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Abstract

Title of Study	Pump Priming SOD for The Big Time – A healtheconomic and patient evaluation in preparation of a multi-centre randomised controlled trial
Abstract and methodological description	ABSTRACT AND STUDY METHODOLOGY IMPORTANCE Dysfunction within the bidirectional communication between the enteric nervous system and the central nervous system is considered to play an important role in the genesis and maintenance of symptoms in chronic visceral pain disorders [1]. Although such disorders are often considered functional in nature, contemporaneous nomenclature refers to these as a disorder of gut brain interaction (DGBI) [2]. Amongst the most incompletely understood of the DGBI are the gallbladder and sphincter of Oddi disorders (SOD) [3].

The Rome criteria defines typical biliary pain as a sense of discomfort located in the epigastrium and/or right upper quadrant associated with other features such as gradual onset, which occurs at different intervals and is severe enough to interrupt daily activity [4]. Frequently, this pain can radiate into the back and/or the right infra-scapular area and be associated with nausea and vomiting. Other distinguishing aspects including the pain not being significantly associated with bowel movements, postural change or acid suppression. The Rome IV process has sought to make the distinction between functional gallbladder disorder, functional pancreatic sphincter of Oddi dysfunction and functional biliary sphincter of Oddi disorder [4].

The modified Milwaukee criteria defines Sphincter of Oddi dysfunction (SOD) Type III as recurrent biliary type pain in the absence of imaging abnormalities or abnormal liver biochemistry. A well performed study has demonstrated that sphincterotomy is not superior to sham treatment in SOD type III patients which has led to the term being largely discarded in favour of the term post-cholecystectomy biliary type pain [5]. Nevertheless, the investigation and management of post-cholecystectomy biliary type pain remains a challenge [6]. For example, endoscopic retrograde cholangiopancreatography (ERCP) and biliary manometry are invasive procedures associated with significant morbidity and are not good at predicting outcomes [7, 8]. Similarly, medical management with neuromodulatory therapy with agents, such as amitriptyline and duloxetine, have a very limited evidence base to date [9, 10]. The lack of therapeutic options in patients with functional biliary pain makes the management of these patients challenging as many are debilitated with pain, with significant impairment to the quality of their lives, dependence on opioids and recurrent hospital admissions. Thus, functional biliary pain represents a significant unmet clinical need.

PILOT DATA

Botox injection to the sphincter of Oddi has been demonstrated to cause a reduction of sphincter of Oddi resting pressures and may exert an antinociceptive effect [11, 12, 13]. A recent meta-analysis of studies evaluating intra-sphincteric Botox injection for the treatment of SOD suggested a pooled efficacy of 49% in completely alleviating SOD-associated pain and a partial improvement of 64% [14].

However, these results, albeit representing a transient benefit, could potentially

offer a framework for management of patients with functional biliary pain, with a study suggesting that repetitive Botox injections can be associated with prolonged symptom control [15]. We have performed a cross-sectional (hypothesis-generating) study of prospectively collected data patients referred to a tertiary centre from 2014-2019. We evaluated 119 consecutive patients (109 females, 10 males, mean age 45 (17-77) years)) who underwent 411 intra-sphincteric botulinum toxin injection procedures (mean 2 (1-15) procedures). 103 patients (87%) had a significant improvement in pain on post procedure review, with 77% and 76% of patients were opioid and admission free respectively. 59% were initiated on tricyclic antidepressants (amitriptyline), 18% on Duloxetine 13% on Pregabalin and 3% on Mirtazapine. Loss of response with the initial dose of botulinum toxin occurred in 56% of patients. Pain control was re-established in 80% of patients in this cohort following botulinum toxin injection at a higher dose.
Nevertheless, our study is not without significant limitations. First, the observational nature of our study design is a critical methodological issue, which has limited us to reporting outcomes rather than any causal effects. Secondly, it is plausible to suggest that there is a significant placebo effect to Botox injection. Placebo responses have been studied extensively in chronic pain syndromes and specifically in irritable bowel syndrome (IBS) and functional dyspepsia [16]. Despite the wide range of placebo responses (3-84%) in IBS, Enck [17] suggested that the true placebo effect of treatments in functional abdominal pain is likely to be around 40%. A therapeutic response of >80% would suggest that the effect of Botox is greater than what one would expect with a placebo and is therefore possibly a true response. Therefore, a well designed randomised, sham-controlled trial will be necessary to objectively evaluate the true effect of Botox injection from any placebo response.

RESEARCH PLAN
The NIHR Research for Patient Benefit (RfPB) programme funds health, public health and social care research covering a wide range of health service challenges. The aim of the programme is to fund topics and research methodologies that increase the effectiveness of NHS services, provide value for money and benefit patients. It is our view, that the objective evaluation of the role of Botox in the management of SOD represents a clinically unmet

need and would be potentially be very attractive to the RfPB programme. However, the RfPB programme remains highly competitive with between 19-21% of submitted applications being funded [18]. An increasing focus of the RfPB programme is public and patient involvement (PPI) and engagement (PPE) in research and health economics. This underpins a commitment to actively involve patients and the public as partners in the processes by which clinical research is identified, prioritised, designed, conducted, implemented, disseminated and evaluated as well as providing a health economic argument for any given intervention. As such, in order to make our subsequent application for a UK and Ireland based definitive randomised, sham-controlled multi-centre trial of botox in functional biliary pain to the RfPB competitive, we are seeking support from the Pancreatic Society of Great Britain and Ireland to fund two complementary work packages.

Work Package 1 – Patient Focus Groups to Explore their experiences and treatment of SOD and to establish their preferred outcome measures for a subsequent clinical trial.
Current patients on our local clinical databases will be invited to take part in a series of focus groups which will be undertaken via MS Teams (given that it is likely that COVID-19 restrictions will be in place for some time to come). Focus groups will facilitated by Dr Farmer who has experience in this type of interaction. He will use a semi-structured topic guide covering the following: experiences and management of SOD; what participants would like to be included in a clinical trial; how to maximise participant recruitment and retention; blinding and acceptance of sham treatment and how best to disseminate the results of the trial in the future. These focus groups will be recorded, and audio will be transcribed verbatim, checked, and anonymised before undergoing thematic analysis to provide a preliminary thematic framework. An additional aim of this work package will also be to identify a patient co-applicant for our future study.

Work Package 2 – Health economic impact of SOD in the UK
The health economic consequences of SOD both from a patient quality of life and a quality adjusted life years perspective (QALY) have not been evaluated. Patients with ongoing pancreaticobiliary pain may present repeatedly to acute

and community providers and may need repeated hospital admissions for pain management. Endoscopic/surgical and pain management interventions carry healthcare resource burden and the impact on front-door services (A&E) can be significant. Moreover, there can be additional psychological, medical and mental health issues that need specialist attention, increasing the burden on healthcare resource. The health economic impact of SOD will be evaluated from a payer-perspective using retrospective data on patient admissions and Hospital Episode Statistics (HES) data to compare. Healthcare utilities will be attributed to patient clinical states and a cost analysis will be performed to understand the financial impact on healthcare resource, with costs per QALYs modelled over a prospective timeframe. Data generated from these analyses will be novel and will be considered for a per-reviewed publication.

Scientific potential – People – Dr Menon and Dr Farmer provide joint tertiary level care to a large cohort of patients across the West Midlands who suffer with SOD. Dr Menon is an active researcher who also has specific endoscopic expertise in the management of patient with functional biliary pain. Dr Farmer has previously organized and delivered a number of research projects, largely focused around visceral pain; a body of work funded by the Medical Research Council. He has also completed the Global Clinical Scholars Research Training Programme at Harvard Medical School. His post-doctoral work has focused on the physiological and electrical modulation of vagal tone in health and disease. Local Research Environment – The project will be based at the Royal Wolverhampton Hospitals which has dedicated clinical research facilities. Given that the focus groups will be undertaken remotely, and the health economics analysis will be informed by existing clinical data, no specific equipment will be needed. Potential benefits to the Pancreatic Society of Great Britain and Ireland – This project has a number of potential benefits to the Pancreatic Society. Firstly, the society will be acknowledged in the academic outputs of this project. Secondly, the society will have aided in making our subsequent application significantly more competitive. Finally, there will be significant reputational benefits to the Society for being associated with the first UK and Ireland trial in this therapeutic area.

PROPOSED TIMETABLE

	Please see GANTT chart below for a proposed timetable. This timetable provides a clear pathway towards our grant application to RfPB. FUNDING REQUESTED AND RATIONALE 1. £2000 for work package 1 to include transcription and thematic analysis – participants to be provided with £20 each vouchers as per Involve guidelines 2. £8000 for data analysis and validation from an external health economic team, access to the HES dataset and assistance with economic evaluation and modelling. ETHICAL APPROVAL FUNDING REQUESTED AND RATIONALE Ethical approval is not required for this study. INSTITUTIONAL APPROVAL Formal institutional approval is not required for these work packages with work package 1 being covered under service evaluation. REFERENCES (separate list)

Timetable

Name	12 months
Date	01/06/22

Funding

Name	Work Package 1
Amount	2000.0

Name	Work Package 2
Amount	8000.0

Details of ethical approval

The study involves focus groups which will be delivered as part of a service evaluation and work package 2 will involve anonymised datasets.

Institutional approval information

Formal institutional approval is not required for these work packages with work package 1 being covered under service evaluation.

Declaration

Confirm Declaration: Yes

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