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REVIEW ARTICLE

# The diagnosis and management of Sphincter of Oddi dysfunction: a systematic review

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**Abstract**
*Objectives* Sphincter of Oddi dysfunction (SOD) is a benign pathological syndrome. The clinical manifestations may be a consequence of an anatomical stenosis or sphincter dysmotility. Manometry is invasive and has an associated morbidity. Non-invasive investigations have been evaluated to ameliorate risk but have unknown efficacy. The review aims to critically appraise current evidence for the diagnosis and management of SOD.
*Methods* A systematic review of articles containing relevant search terms was performed.
*Results* Manometry is the current gold standard in selecting which patients are likely to benefit from endoscopic sphincterotomy (ES). It can, however, be misleading. Several non-invasive investigations were identified. These have poor sensitivities and specificities compared to manometry. There is a paucity of data examining the investigation's specific ability to select patients for ES. Outcomes of ES for Type I SOD are favourable irrespective of manometry. Types II and III SOD may respond to an initial trial of medical therapy. Manometry may predict response to ES in Type II SOD, but not in Type III.
*Conclusions* Non-invasive investigations currently lack sufficient sensitivities and specificities for routine use in diagnosing SOD. Type I SOD should be treated with ES without manometry. Manometry may be useful for Type II SOD. However, whilst data is lacking a therapeutic trial of Botox$^{TM}$ or trial stenting may bean alternative. Careful and thorough patient counselling is essential. Type III SOD is associated with high complications from manometry and poor outcomes from ES. Alternative diagnoses should be thoroughly sought and its management should be medical.

**Keywords** Sphincter of Oddi · SOD · Dysfunction · Review

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## Introduction

Sphincter of Oddi dysfunction (SOD) is the term used to describe the spectrum of motility disorders of the Sphincter of Oddi (SO) encompassing both stenosis and dyskinesia [1]. SOD is estimated to affect 13 % of patients with right upper quadrant pain after cholecystectomy and it is in these patients that most data have been published. It is also thought to affect 0.9 % of patients with an in situ gallbladder [2].

The typical clinical manifestations of SOD are characterised by ongoing biliary-type pain following a cholecystectomy. The differential diagnosis for SOD is summarised in Table 1. The pain has been described using the Rome III criteria for functional gastrointestinal disorders with the characteristics of pain episodes lasting longer than 30 min, building to a steady level and which is severe enough to disrupt daily activities or lead to an emergency department visit [1]. The pain is not relieved by defecation, change in position or acid suppression and no other structural abnormalities can explain the pain. There is a paucity of findings on clinical examination. Biochemical abnormalities include transient increases in liver enzymes or amylase during episodes of pain. Dilatation of the biliary tract or pancreatic duct may also be present. It is using these abnormalities that the Milwaukee classification has been used to describe SOD (Table 2) [3]. The usefulness of the classification has been

**Table 1** Differential diagnosis for SOD

| Differential diagnosis |
|---|
| Gastroparesis |
| Musculoskeletal: fibromyalgia, costrochondritis, trigger points |
| Peptic ulcer disease/reflux |
| Irritable bowel syndrome (visceral hypersensitivity) |
| Cholelithiasis |
| Pancreatitis |
| Coronary artery disease |

the topic of many reviews that call for a revised or modified method with the advent of newer diagnostic and treatment modalities [4].

Currently an abnormally high basal sphincter pressure identified during manometry is the gold standard for SOD diagnosis. However, manometry is invasive and carries a significant risk of pancreatitis [5]. The purpose of manometry is as an aid to predict which patients will benefit from endoscopic sphincterotomy (ES). Numerous less invasive diagnostic methods have been described in the literature but few have been widely adopted. The aims of this study were to critically appraise the available evidence for the diagnosis and management of SOD.

## Methods

A Medline literature search was undertaken using keywords 'sphincter of oddi dysfunction', 'post-cholecystectomy syndrome, 'sphincter of oddi manometry', 'hepatobiliary scintigraphy', 'morphine-prostigmin provocative test', 'magnetic resonance cholangiopancreatography after secretin stimulation', 'Milwaukee classification' and 'endoscopic sphincterotomy'.

Inclusion criteria were any fully published study relating to the diagnosis and management of SOD. Search limits were English language and human studies between 1946 and February week two 2012. All articles retrieved had the references cross-checked to ensure capture of cited pertinent articles.

In total, 86 studies were identified from the Medline search. Twelve were discounted as they were review articles and 23 were excluded as they were irrelevant. Therefore 51 manuscripts were examined and included in this review.

**Table 2** Milwaukee classification

| Criteria |
|---|
| (A) Typical biliary-pain |
| (B) Elevated liver function tests (×2 normal) on 2 or more occasions |
| (C) Delayed drainage of contrast medium at ERCP (>45 min) |
| (D) Dilated common bile duct diameter of >12 mm |
| Classification |
| Type I: Patients corresponding to all 4 criteria (A + B + C + D) |
| Type II: Patients corresponding to A plus 1 or more of B, C, or D |
| Type III: Patients corresponding to A only |

## Results

### Diagnostic methods

Numerous non-invasive methods have been described in the literature to diagnose SOD and predict response to sphincterotomy in an attempt to reduce the morbidity associated with manometry.

*Nardi test (morphine-prostigmin provocative test)* The tests aim to reproduce symptoms and cause increases in hepatic and pancreatic enzymes by stimulating the SO. Five studies were included that investigated this test (Table 3) [6–10]. Three articles found that the test lacked sufficient specificity to be useful [6, 7, 9]. Elevations in enzymes were observed in normal volunteers and the test was poorly reproducible in 50 % [6].

One study found a pathological test result in 83 % and 43 % of patients with an increased or normal SO pressure respectively [8]. A favourable outcome after sphincterotomy was observed in 79 % of patients with a pathological test result. Another study found the test as a screening tool to be useful in combination with manometry for evaluating the sphincter mechanism [10].

*Ultrasound after secretory stimulation* The test aims to trigger symptoms or cause a dilatation of the pancreatic or biliary duct sonographicaly detectable under secretory pressure (induced by a lipid-rich meal, secretin or cholecystokinin). Six studies were identified that investigated this (Table 3) [11–16]. Sensitivity and specificity ranged from 21–88 % and 82–100 %, respectively. This lack of sensitivity correlated with the study by Warshaw et al. that demonstrated a good result of sphincterotomy in 29 % of patients with a negative test [16]. Rosenblatt et al. however demonstrated that 87 % ($n$=13) of patients with an abnormal test had symptomatic improvement after sphincterotomy [15]. Although the test is not invasive, it has been criticised, as the biliary ducts are not visible in up to 45 % of patients due to overlying bowel gas [17].

*Secretin stimulated magnetic resonance cholangiopancreatography (ss-MRCP)* MRCP has largely replaced ERCP in clinical practice for detailing biliary anatomy due to its non-

**Table 3** Non-invasive diagnostic modalities

| Author | Year | Studies conclusion |
|---|---|---|
| Nardi test (morphine-prostigmin provocative test) | | |
| Bozkurt et al. | 1996 | A pathological test result was seen in 83 % and 43 % of patients with increased and normal SO pressures, respectively |
| Madura et al. | 1981 | Nardi remained abnormal in 17.1 % following ES. Nardi test useful in combination with manometry |
| Lobo et al. | 2007 | Lack of sensitivity. ES significantly obtunds the enzymatic and nociceptive responses to the Nardi test in 50 % of patients with SOD |
| Steinberg et al. | 1980 | Poor test. Reproducible in only 50 % |
| Toouli et al. | 2000 | Symptomatic outcome of ES independent of Nardi test result |
| Ultrasound after secretory stimulation | | |
| Catalano et al. | 1997 | Predicts only 57 % of manometry+patients |
| Cavallino et al. | 1994 | Reliability 77-91.5 % |
| Darweesh et al. | 1988 | Sensitivity 67 % (improved to 80 % in combination with HBS), pecificity 100 % |
| DiFrancesco et al. | 1999 | Sensitivity 88 %, specificity 82 % |
| Rosenblatt et al. | 2001 | Sensitivity 21 %, specificity 97 % |
| Warshaw et al. | 1985 | Sensitivity 76 %, specificity 86 % |
| Secretin stimulated magnetic resonance cholangiopancreatography (ss-MRCP) | | |
| Gillams et al. | 2007 | No significant difference between normal volunteers and SOD patients |
| Pereira et al. | 2007 | Sensitivity 37 %, specificity 85 % (type II and III SOD). Sensitivity 62.5 %, specificity 85 % (type II). Diagnostic accuracy was 73 % and 46 % for Types II and III, respectively |
| Testoni et al. | 2008 | Sensitivity 57.1 %, specificity 100 % |

*SO* sphincter of Oddi, *ES* endoscopic sphincterotomy, *SOD* sphincter of Oddi dysfunction, *HBS* hepatobiliary scintigraphy

invasive nature and equivalent diagnostic accuracy. Much like ultrasonography following secretin stimulation ss-MRCP aims to study the biliary ducts after the stimulated increases of secretory pressure. Three studies were identified that utilized ss-MRCP in the diagnosis of SOD (Table 3) [18–20]. One study showed no difference in ss-MRCP results in SOD from normal volunteers [18]. It was not specified to what classification the SOD patients were in. A study by Testoni et al. investigating 37 patients with an intact gallbladder presenting with idiopathic pancreatitis found sensitivities and specificities of 57.1 % and 100 %, respectively [19].

In another article, the diagnostic accuracy of ss-MRCP was demonstrated at 73 % and 46 % in Milwaukee Type II and III categories, respectively, with a global sensitivity and specificity of 37 % and 85 %, respectively [20]. The authors concluded that the test was useful in selecting patients with Type II, but not Type III, disease who would be suitable for sphincterotomy. The study has been criticised, as the 95 % confidence intervals for the positive predictor value were 54–97 % making interpretation of the test 'little better than a coin toss' [21].

*Hepatobiliary scintigraphy (HBS)* HBS assesses bile flow through the biliary tract. It is this test that had attracted the most attention as an alternative to manometry. The criteria used to define an abnormal study varies to include the time to peak, the half time of excretion, the duodenal appearance time (DAT) and the hilum to duodenum transit time (HDTT) making results heterogenous. DAT and HDTT are most widely used [22]. Sostre et al. incorporated six variables to create a scoring system to enhance the tests accuracy and described sensitivities and specificities of 100 % when compared to manometry [23]. The SOD type was not stated in the cohort of patients investigated. Pineau et al. however, using cholecystokinin-stimulated HBS and the scoring system described by Sostre et al. in asymptomatic volunteers, found the specificity to be only 60 % [24].

The results of studies investigating HBS are shown in Table 4 together with Milwaukee classification type. Unfortunately long-term outcomes as per classification are not described making conclusions difficult to reach. HBS appears highly sensitive and specific in Type I disease, where investigation is frequently not necessary, and less so in Type II and III disease. Studies assessing HBS frequently only compared it with manometry and hence there is no way of evaluating whether HBS independently might select patients who are likely to respond to sphincterotomy.

Roberts et al. investigated 17 patients with suspected SOD [25]. Nine of these had Type III disease. The group has abandoned manometry, as they encountered post ERCP pancreatitis in 75 %, in favour of morphine stimulated HBS.

**Table 4** Outcomes of HBS

| Author | Year | *n* | Comparison | Result |
|---|---|---|---|---|
| Bertalon et al. | 2006 | 28 | Manometry | Specificity to exclude disease correctly 92 %; sensitivity for Type I 100 %, Type II and III 50 % |
| Cicala et al. | 2002 | 22 | Manometry and ES outcomes | Abnormal results of HBS matched manometry in 100 % and 64 % of Type I and II, respectively |
| Corazziani et al. | 1994 | 12 (11 controls) | Manometry | Specificity 100 %, Sensitivity 83 % in Type I disease |
| Craig et al. | 2003 | 32 | Manometry | Sensitivity 25-88 %, Specificity 86–89 % in Type II and III disease |
| Darweesh et al. | 1988 | 28 (22 controls) | Manometry | Sensitivity 67 %, Specificity 85 %. Type N/S |
| Drane et al. | 1990 | 10 (31 controls) | Manometry | Type, sensitivity and specificity N/S. HBS and manometry matched in 70 % |
| Farup et al. | | 5 | 'Traditional methods' | Sensitivity 100 % in Type II and I. Specificity N/S |
| Fullarton et al. | 1988 | 10 (20 controls) | Manometry | Abnormal compared to controls. Sensitivity/specificity N/S |
| Grimon et al. | 1991 | 20 (18 controls) | Normal controls | Abnormal results compared to controls. Type N/S |
| Madacsy et al. | 2000 | 20 (20 controls) | Manometry | Sensitivity and specificity 100 %. Type N/S |
| Madacsy et al. | 1993 | 22 (9 controls) | Normal controls | Permits differentiation between stenosis and functional observation |

*N/S* not specified

The HBS was positive in 11 patients who underwent sphincterotomy of which 10 patients had an improvement in symptoms. Another study by Cicala et al. compared both HBS and manometry to outcomes after sphincterotomy in Type I and II disease [26]. Whilst HBS was not as sensitive as manometry in Type II disease it successfully predicted outcomes of sphincterotomy in 93 % of patients compared to 57 % by manometry.

*Manometry* Manometry is seen as the gold standard in diagnosing SOD and predicting a favourable response to sphincterotomy. The techniques of manometry together with the important findings are summarised in Table 5. Table 6 shows the outcomes of studies investigating the results of sphincterotomy where manometry is abnormal. Some authors do not advocate manometry in Type I SOD citing high rates of improvement with sphincterotomy regardless of manometry findings. It may be misleading as normal manometry was encountered in 15–65 % of patients with Type I SOD [27–29]. On multivariate analysis suspected SOD has been shown to be an independent risk factor for pancreatitis post ERCP [30].

*Endoscopic ultrasound (EUS)* EUS is useful for detecting microlithiasis and for assessing ampullary morphology [31]. It is better than trans-abdominal ultrasound for diagnosing

**Table 5** Sphincter of Oddi manometry

| | |
|---|---|
| Technique | |
| The manometry catheter is passed through the working channel of the duodenoscope during ERCP. | |
| A baseline duodenal pressure is measured before cannulation. | |
| The manometry catheter is advanced into the desired duct (biliary or pancreatic) either directly or over a guidewire. | |
| The ductal pressure is measured after cannulation with the manometry catheter. | |
| The catheter is then withdrawn from the duct at 1–2 mm intervals, pausing for 60–90 s when the transducer reaches the sphincter.[a] | |
| Location within the region of the sphincter is recognised by an increase in pressure and is visually aided by the circumferential markers on the catheter. | |
| Measurements | |
| Basal sphincter pressure is the mean pressure reading from 3 pull-throughs. | A basal sphincter pressure of >40 mmHg is the manometric criterion used to diagnose SOD. |
| Manometric tracings are also assessed for evidence of SO dyskinesia. | Rapid phasic wave frequency (>7 phasic waves/min). Also called tachyoddia. |
| | Excessive retrograde phasic wave propagation (>50 % of phasic waves). |
| | High amplitude phasic waves (>300 mm Hg). |

*ERCP* endoscopic retrograde cholangiopancreatogram, *SO* sphincter of Oddi, *SOD* sphincter of Oddi dysfunction

[a] The technique for pull-through may vary depending on the type of catheter used

the cause of biliary obstruction [32]. As the procedure requires specialist equipment and an experienced physician it may not be as widely available as other imaging modalities. Whilst EUS may be as accurate as MRCP in diagnosing the cause of extrahepatic biliary obstruction [33], it is an invasive test and in our opinion of little value in the diagnosis and management of SOD. It may however have a role in assessing patients for an alternative diagnosis to SOD (Table 1).

## Management

*Medical therapy* Medical therapy aims to reduce the resistance of the SO. In theory, pharmaceutical agents would be expected to have more of a role in SO dyskinesia compared to stenosis. Nifedipine, phosphodiesterase type-5 inhibitors, hyoscine butylbromide, octreotide and nitrates have been shown to reduce basal sphincter pressures in SOD and asymptomatic volunteers during 'acute' manometry [22, 34–37]. None of these drugs are specific to the SO and therefore systemic side effects and tachyphylaxis may limit the long-term use of these agents.

Long-term outcomes from regular medical therapy are frequently lacking. A prospective case series by Vitton et al. investigating efficacy of trimebutine and/or a nitrate derivative demonstrated that 50.8 % improved with therapy. Both agents were tolerated by 71.1 % of patients [37]. Complete or partial symptomatic relief per Milwaukee classification was 45 %, 67 % and 71 % for Type I, II and III, respectively. The study was not blinded and therefore placebo effect cannot be excluded.

Other small double-blind, placebo-controlled crossover studies have demonstrated reduced pain severity without cardiovascular side effects with nifedipine in highly selected patients [35, 38]. Symptoms were found to recur after cessation of therapy. The outcomes are not reported per manometry findings and therefore conclusions as to which groups of patients may benefit the most are unknown. Other small studies have demonstrated conflicting results and therefore further placebo-controlled trials are needed [39]. Transcutaneous electrical nerve stimulation and hepatobiliary system specific electroacupuncture applied at acupoint GB 34 has also been shown to reduce SO pressures [40, 41]. Its long-term role in managing SOD has not however been investigated.

*Botulinum toxin (Botox) injection* The use of Botox, a potent inhibitor of acetylcholine release, has been described in several disorders of the gastrointestinal tract such as achalasia and anal fissures. In a case report by Pasricha et al. in two patients with SOD, Botox injection into the SO resulted in a 50 % reduction in basal sphincter pressure [42]. This was sustained for 4 months. Despite these objective findings, neither patient reported sustained improvement in pain even after subsequent ES. The Milwaukee SOD type was not specified.

The only reported case series investigating Botox injection in Type III SOD demonstrated that it could predict those patients likely to gain improvement of symptoms with ES in 92 % of patients ($n=12$, $p<0.01$) [43]. No complications from the use of Botox have been reported.

*Stent trial* There is scanty evidence investigating the use of a short-term stent before ES to predict the outcome of sphincterotomy. Rolny et al. investigated 23 patients with Types II and III SOD and demonstrated that those patients who were symptoms free for at least 12 weeks after trial stenting could predict a favourable outcome to ES [44]. No complications such as pancreatitis were encountered as a result of stent placement.

Another small study has shown similar findings in suspected SOD likely to gain benefit from ES [45]. The group investigated 21 patients in whom a 7 Fr biliary stent was inserted for Type II and III SOD. Rates of pancreatitis following stenting exceeded 38 % however. Severe pancreatitis was seen in 14 %. The reasons for such discrepancy in complications from the study by Rolny et al. have not been examined. It is known that the nature of the patient and activity of the sphincter (in particular, sphincter hypertension) is relevant to post procedure pancreatitis. All of the patients reported by Rolny and Goff had suspected SOD but most had normal manometry but it is not stated if this was restricted to the biliary orifice. Further evaluation of a stent trial is needed.

*Sphinterotomy* Sphincter ablation is usually performed by the endoscopic route. Surgical sphincterotomy is usually reserved when endoscopic therapy is not available or for restenosis after endoscopic intervention. The outcomes of 18 studies reporting efficacy of sphincterotomy are shown in Table 6 [3, 7, 8, 26, 28, 34, 37, 46–53]. Follow-up ranged from a mean 3 months to 3.1 years. Patient numbers ranged from 5 to 237 and included patients with all Milwaukee types of SOD. One paper did not specify the SOD Type as per Milwaukee [47]. Two articles reported results of sham sphincterotomy [3, 7]. Frequently outcomes were not reported per Milwaukee type.

Favourable outcomes are highest in Type I SOD and less so with Types II and III. In patients treated with endoscopic sphincterotomy (ES), complications, where reported, occurred in up to 60 % of patients and included pancreatitis, haemorrhage and iatrogenic visceral perforation. Acute pancreatitis was more common in Type III SOD.

Techniques to reduce the risk of post-procedural pancreatitis have also been described. There are studies demonstrating that pancreatitis following ES may be significantly reduced with a pancreatic stent [54, 55]. In addition, a sham

**Table 6** Outcomes of endoscopic sphincterotomy (ES)

| Author | Year | Design | *n* | Milwaukee type | Intervention | F/U | Outcome (% improved) | Complications |
|---|---|---|---|---|---|---|---|---|
| Farup et al. | 1989 | Prospective | 5 | I and II | N/S | >3 m | 100 % | 60 % (*n*=3); x1 perf, x1 haem, x1 AP |
| Cicala et al. | 2002 | Prospective | 14 | I and II | N/S | 10–13 m | 93 % (*n*=13) | N/S |
| Neoptolemus et al. | 1988 | Prospective | 30 | N/S | B-ES | Median 46 m (10–88) | 63.3 % (*n*=19) | 27 % (*n*=8); ×3 haem, ×4 AP, ×2 perf, ×1 AC |
| Botoman et al. | 1994 | Retrospective | 43 | II (21) and III (2), all man + | N/S | Mean 3.1 years | Type II 68 %; Type III 56 % | Type II 16 % (AP); Type III 15 % (AP) |
| Bozkurt et al. | 1996 | Prospective | 23 | II and III, all man + | N/S | Mean 19 m (8–62) | 83 % | 22 % (*n*=5); ×1 haem, ×4 AP |
| Fullarton et al. | 1992 | Prospective | 10 | II, all man + | B-ES | Median 24 m (12–48) | 80 % (*n*=8) | N/S |
| Geenen et al. | 1989 | Prospective | 47 (24 sham) | II | B-ES | 12 m | 65 % (15); man+91 %; man −42 % | 4 % (*n*=2), AP |
| Kalaitzakis et al. | 2010 | Prospective | 23 | I, II and III. No man performed | B-ES | 15 m (6–35) | 61 % (*n*=14); ecurrence in 64 % | 18 % (*n*=9); ×8 AP, ×1 perf |
| Lin et al. | 1998 | Retrospective | 24 | II, no man performed | B-ES | 18 m | 79 % (*n*=19) | 8 % (*n*=2); ×2 AP |
| Rolny et al. | 1993 | Prospective | 17 | I, normal manometry in 35 % | N/S | 28 m (3–46) | 100 % | 20 % (*n*=3); ×2 haem, ×1 AP |
| Sugawa et al. | 2001 | Retrospective | 8 | I, no man performed | N/S | Mean 26 m | 100 % | 0 % |
| Toouli et al. | 2000 | Prospective | 37 (42 sham) | I (9) and II (72) | B-ES | 24 m | 85 % (*n*=11) man +; 50 % (*n*=12) man − | 9 % (*n*=7) AP |
| Vittan et al. | 2007 | Prospective | 14 | I (4), II (9), III (1) | B-ES, D-ES | 12 m | 86 % (*n*=12) | 14 % (*n*=2) AP |
| Wehrman et al. | 1996 | Prospective | 37 | II (22), III (15), all man + | D-ES | 30 m (6–59) | Type II 60 % (*n*=13); Type III 8 % (*n*=1) | 15 % AP; haem ×4 |
| Freeman et al. | 2007 | Prospective | 121 | I (15 %), II (44 %), III (41 %), all man + | B-ES | 26 m (6–46) | Type I 83.3 %; Type II 69.8 %; Type III 62 % | 18.5 % (*n*=22); ×1 perf, ×18 AP |
| Wehrmann | 2011 | Prospective | 37 | I and II | B-ES, P-ES, D-ES | 2 years | 86 % (32/37) | N/S |
| Heeton et al. | 2011 | Retrospective | 72 | I, II and III. No man performed | B-ES | 18 m | Type I 90.5 %; Type II 75 %; Type III 50 % | None reported |
| Gong et al. | 2011 | Retrospective | 237 | I, II and III | B-ES, P-ES, D-ES | 0.5–7 years | Biliary type 94.8 % (202/213); pancreatic type 76.9 % (10/13); double duct type 63.6 % (7/11) | N/S |

*Man* + manometry positive, *man* − manometry negative, *N/S* not specified, *B-ES* biliary endoscopic sphincterotomy, *P-ES* pancreatic endoscopic sphincterotomy, *D-ES* dual endoscopic sphincterotomy, *perf* perforation, *haem* haemorrhage, *AP* acute pancreatitis, *AC* acute cholangitis

controlled study by Gorelick et al. investigating Botox injection at the time of ES demonstrated a trend towards reduced post-procedural pancreatitis in the Botox group [56].

Long-term outcomes per Milwaukee type

*Type I SOD* This represents a stenosis of the SO and consistently good outcomes are encountered with ES. Improvement was observed in 83.3–100 % of patients with Type I SOD after ES. Frequently manometry was not performed.

*Type II SOD* This represents a functional sphincter disturbance. Table 7 demonstrates the long-term outcomes in patients with Type II disease. ES results in long-term symptom relief in up to 79 % of patients. In the study by Geenen et al., improvement of symptoms in Type II patients with abnormal manometry was observed in 10/11 who had ES compared to 3/12 who had the sham procedure [3]. In those with normal manometry pain scores were similar regardless of intervention. ES was shown to be superior to sham sphincterotomy in Type II SOD ($p<0.0001$, Fisher's exact test). The only other published randomised trial incorporating the sham sphincterotomy was by Toouli et al. investigating outcomes in 81 SOD patients [7]. Data were not separable for the Type I and II groups.

*Type III* Table 6 demonstrates the long-term outcomes in Type III SOD. Five articles report results in which the Type III cohort is described separately. ES was carried out in 18 patients with abnormal manometry and resulted in improved symptomology in 0 to 56 %. The only controlled data in Type III patients (not shown in Table 6) is an abstract by Sherman et al. who demonstrated that ES was not superior to sham sphincterotomy in producing favourable outcomes ($p=0.21$, Fisher's exact test) [57].

ES results in poor long-term outcomes regardless of manometry results. Even with abnormal manometry sustained symptom relief is only found in 8 % [52]. Without ES, patients frequently improve with conservative management. Alternative diagnoses are often made including oesophageal dysmotility/gastroparesis and psychiatric conditions [48].

Freeman et al. performed multivariate analysis to predict response to ES [53]. The group found gastroparesis, daily narcotic use and age less than 40 to be poor predictors of response. Medical therapy was found to resolve or improve symptoms in 57–72 % of patients diagnosed with Type III SOD.

**Table 7** Long-term outcomes in Type III SOD

| Author | *n* | Outcomes |
|---|---|---|
| Botoman et al. | 38 | 55 % had abnormal manometry, 37.5 % ($n=9$) improved after ES. $n=16$ improved without intervention |
| Freeman et al. | 50 | 62 % improved without intervention |
| Kalaitzakas et al. | 21 | 76 % improved with medical treatment. $n=1$ had ES and did not improve |
| Vittan et al. | 14 | 72 % responded to medical treatment. $n=1$ had ES and did not improve |
| Wehrman et al. | 29 | 50 % with abnormal manometry had ES. At 2.5 years follow-up, 8 % had sustained improvement |

*ES* endoscopic sphincterotomy

## Discussion

The aims of the review were to appraise the current evidence for the diagnosis and management of SOD. The review demonstrates that investigations and management must vary depending on the clinical presentation and Milwaukee classification. Consistently favourable outcomes are seen with ES in Type I disease and investigations including manometry are unnecessary, misleading and have an associated morbidity.

The difficulties in diagnosis and management in particular comes with Types II and III SOD. Non-invasive investigations have not yet been proven to have the sensitivities and specificities of manometry. Conclusions however are difficult to make when studies compare abnormal investigation outcomes to manometry and not outcomes of ES. It can be demonstrated that manometry itself, despite being the gold standard, is poor at predicting success of ES especially in Type III SOD where sustained improvement may be seen in only 8 % after ES [52]. The added value of manometry when compared to a clinical assessment such as the Milwaukee classification is open to question. Therefore any novel non-invasive investigation when compared to manometry, already a possible poor measure, will demonstrate disparate results. Likewise, comparing investigational results to outcomes of a procedure that may not be necessary (i.e. ES in Type III SOD) will also be flawed.

Strategies of the investigation and management of Type II SOD is probably the most difficult and controversial area. Placebo controlled randomised trials are lacking. A trial of medical therapy seems appropriate if the side effects are tolerated and may result in a significant number of patients becoming symptom free. Evidence is low level but trimebutine and/or a nitrate derivative appear well tolerated and may result in 67 % of patients sustaining symptom relief [34].

Although further studies are warranted, Botox may serve as a therapeutic trial in those who fail medical management who are considered for ES and who wish to negate the risk of complications from manometry or ES. In addition a trial of stent may help predict the outcomes of ES in those failing medical management but rates of post-procedural pancreatitis may be as high as 38 % [45]. After careful counseling, it may be reasonable to trial Botox or a stent prior to manometry or ES.

There is insufficient evidence that any of the non-invasive investigations are as accurate as manometry in predicting

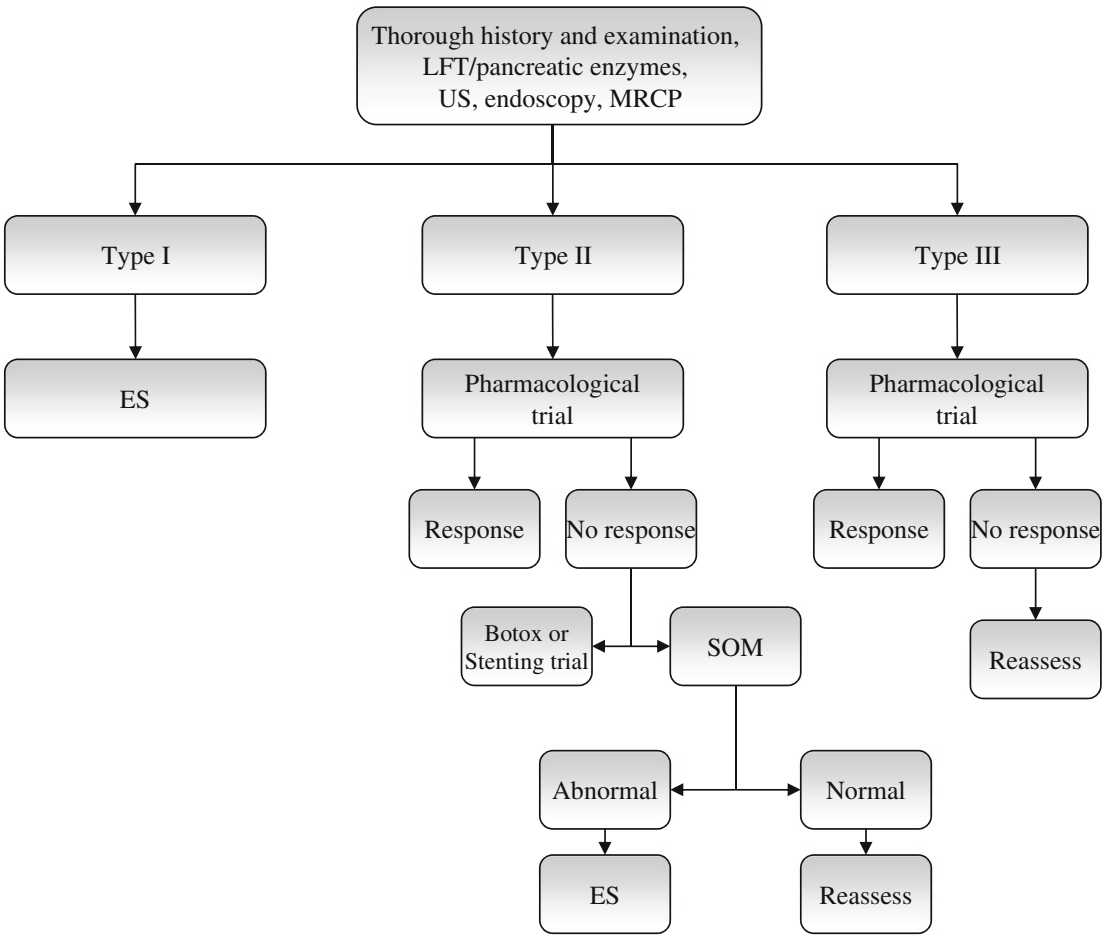
outcomes to ES. The study by Greenen et al. suggests that manometry is necessary to predict the correct cohort of patients to undergo ES and that ES is superior to sham sphincterotomy [3]. Other case series, although not randomised or placebo controlled support reasonable rates of symptom relief with ES with manometry proven dysmotility. After careful counseling of the risks, manometry may be justified in Type II SOD. However even without manometry, favourable outcomes of ES can be observed in 79 % of patients with Type II SOD [50].

In Type III SOD invasive investigation appears unwarranted. Regardless of abnormal results with manometry sustained improvement is poor following ES and may be observed in as few as 8 %. Manometry is associated with the greatest risk of complications in this group and this risk cannot be justified in a disease with a benign course. Symptoms may resolve spontaneously in as many as 69.8 %. An alternative diagnosis should be thoroughly investigated such as gastroparesis or psychiatric conditions that may respond to medical management. There is an increasing prevalence of abnormal psychopathological findings in patients with Type III SOD.

In an attempt to improve on the Milwaukee classification, Gong and colleagues retrospectively analysed the clinical records of 305 patients in China [58]. They suggest the inclusion of two further categories in addition to the biliary and pancreatic types described in the Milwaukee classification. They propose that a double duct-type and biliary and pancreatic reflux-type are included according to anatomy, symptoms, endoscopic evaluation and radiological imaging. Whilst further investigations are needed to determine the its applicability in regions outside China, the classification system described by Gong et al. explains the clinical symptoms of SOD from an anatomical perspective and may be better suited at guiding management decisions.

## Conclusions

In conclusion the classification as described by the Milwaukee Biliary Group can be used to guide investigation and management. An algorithm of investigation and management of




*LFT liver function tests; US ultrasound; MRCP magnetic resonance cholangio pancreatogram; ES endoscopic sphincterotomy; SOM sphincter of Oddi manometry*

**Fig. 1** Algorithm of SOD management

suspected SOD is presented incorporating the Milwaukee classification in Fig. 1. Non-invasive diagnostic investigations have been incompletely studied. Current evidence does not support their routine use due to their low sensitivities and specificities. Type I SOD should be managed by ES without manometry or any other non-invasive investigation. Manometry may result in high rates of complications and should be reserved for suspected type II SOD where a trial of medical management has failed. An alternative to manometry may be a trial of Botox™ or stenting following careful patient counseling. Abnormal manometry or a positive outcome from Botox/stenting may be used to select patients for ES.

Type III SOD does not warrant investigation into SO abnormality. Manometry is associated with unacceptably high risk of complications in this group. Alternate diagnoses should be thoroughly sought and appropriate medical management initiated.

**Conflicts of interest** None.

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