TSMJ

Volume 20 | 2019

20TH ANNIVERSARY EDITION

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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St. James's Hospital, Dublin 8, Ireland

Alternatively, email can be sent to tsmj@tcd.ie.

Current and previous volumes can be accessed at www.tsmj.ie

ISSN 1393-9572 (Print) ISSN 1393-9815 (Online)

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EDITORS' NOTES

This year marked the twentieth anniversary since the founding of the Trinity Student Medical Journal in 1999 under the guidance of Professor Conleth Feighery and Professor Moira O'Brien. The vast progress made in publication, education and research since then and the speed at which research makes it from the bench to print (with early releases online) and then to the patient's bedside is phenomenal.

The TSMJ has been on a journey involving twenty committees, and a mix of conferences, study days, poster competitions, medical art awards, interviews, publication crash courses and journal clubs throughout its time. It has always delivered with physical journal copies being ferried to libraries, lecture theatres and the Trinity College teaching hospitals, as well as the legal deposit libraries.

This years journal highlights some interesting and topical articles; Hazeem Ahmayuddin's case report (completed during an elective) on the management of a primary small cell carcinoma in the subglottis highlights a rare condition, and discusses the urgent need for further trials in the area, and Fátimah Alaya's feature article on the reach of the GDPR that highlights and reflects on the limbo experienced in healthcare research for the last two years. There are two comprehensive reviews; one on the current research in the prodromal phases of Alzheimer's Disease by Tristram Ryan, and the other on the balance between cost and efficacy of the new immune checkpoint inhibitor drugs in cancer therapeutics by now final year student Michael McKenna. And there are many other fascinating reads on reproductive rights, audits based in general practice, palliative care research and approaches and the need to sedating children during MRI studies.

As medicine evolves rapidly, so too does the world of publishing. We are evolving too in the TSMJ and are moving towards online platforms for that last few years. While print editions are key, accessibility and relevance of research relies on online presence and we too must move with the times. Our new website using the Open Journal Systems is soon to go live and will revolutionise the submission process and the ease with which the journal can be accessed, dispersed and referenced.
We are delighted to continue to provide a platform for students in medicine, dentistry and health science fields to publish their research, reviews, case reports and academic efforts that they devote their time to during their undergraduate studies. We are also student run which means that the entire production is a culmination of hard work and volunteered time by students from first year through to final year that are giving of their time and energy to foster others, teaching through editing, providing through production, learning through guiding others and yourself to deliver a product as a team.

The journal would not be here without students to research, authors to write, editors to review, designers to produce, and the numerous researchers, consultants and academics that together support student ventures. We are deeply grateful to all those involved in the Trinity Student Medical Journal, this year, and for every year that has gone before us.

We are pleased to present you with the twentieth edition of the Trinity Student Medical Journal. The topics are varied, thought-provoking and are produced by the talent of the upcoming health scientists, dentists and doctors. We are proud as ever to continue to serve as a platform for student research, student editorial work and student collaboration. Thank you to all our sponsors, supporters, and the School of Medicine for the constant support.

The Editors in Chief
Amy Worrall
Dane Wanniarachige

A Case Report of a Primary Small Cell Carcinoma of the Subglottis

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Abstract

Small cell carcinoma (SmCC) is a type of cancer affecting the subglottic region of the larynx. Subglottic carcinomas represent only less than 5% of laryngeal cancers, with SmCC accounting for only 0.5%. This case report highlights a patient with a rapidly-progressing laryngeal growth that caused a significant airway obstruction within a period of three weeks. Further investigation revealed that the patient was suffering from a rare form of laryngeal neoplasm, which was consistent with a diagnosis of a limited stage primary SmCC of the subglottis. He was then started on a regimen of radiotherapy with concomitant chemotherapy (cisplatin and etoposide) for a duration of two months. Response to therapy was rapid, with a reduction in tumour size. A combination of radiotherapy and platinum-based chemotherapy is currently the modality of choice for treatment, with recent data showing that surgery has a limited role in laryngeal SmCC.

Introduction

Small cell carcinoma (SmCC) is an anaplastic, highly malignant carcinoma, primarily affecting the bronchogenic region of the lung. Histologically, it is composed of small ovoid cells with scanty neoplasm (Stedman, 1990). These cells are characterised by a dominant, deeply basophilic nucleus, with absent or indistinct nucleoli (Stedman, 1990). Small cell carcinoma (SCC) comprises over 95% of laryngeal cancers. The remaining 5% is made up by adenocarcinoma, sarcoma, miscellaneous carcinomas (adenoid cystic, neuroendocrine carcinoma etc.) and the rare variants of SCC – verrucous, spindle and basaloid SCC (Mastronikolis et al., 2008-12). SmCC, which is a subtype of neuroendocrine carcinoma accounts for approximately 0.5% of all laryngeal cancers (Sharma et al., 2014). With regards to location, glottic carcinomas represent the majority of laryngeal cancers (50%-60%), followed by the supraglottic carcinomas (30%-40%), while the subglottic carcinomas are uncommon and comprise 5% or fewer of laryngeal cancers (Mastronikolis et al., 2008-12). Extrapulmonary small cell carcinoma follows a staging classification of either limited or extensive stage. Disease confined to a primary site with or without loco-regional lymph node involvement is classified as limited, while all others are classified as extensive (Doll, 2018).

There is a paucity of literature in this area, with only approximately 200 documented reports of laryngeal SmCC to date worldwide (Raposo et al., 2018). This is a significant barrier to understanding the presentation, progression, treatment and prognosis of this rare condition.

In this report, we examine a case of a subglottic laryngeal SmCC. The patient was treated with radiotherapy, with concomitant cisplatin and etoposide for a duration of 2 months.

Case presentation

A 45-year-old male first presented to the emergency department (ED) with a three-week history of fever, dyspnoea, wheeze and productive cough. The patient reported an acute deterioration of symptoms within the previous two days, with hemoptysis, barking cough and hoarseness of voice, and was diagnosed with a respiratory tract infection (RTI). He was admitted for antibiotic and steroid treatment and discharged after one day. The patient's Eastern Cooperative Oncology Group (ECOG) performance status score was deemed to be 1: symptomatic but ambulatory (Oken et al., 1982). He reported a consumption of four units of alcohol per week for an unknown duration, and a tobacco smoking history of 5.6 pack years. His only past medical history of note was gout.

Investigations

Following the initial presentation, the patient experienced a gradual exacerbation of his symptoms. Over a course of two weeks, the patient presented to ED three times, two times of which he required admission where he was again treated for a RTI. On the fourth hospital presentation, however, a decision was made for a nasal endoscopy to be performed. Endoscopic investigations showed a left subglottic mass causing severe airway compromise and a right vocal cord leukoplakia. This prompted emergency tracheostomy tube insertion. Physical examination found no evidence of cervical lymphadenopathy.

A biopsy of the left subglottic lesion showed a malignant neoplasm in the stroma. Histological examination of this neoplasm revealed cells with large, markedly hyperchromatic nuclei and scanty cytoplasm, forming cords and trabeculae. Mitotic activity was frequent and necrosis was present. Crush artefact and nuclear moulding were evident. There was no evidence of dysplasia in surface stratified squamous epithelium. Immunohistochemical analysis showed that the malignant cells had the following pattern: CKAE1/3 positive, LCA negative, synaptophysin positive, chromogranin negative and had a Ki67 proliferative index which stained >90% of the malignant cells. A computed tomography scan of the neck, thorax, abdomen and pelvis was performed in conjunction with a magnetic resonance imaging of the head and neck. They demonstrated a left-sided subglottic soft tissue mass measuring 2.34 x 1.84 x 1.46 cm which encroached upon and narrowed the lumen to 2.12 mm. There was also evidence of bilateral cervical lymphadenopathy, involving nodes at levels II and III, which ranged from 5.87 mm to 15.8 mm in size, being larger on the right side. There was no radiological evidence of distant metastasis from both imaging modalities. Blood investigation revealed nothing of note; and a test for chromogranin A read a level of 73 µg/L (0-100). A subsequent lymph node biopsy found them to be negative for metastasis. A diagnosis of limited stage primary SmCC of the subglottis was made.

A separate biopsy of the right vocal cord leukoplakia was performed, which then showed squamous dysplasia. Two strips of stratified squamous epithelium was obtained from the site. One of the strips showed slightly thickened squamous epithelial cells with variable nuclear enlargement and hyperchromasia. Few mitotic figures were found in the lower half of the strip. However, there was no evidence of invasive carcinoma from both strip specimens.

Treatment

The patient was subsequently started on a concurrent chemoradiotherapy regimen for a duration of two months. The chemotherapy was given in three cycles. Each cycle consisted of three days of chemotherapy administration. On the first day, the patient received intravenous (IV) etoposide and IV cisplatin, and IV etoposide for the second and third day. Each cycle of chemotherapy was to be given once every three weeks, however, the gap between cycles 2 and 3 increased by four days due to treatment complications which are outlined below. Dosages were administered proportional to body surface area, which was 1.8m^2.

A volumetric arc therapy (VMAT) technique was used to deliver external beam radiotherapy to a dose of 60 Gy at 2 Gy/ fraction. This was delivered five times per week for 6 weeks, totaling 30 fractions. The radiotherapy targeted neck nodes bilaterally as a prophylactic measure, as they are a common site of metastasis (Alpert et al., 2004).

Follow up

The patient was admitted due to complications one week after the second cycle of chemotherapy, following the development of transient neutropenia, thrombocytopenia and oesophagitis. The treatment was temporarily withheld, and the patient received symptomatic treatment, which included antibiotics. Once again, one week after completion of treatment, the patient developed febrile neutropenia and pneumonia. He was readmitted for IV antibiotics and granulocyte-colony stimulating factor (G-CSF). On both occasions, the patient did not require ICU admission. During treatment course, the patient developed radiation dermatitis around the collarbone region of the neck. Other common side effects related to radiotherapy such as mucositis, xerostomia, lymphedema and nausea was not reported. Otherwise, radiological evidence of tumour regression was pronounced (Figure 1).

Discussion

Laryngeal SmCC has been strongly linked to heavy smoking and drinking (Pointer et al., 2017). It is apparent, however, that the patient in this case report reported minimal tobacco and alcohol intake which may suggest another risk factor was at play. The patient's height is 161 cm and he weighs 74 kg, therefore his Body Mass Index (BMI) is 28.5. This would put him under the classification of overweight. Studies have found that diet (Levi et al., 1998), environmental exposure (Sturgis & Pytynia, 2005), oral hygiene (Tezal et al., 2009), gastroesophageal reflux (Zainuddin & Mohd Kornain, 2016), premalignant lesions (Shaw & Beasley, 2016) and HPV infection (Li et al., 2013) are among other risk factors predisposing individuals to oropharyngeal/ laryngeal cancer. Among these, the patient was positive

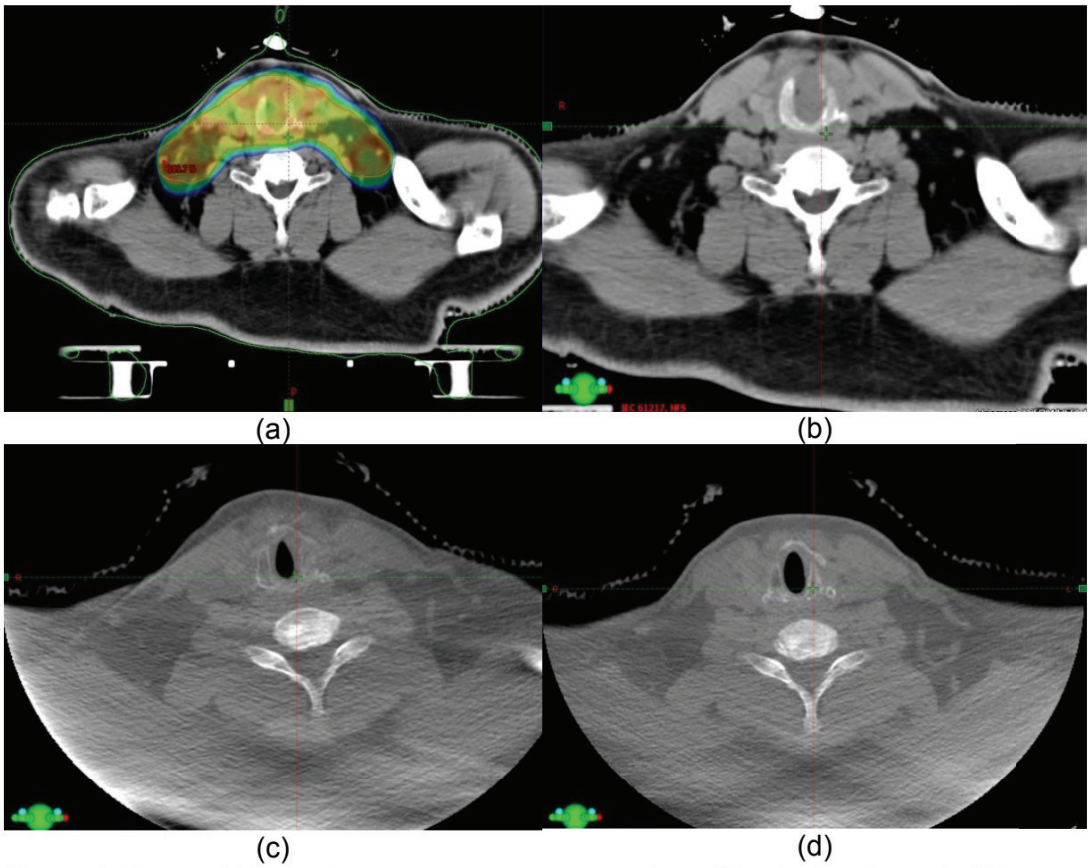

Figure 1: Pre-, middle and post-treatment progression of the lesion through computed tomography scan including an external beam planning for radiotherapy (a) External Beam Planning contour, (b) Pre-treatment, (c) Middle of treatment, (d) Post-treatment

Week 1							Week 2							Week 3						
M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su
Tx	Tx	Tx					Tx	Tx	Tx					Tx	Tx	Tx				
C,E	E	E					C,E	E	E					C,E	E	E				

Table 1. Example of chemotherapy regimereceived by the patient. Tx: Treatment day, C: IV Cisplatin, E: IV Etoposide

for premalignant lesion, which was leukoplakia present at his right vocal cord. Premalignant lesions such as leukoplakia or erythroplakia is very rarely caused by HPV-16 infection (Shaw & Beasley, 2016). Approximately 25% of epithelial biopsy will show dysplastic changes in leukoplakia affected areas (Shaw & Beasley, 2016) and this was histologically evident in our patient.

There are only two other well documented reports of primary small cell carcinoma affecting the subglottis, that is still in the limited stage in the medical literature today. Hence, it is important for every case to be reported so that we could learn its pattern of manifestation. The first case is a 68 year old female presenting with a one week history of progressive dyspnoea and hoarseness of voice with a background of three month history of chronic, non-productive cough (Johnson et al., 1979). The second case saw a 54 year old male presenting with a three month history of progressive dyspnoea with inspiratory stridor and concurrent multiple myeloma (Thompson et al., 1982). Both cases exhibit similar pattern of acute progressive dyspnoea being the chief complaint, which is similar to the patient we are reporting. It is worth highlighting that the patient in this case study also presented with barking cough - a symptom that is predominantly seen in the paediatric population caused by croup or laryngotracheitis. This phenomenon is rarely seen in the adult cohort and is certainly unorthodox to have presented in laryngeal neoplasm.

Historically, SmCC of the larynx follows a treatment regime of either surgery, radiotherapy, chemoradiotherapy or a combination of surgery, radiotherapy and adjuvant chemotherapy (Baugh et al., 1986). Currently, there are no available guidelines as to the management of laryngeal SmCC owing to its rarity. Management decisions have been based on small studies and case reports. Only recently, a meta-analysis found that the addition of surgery to chemotherapy and radiotherapy did not improve survival in patients with locally advanced disease, as compared to receiving only chemotherapy and radiotherapy (Pointer et al., 2017). Further, a retrospective study of 120 extra-pulmonary SmCC patients also concluded that surgical resection was not significantly correlated with recurrence-free or overall survival (SM et al., 2010). Despite the inability of chemotherapy to cross the blood-brain barrier (Wang et al., 2014), routine prophylactic cranial irradiation (PCI) is not recommended due to the low incidence (7.7%) of metastasis to the brain among patients with laryngeal SmCC (Kumar et al., 2015).

There was rapid disease progression in this patient: within three weeks of symptom onset, the patient's airway had narrowed to an extent necessitating emergency tracheostomy. This could partially be explained by the high Ki-67 proliferative index, which is known to predict a worse prognosis in other malignancies (Hoos et al., 2001). Laryngeal SmCC has consistently been reported to have a poor prognosis. The latest data demonstrate a median survival of 17.0 months and a 2-year survival of 40.9%. Other studies have found the 2-year and 5-year survival rates to be 16% and 5% respectively (Pointer et al., 2017). Despite this dismal prognosis, there have been several cases reporting survival times of greater than 47 months. This patient cohort was treated with radiotherapy and concomitant chemotherapy with cisplatin and etoposide (Zhu et al., 2015). Indeed, a 2015 study reported a patient survival time of 99 months when treated with similar chemoradiotherapy regimen (Iqbal et al., 2015).

It is generally agreed, however, that despite concomitant chemoradiotherapy being the standard of care for laryngeal SmCC – it is far from ideal. Therefore, more data are still needed from larger trials and case reports, employing both conventional and more exploratory therapeutic regimes.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Healthcare Difficulties in the Post-GDPR Era

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Abstract

The medical profession centres on the philosophy and principles of providing patients with the best evidence-based care. In doing so, medical clinicians must remain up-to-date with local and international best practice, engage in auditing practice to review and refine practices and engage in an open-relationship with the patient at the forefront of their practice. Protecting the patient encompasses best practice, moral and ethical principle while balancing risk and beneficence and ensuring non-maleficence, justice and patient autonomy. Alongside these aspects, comes the reality of advancing societal requirements which impact on medical practice and governance. The changing dynamic of patient consent that is required with the new General Data Protection Regulation (GDPR) requirements has changed the face of research in Ireland and Europe, with significant implications for research beyond as well. This piece will explore how healthcare data should be available for use for health research without the necessity to seek patient consent.

Introduction

An integral and strongly ingrained feature of being a truly conscientious and excellent doctor centres on protecting the patient (Irish Medical Council, 2016). One could say that this becomes part of our physician's DNA. As we journey through medical school, internship and then climb the ranks, we come to see the patient as a holistic entity rather than simply as a presenting complaint (Beauchamp and Childress, 2008). With that, comes the brave responsibility of upholding confidentiality, empowering the patient and doing no harm. We raise our hands on taking the Hippocratic oath and pledge to always do good in the name of our patients. To do good includes the fundamentals of beneficence, non-maleficence, justice and autonomy (Beauchamp and Childress, 2008). Alongside these ethical and moral pillars, comes the reality of advancing 21st century medical practice and governance. With the current implementation of greater patient security in the form of the General Data Protection Regulation (GDPR) (Health Research Board, 2018), healthcare data and research has been shook-up and demanded to pull its scrubs-up. In the interest of fulfilling these essential criterias, healthcare data should be available for us for health research, without necessarily requiring patient consent. Patient safety will still be maintained with governing bodies such as the Irish Medical Council and Ethics Committees. Necessitating consent will simply hinder evidence based medicine and the much needed advancing care and training, which comes with healthcare data and research.

The Risks

In the past how many times have you quickly glimpsed, scrolled down and clicked on a website or mobile app "Terms & Conditions", simply to move on to the next step? In honesty, we've all done it a million times. Google and Facebook hoard copious amounts of detail about our message threads, websites and links we've visited, all in an effort to study and gain insight to facilitate their products and process (Thielman, 2017). Many don't mind when convenient pops-ups for nearby fertility clinics appear on our screen, how considerate of them to notice that the user is a geriatric want-to-be mother at 38 years with intently ticking ovaries. The irony is that the same openness is far from accepted when it comes to healthcare data and research (Cassell and Young, 2002). The field is almost seen as a looming monster coming to strip patients of their autonomy and rights (Beauchamp and Childress, 2008). Is healthcare-data research truly riskier than other research that analyses our information? Simply because the data is not health or medically related, does not make it less risky (Thielman, 2017). Risk can be defined as the potential to cause harm (Beauchamp and Childress, 2008), a feature which medicine attempts to avoid at every level. Initially consent can appear as a protective means of avoiding risk, especially regarding vulnerable persons (Beauchamp and Childress, 2008). On the other hand, avoiding a risk can itself create an unexpected

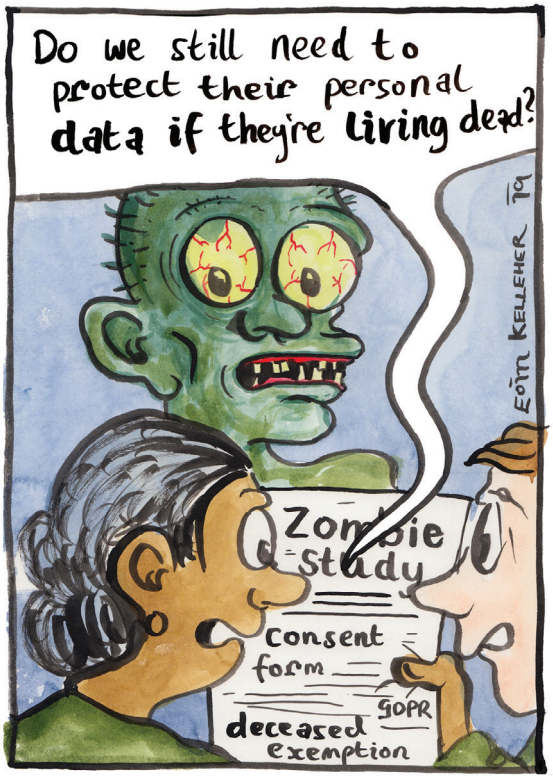
domino effect of further risks. Take the Australian government's approach to schooling and vaccinations; the right to education, safety and autonomy are all upheld by the government, however all citizens are treated equally and required to vaccinate their children prior to schooling. In doing this, there is a more global outlook on preventing risk (Salmon et al., 2006; Kirby, 2017). This is highly relevant in the Irish context with the current outbreak of measles (Lynch, 2018; Ireland, 2019). Accessing existing healthcare data to remedy this current risky wave, with greater vaccine uptake in this case, will greatly benefit the management and prevention of such an outbreak (Lynch, 2018). Having access to healthcare data to improve health research is in essence a means of improving the quality of the overall health system for patients and the practicing clinicians.

Historical Governance

Two years after the second World War, the Nuremberg Code was established to protect patients and vulnerable people from harmful involvement in medical experiments and procedures(The British Medical Journal, 1996). Almost 15 years later, a modified version of the Nuremberg Code was acquired by the World Medical Association, and became the Declaration of Helsinki (The British Medical Journal, 1996). These documents provided the primary fundamentals of consent, ethics in medicine and a stringent focus on ensuring non-maleficence and patient autonomy (Beauchamp and Childress, 2008). The Helsinki Declaration divides research into two forms: therapeutic and non-therapeutic. As per the declaration, "subjects must be volunteers and informed participants in the research project... and each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations, anticipated benefits and potential risks of the study... The subject should be informed of the right to abstain from participation in the study.." (The British Medical Journal, 1996). The model implies that medical research in relation to patient participation is cushioned by safety parameters designed and monitored by protective bodies to enable safe research. Further developing the Helsinki model, interventions used in medical research can be agreed or declined by patients, similar to any other service, regardless of their benefit or impact.

Let's consider a maternity-care case study in Ireland, specifically a series of listeriosis cases amongst a pregnant cohort at the Rotunda hospital. A retrospective review of laboratory investigations confirmed listeriosis in 9 pregnancy-associated cases and concluded that the immigrant population was most at risk (The Irish Times, 2008). The findings highlighted the lack of targeted education in women's mother tongue as well as the lack of written education, leaflets, in multiple languages. Improvements were implemented on a local level in an effort to provide better care to women and babies, especially any at high risk. Such a simple yet incredibly transformative act in medical care could not have been achieved if we followed the Helsinki declaration fully and sought retrospective consent for the analysis of all those women. The declaration, which promotes opting in or out of research, is poorly adapted to guiding this form of healthcare data and research. If women opted out of the retrospective analysis, the possibility of establishing the above findings may have been greatly reduced. Vital aspects such as safe care, beneficence and autonomy would all have been compromised (Beauchamp and Childress, 2008). Autonomy generally refers to one achieving self-governance, determining their own path, as well as taking responsibility for oneself (Beauchamp & Childress, 2008). It may appear challenging to achieve responsibility if women declined being part of the retrospective analysis. The lack of women taking responsibility would greatly reduce the study analysis and compromise the progress which was made, producing the appropriate leaflets. More plainly, would one woman's right to opt-out outweigh the rights of all the other current and future women and babies who could benefit from the knowledge gained? This voice of reason says no. The deeper philosophical principles of such an example can be traced back to John Rawl's theory of utilitarianism (Rawls, 1971). Utilitarianism centres on the principle of doing good for the greater good of the population, unlike Kant's deontological framework which values the individual above all else more (Misselbrook, 2013), the latter of which is much more in line with both the Helsinki declaration and GDPR. Within respecting the patient's rights, one also cannot deny the responsibility that a medical institution has to reviewing their practices, ensuring service quality and improvement, and delivering evidence based medicine. Inhibiting the research and auditing process, which is regarded as a vital step in refining and ensuring best care, by strictly necessitating consent in all uses of healthcare data at such a basic level of medical care,

would only cause overall maleficence and injustice to the public at large (Cassell and Young, 2002).



Modern Governance

In modern 21st century medicine, protecting patients has come in the form of GDPR, the EU's new data protection regulation which came into effect as of May 2018 (The European Commission, no date). It replaces the EU's previous data protection directive and governs the collection, use and storage of all personal data of living individuals. GDPR is highly relevant to medical information as medical data is collected, stored and used manually, handwritten and now digitally in some healthcare units in Ireland. GDPR claims to strengthen a patient's right in relation to their personal health data and forces those who collect, use and disclose such data to be more accountable for their actions (Health Research Board, 2018). GDPR does not differentiate procedural or clinical consent from the use of existing outcomes for ensuring best practice, and this point in particular means that when carrying out research or audits with the intention of publishing the findings publically without specific individual consent from each patient it would be in breach of GDPR (Department of Health Ireland, 2018). This difficulty has already been seen, with the Department of Health having to issue multiple clarifications, and in numerous healthcare services that must audit their services with the intention of publishing data in order to maintain safe standards in medical practice. A health service that has been vocal on the issue is that of the Oncogenetic services in Ireland (Holland, 2018). Standard oncology practice requires verification on the conditions reported in relatives to aid in better diagnosis and treatment. Normally this is achieved through the cancer registry and or death certificates. As per GDPR rules, relatives who have reported having cancer are now required to engage in a data request, alongside proof of identity and official documentation showing proof of address. Dr. Gallagher, a consultant oncologist and specialist in cancer genetics, fears that this process will be viewed by members of the public as "cumbersome"and lead to poor engagement, resulting in a limited ability to verify diagnosis, carrying a detrimental impact to patients and management (Holland, 2018). Placing such a barrier in the face of vital healthcare data, will only hinder much needed advancements, needed to care for such high risk patients.

GDPR

Similar to the Helsinki declaration, the focus of GDPR holds strongly to an individual's right over the collective good. The collective good encompasses other patients and future care which is created on the basis of learning from the present. Furthermore, there is a legal obligation which all practicing clinicians and medical units must uphold, auditing and refining their practice to keep up with local and international best practice (Irish Medical Council, 2016; Royal College of Physicians Ireland, 2018). This is a requirement of the colleges that a physician, surgeon or GP is a member of. Following the introduction of GDPR, it is unclear if GDPR places all these fundamentals of ensuring evidence based care at risk. The reality of GDPR in Irish practice will present itself for physicians and surgeons, at all levels, which are required by both The Royal College of Physicians and The Royal College of Surgeons, respectively, to complete "a minimum of one audit annually" (Royal College of Physicians Ireland, 2018; Royal College of Surgeons Ireland, 2018). While this is part of the professional competence schemes and continuous professional

development, the burden of every doctor across the country seeking retrospective consent for their annual audit means that audits will be compromised, small cohorts will be selected to minimise workload and publication opportunities will be compromised. This will also remove independent and self-directed continuous learning (free of the basic requirements sought by the Colleges), which is a vital stepping stone to becoming a more competent self-starting practitioner. Overall fully engaging with GDPR will potentially change the face of medical training, requiring a more bubble-wrapped or over cautious approach to what should be a two-way process, centred on the pillars of beneficence, non-maleficence, justice and autonomy. These pillars apply not only to the patient, but the pillars also apply to the service provider, the medical clinician. The rights to protection, to best care and working within safe parameters are mutual and finding the balance between the individual's right to consent and the public's right to the best possible health service, which should be based on evidence based medicine, which requires access to healthcare data.

Evidenced-Based Medicine

Evidence based medicine centres on the partnership between hard scientific evidence, clinical expertise, and the individual patient's needs and choices (Grol and Wensing, 2004). Within achieving this, there is a gap between best practice and the reality of providing clinical care. A Lancet study highlighted that up to 20% or more of health care provided is not needed or potentially harmful to patients (Grol and Grimshaw, 2003). The challenge and discrepancy appears to already exist prior to GDPR, despite the best efforts of healthcare research and clinicians. Nevertheless, with the new stringent GDPR legislation in action, the ability to improve the partnership between evidence based medicine and clinical practice may only prove more challenging. If GDPR was to be followed, the reality of only consented patient cohorts in selections will dominant the scene. If health data was reduced to only ever analysing consented patients, results will automatically introduce selection bias. Such data will distort results and ultimately not be representative of the true evidence of the healthcare service. Instead, healthcare data and practice will become based on convenient sampling, rather than truly empirical evidence based medicine, for ultimately safe practice (Cassell and Young, 2002).

Conclusion

Our advancements in modern day medicine have been greatly attributed to evidence-based medicine and healthcare data which is paving the way forward for medical clinicians to provide the utmost best care to all patients. The main means of ensuring this, is maintaining the availability of healthcare data for healthcare research. The importance of this has been seen with the effects of the current Irish meningitis outbreak, the reforms in oncogenic care to follow GDPR rules and the very real negative effects on medical training. Patient safety will always remain at the forefront of the clinician's ethos and practice, with regulatory bodies and best practice ensuring the same (Irish Medical Council, 2016). A more balanced approach could even suggest the possibility of research exemptions, however that may also prove problematic as to then classifying what and how the exemption will be followed through. Going forward, it is integral to ensure that reducing risk and ensuring safety does not in fact lead us into a downward spiral of risk obsession and away from the heart of providing the best evidence-based care. Healthcare data is a necessity for healthcare research, and negatively controlling it with necessitating consent will only comprise what we have trained and worked hard for, safe, up-to-date and effective clinical care.

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DATA PROTECTION OFFICER VISITS...

Balancing the Effectiveness and Costs of Immune Checkpoint Inhibitors in Advanced Cancer

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Abstract

Conventional cancer therapeutics, while having transformed the survival of patients diagnosed with early stage cancer, have failed to produce similar results in patients diagnosed with more advanced cancer. It is for this reason that the arrival of immunotherapy has generated such a visceral interest in the field of oncology. Labelled 'Breakthrough of the Year' by Science in 2013, the field of immunotherapy has continued to grow exponentially, and promising preclinical results have translated into efficacious results in clinical trials, particularly in patients with end-stage disease. This has culminated in an ever-growing list of approvals for agents which have been designed to harness the power of the immune system. Immune checkpoint inhibitors in particular are regarded as potent new tools in the cancer therapeutics arsenal and have produced remarkable results in clinical trials in various cancer types. However, in the context of their increasing use in combination therapy and their remarkably high cost:benefit ratio, it must be asked whether these immune checkpoint inhibitors are a realistic solution to an ever increasing cancer burden. Is their price just a little too steep to pay?

Advanced cancer survival

Improvements in treatment modalities have transformed the survival rates of patients diagnosed with cancer. Cancer survival has more than doubled over the past 40 years (Cancer Research UK 2017a), with cancer mortality predicted to continue to decrease for the majority of cancer types over the next two decades (Smittenaar et al 2016). Unfortunately, these prominent improvements in survival have not translated across to advanced cancers, with stage IV metastatic disease continuing to show poor survival at 1 and 5 years post-diagnosis. Pancreatic cancer, which has the worst prognosis of all cancer types, has shown no improvement in survival in the past 40 years, with only 3% of patients surviving to 5 years (Cancer Research UK 2017b). 5-year survival statistics for stage IV lung cancer have been notoriously difficult to assess because such a small proportion of patients survive beyond 2 years (Cancer Research UK 2017c), while current 5-year survival statistics for Stage IV ovarian and bowel cancer are 4% and 7-8% respectively (Cancer Research UK 2017d-e). The discrepancy in outcomes on the basis of cancer stage is especially prominent when one looks at breast cancer in females, where 99% of Stage I patients will be alive at 5 years compared to 15% of Stage IV patients, and melanoma in males, where 100% of Stage I patients are alive at 5 years compared to 8% of Stage IV patients (Cancer Research UK 2017f-g).

Immunotherapy

Immunotherapy has emerged as potential lifeline for terminal cancer patients and has generated significant interest in both the academic community and the media. In contrast to previous treatment modalities which attacked tumours directly, immunotherapy indirectly targets tumours by potentiating the immune response the body generates against the cancer (Couzin-Frankel 2013). With a history dating back to Virchow's observation of immune infiltrates in tumours and Coley's use of bacteria solutions to generate inflammatory responses against cancer, immunotherapy is currently experiencing a renaissance and multiple types are in development. Promising results have been seen to date with dendritic cell therapy (Schumacher et al 2015), oncolytic virus therapy (Banchereau et al 2005), neo-antigen vaccination (Parato et al 2005) and adoptive cell transfer (Rosenburg et al 2008). However, immune checkpoint inhibitors have emerged as the leading candidates in clinical immunotherapy.

Immune checkpoint inhibitors

The immune system is capable of recognising and

destroying cancer cells, but its activity is moderated by a series of ligand-inhibitory receptor interactions known as immune checkpoints (Pardoll 2012). The purpose of these checkpoints is to maintain self-tolerance and limit collateral damage to normal tissues generated by the immune response. However they can be hijacked by tumours as a means of escaping destruction and ensuring their own survival (Topalian et al 2015). The two major immune checkpoints – cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1) have slightly differing functions (Figure 1). CTLA4 signalling restricts T-cell activity while the immune response is initiated whereas PD1 acts later in the immune response, minimising collateral damage to adjacent tissues during chronic inflammation (Siefker-Radtke et al 2018). Therefore, blockade of these immune checkpoints could intensify the T-cell response and result in tumour eradication.

Efficacy of immune checkpoint inhibitors as monotherapies

The benefits from immune checkpoint inhibitors have been unprecedented in the history of terminal cancer treatment. Their promise was first elucidated with Ipilimumab, a CTLA-4 inhibitor, in metastatic melanoma, a cancer with a notoriously poor prognosis. Ipilimumab treatment resulted in a median overall survival of 10 months compared to a glycoprotein 100 peptide vaccine alternative, which produced a median survival of 6.4 months (Hodi et al 2010). Nivolumab, a PD-1 inhibitor, produced similar results in melanoma, with confirmed objective responses seen in 31.7% compared to 10.6% of the investigators choice-of-chemotherapy (Weber et al 2015). Nivolumab also found utility in NSCLC, with an overall survival rate of 12.2 months compared to 9.4 months in the docetaxel standard-of-care arm (Borghaei et al 2015).

Pembrolizumab, a PD-1 inhibitor similar to Nivolumab, was explored in a wide variety of trials and produced encouraging results in numerous cancer types including NSCLC (Reck et al 2016), melanoma (Robert et al 2015) and urothelial carcinoma (Balar et al 2017a). Pembrolizumab is best known as the first drug in history to receive FDA approval on the basis of a tumour characteristic, receiving approval for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) paediatric and adult solid tumours irrespective of site. Recent focus has shifted to PD-L1 inhibitors, and various agents have produced results comparable to the PD-1 inhibitors. Atezolizumab was the first of these agents to be explored. Promising response rates were seen in a phase II trial of metastatic urothelial carcinoma (Balar et al 2017b) but it ultimately failed to produce prolonged survival in a subsequent phase III trial (Powles et al 2018). However, Atezolizumab found its niche in the Phase III OAK trial, producing more favourable overall survival in NSCLC patients vs docetaxel (Rittmeyer et al 2017). However, to date, no trial has been performed to compare overall survival in NSCLC patients treated with Atezolizumab against those treated with Nivolumab. Results from next-generation PD-L1 inhibitors have been encouraging. The JAVELIN Solid Tumour trial demonstrated potent anti-tumour activity of Avelumab in platinum-refractory metastatic urothelial carcinoma (Patel et al 2018) while the ATLANTIC trial demonstrated a role for Durvalumab

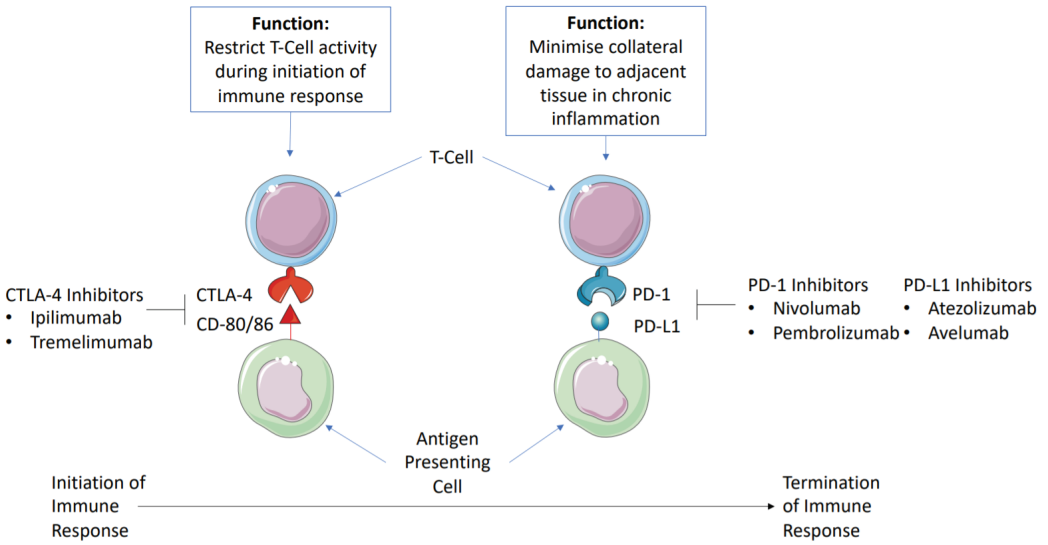

Figure 1: The major immune checkpoints, their functions and how they are targeted

as a third-line or later agent in EGFR-negative NSCLC (Garassino et al 2018).

Resistance to immune checkpoint inhibitors

The problem of resistance to immune checkpoint therapy has begun to emerge as a major limiting factor impeding their effectiveness in monotherapy. While a small proportion of patients maintain a continuous response, two significant subgroups have emerged – those failing to respond from therapy initiation (innate resistance) and those who respond initially but develop resistance over the course of therapy (acquired resistance) (Pitt et al 2016). The causes of resistance are variable and can be broadly divided into 3 main groups – impaired tumour reactive T-cell formation, impaired effector T-cell activation and impaired memory T-cells formation (Jenkins et al 2018) (Figure 2). As such, recent focus has turned towards using immunotherapies in combination therapies for terminal patients.

Combinations of different immune checkpoint inhibitors

Immune checkpoint inhibitors present an exciting avenue for combination therapy, combined either with each other or with alternative forms of therapy. The combinations of different immunotherapies continue to produce promising results, particularly combined Nivolumab-Ipilimumab which was studied first in melanoma. Initially compared against Ipilimumab monotherapy, the combination achieved a higher objective response rate (61% vs 11%) and complete response rate (22% vs 0%), as well as a significant increase in 2-year overall survival (63.8% vs 53.6%) (Postow et al 2015, Hodi et al 2016). Nivolumab-Ipilimumab was also tested against Nivolumab monotherapy, increasing median progression-free survival at initial analysis (11.5 months vs 6.9 months), accompanied by a slight increase in overall survival (58% vs 52%) at the 3-year follow-up (Larkin et al 2015, Wolchok et al 2017).

The scope of the Nivolumab-Ipilimumab combination continues to spread, showing encouraging results in trials of both non-small cell and small cell lung cancer (Hellman et al 2017, Antonia et al 2016a), metastatic renal cell carcinoma (Hammers et al 2017) and metastatic sarcoma (D'Angelo et al 2018). Combinations of newer generation anti-PD-1 and anti-CTLA-4 antibodies are also beginning to emerge such as durvalumab with tremelimumab, which displayed potent anti-tumour activity in a Phase Ib NSCLC study (Antonia et al 2016b). The potential for the combination of anti-PD-1 therapies with antibodies targeting newly discovered immune checkpoint receptors such as Tim-3 and LAG-3 has been promising to date (Sakuishi et al 2010, Woo et al 2012).

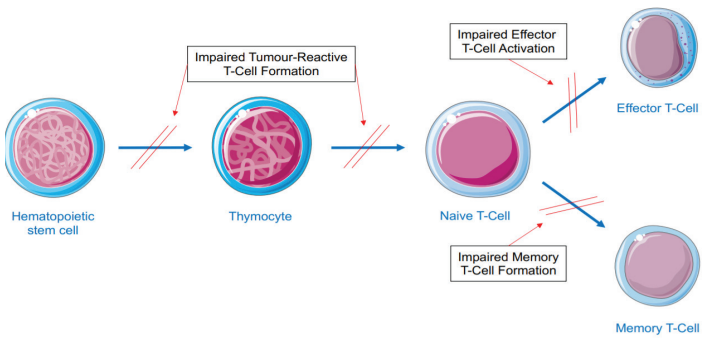

Figure 2: Mechanisms of resistance to immune checkpoint inhibitors

Combinations of immune checkpoint inhibitors with other cancer therapies

Checkpoint inhibitors have also shown promising results in combination with other forms of cancer therapy. Local control and clinical benefit was seen in one study where ipilimumab was combined with stereotactic external-beam radiation therapy (Sundahl et al 2018) while a decreased incidence of brain metastases and favourable survival outcomes were seen in a second study combining either ipilimumab, nivolumab or pembrolizumab with stereotactic radiosurgery (Chen et al 2018). Nivolumab has shown benefit when combined with various chemotherapeutic regimens in NSCLC including gemcitabine/cisplatin, pemetrexed/cisplatin and paclitaxel/carboplatin (Rizvi et al 2016, Kanda et al 2016). While still a relatively new field, checkpoint inhibitors have shown clinical efficacy in early clinical trials with various other agents including anti-angiogenic therapies (Amin et al 2014, Atkins et al 2018), MEK inhibitors (Ribas et al 2015) and BRAF inhibitors (Cooper et al 2014).

Cost-effectiveness of immune checkpoint inhibitors: These promising results have come with a steep price, with immune checkpoint inhibitors rapidly establishing themselves as some of the most expensive therapies available to modern medicine. One study from Switzerland compared the cost-effectiveness

of Nivolumab against Docetaxel for advanced non-squamous NSCLC and found that it was not a cost-effective improvement for patient care, exceeding the willingness-to-pay threshold by almost 78,000 CHF (Matter-Walstra et al 2016). A similar study conducted in Canada found that Nivolumab cost over $150,000 extra per quality-adjusted life year (QALY) compared to Docetaxel in NSCLC (Goeree et al 2016). An Australian Monte Carlo analysis found that Nivolumab was only considered cost-effective if compared against Ipilimumab for BRAF Wild-Type advanced melanoma and Nivolumab was deemed not to be cost-effective against placebo in a US study of its use in second-line metastatic renal cell carcinoma treatment (Bohensky et al 2016, Sarfaty et al 2018). While the relatively recent emergence of checkpoint inhibitor combination therapy leaves a current shortage of cost-effectiveness analysis available, one US study of the Nivolumab-Ipilimumab combination in first line metastatic melanoma found it was not cost-effective compared to Nivolumab monotherapy (Oh et al 2017).

Trends in cancer incidence and cost

The high costs of these checkpoint inhibitors cannot be ignored, especially in the context of current cancer incidence trends. Cancer incidence in Ireland is projected to grow by 84% in females and 107% in males by 2040 (National Cancer Registry Ireland 2014), mirroring trends in the United Kingdom, where incidence is projected to increase by 35% in females and 55% in males by 2030 (Mistry et al 2011). Almost a quarter of the UK population aged 65 years or older in 2040 will be cancer survivors (Maddams et al 2012). Similar statistics are seen elsewhere in the developed world – increases in age-standardised rates of cancer are seen in Australia in both males and females, while the total projected incidence of cancer in the United States is projected to rise by 45% by 2030 (Australian Institute of Health and Welfare 2012, Smith et al 2009). These trends are not restricted to the developed world; the burden of cancer continues to grow in developing countries as a result of aging populations and they will carry a significant proportion of the increases in cancer incidence, morbidity and mortality by 2030 (Thun et al 2010, Kanavos et al 2006).

This rising cancer burden is accompanied by an ever-increasing cost of cancer care. Between 2010 and 2020, the cost of healthcare will have risen by 39% in the United States, reaching an annual expenditure of $173 billion (Mariotto et al 2011). Between 1991 and 2002, the per patient cost of caring for lung, colorectal and breast cancer patients increased by over $7000, over $5000 and over $4000 respectively, and colorectal cancer expenditure alone will have increased by 89% between 2010 and 2020 (Warren et al 2008, Yabroff et al 2008). The average price of cancer drugs per patient per year rose from $5000-10,000 before 2000 to over $100,000 in 2012 and cancer drug expenditure will have risen by 50% over the 10-year period from 2010-2020 (Light et al 2013, Prasad et al 2017). Recently developed immune checkpoint inhibitors are likely to only add to this financial burden further. In NSCLC alone, Atezolizumab is estimated to cost a median of $68,960 per patient, while Pembrolizumab and Nivolumab cost $83,691 and $87,575 respectively for a total course of treatment for each patient (Ogale 2018). The Nivolumab-Ipilimumab combination costs substantially higher at $295,566 per patient and the overall cost of implementing these drugs to tackle metastatic cancer was predicted to cost as high as $174 billion per annum in America alone (Andrews 2015).

Conclusion

The spiralling cost of cancer care has extended from the healthcare provider to the patient themselves. Conservative estimates show that cancer can cost an average patient €832 per month, with 60% of patients experiencing an annual income reduction of over €16,500 (Irish Cancer Society 2015). The cost of new medications is increasingly recognised as a driving force behind the increasing financial toxicity of a cancer diagnosis and it is difficult to imagine that these new high-cost checkpoint inhibitors will do anything other than increase the burden further, on both the state and the patient. With higher cancer expenditure causing patients to delay or forgo treatment, reduce adherence to cancer treatment and increase their risk of bankruptcy, the question must be asked as to whether these expensive immune checkpoint inhibitors are the right step forward in the fight against terminal cancer.

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Should There be a Limit to Reproductive Rights?

Swan Medal Essay Prize

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"Imagine a being who is omniscient, omnipresent and omnipotent. What does such a being lack? The answer? Limitation" (Peterson, 2018). This old Jewish moral teaches an interesting concept: that limitations aren't flawed or restricting, rather beneficial and necessary. Does that hold true for issues on reproductive rights?

Those delving into reproductive rights may naturally jump to the national and international debate of legal and safe abortion. In 2017, the US reinstated its prohibition on American foreign aid to health providers promoting abortion (Sengupta, 2017). In Ireland, the recent campaign to repeal the 8th amendment of the Irish Constitution was successful (Kelly, 2018). However, reproductive rights is an umbrella term; the W.H.O. describes it as encompassing contraception, access to reproductive healthcare, protection from female genital mutilation, and this essays particular topic of interest, freedom from forced sterilization (World Health Organisation, 2009). Forced sterilization is the practice of rendering a person infertile through surgical (vasectomy/ salpingectomy) or other means. Forced sterilization is outlawed in multiple treaties such as the 2011 Istanbul Convention. Article 39 within this treaty references "the following international conducts are criminalised...performing surgery which has the purpose or effect of terminating a woman's capacity to naturally reproduce without her prior and informed consent or understanding of the procedure" (Council of Europe, 2011). This process is claimed to be justified by population control, therapeutic, punitive or eugenic reasons. Should there be total freedom from forced sterilization or are there situations that could justify its usage? This essay will explore multiple groups connected with forced sterilization, such as ethnic minority women, HIV women, Intellectually Disabled (I.D.) people, intersex and transgender people.

UNICEF, WHO, UN Woman, OHCHR, UNAIDS and other organisations wrote cooperatively "Eliminating forced, coercive and otherwise involuntary sterilization: An interagency statement" (World Health Organisation, 2014). It notes that women are particularly targeted by forced sterilization across the globe such as in Uzbekistan and India (Kumar, 1999; Holt, 2012). Ethnic minority women are especially vulnerable. For instance, Romani women were systemically sterilized in the late 1900's in communist countries like the Czech Republic. Allegedly, this was done to disrupt the traditionally high reproductive rate among the Roma population (Denysenko, 2007). Following on from this at the turn of the new century, a total of 5 Romani women brought 3 separate cases in front of the European Court of Human Rights (E.C.H.R). In V.C. vs Slovakia, a woman was forcibly sterilized in 2000 whilst delivering her second child. She was pressured during labour to sign a limited declaration for sterilization under the false pretence that she or her baby would die if she didn't comply. She was unaware what sterilization entailed, later learning that it was not necessary to save her life, but merely as a form of contraception. Given that supposed consent was obtained under a level of unethical duress and misinformation, it was deemed invalid. In 2011 the E.C.H.R. ruled in favour of V.C. based on "her right to private and family life, and her right to freedom from inhuman and degrading treatment." These are expressed under Article 3 and 8 of the European Convention on Human Rights (European Court of Human Rights, 2011; Patel, 2017).

Ethnic minority women aren't the only vulnerable group; women with HIV are also at risk of forced sterilization. The autonomy and freedom of these women can often be overlooked by health-care providers through deception, fear-mongering and misconceptions regarding HIV transmission. Sterilization in this group continues, despite evidence that the simultaneous use of antiretrovirals treatment pre/post pregnancy, and safer infant feeding practices can limit transmission rates to less than 5% (World Health Organization,

2010). These women are being coerced under blackmail threats of not receiving adequate health care, unless they cooperate (Open Society Foundation and Stop Torture Healthcare, 2011). A 2015 study revealed that a quarter of 285 women with HIV from El Salvador, Honduras, Mexico and Nicaragua felt pressured at some point by their health-care provider to undergo sterilization (Kendall and Albert, 2015).

The interagency statement previously mentioned also discusses forced sterilization of people with I.D. People with I.D. may be considered as vulnerable because of their inability to comprehend the consequences of their sexual desires. In the early 20th century, negative eugenics (limit procreation of individuals considered "unfit") was a driving factor for this movement (Friedl, 2015). Justice Oliver Wendell Holmes infamously said in the Buck vs Bell Supreme Court case (1927) "society can prevent those who are manifestly unfit from continuing their kind...three generations of imbeciles are enough" (University of Virginia, 2007). This mentality became recognised as unethical and the practice was made illegal. Following this, the concept of patients' "best interests" came into consideration. It is noteworthy that best interests are not solely medical, but also incorporate emotional and welfare issues. Re F (1990) was one of the first cases to explore this when a 36 year old female with a child's mental age formed a sexual relationship with a fellow inpatient. The concern was that of pregnancy and her inability to cope with motherhood leading to a decision in favour of sterilization (E-law cases, 1990). Whereas in the case of Re A (2000), a 28 year old male with Down Syndrome, the original ruling that sterilization wasn't necessarily in the patients best interests was upheld despite appeal (COURT OF APPEAL, 2000). In terms of minors rulings also vary. In Re D (1976) an 11-year-old girl suffering from Sotos syndrome was going to be sterilised when a psychologist challenged the decision. This resulted in the child being made a ward of the court. The judge refused to approve the operation, citing the welfare of the child, that the operation was premature and would remove the child's basic woman's right to reproduce. However, in contrast, in Re B (1988) the English House of Lords approved the forced sterilization of a 17 year old I.D. girl as she was unable to understand the causal link between sex and pregnancy (COURT OF APPEAL, 1999).

These cases illustrate that there is not one underlying template to follow for all scenarios of I.D. individuals. This ability to differentiate their individual merits and case specifics is a very important safeguard. As one paper argues it is positive that courts have a stricter reign to protect I.D. people and "the only exception should be the particular case in which all medical and social factors having been taken into account..." (Rowlands and Amy, 2017). It is stated that setting the threshold too low could mistakenly hinder someone's reproductive freedom.

Finally, transgender and intersex people are also victims of forced sterilization. A European Union statement on discrimination of trans and intersex individuals states that bias against transgender people "manifests itself most clearly in the enforcement of certain unnecessary, yet obligatory medical treatments and procedures e.g. sterilisation... to access certain rewards... (e.g. change of name and issuance of identification documents in the appropriate gender") (Office for Official Publications of the European Union, 2012). Lee's paper stated that, in 21 Council of Europe countries, proof of sterilization was required in order to change one's legal sex categorization. The author argued that LGBT treaties would need to be established to protect this breach of human rights. (Lee, 2015) The Commissioner for Human Rights of the Council of Europe said this process did not demonstrate respect for individuals, especially because it seemed to make transgender people the only European people under threat of state-enforced sterilization. We are seeing a shift away from this mentality as demonstrated by rulings in the Federal Supreme Court of Germany and the Austrian Administrative High Court that a prerequisite to gender change cannot be mandatory sterilization surgery (Office of the UN High Commissioner for Human Rights, 2013). Intersex children or those born with atypical sexual characteristics may undergo sex normalising surgery or non-medically indicated cosmetic surgery, which may entirely remove their reproductive ability. The argument in favour of this practice is psychosocial, allowing the child to clearly identify themselves as one sex for better social and developmental function. However, Juan E Mendés, the UN Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment condemned this process of non-consensual intervention, which can leave individuals with "permanent, irreversible infertility, and causing severe mental suffering" (Special Rapporteur

Report, 2016). The interagency report recommended that health-care professionals delay interventions until maturity has been reached by the child in order to allow them to participate in informed decision making (World Health Organisation, 2014).

There are various fascinating areas of reproductive rights to debate on. This essay explored multiple groups connected with forced sterilization, such as ethnic minority women, HIV women, I.D. people, intersex and transgender people. It appears that the vast majority of cases that do occur, are unethical and unnecessary. Therefore, people deserve near total freedom from forced sterilization and to have control over their own reproductive rights. It could be argued that there are only a few circumstances where a limit is acceptable, and sterilization may be necessary. Such as cases of intellectually disabled people where thorough evaluation has concluded sterilization is in the patient's best interests. For the majority of other cases, people shouldn't have sterilization forced upon them.

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A General Practice Audit Comparing the Rate of Pneumococcal Vaccine Uptake Among Patients with Diabetes Mellitus, Before and After Intervention

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Abstract

The pneumococcal polysaccharide vaccine was introduced for at-risk groups in Ireland in 1996 and it has been demonstrated that increased vaccination rates result in fewer hospital visits in at-risk groups. An audit was carried out from October 2017 until January 2018 in a rural general practice catering for just over 2,000 patients. It was hypothesised that, from direct observation, there was a lack of uptake of the pneumococcal vaccine in certain at-risk patient groups, such as patients with diabetes mellitus. The findings from this were used to guide intervention aimed at encouraging uptake of the pneumococcal vaccine. Data was collected to include the vaccination status of all patients with diabetes mellitus in the practice. The results showed 89 patients (59.3%) had never received the vaccine. In addition, a further 23 (15.3%) patients were due a booster. From the re-audit, following intervention to encourage uptake, which included direct advice and encouragement from the practice doctors and nurses, in addition to a text message reminder sent to patients, 22 patients attended for vaccination, giving an uptake rate of 19.6%. The ideal scenario is for all patients with diabetes mellitus to be vaccinated which would amount to improved quality of life for patients. Whilst a target of 100% is difficult to achieve, the expectation would be to have the majority of patients vaccinated according to current guidelines. In addition, the practice would ensure compliance with those guidelines and recommendations regarding vaccination and would also generate revenue, which is important in order to maintain a viable business model within general practice.

Introduction

Pneumococcal disease is a bacterial infection caused by Streptococcus pneumoniae, of which there are over 90 serotypes (Habib et al., 2014). S.pneumoniae can lead to significant morbidity and mortality and, in recent times, has become resistant to many antibiotics (Ortqvist et al., 2005). S. pneumoniae is the most common causative agent of pneumonia and also causes a variety of other infections including sinusitis, osteomyelitis, bronchitis and otitis media (Ortqvist et al., 2005). Prevention of disease in patients with diabetes mellitus (DM) through vaccination is recommended as patients with DM are at an increased risk of developing invasive pneumococcal disease compared to those without (Torres et al., 2015). An English record-linkage study identifying and measuring the risk of pneumonia and pneumococcal disease in hospitalised patients with DM found that those admitted to hospital remain at increased risk of pneumococcal infection despite the fact that a national immunisation policy had been in place for more than a decade (Seminog and Goldacre, 2013).

There are two main types of pneumococcal vaccines used in Ireland. The pneumococcal conjugate vaccine (PCV) contains polysaccharide from 13 of the most common capsular types and is recommended for the routine vaccination of all children born on or after 1st October 2010 (HSE National Immunisation Office, Health Service Executive, 2016). The pneumococcal polysaccharide vaccine (PPV) contains purified polysaccharide from 23 of the most common capsular types of S.pneumoniae, thereby covering 85-90% of the serotypes of the bacteria and it is this vaccine which

is recommended for those aged 65 years and over and at-risk adults and children over two years of age (HSE National Immunisation Office, Health Service Executive, 2016). The PPV23 is the vaccine considered in this audit as it pertains to the study population. All patients with DM are recommended to receive the PPV23. If the PPV23 has been administered to a patient under the age of 65 years, it is recommended that they receive a once only booster five years after the first vaccination. If the PPV23 has been administered to a patient over the age of 65 years, no further booster is required (HSE National Immunisation Office, Health Service Executive, 2016). The algorithm for PPV23 administration (Figure 1). Many case control studies have shown the efficacy of the pneumococcal vaccine as being between 56% and 81% (Shapiro, 2012). In addition, a recent systematic review and meta-analysis highlighted significant vaccine efficacy. This study demonstrated vaccine efficacy against invasive pneumococcal disease (by any serotype) of 73% (95% CI: 10-92%) in four clinical trials, 45% (95% CI: 15-65%) in three cohort studies and 59% (95% CI: 35-74%) in three case-control studies. Pooled vaccine efficacy against pneumococcal pneumonia (by any serotype) was 64% (95% CI: 35-80%) in two clinical trials and 48% (95% CI: 25-63%) in two cohort studies (Falkenhorst et al., 2017).

It was hypothesised that, from direct observation, there was a lack of uptake of the pneumococcal vaccine in certain at-risk patient groups, such as patients with diabetes mellitus. Based on this, an audit was carried out from October 2017 until January 2018 in a rural general practice. The findings from this would be used to guide intervention aimed at encouraging uptake of the pneumococcal vaccine among this patient group. Direct advice and encouragement from the practice doctors and nurses, provided to patients during routine consultations, constitutes the primary intervention. In addition, a text message reminder sent to patients would further reinforce the importance of patients keeping their vaccination status up to date and would also capture any patient who was not attending for a routine appointment.

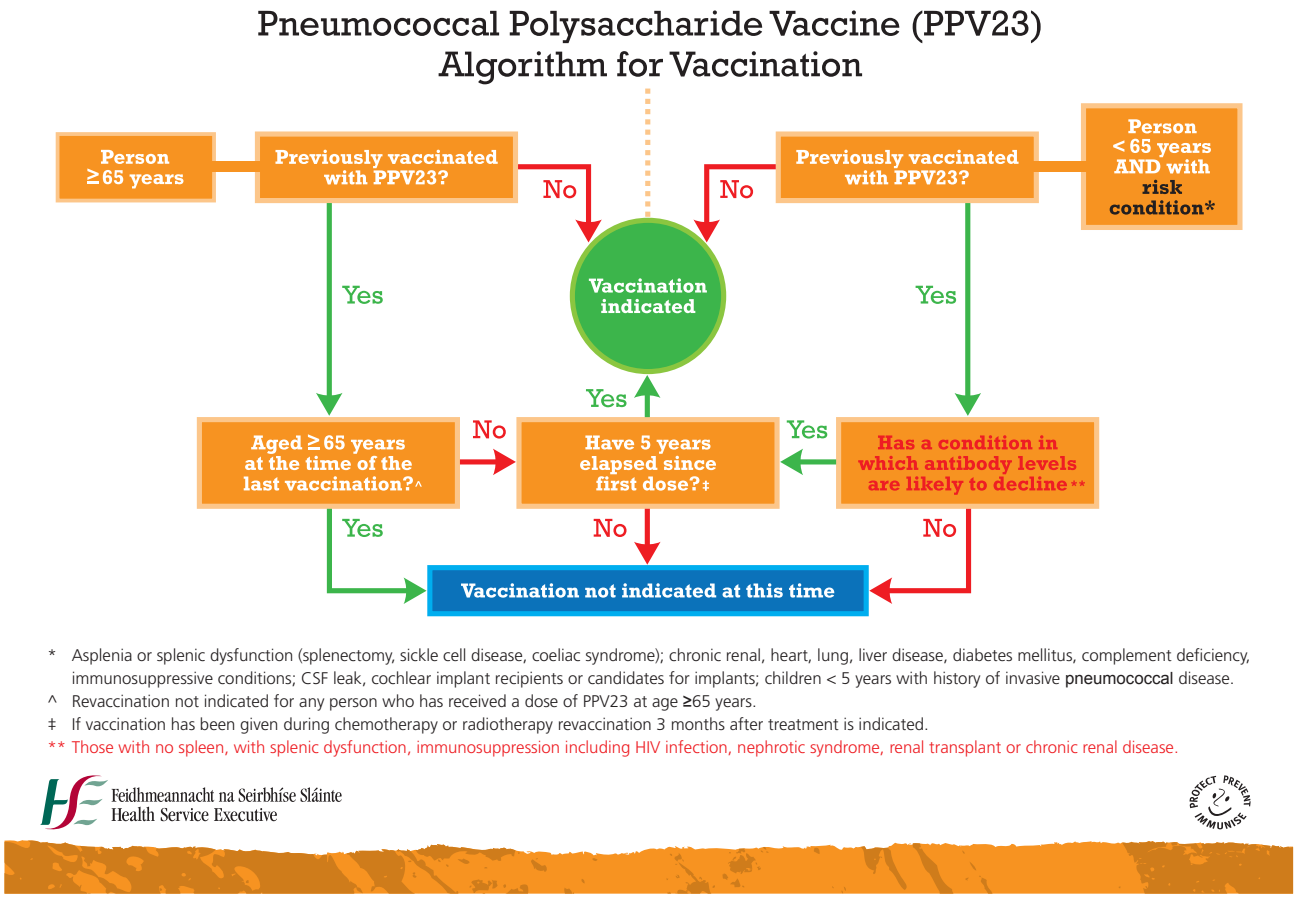

Figure 1: Pneumococcal polysaccharide vaccine (PPV23) algorithm for vaccination (HSE National Immunisation Office, Health Service Executive, 2016).

Methods

During October 2017, the patient list was searched to compile a list of the patients that both attend the practice and have DM. Only active patients in the patient list with type 1 diabetes mellitus, type 2 diabetes mellitus or gestational diabetes mellitus were included. All other patients were excluded. The software package used within the practice for patient record management is SOCRATES. The patient's name, age, date of birth, and their subgroup of disease (type 1 diabetes mellitus, type 2 diabetes mellitus or gestational diabetes mellitus) were recorded. The vaccination history of each patient was examined. It was then noted if they had received the PPV23 in the past and whether they were they under or over 65 years of age at the time of administration.

Direct advice and encouragement from the practice doctors and nurses was provided to patients during routine consultations. In addition, a text message was sent to all patients of the practice with DM to remind those who had either never received the vaccination, or had received the vaccination when they were under 65 years of age and were due a booster, to attend the practice for vaccination at their earliest convenience. The advantages of getting the vaccine, specifically relating to the health benefit of increased immunity, were stated in the text message to encourage patients to attend.

In January 2018, the study population was re-audited to determine the uptake rate following intervention. A list of those patients who had received the PPV23 between 5/10/17 and 12/1/18 was compiled and the uptake rate calculated.

Results

Of the 150 patients with diabetes (3 with type 1 diabetes mellitus, 147 with type 2 diabetes mellitus and 0 with gestational diabetes mellitus), it was found that 61 patients had already received the vaccination, leaving 89 patients unvaccinated. Therefore, at the outset of the audit, before any intervention was performed, 40.7% of patients with DM in the practice had received the PPV23 and 59.3% had never received the PPV23. In addition to those never vaccinated, 23 of those previously vaccinated were under the age of 65 when they received the vaccination, meaning that these patients would be eligible for a booster five years after receiving the initial vaccination. This gives a total of 112 patients who were either immediately eligible to receive the PPV23 or who would be eligible soon (Figure 2).

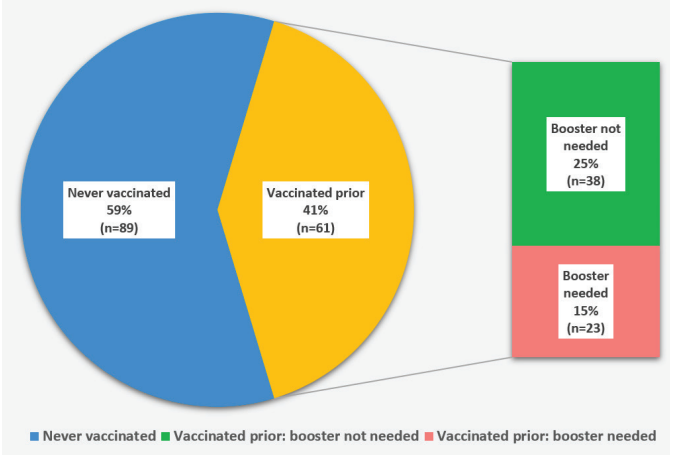

Figure 2: Audit showing percentage of all patients with DM (n=150) who have never been vaccinated with PPV23 prior and also those vaccinated prior and i) not needing a booster and ii) needing a booster.

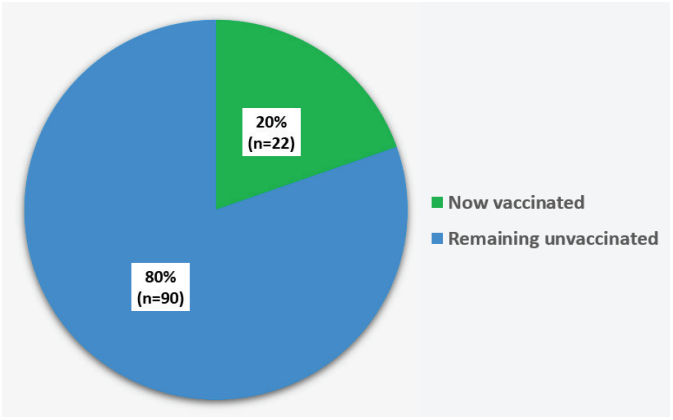

Figure 3: Re-audit showing percentage of patient cohort needing vaccination (n=112) who have or have not been vaccinated with PPV23 following the initial audit and intervention.

From the re-audit, it was found that 22 people from the patient cohort attended the practice to receive the PPV23 between 5/10/17 and 12/1/18. Therefore, from the 112 patients eligible for vaccination, there was a response rate to the initial intervention of 19.6% (Figure 3).

Discussion

The ideal goal is a 100% vaccination rate with PPV23 for patients with DM as this would amount to improved quality of life for patients in terms of reduced morbidity and mortality, reduced general practice visits and decreased hospital admissions. Whilst a target of 100% is difficult to achieve, the expectation would be to have the majority of patients vaccinated according to current guidelines. At the outset of the audit, 40.7% of the study

population had never received the PPV23. However, 22 people from the patient cohort of 112 patients attended to receive the PPV23 after intervention, giving a 19.6% response rate to initial targeting of this patient group. This uptake within a short space of time indicates an improvement and a willingness of the patients to receive the vaccine. There are also benefits for the practice in achieving the target of 100% vaccination among this patient population. In doing so, the practice would become compliant with the guidelines and recommendations concerning vaccination, in addition, the practice would generate revenue, which is important in order to maintain a viable business model within general practice in Ireland.

Without surveying the local study population, it is difficult to determine the exact reasons for lack of uptake of the PPV23. However, previous studies suggest a number of factors. A 2015 study identified two significant predictors which affect the likelihood of vaccination: (i) patients with a greater number of co-morbidities and (ii) vaccine recommendation from general practitioners (Gorska-Ciebiada et al., 2015). Reasons cited by those patients unvaccinated included a lack of information about vaccination and low perceived benefits. An Irish study surveyed patients with DM attending an outpatient clinic regarding their vaccination status and stance (Clancy et al., 2012). This 2012 study demonstrated that vaccine recommendation offered by general practitioners was a significant predictor of pneumococcal vaccine uptake, along with the comorbidity of chronic kidney disease. Both studies therefore demonstrate a key issue relating to vaccine uptake, i.e. recommendation and encouragement by general practitioners. Doctors and nurses within the practice should therefore be encouraged to educate patients on the benefits of receiving the PPV23, thus providing the patient with the relevant information, allowing them to make an informed decision. This has the potential to generate a positive outcome in terms of increasing PPV23 uptake rate and offers a straightforward approach which is easy to implement during the patient consultation.

As a recommendation for the future, it would be advisable to send another message to the patient cohort. Equally, it is important to ensure all patients with DM are advised of the benefits of vaccination during visits to the practice as part of their routine diabetic checks. If there was a levelling off of uptake or it failed to progress at an acceptable speed, it would be important to consider why this is and perhaps identify barriers to patients availing of the vaccination and develop novel ways to encourage uptake.

The immunisation records used for the patients in this audit are those available from the general practice data which dates back to 2002. Unless the patient has informed the practice of having received the vaccination in a different clinical setting, this would not be accounted for in the patient notes and represents one drawback of the audit database. A further limitation was the lack of a target for the desired response rate. Setting a target for further intervention and re-audit would guide intervention and track progress over time.

Conclusion

This audit provides an easy method to target key performance indicators within general practice with a relatively quick turnaround. It was possible to readily identify those patients with DM who had not received the PPV23 at the outset of the audit and then monitor the uptake rate over time. On success of this audit and intervention, this model could easily be adapted to other key targets, including other vaccinations for a range of medical conditions, blood testing, blood pressure monitoring and so on, both at a local and national level.

Acknowledgements

The authors would like to thank the nursing and administrative staff of Market Square Medical Practice for their assistance in accessing the patient files.

Conflict of interest

The authors declare there are no conflicts of interest.

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Managing Anxious Patients Undergoing Magnetic Resonance Imaging: Evidence Versus Common Practice in Ireland

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Abstract

Aim: Adult patients undergoing Magnetic Resonance Imaging (MRI) often experience anxiety prior to and during scanning. While NICE guidelines exist for anxious paediatric patients undergoing MRI procedures, no formal guidelines have been developed for adults. The aim of this study was to compare current practices of managing anxious adult patients undergoing MRI procedures in a selection of Irish hospitals with a reviewed international evidence base.

Methods: A comprehensive literature review was conducted once search terms, the Boolean operators with which to pair them, and the parameters of our search were defined. The Cochrane Database, PubMed, Google Scholar and eMedicine databases were all utilised for the literature review. This knowledge base was then used to create a comprehensive survey, which our team used to conduct phone interviews with nine hospitals throughout Ireland regarding their existing protocols.

Results: The literature demonstrates the benefits of utilising oral, or if necessary, intravenous sedation in anxious patients, despite the potential adverse effects of such. However, no universally-approved or utilised protocols have been established in Ireland. Our survey of nine Irish hospitals found three hospitals with vague and open-ended departmental protocols. The remainder of surveyed hospitals referred anxious patients to their general practitioner for review prior to repeat scans on a case-by-case basis.

Discussion: Our study demonstrates the lack of a nationally implemented formal protocol in Ireland for anxious patients undergoing MRI procedures. Without a formal protocol in place, vague protocols prevail, costing the healthcare system and individual patients time and money. We would aim to build upon this research, consulting with international hospitals to create a formal and robust protocol.

Introduction

Magnetic Resonance Imaging (MRI) is considered to be one of the safest and diagnostically efficacious of all diagnostic radiological procedures (Kanal et al, 2007). Despite the excellent safety profile, anxious adult patients present a unique challenge. Although hospital staff may view an MRI procedure as routine, patients may experience mild, moderate, or severe anxiety. Anxiety and restlessness may result in poor image quality, reducing diagnostic utility of the images, as well as causing psychological and/or physical ramifications (Figure 1). Additionally, poor image quality may necessitate repeat scanning, creating a significant financial burden on healthcare systems. In order to avoid adverse outcomes, non-pharmacological interventions, sedation, and general anaesthetics may be employed. This study aims to examine existing data on MRI sedation options for the anxious adult patient population. Collating this data will allow the formulation of an MRI sedation protocol for anxious adults, which we will compare to current protocols in a surveyed set of Irish hospitals.

An MRI requires patients to remain still for up to an hour in a loud and confined space. Under these circumstances, a patient may be unable to complete the MRI or move too much to obtain viable diagnostic images, requiring a repeat scan, increasing their anxiety. Non-pharmacological techniques such as detailed explanation, sleep deprivation, video-based demonstration, telephone conversation with radiographer, prone positioning, and use of the patient's own music during scanning have all been shown to

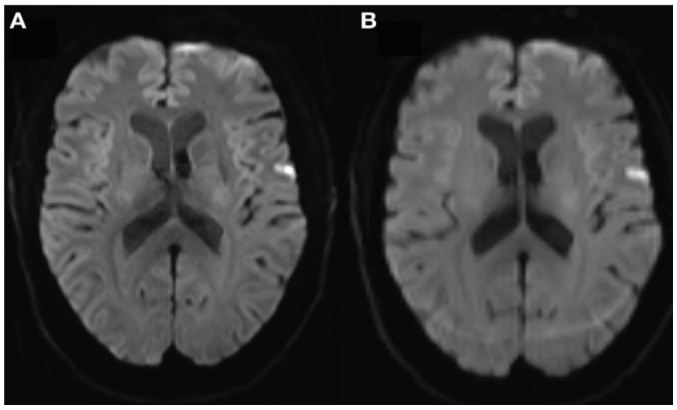

Figure 1: MRI images with, and without movement artifact, demonstrating the need for a movement-free scan to optimize diagnostic quality (Original image demonstrating movement artifact in 68-year-old patient with transient ischaemic attack symptoms lasting two hours, from article: Havsteen et al, 2017).

alleviate anxiety (Tugwell et al, 2017; Munn & Jordan, 2013).

When these non-pharmacological methods fail, the medical team should implement sedation. Although clinical studies regarding sedative drugs are available in the literature, no single drug is recommended as a universal standard (Levati et al, 2004). The choice of the type and level of pharmacological sedation depend on patient age, weight, cooperativity, and medical history. The benefits and the risks of sedation must be weighed against one another for the best patient outcome (Ali et al, 2013; Andre et al, 2015; Nabavizadeh, 2016). Over-sedation in MRI procedures could ultimately result in cardiorespiratory depression, post-procedure nausea and vomiting, disorientation, and sleep disturbance. Conversely, if the patient is inadequately sedated, poor image quality, along with the negative psychological consequences and increased costs due to multiple procedures, may result (Ali et al, 2013; Andre et al, 2015; Nabavizadeh, 2016).

Methods

In order to assess the literature, we found it necessary to define our search terms, the Boolean operators with which to pair them, and the parameters of our search. Our search terms were optimised to answer our research question: "What is the evidence for the use of sedation in anxious patients undergoing MRI?"

Sedation was defined under the search terms; sedation, anaesthesia and anxiolytics. This enabled us to create a wide definition around sedation in order to parse out the most relevant literature. MRI was searched for so as such to exclude other imaging modalities. Articles were analysed for their research methods using the evidence-based medicine pyramid, ranking at its peak meta-analyses and systematic reviews. The Cochrane Database, PubMed and Google Scholar were all utilised, as was eMedicine for its use in providing clinician guidelines. We chose to work through the first twenty results of each search engine, filtering through them by the aforementioned parameters. Duplicate results were then excluded between searches and between databases.Contingent on the findings from this review, a phone survey was created in collaboration with Dr. Anne Buckley (SpR, Radiology). In total, nine radiology departments were surveyed, providing insight into current MRI sedation protocols in Irish hospitals. Firstly, each hospital was asked how many anxious patients they would see per month who required intervention to complete the MRI, or who could not complete the procedure. Each hospital was then asked if they had an official protocol for anxious patients in place. If they had a protocol, they were then asked who administered the protocol and how exactly they did this. If the hospital did not have a formal protocol, they were then asked to explain what practices they employed for anxious patients in this setting. Of note, all hospitals noted that they found explaining the procedure to the patients alleviated anxiety and helped them in completing the MRI scan, regardless of having an existing protocol or not. Furthermore, each hospital was asked a series of questions regarding pharmacological measures employed for anxious patients. This series of questions included: 'Did the department administer sedative medications for anxious patients undergoing MRI?'; 'Was it the department who made the decision to administer sedation or did they refer patients to their general physician for a sedative prescription?'; 'Were sedative medications offered for outpatients only, inpatients only, or both types of patients?'; 'What sedative medications were administered to patients?'; 'What was the route of the sedative medication administration?'; 'What was the timing of administration with regards to the MRI?'; 'If they did not administer any medications, did the department have a referral pathway in place for patients to receive medication from their family practitioner for a future appointment?'.

Results

Findings from Literature Review

Healthcare professionals must record a comprehensive medical history and conduct a thorough clinical examination, including a physical status evaluation (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002). In cases where sedation is deemed necessary, informed consent needs to be obtained from the patient (National Clinical Guideline Centre (NICE), 2010). Specialist advice is recommended before giving sedation if there is a concern about a potential airway or breathing problem. When sedation is necessary, adequate oxygen supply, airway equipment and drugs needed to support life during an emergency, must be readily available (National Clinical Guideline Centre, 2010).

As sedation can be psychologically distressing for patients, especially those with a predisposition to procedural anxiety, it is essential that they are offered information about their role in the procedure and what the healthcare professional will do (National Clinical Guideline Centre, 2010). Radiologists, anesthetists, emergency room physicians, and specialist nurses have administered sedatives in the MRI setting (Arlachov & Ganatra, 2012). Should the sedation team decide to administer sevoflurane, propofol or opioids combined with ketamine, they must ensure that the team member is appropriately trained (National Clinical Guideline Centre, 2010).

Several classes of sedative agents can be used for patients undergoing radiological procedures (Table 1). These include benzodiazepines, barbiturates, intravenous anaesthetics, inhalational anaesthetics and other sedative agents such as dexmedetomidine (Arlachov & Ganatra, 2012). Benzodiazepines are classically used as anxiolytic medications, and in this setting include midazolam, diazepam, lorazepam, and alprazolam (Arlachov & Ganatra, 2012). The literature identifies midazolam as the first-line benzodiazepine for inpatient use, due to its rapid onset of action and short elimination half-life (approximately 1-4 hours), and diazepam as the first-line benzodiazepine for outpatients (The Royal College of Radiologists, 2018). The typical dosing patterns for these medications for adults and geriatric or chronically ill patients have been previously outlined (Irish Pharmaceutical Healthcare Association, 2017; The Royal College of Radiologists, 2018; Medscape, 2018; Prescriber's Digital Reference, 2018). Flumazenil is an effective benzodiazepine reversal agent and may be administered as an IV infusion in the event of an overdose (Arlachov & Ganatra, 2012).

Barbiturates are a class of medications that can be used in the induction and maintenance of deep sedation. However, due to the higher rate of adverse respiratory effects, they are not frequently used (Levati et al, 2004; Mason et al, 2001). Additionally, the general anaesthetics propofol and ketamine are used in radiological procedures (The Royal College of Radiologists, 2018). Propofol is a primary sedative agent that can be used for MRI procedures, and ketamine is a fast acting anaesthetic and painkiller that induces a dissociative state (The Royal College of Radiologists, 2018). Due to the higher risk of adverse effects, these medications should only be administered by anaesthetists (Merola et al, 1995; The Royal College of Radiologists, 2018).

Inhalational anesthetics such as nitrous oxide and sevoflurane can also be used for radiological procedures. Nitrous oxide is a potent analgesic and dramatically reduces patient anxiety, but care must be taken when combining it with other sedatives as this may result in deep sedation (Litman et al, 1998). Sevoflurane can also be used for MRI sedation, but due to its rapid induction of general anaesthesia and short half-life, it is recommended that only anaesthetists administer it. Other sedative agents that have been used, but not rigorously tested, include dexmedetomidine, an alpha-2 agonist with sedative and analgesic properties (Arlachov & Ganatra, 2012).

The current guidelines stipulate that healthcare professionals must "monitor, interpret and respond to changes in depth of sedation, respiration, oxygen saturation, heart rate, pain, coping, distress, three-lead electrocardiogram, end tidal CO_2, and five-minute interval blood pressure readings", for patients undergoing moderate to deep sedation for an MRI procedure (National Clinical Guideline Centre, 2010). Immediately post-procedure patients must be monitored until they have a patent airway, show protective airway and breathing reflexes, are hemodynamically stable and are easily roused.

Survey of Irish Hospitals

Three of the nine hospitals had a protocol in place to

deal with an average of forty-five patients per month whose anxiety was significant and prompted clinicians to consider the use of sedation. Thus, an average of forty-five patients per month required some form of intervention (non-pharmacological or pharmacological), in order to complete the MRI procedure. All three hospitals with a set protocol differed in their approach to anxious patients. Cork University Hospital offered a tiered approach, where non-pharmacological methods were instituted first (verbally calm patient and allow them to bring approved family member or friend into MRI room), followed by oral sedation and then IV sedation if necessary. Letterkenny General Hospital offered only non-pharmacological methods of anxiolysis to patients such as verbal reassurance and a panic button. In order to receive oral sedation patients would be referred to their GP to get a prescription for a benzodiazepine, while IV sedation was not included in the protocol. The Aut Even Hospital in Kilkenny offered many non-pharmacological approaches for anxiolysis, along with elevation to oral sedation if required, but they did not provide IV sedation to patients.

The three hospitals who did maintain a protocol were vague and open-ended in nature, often referring to the judgement of the radiographer. We note that each of these three protocols were determined by a single radiologist or radiographer and were not peer reviewed. In all hospitals, if non-pharmacological procedures did not alleviate anxiety, the decision regarding use of sedation would rest with either the referring team or the patient's GP. Six hospitals would refer patients for whom non-pharmacological methods failed to relieve their anxiety to their GP for the prescription of a sedative medication. In this instance, the hospital often supplied the patient with a suggestion of a particular type of benzodiazepine to mention to their GP. Furthermore, two of the three hospitals with an established protocol and three hospitals without a formal protocol, did not have the capability to offer IV sedation to patients undergoing MRI procedures, highlighting the need for an adaptable protocol which takes into consideration staffing and financial resources.

Drug	Drug Class	Patient	Indication	Route
Midazolam	Benzodiazepine	Adult / Paediatric	Conscious (Light) Sedation	Intravenous
Diazepam	Benzodiazepine	Adult / Paediatric	Conscious (Light) Sedation	Oral / Intravenous / Intramuscular
Lorazepam	Benzodiazepine	Adult / Paediatric	Conscious (Light) Sedation	Oral / Intravenous
Termazepam	Benzodiazepine	Adult / Paediatric	Conscious (Light) Sedation	Oral
Pentobarbital	Barbiturate	Adult / Paediatric	Conscious (Light) Sedation	Oral / Intravenous / Intramuscular
Methohexital	Barbiturate	Adult / Paediatric	Procedural Anaesthesia	Intravenous / Intramuscular
Ketamine	General Anaesthetic	Adult	Procedural Anaethesia	Intravenous / Intramuscular
Propofol	General Anaesthetic	Adult / Paediatric	Procedural Anaethesia	Intravenous
Nitrous Oxide	General Anaesthetic	Adult / Paediatric	Procedural Anaethesia	Inhalational
Sevoflurane	General Anaesthetic	Adult / Paediatric	Procedural Anaethesia	Inhalational
Dexmedetomidine	Alpha-2 agonist	Adult	Procedural Sedation	Intravenous

Table 1: Drugs employed for sedation or general anesthesia.

In each surveyed hospital, all departments favoured explaining the procedure and reassuring the patient in order to help alleviate anxiety. All departments had some informal non-pharmacological procedures in place which were utilised if necessary. Examples include: presence of panic/safety buttons that allow patients to pause the scan and speak with the radiographer; allowing approved family member/friend into MRI room; allowing patient repositioning within the MRI machine. When an anxiolytic or sedative prescription was required, the particular oral benzodiazepine administered varied, and no information could be given regarding dosages, despite the existence of guidelines for such procedures.

Discussion

MRI is a safe, routine and highly accurate procedure, but one that can cause varying levels of anxiety in patients. The literature has described non-pharmacological and pharmacological methods to minimize emotional distress in this patient cohort. Based on this, we believe a definitive and universally accepted MRI protocol would be of value, and that research towards optimizing such a protocol would be beneficial. In order to be effective, this protocol would need to stratify patients based on the severity of their anxiety and on their ASA physical status, as this places restrictions on sedation (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002).

From the results of our preliminary study we offer a potential protocol for use throughout Irish hospitals (Figure 2). We recommend explaining the MRI procedure in the most reassuring and preparative terms for all patients. Prior to an MRI procedure, the patient's GP or the specialist ordering the MRI should assess the patient's periprocedural anxiety. A series of questions regarding previous history of an MRI, how that procedure was tolerated, history of claustrophobia or panic attacks, or any specific medical phobias could flag potential anxiety. If any issues are raised, patients could be provided with more in-depth early non-pharmacological interventions to alleviate potential anxiety (Figure 2). We additionally recommend giving the patient a safety buzzer and the ability to communicate throughout the scan should they feel a sense of discomfort or unease.

Should these measures prove ineffective we recommend using IV sedation with midazolam for inpatients and oral diazepam for outpatients. In those situations where a patient's anxiety cannot be adequately controlled with oral benzodiazepines or the department is conducting an MRI on an inpatient, we recommend treatment with IV sedative medications such as IV benzodiazepines, IV barbiturates (pentobarbital or methohexital), or the general anaesthetics ketamine or propofol if necessary; under the guidance of an anaesthetist. We recommend that those general hospitals in Ireland who do not offer IV sedation for MRI procedures and have patients for who other anxiolytic measures have failed, to refer these patients to a larger tertiary centre.

We believe that to develop a robust and adaptable protocol, further research is required. The focus of this research would compare our proposed protocol with other international evidence-based protocols, as well as examining this protocol's effectiveness when implemented in Irish hospitals.

Limitations

The team was unable to survey all Irish tertiary and general hospitals with an operating MRI machine, potentially skewing the data. The survey was conducted over the phone with a radiographer or radiologist, not formally emailed to radiology departments. Due to time constraints of discussing departmental procedures over the phone, this may have altered operators' answers. Despite asking about sedative medication dosing, none of the departments were able to give a definitive answer to this, stating that it was up to the team caring for the patient. Furthermore, given the difference in hospital size, volume of patients served, and hospital staff available, some hospitals surveyed did not offer IV sedation for patients undergoing an MRI. As these hospitals were not able to provide this service, a formal protocol would necessitate either a referral pathway to a connected centre that offers this service, or an alternative treatment pathway within that centre.

Acknowledgements

We would like to acknowledge the efforts of Dr. Anne Buckley in initiating our interest in this study. We would also like to thank all of the surveyed hospitals for participating in this study.

Conflict of Interest

Authors report no conflict of interest.

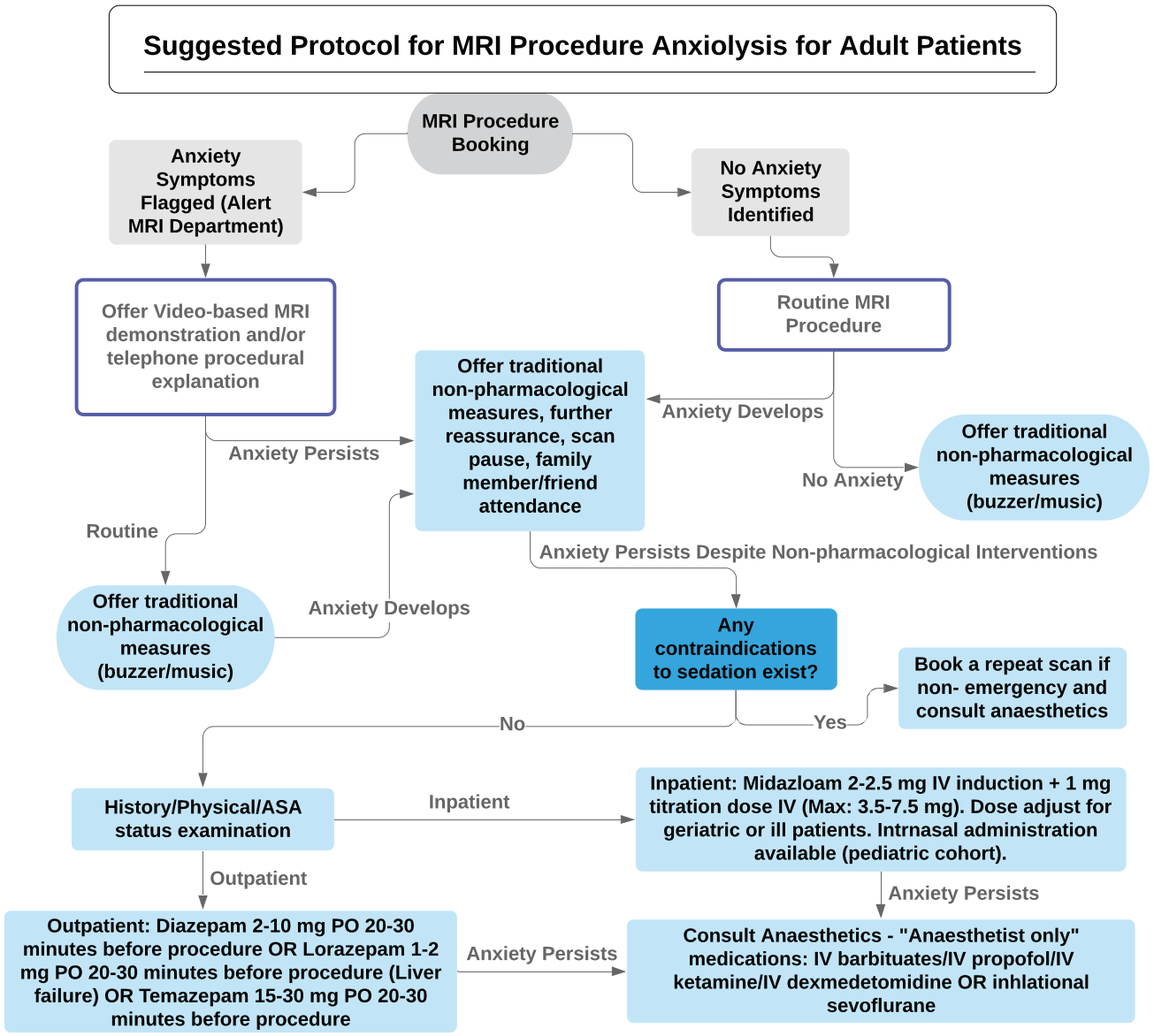

Figure 2: Proposed protocol for the treatment patients.

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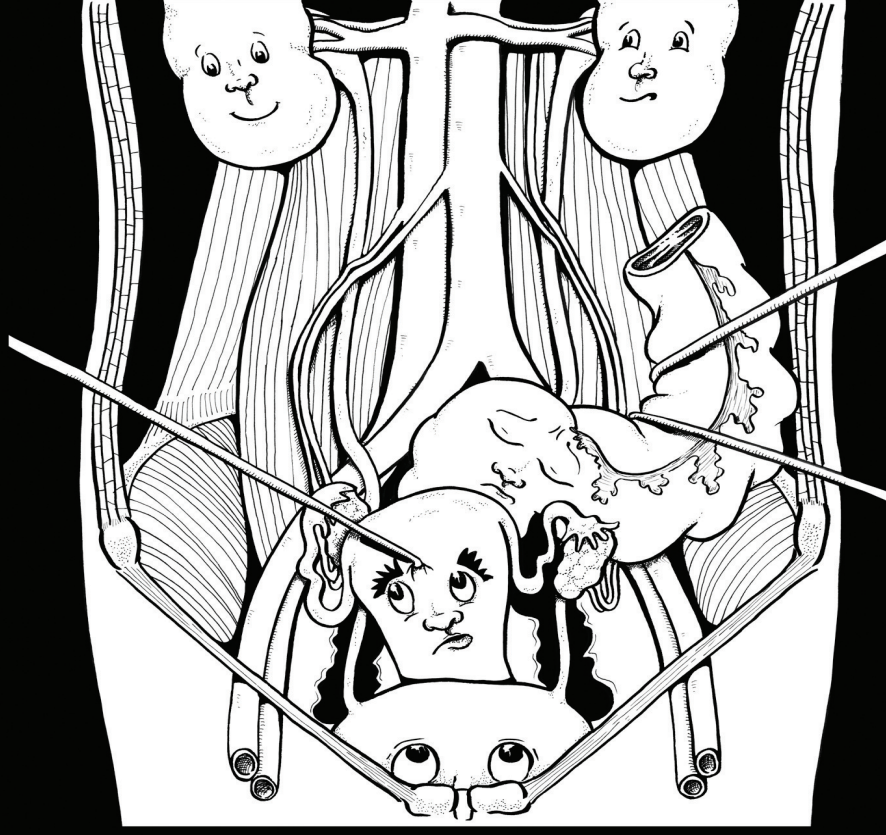
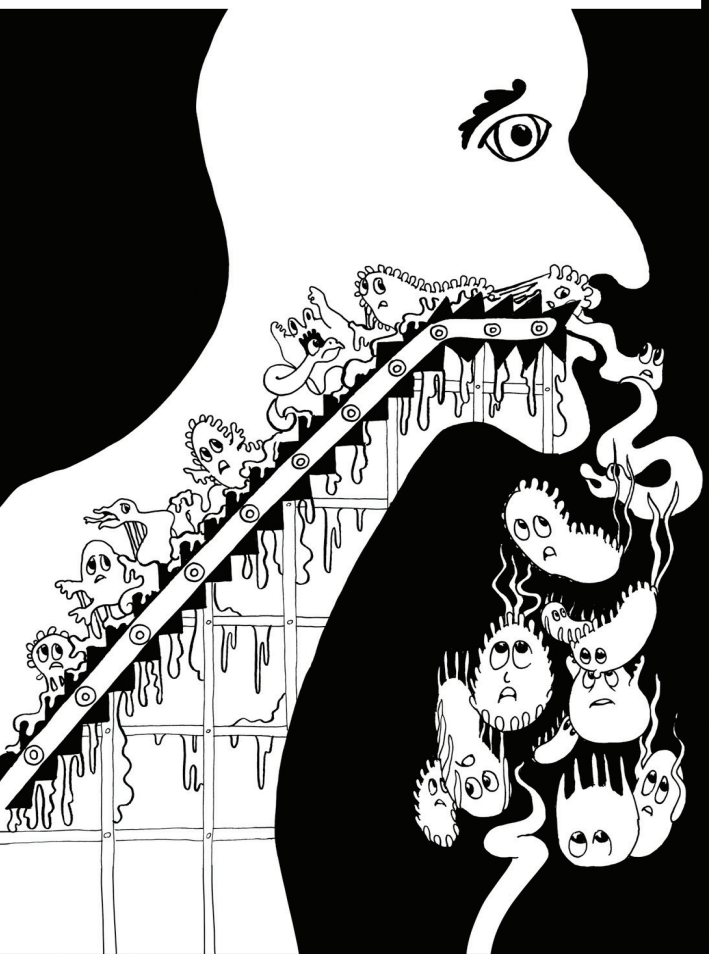
JOURNEY THROUGH THE BODY

A VISUAL EXPLORATION

DR EOIN KELLEHER





AVAILABLE ONLINE AND IN BOOKSHOPS

What is the Evidence for the Pharmacological Management of Nausea and Vomiting in Inoperable Malignant Bowel Obstruction?

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Abstract

The objective is to systematically review the evidence available for the pharmacological management of nausea and vomiting in inoperable malignant bowel obstruction. PubMed, EMBASE and clinicaltrials.gov were searched using the following terms: Nausea, Vomiting, Cancer, Inoperable Bowel Obstruction, Malignant Bowel Obstruction. The search identified 699 studies and 1 from an additional source. With the inclusion and exclusion criteria applied 12 papers were selected. Of the 12 studies, 6 RCTs were identified that compared the somatostatin analogue octreotide or lanreotide. Two of these RCTs also compared octreotide to hyoscine butylbromide, and four with placebo. Octreotide was shown to significantly reduce nausea and vomiting. One study however, found that octreotide did not significantly reduce vomiting compared to a placebo. Prospective studies, retrospective studies and non-randomised clinical trials were also identified. They assessed the use of octreotide, granisetron or olanzapine. They found that there was significant improvement in nausea or vomiting episodes. Despite not being the first line treatment Octreotide appears to be the most studied and researched drug. In all but one study it has been found to have a positive outcome. This review has highlighted the lack of information or research available on other antiemetic or anti-nausea medications, despite their widespread use.

Introduction

The management of bowel obstruction is a common clinical challenge in patients with advanced cancer (Mariani et al. 2012). Inoperable malignant bowel obstruction (IMBO) is a major cause of nausea and vomiting arising on a background of damage to the intestinal epithelium (Mariani et al. 2012). This imposes a complex clinical situation that requires multidisciplinary efforts, including palliative physicians, surgeons and oncologists (Lee et al. 2018). The principal management of IMBO is conservative due to the increased risk of morbidity and mortality associated with surgery (Cousins et al. 2016). Moreover, the value of surgery in alleviating symptoms is questionable (Mariani et al. 2012). Treatment is likely to incorporate intravenous hydration alongside pharmacological treatment and in severe cases, parenteral nutrition (Ripamonti et al. 2001).

Pharmacological treatment includes anti-emetics, antisecretory agents, analgesics and corticosteroids (Cherny 2004). Multiple studies have supported the use of dexamethasone, prednisolone, hyoscine butylbromide, somatostatin analogues, and chlorpromazine in alleviating nausea and vomiting like symptoms (Hardy et al. 1998; Laval et al. 2000; Ripamonti et al. 2001; Mercadante et al. 2000; Mittal et al. 2014; Obita et al. 2016). Metoclopramide along with intravenous PPI's (Proton Pump Inhibitors) such as omeprazole and corticosteroids are also used to alleviate symptoms of nausea and vomiting in IMBO (Tookman 2000; Laval et al. 2000). A nasogastric tube (NGT) might be required to drain stomach contents if drug control does not alleviate symptoms, however this can be particularly distressing for patients. Thus, effective drug therapy in terminally ill patients is needed (Hisanaga et al. 2010). The somatostatin analogue, octreotide, has more rapid effects than hyoscine butylbromide in reducing gastrointestinal secretions (Peng et al. 2015). Octreotide is one of the primary

agents used in IMBO with lanreotide as an alternate. Like the hormone somatostatin, these agents have similar physiological effects including splanchnic blood vessel vasoconstriction, decreased secretions by the intestine and pancreas, lower water and electrolyte absorption in the GI Tract, and changes in gut motility (Gilbar 2000; Obita et al. 2016). Octreotide has emerged as a widely used agent in combination with other anti-emetics and analgesics (M. et al. 2013). However, despite its efficacy, the cost of this agent is higher than other anti-secretory drugs used in IMBO (Mercadante et al. 2000).

Nausea and vomiting are distressing symptoms in patients with advanced cancer (Glare et al. 2011). It requires careful clinical assessment of the patient's symptoms and knowledge of the available therapeutics for palliating them (Glare et al. 2011). To help clinicians utilize the most effective treatments for symptom control, we will examine the pharmacological options investigated in original scientific literature, with the goal of providing optimal palliative care and QOL of patients with IMBO.

Methods

PubMed, EMBASE and clinicaltrials.gov were searched for articles published between 1990 and 2018 (Figure 1). Eligible studies met the following criteria: patients with cancer, over 18, receiving pharmacological intervention for nausea and vomiting related to inoperable malignant bowel obstruction. In order to select for the population of interest, all types of studies were considered, including Randomised Control Trials (RCTs), prospective studies and retrospective studies. Phase II/III clinical trials were also considered. Searches were limited to studies published in the English language and only original research was included. The outcome measured was the improvement of nausea or vomiting after administration of pharmacological intervention.

Studies were excluded if the nausea and vomiting was related to opiate use, chemotherapy or radiotherapy. The following search terms were used: Nausea, Vomiting, Cancer, Inoperable Bowel Obstruction, Malignant Bowel Obstruction (Figure 1). A Boolean

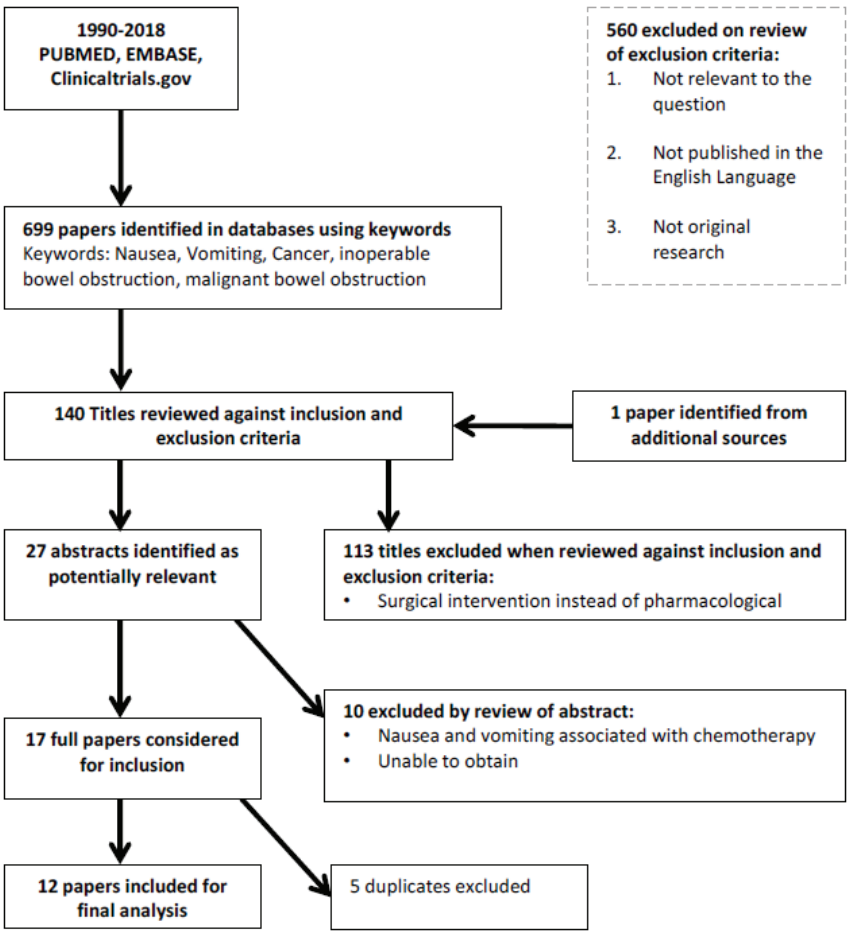

Figure 1. Flow chart of data selection

search strategy, as follows was used: "Nausea" OR "Vomiting", AND 'inoperable bowel obstruction' OR 'malignant bowel obstruction' AND "Cancer".

Data Extraction

Refer to Table 1.

Results

Studies

We identified 699 unique studies through the searches and 1 paper identified by a clinical medicine lecturer within palliative care. Twelve studies were included in the final analysis. Six of these studies were RCTs (Randomised Controlled Trials) investigating pharmacological treatment for IMBO met our inclusion criteria (Figure 1).

Study characteristics

Six RCTs were identified comparing the somatostatin analogue octreotide or lanreotide. Two of the RCTs also compared octreotide to hyoscine butylbromide, and four with placebo. Four of the trials were single centre studies, and two trials were multicentre. The majority of the trials identified were conducted in Europe, with one being performed in China and America. As the studies examined different interventional outcomes and primary/secondary endpoints, it was not possible to perform a meta-analysis.Both studies found that octreotide significantly reduced episodes of vomiting compared with hyoscine butylbromide in patients with advanced cancer. Studies comparing octreotide to placebo found it be more effective in symptom management, however this was only conclusive in two of the three identified due to premature termination of one study. The study by Currow et al 2014, in contrast found that octreotide did not significantly reduce vomiting compared to a placebo.

In addition to the RCTs, 2 prospective studies, 1 retrospective study and 3 non- randomised clinical trials were also identified. Five of these studies assessed the use of octreotide, one assessed the use of Granisetron

Author/Year	N =	Study Design	Primary Outcome	Drug used	Primary Diagnosis	Setting	How Nausea or Vomiting Outcomes Were Measured	Summary and Main Findings
(Hisanaga et al. 2010)	43	Multicentre prospective study	Overall improvement of subjective abdominal symptoms.	Octreotide	Gastric, Pancreatic, Colorectal, Ovarian, Endometrial, Bile duct, Cervical, Gall bladder, and others	Octreotide 300μg/day IV/SC for 3 days. Following an assessment, the dose was adjusted up to 600μg daily if required.	Self-rating scores selected from the MD Anderson Symptoms Inventory and Kurihara's Face Scale. Any change in symptoms was then evaluated on day 8.	Nausea, vomiting and abdominal pain was reduced in 59–72% of the patients.
(Shima et al. 2008)	25	Clinical trial	A change in vomiting episodes after treatment	Octreotide	Gastric, Colon, Ovarian, Pancreatic, Cervical cancers	Octreotide 300μg/day SC for 6 days. Patients who responded to 6-day course continued to receive drug. Dose decreased to 150μg/ day if marked nausea/vomiting.	Number of vomiting episodes and severity per day. Severity was graded using the Toxicity criteria of the Japan Clinical Oncology Group.	44% responded to treatment with resolution or improvement of nausea/vomiting
(Mystakidou et al. 2002)	68	RCT	Improvement of nausea, vomiting and abdominal pain in patients with MBO	Octreotide	GI, Abdomen, and Pelvic cancers	SC Hyoscine Butylbromide 60-80mg/day VS SC Octreotide 600-800 microgram/day.	Patient diary cards	Nausea and vomiting was reduced in the patients receiving Octreotide
(Kubota et al. 2013)	14	Clinical trial	Improvement of oral intake, subjective symptoms, and NGT	Octreotide	Urological cancer	Octreotide 300μg/day SC as a continuous injection.	Grading of Vomiting by World Health Organisation Toxicity Criteria	Overall response rate was 92.8%. 28.6% had "no vomiting". 64.3% had a "reduced vomiting".
(Peng et al. 2015)	97	RCT	Determine whether octreotide or scopolamine butylbromide was more effective at controlling GI symptoms in MBO.	Octreotide and Scopolamine butyl-bromide	Ovarian cancers	Octreotide 0.3mg/day (n=48) or scopolamine butylbromide 60mg/day (n=49) for 3 days through a continuous SC infusion.	Vomiting, nausea, dry mouth, drowsiness, GI secretions via NG tube, and continuous or colicky pain were measured using Likert scales.	Symptoms of nausea and vomiting, and GI secretions, were reduced in the group administered Octreotide in comparison to group given Scopolamine butyl-bromide
(Mercadante et al. 2000)	18	RCT	Octreotide vs. Hyoscine butylbromide as effective anti-secretory drugs for in states of inoperable MBO.	Octreotide and Hyoscine butyl-bromide	Small bowel, vulva, ovarian, pancreas, rectal, breast, liver, stomach cancers.	Octreotide 0.3mg/day (n=9) or hyoscine butyl-bromide (HB) 60mg/day (n=9) SC.	Episodes of vomiting, nausea, drowsiness, continuous and colicky pain were measured using a Likert scale	Octreotide induced a significant reduction in the number episodes of vomiting and intensity of nausea compared with HB treatment
(Tuca et al. 2009)	23	Multicentre Open-label Phase II Clinical Trial	Improvement of symptoms of nausea and vomiting due to inoperable MBO.	Granisetron	GI, Genealogical, and other cancers	Granisetron 3mg/day IV and dexamethasone (4mg IV BD). Optional haloperidol (2.5mg SC) was retained for rescue therapy.	Numeric scale evaluated nausea, pain, asthenia, anorexia at baseline and every 24 hours until four days of treatment.	A significant decrease in the severity of nausea and number of episodes of vomiting. Nausea and vomiting control achieved in 86.9%
(Khoo et al. 1994)	24	Phase I/II Study	Symptom improvement in patients with intractable vomiting, inoperable MBO	Octreotide		SC infusion of octreotide (median initial dose 300, range 100–600μg/day).	Number of vomiting episodes and volume of NG aspirate were measured	Vomiting controlled or the volume of nasogastric aspirate was reduced in 75% of patients.
(Kaneishi et al. 2012)	20	Retrospective study	Assess antiemetic activity of olanzapine in cancer patients with incomplete bowel obstruction.	Olanzapine		2.5-7.5mg/day over a range of 2-60 days.	Two doctors interpreted the electronic charts of 20 patients. The severity of symptoms was evaluated on a scale of 0 to 3	90% had decreased intensity of nausea and frequency of vomiting decrease from an average of 1.1 times/day to 0.3 times/day
(Mariani et al. 2012)	80	Randomized, DB, Placebo Controlled Phase III Study	Reduction in number of vomiting episodes and/or NG volume aspirate.	Lanreotide	Peritoneal carcinomatosis	30mg injection of lanreotide microparticles (n=43) or placebo (n=37) every 10-days until they requested to stop or died	Visual analogue scales for nausea. Episodes of vomiting per day, volume of NG aspirate.	Symptom control was better in the group receiving lanreotide.
(Novartis, 2011)	64	Randomised Interventional DB, Controlled Trial	Treatment of symptomatic inoperable bowel obstruction in peritoneal carcinomatosis	Octreotide	Peritoneal carcinomatosis	Octreotide long-acting release 30mg IM/28days for 90days, and immediate-release Octreotide 600μg/day SC BD/TDS or IV 24-hrs	Number of vomiting episodes per day and volume of NG aspirate was measured.	Study was terminated prematurely due to low enrolment
(Currow et al. 2015)	87	Randomised Control Double blind study	Patient-reported days free of vomiting at 72 hrs	Octreotide		SC infusion of octreotide (600 mg/24 hours) co	Number of days free of vomiting	17 octreotide patients had 72 hrs free of vomiting, compared to 14 placebo patients. No significant difference comparing treatments.

Table 1. Table of articles and data extraction from the papers selected for full analysis.

and one also assessed the use of Olanzapine (Table 1). Each of these studies found that there was significant improvement in nausea or vomiting episodes.

Demographics

The number of patients per study averaged at 47 (range: 14-97). All studies focused on the treatment of nausea and vomiting related to IMBO. Nausea related to chemotherapy and pain management was excluded from consideration. Primary diagnosis ranged hugely in the total patient cohort, but abdominal and pelvic cancers were the most frequently occurring. The route of administration was predominantly subcutaneous infusion (Hisanaga et al. 2010; Shima et al. 2008; Mystakidou et al. 2002; Kubota et al. 2013; Peng et al. 2015; Mercadante et al. 2000; Khoo et al. 1994; Novartis Pharmaceuticals 2011). Due to the nature of the symptoms being examined, oral medication was not an option apart from in the case of olanzapine (Kaneishi et al. 2012). In some cases, intramuscular injection (Mariani et al. 2012; Novartis Pharmaceuticals 2011) and intravenous administration (Novartis Pharmaceuticals 2011; Tuca et al. 2009; Hisanaga et al. 2010) were used.

Assessment of symptom severity and improvement also varied between papers. Four studies used a Likert scale, with scores ranging from 0-3 based on severity. Two used diary cards and two others used the WHO vomiting toxicity criteria. Patient questionnaires, nasogastric aspirate volume and the MDASI (MD Anderson Symptoms Inventory score) and Face Scale Score were used one time each.

Discussion

IMBO is a complex clinical challenge in many advanced cancers. The management of this issue appears to involve multidisciplinary efforts and there is little guidance in treatment based on the current literature. This review analysed the pharmacological management of preventing vomiting and nausea in IMBO. Twelve papers were identified that fit our inclusion criteria, from an original 140 reviewed against inclusion and exclusion criteria.

The Oxford Handbook of palliative care outlines the current choices of antiemetic drugs in IMBO. It recommends cyclizine, Hyoscine butylbromide, octreotide or ondansetron, which can all be given subcutaneously to manage the symptom of vomiting (Tookman 2000). This should follow the use of metoclopramide, cyclizine or haloperidol as first line followed by a combination with ondansetron or cyclizine to alleviated emesis (Tookman 2000). Broad-spectrum antiemetics such as levomepromazine can also be employed (Tookman 2000). On reviewing the current treatment guidelines, it is surprising that other antiemetic agents were not identified by the search. Despite not specifying a particular pharmacological intervention in the search, 9 out of the 12 papers focussed on octreotide. This highlights the need for further research regarding these medications to confirm their clinical efficacy, as little information is currently freely available (Tookman 2000).

As discussed previously, octreotide was the primary agent investigated to manage symptoms in IMBO in the majority of studies. Lanreotide, hyoscine butylbromide, olanzapine and granisetron were also shown to have clinical benefit however more research is needed to confirm their efficacy in clinical practice. As the average number of participants in each of the trials was only 47, further research with larger cohort studies, ranging from multi-centre to international studies is needed to ensure primary endpoints can be assessed (Table 1).

The study by Currow et al 2015 was the only study identified which highlighted that Octreotide, when compared to a placebo, did not significantly reduce nausea and vomiting (Currow, 2015). As a randomised control trial, it was well designed and the results do carry significance, however it is not sufficient to invalidate the other trials, which all found positive outcomes. The trial did find that vomiting episodes were reduced, however it was not statistically significant. The trial assessed improvement after 72 hours and this may not be a sufficient time frame for clinically significant results to occur. The outcome may have been different if the patients had been followed for a longer period of time. In general, most studies have shown that octreotide has a positive response for the treatment of nausea and vomiting. It has also very few side effects and so can be safely given. Furthermore, the side effects that do occur cannot always be linked directly to octreotide due to the nature of patients being on multiple medications and having complicated illnesses.

In a number of studies, there was continued co-administration with other antiemetics such as prochlorperazine or haloperidol. In one study their use was continued and only had to be documented until

day 4, until the first assessment had been completed. Following this there was then no restriction on their use and symptoms were reassessed at day 8 (Hisanaga et al. 2010). This co-administration has the potential to bias the results. It also highlights the difficulty of studies within palliative care, as ideally the effect would be determined in isolation, however this is not always possible or ethical in patients with terminal illness.

In addition, a limitation in the cohort of patients examined is the type of scale used to determine symptom severity. Some of the studies utilised a likert scale. The Likert scale is used to represent a person's attitude to a topic, in this case vomiting and nausea. It ranges from 0-3 with 0 represent no response, 1 slight response, 2 moderate response and 3 severe response (Peng et al. 2015; Mercadante et al. 2000). There is potential for bias using this scale as what one patient deems a slight response, another may think is severe. However, the goal of treatment is to improve how a patient feels about their illness and not what patient has more severe symptoms. In the multicentre prospective study on efficacy and safety of octreotide for inoperable malignant bowel obstruction, the Face Scale Score was used in conjunction with an MDASI score, which is an 11-grade numerical scale. In this study, the MDSAI score showed significant improvement with octreotide treatment, however the improvement was less significant when using the Face Scale score. This may be due to the subjective nature of the Face Scale Score and that quality of life and therefore happiness may be reduced due to disease progression and not because of nausea and vomiting. This also highlights the disparity between assessment methods, and further research is needed to find a suitable, less subjective assessment method, which would allow easier comparison between studies (Hisanaga et al. 2010).

Grading of vomiting by the WHO toxicity criteria and the method of counting the number of vomiting episodes were other methods used, we found these methods were less subjective and so gave a more accurate description of a drug's efficacy. However, the method of counting the number vomiting episodes did not always quantify the volume of vomit produced and therefore comparison is made more challenging (Kubota et al. 2013; Peng et al. 2015; Khoo et al. 1994; Mariani et al. 2012).

In undertaking this review it has highlighted that the area of palliative medicine in general is difficult to research due to ethical obstacles and patients' medical conditions. A study by Chan et al, 2014 highlighted the barriers that are difficult to overcome in regards to research within palliative care. Within this study they systematically identified barriers by interviewing 61 lead researchers within the palliative care field. One of the key challenges identified was the study population and topic. Within the interview one researcher stated "The work we do by its nature is challenging and always will be. It's hard work to do research with such a vulnerable patient population and their families. It's hard to recruit them, it's hard to follow them." The study also identified the other unique challenges that face researchers within this setting and how often doctors are very reluctant to change their standard practices of care within a very distressed, vulnerable and dying population (Chen et al. 2014).

We found a high attrition rate in many of the studies and trials due to decline in patient's well-being and death during the study. This is demonstrated by the multi-centre prospective study determining the efficacy and safety of octreotide for inoperable malignant bowel obstruction (Hisanaga et al. 2010). This study had an attrition rate of 13% (n=6). Initially 49 patients were enrolled, however 3 ineligible patients were excluded due to delirium or lymphoma. A further 3 patients were discontinued due to reduced consciousness, protocol violation or not all data was available (Hisanaga et al. 2010). This is also apparent in those trials terminating prematurely due to high patient withdrawal (Novartis Pharmaceuticals 2011).

Conclusion

In conclusion, octreotide appears to be the most studied and researched drug, despite not being the first line treatment. In all but one study it has been found to have a positive effect on nausea and vomiting in patients with malignant bowel obstruction. It must be noted however that there is a lack of information or research available on other antiemetic or anti-nausea medications. Furthermore, a key limitation is also the small numbers participating in the trials, however due to the nature of the illness it may still prove challenging to recruit participants on a larger scale. It may also be advantageous for a more reliable and less subjective scale or assessment method to be produced. This would allow more comparison between studies and remove bias, leading to more meaningful results.

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REVIEW

Cutting Edge of Alzheimer's Disease Research: Literature Review for the Changes in Brain Function in the Prodromal Stages of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder that is estimated to affect 44 million people worldwide, and the global incidence of AD is expected to triple by 2050, thus making it a major current topic with the ageing global population. Whilst symptoms generally present late in life, many details of AD pathogenesis remain unclear. Current thinking suggests cognitive tasks are performed not by individual brain regions working in isolation, but by functionally connected networks. Hence AD research is turning to the study of large-scale networks such as the Default Mode Network (DMN), primarily involved in processing memories, which is observed as the first locus of the disease. Consequently, there is a paradigm shift towards focused research on earlier stages. Mild cognitive impairment (MCI) is a prodromal stage of AD, displaying cognitive deficit but neither marked functional impairment nor satisfying established clinical criteria for dementia or probable AD. MCI subjects are at risk of AD but otherwise are unimpaired in daily living. It is noted that if MCI is a portal into potential AD, the field must work towards a better understanding of the MCI stage and emerging therapies for MCI. Thus, there is a clear need to make use of the data freely available from the ongoing Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate changes in network function in the prodromal stages of AD with the ambition of gaining a better understanding of the MCI stage of AD.

Introduction

AD is a complex neurodegenerative disorder characterized by an accumulation of ß-amyloid (Aß) plaques and neurofibrillary tangles (NFTs) comprising tau amyloid fibrils leading to memory impairment and other cognitive problems (Weiner et al., 2015; Petersen, 2003; Huang et al., 2018). One of the most common dementia diseases, AD has swiftly become a serious health problem for ageing populations around the world (Jiang et al., 2015). According to the 2014 World Alzheimer report, the cost of dementia was more than US$600 billion in 2010 (Weiner et al., 2015). Many details of AD pathogenesis remain uncertain with symptoms usually starting around the age of 65 years, except in 5.5% of patients with early onset (33–60 years) autosomal-dominant AD (Badhwar et al., 2017; Zhu et al., 2015).

The brain is organized into large-scale networks, collections of widespread brain regions showing functional connectivity (Riedl et al., 2016). Networks can be determined based on similarity in grey matter structure between brain areas as measured with structural magnetic resonance imaging (sMRI) (Dicks et al., 2018). Current thinking suggests that cognitive tasks are performed not by individual brain regions working in isolation, but by functionally connected networks (Riedl et al., 2016). One such network is the DMN – which is activated during internally-oriented tasks such as daydreaming, envisioning the future, and retrieving memories (Riedl et al., 2016). The DMN is usually affected in the earliest stages of AD before networks involved in visual-spatial, sensorimotor,

language, behavioural, and executive faculties decline as a function of targeted AD pathophysiology (Jones et al., 2017). Put simply, AD targets the interconnectivity element between networks. Network analysis can provide insight into key organizational principles of brain structure and help identify structural changes associated with brain disease (Raj and Powell, 2018).

There is currently no known long-term treatment that slows the progression of AD (Weiner et al., 2015). Drugs available for AD provide limited short-term treatment of symptoms such as reducing rate of memory loss and confusion. Trials of disease-modifying therapies for AD dementia patients have been unsuccessful, likely because intervention at this stage is too late to affect the neurodegenerative process (Badhwar et al., 2017). Focus now is on therapeutic intervention at the MCI and/or preclinical disease stages, with delay of dementia onset constituting a major clinical endpoint for clinical trials (Badhwar et al., 2017). MCI is a prodromal stage of AD, displaying cognitive deficit but neither marked functional impairment nor satisfying established clinical criteria for dementia or probable AD (Huang et al., 2018; Dicks et al., 2018).

Alzheimer's Disease

Ich habe mich sozusagen selbst verloren.

This phrase, translating as "I have lost myself, so to speak", was uttered by Auguste Deter to Alois Alzheimer in a Frankfurt asylum in 1901 in recognition of her strange behavioural symptoms and short-term memory loss (Maurer et al., 1997). Upon Deter's death on 8 April 1906 at the age of 55, Alzheimer brought her medical records and brain to his Munich laboratory where he identified amyloid plaques and NFTs, the same characteristics used to diagnose AD today (Maurer et al., 1997).

The initiating event in AD is related to abnormal processing of the Aβ peptide, ultimately leading to formation of Aβ plaques in the brain (Jack et al., 2010) (Figure 1). This process occurs while individuals are still cognitively normal. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes (Jack et al., 2010). This neurodegeneration is accompanied by synaptic dysfunction (Jack et al., 2010). The neuropathology typically begins in the

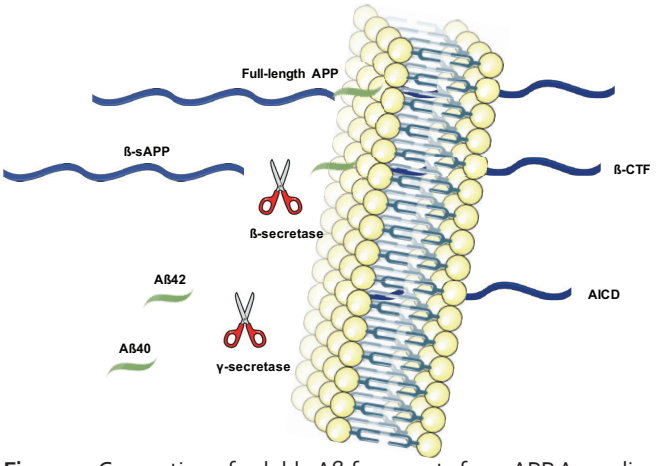

Figure 1. Generation of soluble Aß fragments from APP.According to the Aß hypothesis, AD begins with the abnormal processing of the transmembrane Aß precursor protein (APP). Proteolysis of extracellular domains by sequential ß and γ secretases results in a family of peptides that form predominantly ß-sheets, Aß. The more insoluble of these peptides, mostly Aß42 (a more fibrillogenic form of Aß), have a propensity for self-aggregation into fibrils that form the senile plaques characteristic of AD pathology (Weiner et al., 2015).

entorhinal cortex – located in the medial temporal lobe – and hippocampal formation; consequently, and as the hippocampus is responsible for memory retention, the corresponding clinical symptoms include early signs of memory dysfunction (Petersen, 2003).

Historically AD has been viewed as a disease of abnormally aggregated proteins by pathologists and molecular biologists and a disease of clinical symptoms by neurologists and psychologists (Jones et al., 2016). A complementary way to view the disease is through a pathological interaction between the microscale proteinopathy and macroscale brain networks leading to characteristic cascading failures that impart clinical symptomatology (Jones et al., 2016). Bridging the divide between these scales has been elusive, but the study of brain networks appears to be a pivotal inroad to accomplish this task (Jones et al., 2016).

NFTs follow a stereotypic topographic progression pattern, first appearing in the brainstem and transentorhinal area, then progressing to the hippocampus (Jack and Holtzman, 2013).

Risk Factors

Risk factors for AD, include age, family history, and head injury, as well as midlife hypertension, stroke, diabetes, midlife hypercholesteraemia, and a low level of education, and most notably late-onset AD

(LOAD),(Ballard et al., 2011). Meta-analyses and systematic reviews provide robust evidence that cognitive reserve, physical activity, exercise, midlife obesity, alcohol intake, and smoking are the most important modifiable risk factors for AD (Ballard et al., 2011). A further risk factor is depression (Weiner et al., 2015; Arnold et al., 2012). The number of modifiable risk factors is notable. However, the amount of risk of AD that is attributable to genetics is estimated to be around 70% (Ballard et al., 2011).

Genetics

The ε4 allele of Apolipoprotein E (APOE) is the largest known genetic risk factor for AD (Baik et al., 2016). Further genes implicated in AD are familial mutations of APP and Presenilin (PSEN) which result in Aß plaques being generated and deposited in neural cells (Jiang et al., 2015). Other genes implicated in AD have been comprehensively reviewed elsewhere (Ballard et. al., 2011).

Early-Onset versus Late-Onset AD

AD is commonly categorized clinically as either early-onset (pre-age 65) or late-onset.

Early-onset AD is uncommon (Jack and Holtzman, 2013). A proportion of such cases occurs in individuals with autosomal-dominant mutations in one of three genes: the APP gene on chromosome 21, PSEN1 gene on chromosome 14, or PSEN2 gene on chromosome 1 (Jack and Holtzman, 2013).

LOAD accounts for the overwhelming majority of cases (Jack and Holtzman, 2013). While most autosomal-dominant AD is usually believed to be caused by overproduction and subsequent aggregation of Aß42 from the beginning of life, LOAD may most often be a disease of inadequate Aß clearance, again leading to increased aggregation and accumulation (Jiang et al., 2015; Jack and Holtzman, 2013). As mentioned earlier, genetics plays a very important role in AD risk: the ε4 allele of the APOE gene is the major known genetic risk factor (Jiang et al., 2015; Jack and Holtzman, 2013). The ε4 allele of APOE increases the risk of developing AD by greater than 20% and also lowers the mean age at onset of the disease in a dose-dependent fashion (Jack and Holtzman, 2013; Baik et al., 2016). The major mechanism by which APOE ε4 contributes to AD pathogenesis appears to be by modulating the aggregation and clearance of the Aß peptide, leading to increased deposition, which implicates this pathway in causation of late-onset AD (Jack and Holtzman, 2013; Ballard et al., 2011). Thus, from a genetics standpoint, sporadic AD is complex.

By the late 70s, approximately 97% of the population has some tauopathy, while only 17% have Aß deposits (Jack and Holtzman, 2013). Definitively identifying the initiating event in the molecular cascade that eventually leads to clinical and pathological AD has been controversial for decades (Jack and Holtzman, 2013). The amyloid cascade hypothesis, first proposed by Glenner and Wong in 1984, assumes serial causal events initiated by abnormal Aß production/aggregation (Glenner and Wong, 1984). A sequence of pathological

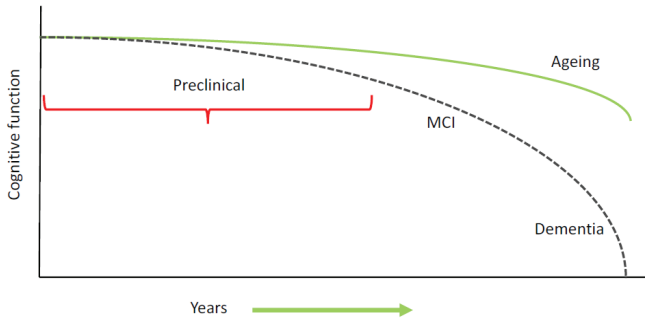

Figure 2. The Continuum of Alzheimer's Disease. The neuropathological changes in AD are thought to occur many years before the onset of clinical symptoms (Adapted from Sperling, 2011 and Kehoe et al, 2014).

events proposed by Price and Morris in 1999 for LOAD seems best to explain the fact that while small amounts of medial temporal tauopathy often precede amyloid plaque formation, Aß seems to drive the progression of the disease (Jack and Holtzman, 2013; Baik et al., 2016).

Mild Cognitive Impairment

The most noticeable deficit in pre-dementia subjects is short-term memory loss, but these first prodromal first symptoms are often mistakenly attributed to ageing or stress (Waldemar et al., 2007). This preclinical, or prodromal, stage of the disease is also termed MCI (Weiner et al., 2015; Arnaiz and Almkvist, 2003) (Figure 2).

MCI represents a transitional state between the cognitive changes of normal ageing and very early dementia (Grundman et al., 2004). Originally defined in 1999, MCI is a condition in which subjects are usually only

mildly impaired in memory with relative preservation of other cognitive domains and functional activities and, therefore, do not meet the criteria for dementia (Weiner et al., 2015). Risk factors of both dementia and MCI are considered to be the same, although individuals with MCI have increased oxidative damage in their nuclear and mitochondrial brain DNA (Wang et al., 2006).

Epidemiological studies of participants aged 70 to 89 years who were nondemented found the prevalence of MCI in this population to be approximately 15%, with an approximate 2:1 ratio of two identified phenotypes: amnestic and non-amnestic (Weiner et al., 2015). MCI patients progress to AD at a yearly rate of 10% to 15%, and predictors of this conversion include whether the patient is a carrier of the ε4 allele of the APOE gene, brain atrophy, and Aß deposition (Weiner et al., 2015).

In America, the National Institute on Aging-Alzheimer's Association has developed criteria for MCI due to AD that use biomarkers to determine the likelihood of AD pathology and classify patients accordingly (Weiner et al., 2015). MCI patients are not characterized by a significant decrease in structural connectivity, unlike AD patients, suggesting integrated structural/functional connectomics could provide a useful tool for assessing disease progression from MCI to AD (Palesi et al., 2016).

Criteria for MCI

Typically, the earliest presentation of MCI involves forgetfulness (Petersen, 2003). The individual will have memory complaints, preferably corroborated by an informant (Petersen, 2003). Other criteria for MCI include normal general cognition, not demented, objective memory impairment in line with the individuals age and education, whilst also maintaining activities of daily living. Currently, there are three documented types of MCI (Petersen, 2003) (Table 1).

Current Therapies

There is no proven therapy for MCI (Petersen et al., 2018). Grundman et al. speculates that as MCI may represent a prodromal state to clinical AD, treatments proposed for AD, such as antioxidants and cholinesterase inhibitors,

Type of Mild Cognitive Impairment	Deficit
Amnestic MCI	Memory complaint, preferably corroborated by an informant. Objective memory impairment for age and education. Normal general cognition, with preserved activities of daily living. Not demented.
Multiple-domain MCI	Subjects who have mild cognitive deficits in more than one cognitive domain but not of sufficient severity to constitute dementia
Single non-memory cognitive domain MCI	Presents with an early impairment in a single non-memory cognitive domain

Table 1. Types of MCI (Petersen, 2003).

Sponsor	Duration	Number of Participants	Endpoint	Agent
ADCS	3 years	769	AD	Vitamin E and Donezepil
Merck	2-3 years	1200	AD	Rofecoxib
Novartis	3-4 years	1018	AD	Rivastigmine
Janssen	2 years	780	Symptoms	Galantamine
Pfizer	24 weeks	269	Symptoms	Donezepil
UCB	1 year	200	Symptoms	Piracetam
Cortex	4 weeks	160	Symptoms	Ampakine

Table 2. A Summary of Clinical Trials in Mild Cognitive Impairment (Petersen, 2003).

may be useful in MCI (Grundman et al., 2004) (Table 2). The lack of an available therapy for MCI, combined with an urgent requirement to understand fully the concept and mechanisms of this stage of AD, urgently warrants further studies. If MCI is a portal into potential AD, the field must work towards a better understanding of the MCI stage and emerging therapies for MCI.

Large-scale Brain Networks

Mapping the network structure of the brain is often done via a method called tract tracing (Sporns, 2013). It has an important role to play for the study of anatomical connections in animal models, particularly in non-human primates, and is of vital importance for validating anatomical data derived from noninvasive imaging technology (Sporns, 2013).

Default Mode Network

First described by Greicius et al. in 2004 as the first resting-state network (RSN) implicated in AD pathophysiology (Brier et al., 2014b), the DMN has distinct subsystems with unique functional-anatomic connectivity, cognitive associations, and responses to Alzheimer's pathophysiology (Jones et al., 2016) (Table 3). These distinctions provide a window into the systems-level pathophysiology of AD (Jones et al., 2016).

The PCC is activated in all tasks involving the DMN, including those related to the self, to others, memory, thinking about the future, and spatial navigation. The mPFC processes personal and emotional information, whilst the angular gyrus connects perception, attention, and spatial cognition (Andrews-Hanna et al., 2014) (Table 3).

The dorsal medial subsystem is involved in social directed thought such as determining or inferring the purpose of others' actions, the theory of mind, and retrieval of social semantic and conceptual knowledge (Andrews-Hanna et al., 2014) (Table 3).

Functional Hubs: (information regarding the self)	Dorsal Medial Subsystem: (thinking about other)
Posterior cingulate cortex (PCC) and precunus Medial prefrontal cortex (mPFC) Angular gyrus	Functional hubs Dorsal medial prefrontal cortex Temporoparietal junction Lateral temporal cortex Anteruir temporol pole

Table 3. DMN: Functional hubs (Andrews-Hanna et al., 2014) and Dorsal medial subsystem (Andrews-Hanna et al., 2014).

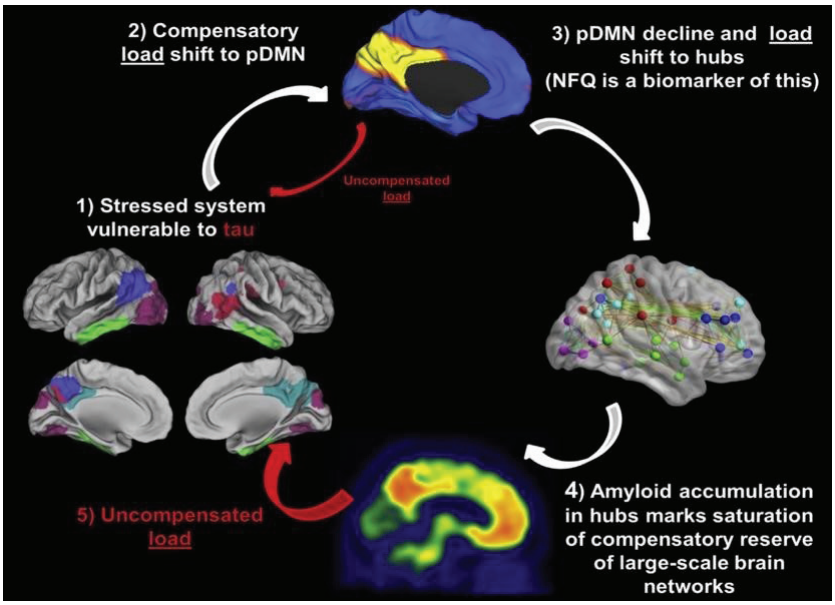

Figure 3. A schematic of the hypothetical model relating large-scale brain networks, beta-amyloid, and tau across the AD spectrum (Jones et al., 2017).

Reduced DMN connectivity as measured by functional MRI (fMRI) has arguably become the hallmark fMRI biomarker of AD (Kehoe et al., 2014). Using ADNI data, it has been found that the posterior DMN fails before measurable amyloid plaques and appears to initiate a connectivity cascade that continues throughout the disease spectrum (Jones et al., 2016; Sperling et al., 2010). High connectivity between the posterior DMN and hubs of high connectivity is associated with amyloid accumulation (Jones et al., 2016; Sperling et al., 2010) (Figure 3). This supports a system model best characterized by a cascading network failure, with the failure beginning in the posterior DMN, which then shifts processing burden to other systems containing prominent connectivity hubs (Jones et al., 2016; Sperling et al., 2010).

Pathophysiological Changes in the Brain

The initial changes seen in the brain are alterations in CSF-based Aβ42, followed by an increase in amyloid as measured by PET with alteration in CSF-based tau. This leads to changes in neuronal function occasioning cognitive impairment and the appearance of the symptoms of AD (Kehoe et al., 2014). The most consistent sMRI finding is reduced volume of the hippocampus and entorhinal cortex in individuals at an increased genetic risk of AD without any overt symptoms; reduced hippocampal volume in individuals with amnestic MCI is predictive of conversion to AD (Kehoe et al., 2014; Appel et al., 2009; Weiner et al., 2015). The location of these grey matter changes mirrors the appearance of NFTs in these regions early in AD and supports the observance of severe memory impairment as the quintessential neuropsychological symptom of the disease (Kehoe et al., 2014; Appel et al., 2009). Thus, hippocampal volume is currently being considered for inclusion in trials to detect prodromal AD (Kehoe et al., 2014).

Conclusion & Value of Research Area

The translational end result of this research is that only five medications are currently used to treat the cognitive problems of AD: four acetylcholinesterase inhibitors and an NMDA receptor antagonist, although the benefit from their use is small (Prescrire Int., 2012). No medication has been clearly shown to delay or halt the progression of the disease (Prescrire Int., 2012). Each new hope – such as the recent case of Solanezumab (Eli Lilly, 2016) – has focused on patients who are beyond the prodromal stages of AD. Each drug has disappointed in clinical trials.

The logical conclusion for this is that research has focused on too late a stage of the disease for effective therapies to make meaningful impact. There has been a recent paradigm shift towards focusing on MCI, the prodromal stage of AD. Catching the disease before the onset of pathological proteinopathies and functional connectivity breakdown appears to make much more sense.

Thus, research is starting to focus on subjects with MCI, who are at risk of AD but otherwise are unimpaired in daily living. In conclusion, we are left with the pressing requirement to gain a greater understanding of network analysis and interconnectivity, with a further aim to investigate if the changes in network function are predictive of the longitudinal clinical development of MCI subjects and their cognitive impairments.

Acknowledgements & Conflict of Interest Statement

It is a pleasure to acknowledge the input and support of Dr Arun Bokde in guiding this review, and I record my gratitude to Dr Eric Downer for his constant support throughout my undergraduate degree. I add my thanks to Alyssa Kramer for her clear and most helpful editing of this review.

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Obstetrics and Gynaecology – a Surgical or Medical Specialty?

Obstetrics and Gynaecology Essay Prize

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The distinction between medical and surgical approaches to disease has been a cornerstone to medical practice since its conception, the long-standing divide between the medical and surgical specialties well established, each accompanied by their own set of strengths, stereotypes and clichés. Few medical professions are boastful of combining both qualities; ENT, ophthalmology, and obstetrics and Gynaecology are the main culprits to spring to mind. However, obstetrics and gynaecology is particularly of interest, although historically bringing together medically inclined obstetricians and surgically keen gynaecologists (Smith, 1996), the rift was still evident. In modern days, increasing complexity, advancing technology, and demographic and financial changes, have altered the balance between the two, involving increasing medical expertise in gynaecology and surgical intervention in obstetrics, with a new balance to be struck and a new art to be perfected.

Obstetrics and gynaecology is a unique specialty, in that it has been established with women as its focal point, rather than disease or organ (Smith, 1996); obstetrics focusing on pregnancy, childbirth and the postpartum period, gynaecology ensuring the health of the female reproductive system, vagina, uterus or ovary (Impey and Child, 2017). Although various countries focus on differing subspecialties, the main aspects often covered are gynaecological oncology, maternal-foetal medicine, urogynaecology, reproductive medicine, and female pelvic medicine and reconstructive surgery, and sexual and reproductive health (Hapangama & Whitworth, 2006).

As these sub-specialties develop and become fixed divisions, doctors become more specialised in one particular field, which although allows for more in depth and specialised treatment and management, also further deepens the wedge between medicine and surgery in the obstetrics and gynaecology department. Although, historically, it was possible to clearly differentiate between them and query whether obstetrics and gynaecology is a more medical or surgical field, perhaps with brisk advancements and modified management, the question ought to evolve too, to look at obstetrics and gynaecology as an art, encompassing aspects of both qualities.

Modern advancements have changed the shape of medicine in general already; previous treatments requiring surgery are now managed medically. Major surgeries are being discarded in favour for minimally invasive operations such as "keyhole" techniques and laser treatments. Moreover, there is an augmenting number of at home treatments being offered for diseases once deemed to be hospitalization critical (Timmins, 2012). Such changes are equally seen, if not more, with obstetrics and gynaecology.

Indeed, with new endoscopic equipment, imaging technology and drug treatment (Kelleher & Braude, 1999) gynaecology has been vastly altered, streamlining it to a gentler, more medically orientated sub-specialty. Instead of major gynaecological surgeries to treat gynaecological cancer and menorrhagia, women are expecting laparoscopic and hysteroscopic surgeries, medically conservative management, and less invasive treatments. For example, large uterine fibroids can now be treated medically with gonadotropin releasing hormone analogues, and ectopic pregnancies, frequently diagnosed earlier with transvaginal ultrasonography and quantitative measurements of human chorionic gonadotropin concentrations, are managed conservatively with methotrexate injections, or by laparoscopic surgeries (Kelleher & Braude, 1999). Furthermore, there are increasing numbers of non-surgical procedures performed in gynaecology, such as colposcopies and dilation and curettage (Minig et

al. 2016). Despite this, surgery continues to be the standard care for many gynaecological malignancies, especially the more aggressive cancers such as ovarian and cervical (Collins et al. 2013)

Similarly, obstetrics has deviated from the previously medicine heavy management, to a more surgically based response. While caesarean sections can be crucial intervention to reduce the morbidity and mortality of the mother and child, the procedure previously was performed only when medically necessary. However, since the turn of the millennium, the frequency of caesarean sections has increased rapidly, in both developed and poorly developed countries (WHO, 2015). In 2018, the Lancet identified that more than 21% of births in 2015 were caesarean sections, a figure that had doubled since 2000 (Boerma, 2018), figures unjustifiable by the World Health Organization (WHO, 2015). This surgical procedure has taken preference over the medically-dominated forceps, vaginal breech delivery and vaginal birth after caesarean sections in some countries (Purandare, 2011). However, the skills in manoeuvring an infant during the obstetrical complication of shoulder dystocia or vaginal delivery of multiple gestations cannot be overlooked or merely replaced with surgery.

> **". . . perhaps with brisk advancements and modified management, the question ought to evolve too, to look at obstetrics and gynaecology as an art, encompassing aspects of both qualities. "**

Technology has also expanded exponentially in the field of treating infertility; artificial reproductive technology is the new foundation to treat infertile women, and this too, has changed the management and treatment for women. In-vitro fertilization, IVF, a name increasingly commonplace in our society, has permitted previously sterile couples to procreate, a task handed to obstetrics and gynaecology doctors. This procedure combines the medical treatment of fertility hormones and the surgical extraction of eggs through the pelvic cavity under ultrasound imaging, terminating with insertion of the newly fertilized embryos into the woman's uterus, and thus would combine both aspects of medical and surgical traits.

All of these advancements in technology, treatment and management beg the question of whether this segregation between the specialties, of medically or surgically weighted preference, is necessary in our modern and rapidly changing society, or if these labels detract from the best possible patient care, and the importance of the art of obstetrics and gynaecology instead. In this oscillating medical world, perhaps obstetrics and gynaecology, rather than claiming to be one or the other, can claim to be an amalgamation of both medicine and surgery.

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Follow-up of Cardiovascular Risk Following Complicated Pregnancy: a Single Centre Audit

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Abstract

Introduction: Gestational diabetes mellitus, pregnancy-induced hypertension and pre-eclampsia are associated with significant long-term cardiovascular and metabolic risk to the woman. Aims: The primary aim of this audit was to determine whether women who develop these pregnancy-related complications were followed up by their general practitioners (GPs) with respect to cardiovascular risk after delivery. Another aim was to assess whether the condition was communicated from the maternity health care to the GP on discharge letter. Methods: The audit was carried out using a structured search via the general practice electronic health record system. Conclusions: This audit found a deficit of follow-up monitoring of blood pressure and glucose tolerance of the women in our study and deficient communication of the complication experienced from the hospital to primary care. These findings suggest that there is a lack of appreciation of the impact of pregnancy-related cardiovascular and metabolic complications on future maternal health.

Introduction

Cardiovascular complications of pregnancy include the development of gestational diabetes, pregnancy-induced hypertension and pre-eclampsia. These complications not only affect maternal and fetal health during the pregnancy, they also signal significant long-term cardiovascular and metabolic maternal risk. It has now been established that women who develop gestational diabetes mellitus (GDM) have at least a seven-fold increased likelihood of developing type 2 diabetes later in life, compared to those with a normoglycemic pregnancy (Bellamy et al., 2009). It has similarly been shown that women who experience pregnancy-induced hypertension (PIH) and Pre-Eclamptic Toxaemia (PET) are at a greater risk of cardiovascular disease (CVD) later in life, with four times the risk of hypertension and twice the risk of ischemic heart disease, stroke and venous thromboembolic events (Bellamy et al., 2007).

The reason for this association between pregnancy disorders and cardiovascular disease is not yet fully elucidated. The two leading possibilities are that: Firstly, that preeclampsia and cardiovascular disease share common risk factors that are unmasked by preeclampsia or secondly, that residual endothelial "damage" from preeclampsia leads to cardiovascular disease in later life (Roberts et al., 2010). In either case, pregnancy can be viewed as a screening test for a woman's future CVD risk by identifying an underlying predisposition to cardiovascular and metabolic disease (Nijdam et al., 2009, Mosca et al., 2011). Early identification and primary prevention of at-risk women may decrease CVD incidence by stimulating active monitoring and the early employment of primary preventative strategies. However, there is insufficient awareness about the implications of these disorders on future health among women and their health care providers, both in hospitals and in the community (Viana Pinto et al., 2014).

Young women of childbearing potential typically score as low-risk in currently used cardiovascular risk assessment tools such as SCORE and QRISK (Anderson et al, 2015). However, these tools do not take into account any obstetric complication history. Lack of awareness among physicians, lack of communication between primary care and maternity hospitals and the omission of the obstetric history from CVD risk assessment tools may result in a lost opportunity for early detection and targeted primary or secondary prevention of cardiovascular disease in these women.

Audit Objectives

We hypothesised that despite evidence that complications during pregnancy affects future maternal

health, there would be a dearth of follow up of the woman's cardiovascular risk factors. The aims of this audit were to determine whether women who develop gestational diabetes, pregnancy induced hypertension, pre-eclampsia and eclampsia, were followed up by their general practitioners (GPs) with respect to cardiovascular risk after delivery. Another aim was to assess whether the condition was communicated from the maternity health care provider (HCP) (either a midwife or obstetrician) to the GP in the discharge letter.

Methods

Keywords were used to search for patients within the practice's electronic patient health record (EPR), using health-software Socrates, between the period of 1st April 2008 and 1st April 2017. Patients who were coded as having experienced a pregnancy during this time were identified and their files were reviewed. Cases were included if the pregnancy was complicated by GDM, PIH, PET or eclampsia and were excluded if the pregnancy occurred before the woman joined the practice. Data was gathered about the year of the pregnancy complication, whether the complication was noted on the discharge letter, whether the woman's blood pressure was measured and recorded at the six-week postnatal check, and whether an Oral Glucose Tolerance Test (OGTT) was carried out within six months post-delivery. It was also noted whether the woman had formal total CVD risk assessment (such as QRISK) as a marker for cardiovascular health monitoring.

Results

186 pregnancies were identified within the practice EPR over the specified period. 34 cases were found to have experienced either PIH, PET or GDM during the study period and were included in the analysis. All deliveries occurred within hospitals and had a maternity care discharge letter on file. Of the 34 identified pregnancies, 24 had GDM alone, one had PIH alone, six had both GDM and PIH while 3 were coded as PET. No cases of eclampsia were coded. (See Figure 1.)

The pregnancy complication was recorded in 8 (23.5%) of the hospital discharge letters. Maternal blood pressure was taken and recorded in 19 of 33 cases (57.6%) at the six-week postnatal visit, with one woman moving away for the GP area during this time.

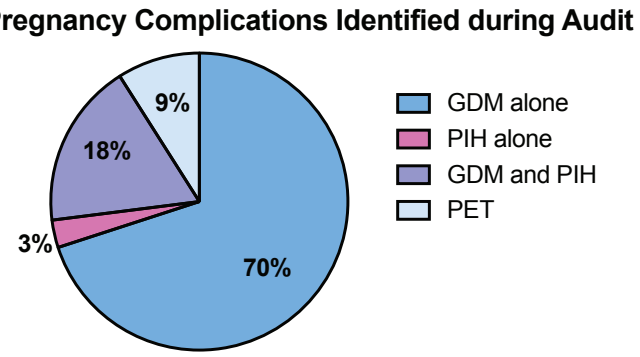

Figure 1. Cardiovascular complications of pregnancy identified in this audit. GDM - Gestational Diabetes Mellitus, PIH - Pregnancy-Induced Hypertension, PET - Pre-eclampsia Toxaemia.

Of those diagnosed with GDM, OGTTs were carried out within six months of delivery in 17 (56.6%). In contrast, among the women diagnosed with a complication other than GDM, none had an OGTT. It was found that 16 women (47%) had a lipid profile on file, while 20 (58.8%) had their BMI recorded. No woman had a formal total cardiovascular risk calculation on file (e.g. SCORE).

Discussion

Obstetric complications represent cardiovascular risk factors unique to women. The relative importance of this has recently been highlighted with the inclusion of pre-eclampsia as a major risk factor for cardiovascular disease among women in the 2011 update of the American Heart Association guidelines (Mosca et al., 2011). Early identification of individuals at risk of cardiovascular disease allows for timely lifestyle and medical intervention. However, a lack of awareness among physicians involved in postpartum care of the importance of these factors results in an under-estimation of the woman's risk.

The Centre for Disease Control estimates the prevalence of GDM to be up to 9% (DeSisto et al, 2014). This study identified 30 cases of GDM from 186 pregnancies, yielding a rate of 16.1%. The prevalence of hypertensive disorders of pregnancy (PIH and PET) is estimated to be between 5-10%, similar to a frequency of 11 cases (5.91%) in this study (Duley, 2009). The differences in prevalence between populations, particularly with respect to GDM, likely arises as a result of this study's small sample size. This study found only 53% of hospital discharge letters conveyed information relating to the woman's complication of pregnancy. This is very

similar to an Ontario-based study which found only 58% of obstetricians regularly inform GPs that a woman has experienced PIH, and only 36% highlight the subsequent increased lifetime risk of hypertension and CVD (MacDonald et al., 2007). There was a deficit of follow-up monitoring of BP and glucose tolerance of the women in our study. These findings suggest obstetricians and GPs are either unaware, undervalue, or lack resources to focus on the future health implications of these disorders of pregnancy. It is noted that the Irish national Mother and Infant Scheme does not provide any extra visits for postpartum OGTT and hypertension monitoring and therefore this lack of resourcing for care provision is likely a significant factor in impeding cardiometabolic evaluation following pregnancy.

To our knowledge, this is the first study undertaken in an Irish primary health care setting which looks at the monitoring of cardiovascular risk factors among women who have been identified as being potentially at an increased risk of CVD morbidity in the future. This audit highlights that awareness needs to be raised among clinicians regarding the importance of the obstetric history in determining CVD risk. In addition, CVD risk assessment tools should be updated to reflect this new understanding.

Guidelines are required which would standardise timelines for postpartum risk assessment by GPs. Research is required to identify the best method of ensuring follow-up, as studies have shown that among women who have a pregnancy-related CVD risk, attendance to maternity hospital appointments tends to be poor, particularly among PIH and GDM groups (Nowik et al., 2016). Potential methods to improve this would be standardised incorporation of postpartum risk factor screening as a part of primary care practise, such as at the six-week baby check and vaccination visits. Another option would be the utilisation of mHealth (mobile health) strategies to increase maternal health focus in the busy postpartum period.

Methods to improve communication between the hospital maternity care team and the woman's GP with respect to complications of pregnancy encountered should be explored. This is important as it provides an opportunity for the maternity care team to re-emphasise the potential future health implications of these complications to the GP. A potential change would be the use of discharge letters with a simple tick-the-box option for common complications such as PIH. It is intended to repeat the analysis with the inclusion of multiple primary care centres, in both urban and rural areas, to increase the data power. This would enable a confirmation and a better estimation of the follow-up and communication deficit.

Limitations

Limitations of this study include that this was a single centre study and relied on the coding of complications by GPs. It is likely that there are other cases of these conditions, not captured in this audit, which were not coded. In addition, it is possible that GPs are less likely to record negative findings as often as positive ones, which would lead to a systematic underestimation of risk management by GPs. The audit was based on a small sample size, which limits its power.

Conclusion

It is now understood that certain obstetric complications place women at increased risk for cardiovascular and metabolic disease in the future. This study identified a deficit in the follow up of women who have experienced such complications in the postpartum period. It has also highlighted a deficiency in communication between primary and obstetric care practitioners. Much remains to be done to promote awareness regarding the association of certain complications of pregnancy and future cardiovascular risk. In addition, a standardisation of discharge letters with the inclusion of any complication experienced is recommended. Further research is needed to establish the most appropriate level and frequency of monitoring these women require in the months and years following the pregnancy.

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Understanding Ageism

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As I waited for the tram on a windy day in Dublin, I noticed an older man wearing a flat cap shuffling unhurriedly towards the busy platform with a noticeable parkinsonian gait. The tram slowed to a halt and as soon as the doors opened, a gust of wind blew the gentleman's hat upward and behind him into a parking lot enclosed by a tall iron fence.

"My hat, my hat!" he cried out. I noticed that several passengers looked over their shoulders as they boarded, but most did not give it a second thought as the doors closed, leaving the man in a new crowd of bustling people eager to reach their next destination.

Ageism is predominantly defined as negative attitudes toward older adults[1]. In Robert Butler's (1969) paper where he first coined the term ageism[2], he says that the attitude "reflects a deep seated uneasiness on the part of the young and middle aged – a personal revulsion to and distaste for growing old, disease, disability; and fear of powerlessness, uselessness, and death." This predisposition manifests like other forms of discrimination, where a group is considered to be different or "other." As a result, older persons are "categorized as senile, rigid, and old-fashioned in morality and skills... we subtly cease to identify them as human beings, which enables us to feel more comfortable about our neglect and dislike of them[2]."

In an opinion article about ageism in healthcare, Dr. Kenneth Rockwood, a Canadian geriatrician, recalls this discussion with a trainee doctor: healthcare is overstretched, she argued. "We can't do everything for everyone, so why spend money on old people, who have little chance of benefit?" For her, ageism is not all that bad — in fact, it is a practical response to limited resources.[3]

The student doctor's attitude is embedded in the philosophy of utilitarianism – patients who can contribute more to society should be given priority. In a study by Wiseman (2007), utilitarian attitudes were exhibited by university students who were asked to triage healthcare situations – as opposed to a more egalitarian approach that supposes all people are of equal worth. In a response to a survey asking introductory psychology students to rank the priority for treatment of a hypothetical patient with kidney disease, participants favored patients who were young, had children, and were mentally healthy[4].

The irony of this attitude, of course, is that ageism is one form of prejudice against our own selves, specifically our "feared future self[5]". This attitude persists despite the understood inevitability of aging and our exposure to the scale at which it is occurring. The World Health Organisation estimates that the population of people over age sixty will reach two billion by 2050 – composing 22% of the global population[6]. One explanation for the cultural willingness to maintain such an attitude is the Terror Management Theory. This theory suggests that a fundamental function of societal ageism is to protect ourselves from the anxiety of our own mortality. Because of the association between age and death, ageism allows "the younger person to deny the reality that they too will eventually become part of that outgroup[5]."

As the world transitions to accommodate the realities of normal aging, there are stark consequences of this pervasive prejudice toward older adults. Compared to other forms of discrimination such as sexism and racism, not only is ageism socially acceptable, it is strongly

institutionalized, undetected, and unchallenged[7]. These attitudes are so deep-seated that older people internalize them and hold negative self-views that affect their well-being[8]. It is therefore critical not only to account for these stereotypical concepts of an older person, but also determine how they are detrimental in healthcare – stereotypes by definition fail to recognize the complexity and variation within a population. In Jan Baars' (2012) Aging and the Art of Living the author was shocked by the treatment of the elderly as "almost another species who were mainly of interest as objects of care[9]." Conceptualizing older adults in single-dimensional views such as "demented" or even "wise," undermines care that should be "embedded in the life of persons with dignity in their own right, not simply problematic beings needing care." He says that carers for this population should regard patients as "socially located, vulnerable, and unique individuals ready to live possible futures filled with perils and promise[9]." Ageist societal conceptions have negative impacts on health – those who hold negative views of self have poorer recovery from disability. Furthermore, these values are embedded in the institution of healthcare, resulting in poorer health outcomes[7].

How Can We Combat Ageism?

While volunteering in a long-term care center a few years ago, I spent some time with a pleasant gentleman named Walter. The octogenarian, now confined to a wheelchair, told me his story: his wife had died a few years ago, he had buried one of his children, and many of his closest friends were now gone. But despite his hardships and his loneliness, Walter was friendly and gentle and exuded warmth. Every day, I would take Walter out to the courtyard where he enjoyed the sunshine and we would chat. He told me about his passion for music, and how he played piano in bars and clubs when he was a younger man, "We called it pop music, it's different from what the pop music is now," he said.

I asked him if he knew there was a piano in the gymnasium, which he was surprised to hear. I will never forget the first time I excitedly wheeled Walter down to the piano. I removed the bench and rolled his wheelchair into the proper position. Without missing a beat, his fingers danced on the keys and a crowd slowly gathered around the piano of other patients and residents smiling and clapping their hands. Walter was beaming. For the rest of my time in that center, the favorite part of my day was taking Walter down to the piano whenever he asked, to be treated to a display of the beauty and compassion of a man through his music.

To see an older adult as less than what they are – an amazing human being – is not only detrimental to them, but to ourselves. When my grandmother was dying in Sri Lanka, the last time my family visited, I watched my dad transfer her emaciated body from the wheelchair to the bed and clear her airway with a suction catheter. This was not just a frail old woman, who could barely speak and was dependent on caregivers. It was a woman who gave birth to and raised nine children from a small mountain village in Sri Lanka. A woman who saw me grow up and took care of me. A woman who, despite the language barrier, I loved to make laugh with my goofy behavior. She was my grandmother.

According to Butler[10], "Ageism allows the younger generations to see older people as different from themselves; thus, they subtly cease to identify with their elders as human beings."

Evidence suggests that overcoming future-self discrimination is quite intuitive. The more time people spend caring for older adults, the more these ageist attitudes recede. In Lytle and Levy's (2017) study[11] that tested The Positive Education about Aging and Contact Experiences (PEACE) model, they determined two key factors for reducing ageism: education about aging, and extended contact. In Jonson's (2012) article published in The Gerontologist[12] he suggests that society is struggling to update the stereotypes of old age, "a misunderstanding that can be corrected with factual information…The health, mental abilities, financial security, social activity, and life satisfaction of older people has increased, but most people have not heard the good news." Research also suggests that negative attitudes stem from a lack of positive contact between group members. Positive contact with older adults is associated with less ageism, with the strongest effect observed for close relationships such as friendships. This exposure allows for individual identities to become more salient with a richer, more holistic view of individuals[12].

In 2016, the World Health Organization adopted the first global strategy and plan of action on ageing and health[13], which spans a fifteen year period and calls for a global campaign to combat ageism. The campaign seeks to inform the public about the individuality of

older persons, influences on health, and aspects of healthy aging. The program mandates changes in societal attitudes, more accessible environments, and changes to health care systems that align with the needs of older people.

If all healthcare workers – not only geriatric practitioners – are attuned to these needs, patients are treated holistically, with both medical and psychosocial needs accounted for. I had the pleasure of hearing the colorful stories of many patients and getting to know them as human beings rather than "objects of care." Patients leaving the hospital showed so much gratitude, and each day I walked away feeling fulfilled. While it may not be for everyone, I can understand why geriatricians are ranked as the subspecialty with the highest job satisfaction[14]– and maybe this should be another selling point for a career that is overlooked in a profession where burnout is so prevalent.

On that windy day in Dublin, I stopped for a moment when I saw the man's hat blow off on the platform, and I ran around the enclosed part of the parking lot until I could enter it. I picked up his hat and handed it to him through the gap of the iron fence.

"Thank you, God bless you," the man said.

When I came back around to the platform, I chatted with him for a few moments until the next tram arrived and he shook my hand. I will not forget how appreciative he was of such a small gesture. I can only hope that when I am in that man's shoes someday,
others would take the time to do the same.

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Early Satiety in Cancer: A Clinical Review of Definition and Therapeutic Management

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Abstract

Early satiety is defined as the desire to eat with the inability to eat appropriate amounts due to premature fullness. Although a common symptom of cancer, it is rarely recognised in medical practice and poorly elucidated in the literature. This review highlights the importance of early satiety in cancer, and outlines appropriate treatment. A literature search was conducted using EMBASE, CINAHL and SCOPUS. The search was limited to articles available in English and peer-reviewed journals. Articles were screened in four stages by two independent reviewers and the Preferred Reporting Items for Systematic Reviews (PRISMA) was used. 486 articles were identified, of which, five full-text articles were included in the study. The literature outlined that targeting central and peripheral mechanisms are key to symptom management. Peripherally-acting prokinetics such as metoclopramide are considered first line therapy. Agents that target gastric accommodation such as clonidine, sumatriptan and sildenafil may also be useful. Centrally acting pharmacological agents associated with digestion may be effective. Centrally acting agents include: progesterone receptor agonists, cannabinoids and ghrelin agonists. Overall, early satiety is an under-recognised, but important symptom in cancer. Due to the limited studies available, the efficacy of treatments are not well established. High quality studies outlining appropriate therapeutic management are necessary to establish standardised treatment protocols.

Introduction

In advanced cancer states, early satiety appears to be a key determinant of anorexia severity (Walsh et al. 2000). Anorexia is a common symptom in cancer and has significant consequences for morbidity and quality of life (QOL) (Laviano et al. 2017). However, early satiation is poorly defined and under-recognized in medical practice. Diverse descriptors such as "abdominal fullness", "easy filling" or "filling quickly" have been used (Theologides 1979). The present review aims to define early satiety, describe its pathophysiology and conduct a literature review of appropriate therapeutic management.

Definition

Early satiety is a desire to eat, followed by an inability to eat appropriate portions due to a premature sense of fullness (satiety), with consequent decreased food intake (Theologides 1976; Sarhill et al. 2003). It occurs in an anorexia-cachexia cluster of symptoms along with taste changes and weight loss (Aktas et al. 2014). Clinically, early satiety is often misclassified as anorexia or nausea; however it is a distinct symptom that can occur in their absence (Theologides 1979; Theologides 1976).

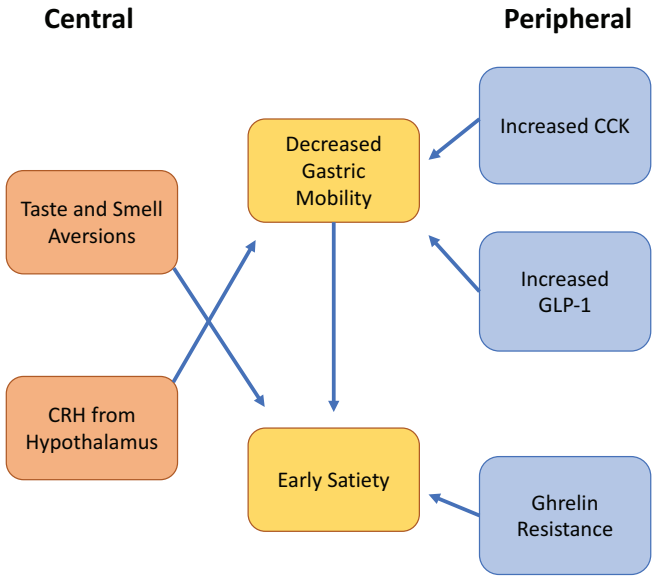
Prevalence

Early satiety is one of the ten most prevalent symptoms in advanced cancer, experienced by 51% of patients (Walsh et al. 2000). This symptom is more common in females and has not been linked to any specific primary cancer site or anti-cancer therapy (Davis et al. 2006; Walsh et al. 2000; Nielsen et al. 1980; Donnelly et al. 1995). It is an independent prognostic indicator of life expectancy (Walsh et al. 2000). Further, patients rarely volunteer information about the symptom spontaneously (Walsh et al. 2000). Consequently, it remains under-treated and poorly understood (Walsh et al., 2000).

Pathophysiology

The pathophysiology is ill-defined but appears to involve both central and peripheral mechanisms (Figure 1). Centrally, food intake is tightly regulated to match energy expenditure to body weight (Davis et al. 2006). Taste and smell aversions reduce food consumption and promote satiation (De Graaf et al. 1999; de Graaf et al. 2004). Corticotropin-releasing hormone (CRH) secreted from the hypothalamus reduces gastric motility and may induce satiety (Beglinger & Degen 2002).

Peripherally, food ingestion induces satiety signals from the gastrointestinal tract (Woods 2004). Important mediators include cholecystokinin (CCK), glucagon-



like peptide 1 (GLP-1), and ghrelin. Most of these elicit satiety as a meal progresses (Woods 2004). CCK is released from the small intestine due to fat and protein intake (Davis et al. 2006). GLP-1 is associated with fat and carbohydrate consumption and released by the ileum (Davis et al. 2006). Both CCK and GLP-1 inhibit gastric emptying, promote satiety, and reduce food intake (de Graaf et al. 2004; Woods 2004; Wilson et al. 2002). Conversely, ghrelin is a stomach hormone that stimulates appetite and gastric motility (Edholm et al. 2004; Davis et al. 2004). Elevated ghrelin levels occur in advanced cancer but there is resistance to ghrelin-associated appetite stimulation (Davis et al. 2006).

Inflammatory cytokines may play a role in the pathogenesis of early satiety in cancer. Studies have demonstrated that tumour associated pro-inflammatory cytokines, tumor necrosis factor-α (TNFα), Interleukin (IL)-1 and 6, and vascular endothelial growth factor (VEGF)-A and VEGF-C are key mediators in cancer-associated anorexia (Davis et al. 2012). Furthermore, early satiation occurs in insulin-dependent diabetes mellitus as a complication of diabetic autonomic neuropathy (Hasler WL 2008; Patrick et al. 2008). There is some evidence of autonomic dysfunction in non-diabetic cancer patients perhaps as a paraneoplastic syndrome (Donthireddy et al. 2007). It is presumed that early satiety reflects gastric dysmotility. Early satiety is a complex multifactorial symptom and appropriate treatment should target both its central and peripheral aetiologies.

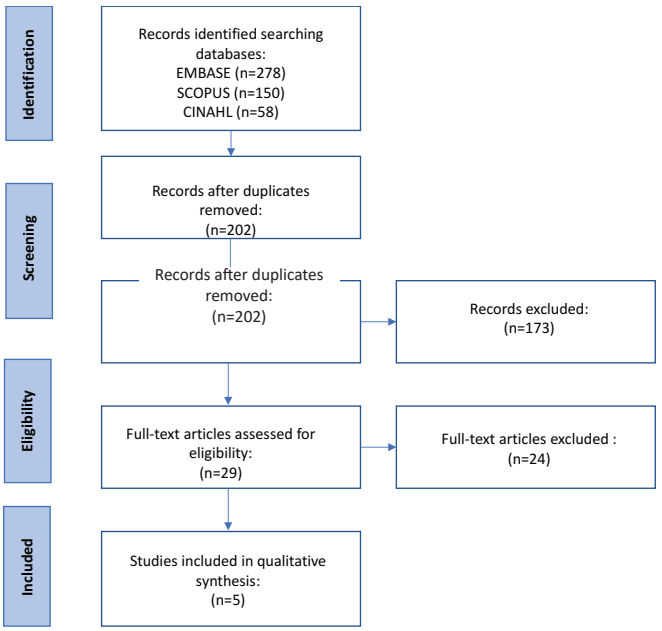
Methods

Literature Search

A systematic literature search was conducted using three electronic databases: EMBASE, CINAHL and SCOPUS. Variations of the following keywords were used: early, premature, satiety, satiation, fullness, and cancer. The search was limited to peer-reviewed journals and texts available in English language.

Study Selection

The review had four stages. To reduce selection bias, each stage was conducted independently by two reviewers. The reviewers screened eligible studies and papers were excluded if they did not pertain to therapeutic management or have full-text available. Articles were also excluded if they did not study the correct population or evaluate early satiety as a primary symptom.



Results

A total of 486 articles were identified and 284 duplicates removed. After screening titles and abstracts, 173 articles were excluded. Twenty-four articles were excluded after full-text assessment. Results were reported by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Figure 2). Five items (three original articles and two reviews) were included and full analysis was conducted (Table 1).

Source	Intervention	Study Sample / Literature Reviewed	Study Design	Limitations	Outcomes
Davis et al. 2006	None	Defining early satiety in advanced cancer	Narrative Review	Selection bias Publication bias Qualitative rather than quantitative	Treatments: small frequent meals, increased dietary fat, megestrol acetate, cannabinoids, ghrelin agonists, prokinetic agents (domperidone; metoclopramide)
Davidson et al. 2007	None	Treatments for ingestive behaviour in critical disease states (included cancer)	Narrative Review	Publication bias Selection bias Qualitative rather than quantitative. Conclusions related to all critical disease, not cancer-specific.	Treatments: cannabinoid agonists, ghrelin, megestrol acetate, thalidomide
Andrew et al. 2008	Clinical audit of cancer symptoms and drug history	Advanced cancer with cachexia syndrome (n=32)	Clinical Audit	Small sample (n=23) Did not evaluate treatment effects	Identified early satiety as a common symptom. Treatments: domperidone and metoclopramide
Chasen et al. 2011	OHR118- novel peptide nucleic acid, (TNF-alpha and IL-6) immunomodulatory effects	Advanced cancer with anorexia (n=21; 15 males, 6 females)	Non-randomised interventional study	Small study (n=8 completed) Non-randomised No control Short term study	Effectiveness not established. Significant appetite increase (p=<0.01) (n=8). Total PG-SGA score improved (p ≤ 0.01). Early satiety improved on the DSSI** (p=0.04).
Davis et al. 2012	Thalidomide, (TNF-alpha and IL-1) immunomodulatory effects	Advanced cancer with anorexia (n=35)	Non-randomised, phase II study	Small study (n=33 completed) Non-randomised No control Short term study	Effectiveness not established. 16 non-responders, of these, 4 who were uptitrated responded. Side effects: constipation, dry mouth, pruritus. Early satiety by the CAT significantly improved (p<0.05).

Table 1. Detailed Source Extraction. PG-SGA- Patient Generated Subjective Global Assessment score, **DSSI-Dyspepsia Symptom Severity Index, CAT- Categorical Scale

Discussion

Limited recognition and understanding of early satiety is reflected in the paucity of studies available. Few studies identify and examine effective therapeutic management. Limitations in the literature were identified (Table 1). Evidence was limited by poor follow-up attributable to high mortality in this cohort. In addition, much of the literature evaluates cachexia treatment, which although related, presents different therapeutic challenges. This literature was not included in our study.

Validated assessment tools for symptoms in advanced cancer symptoms rarely include early satiety, so it is difficult to assess treatments reliably. In Davis et al. 2012, the categorical scale (CAT) was used, however it has poor sensitivity (Davis et al. 2009). In addition, the Patient Generated Subjective Global Assessment (PG-SGA) includes early satiety as a symptom, but does not quantify it (Bauer et al. 2002). Early satietyhas been identified as an "Orphan" cancer symptom. As it occurs as part of a four-item anorexia-cachexia symptom cluster, there is the possibility that they share a common pathophysiology. Effective management of early satiety might improve not just satiety but other closely related symptoms.

Non-Pharmacological Management

With regard to central and peripheral mechanisms, early satiety can be targeted with non- pharmaceutical and pharmaceutical interventions. In terms of conservative management, various strategies can be used. There is a clinical variation in appetite of cancer patients, thus it is recommended to make breakfast the main meal of the day (Davis et al. 2006). Alternatively, it has also been proposed that frequent small meals throughout the day may help reach minimum daily calorie requirements (Davis et al. 2006). Lipid-rich meals cause less satiation

than protein or carbohydrate (Davis et al. 2006; Blundell et al. 1996). Colder food temperatures may also reduce food aversion (Davis et al. 2006). Further, emotional stress and anxiety contribute to early satiety, and psychiatric intervention can be helpful in these patients (Andrew et al. 2008).

Pharmacological Management

Megestrol acetate acts predominantly as a potent progesterone receptor agonist. It has a positive effect on the common symptoms of food aversion including taste and smell changes (Davis et al. 2006; Thorne et al. 2015). Cannabinoids like nabilone down regulate hypothalamic CRH and improve energy intake, thus may help improve satiety (Davis et al. 2006; Thorne et al. 2015). In a randomised, placebo-controlled, cross-over clinical trial, the effects of ghrelin were evaluated based on energy intake and meal appreciation using the visual analogue scale. Overall, ghrelin increased energy intake by 31% and a significant increase in meal appreciation score ($P = 0.02$) was observed (Neary et al. 2004). An additional study also concluded that ghrelin could be an effective, well-tolerated treatment for cancer-associated early satiety (Davis et al. 2006).

Cancer patients with severe early satiety have decreased gastric motility (Davis et al. 2006). A study identified in the present review recommended prokinetics, such as metoclopramide and domperidone for pharmaceutical management (Andrew et al. 2008). This particular study quantified symptom burden and audited prescribing in cancer patients with anorexia–cachexia syndrome (ACS) symptoms (Andrew et al. 2008). Seventy percent (n=23) of those audited had early satiety as a primary symptom by the PG-SGA tool and overall early satiety was identified as an unmanaged symptom. Commencing or increasing the dose of a prokinetic such as metoclopramide and domperidone was recommended (Andrew et al. 2008).

The immunomodulatory effects of OHR118, a novel broad spectrum peptide nucleic acid, on TNF-α and IL-6 were investigated in a small phase II non-randomised study (Chasen et al. 2011). Patients received daily, subcutaneous injections (4.0mL) of OHR118 and the effects on appetite, early satiety, and nutritional intake in advanced cancer were explored in 21 patients (Chasen et al. 2011). Early satiety improved significantly on the Dyspepsia Symptom Severity Index (DSSI). However, of the 21 patients enrolled, only eight continued with OHR118 treatment to completion (Chasen et al. 2011). A larger, randomised clinical trial should validate these findings.

Thalidomide, a TNF-α inhibitor, is an additional immunomodulatory drug associated with improved appetite. A two-stage phase II dose titration study (n=35) assessed appetite response in cancer-associated anorexia (Davis et al. 2012). The severity of early satiety, measured by the CAT, significantly improved ($P<0.05$) after two weeks treatment (Davis et al. 2012). However, many were non-responders (n=16) (Davis et al. 2012). A larger study is required.

Other potential agents such as clonidine, nitroglycerin, sildenafil, or sumatriptan have been outlined in the literature (Davis et al. 2006). These may help to improve gastric accommodation (Davis et al. 2006). In addition, hypersensitivity due to increased enteric afferent signals may be blocked by asimadoline (Delgado-Aros et al. 2003). The effectiveness of these treatments, however is unclear (Delgado-Aros et al. 2003; Davis et al. 2006).

Conclusions

Early satiety is a complex multifactorial symptom and appropriate treatment should target both its central and peripheral aetiologies. Despite its high prevalence, significant association with anorexia, and poor prognosis, early satiety is rarely identified or treated in advanced cancer. Limited high quality studies have specifically evaluated management. Future research should establish both a standardised treatment protocol and a validated tool for long-term assessment. Randomised control trials of large patient populations should be conducted to specifically evaluate the efficacy of proposed therapies. Translational research of the pathophysiology of early satiety may improve the understanding of this neglected symptom and uncover novel therapeutic pathways. Overall, improved recognition and management of early satiety may significantly enhance the quality of life in patients with advanced cancer.

Conflict of Interest Statement

There are no conflicting interests that may have influenced this work.

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