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The Trinity Student Medical Journal is intended to provide an inclusive vehicle for students to communicate current medical research, opinions and thoughts to other students, faculty members and faculty of affiliated hospitals and institutions. We publish articles relating to many aspects of medicine including scientific research and clinical experience. Articles are accepted from students in medicine and other related fields, as it is our view that medicine is the meeting point of many disciplines. The aim of the Journal is to provide a medium that is responsive to the rapidly changing face of contemporary medicine, and is able to grow and expand as rapidly as the subject.

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Getting bit by the research bug: Why medical students should get published.

Kaie Rosborough

As a final year medical student in the midst of applying for further training after graduation, I find myself simultaneously grateful to have lines beneath the 'Research & Publications' heading of my CV and proud of the work that I have produced and published. While publication is certainly an effective means of career advancement, I feel the benefits of participating in research as a medical student extend far beyond CV development. As medical students, we are often encouraged by academic staff to publish scientific literature, but we are rarely instilled with the value of conducting this research and the potential impact of our work.

At the forefront, the underlying currency of medicine is knowledge. As clinicians, how we trade this knowledge is through research and its final product, scientific publication. We gain knowledge from the work of others and use this information to guide how we care for our patients every day. My enthusiasm for research lies in the opportunity to add a small brick to the wealth of information that forms the foundation of medical practice and drives changes in patient care. Active involvement of medical undergraduates in research is essential to prepare the next generation of scientifically-oriented physicians. My goal as Editor-in-Chief of the Trinity Medical Student Journal (TSMJ) is to cultivate an environment that supports student research, encourages scientific literacy, and fosters a culture of evidence-based medicine.

The publication of a medical article requires much more than just writing an article. Writing case reports entails finding an interesting case, doing a literature search, collating medical information, choosing a journal and writing up an interesting case and responding to reviewers' comments. Writing audits or research reports requires involvement in study design, data collection, analysis and interpretation, as well as drafting and editing the full article. By the time an individual has gone through these steps, they will have undoubtedly enhanced their understanding of their particular topic. Completing a project from inception to publication develops a sound understanding of research methodology and critical thinking skills, but also patience, humility and determination. While students may not be considering research careers, they will certainly develop an appreciation of the value and limitations of medical research, as well as the skills to critically evaluate evidence and apply it to their clinical practice.

Part of the beauty of medicine as a career path is the concept of lifelong learning. By prioritizing research alongside their medical education, students have the unique opportunity to receive mentorship from senior physicians. Lifelong learning to me also implies lifelong teaching; all members of the medical field have plenty to learn from each other—even medical students can teach their peers and seniors. Publications provide medical students a valuable opportunity to share their knowledge.

At this early stage in your careers, may you all be bitten by the "research bug" and seek out research experience as an undergraduate medical student. Internalize the spirit of enquiry: ask questions, critically appraise the literature, seek out the answers, and find mentors in your chosen field. It is my hope that by providing opportunities for students to engage in the publication process, I am instilling passion in future physicians to use it for meaningful advancement of their own careers, and also of the profession as a whole.

What is the Evidence for Endoscopic Therapy for Pain Relief in Chronic Pancreatitis?

Azreena Burukan, Joshua Skeens, Andrew Butler, Emily Vickery, Emily Tone, Jack Tyrrell, Niall O'Sullivan and Donal O'Connor

Background

The objective of this study was to evaluate the efficacy of endoscopic therapy for pain relief in patients suffering from chronic pancreatitis. Following an initial search, 25 papers met the inclusion criteria and were selected and reviewed.

Introduction

Chronic pancreatitis (CP) has two fold increased prevalence of 11.7 to 13.4 per 100,000 population (Duggan et al., 2016), and requires national attention. The highly variable levels of pain exhibited by patients (Manes et al., 1994) has led to investigation into the efficacy of pain management for CP.

Endoscopic therapy in pain management of CP involves Endoscopic Retrograde Cholangio-pancreatography (ERCP) and Endoscopic Ultrasound (EUS) procedures. All procedures require the use of an endoscope, which is passed through the mouth, oesophagus, stomach, and into the duodenum where it can access the Common Bile Duct (CBD) and Main Pancreatic Duct (MPD). ERCP involves the injection of contrast to visualise the biliary tree and pancreas for endoscopic sphincterectomy (CBD or MPD sphincter) and to insert duct stents for dilatation of strictures and the removal of calculi in the ducts. Extracorporeal shock wave lithotripsy (ESWL) is promoted for calculi larger than 5 mm, which encompass the use of magnetic waves to break down calculi for removal via ERCP. EUS can also be used for coeliac plexus block in order to achieve pain relief.

In this paper, a systematic review was performed to assess therapies for pain relief in CP. The objectives were: - 1) to assess current literature regarding the authenticity of endoscopic therapy and 2) whether other forms of intervention showed a greater efficacy in pain relief, with the aim of attaining the highest levels of evidence (IA) and recommendations (A), as stated in "The Oxford levels of Evidence 2". This paper analysed 25 papers; three were randomized control trials (IB), with the remaining papers representing targeted studies exhibited level IIB evidence. Therefore, through the homogeneity of the results provided below, this paper falls under level IIA evidence and Grade B recommendation.

Chronic pancreatitis

Aetiology

CP is a chronic inflammatory disease of the pancreas that leads to fibrosis and scarring of pancreatic parenchymal tissue and pancreatic ducts. The disease progression typically causes pain, with Goulden et al. (2013) recording it as the primary symptom for 80-90% of recorded chronic pancreatitis hospital admissions.

Bornman et al. (2003) highlighted the large variation in the level of pain witnessed by patients with similar anatomical and morphological changes brought about by the disease, thereby demonstrating the classification of the disease as a complex pain syndrome. The pain is noted as radiating from the epigastric region to the back, with acute severe episodes. Most CP patients complain of postprandial pain. Pain as a result of CP can be due to anatomical reasons, such as: enlargement of pancreatic and common biliary duct, due to calcifications, which (Figure 1) can lead to increased intraductal pressure causing hypertension and ischemia, due to bile duct or pancreatic duct stenosis. Pain can also be caused by the involvement of neuronal tissues, as a result of inflammation of visceral tissue in disease progression, leading to increased nociceptive sensitisation of the tissue (Hoogerwerf et al., 2001). Furthermore, there has been a promotion that defective centres of the brain involved in the regular immune response mediated by inflammation cause further sensation of pain and visceral inflammation (Fregni et al., 2007). The unpredictable origin of pain makes further research in this area a necessity.

Chronic alcohol abuse is the most common cause of CP (Tsujimoto et al. 2008). It is theorised that the oxidation of ethanol to acetaldehyde activates pancreatic stellate cells prematurely resulting in increased oxidative stress and signalling of the fibrogenic pathway (Pezzelli et al., 2009). Other causes include familial pancreatitis, autoimmune diseases, and cystic fibrosis. It can also be idiopathic (PubMed Health, 2017).

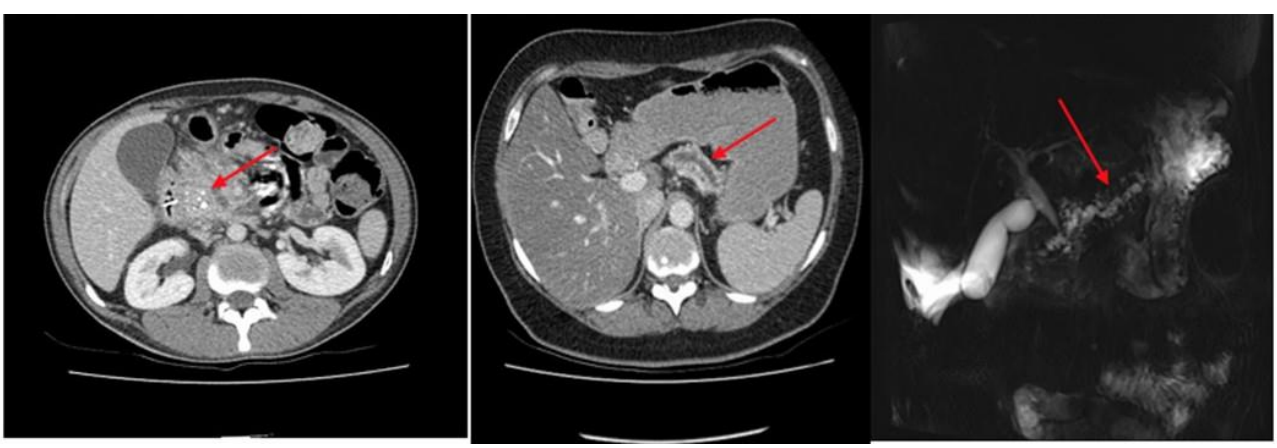

Figure 1. Computer Tomography (CT) showing calcifications and enlarged head of pancreas (left), dilated MPD and atrophic pancreas (centre) and dilated tortuous main pancreatic duct (right). Courtesy of Dr. Donal O'Connor; Senior registrar.

Complications

CP encompasses both mechanical and functional complications. Mechanical complications include chronic pseudocysts that develop in 10% of patients with CP, gastric outlet obstruction, and common bile duct stenosis (D Freedman et al., 2017). Less commonly reported complications include post-Endoscopic cancer.

Chronic pain is the most common complication associated with CP (EL, 1998). It can be the most challenging complication to treat (Gachago et al, 2008) and is associated with poorer psychological quality of life and endorsement of depressive symptoms (Balliet et al., 2012).

The mechanism underlying the pathogenesis of CP pain is still not precisely known. The most widely accepted "Plumbing" Theory states that fibrotic obstruction causes an increase in intraductal or parenchymal pressure (Schou Olesen et al., 2015),similar to "compartment-like syndrome". Patel et al., (1995) documented decreased blood flow and increased acidic metabolites of an animal CP model upon stimulation, which could account for pain. Swelling of the pancreatic head can also result in hypersensitisation of the celiac plexus and hence this is a common site for neurological blockade therapy. (Schou Olesen et al., 2015). Numerous other theories are summarised in Figure 2.

Pain Relief

As discussed above, we will be focusing on pain relief for CP via ERCP and EUS. There are, however, other forms of treatment such as pharmaceutical, neurological, and surgical treatments.

Proton pump inhibitors are thought to reduce intra-pancreatic pressure by suppressing acid secretion. Yoo J. et al (2012) found that the use of pantoprazole shorten hospital stays as well as the time taken for pain relief to take place.

It is advised to cease all alcohol intake completely, if possible, to avoid recurrent attacks. Opioid analgesics can also be used to relieve pain in chronic pancreatitis. Wilder-Smith et al (1999) found that 67% of patients rated their analgesia 'excellent' after 4 days of treatment with tramadol, but this amount was significantly lower in patients taking morphine (20%).

Neuropathic analgesics such as gabapentin and amitriptyline may also be used, although relief from pancreatic pain wouldn't be their primary indication for use. Neurological treatment includes endoscopic ultrasound coeliac plexus block (EUS-CPB). Santosh D. et al (2009) found that 70% of patients reported improved pain scores after undergoing EUS-CPB with bupivacaine and Triamcinolone.

There are a number of surgical interventions including the classic Whipple procedure to the newer duodenum preserving procedures developed by Frey and Beger, among others. In an 85 patient study, patients underwent either a classic Whipple procedure or a duodenum preserving procedure for pain in chronic pancreatitis. 67% of the patients who underwent the whipple procedure were pain free 66 months postoperatively and similarly 67% of patients who underwent the Frey and Beger procedure were pain free for the same length of time on average.

Method

In order to gather evidence for the use of endoscopic therapy for pain relief in CP, we conducted a systematic literature review and focused on recently published guidelines for management of pain in CP. In accordance with HaPanEU guidelines, published in 2016, studies were sourced through the online search engine, PubMed. The terms used when searching the database were: chronic pancreatitis, pain management, and endoscopy. We also included current reviews from the Lancet, the World Journal of Gastroenterology, Elesivier, Science Direct, Cochrane library, Gastroendo News and the Gastrointestinal Endoscopy Clinics of North America. For the purpose of our investigation we included 25 papers, which studied the efficacy of endoscopic intervention in the management of pain in chronic pancreatitis. We were particularly interested in those, which compared their results using the Izbicki pain score (Izbicki et al. 1998). We excluded literature which discussed acute pancreatitis and pseudocyst drainage, and those which did not focus on management of chronic pain. We excluded all papers which discussed biliary obstruction. Due to limited material available we decided to exclude systematic literature reviews from our study material. All material used for the purpose of this review is lawfully sourced and referenced appropriately.

Results

A systems-review of 25 papers evaluated the use of endoscopy in the treatment of chronic pancreatitis for pain relief as shown in Table 1. The total number of patients is 3892. Pain relief averaged 70.8% through endoscopy treatment where the highest rate of pain relief achieved was 94% while the lowest was 30.4%.
The endoscopic treatment that was looked in this study ranges from EUS, ERCP and ESWL. Significance on pain relief between the different types of endoscopic treatment cannot be commented.

Pain relief was not achieved in about 28.1% where the highest rate that failed to relieve pain was 69.9% and lowest was 6%. Further treatment is required in 41% of patients, in which 25.2% underwent surgery, 44.53% of the patients had repeated endoscopic treatment, and 30.25% had to use analgesia to control their pain. 27% of patients had an endoscopic- related complication.

According to Cervero F and Laird JSM 1999, the pain that is experienced by patients with CP is abdominal pain that radiates to the back and hypogastric region. The pain is exacerbated when they eat, hence they avoid eating. The pain does not resolve and is constant. They get unexpected pain suddenly and when this is not elevated by analgesia, patients seek medical attention. When endoscopic intervention does not relieve this pain, then further intervention is needed.

Discussion

In a study by Dite P et al, 2003, complete relief was seen in 37% of the patients that underwent surgical intervention whilst only 14% was seen in endoscopic intervention. Cahen DL et al and Ahmed AU et al ., 2012 found long-term pain relief was higher amongst surgical patients 5 years post intervention compared to endoscopic patients. Longitudinal studies conducted by Ammann RW et al, 1984, 1994, showed that 40-75% of patients require surgery after endoscopic intervention due to continuing pain.

Rutter et al. (2010) reported endoscopic therapy in treatment of chronic pancreatitis improved overall quality of life. This included reduced hospital stays, reduced follow up procedures and a longer period between relapsing of symptoms in patients. Although surgery was deemed to have greater clinical outcomes with regard to improving overall quality of life (Rutter et al. 2010). Based on these findings and considering pain management in chronic pancreatitis as a whole, it would therefore be logical to assume surgery as a first line therapy in all patients with chronic pancreatitis. However, there are instances where endoscopic therapy supersedes all other treatments and these

are mainly due to an obstacle in the main pancreatic duct (Dumonceau 2010).

One way pain relief can be achieved is through endoscopic ultrasound (EUS)-guided celiac plexus block which is often reserved and used in patients with chronic pancreatitis. According to Le Blanc et al. 2009, EUS guided celiac plexus block gives an average pain relief for about 4 months and has an overall response rate of 50-55%, which is deemed to be short term pain relief. Puli SR et al. 2009 mentioned that the rate of complication of the neurolysis is very low and though it depends on technique about 60% of pain relief is seen. Ahmed Ali et al, 2015 and Cahen DL et al, 2007 agree that treatment given surgically has a better outcome compared to an endoscopic approach. Although there are various surgical methods that are available for CP, Diener MK et al. 2017 found that the pancreaticoduodenectomy and the duodenum preserving pancreatic head resection procedures have similar outcomes for pain relief.

Pancreatic Calculi can deposit in the Main Pancreatic Duct (MPD), its side branches or parenchyma and cause these areas to become hypertensive, potentially leading to pancreatic ischaemia and resulting in severe pain in some cases (Tandan et al. 2013). Three or more stones blocking the MPD and a Pancreatic Duct stone (PDS) with a diameter of ≤ 10mm indicates endoscopic treatment. Small calculi can be extracted by ERCP following initial fragmentation by Extracorporeal Shock wave lithotripsy (EWSL) to <3mm diameter (Liu et al. 2010). ESWL is a high intensity magnetic shock wave treatment performed that shatters pancreatic stones, and stones >5mm are indicated for its use (Tandan et al. 2010). Some studies suggest that ESWL is effective as a sole therapy for pancreatic caliculi, with higher costs and longer hospital stays associated with the adjunctive therapy (Tandan et al. 2013)

A prospective cohort study carried out over a 15 year period made an incredibly strong case for the use of ERCP to decompress the main pancreatic duct. Gabrielli et al (2005) achieved sufficient drainage and"complete clearance" of the MPD through the placement of these plastic stents- with a reduction in the diameter of the MPD and a complete relief of pain achieved in all patients. Only four patients were admitted to surgery after relapses of pain from the procedure, and there were 10 relapses of pain related to the placement of plastic stents. A more recent systematic literature review validates the findings of Gabrielli's study by suggesting that MPD strictures be treated with single large plastic stents for "1 year". In the case of unsuccessful ERCP, EUS-guided drainage of the pancreatic duct is recommended (Seican and Vultur 2014). Dumonceau stated that endoscopic therapy -ERCP with EUS-guided drainage of the MPD if unsuccessful - is a "first line therapy for painful chronic pancreatitis", when the MPD is obstructed. Dumonceau also recommends that in the case of an unsatisfactory clinical response, an MDT approach be adopted with the potential for surgery to be carried out on the patient at this stage.
As the role of endoscopic therapy has not yet been well defined in both treatment and control of pain in CP, one must consult the most recently published guidelines before making a clinical decision due to the invasive nature of the procedure. The Spanish Pancreatic club outlines how a clinician must be aware of the various limitations of endotherapies (E. de Madaria et al. 2010):

(i) There is no randomised control trial comparing pharmacological vs endoscopic or surgical treatment of pain in CP

(ii) It is difficult to ascertain how effective EDT in treating pain long term, as the long term pain profile with or without EDT is not well defined (Ammann and Muellhaupt, 1999).

(iii) Endoscopic therapy has to be carried out by extremely qualified and skilled clinicians. This challenge would potentially be avoided administering medication.

Izbicki JR et al. 1998 argues the reduction of pain in patients who received endoscopic treatment is because the treatment procedure was unclear and there was no evidence that pain was measured. There are only 2 randomised controlled studies in the literature comparing endoscopic therapy with surgical drainage of the pancreatic duct in CP. (Table 1).

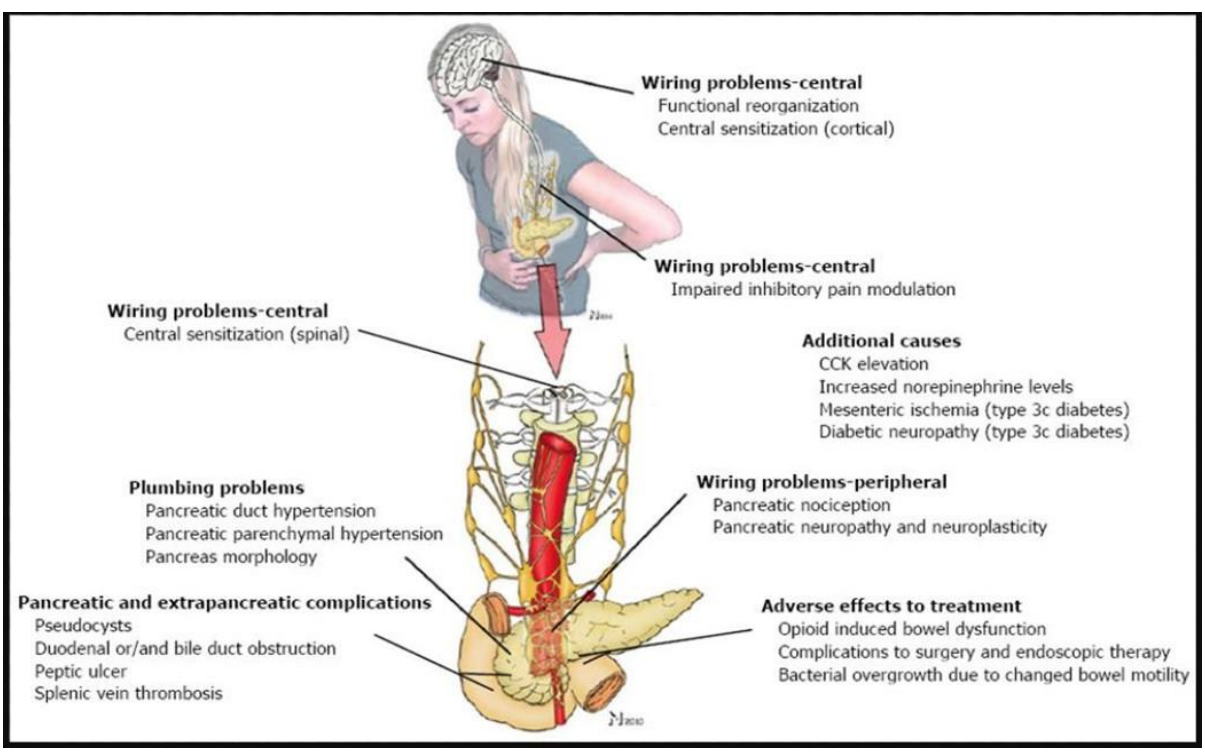

Figure 2. Pain mechanisms in chronic pancreatitis (Poulsen, 2013)

Table 1 - Characteristics of 25 included studies.

Study title	Author	Year of publication	Country of publication	Type of study	Level of evidence
Endoscopic versus Surgical Drainage of the Pancreatic Duct in Chronic Pancreatitis	Cahen et al	2007	Netherlands	Randomised Trial	IB
Endoscopic stenting for pain relief in chronic pancreatitis: Result of a standardized protocol	Ponchon et al	1995	France	Prospective study	IIC
Stenting in severe chronic pancreatitis: result of medium-term follow up in seventy-six patients	Cremer et al	1991	Belgium	Prospective study	IIB
A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis	Dite et al	2003	Czech Republic	Prospective Randomised Trial	IB
Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicentre survey	Inui et al	2005	Japan	Retrospective Multicentre study	IIB
Long-term clinical outcome after endoscopic pancreatic ductal drainage for patients with painful chronic pancreatitis.	Delhaye et al	2004	Belgium	Retrospective Study	IIB
Long-term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones	Tadenuma et al	2005	Japan	Prospective Study	IIB
Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi - a large single centre experience	Tandan et al	2010	India	Prospective Study	IIB
Long Term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific	Seven et al.	2012	United States of America	Retrospective Chart Review	IIB
Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy	Adamek et al.	1999	Germany	Prospective Study	IIB
Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis	Brand et al.	2000	USA	Prospective Study	IIB
Long-term Outcomes of Endoscopic vs Surgical Drainage of the Pancreatic Duct in Patients With Chronic Pancreatitis	Cahen et al	2011	Netherlands	Prospective Randomised Trial	IB
Endoscopic Stent Therapy in patients with chronic pancreatitis: A five year follow up study	Weber et al	2013	Germany	Prospective Study	IIB
Endoscopic Treatment of Chronic Pancreatitis: A Multicentre Study of 1000 patients with long term follow up	Rösch et al	2002	Germany	Prospective Multicentre study	IIB
Ultrasound-guided extracorporeal shock wave lithotripsy of pancreatic ductal stones: six years' experience.	Johanns et al	1996	Canada	Prospective Study	IIB
Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones	O'Hara et al	1996	USA	Prospective Study	IIB
New modalities of treating chronic pancreatitis	Grimm et al	1989	Germany	Prospective Study	IIB
Endoscopic pancreatic stent drainage in chronic pancreatitis and a dominant stricture:	Binmoeller et al	1995	Germany	Retrospective Study	IIB
Role of pancreatic duct stenting in the treatment of chronic pancreatitis	Vitale et al	2004	USA	Prospective Study	IIB
endoscopic treatment of chronic pancreatitis	Bartoli et al	2005	France	Retrospective Study	IIB
Long-term outcome after pancreatic stenting in severe chronic pancreatitis.	Elefthiriadis et al	2005	Belgium	Retrospective Study	IIB
Interventional endoscopic therapy in chronic pancreatitis including temporary stenting: a definitive treatment?	Farnbacher et al	2006	Germany	Retrospective Study	IIB

Endoscopic treatment of painful chronic pancreatitis: evaluation of a new flexible multi perforated plastic stent.	Boursier et al	2008	France	Retrospective Study	IIB
Outcome following endoscopic stenting of pancreatic duct strictures in chronic pancreatitis.	Topazian et al	2005	USA	Prospective study	IIB
Endoscopic treatment of the main pancreatic duct: correlations among morphology, manometry, and clinical follow-up	Renou et al	2000	France	Prospective study	IIB

Table 2 - Outcomes of studies for pain relief of CP via endoscopic therapy, including further forms of treatment

Author	# of patients	Pain relief achieved							
		Yes		No				Complications after endoscopic intervention	
		# of patients	% of patients	# of patients	% of patients	Intervention	# of patients	% of patients	# of patients	% of p atients
Cahen et al	39	21	53.80	19	46.10	Converted to surgery	4	10.30	18.00	46.20
Ponchon et al	23	7	30.40	16	69.60	Use of analgesia	14	60.90	10.00	43.50
Cremer et al	76	72	94.00	4	6.00	Converted to surgery	1	15.00	-	-
Dite et al	140	-	46.00	-	54.00	-	-	-	-	39.00
Inui et al	555	428	77.10	127	22.90	Converted to surgery	22	3.96	35.00	6.30
Delhaye et al	56	37	66.00	19	34.00	Converted to surgery	12	63.00	14.00	25.00
Tadenuma et al	117	49	70.00	21	30.00	Repeated endoscopic treatment	21	30.00	-	-
Tandan et al	1006	711	84.00	135	16.00	-	-	-	71.00	7.10
Seven et al	120	60	50.00	60	50.00	Repeated endoscopic therapy and surgery	-	-	-	-
Adamek et al	80	61	76.20	19	23.70	Converted to surgery	8	10.00	6.00	7.50
Brand et al	38	17	45.00	21	55.00	Unknown	-	-	-	-
Cahen et al	31	18	58.10	13	41.90	Converted to surgery	9	47.40	13.00	68.42
Weber et al	19	17	89.40	2	10.60	Use of analgesia	3	15.80	6.00	31.60
Rösch. et al	1018	-	65.00	-	35.00	Converted to surgery	-	24.00	-	40.00
Johanns et al	35	29	82.80	6	17.10	-	-	-	-	-
O'Hara et al	32	25	79.00	7	21.00	-	-	-	-	-
Grimm et al	61	50	82.00	11	18.03	Repeated endoscopic therapy	-	-	-	-
Binmoeller et al	93	69	74.00	13	14.00	Repeated endoscopic therapy	11	11.80	6.00	6.45
Vitale et al	75	62	83.00	13	17.00	Use of analgesia	55	73.30	-	-
Bartoli et al	39	34	87.20	5	12.80	surgical treatment	4	10.20	3.00	7.00
Elefthiriadis et al	100	62	62.00	30	30.00	repeated endoscopic therapy	34	34.00	38.00	38.00
Farnbacher et al	98	65	66.00	33	34.00	Repeated endoscopic therapy and surgery	39	39.70	31.00	31.60
Boursier et al	13	11	85.00	1	7.69	Repeated endoscopic therapy	1	7.69	4.00	10.00
Topazian et al	15	13	87.00	2	13.00	Repeated endoscopic therapy	-	36.00	-	-
Renou et al	13	10	76.90	3	23.00	-	-	-	-	-

Table 3 - Compiled data from all 25 studies

Criteria	Number of patients (%)
Pain relief achieved	1928 (70.8%)
Pain relief not achieved	580 (28.10%)
Complication	255 (27.00%)
Further treatment	238 (41.00%)
Surgery	60 (25.21%)
Additional endoscopic therapy	106 (44.53%)
Use of analgesia	72 (30.25%)

In Ireland, most specialists are unaware of any specific guidelines to follow in the management of CP, highlighting the caution that needs to be exercised when selecting patients for endoscopic therapy (Ní Chochubhair et al. 2016).

The National Institute for Healthcare Excellence (NICE) recommends surgical treatment before endotherapy in control of pain in CP (NICE 2010). However, main pancreatic duct strictures are to be treated with "multiple plastic stents". One study showed that strictures were resolved in 95% of patients 24-48 hours following stent removal (Nyguyen-Tang and Dumonceau 2010).

Future Direction

When looking at future considerations for therapy in pain management of Chronic Pancreatitis, it is difficult for us to make a clinical recommendation on when to use endoscopic therapy, surgery, or pain medication, when the patient cohorts are so ill-defined due to heterogeneous nature of the condition. The aetiologies of chronic intractable pain in CP are still not fully understood, therefore the indications and guidelines for therapy are currently lacking.

Therefore, to expedite and improve our understanding on how to manage pain in CP more efficiently and cost effectively- with lower risks of morbidity and mortality, fewer complications and a higher quality of life- future clinical trials must focus on establishing the causes of pain in chronic pancreatitis. This is partly the reason why Irish gastroenterologists and those around the world are still at odds when it comes to deciding on the correct treatment protocol for each chronic pancreatitis patient. In Ireland, no study has been carried out on the "prevalence, incidence and aetiology of Chronic Pancreatitis" (Duggan 2014).

By understanding how alcohol and other risk factors are involved in the pathogenesis of Chronic Pancreatitis, e.g. by laying down of fibrotic tissue in the parenchyma of the pancreas (which can lead to Main Pancreatic Duct strictures), we will have a better knowledge on how best to manage pain in Chronic Pancreatitis. Much of the ambiguity in the two randomised controlled trials by Cahen et al and Dite et al over the preferred therapy in CP, centres on a lack of understanding of the aetiologies and pathogenesis of both pain in Chronic Pancreatitis and Chronic Pancreatitis as a whole. Taking the Dite study it was concluded that surgery is the preferred method of "long-term pain reduction" in Chronic Pancreatitis. However, it is recommended that endotherapy be offered as a first line therapy, with surgery required in the case of "failure and/or recurrence". In more recent years this method has been widely adopted as the "step-up approach"; with medication being first line, then endotherapy, and in those unresponsive to the latter methods, surgery (Windsor and Reddy 2017). Although Dite acknowledges the shortcomings of this recommendation by stating that patient selection criteria for endotherapy needs to improve in order to"maximize results", no suggestion is given as to how these patients might be appropriately stratified for treatment.

A greater understanding of the aetiologies and pathogenesis of pain in Chronic Pancreatitis would hugely ameliorate the guidelines for therapy. By knowing which procedure is best suited to each patient subgroup (classified based on aetiology and/or pathogenesis), the step-up approach would be avoided in most cases. The results would not only improve patient outcomes, but it would significantly reduce costs associated with therapy and reduce the amount of invasive procedures needed to treat pain in Chronic Pancreatitis.

Conclusion

In conclusion, by carrying out a systems review with multiple studies, we agree that surgical route of treatment has better long term pain relief compared to endoscopic intervention basing our evidence mainly on two randomised controlled trials. Furthermore, endoscopic therapy has a high failure rate and often necessitates further surgical management. A multidisciplinary approach is best advised when selecting the appropriate patients for endoscopic therapy in pain relief for chronic pancreatitis.

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Autoimmune Encephalitis
Pathophysiology, Diagnosis and Treatment

Matthew Coalter and Jean Dunne

Autoimmune encephalitis is a family of similar neuropsychiatric diseases presenting with a range of symptoms including subacute dysfunction in memory, decreased cognition, psychosis, refractory seizures, and encephalomyelopathy. During the initial investigation, infectious and medical causes of encephalitis must be ruled out and autoimmune aetiologies explored. Patients will often have a characteristic clinical history and findings, CSF pleocytosis, MRI T2-FLAIR, especially in temporal lobes and limbic system, and EEG changes. Specific autoantibodies can be detected using commercial laboratory tests with high sensitivity and specificity. The diseases can largely be broken down into group I encephalitides with autoantibodies against intracellular synaptic proteins, and group II encephalitides with autoantibodies against neuronal surface proteins. When a diagnosis is suspected, patients should receive first-line steroids and IVIG. If this fails, second-line immunotherapies rituximab and cyclophosphamide are recommended. The majority of autoimmune encephalitides have an association with various tumours and are therefore paraneoplastic syndromes in many patients. Comprehensive screening for cancer should be carried out in all patients, focusing on the specific cancer association, and appropriate cancer treatment can help ease neurological symptoms. Outcomes vary by disease and recovery is usually slow. This is a relatively newly recognised disease and new research is vital to increase recognition and form treatment strategies to best deal with this underdiagnosed condition. This is a review of the literature on the pathophysiology, diagnosis and treatment of autoimmune encephalitis.

Introduction

Autoimmune encephalitis is a family of similar neuropsychiatric diseases with different pathophysiology. It is important to identify the exact type of disease in order to best diagnose and treat a patient. Often the diagnosis can be challenging as many of the symptoms overlap, and many autoimmune, and even infectious encephalitides may be confused. While clinical presentations vary, in general, there is a subacute dysfunction in memory and decreased cognition. Certain types are often associated with underlying malignancy and therefore are paraneoplastic conditions, while others are seen without cancer in the body. Paraneoplastic forms are comparable to more well-known diseases such as Lambert-Eaton myasthenic syndrome (LEMS) where antibodies are formed against presynaptic voltage-gated calcium channels leading to muscles weakness. Like many of the autoimmune encephalitides, LEMS is often seen on a background of small cell lung cancer (Petty, 2007).

Autoimmune encephalitis was first described in 1968 as a paraneoplastic syndrome causing damage and inflammation of the temporal lobe and limbic structures with progressive memory loss seen in some patients with lung cancer (Corsellis, Goldberg, & Norton, 1968). Later in 1988, when brain imaging became widely available, this inflammation could be picked up using MRI to visualise T2-weighted hyperintense regions in the limbic system and temporal lobes on a patient by patient basis (Kohler, Hufschmidt, Hermle, Volk, & Lücking, 1988). Larger studies were done, and a pattern began to emerge of similar T2-FLAIR signal changes, and diagnostic criteria were established in 2000. In 2007 these criteria were altered to include the non-paraneoplastic forms of limbic encephalitides (Tüzün & Dalmau, 2007). Josep Dalmau can almost be considered 'the father' of autoimmune encephalitis for his discoveries in this field and many of the papers referenced in this review include him as a lead or co-author. In 2016, many of the world leaders in this field came together to publish updated guidelines. They felt the need for more widely usable criteria, as antibody testing is frequently initially outside the reach of many hospitals. They describe the criteria for possible autoimmune encephalitis if a patient has all 3 of the following:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status, or psychiatric symptoms.

2. At least one of the following:

   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm3)
   - MRI features suggestive of encephalitis

3. Reasonable exclusion of alternative causes (Graus et al., 2016).

Groups of Autoimmune Encephalitis

Autoimmune encephalitides can be grouped based on the antibody present. Group I autoimmune encephalitides have antibodies to intracellular antigens, like anti-Hu. They are most often paraneoplastic, mediated by cytotoxic T-cells and have a limited response to treatment. For this reason, and the fact that the neuronal damage tends to be irreversible, they have worse clinical outcomes than group II encephalitides. As the damage is largely caused by T-cells, the antibody levels are less correlated with disease severity but may be useful as tumour markers (Dalmau & Bataller, 2006). Focusing on anti-Hu encephalitis, it was discovered in 1985 in two patients with subacute sensory neuronopathy (a form of polyneuropathy due to neural degeneration (Zuberbuhler et al. 2015)) with a previous diagnosis of small cell lung cancer (SCLC). This is an aggressive neuroendocrine lung cancer which metastasises early and is associated with various paraneoplastic syndromes. An immune response is generated when Hu proteins are expressed on cancer cells such as SCLC. Hu protein is normally only found in the nuclei of neurons of the central and peripheral nervous system, i.e. immune privileged environments. T cells are activated and anti-Hu antibodies are produced (Bernal et al. 2002). Studies have shown that T-cells are central mediators of the disease and are present at higher levels in the CSF of patients with anti-Hu encephalitis than controls with SCLC without neurological disease (De Jongste et al. 2013). CD8+ T cells infiltrate affected tissue and are found in close proximity to damaged neurons at autopsy (Jean et al. 1994). These results suggest that T cells are central to the immune response in the CNS.

Group II diseases have antibodies which target cell surface neuronal antigens such as anti-NMDAr encephalitis. They are less likely to be paraneoplastic, more responsive to therapy and have antibodies as the central mediator of their pathogenicity (Bien et al., 2012). Due to this direct link between antibody titre and disease activity, the levels can sometimes be monitored for treatment response, severity and recurrence. Patients with this group of antibodies may have systemic autoimmune disease, experience symptoms following viral infection or vaccination, or have an idiopathic aetiology (Glaser et al., 2003). Focusing on anti-NMDAr encephalitis, it is mediated by IgG1 and IgG3 antibodies against the GluN1 subunit of the NMDAR (Dalmau et al. 2008). These antibodies have been shown to be pathogenic and crosslink the NMDAR

causing its internalisation. This leads to less receptor at the synapse and less NMDA mediated signalling. Secondly, they also directly antagonise signalling at the receptor, similar to pharmacological antagonists PCP and ketamine (Moscato et al. 2010). They have been shown to be pathogenic when passively transferred into the brains in rodent experiments (Planagumà et al. 2015). An ovarian teratoma can express the onconeural antigen NMDAR, and antibodies can be formed and subsequently cross the BBB and cause neural damage. However in one study only 45% of women with anti NMDAR encephalitis were found to have an ovarian teratoma (Florance et al. 2009). Therefore, there must be another mechanism of antibody production.

Diagnosis

Clinical

Symptoms can be generalised or patient specific. Generally, symptoms include loss of cognition, memory (especially anterograde) or consciousness, and psychiatric symptoms such as mood swings, psychosis, compulsive behaviours and hallucinations. In some cases, more idiosyncratic symptoms can appear, such as ocular symptoms in anti-Ma associated encephalitis (Rosenfeld, Eichen, Wade, Posner, & Dalmau, 2001). Certain encephalitides may present within a syndrome of symptoms. For example, some cases of Morvan's syndrome are caused by anti-Caspr2 antibodies, a subtype of anti-VGKC encephalitis. This presents as neuromyotonia, neuropsychiatric features, autonomic dysfunction and neuropathic pain (Josephs et al., 2004). Anti-Caspr2 antibodies also cause some cases of Isaacs syndrome which presents as peripheral nerve hyperexcitability, twitching, stiffness and cramps (Irani et al. 2010). Table 1 shows key features which may (or may not) be visible in the presentation of each type of autoimmune encephalitis.

The collection of symptoms, along with the medical history focusing on any cancers, as well as the age and sex of the patient can help to guide the laboratory and radiologic tests which should be ordered. If a patient has not been previously diagnosed with a solid tumour, a full screen with CT, MRI or PET is recommended as many of the diseases are paraneoplastic. Children have more motor symptoms and fewer psychiatric symptoms than adults, and thus chorea or other movement disorders may be seen in this cohort (Armangue et al., 2013).

Laboratory

From a biochemical perspective, blood and CSF samples are often sent for analysis. A full blood count performed along with a lumbar puncture and subsequent CSF differential cell count. Common CSF findings in autoimmune encephalitis can help to reach a diagnosis. A mild lymphocytic pleocytosis (<100 WBC/µL) is seen in 80% of patients. A raised protein count (<150 mg/dL), normal glucose and an elevated IgG with oligoclonal bands

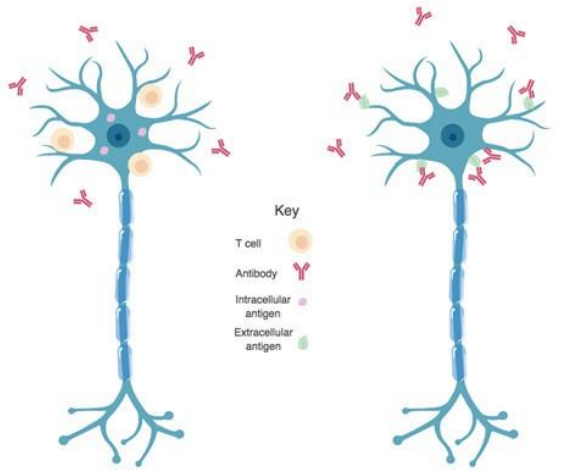

Figure 1: (left) T cell and antibody activity to intracellular antigen in group I autoimmune encephalitis. (right) Antibody attack on extracellular antigens in group II autoimmune encephalitis.

are also seen frequently (Tüzün & Dalmau, 2007).

With suspected AI encephalitis, an antibody panel is requested. In recent years, tests have improved in specificity and sensitivity for the detection of specific intracellular and neuronal surface antibodies. It is important to detect the antibody early in order to characterise the disease and to determine management strategies. Broad-spectrum commercial tests for relatively common antibodies should be carried out before specific tests for rarer antibodies, if the former is negative. Both the serum and CSF of the patient must be tested, with clinical justification based on the fact that in 14% of anti-NMDAR encephalitis patients the serum is negative for specific antibodies which are found to be present in the CSF (Gresa-Arribas et al., 2014). Only testing serum would give a false negative for this group. On the other hand, patients with positive serum and negative CSF may have degenerative or psychiatric pathologies (Zandi et al., 2015). When antibodies are found in both CSF and serum, titres can be used to estimate intrathecal production levels.

Antibody tests are central to the classification of these diseases, but results have to be analysed carefully and positive findings do not always equate to a diagnosis. In group II encephalitides such as anti-NMDAR encephalitis, IgG antibodies are pathogenic and diagnostic whereas IgM or IgA are seen in other psychiatric diseases and even in up to 10% of the healthy population (Jearanaisilp, Sangruji, Danchaivijitr, & Danchaivijitr, 2014). While it may be presumed that antibody titres correlate with disease severity and treatment response in other AI conditions, this is rarely the case here. In most of the diseases the only occasions they are useful is when comparing a single patient's CSF antibody titres over the disease course, to analyse treatment response or relapse. However, clinical wellbeing of the patient is still a better measure of the disease (Gresa-Arribas et al., 2014). Furthermore, testing for an antibody that is known to be pathogenic does not mean that it is pathogenic in every positive case. Looking at anti-GAD antibodies, a positive result can mean 3 things. The antibodies may be pathogenic and cause SPS, encephalitis or cerebellar degeneration. They may be found together with anti-GABA-B receptor antibodies which are actually the pathogenic antibody. Or lastly, they may be found in T1DM in patients without neurological disease (Tohid, 2016).

Group I		Group II	
Encephalitis Antibody	**Symptom**	**Encephalitis Antibody**	**Symptom**
Hu	Sensory neuronopathy	NMDAR	Prodrome + psychosis
Ma	Ophthalmoplegia	VGKC	REM sleep disorder
CV2/CRMP5	Sensorimotor neuropathy	GABAr	Seizures
SOX1	LEMS	AMPAr	Psychosis
GAD	T1DM + Stiff person syndrome (SPS)	GlyR	Motor/SPS

Table 1: Types of autoimmune encephalitis (named by antibody produced) and their distinguishing symptoms often seen uniquely in patients with this form of AI encephalitis

Neuroimaging

MRI is the primary imaging modality used in patients with suspected AI encephalitis. MRI changes are frequent but can often be similar to changes seen in other encephalitic causes like Herpes Simplex Virus (HSV) and so may be nonspecific (Sili, Kaya, & Mert, 2014). Findings vary by type of encephalitis as highlighted by Kelley et al. published in the American Journal of Neuroradiology (Kelley et al., 2017). Most classically seen are T2-FLAIR (fluid-attenuated inversion recovery) hyperintense lesions in temporal lobes and limbic structures. It is important to note that a negative MRI does not exclude the diagnosis of autoimmune encephalitis.

Electroencephalogram (EEG) is an alternative neuroimaging test used to aid diagnosis. EEG can help to exclude other causes of symptoms like seizures and diagnose and aid prognosis of certain types of autoimmune encephalitis. In classic limbic encephalitis, EEG can detect epileptic foci in one or both temporal lobes, or focal or generalised slow activity (Lawn, Westmoreland, Kiely, Lennon, & Vernino, 2003). When EEG detects an extreme delta brush pattern it can be suggestive of anti-NMDAR encephalitis and prompt antibody testing (Schmitt et al., 2012). EEG can also be used to determine the aetiology of refractory epilepsy or status epilepticus in which no response is seen to anti-epileptic treatments. Anti-GABAr encephalitides are the most heavily linked autoimmune encephalitis to seizure activity (Lancaster et al., 2010).

Exclusion of other diseases

As autoimmune encephalitis is a rare diagnosis, more common diseases must be considered and ruled out. Many forms of encephalitis, along with other similar pathologies, can present with comparable features and there are various tests which must be done to elicit the aetiology of these symptoms. Firstly, as infectious causes of encephalitis are prevalent, patients will likely be screened for Herpes simplex virus (HSV) encephalitis, the most common cause of viral encephalitis. This test is done by PCR of CSF and has 94% sensitivity and 98% specificity but only after 24 hours of onset (Weil, Glaser, Amad, & Forghani, 2002). For this reason, patients may be empirically started on acyclovir. Other viral causes which may be screened for include Varicella zoster, Enterovirus, West Nile virus, and Japanese encephalitis (Venkatesan, 2015). Bacterial causes include Listeria, Streptococcus, Syphilis, Lyme disease, and Tuberculosis. Fungal causes include Cryptococcus and Aspergillus and are found more commonly in immunocompromised patients (Venkatesan, 2015). As some of these causes are endemic in certain regions and depend on the host being immunocompromised in most cases, gaining a comprehensive medical and travel history from the patient is important. These infectious agents can be detected through PCR, serology for antigen or antibody, or culture. To effectively test for many agents at once, next generation sequencing techniques have been developed. These methods, like metagenomics deep sequencing of CSF, can screen for 100s of pathogens at once and speed up the diagnosis of the infectious agent (Wilson et al., 2014). Interestingly, 20% of patients with HSV encephalitis develop antibodies to the NMDAR (Armangue et al., 2015). This explains the previously mysterious condition of relapsing neurologic symptoms post HSV encephalitis which occur as psychiatric, cognitive or movement symptoms a few weeks after acyclovir treatment. This is a now well-established link showing a CNS viral infection triggering an autoimmune encephalitis. The mechanism behind this is likely to be inflammatory damage by the virus exposing the NMDAR to immune cells and stimulating an inflammatory response. This presentation likely occurs in the deep cervical lymph nodes which receive antigens from the CNS (Ransohoff & Engelhardt, 2012).

As well as infectious causes, other medical and autoimmune causes must also be excluded. Wernicke's encephalopathy, mostly seen in alcoholics, can mimic autoimmune encephalitis. If this is likely, thiamine supplementation will be carried out without waiting for lab results as fast treatment is necessary to avoid long term damage (Lallas & Desai, 2014). Other medical diseases which can present similarly are serotonin syndrome, and neuroleptic malignant syndrome. There are certain autoimmune diseases, which are not autoimmune encephalitides, that can present similarly. These include multiple sclerosis, encephalomyelitis, and neuropsychiatric lupus seen in the form of antiphospholipid syndrome. These will likely have other symptoms present, and so a full history and examination is important. They will also have different findings on MRI (Lancaster, 2016).

Treatment

Timely treatment is hugely important in these diseases to prevent further deterioration and long-term damage. When autoimmune encephalitis is strongly suspected or confirmed, empiric treatment will be commenced, often before any specific antibodies are detected. First-line treatments usually include steroids and/or intravenous immunoglobulin (IVIG). Steroids help to reduce the cerebral inflammation in AI as well as other causes of encephalitis. However, steroid do carry the risk of systemic side effects and are contraindicated in certain patients due to conditions such as peptic ulcers, hypertension, osteoporosis and diabetes mellitus (Kopera, 1993). IVIG also reduces inflammation by blocking Fas-mediated cell death, increasing the expression of the inhibitory Fc receptor on APCs, and shortening the half-life of autoreactive antibodies (Nimmerjahn & Ravetch, 2007). If the disease is suspected

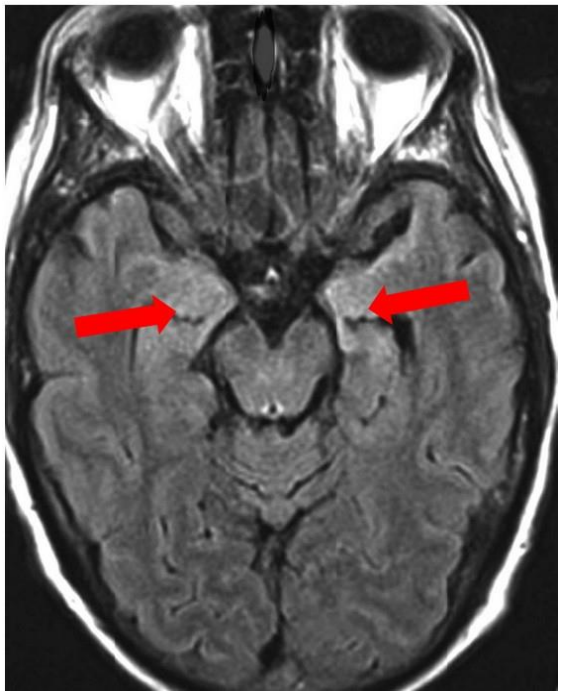

Figure 3: MRI of a patient with NMDAR encephalitis showing increased signal intensity bilaterally in the medial temporal lobes and hippocampi. Image taken from (Zhang et al. 2013)

to be a group II encephalitis, plasmapheresis is sometimes carried out to remove the pathogenic antibodies. IVIG and plasmapheresis are unlikely to worsen the disease if it turns out to be infectious (Lancaster, 2016). One major problem with these first-line treatments is that they do not reduce intrathecal antibody production (Furneaux, Reich, & Posner, 1990). First-line immunotherapy such as steroids have been shown to be limited in their efficacy in autoimmune encephalitis (Shin et al., 2018). At least half of patients are put on second line agents for this reason.

Second-line treatments are employed in patients unresponsive to first-line treatments. These include the immunotherapies of anti-B cell monoclonal antibody rituximab, or the anti-T cell drug cyclophosphamide (Lancaster, 2016). If a tumour is already diagnosed or newly detected it will be removed if at all possible. This usually helps to stabilise the disease aggressiveness (Alamowitch et al., 1997). Second-line treatments also share the problem of not targeting intra-thecal antibody production. Rituximab targets CD20 on B-cells to eliminate these cells, but the mature plasma cells within the CNS do not express CD20 and are therefore resistant (Martinez-Hernandez et al., 2011). Blood brain barrier (BBB) penetration of these second-line therapies is also limited (Dalmau, Geis, & Graus, 2017).

As previously mentioned, patients presenting with autoimmune encephalitis are likely to have a concurrent tumour. For this reason, a full cancer screen should be carried out, targeted to the diagnosis, e.g. ultrasound of testicles for Anti-Ma associated encephalitis. This should be done at presentation, and at follow-ups over the next 24 months, as tumours may be undetectable initially. It is vitally important to detect and address the cancer at the onset of treatment for a number of reasons. Firstly, treating the tumour may help the neurological symptoms. Secondly, coordination between tumour therapy and immune therapy may be important. Lastly, treatments with some immunotherapy agents may delay or complicate the diagnosis of certain cancers like lymphoma (Lancaster, 2016). For group I encephalitides, detection of the antibody may occur in certain cancers in the absence of encephalitis. If the antibody is detected by chance, or when investigating another disease, tumour screens should still be carried out. For group II encephalitides, presence of the antibody in the CSF usually indicates neurological disease, and likewise, the relevant tumour tests should be performed. On the other hand, patients with likely autoimmune encephalitis or cerebellar degeneration without identifiable antibodies should still be broadly screened for cancer (Lancaster, 2016).

More research is needed into many aspects of the treatment of autoimmune encephalitis. Further clarifying the pathophysiology of the specific types of autoimmune encephalitis will allow more targeted therapies and improve responses, especially for group I encephalitides. RCTs comparing individual first and second-line treatments are also needed to produce evidence bases guidelines for physicians attempting to treat these diseases. For now, prompt initiation of first-line therapies with appropriate monitoring and transfer to second-line drugs, along with tumour identification and resection, is the best treatment strategy.

Concluding Remarks

Autoimmune encephalitis is a relatively novel but important consideration on the list of potential diagnoses for a patient presenting with a range of neurological or psychiatric symptoms. It is not one disease but a family of similar diseases within two major groups. Many of the types are paraneoplastic or can occur in the absence of cancer, but careful tumour screening is usually warranted at presentation and at later follow-ups. The diagnosis relies on the initial clinical history and examination, laboratory findings and neuroimaging. Many other diseases, like infectious and medical encephalitides can present in similar ways and must be excluded. While the diagnosis of autoimmune encephalitis is frequently overlooked, early recognition and treatment is key to effective management in these patients. Current treatments consist of first-line steroids, IVIG and plasmapheresis, moving onto second-line immunotherapies, but this varies with aetiology and health of the patient.

New research in the last 5 years has identified many new autoantibodies and this is predicted to continue in coming years. This allows the correct identification of many diseases with previously unknown aetiologies as autoimmune. There is a need for new research into treatments, especially those which target the intrathecal synthesis of autoantibodies, as well as treatments to improve outcomes for the encephalitides with antibodies to intracellular antigens. For these group I encephalitides, better understanding of the role of T cell autoimmunity is needed to develop and utilise anti-T cell therapies in these diseases. Further large studies are needed to improve the classification of individual types of autoimmune encephalitis to allow for better diagnostic guidelines within the field. Currently, there are 7 clinical trials ongoing or recruiting into various aspects of autoimmune encephalitis listed on clinicaltrials.gov, and these will only help to improve understanding and outcomes in these relatively novel but devastating diseases.

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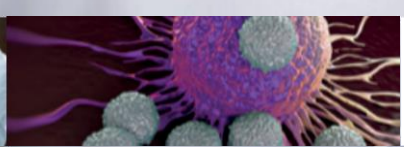

Assisted Dying? An Ethical Exploration of some Concerns around Legalisation

Amy P Worrall

From its Greek origins euthanasia, a 'good death' has come to have a multitude of meanings in a modern context such as a merciful death, the 'ending of suffering', 'palliation' or even 'assisted-suicide'. The issue of euthanasia, is by no means simple, and there is often a propensity to focus on the historical and philosophical. The modern worldwide flourish of scientific research has, thus far, failed to find answers to much of the unknowns surrounding death and dying. Even the precise physiology, underpinning the decline of the autonomic system, remains elusive and contentious.

While traditionally most, if not all, forms of euthanasia were considered 'immoral', much of the contemporary assisted-dying discussion revolves around a more modern interpretation of euthanasia, where due consideration is given to the voluntary or involuntary nature of assisted-dying, and the intention of the active or passive action. The types of assisted-suicide will be discussed, followed by some of the ethical concerns surrounding practical and legislative implementation of euthanasia.

Voluntary active assisted-dying (VAAD) is the active assisting of a patient to take their life, on the basis of a request to do so. Passive voluntary assisted-dying (PVAD) is the more passive provision of tools, such as writing a prescription, providing medication, that a patient can use themselves to take their own life, on the basis of a request from the patient.

It is worth acknowledging that both of these, VAAD/PVAD, rely on the patient having an understanding of the process to make it voluntary. Involuntary assisted dying also exists, both actively (where a physician might administer drugs resulting in the patient's death, with or without 'double effect', Double effect is a principle that says it is permissable to act in a way that may have both good and bad consequences, as long as the bad effect is not intended) and inactively, where a physician prescribes medicines that can result in death, but does not inform the patient of this eventuality. It is these latter two scenarios of involuntary assisted dying that troubles many when faced with the possibility of legislating for euthanasia in any form (Bishop, 2006b). This worry stems from the potential to abuse a system where VAAD and PVAD may be legislated for, but be exercised on those who have not voluntarily requested it.

Beyond the obvious ethical questions of autonomy, non-maleficence, beneficence, mercy and utility, which Hume, Rawls and many others discuss, there are distinct ethical issues that arise when it comes to legislating and implementing a formal procedure for assisted-dying. In Europe: Belgium, Luxembourg and the Netherlands all have legalized certain forms of euthanasia, and most work within the constraints of a medical model. These medical models often relate to patients who have capacity, who are terminally ill and who have requested assisted-dying (Hurst & Mauron, 2003).

A framework exists of ethical decision-making that identifies four topics for consideration in medical models. Similar systems, or variants of this model, are used in the European states that facilitate medically-modelled euthanasia. The four domains are: the medical indication, the quality of life, the patient's personal preference or previously expressed preference, and contextual considerations (Jonsen, Siegler, & Winslade, 2010). The model accounts for the principles of beneficence, non-maleficence, autonomy and the principles of justice.

Models provide structure and the necessary framework to make as many of the difficult decisions as objective as possible. There is always a risk here that physicians, in spite of the more objective scales, grades and formulaic tools of a framework, could run into trouble have difficulty with subjective judgements, making decisions based on futility, or in more sinister contexts skewing discussions and pressurising patients and families into making 'involuntary' decisions. It would be hard to refute the genuine risk that legislating for VAAD/PVAD might come with increased frequency of involuntary VAAD/PVAD, though the absence of them poses a continued failure to provide justice and fairness, and fails to acknowledge harms within the status quo.

It would also be naïve to suggest that VAAD and PVAD do not occur outside of a legal framework, including in Ireland, in both voluntarily and involuntary contexts. Martha Minow, Professor of Law in Harvard asks, which 'lie' is more beneficial: the lie that VAAD/PVAD does not occur at all, or the lie that 'institutional powers' would be able to prevent all vulnerable from ever succumbing to involuntary VAAD/PVAD (Bishop, 2006a)?

The fallacy that VAAD and PVAD do not occur is what allows society, the judiciary and healthcare professionals to turn a blind eye, or sympathetic glances, to cases where we might judge the situation to be understandable or warranted. The recent Irish case of Bernadette Scully, a GP that was accused of over-sedating her daughter who had microcephaly and severe epilepsy, is an example of appropriate prosecution (Cullen, 2016). However, the media and much of society rationalized the circumstances, intentions, purpose and the means that justified the actions in this scenario. The lack of legislation here results in politicians, prosecutors, the judiciary, medical professionals and the public to ignore cases of involuntary VAAD/PVAD, and avoid putting in place processes that might protect patients, physicians and the most vulnerable in society.

Would the provision of VAAD/PVAD legislation for those voluntarily seeking it, outweigh the inevitable risk and potential for those vulnerable among us to have VAAD/PVAD occur involuntarily, and illegally? In the absence of legislation, the greatest fault is the injustice and lack of fair and objective treatment of those at risk of involuntary VAAD/PVAD occurring and human subjectivity deciding who and when is prosecuted, sentenced, judged and/or held accountable. The risk that solitary human decisions; a doctor in a room, a judge on a bench, a Garda choosing to report a crime or not, might be the difference between prosecution or ignorance is not morally defendable. Due consideration to the ethics of accepting the status quo must also be deliberated.

Is there a role for a prescriptive legislation for VAAD and PVAD, or is there an alternative? Switzerland is of interest in this discussion. Swiss law classifies euthanasia as 'murder upon request by the victim', and thus finds euthanasia to be a type of murder, and consequently illegal. However, an exception clause legislates and condones assisted-suicide if motivated by altruistic intent. The Swiss model differs to the other European states, as well, in that it does not fall under the 'physician's role' or a medical model of ethical decision-making (Hurst & Mauron,

2003).

In light of this, one might wonder where the benefits and risks lie on the subject of legislating for assisted-dying? Should legislation be directly legalising of VAAD/PVAD, or should it be like a Swiss model with a 'Save and Except' clause. And while the government, medical authorities and other institutional powers can never really ensure there is no risk, Huxtable argues that there is a need to end "uncertainty, obfuscation and injustice". He believes this is to be through legislation, although he remains open to the shape that legislation should come in (Huxtable, 2004).

To digress, is there instead an alternative to euthanasia, and is there an ethical obligation to pursue alternatives? One might wonder if what we need most is a modern ars moriendi, a guide to the art of dying. Sean O'Mahony argues that the Irish ritual itself of dying is uniquely important and should continue to carry significance (O'Mahony, 2016), while Caitlin Doughty argues that the Irish, Muslim and Jewish approaches to death are healthy and human, and should be conserved, rather than be hidden from (Doughty, 2015).

The process of dying itself is at the heart of the euthanasia argument and our deep-rooted fear of pain and suffering. Some argue that legislating for euthanasia would morally desensitise death (Hurst & Mauron, 2003), while others believe that the transcendent meaning of humanity, independent of religion, is lost if leaving this world becomes mechanistic and perfunctory (Bishop, 2006b). "[Life isn't] about avoiding suffering" said Paul Kalinathi in his posthumously-published reflection When Breath Becomes Air (Kalinathi, 2016).

However, irrespective of these musings, in an Ireland where several high-profile cases have escaped prosecution - or as with Dr. Scully avoided sentencing. It is clear that the absence of legislation allows a blind eye to be turned on an important issue. for the turning of a blind eye to the issue. This reality could be an even greater immorality to those vulnerable that are not currently protected by the institutional powers, that might have some power to prevent involuntary VAAD/PVAD if it were to be legislated for.

To conclude, in progressing forward we might consider that legislating for assisted-dying might be a more egalitarian option, that treats all citizens equally, judges them as objectively as our institutions can ensure, and does so in an attempt to avoid negating the rights of those most vulnerable in society. We must consider the ethics of the act of VAAD/PVAD itself, but also consider the ethical implications for the implementation of assisted-dying legislation. Indeed, there is an obligation to consider ethics grounded in the reality and context in which the intended action is expected to operate within.

"It is not because things are difficult that we do not dare, it is because we do not dare that they are difficult." ~Lucius Annaeus Seneca

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Cancer Pain Management at a Specialist Palliative Care Inpatient Unit: An Audit

Sadhbh Dalton, Cormac Jones, Robert Power, Des McMahon, Michelle Barrett, Pauline Uí Dhuibhir and Declan Walsh

Cancer pain is prevalent and burdensome in a palliative care setting and managed pharmacological and through non-pharmacological means. There is variance in how effectively cancer pain is managed, and to address this the 'Pharmacological Management of Cancer Pain in Adults' was published by the Department of Health in November 2015. To assess adherence to the standards defined by the 'Pharmacological management of Cancer Pain in Adults'. Our study audited the implementation of these guidelines regarding recording pain, administering analgesics, dealing with side effects and opioid toxicity. Three researchers reviewed the charts of 100 consecutive cancer admissions between 01/09/17 and 31/12/17 in a Dublin hospice. This Information was used to assess adherence to 15 audit standards. Of the 15 audit standards examined, 9 met this goal of 100% compliance. 3 of the remaining 6 standards had a compliance equal or greater than 90%. There is a high degree of compliance in the assessment and management of cancer pain. Where compliance is not 100% clinical practice should be reviewed or feedback given on the audit tool. Future research should focus on completing the audit cycle, and further audit in a community or acute hospital setting.

Background

Cancer Associated Pain

Pain is defined as the unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage (Merskey et. al, 1986). Pain is subjective, but the patient is the prime assessor of their own pain. It can be graded by predefined categories and treated accordingly. Pain affects 80% of cancer patients with advanced metastatic disease (Cleeland et. al,1994). Over 1/3 of cancer pain is graded as moderate or severe (Van der Beuken et. al, 2007). Cancer pain can be acute, chronic or acute-on-chronic known as breakthrough or incident pain (Watson et. al, 2009). Cancer pain can be categorised as neuropathic or nociceptive. Neuropathic pain is a result of nerve damage to the central or peripheral nervous system and is described as shooting, burning or stinging. Nociceptive pain may be somatic (bone and soft tissue), or visceral (including hollow viscus) (Watson et. al, 2011). Psychological, social and spiritual distress can impact the individual's pain experience and in severe distress can culminate in 'total pain.' Hence these dimensions must be addressed as part of any comprehensive pain assessment (Twycross et. al, 2009).

Analgesic Use

Analgesics are used to treat cancer pain. The WHO (1986) developed a three step 'analgesic ladder' to guide the treatment of cancer pain according to its severity (Table 1).

As cancer pain is often moderate or severe in advanced disease, opioids are the most commonly prescribed analgesic. It is recommended that both background (long-acting) and breakthrough (short-acting) preparations are prescribed. Oral administration is the preferred route, but if not tolerated, subcutaneous or transdermal administration is employed (Radbruch et. al, 2011). If pain control is inadequate or side effects intolerable, opioids can be switched to an alternative opioid from the same ladder step. This is called opioid rotation and occurs in 20-44% of cancer patients (Sarhill, 2001).

Opioid side effects include constipation, delirium, dry mouth, nausea, neuropsychological symptoms, respiratory depression and sedation (Stone et. al, 2011). Symptoms of toxicity include delirium, hallucinations, myoclonus, respiratory depression and may be precipitated by hepatic or renal impairment (Watson et. al, 2011). There is also evidence that improved cancer pain management can increase quality of life by more than the pain reduction alone. This is due to 'symptom clustering,' whereby pain can worsen depression, fatigue and other symptoms in a cancer setting (Aktas et. al, 2010).

Despite the significant burden of cancer pain, there is variation in how adequately pain is managed. Estimates of unsatisfactory pain relief range from 12% in Germany (Zech et. al, 1995) to 43% in Italy (Cascinu et. al, 2003). Due to this prevalence, importance and variation, development of a national clinical guideline on cancer pain management was necessary.

Audit Standards

Work began on The National Clinical Guideline No. 9, entitled 'Pharmacological management of Cancer Pain in Adults' in 2011. A formal literature review of publications between 01/01/2011 and 31/12/2014 was undertaken, and the evidence was graded from level 1-5 according to SIGN 106 guidelines, The National Comprehensive Cancer Network guidelines, Palliative Adult Network Guidelines (3rd edition) and Oncology Nursing Society guidelines. After extensive consultation, 42 recommendations were made and the strength of recommendation was graded from A-D based on the evidence level. The Guidelines were devised in November 2015 and are due for formal review in 2018 (Lucey et. al, 2015).

Need for Audit

The Guidelines include an audit recommendation, which includes 18 audit questions based on the 42 evidence-based conclusions. Prospective audit is recommended where possible. The National Clinical Effectiveness Committee website includes an electronic audit tool, baseline assessment and action plan template which were also used. We used the Guideline Audit Tool to evaluate pain assessment and management at Our Lady's Hospice and Care Services (OLH&CS). To the best of the authors' knowledge, this is the first audit on this topic carried out since guideline publication. We conducted the audit by means of retrospective chart review and made some minor alterations, namely defining 'poor controlled pain' and 'uncontrolled pain'.

Methods

Objective: To audit cancer pain assessment and management in OLH&CS according to the 18 audit standards specified by the National Clinical Guideline (Appendix 1).

Literature review

A PubMed search was conducted to identify the recent literature in relation to opioid toxicity and side effects from 31/12/2014

WHO analgesic ladder	Score on numerical rating scale	Analgesic of choice
Step 1: mild pain	1 to 2 out of 10	Non-opioid (Paracetamol/NSAID) +/- Adjuvant
Step 2: mild to moderate pain	3 to 6 out of 10	Weak opioid (Codeine/ Tramadol*) +/- Non-opioid +/- Adjuvant
Step 3: severe pain	7 to 10 out of 10	Strong opioid (Morphine sulphate/ Oxycodone/ Hydromorphone/ Fentanyl) +/-Non-opioid +/- Adjuvant

Table 1: WHO analgesic ladder (Lucey et. al, 2015).

(when the Guidelines were published) to March 2018. MeSH search terms "cancer pain" and "opioid toxicity" yielded 186 articles. 'Cancer Pain' and symptoms of 'Pruritis', 'Nausea', 'Delirium' and 'constipation, yielding 42 articles.

Sampling and Data collection

Three student researchers conducted a retrospective chart review of 100 consecutive cancer patients. The healthcare charts of patients admitted to the inpatient palliative care unit from 01/09/17 to 31/12/17 were examined.

The Guideline does not define 'poorly controlled pain' which we defined as three doses of PRN opioid over 24 hours required, for more than three days in a row.

The Guideline also did not define moderate to severe hepatic impairment. We defined this as altered liver function tests, as well as signs of encephalopathy, jaundice, or ascites (Watson et. al, 2011).

The most recent admission in the patient healthcare records (clinical narrative, admission proforma/notes and medication Kardex) was scrutinised to establish documentary evidence of the 18 standards. The audit timeframe was seven days from the first reported episode of pain. All relevant data was recorded onto an audit proforma. Patient demographics (age, gender, primary cancer diagnosis and reason/outcome of admission) were recorded. Whether an admission proforma was used or not was also recorded.

Each chart required 30 minutes to examine and was checked once, while two clinicians reviewed a sample of 20 charts to check consistency. The 100 charts required 35 hours between the three student investigators.

Ethical consideration

The OLH&CS Healthcare Audit Committee reviewed and approved the project proposal.

Statistical analysis

Data was recorded, analysed and presented using Microsoft Excel.

Results

Demographics

100 admissions were reviewed in the audit. Of these, 45 were male and 55 female. The median age was 70, range 21-94. 59 of the admissions had an admission proforma completed, while 41 did not. Patient demographics are presented below (Figures 1-3).

Discussion

Compliance with audit standards

The National Clinical Programme for Palliative Care recommends compliance of 100%. Of the 15 audit standards examined, 9 met this goal. This reflects a high level of adherence to the Cancer Pain guidelines.

Use of admission proforma

Use of an admission proforma improved compliance to certain standards. This includes audit standard 3, where proforma use increased the assessment of anxiety, depression or spiritual distress from 72% to 100% (figure 3). In audit standard 9, use of a proforma improved delirium assessment as a sign of opioid toxicity from 62% to 80%.

Audit standards not met

Audit standards 1, 4, 9, 10, 11, 14, 17 were not fully met. Clinical practice may have in fact met the standard, but this was not possible to determine from the documentation analysed. Moreover, there may have been good clinical reasons to depart from the recommended audit standard. Relating to the audit tool itself, a yes/no audit question format proved difficult to apply to certain standards. For example, some audit standards (13, 14, 17) asked that a certain intervention be "considered". It is possible that an intervention was considered and decided against, but this could not be accounted for in the yes/no format.

Audit standards 1-4: Principles of Pain Management

In this category audit standards 1 and 4 were not met. Audit standard 1 had a very high compliance rate of 98%. Therefore, there is scope for review in the implementation and re-audit components of the audit cycle to see if

100% is achievable. Audit standard 4 had a compliance rate of 87%.

However, this relied on our definition of 'consecutive reports of poorly controlled pain' which was not defined in the guidelines. There also may be clinical reasons why in individual cases an opioid increase/addition or another analgesic was not appropriate.

Audit standards 5-12: Opioids

In this category audit standards 9, 10 and 11 were not met. Audit standard 9 had a high compliance of 97% and it is hoped that on completion of the full audit cycle that this will increase to 100%. Audit standard 10 (ii) was not met (Figure 5). These findings will be of interest to the clinical team of OLH&CS and it may be appropriate to review how such symptoms are recorded. Audit standard 11 had a compliance of 69% however there may be good reasons why this does not meet the standard. For example, it is possible that it was felt clinically that further opioid titration was more appropriate than opioid rotation.

Audit standards 13-16: Non-opioid Pharmacological Management

In this category audit standard 14 was not met, with a compliance of 5%. There are several possible reasons for this low adherence. The audit standard recommends that bisphosphonates should be 'considered' but insufficient

evidence precludes use as first line therapy. As discussed above, it is possible that bisphosphonates were considered for use but decided against. Also, the question from the audit tool only asked whether bisphosphonates were prescribed or not, which may not have accurately represented the audit standard.

Audit standards 17-18: Renal and Hepatic Impairment

In this category audit standard 17 (ii) and (iii) were not met, with compliance of 90% and 75% respectively. As discussed above, we were limited to checking what medicine was prescribed, rather than considered. We also could only check if dose reduction was done, rather than considered.

Limitations of Research

One limitation that arose during the auditing process was the issue of documentation. Particularly for the assessment of pain it is likely that our results do not reflect how pain was actually assessed, only what was recorded in the healthcare record. There were also difficulties locating the relevant data in each individual record.

There were challenges with the audit tool itself. Lack of clarity with terms such as "considered" rather than documented or recorded lead to subjective interpretations of the questions which may lead to problems with re-audits in the future.

This audit was intended to assist healthcare professionals to reflect on their own practice. Therefore, the clinical audit guidelines are written assuming that those carrying out the audit are clinicians and our status as medical students was a limiting factor.

Clinical Implications

It appears the consistent use of a proforma on admission can improve either documentation or assessment of pain and opioid toxicity (Figure 3). This is particularly true with anxiety, depression, or spiritual elements to pain, in addition to delirium as a sign of opioid toxicity. The proforma itself may be modified to include a more structured pain assessment under the 8 criteria, as well as a focused assessment on sedation.

In areas where compliance was less than 100%, it is important to examine if practice needs to be reviewed or if feedback on the audit tool may be more appropriate. In some standards such as audit standard 3 practice may need to be reviewed or documentation improved. For others, like audit standard 14 feedback on the audit tool may be more beneficial.

Research Implications

To the best of the authors' knowledge, this is the first audit to be completed based on these guidelines. This is useful for future elements and iterations of the audit cycle as it outlines some shortcomings of the included audit tool. A future study could audit the same guidelines, but in a community or acute hospital setting instead of a hospice. This would gain insight into the compliance with standards like audit standard 2, which was not possible in this study.

Conclusion

After auditing the cancer pain management at this specialist inpatient palliative care unit, the research team can conclude:

1. There is a high degree of compliance of OLH&CS in the assessment and management of cancer pain.

2. Where compliance not 100%, clinical practice should be reviewed or feedback given on the audit tool.

3. Future research should focus on auditing the same guidelines but in a community or acute hospital setting. This would investigate compliance with standards that could not be assessed in OLH&CS.

4. The audit cycle should be completed by a second chart review after the results of this study have been considered and an action plan put in place.

Acknowledgements

Our thanks to Professor Declan Walsh, Dr. Des McMahon, Michelle Barrett, Pauline Uí Dhuibhir, Jennifer Dempsey and Staff of Our Lady's Hospice and Care services.

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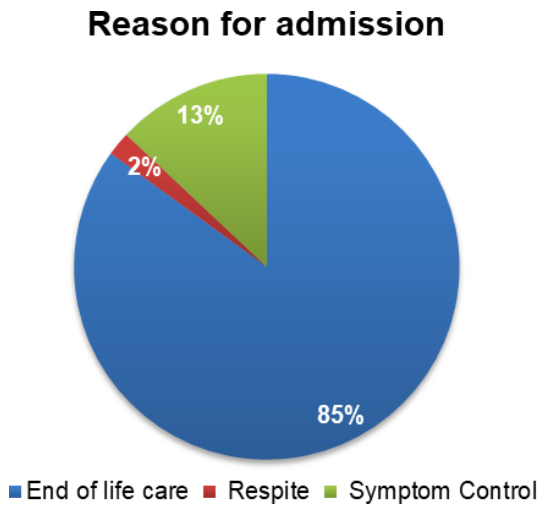

Figure 1: Reason for patient admission

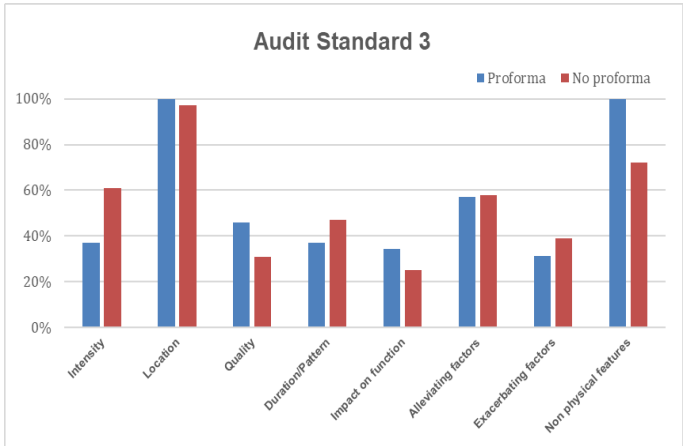

Figure 4: Audit Standard 3 Compliance. 'Non-physical features' refers to the presence of anxiety, depression or spiritual distress.

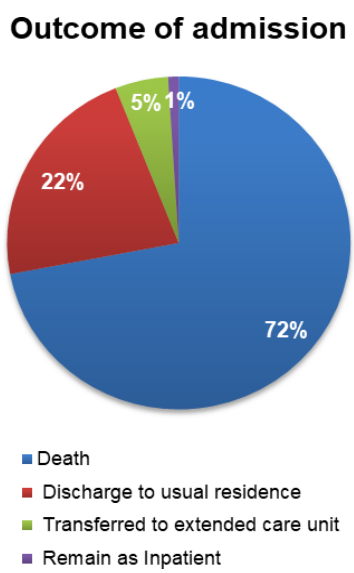

Figure 2: Outcome of admission

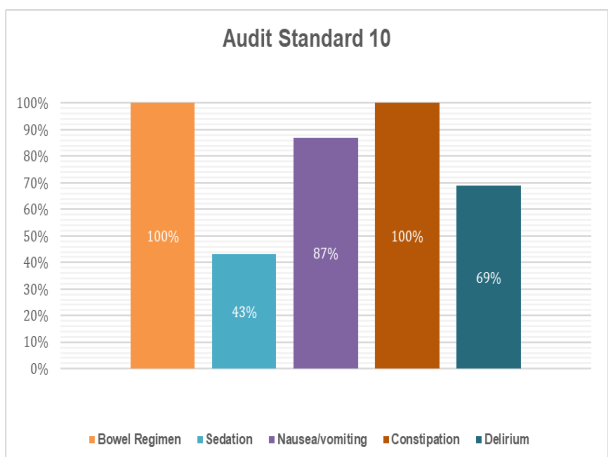

Figure 5: Audit Standard 10 Compliance.

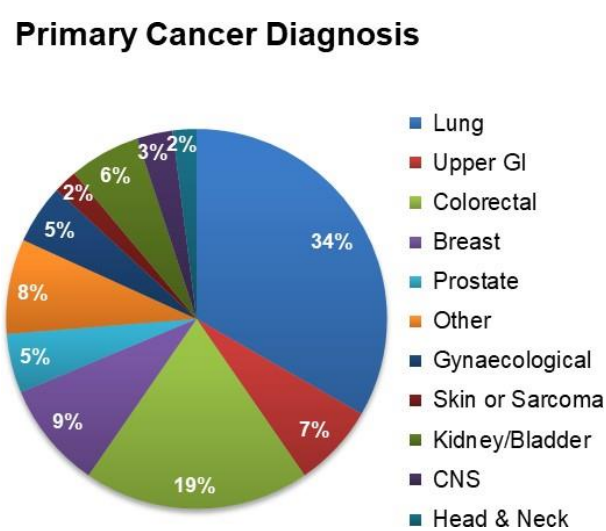

Figure 3: Other diagnoses: mesothelioma myeloma, lymphoma, thyroid carcinoma.

Appendix 1: Audit standards

	AUDIT STANDARDS
	Address physical, psychosocial, emotional and spiritual domains
	Patient given appropriate information about pain management encouraged to participate.
	Pain assessment to include: • Intensity • Location • Quality • duration/pattern • impact on function • exacerbating factors • relieving factors • presence of anxiety, depression or spiritual distress
	Pain managed in accordance with the WHO cancer pain relief guidance. a. Poorly controlled pain defined as ≥3 breakthrough opioid doses in 24-hours
	Weak opioids for mild/moderate pain +/- non-opioid analgesic. Unless specific patient-related issues, use codeine and codeine/paracetamol combinations in preference to tramadol or tapentadol.
	Oral morphine sulphate, hydromorphone and oxycodone for moderate to severe pain. Consider opioids with lower acquisition costs when all other costs are equal.
	Oral route if practical and feasible. Other options: subcutaneous, intravenous, trans mucosal, transdermal, topical and spinal routes.
	Transdermal route suitable for stable pain. Titrated to adequate pain relief with oral/parenteral opioid pain prior to initiation of transdermal patch. Prescribe breakthrough medication also.
	When starting strong opioids, offer patients regular oral morphine, with rescue doses of oral immediate-release morphine for breakthrough pain.
	Anticipate, monitor & manage opioid side-effects
	Opioid rotate if pain poorly controlled, or side-effects intolerable.
	Evidence-based dose conversion ratios to apply. Dose titration as needed.
	For neuropathic pain, consider anti-epileptic and antidepressant medications. Monitor side effects.
	Consider bisphosphonates for pain associated with bone metastases (Limited evidence)
	Methadone may be used moderate or severe pain. (Specialist advice only)
	Spinal opioids require specialist input
	Renal impairment: Use opioids with caution, but don't delay use. Consider reduced doses/frequency. Specialist advice in moderate/severe impairment. Monitor for toxicity. Safest opioid for Stage 4 or 5 kidney disease: Alfentanil and fentanyl (estimated glomerular filtration rate <30 ml/ min/1.73 m^2). Paracetamol is non-opioid of choice for mild/moderate pain. Adjuvant analgesics may require dose adjustment.

A Peculiar Cause of a Watery Eye

David Lennon, Conor Lyons and Michael O'Rouke

Introduction

Sarcoidosis is a multisystem disorder characterised by non-caseating granulomatous inflammation with a wide variety of potential presentations. The cause of the disease is largely unknown, however, CD4+ T cells are thought to play a role in the excessive inflammation within tissues. Sarcoidosis incidence is globally estimated at 16.5/100,000 for men and 19/100,000 for women (Hillerdal et al, 1984). The most common manifestation of sarcoidosis is pulmonary sarcoidosis. It is estimated that 90% of patients will have an abnormal chest x-ray with bilateral hilar lymphadenopathy, pulmonary infiltrates or fibrosis (Merck, 2018). Other less common presentations include sinonasal, ocular, dermatological, cardiac muscle or bone involvement. A recent study aiming to determine cause of death in patients diagnosed with sarcoidosis, the most prevalent determinants of mortality were shown to be respiratory and cardiac failure as a result of sarcoid spread (Swigris et al, 2011). This highlights the importance of recognising and treating sarcoidosis early. The following case is an example of how sarcoidosis may not present in a classical manner, requiring an open mind and lateral thinking to arrive at the correct diagnosis.

Case

A 28-year-old male presented to the emergency department at the Royal Victoria Eye and Ear Hospital with a two-day history of painful, red swelling inferomedially in the left lower lid. The patient also reported a background history of left sided epiphora (eye watering) for the preceding eight months. This had been treated by his general practitioner with chloramphenicol drops, a topical antibiotic commonly used to treat eye-related infections. The patient was otherwise well with no other symptoms and no past medical history of note. There were no other findings on review of his other organ systems.

On examination, a 15 mm erythematous swelling was present below the medial canthus of the lower left lid. With mild pressure, mucopurulent material was expressed from the lower punctum. He was afebrile at roughly 37°C and vitals were within normal limits. He was prescribed oral co-amoxiclav and advised to continue with chloramphenicol drops.

The following day the patient returned with worsening pain in his lower lid and associated epiphora reporting malaise. On examination the swelling had increased in size and temperature was elevated to 38°C. The area was incised and the mucopurulent contents were sent for culture and sensitivity. The patient was admitted for intravenous (IV) co-amoxiclav for 48 hours and then discharged home on oral antibiotics. Three days following the course of IV antibiotics, the swelling, erythema and pain described were resolved. Due to scarring of the nasolacrimal duct from the infection, a dacryocystorhinostomy (DCR) procedure was scheduled for one week later.

The procedure performed via endoscopic approach to create a new nasolacrimal duct. During the DCR procedure, friable nasal mucosa was noted by the surgeon and a biopsy was sent for pathology consult. At this point, it was suspected that there may be an underlying disease causing this presentation. Bloods were taken post-operatively and a routine blood profile was ordered. Anti-neutrophil cytoplasmic antibodies (ANCA) and angiotensin converting enzyme (ACE) were also requested as both biomarkers can be useful in predicting the presence of certain systemic diseases. ANCA antibodies are present in various vasculitides (inflammatory conditions of blood vessels) and ACE is elevated in sarcoidosis. Due to the suspicion that sarcoidosis may be present, a chest x-ray was also ordered to establish pulmonary findings. A computed tomography (CT) sinus was requested to visualise the soft tissues of the nasal cavity.

Two weeks post-DCR, the patient re-presented to the emergency department with recurrence of left sided lower lid swelling. Oral co-amoxiclav was prescribed however swelling persisted despite antibiotic therapy. Results from investigations carried out at the time of surgery displayed raised calcium and ACE levels with bilateral lung hilar lymphadenopathy on chest x-ray (Figure 1). Results from the biopsy taken during the DCR displayed noncaseating, granulomatous inflammation of nasal mucosa. The combination of the x-ray, histology and biochemical findings make the diagnosis of sarcoidosis definitive. Granulomas present in sarcoidosis produce excessive amounts of ACE resulting in characteristic elevated levels, similarly the increased inflammatory activity results in high serum calcium levels. The patient was prescribed a tapering course of oral prednisolone and referred for respiratory opinion to further investigate the chest x-ray findings. At the latest review six weeks post-op, pain, swelling and erythema of the left lower medial canthal area had improved and the patient was tapered off oral prednisolone.

Sinonasal Sarcoidosis (SNS)

Separate studies carried out by Aubart (Aubart et al, 2004) and Yanadağ (Yanadağ et al, 2006) found the prevalence of sinonasal mucosa inflammation in sarcoidosis to be as uncommon as 1% amongst patients with sarcoidosis. These patients can present with nasal crusting, congestion, epistaxis, pain or anosmia. On examination, patients with SNS are found to have friable nasal mucosa, nasal polyps, or characteristic submucosal nodularity (McCaffery and McDonald, 1983).

However, the patient did not have nasal polyps or submucosal nodularity as the only clinical finding to suggest underlying disease was abnormally friable nasal mucosa. Clinicians should be aware of variable presentations, being especially vigilant in cases which encounter unexpected

Stage	Disease Progression	Suggested Treatment
I	Mild reversible disease, paranasal sinuses not involved	Saline nasal spray with nasal irrigation and topical nasal steroids
II	Moderate disease, potentially reversible, sinuses and paranasal sinuses involved	Stage I therapy combined with intra-lesional steroids
III	Severe and irreversible nasal and sinus disease	Stage I and II therapy combined with systemic therapy

Table 1. Proposed grading system by Krespi.

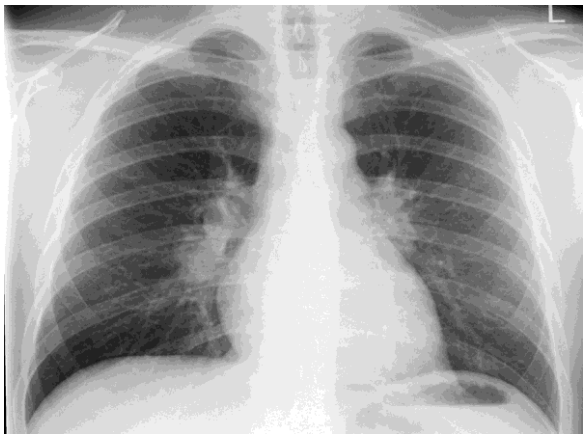

Figure 1; Chest X-Ray displaying characteristic bilateral hilar lymphadenopathy and reticulonodular opacities.

complications, such as recurrent infections as with the present case.

There have been attempts to classify SNS in order to determine the best treatment regimes, such as the system proposed by Lawson in 2014 (Lawson et al, 2014). This system divides SNS into four subgroups: hypertrophic, atrophic, destructive and nasal enlargement. However, due to gaps in the scientific literature regarding SNS, a robust treatment algorithm that is unanimously accepted does not exist. This is mostly due to the rarity of the disease subtype and the subsequent lack of clinical trials.

The natural progression of SNS without any other systemic involvement is different to regular systemic sarcoidosis. SNS is associated with greater morbidity than classical sarcoidosis. A case series demonstrated that patients with SNS required systemic treatment (corticosteroids / immunosuppressants) more often than those without sinonasal involvement (100% vs. 57.7%) and a longer duration of treatment (88 months vs 22 months). The same study showed that the number of patients who underwent spontaneous remission (cessation of disease process without treatment) were significantly fewer in the SNS cohort at 10 years (6.2% vs. 55.7%) (Aubart et al, 2004).

Management

Many sarcoidosis cases are detected incidentally and are asymptomatic, in which the patient's treatment consists primarily of monitoring for deterioration. Currently, there are no universally accepted guidelines for the treatment of symptomatic sarcoidosis with sinonasal involvement. Oral steroids are the mainstay of treatment for most patients as the anti-inflammatory effect is effective in treating granulomatous inflammation (McKinzie et al, 2010). Topical nasal corticosteroids can augment treatment and control local inflammatory processes. Nasal irrigation and emollients also play important roles in symptom management.

If necessary, systemic steroids may be combined with topical therapy (Broaddus et al, 2015). If the disease requires prolonged systemic steroid use, a steroid sparing agent should be used instead. Cytotoxic therapy like methotrexate or azathioprine may be used in these cases, as can anti-tumour necrosis factor (anti-TNF) agents such as adalimumab (Callejas-Rubio, 2008). It has also been shown to be possible in certain situations for disease to regress spontaneously. Antibiotics are used to treat secondary infections related to mucus stasis or sinus obstruction.

Surgery may also be required to treat sequelae such as dacryocystitis that can arise as a result of inflamed tissue. If the sequelae of SNS damage nasolacrimal ducts as in this case, they must be repaired via DCR to achieve satisfactory long-term outcomes. The DCR enables ocular secretions from the eye to the nasal cavity by creating a new channel which is kept patent post-operatively with O'Donoghue tubes until the channel heals sufficiently to remain patent without supports. The O'Donoghue tubes are then removed during an outpatient procedure at a later date. In 1995, a grading system was proposed in by Krespi (Krespi et al, 2005) as a guide for determining management. The system grades disease severity according to nasal involvement and gives suggested guidelines to treatment.

Conclusion

Diagnosis of SNS can be delayed or missed entirely without thorough examination. The presented case demonstrates that nasolacrimal or ophthalmological features may be the only presenting symptoms. An extensive systems review including exploration of symptoms including nasal congestion, epistaxis, epiphora, anosmia would enable the clinician to query the possibility of SNS. Recognition of this entity is important as treatment significantly reduces morbidity and mortality in patients.

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Kielland's Forceps: A Necessary Revolution? Ethical Dilemmas in Obstetrics and Gynaecology

Robert A. Farrell

The Kielland's forceps has been controversial since its inception. The unparalleled range of movement offered by its unique design made it for a time the instrument of choice for occipito-transverse arrest in the second stage of labour. In recent decades use of the Kielland's forceps declined significantly following a series of damning case reports linking its use to significantly poorer neonatal outcomes, and now many obstetric trainees are not trained in Kielland's deliveries. However, these case reports have never been replicated, and modern evidence now suggests that the not only is the Kielland's forceps equivalent in neonatal and maternal outcomes to other forms of vaginal delivery for transverse arrest, but also that is significantly less likely to fail preventing the substantially poorer outcomes associated with sequential instrumentation, or emergency Caesarean section. The potential reintroduction of structured training in Kielland's delivery raises ethical concerns regarding training related risk, and whether the profession has accurately quantified the potential risks involved. However, modern evidence broadly supports a positive balance of risk and favours the widescale reintroduction of the Kielland's forceps.

Introduction

The Kielland's forceps has been controversial since its inception. The unparalleled range of movement offered by its unique design made it for a time the instrument of choice for occipito-transverse arrest in the second stage of labour. In recent decades use of the Kielland's forceps declined significantly following a series of damning case reports linking its use to significantly poorer neonatal outcomes, and now many obstetric trainees are not trained in Kielland's deliveries. However, these case reports have never been replicated, and modern evidence now suggests that the not only is the Kielland's forceps equivalent in neonatal and maternal outcomes to other forms of vaginal delivery for transverse arrest, but also that is significantly less likely to fail preventing the substantially poorer outcomes associated with sequential instrumentation, or emergency Caesarean section. The potential reintroduction of structured training in Kielland's delivery raises ethical concerns regarding training related risk, and whether the profession has accurately quantified the potential risks involved. However, modern evidence broadly supports a positive balance of risk and favours the widescale reintroduction of the Kielland's forceps.

The Evidence for Kielland's Forceps

The Kielland's forceps has divided professional opinion since it was first presented by Christian Kielland in 1916 (Dunn, 2004). Indeed, Kielland's own hospital, the Kristiania in Oslo, did not begin widespread use of his forceps until 1930 (Hem, 2001). The innovative design of his forceps, a relatively straight profile with a gentle backwards pelvic curve and a unique sliding lock, allows rotation alongside correction of foetal asynclism, and made the Kielland's forceps the instrument of choice for arrested descent in occipito-transverse positions (Dunn, 2004). However, a series of case reports cast grave doubts over the neonatal mortality associated with Kielland's forceps use, and many training centres have since discontinued teaching the technique, with as many as 31% of UK units not supporting Kielland's delivery (Al Wattar, Mahmud, Janjua, Parry-Smith, & Ismail, 2017; Chiswick & James, 1979). Now, mounting evidence of the Kielland's forceps' safety in expert hands, and concern over the increasing recourse to emergency Caesarean section (C.S.) in cases of transverse arrest have prompted discussion of the reintroduction of the Kielland's forceps to general obstetric practice (Nash, Nathan, & Mascarenhas, 2015). This article explores the evidence supporting and opposing the use of the Kielland's forceps, with review of the ethical obstacles in its reintroduction.

The Evidence Against Kielland's Forceps

Malposition of the foetal head occurs in 4.4% of live births, and is now the most common indication for second stage C.S. (Tempest, Hart, Walkinshaw, & Hapangama, 2013). However, emergency second stage C.S. are associated with a maternal and neonatal complication rate of between 32.6%-57% (McKelvey, Ashe, McKenna, & Roberts, 2010). Alternatives to emergency C.S. in cases of malposition include the rotational ventouse, the Kielland's forceps, and manual rotation. There are few studies that have compared these three modes of vaginal delivery in cases of foetal malposition, and no significant differences were observed in either neonatal or maternal morbidity between the techniques (Bahl, Van de Venne, Macleod, Strachan, & Murphy, 2013). However multiple studies have observed that neonatal and maternal outcomes are substantially worse both in emergency C.S. following failed instrumentation, or following sequential instrumentation (Burke, Field, Mujahid, & Morrison, 2012; Tempest et al., 2013).

Attention then must be turned to the failure rate of each method. The failure rate of manual rotation is reported as 4.8%, however the technique is poorly generalisable and subject to strict entry criteria (Bahl et al., 2013). Failure rates of Kielland's forceps delivery are reported to be between 3.7%-10.4%, whereas rotational ventouse failure rates range from 22.4%-43.7% (Nash et al., 2015). Rotational ventouse techniques have become the favoured technique of operative vaginal delivery for foetal malposition, yet they are between 2 and 12 times more likely to fail, requiring sequential intervention which significantly increases morbidity.

Ethical Considerations

If used correctly, the Kielland's forceps has the capacity to reduce both maternal and neonatal morbidity through a technique that is no more dangerous than other modes of operative vaginal delivery already in use (Bahl et al., 2013). However, the major obstacle to its reintroduction and an area for great ethical concern is that the Kielland's forceps is not today in widespread use, that there is a generation of obstetricians untrained and unskilled in its use (Al Wattar et al., 2017). Articles have also raised doubts about whether we can accurately diagnose long term consequences of forceps delivery, and whether this uncertainty should limit support for reintroduction (Dietz, 2015).

Nearly all studies of the efficacy and safety of Kielland's forceps report their use by skilled practitioners, not by trainees. Inexperience with the forceps is associated with increased rate of all complications particularly OASI, which in one case series, occurred in 2.1% of consultant led deliveries, and 8.1% of trainee led (Josephs, Denison, Akolekar, Cooper, & Stock, 2010). Concerns were raised as early as 1999 that training programs did not provide sufficient skills to guarantee safe use of the Kielland's forceps (Robson & Pridmore, 1999). Is it ethically justifiable to expose patients to this increased risk of morbidity while a generation of obstetricians retrain?

The most compelling refutation of this concern is the very institution of medical education and training. We expose patients to doctors who are less experienced than their senior colleagues at all stages of their training. These doctors are more prone to misjudgements and errors, but we accept the risk that they may commit errors, for the benefit of having experienced doctors in the future (Lewis et al., 2014). There are few differences between the junior doctor, unskilled but training; and the senior obstetrician, unskilled but training. Both are striving to deliver better patient care, both are more at risk of making errors, but both act under supervision of training schemes which will reduce this risk. Why then would we not consider reintroducing the Kielland's forceps justified as another facet of medical education where risk is increased temporarily in pursuit of better outcomes in the future? The need for competent supervision demands a degree of urgency in reintroducing Kielland's training. As time progresses fewer experienced consultants will be available to supervise training, and while useful and effective, simulation training such as the RCOG's ROBuST program cannot replace oversight by an experienced clinician (RCOG, 2015).

It is accepted that forceps deliveries are associated with increased rates of pelvic floor injuries including OASI and levator ani avulsion injuries (Johanson et al., 1999). However, some authors have, controversially, raised concerns over whether clinical diagnosis of these conditions is sufficiently sensitive, and that reported figures may be a gross underestimation (Dietz, 2015). Although there is no Kielland's specific data, imaging studies have identified OASI in up to 60% of women after forceps delivery, and levator ani avulsion in 30-65% of women (Cassado Garriga et al., 2011; Kearney et al., 2010). Both conditions are associated with serious, significant, often recurrent, morbidity (Dietz, 2015). Thus, is it ethically justified to utilise a technique in which more than 50% of women may suffer serious complications?

These reports of increased complications are themselves fraught with uncertainty, reporting accurate diagnosis of a condition they themselves admit is difficult if not impossible to diagnose (Kearney et al., 2010). How then to proceed? Any strategy must focus on empowering patients, presenting them with both the risks and benefits, and allowing them, in concert with their obstetrician to come to an informed decision. The already poor public image of the Kielland's forceps, and of forceps in general, necessitates considered and careful discussion by skilled and empathetic clinicians to ally patient fears and to bring forth the true risks and benefits. (Murphy & Liebling, 2003). Patients should be aware that all medical procedures are carried out with some degree of uncertainty, however, proceeding is justified by the weight of evidence supporting the intervention's therapeutic benefit, and confidence that the balance of risk is favourable. Most modern evidence supports a positive balance of risk for Kielland's forceps delivery, and it would seem unethical to ignore its potential to greatly improve patient outcomes (Burke et al., 2012; Macleod et al., 2013).

It would therefore seem ethically imperative, that the use of Kielland's forceps be encouraged by training authorities and indeed UK trainees are enthusiastic to train in Kielland's delivery (Al Wattar et al., 2017). When used correctly, they are no more dangerous than any other form of operative vaginal delivery, and are far less likely to fail, preventing sequential instrumentation. Therefore, if we are truly to respect the doctrine of non-maleficence, then it becomes imperative that we support the reintroduction of Kielland's forceps in order to prevent sequential instrumentation and potentially devastating outcomes.

Conclusion

The Kielland's forceps has been controversial since its inception. A series of damning case reports linked its use to significantly poorer neonatal and maternal outcomes, and resulted in the forceps nearly disappearing from obstetric practice (10). However, in recent years new analysis has supported the skilled use of the Kielland's forceps, as both equivalent in safety to other rotational techniques, and significantly less likely to fail, thus reducing sequential interventions. The reintroduction of the Kielland's however raises several ethical concerns: is it justifiable to accept potentially poorer outcomes during the training period in exchange for future more favourable outcomes? And, is it appropriate to proceed with the reintroduction of the forceps when there exists uncertainty regarding potentially significant complications? The uncertainty regarding complication and training related morbidity will always exist in healthcare. Moreover, advances in maternal and neonatal outcomes with skilled use of the Kielland's forceps makes its reintroduction ethically and clinically justified.

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HPV-associated Oropharyngeal Cancer: A Distinct Clinical Entity

Katherine Hughes

It is now widely accepted that cervical cancer cannot develop in the absence of Human papillomavirus (HPV) infection. Less well known is the link between HPV and oropharyngeal cancer (OPC). With falling smoking rates, OPC rates were expected to decline. However this has not occurred, potentially due to a rise in HPV-associated OPC. This literature review aims to provide a summary of the most recent data regarding risk factors, biomarkers and prognosis for HPV-positive OPC, and to compare these findings with HPV-negative OPC. In light of its improved prognosis, this paper will also discuss the potential merits of treatment de-escalation in cases of HPV-positive OPC. A search was carried out on PubMed with the keywords Human papillomavirus, oropharyngeal cancer, and head and neck cancer. The search focused on papers published in the past 5 years but did not exclude seminal or relevant studies published earlier. Conclusion: HPV-associated oropharyngeal cancer should be recognised as a distinct clinical entity, which stands in contrast to HPV-negative OPC with regards to its aetiology, risk factors, chemotherapy and radiation therapy sensitivity and therefore also prognosis. More research is required to determine appropriate treatment and public health strategies.

Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus with over 100 genotypes, of which approximately 15 are considered to be oncogenic (Munoz et al, 2003). The causal relationship between HPV and the development of cervical cancer is now well established. In 1999, Walboomers et al. published findings that HPV infection is related to cervical cancer in 99.7% of cases, resulting in HPV being labelled a 'necessary cause' of cervical cancer (Walboomers et al, 1999). As a result, it is now widely accepted that cervical cancer cannot develop in the absence of HPV infection. This finding is of significant clinical importance, particularly with regards to implementation of public health campaigns. In Ireland, the HPV vaccine was introduced in 2010 for all girls in their first year of secondary school to induce HPV immunity in young women prior to virus exposure (usually before they become sexually active). This national initiative is supported by findings that the quadrivalent HPV vaccine against serotypes 6, 11, 16 and 18 was able to reduce rates of HPV infection by 90% and of high-grade cervical changes by 85% (Garland et al, 2016).

While the connection between HPV and the development of cervical cancer has now been proven beyond reasonable doubt, evidence for relationship between HPV and OPC is less well-known. However, it has been suggested that OPC will overtake cervical cancer as the most common HPV-related cancer (Chaturvedi et al, 2011). OPC is a cancer of the head and neck, with over 90% of head and neck cancers being of the squamous cell carcinoma (HNSCC) type. It has been found that the incidence of HNSCC has remained largely static in recent years. This is a surprising result, as traditionally HNSCC has been most strongly associated with tobacco smoking, and with decreasing smoking rates in the developed world one might expect to see a subsequent overall decrease in HNSCC rates (Ng et al, 2012). However, the decrease in smoking rates appears to have been balanced by an increased relative contribution to HNSCC by HPV-associated OPC, even being described as an 'epidemic' by some authors (Gillison and Shah, 2001; Pytynia et al, 2014; Okami, 2016).

HPV was initially thought to be the causative agent in only a minority (approximately 16-25%) of OPC cases (Gillison et al, 2000). However, evidence now suggests that HPV prevalence in OPC may be as high as 72%, with up to 90% of these cases being caused by serotype 16 (Leoncini et al, 2014; Kreimer et al, 2005). As HPV-positive rates increase across the world, HPV-negative (smoking-related) OPC rates have decreased by over 50%, much like other types of HNSCC (Maasland et al, 2014). Taking into consideration the striking increase in HPV-associated OPC rates, the remainder of this paper will briefly focus on the most recent data about risk factors and prognosis in relation to HPV-associated OPC. This paper will also discuss the potential merits of treatment de-escalation and vaccine prevention in cases of HPV-positive OPC.

Methods

A literature review was conducted using the biomedical search tool PubMed using keywords oropharyngeal carcinoma, human papillomavirus, HPV carcinogenesis, HPV biomarkers, OPC prognosis, HPV vaccination. An analysis on the current understanding of Human Papillomavirus and its role in oropharyngeal carcinoma was then carried out. Aspects such as risk factors for infection, pathogenesis, biomarkers, treatment and vaccination were considered.

Discussion

Risk factors for Oropharyngeal Carcinoma

Tobacco and alcohol consumption have long been associated with HNSCC (Leoncini et al, 2014; Maasland et al, 2014; Wyss et al, 2013; NIH, 2009). Thus patients with OPC in the 20th century characteristically were middle aged, of a low socio-economic status and smoked or drank alcohol. However, with the proportion of OPC attributed to HPV infection on the rise, the demographic characteristics of people diagnosed with OPC have shifted significantly. Patients now tend to be younger, with the primary risk factor being their level of sexual activity.
Genital HPV infection is the most commonly acquired sexually transmitted infection (Ankit et al, 2013). The incidence of oral HPV is on the rise, and disproportionately affects the young (30-50 years), leading to an increased rate of HPV-associated OPC in this group (Nguyen et al, 2010).

This pattern is hypothesised to result from changing patterns of sexual behaviour among younger generations. It has been observed for many years that increased sexual activity was correlated with an increased risk of developing OPC. With the development of technology to detect HPV DNA in mucosal cells, it has now been demonstrated that the above observation had been serving as a marker for an increased risk of exposure to HPV and thus an increased possibility of developing OPC. A case-control study in the USA found that recent oral sex and tongue-kissing were both connected with HPV infection of the oral mucosa, independent of vaginal sex (Jones, 2015). It was suggested that the relative popularity of oral sex among young adults may account for the rise in HPV-associated OPC in this age group (Nguyen et al, 2016).

A recent systematic review found that not only is oral sex a risk factor for developing HPV-associated OPC, but that the number of lifetime sexual partners also carries risk (Chancellor et al, 2016). The review notes, however, that some of the studies were poorly controlled.

For HPV to cause infection it must access the basal epithelioid cells (Cox, 2006), which is increased in likelihood by damage to

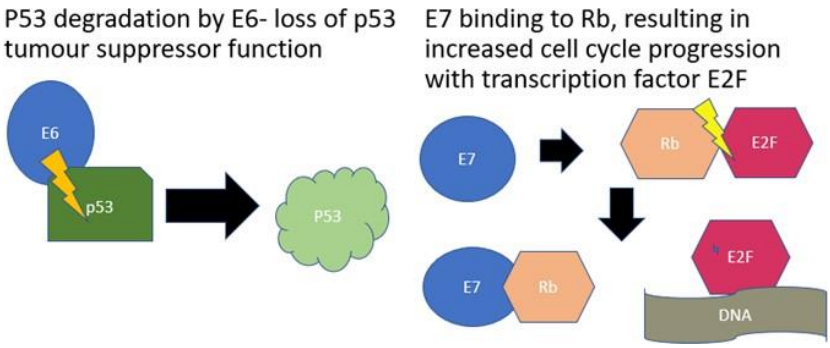

Figure 1: HPV DNA integrates into host DNA and amplifies transcription of oncogenic proteins E6 and E7. These proteins downregulate the action of tumour suppressor genes p53 and Rb, resulting in uncontrolled proliferation and thus cancerisation of the epithelial tissue.

the epithelium (Bui et al, 2013). Therefore, poor oral hygiene, chronic ulceration and inflammation might increase the ability of HPV to enter oral mucosa cells and cause infection, and thus increase the risk of OPC. Further studies are needed to clarify the exact risk oral sex, number of sexual partners and oral mucosal health play in the development of HPV-associated OPC.

Differentiating HPV-positive and HPV-negative Oropharyngeal Carcinoma

It has been found that the prognosis of an OPC diagnosis differs considerably depending on HPV status, making the distinction between the two aetiologies clinically significant (Weber et al, 2010). Research in the last decade has centred on the characterisation of proteins associated with HPV infection and carcinogenesis in an attempt to find suitable biomarkers to differentiate the two forms of OPC.

It has been found that HPV DNA integrates into host chromosomes and upregulates the production of several oncoproteins, such as E6 and E7 (Refer to Figure 1). P53 is a protein known as the 'guardian of the genome', which acts to induce apoptosis in damaged cells and therefore prevents cancer. E6 is upregulated by HPV and inhibits p53's protective actions.

P16 is a cyclin-dependent kinase (CDK) inhibitor, which acts as a check point inhibitor to control proliferation. P16 normally prevents Retinoblastoma protein (pRb) phosphorylation. This unphosphorylated pRb associates with E2F, a transcription factor, and prevents E2F from inducing cell proliferation. In a HPV-infected cell, oncoprotein E7 is produced, which causes dissociation of the pRb-E2F complex. This free E2F increases unregulated cell cycle progression and thus carcinogenesis (Zhang et al, 1999). P16 expression is reactively upregulated in HPV-associated OPC an attempt to counteract this E7-induced cell proliferation (Lewis James et al, 2013). Thus HPV-positive oncogenesis is characterised by p53 degradation, pRb inhibition and p16 upregulation. In contrast, HPV-negative (tobacco-related) OPC is typified by p53 mutation and p16 down-regulation (Elrefaey et al, 2014). Updates to the staging of OPC were devised in 2017 by the American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section to reflect these differences (Lydiatt et al, 2017). The AJCC found the tumour suppressor protein p16 to be a reliable surrogate biomarker and an independent prognostic factor in HPV-positive OPC. Identifying HPV-positive OPC via P16 immunohistochemical staining is also endorsed by the AJCC as it is an inexpensive test has near global availability, allowing for international adoption. Hence, OPCs are now staged according to two distinct sets of guidelines, depending on whether or not they overexpress p16.

Improved Prognosis for HPV-positive OPC

HPV-positive OPC is has been found to have a favourable prognosis when compared with HPV-negative OPC. For example, one study reported a 3-year overall-survival rate of 82.4% in the HPV-positive subgroup and 57.1% in the HPV-negative subgroup (Weber et al, 2010. High levels of p16 expression is associated with locally advanced stages of HPV-positive OPC at diagnosis. Paradoxically though, p16 expression has been shown to be an indicator of good prognosis (Weinberger et al, 2006).

There are several theories about why this may be. When considering the risk factors highlighted above, it is clear that the increase in popularity of oral sexual activity among young adults results in an increase exposure of HPV and thus increased risk of HPV-positive OPC among that age group. In contrast, patients with HPV-negative OPC tend to be of an older age group with a long history of tobacco and alcohol use (Nguyen et al, 2010). This raises the likelihood of co-morbidities as well as field cancerization (for example, smoking may result in a concurrent HNSCC and lung carcinoma). These demographic factors can strongly influence the prognosis of the respective OPC groups. HPV-positive OPC is mainly characterised by inhibition of tumour suppressor genes p53 and Rb without somatic mutation. In comparison, HPV-negative oncogenesis usually results from several mutations, especially in p53 and upregulation of epidermal growth factor receptor (EGFR). EGFR overexpression is correlated with high rates of recurrence and distant metastases. Thus, multiple and variable mutations in the HPV-negative OPC group may lead to poor treatment response and prognosis (Elrefaey et al, 2014).

The increased survival rate of HPV-positive OPC has also been attributed to the increased chemo-radiation therapy (CRT) sensitivity profile of HPV-positive OPC. Genome-Wide Association Studies have found that cells which express high levels of histone binding protein RBBP4 tend to be RT-sensitive (Ng et al, 2012), and studies have demonstrated an upregulation of RBBP4 in HPV-positive OPC (Lohavanichbutr and Houck, 2009; Kim et al, 2014). In addition, low p53 expression levels, as seen in HPV-positive OPC, correlated with a complete response to induction chemotherapy. Conversely, HPV-negative patients were found to highly express class III beta-tubulin, which was associated with a poor 3 year overall survival (Kim et al, 2014). Studies such as these highlighted the fact that HPV-positive and -negative OPC are distinct cancer disorders with respect to aetiology, prognosis and treatment.

Current & Future Treatment Regimens

Until recently, patients who present with OPC are treated similarly regardless of their HPV status, with surgery, radiotherapy and chemotherapy. This multi-modal approach

of surgery and CRT was associated with significant morbidity and mortality. Pauloski et al. studied the long-term sequelae of oropharyngeal surgery and found that the level of speech impairment and intelligibility was associated with the volume of tongue and soft palate removed (Pauloski et al, 1998). Nguyen et al. looked at acute and chronic toxicities in patients who underwent CRT for OPC. They noted significant mucositis, dysphagia, speech impairment, and high levels of haematological effects such as anaemia and neutropenia. Oesophageal strictures and chronic dysphagia with associated aspiration were also found, both of which can require long-term gastrostomy tubes (Nguyen et al, 2007). It is clear then that surgery and CRT for OPC is not without risks and complications, thus a decrease in intensity of these therapies would be beneficial to a patient provided their cancer control is not compromised.

Considering the difference in CRT sensitivity between HPV-positive and HPV-negative OPC, it is reasonable to question if current treatment regimens are more intense and toxic to HPV-positive OPC patients than is necessary to achieve a cure. A less noxious regimen may be more suitable for patients with HPV-positive OPC.

Methods in achieving cure without excessive toxicity can range from altering the chemotherapeutic agent, radiation dose, or the use of less-invasive surgical techniques. However, the benefit of less intense treatment for some must be balanced against the risk of cancer spread in others. Therefore, there needs to be an accurate method of choosing patients for whom treatment de-escalation would be appropriate. Several trials are underway to try and clarify these issues, such as the De-Escalate study and the QUATERBACK trial (both in Phase 3), and the PATHOS study (currently in Phase 2). Time will tell if any or all of these toxicity-sparing tactics are defensible.

Prevention

The HPV vaccine is indicated among young girls as a prevention strategy for cervical cancer. Randomised controlled trials have supported both the bivalent HPV16/18 vaccine (Ceravix) and the quadrivalent HPV 6/11/16/18 vaccine (Gardasil) against cervical, vaginal, vulvar, and anal infection in women (Munoz et al, 2010; Kreimer et al, 2012). The vaccine is typically administered to girls before the age of 15 years; statistically prior to viral exposure via sexual contact.

Several studies, such as Chaturvedi et al. in 2011, have demonstrated that by 2020, OPC is set to surpass cervical cancer as the most common HPV-associated cancer (Chaturvedi et al, 2011). In addition, the majority of HPV-positive OPC is expected to occur among the male population. Perhaps, then, the indication for the vaccine should also be carefully considered. It would seem logical to include males in the vaccination program in light of this evidence in order to tackle what is rapidly becoming the most common HNSCC. This change was supported in 2011 by the Centre for Disease Control (CDC), who recommend that HPV vaccination should include males under 12 years (Gillison and Shah, 2001).

However, this CDC recommendation has yet to be implemented in Ireland, and the decision of whether to fund a broadened vaccination program will inevitably be driven by the efficacy and cost-effectiveness of such an initiative. A systematic review published in 2017 found that inclusion of non-cervical HPV-associated cancers in economic assessment suggests the measure would be cost-effective and supports the expansion of the HPV vaccine to include boys (Anita et al, 2017). With respect to efficacy, HPV vaccination has been shown to reduce prevalence of oral HPV infection, and thus may be effective at reducing HPV-mediated oral carcinogenesis (Herrero et al, 2013). Further research is needed to determine the true efficacy of the HPV vaccines in reducing HPV-positive oropharyngeal carcinoma. However, given the vaccines' effectiveness against cervical and other genital lesions, it seems likely that the vaccine will be effective in this respect.

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Open vs laparoscopic hernia repair for unilateral inguinal hernia, are there better outcome with development in skills?

Abidur Rahman, Alice Titiloye, Leah Carroll, Christopher O'Loughlin, Niall O'Donnagain, Niall Hickey, Hugo Temperley and Yasir Bashir

Inguinal hernia refers to the protrusion of bowel or omentum through a weakening in the abdominal wall – specifically the inguinal canal. The gold standard treatment for bilateral inguinal hernia is laparoscopy. However, there is presently no consensus in the gold standard surgical method of unilateral inguinal hernia treatment. Unilateral inguinal hernias have been shown to be effectively treated in both open and laparoscopic fashion. Intrigued by this dichotomy in treatment for the ailment, we investigated the effectiveness of both procedures over two time periods (2000-2005 vs. 2012-2017) for the treatment of unilateral inguinal hernia. The primary outcome measure that was used for comparison was recurrence rates. The 2000-2005 period exhibited a lower recurrence rate for open procedure whereas the 2012-2017 period favoured the laparoscopic technique. However, these observed differences were not statistically significant in favouring one technique over the other.

Introduction

The word 'hernia' is derived from the Latin word 'rupture' and describes the event where an organ protrudes through the cavity in which it should be contained (Sangwan et al., 2013). There are various types of hernias such as inguinal, ventral, femoral, umbilical, epigastric, hiatal, which can be described based on their characteristics including direct, indirect, acquired, congenital, reducible and nonreducible (Miserez et al., 2007). If an abdominal hernia cannot be reduced, the herniated contents can become incarcerated in the abdominal wall (Hjaltason, 1981). This requires surgical intervention as an incarcerated hernia can become life threatening if blood flow is cut off to the externalized tissue and the hernia becomes strangulated (Gallegos et al., 1991).

We have chosen to specifically focus on unilateral inguinal hernias. An inguinal hernia is defined as a protrusion of tissue from the abdominal cavity through a weakened space in the inguinal canal. Inguinal hernias occur ten times more frequently in men than women, with 27% of males experiencing herniation in their lifetime (Jenkins and O'dwyer, 2008). An inguinal hernia occurs above the inguinal ligament and can be subdivided into direct and indirect variants. Direct inguinal hernias occur when bowel projects through a weakened section of abdominal muscle along the inguinal canal medial to the inferior epigastric vessels (Stein, 1946). An indirect inguinal hernia occurs when the opening of the inguinal canal remains patent after birth, allowing passage of bowel through the canal lateral to the inferior epigastric vessels (Gilbert, 1989). Corrective surgery is required when simple conservative management by reduction and watchful waiting fails.

This paper focuses on the recurrence rates in unilateral inguinal hernia surgical repair, specifically Open approach and the Laparoscopic approach. The Lichtenstein open method involves using a polypropylene mesh to bridge the defect rather than sewing the two sides together (Schmedt et al., 2005). Hernias can also be repaired laparoscopically by passing the endoscope and instruments through one, three or four small incisions, dissecting the area and repairing the hernia with mesh from the inside of the abdomen. We wish to investigate whether recurrence rates have changed from the years 2000-2005 and 2012-2017 in order to establish whether procedural and technological improvements in both surgeries has led to better patient outcomes.

Methods

PICOS

The study will examine research articles published during the time periods of 2000-2005 and 2012-2017 inclusive in order to compare the aforementioned surgical techniques. The study aims to determine if there is a significant difference between the two techniques in rates of hernia recurrence. Furthermore, we will also examine the costs associated with the procedures as a secondary outcome. We performed a systematic review, utilizing Cochrane, Web of Science, EMBASE, and Ovid Medline databases to retrieve research articles. The search strategy was based on using keywords that related to inguinal hernia, the surgical techniques used for its treatment, and complications following the surgery. The surgical techniques that were used included laparoscopic (total extraperitoneal and transabdominal preperitoneal techniques) and open incision procedures. The surgeries were separated into these two categories, in an attempt to compare the complications rates - primarily recurrence rates post-surgery. The complete search criteria can be seen in Figure 1.

Selection Criteria

A subject librarian carried out a search on Cochrane, EMBASE, Ovid Medline and Web of Science using the keywords; 'unilateral inguinal hernia', 'laparoscopic surgery', 'open surgery', 'inguinal' and 'hernia', which yielded an initial result of 3,776 articles. These were uploaded to endnote and the duplicates were removed. The remaining papers were then uploaded to Covidence™ (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org) for further screening. The articles were initially screened based on the title and abstracts. After this initial selection process, complete versions of the selected publications were retrieved for a full text review. The entire selection process was performed by two independent authors in duplicate and any conflicts were resolved by a third member of the group to prevent selection bias.

We included articles that investigated the long term outcomes of patients undergoing unilateral inguinal hernia surgery. The papers were required to compare laparoscopic and open surgical procedures and report recurrence rates amongst the two techniques in the long term. Studies were excluded if they did not report the outcomes of unilateral inguinal hernias, if the studies were not available in English, and if the study was published outside of the target years (2000-2005 and 2012-

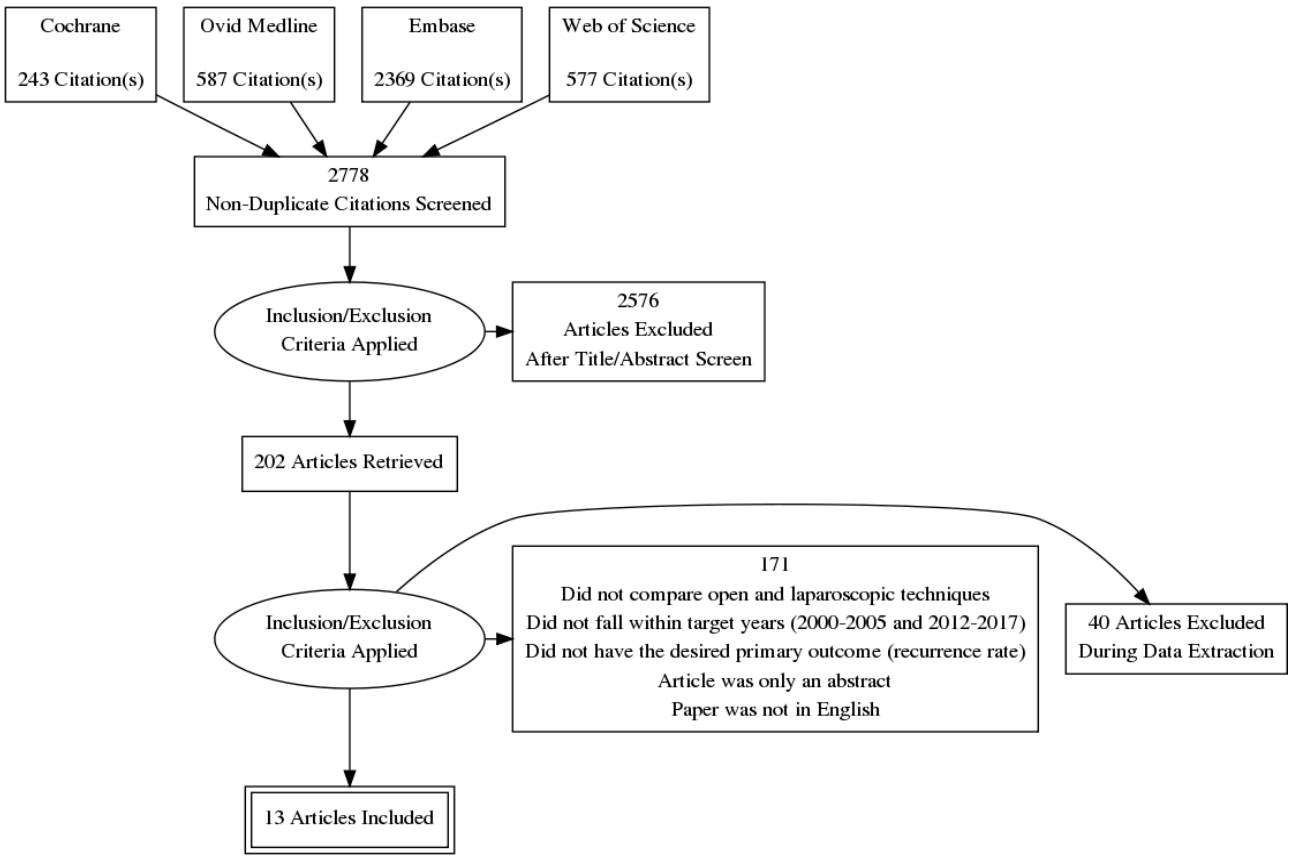


Figure 1: PRISMA flow diagram for article selection for the systematic review

2017). Any publications that were presented as only abstracts or conference proceedings were not included, as it was not possible to extract the necessary information required for the overall analysis.

Data extraction

Included studies were first separated into two groups according to publication year: 2000-2005 and 2012-2017 inclusive. The data from the selected studies were extracted according to the type of procedure performed. Data extraction primarily focused recurrence rates between open and laparoscopic surgeries performed as well as costs in these populations.

Data Analysis

The collected data from the papers selected for analysis were assessed according to the time of publication. The data sets were analysed by comparing recurrence rates from open and laparoscopic procedures and forest plots were created for each time-frame.

Results

The selected search criteria yielded thirteen articles that fulfilled our inclusion standards. The total number of subjects in the eight studies conducted between 2012 - 2017 was 1,208,024 with a range from 185 to 125342 patients. The five studies conducted between 2000 - 2005 had a total of 4,433 subjects with individual studies having 50 to 1777 subjects.

The cumulative results from the selected studies demonstrated that the recurrence rates are not constant. However, the

Author	Year	Procedure Type	No. of unilateral hernias	Recurrence Rates	Cost
McIntosh et al.	2001	OH: 302 LH: 308	610	OH: 0 LH: 1.9%	OH: £788.89 LH: £1112.64
Wright et al.	2002	OH: 151 LH(TEP): 149	210	OH: 2% LH: 2%	LH > OH due to costs of instruments
Lal et al.	2003	OH: 25 LH:25	50	OH: 0% LH: 0%	
Winslow et al.	2004	OH: 1476 LH: 301	1777	OH:5% LH: 3%	
Neumayer et al.	2004	OH: 834 LH: 862	1696	OH : 4.9% LH : 10.1%	

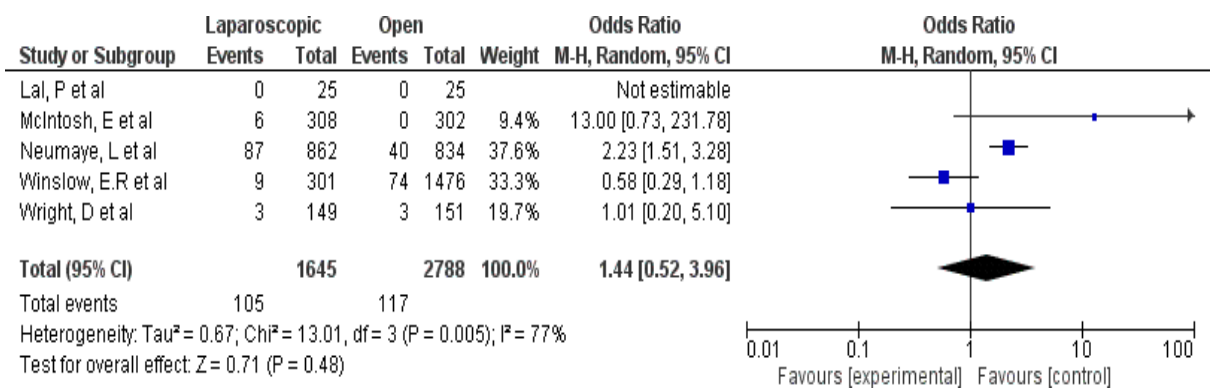
Table 1: Papers included from the time period 2000 - 2005 OH – open hernia repair; LH – laparoscopic hernia repair;

TAPP – transabdominal pre peritoneal hernia repair; TEP – Total extra peritoneal hernia repair;

Table 2: Papers included from the time period 2012 - 2017

Author	Year	Procedure Type	No. of unilateral hernias	Recurrence Rates	Cost
El-Dhuwaib et al.	2013	OH: 117,234 LH: 8,108	125, 342	OH: 2.1% LH: 4%	-
Abbas et al.	2012	OH: 97 LH(TAPP) : 88	185	OH : 5.2% LH: 3.4%	-
Wang et al.	2013	OH: 84 LH: 84 (TAPP); 84 (TEP)	252	OH: 4.76% LH: 0%	OH: 5852±864 RMB TAPP: 9504±1132 RMB TEP: 9351±985 RMB
Khan et al.	2013	OH: 44 LH(TAPP) : 46	90	OH: 12% LH: 3%	OH: 6180±1409.73 PKR LH(TAPP): 13040± 2166.15 PKR
Li et al.	2013	OH: 952 LH: 504	1456	OH: 0.6% LH: 1.2%	-
Ashfaq et al.	2014	OH: 59 LH:44	96	OH: 3% LH: 0%	-
Vigneswara et al.	2015	OH: 91 LH: 380	337	OH:2.5% LH: 2.5%	-
Zhu et al.	2017	OH: 923 LH: 202	998	OH: 0.46% LH: 0.64%	-

OH – open hernia repair; LH – laparoscopic hernia repair; TAPP – transabdominal pre peritoneal hernia repair; TEP – Total extra peritoneal hernia repair; RMB – Chinese yuan; PKR – Pakistanirupee



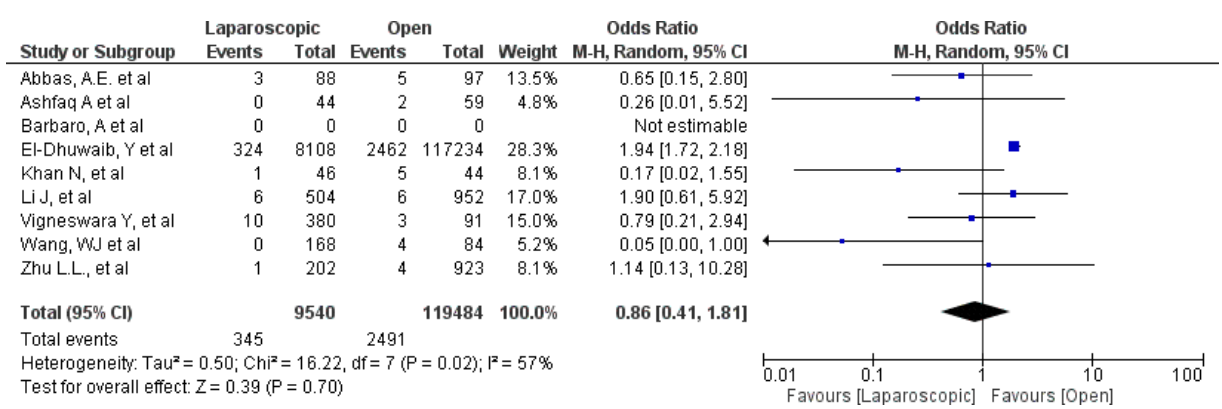


Figure 3: Forest plot depicting the data extracted from the 2012 – 2017 papers

majority of papers from Table 1 indicate that between 2000-2005 recurrence rates were lower in open inguinal hernia repairs compared to laparoscopic techniques. This is highlighted most clearly by Neumayer et al. who demonstrated a recurrence rate of 4.9% in open repairs compared to 10.1% in laparoscopic repairs (Neumayer et al., 2004). Furthermore, when examining the papers that assessed the costs associated with the procedures, it is evident that the laparoscopic repair was more expensive, likely attributable to the cost of the instruments used in the procedure and lack of availability of resources.

In the data sets obtained from 2012-2017 inconsistency in recurrence rates is also observed. The majority of the studies reported either lower recurrence rates for the laparoscopic procedure or similar recurrence rates, suggestive of an improvement in post-surgical complications from the 2000-2005 time period. El-Dhuwaib et al. show a lower recurrence rate for the open procedures, however this data takes surgical procedures conducted over a large time period starting from early 2000 (El-Dhuwaib et al., 2013). For this reason, the results from the study need to be assessed carefully as it has surgical data that coincides with both of our time periods of interest. Khan et al demonstrated a substantially higher recurrence rate in open hernia repairs (12%) in comparison to laparoscopic repairs (3%), however their sample size was small (Abbas et al., 2012). The costs for the surgeries were also examined whenever possible and it was consistently shown that laparoscopic repair remains more expensive than open repair.

Figure 2 depicts the five studies included from between the years 2000 to 2005. The result of this meta-analysis is that the results did not display a statistically significant difference between the open and laparoscopic techniques - summary evaluation crosses the line of no effect (P = 0.48) but still favouring the open technique. The level of heterogeneity in the data from 2000-2005 is 77%. According to the data collected as shown in Figures 2 and 3, it is evident that there were higher recurrence rates in the laparoscopic method between 2000-2005 before the paradigm shifts towards lower recurrence rates in the laparoscopic method between 2012-2017. The odds ratio interprets the odds of recurrence of symptoms in laparoscopy and illustrates lower recurrence rates between 2012-2017 compared with 2000-2005. The data does not meet statistical significance since the 95% confidence interval crosses the midline making it non-equivocal.

Discussion

This study investigated which surgical procedure for unilateral hernias had the most favorable outcomes. Studies published in 2000-2005 and 2012-2017, comparing open versus laparoscopic surgeries for unilateral inguinal hernias were identified and analysed. This project focused on recurrence rates to determine which procedure type that had the more effective outcomes. While research has shown that in treatment of bilateral hernias, the laparoscopic method has been recommended as the 'gold standard', studies examining a potential best approach for unilateral hernias are limited because of the lack of widespread consensus (Wauschkuhn et al., 2010; Saleh et al., 2014).

Based on the results above, in the years 2000 - 2005, the open method was favoured when compared to the laparoscopic, as it produced lower recurrence rates and was more cost effective. This may be due to the fact that during this time, laparoscopy was relatively new and limited to surgeons who were experienced and trained to use it. Conversely the open method was readily available and had been used extensively by general surgeons up until the invention of laparoscopy.

For the years 2012 - 2017, the trend shifts towards laparoscopy as the preferred approach. Over the course of this time period, laparoscopy produced lower recurrence rates when compared to that of the open method. The number of laparoscopic hernia repair procedures has increased and therefore more surgeons have gained experience and training in the laparoscopic procedures. This has led to a shift in the favoured treatment as it is less invasive (minimizes infection risk due to exposure), is associated with a shorter duration of hospital stay and has been shown to minimize postoperative pain (Cavazzola and Rosen, 2013).

Although both time periods favour different approaches, the statistical evidence for both remains insignificant. There are a number of potential causes for this insufficient statistical evidence. Firstly, the search criteria for this topic was highly specific, each study had to include an open vs. laparoscopic comparison in recurrence rates for unilateral inguinal hernias during the specific time periods stated above which narrowed down the eligibility of studies from the original 3776 papers found from the search. It is clear that laparoscopy has come long way since its introduction into surgery, however the results of this study highlights that in the case of repair of unilateral inguinal hernias, more comprehensive comparative research needs to be carried out in order to concretely determine whether laparoscopy is ideally the best method of treatment for unilateral hernias in most cases.

Conclusion

Our study attempted to elicit the safest surgical approach when treating unilateral inguinal hernias, comparing the open method to a laparoscopic approach using recurrence rates as primary outcome and cost as a secondary outcome. Research papers selected focused on these outcomes during two time periods (2000 – 2005 and 2012 -2017).

Based on our research, it was apparent that between 2000-2005 shifted towards the open technique, whereas between the years 2012 – 2017 surgeons favoured the laparoscopic technique. However, in neither case was statistical significance shown following statistical analysis. We ultimately concluded that more comprehensive comparative research is required to unequivocally state that the laparoscopic technique is superior to the open for the repair of unilateral inguinal hernias.

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“Go mór i mbéal an phobail” – antidepressants and their effects on the mouths of the public.

Mairéad Kelly

Introduction

In recent years, the treatment mechanisms at the disposal of the treating practitioner for mental illness have evolved greatly. The most significant of these for the dental clinician is the use of antidepressant medications which have both direct and indirect implications for dental treatment. It is therefore imperative that the dentist is confident in the management of these patients and the particular set of complications they may present with.

Given the high incidence of these disorders, it is of the utmost importance that the dental practitioner is equipped with the required skillset to adequately manage these patients, and provide them with lifelong holistic care that takes their mental disorder and its implications for treatment into consideration. In 2004, depression was found to be the fourth leading cause of disease burden worldwide and the reported prevalence of depressive episodes found in this study was 16 per 100,000 per year for males and 25 per 100,000 per year for females (Üstün et al, 2004).

On a European Scale, a study including rural and urban areas within Ireland, Spain, the UK, Norway and Finland demonstrated a prevalence of 8.56% of depressive disorders within a 12-month period (Ayuso-Mateos et al, 2001). Due to the high prevalence of depressive disorders in the general population, the dental practitioner is likely to encounter patients suffering from these conditions. In addition to this, the prevalence of depressive disorders in younger age groups has become apparent in recent years. In particular, three quarters of all mood disorders manifest by the age of 24. It is therefore of the utmost importance that the dentist is aware of the implications of these conditions and their management for the dental health of the patient. (Kessler et al., 2005).

Ultimately, a history of a common mental disorder should affect a dentist’s management of a patient for a host of pertinent reasons; depressive disorders have frequently been associated with poor oral health, with various studies showing links between depressive disorders and caries, periodontal disease, tooth substance loss and tooth erosion (Delgado-Angulo et al., 2015; Khambaty and Stewart, 2013; Anttila et al., 2001). Furthermore, independent of this increase in dental pathology, patients with mental illness may have an exacerbated perception of dental pain and thus a greater incidence of dental phobia (Kisely, 2016).

The international classification of mental diseases (ICD-10) breaks down mental diseases into various subcategories and the disorders that are the main focus of this review (depression, generalised anxiety disorder and panic disorder) are categorised within this as common mental disorders.

Taking the above factors into consideration, it is apparent that an increased incidence of pathology in the dentition, compounded by dental phobia preventing routine dental examination makes care for these patients both more complex and more urgent. Correct identification of these patients as being at a higher risk of developing dental pathologies, and adaptation of treatment plans to allow consideration of this allows for a more comprehensive approach to patient care.

The treatment of mental illness and its oral implications

Mental health disorders, such as depression and anxiety, are managed using a variety of treatment modalities, the most significant of which to the dental practitioner being pharmacological treatment. Since various antidepressant medications are available, the pharmacological agent is selected based on the patient’s symptoms and the side effects profile of the drug. In 75% of cases, antidepressant therapy is an effective treatment modality, and therefore is encountered with relative frequency by dentists (Agency for Health Care Policy and Research, 1993).

The major medications prescribed for depressive disorders include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and atypical antidepressants (Snow et al., 2000). SSRIs are also commonly prescribed medications for panic and anxiety disorders (Bandelow et al., 2013).

TCAs were previously the first line drug for the treatment of depression for over a decade, and are still widely in use today (Goldman et al., 1999; Williams et al., 2000).
The SSRI class of drugs are currently the first line of pharmacological treatment for both depressive disorders and panic disorders (Majeroni & Hess, 1998; Kasper & Resinger, 2001). However, although the side effects associated with SSRIs are substantially less debilitating than those of the TCAs, they do nonetheless exhibit some important side effects that may affect the dental practitioner (Edwards and Anderson, 1999) (Spigset, 1999).

The atypical antidepressants have been found to be equally effective as the SSRIs and are also considered first line drugs for mild to moderate depression (Horst and Preskorn, 1998).

The major orofacial side effects of TCAs, SSRIs and atypical antidepressants are outlined in table 2 below. The effects and implications for dental practitioners of each of these drugs is the main topic of interest in this literature review.

Orofacial implications and dental management

A significant number of the drugs discussed in this review have anticholinergic or sympathomimetic effects. Although necessary for the management of depressive and panic disorders, these systems play a major role in the proper functioning of the body and it is therefore unsurprising that they can cause a wide range of side effects.

Pathophysiology

Throughout the literature, the most frequently cited oral implication of antidepressant use is xerostomia, which is defined as a subjective alteration in salivary flow (Saleh et al., 2015). Saliva serves many functions in the oral environment, including moistening and lubricating, taste and smell, digestion, protection of the oral mucosa and oesophagus and tooth protection (Dawes et al., 2015). The TCAs decrease salivary flow by blocking the effects of acetylcholine on muscarinic M3 receptors, which in turn decrease parasympathetic stimulation and decrease stimulation of the salivary glands (Del Vigna de Almeida et al., 2008). SSRIs and atypical antidepressants have sympathomimetic effects. It has been suggested that

ICD-10 Diagnosis	Definition
Depression	A depressive episode, with three typical symptoms of depression and at least four common symptoms where the minimum duration of the depressive episode is at least two weeks. - A depressive episode is defined as depressed mood, loss of interest, and reduced pleasure and energy, leading to increased fatigability and decreased activity
Generalised Anxiety Disorder	Generalised and persistent anxiety, but not restricted to or even strongly predominating in any particular environmental circumstances
Panic Disorder	Panic disorder is defined as a complex mental illness in which a person experiences recurrent and unexpected panic attacks which are not associated with any external event or situation

Table 1. ICD- 10 Classification of mental diseases

this increase in stimulation of the sympathetic system acts on central nervous system adrenoreceptors and indirectly acts on protein secretion of noradrenaline. This in turn inhibits saliva secretion by the salivary glands (Del Vigna de Almeida et al., 2008).

Salivary glands, which are controlled exclusively by neurotransmitters, consist of epithelial cells that excrete fluid and exocrine proteins that serve various functions intraorally. Antidepressant drugs affect the muscular veins and myoepithelial cells, which directly influence the blood circulation of glandular tissue (Sreenby and Schwartz, 1986; Vissink et al., 1992). As such, anticholinergic medications and those that alter adrenergic stimulation of the glands change the composition of the saliva that is secreted as well as decreasing its volume. It has been reported that patients find the change in salivary secretion and composition caused by anticholinergics to be more debilitating than those changes caused by other mechanisms (Vissink et al., 1992).

In addition to this, the reduced resting salivary flow impairment has been seen to return to normal range upon cessation of medication. Interestingly, these medications exhibit a dose-response relationship – the greater the dose of the drug, the more severe the side effects. TCAs exert the greatest xerostomic effect, due to their anticholinergic action (Del Vigna de Almeida et al., 2008) (Hunter and Wilson, 1995). It is uncertain whether it is the decrease in quantity or quality of the saliva that causes patients to complain of the symptoms of dry mouth, although studies suggest that fewer salivary mucins within the saliva secreted is the primary cause of discomfort related to xerostomia (Anttlia et al., 1998).

Saliva is a key component in the mechanisms by which taste occurs. It provides the fluid in which food components and tastants are dissolved and carries these to the taste buds to allow the sensation of taste. A dry oral environment can cause damage to the taste buds, increasing their threshold for taste (Matuso, 2000). Given that dysguesia is another reported side effect of many antidepressant medications, taste sensation in these patients can be significantly altered.

Treatment

Treatment of xerostomia experienced by patients can be achieved by several mechanisms, many of which can be utilised concurrently. Given the potential for medication interaction with antidepressants, prescription of medications such as pilocarpine, which is a parasympathetic stimulant, are inadvisable. Although these medications can successfully be used in the treatment of patients experiencing dry mouth due to other aetiological factors (Saleh et al., 2015), their mechanism of action precludes their use in the treatment of those receiving antidepressant therapy. Therefore, the most effective management of xerostomic symptoms is by use of local salivary substitutes.

Although plain water is an effective salivary substitute in many cases, salivary substitutes containing components such as carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxyethylcellulose, linseed oil or polyethylene oxides give a higher viscosity and therefore greater mucosal protection (Vissink et al., 2010) (Hahnel et al., 2009). Such agents have no known interaction with antidepressant medications and can provide significant relief from the sensation of a dry mouth that is the presenting complaint of many patients.

Pathophysiology

The presence of fermentable carbohydrates in the oral environment is one of the primary aetiological factors of dental caries. Saliva's function in removing debris and the food bolus from the oral cavity is compromised in those with decreased salivary flow, regardless of the aetiology of the dry mouth. Due to prolonged retention of sugars containing fermentable carbohydrates, the caries risk in this cohort of patients is elevated (DaSilva et al., 2011).

Saliva functions as a buffer thanks to the presence of bicarbonate ions that neutralise acid in the oral environment and in the oesophagus following deglutition. Furthermore, carbonic acid, formed by the protonation of bicarbonate ions, reacts to form water and carbon dioxide. This reaction is catalyzed by carbonic anhydrase VI, which is also contained in the saliva (Kivela et al., 1999). This provides protection against acid attack orally, and is a protective factor in patients who are at risk of dysplastic change in the oesophagus due to gastro-oesophageal reflux disease. Salivary mucins may also help to replenish the lining mucous layer in the oesophagus (Sarosiek and McCallum, 2000; Kongara & Soffer, 1999).

Specific Compound	Xerostomia	Dysguesia	Stomatitis	Gingivitis	Glossitis	Tongue Oedema	Bruxism	Sialadenitis	Others
TCA									
Amitriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Clomipramine	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Oral Ulcers, Dysphagia
Desipramine	Yes	Yes	No	No	No	Yes	No	Yes	Facial Oedema
Doxepin	Yes	Yes	Yes	No	No	No	No	No	No
Imipramine	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Nortriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Protriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Tripramine	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
SSRI									
Paroxetine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Dysphagia
Sertraline	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Dysphagia, Gingival Hyperplasia
Flovoxamine	Yes	No	Yes	Yes	Yes	No	No	No	No
Fluoxetine	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Citalopram	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Atypical									
Bupriopion	Yes	Yes	Yes	No	Yes	No	Yes	No	Dysphagia
Maprotiline	Yes	Yes	Yes	No	No	No	No	Yes	Dysphagia
Mirtazepine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Facial Oedema
Nefazodone	Yes	Yes	Yes	Yes	Yes	No	No	No	Oral Ulcers
Trazodone	Yes	Yes	No	No	No	No	No	No	Sinusitis
Venlafaxine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Dysphagia

Table2 – the main orofacial effects of Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors and Atypical Antidepressants

The mechanism by which caries cause demineralisation of the dental hard tissues is by the production of bacterial acidic metabolites (Stookey, 2008). When patients who are taking antidepressant medications experience a lower quantity of saliva, this buffering effect of the saliva is diminished, along with its other protective effects.

The epidemiology of dental decay is typically measured by the number of decayed, missing and filled teeth in the dentition, abbreviated to DMFT. Many studies have investigated the relationship between dental caries and mental illness, with a wide range of results and conclusions. However, there is sufficient evidence to support a positive correlation between the factors. Those with depression and anxiety do indeed have an increased risk of developing dental caries, more specifically having a higher DMFT value than the control cohorts (Anttila, et al., 2001; Delgado-Angulo et al., 2015; Kruger et al., 1998; Shah et al., 2012).

Treatment

With the increased DMFT scores observed in patients with mental illness as well as the increased caries risk due to decreased salivary flow and dry mouth, caries prevention should be a priority for the dental practitioner in these cases. The use of oral hygiene education, home oral hygiene maintenance, increased fluoride use, and antimicrobial mouthwash use to decrease this caries risk have all been shown to be effective (Friedlander and West, 1991). More frequent dental recall times, examination and interventions such as scaling and topical fluoride application will also ensure the maximisation of oral health in this patient cohort (Friedlander and Mahler, 2001).

Of significant concern to dental practitioners is the interaction between antidepressant medications and those prescribed by the dentist. Given both the broad range of medications prescribed by the dentist and the broad range of antidepressant medications, the propensity for drug interaction is vast.

Commonly prescribed antibiotics in the dental setting include the macrolide group, of which erythromycin and clindamycin are members. These antibiotics are the first line of treatment for dental infection for patients with an allergy to the penicillins. Azole antifungal medications are used in the treatment of candida infections and are commonly prescribed by dental practitioners. Both the macrolides and the azoles are metabolised by the CYP450 enzymes in the liver, but it is their inhibitory effects on these enzymes that pose a risk to the patient. Benzodiazepine medications are also metabolised by CYP450 and so its inhibition can significantly affect the bioavailability of the benzodiazepine group (Hersh, 1999). By increasing the bioavailability of benzodiazepines, this interaction could result in overdose and CNS depression.

Post-operative pain in dentistry often results in the prescription of analgesics. When this pain is severe, the prescription of opioid analgesics such as codeine, hydrocodone or tramadol is quite common. However, prescription of opioids with CNS depressants or monoamine oxidase inhibitors has been shown in some studies to cause a life-threatening interaction (Haas, DA., 1999). The use of local anaesthetics is generally considered safe, although care should be exercised with those patient receiving treatment by medications affecting the adrenergic system. Adrenaline within a local anaesthetic cannot bind to alpha-1-adrenergic receptors in patients receiving medications that block alpha-1- adrenergic receptors. The adrenaline then binds to alpha-1-adrenergic receptors instead causing vasodilation and resulting in hypotension (Keene et al., 2003). Therefore, consideration should be given to the medications being taken by the patient prior to administration of local anaesthetics containing adrenaline in their formulations or use of haemostatic agents containing adrenaline.

Conclusion

Due to the prevalence of depressive disorders in the general public, the dental practitioner is likely to encounter patients suffering from these conditions. Since anti-depressant drugs can cause an array of side effects, it is important for the practitioner to understand the pharmacology and mechanisms of action of these treatments.Xerostomia, increased caries risk, orthostatic hypotension and interactions with other drugs mean that these medications can be detrimental to oral health and can result in adverse reactions in dental practice that can be potentially life threatening.

The impact of antidepressant use on patient management highlights the importance of obtaining a thorough medical history. Disclosure of a history of mental illness and antidepressant use on a patient's behalf may be difficult and therefore, a positive relationship with the practitioner, exhibiting a non-judgemental attitude and a supportive environment is also of the essence. These patients are inevitably encountered in practice with great frequency and so, knowledge of these medications and their orofacial manifestations and implications for treatment are imperative for the dental practitioner.

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Prevalence of Non-Prescribed Drug Use in Hospital Patients Assessed by Urine Toxicology Testing

Nada Bochor, Ronan Doherty, Ciara Quigley and Gerard Boran

To analyse the results of a survey for non-prescribed drug use in selected patient populations in Tallaght University Hospital to determine the patterns of drug use by urine toxicology testing.Urine toxicology screening results done by the Alere Triage® TOX Drug Screen Meter were extracted from the Clinical Chemistry Lab database from the 5th of March to the 23rd of March at Tallaght University Hospital. Results were analysed to determine which drug tested positive most commonly. Benzodiazepines were the most prevalent drugs of abuse in urine toxicology, accounting for 25.62% of all positive results, this was followed by Cannabis and Amphetamines with 21.67% and 20.20% respectively. The largest age group that presented was between 30-39 inclusive. Benzodiazepines are the most prevalent positive result in drug of abuse screens in Tallaght University Hospital and the 30-39 age group contained the most positives and number of samples sent for toxicology analysis, supporting the claims of recent literature.

Introduction

According to the All-Ireland Drug Use Survey (National Advisory Committee on Drugs and Alcohol (NACDA), 2016), the levels of illegal drug use in Ireland have risen over the past decade and those aged between 15 and 24 have the highest use of non-prescribed drugs. The percentage of Irish people aged 15-64 saying that they had used an illegal drug at least once in their life rose from 18.5% in 2002/03 to 30.7% in 2014/15, with increases reported at each intervening survey (McKinney, 2017). Cannabis has been reported to be the most commonly used drug, with 27.9% of respondents between the same age group having reported use in 2016 (Brennan, 2016). This study aims to analyse the results of a survey for non-prescribed drug use in selected patient populations in Tallaght Hospital to determine the patterns of drug use by urine toxicology testing. Urine drug screen (UDS) immunoassays are a quick and inexpensive method for determining the presence of drugs of abuse (DOA). Therefore, testing will be performed by the Alere Triage® TOX Drug Screen Meter, which provides rapid and sensitive urine screening of up to 11 drug classes at once (Table 1). The results of a toxicology screen include a "POS" or "NEG" reading for Paracetamol (APAP), Amphetamines (AMP), Methamphetamines (mAMP), Barbiturates (BAR), Benzodiazepines (BZO), Cocaine (COC), Methadone (MTD), Opiates (OPI), Phencyclidine (PCP), Tetrahydrocannabinol (THC) and Tri-cyclic Antidepressants (TCA).

Methods

The primary investigation undertaken involved a comprehensive review of urine
toxicology samples received into the department of Clinical Chemistry at Tallaght University Hospital. Samples were collected over a 19 day period from the 5th of March to the 23rd of March and screened in the lab for a panel of 11 drugs of abuse (Table 1) using the Alere Triage® TOX Drug Screen. Initially there were forms distributed to the Emergency Department and Department of Psychiatry that were to be filled out for each sample sent to the lab by clinical staff, this form contained basic patient information along with known drug use and the reason for their toxicology screen request. The form also contained a tick box giving the option for the extended drug panel that would be conducted in Birmingham, this acted to gain consent and as a fail-safe to guarantee that samples would be available to send for further analysis as the study was pending ethical approval.

Ethical approval was granted by the SJH/AMNCH Research Ethics Committee and provided for submission of all samples received during the research period for extended DOA screening in Birmingham.

Over the course of the study we received a yield of 154 urine samples, 7 (4.54%) of which were unsuitable for analysis due to leakage in transit. Of these 7 spoiled samples, 4 were reordered soon after while the remaining 3 patients did not have a further sample submitted to the lab for analysis.
The Alere Triage® is very simple to use, a sample of urine is taken up by a small pipette with an overflow bulb to ensure the correct amount and no more is used. This sample is released into one end of a TOX Drug Screen cartridge that has just been removed from its packaging. The cartridge is then inserted into the device and the assay is run. This can take about 15 minutes from the moment the sample is placed in the cartridge, a significant amount of this time is taken up by the time it takes the sample to fully pass through the cartridge, therefore preparing a few samples simultaneously will allow quicker analysis following completion of the first screening. The device produces a printout for each sample that details the 11 drug panel and a positive/negative reading for each. The threshold values are also listed, however the result does not give a quantitative value for each sample.

Each sample received was also aliquoted twice, both aliquots into a 10mL sealed tube and labelled with the lab number as a unique patient identifier. One set of these aliquots was to be sent to a laboratory in Birmingham where an extended drug panel was offered. The second set of aliquots was frozen and stored, for potential future analysis should it be required.
Clinical data for selected patients was also extracted from the Emergency Department database Symphony, this allowed for the correlation of history, symptoms and diagnoses with the toxicology data returned from that patient's sample.

Results

A total of 154 urine samples were received mainly from the Adult Emergency Department and the Paediatric Emergency Department with some samples also collected from Psychiatry and from various wards around the hospital. Upon analysis using the Alere Triage® TOX Drug Screen results were tabulated and key data was extracted that can be seen in Figures 2-4. It can be noted that Paracetamol (APAP) is the most commonly returned positive from ages 10-29, thereafter, Benzodiazepines (BZO) become the most prevalent (with the exception of the 60-69 bracket where THC was equally prevalent) (Figure 2). Examining drug prevalence, without the age breakdowns, it can be seen that Benzodiazepines remain the most prevalent across all positive samples with a total of 52 (25.62%) (Figure 2). THC was the second most prevalent, followed by Paracetamol with 44 (21.67%) and 41 (20.20%) positives, respectively. There were no samples that tested positive for Phencyclidine (PCP) and very few that returned positive results for Amphetamine (AMP) 1, Barbiturates (BAR) 1, Tricyclic Antidepressants (TCA) 2, or Methamphetamine (MAMP) 2. Overall there was quite a diverse breakdown in the return of positive results.

Analysing the gender breakdown, it is indicated that any given male sample is more likely to be positive for at least one DOA than a female sample. Analysis of multiple positive results for a single sample was also undertaken. 27 (34.62%) of the 78 male

samples were positive for one drug only, this number was 13 and 14 for 2 positives and 3 in a given sample respectively. It is also of note to see that two samples returned a positive result for 5 DOA, one of these samples was from a patient on 50mg of Methadone weekly with a Methadone overdose listed as the likely diagnosis on sample's request form. The female samples returned a slightly different data set; while there were no patients with a positive for 5 DOA, there were 4 samples that presented with a positive result for 4 DOA (2 of these were from the same patient), while no males presented with 4 positive DOA readings. One of these patients was noted to have been brought in by ambulance after collapse with a suspected overdose of 6 tablets of Lyrica and Diazepam, and 90 mL of Methadone. She was known to be on Methadone therapy.

Discussion

The 2016 Report of Tallaght Drug & Alcohol Task Force to the Drug Programmes Unit, Department of Health (Tallaght Drug & Alcohol Task Force (TDATF), 2016) gives a further insight into some of these trends and is the most recent version available. Data suggests that throughout the period of 2016 as a whole Tallaght had the second highest number of people using methadone treatment services in the country at 731 individuals (6.4%), with 676 undergoing treatment at the end of year (8.8%). These figures were second only to North Inner City Dublin at 982 (8.6%) for the year in total and 889 (8.8%) at the close of the year. The same report also details information gathered from the

National Drug Treatment Reporting System (NDTRS) in 2015 where outcomes from patients (268) attending any form of drug rehabilitation services were analysed. The predominant positive outcomes were: "Treatment Completed" and "Transferred Stable" with 61 and 24 patients respectively. The most prevalent negative outcomes were "Client did not wish to attend further treatment sessions" at 54, "Client refused to have further sessions (or did not return for subsequent appointments)" at 92, and "Premature exit from treatment for non-compliance" at 11, totalling off at 157, significantly higher than the cumulative positive outcomes. Only a single patient received rehabilitation treatment for the use of benzodiazepines in 2015, this result comes as a surprise based on its growing prevalence and the findings of this paper's findings. The National Advisory Committee on Drugs and Alcohol published their most recent drug prevalence report in 2016 (National Advisory Committee on Drugs and Alcohol (NACDA), 2016) detailing cannabis as the most prevalent illegal drug in Ireland with increases in lifetime prevalence (25.3% to 27.9%), last year prevalence (6% to 7.7%) and last month prevalence (2.8% to 4.4%) since its previous report in 2012 (National Advisory Committee on Drugs and

Alcohol (NACDA), 2012). These results are the nationwide figures, however in the regional reports contained within, the South West Regional Drug Task Force, of which Tallaght is within its catchment area, showed similar trends. This differs from the results detailed figure 1.1 of this report, which suggests benzodiazepines to be the most prevalent drug, with cannabis coming second, narrowly followed by amphetamines. This could indicate that there has been a significant shift in drug prevalence since the 2012 publication. Internationally however cannabis remains as the leading illicit drug internationally with an approximated 162 million adult users in 2004 (Hall & Degenhardt, 2007).

Conclusion

154 urine samples were collected over a 19-day period in Tallaght University Hospital for toxicology screening. The most prevalent drug of abuse class was found to be benzodiazepines, with 25.62% of samples testing positive; this was followed by THC (21.67%) and paracetamol (20.20%). No samples during this period tested positive for phencyclidine (PCP). Drug abuse in the age group of 30 – 39 years old was ascertained to be most prevalent, with 66 positives recorded from 35 samples. Patterns of drug use varied between age ranges, with paracetamol (APAP) most common in 10 – 29 year olds and with THC equal in prevalence to benzodiazepines between the ages of 60 and 69, with benzodiazepines the most prevalent overall. Gender analysis found a higher percentage (71.79%) of males than females (61.84%) tested positive for at least one drug. The majority (34.62%) of male samples were positive for one drug only as opposed to females, where two positives were most commonly observed (26.32%). The highest number of positive results from a single sample was observed to be 5 among males and 4 among females. These findings give an overview as to current patterns of drug abuse in Tallaght and the surrounding area, and patterns of prevalence can be seen to be similar to those observed in a similar study (Rajasingam & Gallagher, 2015).

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Drug	Drug Code	Threshold Concentration
Acetaminophen/Paracetamol	APAP	5 µg/mL
Amphetamines	AMP	1000 ng/mL
Methamphetamines	mAMP	1000 ng/mL
Barbiturates	BAR	300 ng/mL
Benzodiazepines	BZO	300 ng/mL
Cocaine	COC	300 ng/mL
Methadone	MTD	300 ng/mL
Opiates	OPI	300 ng/mL
Phencyclidine	PCP	25 ng/mL
THC	THC	50 ng/mL
Tricyclic Antidepressants	TCA	1000 ng/mL

Table 1. Threshold concentrations for the 11 DOA classes tested for by Alere Triage Tox Drug Screen

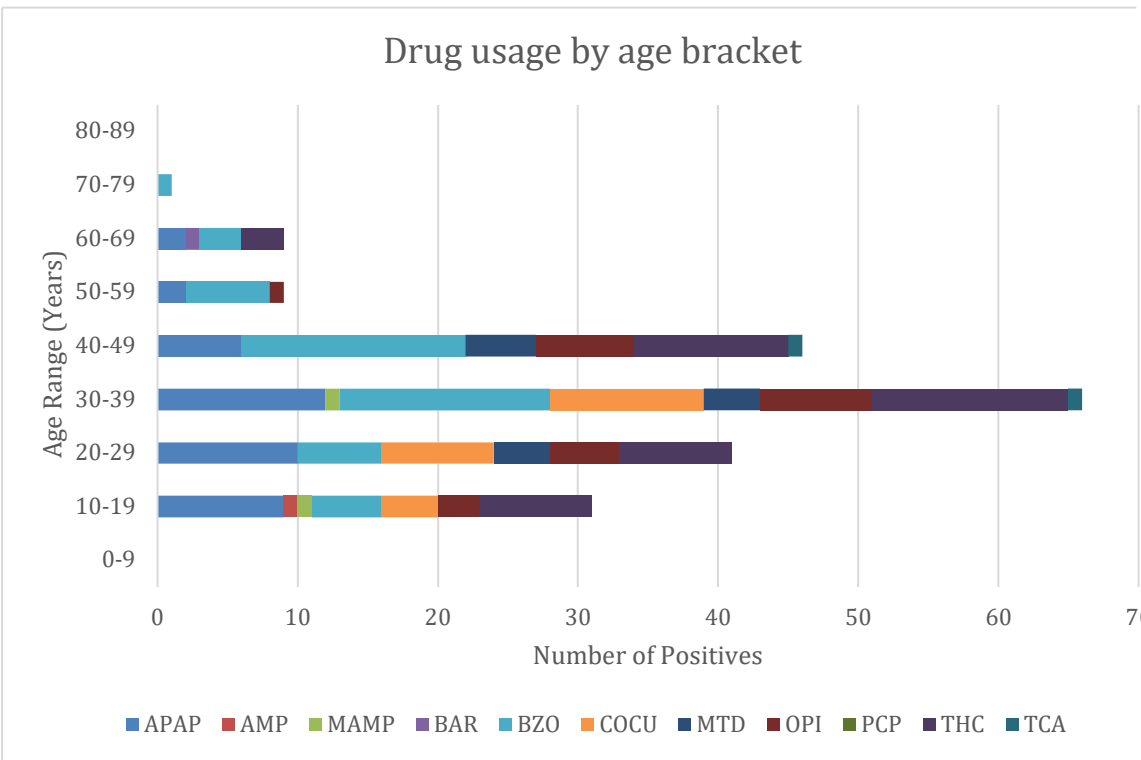

Figure 2. Drug useage by age bracket

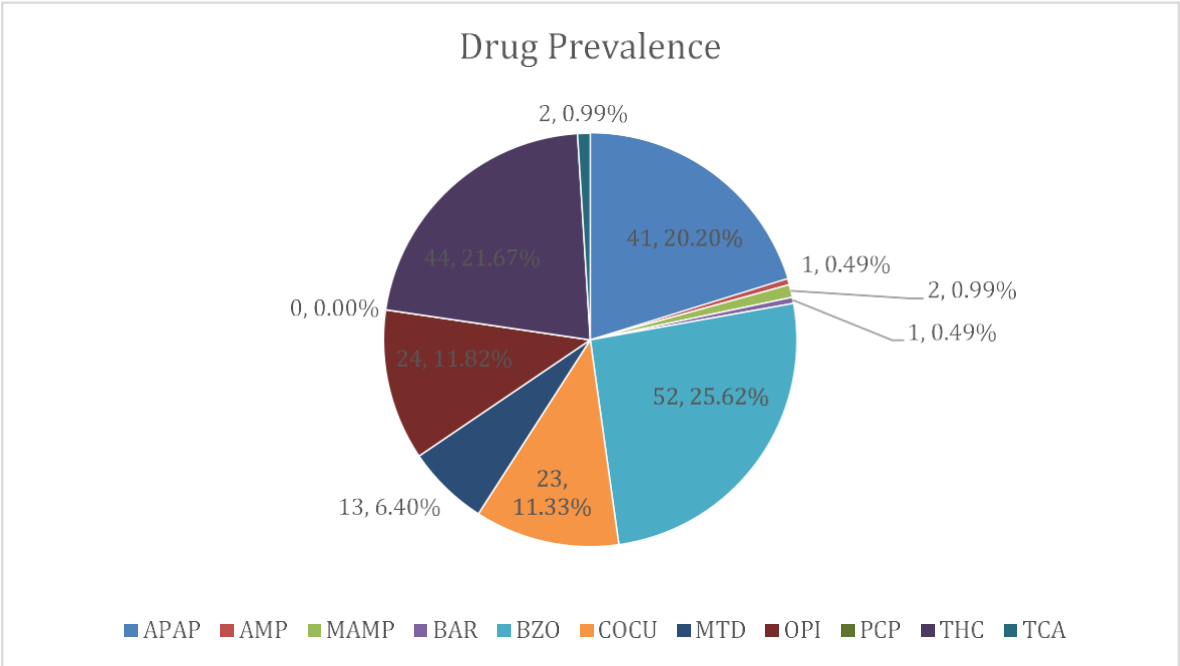

Figure 3. Drug prevalence of 11 DOA classes tested in 154 patient samples.

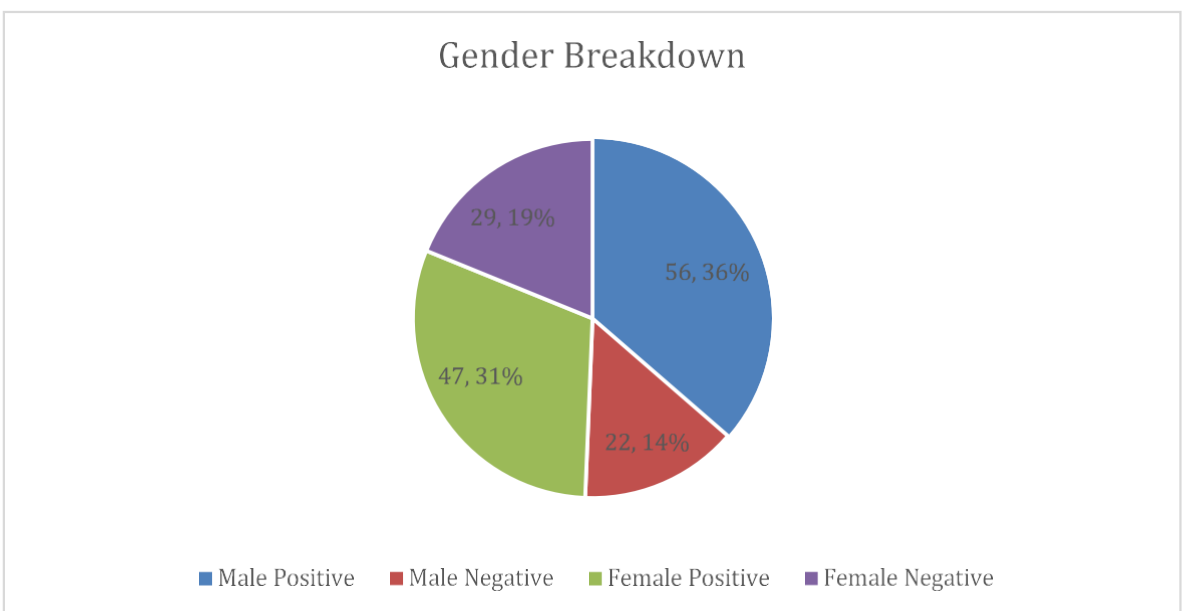

Figure 4. Percentage of males and females testing positive and negative for one or more DOAs

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