyzed in a number of ways using less stringent criteria for outcome and the results were unchanged.

Even if manometry is imperfect but some patients respond to therapy, why not still perform manometry or empiric biliary sphincterotomy on Type III patients? The primary reason to avoid ERCP and manometry is the risk of pancreatitis as these patients have the highest risk for pancreatitis<sup>[35]</sup>. In addition, even when performed in expert hands such as by the investigators in EPISOD, the rate of pancreatitis despite use of pancreatic stents was 12% and in this group, 2 patients had a perforation and surgery was required in one; there were no deaths.

While not perfect, the EPISOD trial is the best study we have regarding efficacy- or lack thereof- for interventions in type III SOD. The study has been criticized for the use of a new scoring system termed the RAPID system which had not been used previously but does measure the burden of intermittent pain. Approximately 1/3 of the patients had irritable bowel syndrome which could be a confounder. However, we recognize that many patients with SOD have other GI complaints. Regardless, given the quality of the study with the caveats as noted, the results really call into question whether SOD Type III is even a disease.

If not the sphincter, then what is the cause of pain? Even in patients who report a response, pain is often still present suggesting that other causes must be considered<sup>[36]</sup>. Significant psychological comorbidity has been identified in these patients and could be a major contributor to or cause of pain. Indeed, a number of studies have suggested psychosomatic disorders, central sensitization, and even potentially visceral hyperalgesia<sup>[37-40]</sup>. As is common in many patients with functional gastrointestinal disorders, prior

sexual abuse, or other abuse, has been found<sup>[41]</sup>. Such psychological comorbidity is important to appreciate given the potential role for medical therapy as has been shown for other functional GI disorders<sup>[42]</sup>.

## OTHER MECHANISMS OF PAIN

An important physiologic study performed a decade ago suggests potential mechanisms for right upper quadrant or "biliary type" pain in SOD type III<sup>[40]</sup>. These investigators studied 11 patients with post-cholecystectomy abdominal pain as well as ten controls with balloon distention studies of both the duodenum and rectum to evaluate this visceral pain perception. Psychological testing was also performed. They found that in patients referred with SOD Type III, duodenal but not rectal hyperalgesia was shown as compared to controls. Furthermore, duodenal distention reproduced symptoms in all but one of the patients. Psychological testing showed high levels of somatization, depression, obsessive compulsive behavior, as well as anxiety. These provocative findings thus suggest that patients with SOD Type III may have a functional abdominal pain syndrome related to visceral hypersensitivity.

## ROLE OF MEDICAL THERAPY

A variety of medical therapies have been tried some of which have shown efficacy in uncontrolled studies<sup>[32,43]</sup>. Smooth muscle relaxers such as nitrates and nifedipine have been used with moderate success. Antidepressant medications like amitriptyline have been used most commonly and should be titrated to effect. When using such medical therapies, response rates similar to sphincterotomy have been reported from retrospective uncontrolled studies<sup>[32,43]</sup>. A novel therapy includes injection of botulinum toxin into the sphincter<sup>[44]</sup>. This could perhaps result in sphincter relaxation and in one study such a clinical response predicted a response to sphincterotomy. Nevertheless, given the results of the EPISOD study, the findings of any uncontrolled non-blinded study should be questioned. Thus, given the results of EPISOD, medications should be given and we typically would use antispasmodics - (hyoscyamine) for those in whom the abdominal pain has a crampy component. In addition, we use low dose antidepressants such as amitriptyline especially for those with chronic almost constant pain. Although not discussed, the use of psychological counseling may be appropriate as well given the frequent psychiatric issues in patients with functional abdominal pain.

## CONCLUSION

Based upon EPISOD, at this juncture, sphincter of Oddi Type III likely does not exist as a true pancreaticobiliary disease and these patients should be categorized as having functional abdominal pain<sup>[45]</sup> rather than a true pancreaticobiliary disorder<sup>[4]</sup>. Also, given the

findings of EPISOD, the current classification system for SOD requires a reevaluation. When faced with such patients, medication trials and reassurance would be important in the Type III patient. ERCP should be avoided given the low yield<sup>[46]</sup> and high potential for pancreatitis<sup>[35,47]</sup>. In such patients, EUS also has a relatively low yield<sup>[48]</sup>. For those in whom abnormal liver tests reproducibly occur during pain or in whom bile duct dilation is present (Type II SOD), empiric biliary sphincterotomy may be appropriate taking into account the risk of pancreatitis, and measures to prevent post-ERCP pancreatitis must be followed<sup>[35,49]</sup>. Such an empirical approach to the Type II patient may be cost effective<sup>[50]</sup>. Patients with abnormal liver tests and a dilated bile duct (Type I) should undergo biliary sphincterotomy and manometry is not needed. Further work is necessary to better define other mechanisms for pain, the ideal methods to identify psychological issues which may require specific treatment, and to identify novel therapies for abdominal pain syndromes.

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