On the day the completion of the Human Genome Project was announced, the President of the Royal Society, Lord May of Oxford, pointed out that humans share about 50% of their genes with bananas. The parallels between our genome and those of other species are remarkable. Approximately 40% of our genes are shared with yeasts, 60% are shared with worms and about 80-90% are shared with mammals, such as mice or rabbits. Around 99% are shared with chimpanzees and other great apes. The difference in the genome between ourselves and chimpanzees are therefore tiny compared with the overwhelming overall differences. However, they are crucial because they make humans 'human.'

It has become evident that the two 'genomes' that each of us carry, inherited from our parents, differ from each other and from the genomes of other humans, in terms of single changes in nucleic acids. The 21st century has witnessed exponential growth in the identification of these so-called single nucleotide polymorphisms (SNP). The International SNP Map Working Group estimates that they have identified 1.42 million SNPs within genes.[1] However, the main use of the human SNP map will be in delineating the contributions of individual genes to diseases that have a complex, multi-gene basis. Knowledge of genetic variation already affects patient care to some degree. For example gene variants lead to tissue and organ incompatibility, affecting the success of transplants. The mainstay of medical genetics has also been the study of the rare gene variants that are the basis of inherited diseases such as cystic fibrosis. The most valuable aspect of variation in genome sequences underlie differences in our susceptibility to, or protection from all kinds of diseases including the age of onset, severity of illness, and how our bodies respond to treatment. Therefore, by comparing patterns and frequencies of SNPs in patients and controls, researchers can identify which SNPs are associated with which diseases.

The clinical application of SNPs is currently being investigated in two projects here at Trinity College, the LIPGENE Project and the IMAGE Project. LIPGENE is an ambitious five-year interdisciplinary research project aiming to reveal the link between genes and obesity. It involves a consortium of 25 research laboratories across Europe, led by Professor Michael Gibney and Dr. Helen Roche of the Institute of Molecular Medicine and the Department of Clinical Medicine. A primary focus of LIPGENE will be to identify interactions between dietary lipids and SNPs involved in the development of the 'metabolic syndrome'. The IMAGE (International Multicenter ADHD Genetics) Project is another ambitious collaboration between the Neuropsychiatric Genetics Group, led by Professor Michael Gill of the Department of Psychiatry, the Institute of Psychiatry in London, Harvard Medical School and clinical centres throughout Europe. One of the aims of this project is to identify SNPs in the genome that predispose and lead to the development of attention-deficit hyperactivity disorder (ADHD). The genetic basis of obesity and ADHD is explored further in this issue of the TSMJ.

Finally, we should pay heed to Aravinda Chakravarti's warning in the issue of *Nature* which announced the completion of the Human Genome Project, *"To some, there is a danger of genomania, with all differences (or similarities, for that matter) being laid at the altar of genetics. But I hope this does not happen. Genes and genomes do not act in a vacuum, and the environment is equally important in human biology."*[2]

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Cerebral Vein Thrombosis in St. James's Hospital: Incidence, predisposing factors and sequelae

Niamh Appleby

5th medical year

Abstract:

Background: Thrombosis of the cerebral veins and sinuses is a cerebrovascular disorder most commonly affecting young adults. Underlying risk factors for cerebral vein thrombosis (CVT) are identified in 85% of patients. This study aims to identify the underlying risk factors in a cohort of patients with a diagnosis of CVT and identify risk of recurrent events.

Methods: A retrospective analysis of data from a cohort of 12 patients with a diagnosis of cerebral vein or sinus thrombosis was performed.

Results: 12 patients (10 female, 2 male, median age 30.5 years) with cerebral vein or sinus thrombosis were identified. Ten patients (83%) had a known risk factor for CVT. Thrombophilia (genetic or acquired), use of oral contraceptives, pregnancy and post-partum and infection were the most commonly identified risk factors. Two patients (17%) experienced a recurrence of CVT.

Conclusion: The mode of presentation of CVT and its risk factors identified here are similar to those described in international studies. No woman with intrapartum CVT has experienced a recurrence thrombosis to date. Further data is required to provide evidence based management guidelines for the subgroup of women who present with CVT during pregnancy and for the group of women with a history of CVT who become pregnant subsequently.

Introduction:

Cerebral vein thrombosis (CVT) is a potentially life threatening form of thrombosis which affects the venous system of the brain. It is one cause of stroke in young adults, predominately young women[1, 2]. While it would be likely that the clinical phenotype of CVT in Ireland mirrors the international experience, few data exist. International information is scarce regarding the likelihood of recurrence and optimal management of cerebral vein thrombosis during pregnancy.

The annual incidence of CVT is approximately 3-4 cases per million. The frequency of cerebral vein thrombosis is increased in the peripartum and post partum period to between 12 and 13.1 cases per 100,000 deliveries[1, 4].

Thrombosis of the cerebral veins leads to venous obstruction, followed by local brain oedema and venous infarction. Thrombosis of the major venous sinuses disrupts the circulation of cerebrospinal fluid, causing intracranial hypertension[1]and in most patients, both processes occur simultaneously. The most frequently identified sites of cerebral vein thrombosis are the lateral and sagittal sinuses[1, 2].

A prothrombotic risk factor is identified in 85% of patients with sinus thrombosis[1]and patients with CVT usually have multiple risk factors[2]. Thrombophilic states (both genetic and acquired) and use of the oral contraceptive pill (OCP) are the most commonly identified risk factors. A recent Italian study found that oral contraceptive use is strongly and independently associated with cerebral vein thrombosis. In addition, the combination of a prothrombin gene mutation and use of OCP further

increased the risk of sinus thrombosis[3]. Mechanical causes of sinus thrombosis include head injury, direct trauma to the sinuses or jugular veins, neurosurgical procedures and lumbar puncture[1]. Pregnancy related hypertension and caesarean delivery are associated with intracranial venous thrombosis in the peripartum and post partum period [4]. A significant minority (12.5%) of cases had no known risk factor[2].

The clinical presentation of cerebral vein thrombosis is highly variable.
Severe headache is present in approximately 90% of adult patients with sinus thrombosis. Cerebral lesions and neurological signs develop in between one third and one half of patients and seizures occur in about 40% of patients[1, 2].

CT scanning is useful in the initial assessment and helps exclude other acute cerebral disorders, however CT results may also be normal[1]. While MRI in combination with magnetic resonance venography is the most sensitive imaging technique for the diagnosis of sinus thrombosis[1], cerebral angiography provides more detailed imagery of the cerebral veins and represents a useful diagnostic tool in cases were CT or MRI results are ambiguous[1].

The combination of raised intracranial pressure and venous infarction means that patients are at risk of death from cerebral herniation. Management options to prevent or reverse cerebral herniation include administration of intravenous mannitol surgical removal of the infarct or decompressive hemicraniectomy[1]. Anticoagulation with heparin is widely used to halt the progression of the thrombosis and prevent pulmonary embolism[1, 2]. However, venous infarcts may become haemorrhagic and the optional duration of treatment is unknown. Endovascular thrombolysis has been used in some centres.

CVT is associated with significant morbidity and mortality, the latter ranging from 8% to 30% [2,5]. One recent study found that 36% of survivors of CVT had some neurological impairment, though 22% of these were mild[2]. Coma, cerebral haemorrhage and malignancy have been identified as risk factors for death or dependence [2,6]. In the same study, 2.2% of patients suffered a recurrent sinus thrombosis while 4.3% had another thrombotic event[2].

Aim of Study:

To identify the underlying risk factors in a cohort of patients diagnosed with CVT and to identify the risk of recurrent thrombotic events, particularly in women during pregnancy and in the post-partum period.

Methods:

Data were collected retrospectively from a cohort of 12 patients referred to the National Centre for Hereditary Coagulation Disorders, St. James's Hospital between 1995 and 2005. Patients with a diagnosis of cerebral vein or sinus thrombosis made on CT, MRI or MR angiography were included. Underlying prothrombotic risk factors and precipitating factors were sought.

Results:

Table 1: Demographic Features of Patient Group

	Number of Patients	Percentage of Cases

Female	**10**	**83%**
Male	**2**	**17%**
Age Range = 13-46 years		
Median Age = 30.5 years		

(percentages given as the nearest whole number)

Twelve patients were included in the study, of which 10 cases were female. Median age at diagnosis was 30.5 years, with a range of 13 to 46 years. Demographic data on the patient population is outlined in Table 1. Data on clinical presentation are shown in Table 2 below.

Table 2: Presenting Symptoms: *(data available for 11/12 patients)*

Presenting Symptoms	**Number of patients**	**Percentage of Patients**
Headache	8	67%
Unilateral Limb Weakness	3	25%
Meningism	2	17%
Cranial Nerve Palsy	2	17%
Seizure	2	17%
Loss of Balance/ Fall	2	17%
Unconsciousness	1	8%
Confusion	1	8%
Visual Loss	1	8%
Sensory Symptoms	1	8%
Vomiting	1	8%

(percentages given as the nearest whole number)

Location of Thrombosis in the Major Cerebral Veins and Sinuses:
Of the 12 patients in the study one third had thrombosis at a single site and one third had thrombosis with extension to another site. Location of the thromboses is described in Table 3. One third (4 patients) had evidence of underlying cerebral ischemia on imaging, of these 4 patients, only 1 developed long term neurological sequalae (epilepsy).

Table 3: Location of Thrombosis on Imaging
(Data available for 12 patients. Thrombus may affect more than one site)

Location of Thrombosis	**Number of Patients**	**Percentage of Cases**
Superior Sagittal Sinus	6	50%
Transverse sinus (left or right)	7	58%
Jugular Veins	1	8%
Cavernous Sinus	1	8%
Occipital Sinus	1	8%
Central Thoracic Veins	1	8%
Brachial Subclavian	1	8%

(percentages given as the nearest whole number)

Risk Factors:

Risk factors for cerebral vein thrombosis are summarised in Table 4. Ten of 12 patients (83%) had an identifiable risk factor for CVT. Of these 10 patients with identified predisposing factors, 4 patients had two risk factors and 1 patient had 3 or more risk factors. Thrombophilia screening was performed in 11 cases. Genetic and acquired thrombophilia was found to be the most common risk factor, followed by pregnancy and the post-partum state, infection and use of the OCP. In 2 cases no known risk factor was identified. Oral contraceptive use was identified has a risk factor in 3 cases, in 2 of these, use of the OCP was the only risk factor identified. Pregnancy was a risk factor in 2 cases, where CVToccurred at 31 weeks and 37 weeks gestation respectively. A third case was post partum.

Table 4: Risk Factors for Cerebral Vein Thrombosis Identified
(percentages given as the nearest whole number)

Risk Factor	Number of Patients	Percentage of Cases
None Identified	**2**	**17%**
Thrombophilia	**4**	**33%**
Genetic prothrombotic states	*3*	*25%*
Protein S deficiency	1	8%
Prothrombin mutation	1	8%
Antithrombin deficiency	1	8%
Acquired prothrombotic states	*1*	*8%*
Antiphospholipid antibodies	1	8%
Vasculitis	**1**	**8%**
Beçhets disease	1	8%
Pregnancy & post partum	**3**	**25%**
Infection	**3**	**25%**
Systemic Infection	2	17%
Sinusitis	1	8%
Oral Contraceptive Use	**3**	**25%**
Corrected OCP*		**50%**

Excluding male or pregnant cases. Half of non-pregnant female cases used the contraceptive pill

Management of Patients with Cerebral Vein Thrombosis:
Data were available for 11 cases.
All were initially anticoagulated with heparin. One case was given endovascular thrombolysis with urokinase, complicated by the development of a retroperitoneal haematoma. No patients required neurosurgical intervention. Five patients remain on lifelong anticoagulation with warfarin, and three patients remain on lifelong aspirin.

Outcome for Patients with Cerebral Vein Thrombosis:
Six of the12 patients developed long term neurological sequalae. The various types of neurological sequalae are outlined in Figure 1 (below). Thrombotic events and seizures occurring during follow-up are outlined in Table 5.

Figure 1:Long Term Neurological Sequalae

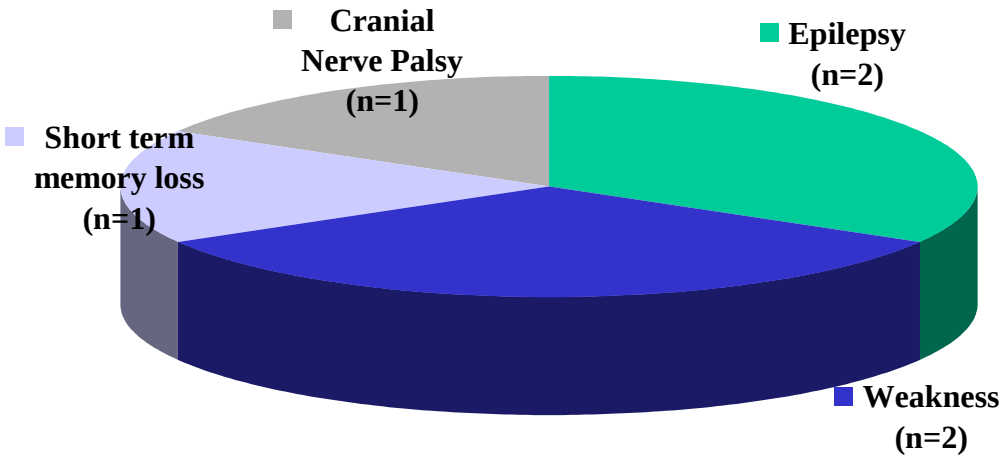

Table 5: Events during follow-up
(percentages given as the nearest whole number)

	Number of Patients	Percentage of Cases
Recurrent sinus thrombosis	**2**	**17%**
Other thrombotic events*	**2**	**17%**
Deep vein thrombosis	2	17%
Pulmonary embolus	2	17%
Seizures	**2**	**17%**

** 2 cases developed both deep vein thrombosis and pulmonary embolus*

Cerebral Vein Thrombosis and Subsequent Pregnancy:
Of the 10 women in our cohort, 3 have had subsequent pregnancies, one of whom has delivered a healthy baby with no recurrent thrombotic events. She received prophylactic heparin during the postpartum period only. The other two women have not yet delivered.

Discussion:
This study shows that the St. James's experience with cerebral vein thrombosis is broadly consistent with published work on the topic, where the patient population (83% female, median age 30.5 years) mirrors the international experience [1, 2]. Headache was the commonest presenting feature, though at 67% was lower than the 88.8% - 90% reported in previous studies [1, 2]. The transverse sinus was the most commonly observed site of thrombosis, followed by the sagittal sinus. These findings are consistent with those described in the International Study on Cerebral Vein and Sinus Thrombosis (ISCVT) [2]. The vast majority (83%) of patients had an identifiable risk factor and half of these had more than one risk factor. Thrombophilia and oral contraceptive use were the most frequently identified risk factors. The use of the OCP has been found to be strongly associated with sinus thrombosis. Moreover, the combination of the prothrombin gene mutation and OCP has been found to increase the risk of cerebral vein thrombosis further[3]. Infection was reported as a risk factor in 25% of St James's cases compared with 12% of ISCVT cases[2].

No deaths occurred in our cohort. However, our patient population included only cases of CVT who survived the initial event to be referred to the National Centre for Hereditary Coagulation Disorders.

The International Study on Cerebral Vein and Dural Sinus Thrombosis found that following CVT (median follow-up of 16 months), 57.1% of patients had no signs or symptoms, 22% had minor residual symptoms and 7.5% had mild impairments. Moderate residual impairment was found in 2.9% of the patient population and 2.2% were severely handicapped. Six patients (50%) in the St. James's Study had some residual signs and symptoms. Seizures were reported in 17% of St. James's patients following cerebral vein thrombosis, somewhat higher than the 10% reported in the ISCVT. The absence of data on the severity of the neurological sequalae and their impact on the patients living made further comparison of the long-term effects of CVT with previous published studies difficult.

The rate of recurrence of both CVT and other thromboses is higher in this study than that observed in international studies. Both cases with subsequent thrombosis had their initial cerebral vein thrombosis in 1995.

Following their CVT, 5 patients remain on lifelong warfarin while 3 are on aspirin.

The lack of recurrence of CVT during pregnancy is encouraging. However, our sample size was small. Previous CVT, including puerperal cerebral thrombosis is not considered a contraindication to pregnancy[2, 7].

Finally, we have identified a need for a national database of CVT occurring during pregnancy. Little evidence is available to guide management of these patients both during their pregnancy and in the post partum period. Currently, it is uncertain whether they should receive prophylactic heparin during pregnancy.

Acknowledgments

With thanks to Fionnuala ní Ainle, Specialist Registrar in Haematology. This article is based on data presented to the Haematology Association of Ireland in November 2005.

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Nature or Nurture? A Review of the Aetiology, Diagnosis, and Treatment of Attention Deficit Hyperactivity Disorder

Simon Bull

4th year Neuroscience

Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioural disorder characterised by developmentally inappropriate levels of hyperactivity, impulsiveness and inattention. Heritability data from twin studies of ADHD attribute about 75 percent of ADHD aetiology to genetic factors. The remaining 25 percent is attributed to environmental influences. ADHD affects 3 to 5% of children and a smaller percentage of adults. Diagnosis is based on criteria from the DSM-IV or ICD-10 and determined by a complete physical and behavioural evaluation. Psychoactive medication is consistently the most effective approach to managing ADHD and many effective pharmacological treatments are currently available.

Introduction

ADHD is a neurobehavioural disorder that affects both children and adults. It was first identified over a century ago by Dr. Heinrich Hoffman in children who acted impulsively and had significant behavioural problems. Research later determined that the behaviour was not caused by poor child rearing, but by a genetic predisposition. Sir George F. Still described the genetic predisposition in a series of lectures he presented to the Royal College of Physicians in England in 1902. Since that time, thousands of studies have been performed concerning ADHD.

Formerly, ADHD was known as Attention Deficit Disorder (ADD) but was renamed ADHD in 1994 to encompass the hyperactivity which may present in the disorder. The main symptoms of ADHD are hyperactivity, impulsiveness and inattention. Typical symptoms include excessive running and climbing, squirming in seat, careless mistakes on assignments, difficulty awaiting turn, and excessive talking. The child displays these symptoms in the classroom and home. The prevalence of ADHD is between 3 to 5% of school children worldwide[1]. It was recently estimated to occur in 5 to 10% of Irish children[2]. Boys are approximately three times more likely to have ADHD than girls, although the reason for this is not understood[3].

Theories of Causation

No definitive cause has been established for ADHD. The disorder cannot be identified by any distinct genetic, environmental, or neurobiological factors[4]. Family, twin and adoption studies have indicated that ADHD has a strong genetic foundation. It has been firmly established that ADHD is not simply the result of a poor social environment; however there is a correlation between specific environmental factors and ADHD. Finally, neurobiological studies indicate that ADHD may be caused by alterations in neurological

circuitry or specific structural changes in the brain. Ultimately, ADHD is most likely due to an interaction between these factors in genetically predisposed individuals.

For decades, research has shown that ADHD is primarily the result of genetic factors and is transmitted in families. ADHD occurs 5 to 7 times more frequently in family members with the disorder[5]. A recent longitudinal study showed that the parents of children with ADHD had significantly increased rates of ADHD as compared with the parents of children who did not have ADHD[6]. The child of an adult with ADHD has approximately a 25% chance of developing ADHD[7]. In agreement with these findings, studies found that adoptive relatives of children with ADHD are less likely than biological relatives to have the disorder or associated syndrome. A large scale study identified a 75 to 91 percent heritability across familial relationships (twin, sibling, and twin-sibling)[8]. This finding, along with numerous other studies, estimates the heritability to be 0.76 on average (Figure 1)[9]. A twin study reported a monozygotic probandwise concordance rate of 51 percent and dizygotic concordance rate of 33 percent[10]. Together, these studies provide compelling evidence that ADHD is a highly heritable disorder. Although no single genomic region is responsibility for ADHD, a number of genetic abnormalities have been associated with the disorder.

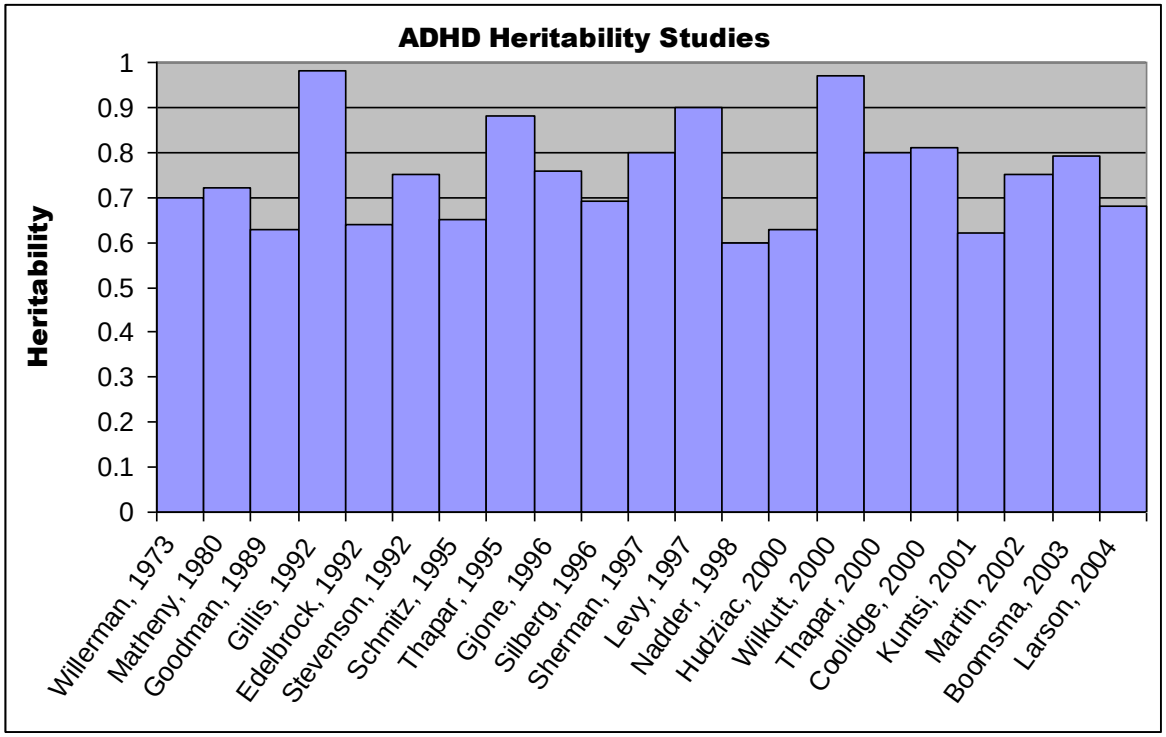

Figure 1[9]. This figure demonstrates the correlation in data from heritability studies.

Linkage findings provide evidence of a susceptibility locus on chromosome 16p13. A polymorphism in the GRIN2A (glutamate receptor, ionotropic, N-methyl D-aspartate 2A) gene, which maps to this locus, has been associated with increased risk of ADHD[11, 12]. Despite findings such as this, genomic regions implicated by linkage studies do not show significant correlations and several different loci have been connected with ADHD. These include 5p13, 5q33.3, 6q12, 7p13, 9q33, 11q22, 15q15 and 17p11[9]. Given the absence of repeated results across the spectrum of studies to date, it is reasonable to speculate that

genes with moderately large effect do not exist and that predisposition to ADHD is the result of a combination of genetic factors.

Meta-analyses have implicated polymorphisms in dopamine receptors *DRD4*, *DRD5* and the dopamine transporter *SLC6A3*. DRD4 is also prevalent in the frontal-subcortical networks that are implicated in ADHD pathophysiology[9]. Imaging studies of adults with ADHD have demonstrated a reduction in dopamine-transporter binding[9]. Accordingly, the dopamine tranporter is a primary target of the most frequently prescribed pharmacological treatments, methylphenidate and amphetamine.

There are multiple environmental factors which contribute to the risk of developing ADHD. The child is most vulnerable in utero where chronic exposure to certain toxins, including alcohol, nicotine and cocaine, is associated with an increased risk of ADHD. Delivery complications also increase the risk of ADHD. This includes foetal hypoxia, premature delivery and significantly low birth weight[9, 13]. Notably, the basal ganglia, which are associated with ADHD, are particularly sensitive to hypoxic insults[9].

Postnatal environmental conditions have also been associated with ADHD. Rutter *et al* found that combinations of family environmental risk factors, rather than any one factor, contribute to the postnatal incidence of ADHD[14]. The risk factors include a large family size, maternal mental disorder, paternal criminality, severe marital discord, low social class and foster care placement[15]. It is not suggested that these risk factors cause ADHD, but that there is a positive correlation between their presence and the presence of ADHD. Systematic studies discredit theories contending that particular foods or additives or excessive television viewing contribute to ADHD[9]. Despite being associated with ADHD, lead contamination is not found in most children with ADHD and many children with high lead exposure do not develop ADHD[9].

There are two currently held neurobiological models to explain ADHD. The Neuro-Cognitive Model describes ADHD as an executive dysfunction caused by disturbances in the fronto-dorsal striatal circuit and associated dopaminergic branches (e.g. mesocortical pathway). A second account sites altered reward pathways (e.g. delay aversion). These implicate fronto-ventral striatal reward circuits and the meso-limbic branches that terminate in the ventral striatum, particularly the nucleus accumbens. Previously, these models were thought to be competing. However, they are now regarded as complementary accounts of two psycho-patho-physiological subtypes of ADHD with different developmental pathways, supported by different cortico-striatal circuits and modulated by alternative dopaminergic pathways[16]. Both models result in a reduction in attention-monitoring processes, inappropriate cognitive responses and behavioural impulsiveness. Many scientists now believe that cognitive disinhibition is the root cause of ADHD[5, 17].

Scientists have examined the brain's anatomy in order to find further information as to the aetiology of ADHD. Electroencephalogram (EEG) studies show that over 90% of children diagnosed with ADHD demonstrate regulation disturbances in the prefrontal and sensorimotor cortices along with inhibited activity in all cortical areas. These children may be experiencing delayed maturation of the neural pathways because the regulation disturbances were seen in younger children's brains (<8yrs). The average total brain volume of boys with ADHD was found to be 5 percent smaller than that of the control group. The two anterior regions of the corpus collusum, the rostrum and the rostral body, have smaller areas in boys with ADHD compared with the control group[5, 18]. When

compared with controls, ADHD boys were also found to have a smaller right globus pallidus volume, a smaller left caudate volume[19], a smaller right anterior frontal region and a reversal of normal lateral ventricular asymmetry[20]. PET studies have shown that brain activity in adults with ADHD were significantly lower than control groups. The failure to adequately metabolise glucose was also implicated as a direct contributor to ADHD[5]. While these findings support the hypothesis that anatomical and physiological brain abnormalities are the basis of ADHD, no unique brain pattern has been identified. Slight variations of brain size and structure occur normally in the population. ADHD brains still have the same neurological and developmental features as the rest of the population.

Diagnosis

The two main sets of diagnostic criteria for ADHD are the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) from the American Psychiatric Association and the International Classification of Mental and Behavioral Disorders 10th edition (ICD-10) published by the World Health Organisation. The two sources provide similar criteria for diagnosis of ADHD. The DSM-IV subdivides ADHD into three main categories; inattentive type, hyperactive-impulsive type and combined type. According to a recent study, more children meet the DSM-IV criteria for ADHD diagnosis than the ICD-10 criteria[21]. Therefore, children who have ADHD under the DSM-IV criteria may not be diagnosed under the ICD-10 criteria. This study illustrates the fine line in diagnosis and therefore the importance of a thorough examination. Accurate diagnosis of ADHD is dependent on a lengthy and systematic process that rules out other possibilities. The medical practitioner must therefore be cautious and diagnosis should not be hasty.

Inattentive type

In this subtype, inattention is present without impulsivity or hyperactivity. Children with this form of ADHD tend to be slow moving, slow thinking and sluggish in general. They have trouble with sustained concentration during tasks and play activities, resulting in apparent listening problems. Children with ADHD have difficulty paying attention to detail which is integral to schoolwork and other activities involving organisation. They often lose equipment necessary for completion of tasks and appear forgetful[3].

Hyperactivity-impulsive type

Hyperactivity and impulsivity are present in this subtype without inattention. It is characterised by excessive talking and fidgeting. A child with this form may interrupt or intrude frequently and has difficulty waiting for his or her turn. The child has great difficulty controlling immediate reactions and thinking before acting. Teenagers and adults express feelings of internal restlessness and report that they must remain occupied and often try to do several things simultaneously[3].

Combined type

The combined type includes a combination of symptoms from the other two types including inattention, hyperactivity and impulsiveness. It is the most prevalent form of ADHD. The synergy of symptoms results in exponential problems for individuals with this subtype of ADHD[3].

All of these symptoms can mimic childhood behaviours making diagnosis difficult. In order for a child to be diagnosed with ADHD, symptoms must be displayed from one of the ADHD categories before the age of 7. The behaviours must be more severe than those

displayed by children of the same age and must last for at least 6 months. Symptoms should be present both at home and school. No simple medical test exists to detect the presence of ADHD. One tool to aid in diagnosis is the Conners' hyperactivity index, which includes a patient and teacher rating scale. A complete physical and behavioural evaluation is also required for diagnosis to rule out any organic cause. It is also important to rule out the possibility that the behaviour is stress induced such as parental marriage breakdowns, illnesses or any other significant events. Behavioural changes resulting from such traumatic events are not an indication of ADHD. Additionally, children with high IQ's can display characteristics similar to those of ADHD including emotional responses, imagination and resistance to authority[22]. Awareness and thorough investigation of this is necessary to avoid the risk of misdiagnosis.

Many children with ADHD remain undiagnosed and untreated. This is most common in children with the inattentive form of ADHD. They do not show the problems of hyperactivity or impulsiveness associated with the hyperactive-impulsive type. As a consequence, these children are generally better behaved and do not present a problem in school or at home. Research has shown that girls, especially those with the inattentive type of ADHD, are at greater risk of being overlooked. Girls are more likely to become passive and withdrawn, while boys are likely to act out and misbehave[3].

Under DSM-IV criteria, diagnosis with a subtype requires presentation of 6 or more of its specific criteria for at least the past 6 months to a degree that is maladaptive and inconsistent with the developmental level for the childs age. Combined type must meet the criteria for both of the other subtypes. Some hyperactive-impulsive or inattentive symptoms that caused impairment must have been present before age 7 years and must present in two or more settings (e.g., at school and at home). There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning. The symptoms must not be better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder) and do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder or other Psychotic Disorder[23].

The DSM-IV criteria for inattentive type ADHD are: (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities (b) often has difficulty sustaining attention in tasks or play activities (c) often does not seem to listen when spoken to directly (d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions) (e) often has difficulty organizing tasks and activities (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools) (h) is often easily distracted by extraneous stimuli (i) is often forgetful in daily activities[23].

The criteria for hyperactivity-impulsivity type ADHD are**:** (a) often fidgets with hands or feet or squirms in seat (b) often leaves seat in classroom or in other situations in which remaining seated is expected (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) (d) often has difficulty playing or engaging in leisure activities quietly (e) is often "on the go" or often acts as if "driven by a motor"(f) often talks excessively(g) often

blurts out answers before questions have been completed (h) often has difficulty awaiting turn (i) often interrupts or intrudes on others (e.g., butts into conversations or games)[23].

Associated Problems

Longitudinal studies have shown that children with ADHD are more prone to learning, behavioural and emotional problems during childhood and adolescence. Childhood ADHD pre-disposes to specific disadvantages such as less formal schooling (2 years less, on average)[24]. Children diagnosed with ADHD are more likely to fail academically in school despite scoring in the average to above average range on standardised ability tests and achieve a lower occupational status [25].

People with ADHD are more likely to have co-existing or associated psychiatric problems. Studies have shown that about 50-60 percent of children with ADHD also have oppositional defiant disorder (ODD), about 50 percent meet the criteria for conduct or mood disorder, 18% experience depression and 25% have anxiety disorders. The person may have difficulty in various social settings, in particular those where co-occurring conditions are present[5, 26]. Children with ADHD are also more likely to have tics[26], problems with motor co-ordination, psychosocial functioning and sleep[27]. For these reasons, it is accepted that treatment is necessary to manage ADHD and reduce the possibility of adverse outcomes.

Treatments

Many treatments are currently available for ADHD. These treatments consist of three general approaches; pharmacological therapy, behavioural treatment and a combined approach. Over the past decade, numerous scientific studies have examined each treatment to establish which are most effective. Pharmacological treatment has a greater effect on behaviour than counselling, however counselling results in better educational outcomes [28]**.** Results from a large scale study showed that both the pharmacological and combined approaches show a significantly greater improvement in ADHD symptoms than behavioural treatment alone [29]. There is still an ongoing debate as to which drug is the most effective for general ADHD treatment. Since each approach has its strengths and weaknesses, it is prudent for healthcare specialists to decide treatments on a case-by-case basis. The American Academy of Pediatrics (AAP) issued modern clinical practice guidelines for the treatment of school-aged children (six to 12 years) with ADHD in 2001. Clinical guidelines are also being developed by the National Institute of Clinical Excellence (NICE) in the UK for treatment of ADHD [30].

Pharmacological therapy

Stimulants

Stimulant drugs are by far the most popular class of drugs used to treat ADHD in adults and children. They account for about 75% of the medications prescribed for children [31]. Stimulants are the most effective treatment of ADHD, producing significant relief of symptoms in 75 to 90% of children.

Methylphenidate hydrochloride (Ritalin)

Methylphenidate is the most widely used drug for the treatment of ADHD. It provides safe, effective relief from the symptoms of ADHD with improvements in social interactions, academic performance and self-esteem. It decreases impulsivity and hyperactivity while also increasing attention. Methylphenidate is a psychomotor stimulant which has pharmacological similarities to the amphetamines, although the drugs differ in their neurochemical mechanism of action. Methylphenidate appears to enter the brain primarily by passive diffusion. It then enhances dopaminergic transmission in a dual action, augmenting dopamine (DA) release while simultaneously inhibiting dopamine reuptake transporters. This is done with potency comparable to that of cocaine but without activating the reward circuitry that leads to addiction in cocaine users[32].

Analogous to its effects on dopaminergic pathways, methylphenidate is also thought to increase CNS synaptic concentrations of noradrenalin (NA) by inhibiting the NA reuptake transporters[33]. In addition, research has suggested that methylphenidate indirectly increases cortical acetylcholine levels by stimulating cortical dopamine D1 receptors. It is not thought to affect the serotinergic pathways or their transporters. It is postulated that the therapeutic relief provided by methylphenidate is mediated by its effects in the CNS on DA concentrations and to a lesser extent NA concentrations. Methylphenidate also significantly increases the rate of glucose metabolism in the cerebellum and decreases it in the basal ganglia. It has been suggested that the increased metabolism seen in the cerebellum is the result of DA or NA concentration changes [34, 35]. Methylphenidate's activation of cerebello-thalamo frontal circuits may be a contributing factor in its therapeutic effects since the cerebellum plays an important part in higher cognitive functions such as learning, memory and attention[32].

Adverse effects include headache, insomnia, abdominal discomfort, diminished appetite, weight loss and increased nervous behaviours. The majority of these effects are mild and dissipate with cessation of treatment. However, potentially dangerous affects on the heart rate and blood pressure can occur due its action as an agonist at NA post synaptic terminals. Caution must be used in treating patients with coexisting heart conditions. Other contraindications include use with Monoamine Oxidase (MAO) inhibitors since high doses of methylphenidate also inhibit monoamine oxidase, possibly leading to hypertensive crisis. Methylphenidate can also cause a transient increase in intraocular pressure and must be used with caution in patients with glaucoma[32]. As with other psycho-stimulants, 'behavioural rebound' may occur after about 5 hours when the medication effect diminishes leading to increased irritability, over talkativeness, excitability and hyperactivity. However, this rebound can be controlled by administration of a small dose of methylphenidate. Despite previous reports which suggested that stimulants may intensify tics in children with ADHD, a recent study provides evidence that methylphenidate may actually be used to treat these children[36]. Methylphenidate is a controlled substance with potentially addictive properties and therefore constitutes an abuse liability.

The dosage of methylphenidate can vary from about 10 mg/day up to a maximum of 60mg/day. Methylphenidate has a short half life of approximately 2.5-3 hours and therefore is usually taken in two or three doses during the day. The Concerta brand of methylphenidate consists of coated beads that dissolve at different rates to provide a steady response that can last up to 12 hours.

Dextroamphetamine sulphate (Dexedrine)
Dextroamphetamine is another stimulant commonly used for treatment of ADHD. It acts by a mechanism similar to methylphenidate, stimulating DA release and reducing reuptake. Side effects are similar to those of methylphenidate although it may cause a more severe headache[37]. Dextroamphetamine observes the same contraindications as methylphenidate. It has a short half life of 4-6 hours and is taken in two or three daily doses. Dextroamphetamine therapy may be initiated with a dose of 2.5 mg/day and increased to the required level, but may not exceed a maximum dose of 40mg/day in children.

Amphetamine Salts (Adderall)
Adderall is commonly used to treat ADHD. It is a mixture of amphetamine salts consisting of three forms of d-amphetamine and one of 1-amphetamine. Studies have shown that Adderall is at least as effective as methylphenidate at reducing ADHD symptoms and improving academic performance[38]. It is twice as potent, although doses higher than 7.5mg/day do not produce incremental improvement. Its dose range is between 2.5mg/day and a maximum of 40mg/day. Its effects are longer lasting than methylphenidate due to its longer half life of 6 or 7 hours[26]. Similar to methylphenidate, Adderall produces side effects including restlessness, dizziness, headache, insomnia, dryness of the mouth and weight loss. Sudden death has occurred in some patients taking this medication, which has resulted in the suspension of sales in some countries.

Antidepressants
Tricyclic antidepressants (TCA) such as desipramine (Norpramin) and imipramine (Tofranil) are used for the treatment of ADHD when psychostimulant use has proven ineffective. The therapeutic relief provided by TCA's is postulated to be mediated by its CNS inhibition of both serotonin and noradrenalin reuptake which thereby increases their concentration and enhances their transmission. TCA's also stimulate phospholipase C (PLC) and the production of the second messenger inositol 1,4,5-trisphosphate (IP3). PLC activation leads to the activation of diacylglycerol (DAG) and protein kinase C (PKC) production. It is postulated that this pathway modifies the activity of glutamatergic neurons[39].

Studies comparing the efficacy of TCA's with psychostimulants have yielded inconclusive results[40]. They have longer half lives of about 24 hours and can therefore be given once daily. Behavioural rebound is not as problematic with TCA's as with stimulants. TCA's are especially useful when treating children with ADHD and concomitant depression. Side effects of TCA use in children can be substantial and include dry mouth, constipation, decreased appetite, fatigue, headaches, abdominal discomfort, dizziness, insomnia and increased blood pressure. TCA's should not be used concurrently with MAO inhibitors.

Desipramine is the most studied and the most popular TCA used for ADHD. It significantly improves behaviour in doses ranging from 1–3.5 mg/kg/day. The most serious side effect of desipramine and other TCA's is cardiotoxicity, most commonly presenting as sinus tachycardia. It is recommended that children receive an electrocardiogram (ECG) before administration of TCA's, as well as before dose changes.

Bupropion (Wellbutrin) is an antidepressant medication that is used as a second line treatment for ADHD. It affects the noradrenergic and dopaminergic systems and has been shown to ameliorate the symptoms of ADHD. Bupropion has greater efficacy than Pemoline and clonidine but is not as effective as methylphenidate or dextroamphetamine.

Bupropion is given in a daily dosage range of 50-300 mg (3.0 to 6.0 mg/kg/day) as Wellbutrin, although several formulations are available. Side effects include seizure activity in 0.1% of patients prescribed with dosages under 300 mg/day. The risk of seizures are reduced if bupropion is taken in doses over 8 hours apart, medication is slowly titrated upward in dose, sustained release (SR) formulation is used, and the regular formulation is not administered in high doses. Bupropion is contraindicated in patients with epilepsy or eating disorders. Drug interactions are minimal and it does not lead to cardiac conduction delays[41].

Antihypertensive Agents

Clonidine (Catapres) and guanfacine (Tenex) have been shown to be somewhat effective in the management of ADHD. They are central acting alpha2 adrenergic receptor agonists and bind to the presynaptic terminal to produce inhibition of adenylate cyclase and a subsequent decrease in cAMP formation. This results in inhibition of noradrenaline (NA) and acetylcholine (Ach) release.

Clonidine has a dose range of 0.05 mg/day to 0.3 mg/day while guanfacine's dose range is between 0.5 mg/day and 3.2mg/day[42]. Side effects are generally limited and may include sedation, hypotension, headache, dizziness, stomach-ache, nausea, depression and cardiac arrhythmias[43]**.** Patients should have their blood pressure, pulse, liver function tests and ECG closely monitored[44]. Contraindications include use with other antihypertensive drugs such as beta blockers. Also, the drugs should not be abruptly discontinued due to risk of rebound hypertension[26].

New drug treatments - Atomoxetine (Strattera)

Atomoxetine is the first non-stimulant drug approved for use in children, adolescents and adults, for the treatment of ADHD [45, 46]. The American Academy of Child and Adolescent Psychiatry recently approved Atomoxetine as a first line treatment for ADHD[47.] Atomoxetine provides relief of core symptoms of ADHD and also improvements in social and family functioning and self-esteem. Its mechanism of action is the selective inhibition of noradrenalin reuptake through inhibition of the presynaptic NA transporter. Atomoxetine has a low affinity for various receptors, such as cholinergic, serotonergic, adrenergic, and histaminic. The recommended dose is 1.2 mg/kg/day in children and adolescents weighing less than 70 kg and 80mg/day for children, adolescents and adults weighing over 70kg[45]. A single daily dose provides continuous symptom relief throughout the day.

Clinical trials have shown Atomoxetine to be safe and well tolerated in the short term but studies examining long term use are unavailable[45]. Atomoxetine is not a controlled substance and carries a negligible risk of abuse. Adverse effects include appetite loss, stomach ache, headache and nausea. These effects are mostly mild and temporary in nature. Modest increases in heart rate and blood pressure were also reported but steadily decreased after cessation of treatment[48]. Other drugs, such as selective serotonin reuptake inhibitors may increase the blood level of atomoxetine and intensify its actions by competing for the attention of liver enzymes that metabolize it. Overall, atomoxetine represents an important advance in the pharmacological treatment of ADHD.

Discussion

ADHD is caused by a combination of genetic and environmental risk factors. These contribute approximately 75% and 25% respectively to ADHD susceptibility. The presence of certain genetic variations influences brain development in such a way that children with these configurations are more likely to develop inattention, hyperactivity and impulsivity. Environmental factors can exacerbate these behaviours. However, it is not yet known which environmental factor has the most prominent effect on each genetic continuum of ADHD.

Research into the genetic aetiology of ADHD has enhanced understanding of the disorder and resulted in an increased appreciation of the genetics involved. The multifactoral model of ADHD maintains that ADHD cannot be attributed to a single inherited gene, but is a complex disorder caused by a combination of genetic and environmental risk factors. Despite the identification of specific risk factors, their exact contribution and specific interaction have yet to be determined. If an individual's cumulative susceptibility exceeds a certain threshold, he or she will manifest the symptoms of ADHD[9]. In the future, genetics may provide an avenue of very early diagnosis, even before the symptoms of the disorder present. However, more work is required before data can provide a new diagnostic approach for ADHD. A better appreciation of the genetics involved in ADHD susceptibility may allow for the selective use of medications which are more suited to the specific gene and neurobiological differences of each individual with ADHD.

Similarly, brain imaging studies have been useful in providing information on both the structural and functional characteristics of the brains of people with ADHD. Emerging knowledge of the cause and pathophysiology of ADHD is creating an improved understanding of the underlying neural mechanism involved. This should allow for improvements in both diagnostic and treatment strategies[9].

Given the prevalence of ADHD among school aged children, primary care clinicians should have a strategy for diagnosis and long term management of the condition. The practice guidelines issued by the AAP provide a solid framework for the treatment of children with ADHD without major co-morbidity. According to the AAP, physicians should recognise ADHD as a chronic condition, the treatment of which requires partnership with the family, child, teachers, nurses, psychologists and counsellors. The physician must serve as a source of information for the family and child while co-ordinating resources as necessary. As with other chronic conditions, new data may impact upon the treatment of ADHD and physicians should therefore closely monitor the literature. Given that the primary symptoms of ADHD impact the child's performance in various circumstances, the main focus of treatment should be to maximize function. The AAP recommends that treatment plans be tailored for each child to achieve between three and six specific changes such as improvements in relationships, self-esteem and school performance, and a decrease in disruptive behaviours[49].

The AAP guideline recommends methylphenidate or dextroamphetamine (short-, intermediate-, and long-acting formulations) stimulants as the first-line treatment. Based on data indicating that the majority of children who do not respond to one stimulant will respond to an alternate one, the AAP recommends that if one stimulant does not work at the highest feasible dose, the physician should recommend another. Nonstimulant medications do not fall within the scope of the guidelines. The only other medications indicated for ADHD in the guideline are the tricyclic antidepressants (imipramine,

desipramine) and bupropion. Physicians are advised to titrate upward from an initially low dose so as to achieve the highest efficacy with minimal side effects. If adverse effects or no further improvement occurs, a downward titration is recommended. Behavioural therapy has also been advocated as a separate treatment or in addition to medication[49].

Psychoactive medication has consistently proven to be the most effective approach to managing ADHD. A wide range of very effective pharmacological treatments are currently available for the management of the disorder. Stimulants such as methylphenidate and Adderall have proven very capable first line medications for ADHD treatment and are supported by a number of other pharmacological options. Atomoxetine provides a novel non-stimulant ADHD treatment for all ages. It has recently been accepted as a first line treatment and may yet surpass stimulants in terms of use.

The AAP recommends a series of follow up visits with the child to determine if target outcomes have been achieved and whether or not adverse effects exist. Information from parents, the child, teachers, and any other professionals involved can be used for this assessment. In cases where the selected treatment plan for a child with ADHD has not met target outcomes, physicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions[49].

Although the parameters of the disorder are vague and diagnosis can sometimes be difficult, it is very important to identify and treat people with ADHD. With the help of their medical practitioner, most people can find the treatment which is right for them. Successful treatment is paramount to allowing sufferers of ADHD to break free from the constraints of the disorder and fulfil their potential. Research continues to unravel the intricacies of ADHD and may provide scope for the introduction of early behavioural treatments in the future to tackle the disorder before its symptoms even present.

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Statins: the future of Alzheimer's disease treatment?

Florence O'Connell

4th Year Physiology (Medical Moderatorship)

ABSTRACT

Emerging research indicates that the pathological basis of Alzheimer's disease maybe inflammatory in origin, possibly mediated through the pro-inflammatory cytokine, interleukin-1beta. Statins are a class of drugs which reduce circulating lipid levels. There is also evidence that they may have anti-inflammatory properties. This review assesses new evidence that statin therapy may have a role in the treatment of Alzheimer's disease.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common age-related neurological disease. It is responsible for 65-75% of all incidences of dementia (1) and affects 27.7 million people world-wide, costing an estimated $156 Billion annually (2). AD occurs mainly in those over 50 years of age. However in those aged 30-40 a familial form of the disease has been identified, termed *early onset Alzheimer's disease* (EOAD). This inheritable form of the disease is linked to autosomal dominant gene mutations on chromosomes 1, 14 and 21, responsible for coding proteins related to the production of neuritic plaques including, presenilin 2 (PS2), presenilin 1 (PS1) and amyloid precursor protein (APP) respectively (3). However, EOAD accounts for only 2% of all AD cases. The more common sporadic form of the disease, termed *late onset Alzheimer's disease* (LOAD), occurs after the age of 60 years. At 65 years the prevalence of AD is approximately 10%, increasing to 49% by 85 years (4). The aetiological factors involved in AD are complex and multifactorial, encompassing, lifestyle, diet, trauma and genes, including ApoEε4 on chromosome 19
(5).

Pathophysiology of AD

The pathological hallmark of AD is the development of neurofibrillary tangles and senile plaques containing amyloid-β protein (Aβ). These occur throughout much of the neocortex and hippocampus (6). Production of neurofibrillary tangles within neurones is now understood to occur when the microtubule-associated protein, Tau, is converted to a

hyperphosphorylated form. This leads to dissociation and aggregation of Tau within nerve dendrites and axons, resulting in catastrophic loss of microtubular structure (7). There is a growing body of evidence to suggest that this occurs as a result of Aβ protein production. The mechanism by which this may occur is via cyclin-dependant kinases. In post-mitotic cells such as neurones, their importance may be related to their ability to regulate processes in the cell nucleus and in cytoskeletal organisation. Cyclin-dependant kinase 5 (Cdk5) is one such kinase thought to play a role in Tau phosphorylation both constitutively in normal neurons and with increased activity in AD (8). Toxicity of Aβ alters intracellular calcium homeostasis leading to activation of calpains, a family of calcium-dependant proteases. Calpains cleave p35 (Cdk5 activator) to p25, leading to increased activity of Cdk5 which hyperphosphorylates Tau (8). Thus, Aβ is central to the pathophysiological aberration in AD.

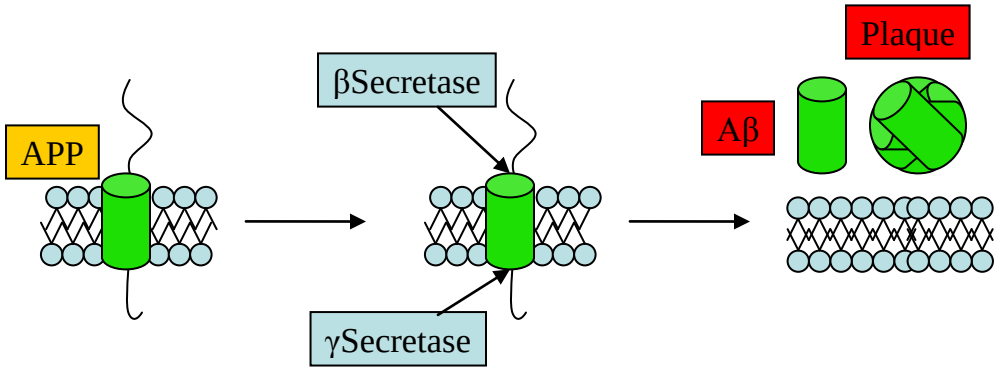

Figure 1. Aβ production results from abnormal clevage of amyloid precursor protein.

Aβ is produced by proteolytic cleavage of the integral membrane glycoprotein amyloid precursor protein (APP) by β- and γ-secretases leading to release of Aβ from the neuronal membrane (Figure 1). Extracellular Aβ aggregates leading to the formation of amyloid plaques. There are a number of mechanisms by which Aβ may exert its neurotoxic effects. One mechanism, which has received much attention in the literature over the last number of years, is inflammation.

Microglia are the major resident immunocompetent cells in the brain. Activated microglia undergo both morphological and secretory changes. Morphological changes include adaptation to an amoeboid appearance and expression of a number of cell surface

proteins including major histocompatability complex type II (9). These proteins confer antigen presenting properties on microglia. Secretory changes include the expression and release of known pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interferon gamma (IFN-γ) (9).

IL-1β is the most studied pro-inflammatory cytokine in the body. It is produced in a biologically inactive, pro-IL-1β form and activated following cleavage by caspase-1 (10). IL-1β is constitutively expressed in the brain at low levels but following an exogenous or endogenous insult there is an increase in production, release and activity of the molecule. Upon binding to the membrane-bound type I IL-1 receptor (IL-1R1) and association with an accessory protein, a complex permitting intracellular signalling is formed (11). Neurones, glia and invading immune cells all express the IL-1R1 and have been shown to increase activity of the mitogen activated protein kinase (MAPK) signalling cascade on binding with IL-1β (11).

Increased expression of IL-1β has been linked with neurodegenerative disorders such as AD (12). Il-1β has been shown to trigger cell death in primary cultures of human fetal neurons (13). Intracerebroventricular injection of Aβ increases the activation of c-Jun N-terminal Kinase (JNK), a MAP kinase, in rat hippocampus. This results in a decrease in cell survival and long-term potentiation, an electrophysiological model of synaptic plasticity and memory. It has been suggested that this decrease in hippocampal plasticity is dependent upon IL-1β-triggered JNK activation (14).

The increasing realisation that inflammation maybe a significant component in AD, may lead to novel therapeutic strategies in the future. Various forms of immunotherapy, including Aβ vaccination, are currently under investigation (15). One of the most promising emerging treatments is the class of lipid-lowering drugs, statins.

Statins

Statins are a class of drugs which inhibit the enzyme, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase. Lovastatin, the first member of this class, was

introduced in 1987. The licensed indication for statin therapy is in the management of hyperlipidemia. The conversion of HMG-CoA to mevalonate via the enzyme HMG-CoA reductase is the rate limiting step in cholesterol synthesis. Statins act by competitively and reversibly binding the dihydroxy heptanoic/heptenoic acid side chain to HMG-CoA reductase on endoplasmic reticulum and peroxisomes, decreasing mevalonate production and thus cholesterol synthesis (Figure 2) (16). This decrease in intracellular cholesterol levels leads to an increase in production and insertion of low-density lipoprotein receptors into the cellular membrane and a decrease in circulating lipid levels. It has been widely shown that statin therapy reduces the 5-year incidence of major coronary events, coronary re-vascularisation, and stroke (17). However, simultaneous inhibition of isoprenoid production may have an anti-inflammatory effect (18).

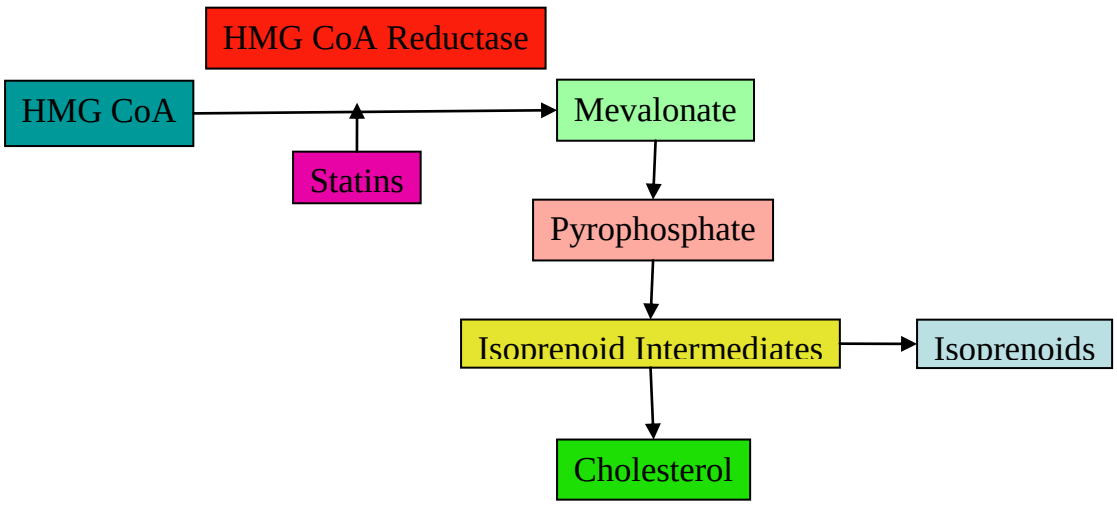

Figure 2: Statins competetively inhibit the enzyme HMG-CoA reductase.

The first indication that stains may have anti-inflammatory properties was a randomised study on cardiac transplant rejection and statin treatment (19). Previous work *in vitro* had shown a decrease in natural killer cell cytotoxicity with statins (20) and the aim of the study was to investigate if this had an application *in vivo*. The results of the study using pravastatin to control post-transplant hypercholesterolemia showed cholesterol-independent effects. These included less frequent cardiac rejection and a decrease in

natural killer cytotoxicity. Coupled with the beneficial effects on cholesterol levels this led to increased survival and lower incidence of coronary vasculopathy (19).

Statin inhibition of mevalonate production also affects the production of isoprenoids. Isoprenoids are critical in the covalent addition of lipid moieties (prenylation) to regulatory proteins (21). Prenylation by the mevalonate products farnesyl diphosphate and geranylgeranyl diphosphate contribute to the regulation of cell signalling and trafficking. The small G-proteins are important substrates of isoprenoid modification, and isoprenylation is critical their role in cytoskeletal rearrangement, cell motility, phagocytosis, intracellular trafficking, transcriptional regulation, cell growth and development (22).

The Rho family of G-proteins regulate the actin-based cytoskeleton with RhoA, Rac and Cdc42 leading to stress fibre, lamellipodia and filopodia formation respectively (23). The Rho family are also important in inflammatory signal transduction cascades with RhoA, Rac and Cdc42 participating in the signalling pathway required for nuclear factor-kappa B (NF-κB) activity leading to cytokine and chemokine release and JNK pathway activation (24). Statin inhibition of isoprenylation is thus one of the many means by which stains are thought to exert an anti-inflammatory effect.

Stains and Alzheimer's Disease

To date, the strongest population-based evidence suggesting a beneficial effect of statins on AD was an observational study published in 2002. A reduction in the incidence of AD by up to 70% was seen in patients receiving statin therapy independent of their lipid-lowering properties (25). Further to this, preliminary results from a pilot proof-of-concept randomised study has shown a cognitive benefit in mild to moderate AD in those receiving 80 milligrams of atorvastatin a day compared to those with AD receiving placebo (26). Several mechanisms have been suggested as to the mechanism of action of statins in AD including, a reduction in brain cholesterol (27), alteration in metabolic enzyme pathways shifting APP cleavage along the β-secretase pathway (28), alteration in the vasculature (5), alteration in the isoprenoid pathway (29) and alteration in

inflammatory pathways (30). Of these theories, isoprenoids and inflammation have received the most attention.

Two papers investigating the role of statin-mediated G-protein inhibition have recently been published. The first attempted to define the mechanism of statin action in AD. In BV-2 mouse microglia cultures and human THP-1 monocyte cell lines it was found that simvastatin inhibited the production of IL-1β following Aβ exposure. To establish if this was cholesterol-dependant, cholesterol levels after statin treatment were measured and shown to be unchanged. Subsequent cholesterol supplementation did not attenuate the simvastatin-mediated reduction of IL-1β (29). It was therefore postulated that blockade of cholesterol biosynthesis does not account for the anti-inflammatory effects of simvastatin. A further hypothesis that lipid intermediates in the cholesterol synthesis pathway may be exerting a pro-inflammatory effect was tested. It was shown that supplementation with these lipid intermediates did not attenuate the anti-inflammatory actions of simvastatin. Using an inhibitor of geranylgeranyl transferase, it was shown that inhibition of isoprenylation attenuates the production of IL-1β following Aβ exposure. This suggests a role for geranylgeranylated proteins such as the Rho family of G-proteins including Rho, Rac and Cdc42. Using a specific clostridial toxin inhibitor of the Rho family of GTPases it was shown that Aβ-induced production of IL-1β was significantly reduced. This is strong evidence for the role of G-proteins in statin-mediated attenuation of AD pathology (29).

The second paper investigated at the mechanisms by which statins may inhibit G-protein function in an effort to delineate altered G-protein regulation and localisation. They report that stain-mediated inhibition of isoprenylation prevented Rho family members from interacting with a negative regulator, the Rho guanine nucleotide dissociation inhibitor (RhoGDI) which lead to an increase in GTP-loaded G-proteins. Lack of isoprenylation also prevented translocation to the plasma membrane thus limiting effector-interaction and decreasing functional signalling, suggesting that the beneficial effects of stains in reducing the risk of AD may arise in part from inhibition of microglia-medicated inflammatory responses (31).

Conclusion

AD is the most common age-related neurological disease. Since it was first described by Alois Alzheimer in 1907 there has been a vast increase in our knowledge of the aetiology and pathophysiology of the disease. With an increasingly elderly population, research has focused on developing treatments that can slow or prevent the progression of AD. One therapeutic strategy that shows particular promise, are statins. These lipid lowering agents are now known to have pleiotropic effects, which may have a role in decreasing the inflammation associated with AD. The beneficial effects of statin treatment on AD appear very promising, although the precise mechanism by which these effects are achieved remain to be elucidated.

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The Aetiology and Management of Gastric Carcinoma in Japan

Satoko Tomiyama

5th Year Medicine

Abstract

With the rapid development of modern technologies, Japan has increased its population's average lifespan to become the longest in the world. Since 1981, its industrial lifestyle has seen cancer as the leading cause of death in Japan, accounting for 31.1% of the total number of deaths in 2004. Gastric cancer ranked first in morbidity until replaced by lung cancer in 1992.[1] However, it still remains an important malignancy with significant geographical, ethnic, cultural, and socioeconomic differences in distribution. Although genetic factors can predispose individuals to contracting the disease, the environment, particularly diet, contributes to between one-third and one-half of all gastric cancers.[2]

There are three distinct approaches to gastric cancer treatment in Japan: endoscopic, surgical and oncological. This article describes the techniques employed in the treatment of gastric cancer in Japanese hospitals in the context of its aetiology.

Introduction

Gastric cancer is the second leading cause of cancer deaths, with Japan having the highest global mortality rate.[3] While the Japanese possess the longest average life span (81 years) in the world, more than 100,000 Japanese are diagnosed with gastric carcinoma each year.[1,4] A definitive carcinogen remains to be identified, but multiple factors have been recognized to contribute towards its pathogenesis. These include a high salt intake, high prevalence of *Helicobacter pylori* infection and atrophic gastritis, low consumption of vitamins A and C, and smoking.

Nearly 500 gastrectomies are carried out at National Cancer Centre Hospital (NCCH) in Tokyo per year.[4] This hospital has a well-reputed gastrointestinal (GI) team subdivided into endoscopic, surgery and medical oncology divisions. This method allows each division to focus their efforts on a specialized task and may offer more treatment modalities than a non-divided GI team.

Pathogenesis

Dietary Considerations

It is well recognized that malignant mutation in gastric cancer occurs over a long period of time. Therefore, it is difficult to separate familial and environmental factors in its pathogenesis. Despite a large number of studies on aetiologic factors, the definitive carcinogens are not yet established. Certain environmental and genetic are associated with increased risk of gastric carcinoma formation. Dietary considerations include high salt and nitrate consumption from food preparation and preservation techniques, low supply of vitamins A and C due to poor consumption of fruit and vegetables, lack of refrigeration and water sanitation, cigarette smoking, and *Helicobacter pylori* infection.[3]

Regional distribution of gastric cancer matches the salt consumption rate within Japan. The Tohoku district, which has the highest salt consumption, also sees the highest incidence of gastric cancer. The colder locale increases the frequency of smoking and salt-curing food preservation methods, exposing its population to saltier foods.[4] Contact with N-nitroso compounds in fertilizers and pickled foods common to the Japanese diet also correlates with an increased risk of gastric cancer.[14] In contrast, green vegetable consumption among Japanese people is low.[4] Diets low in vegetables, fruits, milk and vitamin A have been associated with increased risk for gastric carcinoma,[10] as these foods have a protective effect.[3]

In particular, the antioxidant properties of vitamin C may have a preventative role against damaged caused by *H. pylori*.[10] Although the mechanism of *H. pylori* influence on the progression to gastric carcinoma is unclear, infection increases the incidence of atrophic gastritis, metaplasia and dysplasia. Gastric adenocarcinomas of the stomach body and antrum are profoundly associated with *H. pylori* infection. The bacteria is present in approximately eighty percent of Japan's population.[3]

The influence of the Japanese diet in relation to gastric cancer incidence is supported by a number of migration studies. Emigration to geographically lower-risk areas decreased the risk of gastric cancer to a level halfway between that of Western and Japanese values.[3] The incidence rates of Japanese living in Hawaii are 24.3 and 11.1 in males and females, respectively.[7] While these rates are one-third of those found in the Japanese population, they are nonetheless three times the risk of the American Caucasian population.[2] The incidence of gastric cancer is also high in second-generation offspring who continue to consume a Japanese-style diet, whereas low in those who adopted a Westernized diet.[3] The mortality rate of subsequent generations born in the US continues to decline towards the lower rate of US Caucasians.[8]

Genetic Polymorphisms

Although a genetic predisposition to gastric carcinoma has been frequently confirmed,[15] the mechanisms by which genes exert their influence are not well-understood. Certain factors include Type A blood, pernicious anaemia and family history.[3] A familial risk for chronic atrophic gastritis, which is a precursor for gastric carcinoma, has been associated with a number of cases.[16] Gastric carcinoma has been associated with certain hereditary syndromes: hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome.[10]

DO A REFERENCE CHECK! ENGLISH TOO GOOD?

The interleukin 1 beta (IL-1beta) gene has been postulated as a candidate gene which may affect the clinical consequences of *H. pylori* infection. It is upregulated by infection, is strongly pro-inflammatory, and is the most potent acid inhibitor known.[19] Certain polymorphisms of the IL-1beta gene (carriers of IL-1B-551 *T) and the IL-1 receptor antagonist gene (IL-1RN*2/*2) have been associated with a high risk of gastric carcinoma. Host genetic factors that influence IL-1beta may determine why some individuals infected with *H pylori* develop gastric carcinoma while others do not.[17]

Treatment Methods

Endoscopic Mucosal Resection (EMR)

Endoscopic Mucosal Resection (EMR) is an endoscopic alternative to invasive surgery for early gastric cancer (EGC). EGC is defined as a cancerous lesion confined to the mucosa or submucosa regardless of the presence of perigastriac lymph node metastases (LNM).[19]

Japanese people are now aware of the high incidence of gastric tumours. Most cases are discovered incidentally through routine screenings using oesophagogastroduodenoscopy during annual checkups. While mass-screening programmes using barium meal ingestion may be performed, Gotoda mentions that only 10% of gastric carcinomas are detected by this method. More than 50% of all gastric cancers identified in Japan are EGC, versus 5% or less in the West.[19] For EGC, it is more sensible to offer a local treatment rather than radical surgery in terms of high risk of complications and poor quality of life following the operation.[19] EMR, therefore, has become more widely used

in recent decades.

The original criteria for tumours amenable to EMR include elevated lesions less than 2 cm in size, depressed lesions less than 1 cm in size with no ulceration, and well-differentiated lesions. It must be emphasised that EMR can be performed only when the possibility of LNM has been excluded.[19]. The presence of LNM plays an important role in patient prognosis, and accurate histological assessment is required prior to the procedure.[5] However, it can be difficult to define the degree of mucosal invasion. In fact, 20 percent of pre-treatment diagnoses are incorrect. Overall, 5-year survival for EMR is similar to the outcome with more invasive gastrectomy.[19] With EMR, the recurrence rate is 4.2%, requiring repeat mucosectomy; however, the cumulative cure rate is between 90 and 100%.[5]

Fig. 1 Schematic drawing of the strip biopsy of EMR. **(a,b)** The lesion is identified and saline is injected into the submucosal flat to elevate the tumour. **(c)** The snare is placed around the lesion, which is elevated by use of the grasping forceps. **(d)** The snare is tightened around the base producing a polyp, which is removed with diathermy.[22]

FIG 2 (Credit: Gotoda)

Endoscopic Submucosal Dissection (ESD)

Another endoscopic procedure has been introduced into the NCCH called 'endoscopic submucosal dissection (ESD),' which utilizes an insulation-tipped (IT) needle knife. ESD enables larger en-bloc resection than EMR, and is associated with fewer local recurrences. It also offers precise and complete histological assessment.[23] It is especially beneficial for performing one-piece resection and lowering recurrence rate. ESD operations use an IT knife, hook knife and flex knife, followed by marking, injection, pre-incision, mucosal cutting, submucosal dissection and endoscopic management for complications.[19,23]

Fig 3: Mucosal cutting and Submucosal dissection using IT knife
ICC 200; Endocut 80W effect 3, VIO 300D; Dry cut 50W effect 4 (Credit: Gotoda)

Surgery

At NCCH nearly 500 patients undergo gastrectomies each year. Gastrectomy with

extended lymph node dissection (D2 gastrectomy) has been the gold standard of surgery in Japan. More than two-thirds of the stomach is usually dissected, with over 25% of operable gastric cancers accompanied by seven to fifteen LNM.[24] Japanese doctors number the lymph nodes surrounding the GI tract into 16 groups in order to identify the LNM more efficiently.

Fig 4

CUT THIS OUT? DO WE REALLY NEED AN EXPLANATION OF TNM INCLUDED?

A modified TNM classification is commonly used for gastric carcinoma in Japan. T categories demonstrate the areas into which tumours invade, N categories indicate the numbers of lymph nodes involved, M1 shows metastasis to other organs, H1 demonstrates hepatic metastasis, P1 is peritoneal dissemination and CY1 indicates the presence of cancerous cells. T1 denotes invasion to the lamina propria and submucosa, T2 to the muscularis propria and submucosa, T3 involves penetration into the serosa, and T4 indicates invasion into adjacent structures. Nodal involvement is broken into subgroups N0 for no lymph node involvement, N1 for 1-6 nodes involved, N2 for 7-15 involved, and N3 for greater than 15 affected. [26]

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Table 1 Stage Grouping for Gastric Cancer

	N0	**N1**	**N2**	**N3**
T1	Ia	Ib	II	IV
T2	Ib	II	IIIa	IV
T3	II	IIIa	IIIb	IV
T4	IIIa	IIIb	IV	IV
H1,M1 P1, CY1	IV	IV	IV	IV

Source: Japanese Classification of Gastric Carcinoma (1999)

CUT GRAPH OUT?

Although there are no significant long-term survival differences between limited LN dissection (D1) and extended LN dissection (D2) in Europe, it should be considered that the skills and experience of doctors may vary. Comparison studies reveal that the

hospital mortality rate of patients under 70 years old is 5.9% in the Netherlands, versus 0.8% in Japan.

Table 2 Survival rates (%) of Stomach cancer at the National Cancer Center Hospital (1990 ~ 1994)

Stage	No. of cases	1-year	2-year	3-year	4-year	5-year
I	757	97.9	96.8	94.3	92.6	91.2
II	122	95.7	90.4	86.1	82.7	80.9
III	187	84.5	66.3	61.3	56.0	54.7
IV	224	55.2	26.8	15.7	9.4	9.4
Total	1,290	88.3	79.7	75.5	72.6	71.4

Source: Gastric Cancer Research Group, National Cancer Centre Hospital (new cases admitted during 1990-4)[26]

From the latest statistics at the NCCH provided in Table 2, D2 gastrectomy has provided good therapeutic outcome for patients with EGC, especially in those contracting Stage I or II stomach cancers.[26] The overall 5-year survival rate is 96%, and the surgery mortality rate less than 2%.[24] This suggests that good prognosis using this method has been achieved.

Chemotherapy

Approximately 49,500 patients with gastric carcinoma die yearly in Japan.[1] Some may have suffered a relapse gastric carcinoma after successful surgery, with or without metastases into adjacent organs. Others may have had an aggressive gastric carcinoma which invaded other organs (Stage IV). For these advanced gastric cancers (AGC), the surgical approach is of little or no benefit, and curative treatment becomes impossible. Only chemotherapy can improve patients' quality of life and prolong survival.

Chemotherapy is a systemic treatment which targets not only cancer cells but normal cells as well.[28] Adverse effects include nausea, vomiting, diarrhoea, fatigue, alopecia, numbness and pigmentation in the extremities, anaemia, leukopenia and increased fragility of the nails. Randomly controlled trials comparing the benefits of chemotherapy and supportive palliative care have shown a significant difference in the

median survival time (MST) to be 6-9 months versus 3-4 months respectively.[28]

The development of new agents and different drug combination regimens has brought about major improvements to the treatment of AGC in the last decade. However, no universal "gold standard" currently exists. Single use of chemotherapeutic agents (e.g. 5-FU (fluorouracil), mitomycine C, CDDP (cisplatin), irrinotecan (CPT-11), docetaxel, paclitaxel, tegafur/ uracil, 5'-doxifluridine, and S-1) and combinations of these agents (i.e. 5-FU + CDDP, methotrexate (MTX) and 5-FU + leucovorin, 5-FU + l-leucovorin (l-LV), and irrinotecan + CDDP) are widely used throughout the world. FAMTX (5-FU+ ADM + MTX) are most commonly used in Western countries.[28] S-1 has become one of the standard agents for AGC in Japan, where it was initially developed. S-1 is a novel oral fluoropyrimidine derivative, in which the oral 5-FU prodrug, tegafur, is combined with two 5-FU modulating substances - gimeracil (5-chloro-2,4-dihydropyridine) and oteracil (potassium oxonate) at a molar ratio of 1: 0.4: 1. It was designed to improve antineoplastic activity while reducing side effects, particularly GI disturbance.[31] As it is the very first oral alternative to the conventional intravenous administration of 5-FU, a large number of studies have been performed. The MST of S-1 is 7-8 months, which is comparable to that of 5-FU, and its response rate (RR) reaches 50%.[24]

Combination therapies improve the chances of survival in comparison to use of the single-agent 5-FU.[29] A combination of 5-FU + anthracyclines + CDDP achieves the best survival rates. In particular, the ECF combination (epirubicin + CDDP + continuous infusion of 5-FU) is tolerated best by patients.[29] Thus, ECF therapy has been recommended as a new standard regimen in Europe.[28] In the USA, there is also a shift towards using DCF (docetaxel + CDDP + 5-FU) as a new standard of chemotherapy.[30] In contrast, a randomized phase III trial of combination 5-FU + CDDP (FP) therapy versus 5-FU alone was carried out by the Japan Clinical Oncology Group (JCOG), and found in favour of treatment with 5-FU alone.[30] The JCOG study concludes that 5-FU alone should remain as a standard treatment for advanced gastric carcinoma .[32] However, the results of emerging studies may suggest new gold standard chemotherapy regimens for AGC treatment in Japan.

Conclusion

With the improvement of conventional therapy and the development of new therapies, the mortality rate of gastric cancer has gradually decreased over the last decade. This is

mainly due to a decrease in incidence, not a favourable change in curability rates.[31] The high incidence in Japan may be related to several environmental factors, including high consumption of salt, *H. Pylori* infection, cigarette smoking, family history, and low intake of ascorbic acid, carotene and vitamin E. Therefore, it has been postulated that ascorbic acid supplementation or eradication of *H Pylori* infection may reduce the risk of developing gastric carcinoma.[10] Migration studies also indicate that environmental factors play an important role in the aetiology of gastric carcinoma.[2,3]

There are three distinct approaches to gastric cancer in Japan: endoscopic mucosal resection and endoscopic submucosal dissection, D2 gastrectomy and chemotherapy. The surgical procedures for early gastric carcinoma result in good survival rates. However, mean survival time for advanced gastric carcinoma treated with chemotherapy is low, at 6-9 months on average and 9-11 months at longest.[24] Chemotherapy agent used in Japan, S-1, has the advantage of being safely administered orally, with a moderate response similar to that of 5-FU.[28,30] It should be considered that the efficacy of the drug may vary depending on ethnic origin. The toxicity profile of Caucasian patients with gastric cancer differs from Japanese patients, and Caucasians present with more diarrhoea and hand-foot syndromes, but less myelotoxicity.[31] These highlight the need for further global studies regarding treatment approaches towards gastric cancer.

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The Changing Pattern of Homicide in Ireland

Bernadette Brady and Lindsey Clarke
6th year Medicine

ABSTRACT
Objective: To study the pattern of homicides (encompassing both murder and manslaughter) in the Republic of Ireland in the years 1994 and 2004. **Methods:** Data was obtained from the Office of the State Pathologist, the Technical Bureau of An Garda Siochána and the Central Statistics Office. **Results:** Approximately three-quarters of victims were found to be male in both 1994 and 2004. In 1994, 100% of victims were of Irish nationality compared with 85% of Irish nationality in 2004. 16 of 24 total homicides in 1994 were in County Dublin, with 21 of 45 total homicides taking place in the same county in 2004. Gunshot wounds accounted for 8 of a total 24 deaths by homicide in 1994, while blunt force trauma and stab wound(s) each accounted for 10 of a total 45 deaths by homicide in 2004. **Conclusion:** The proportion of male homicide victims has remained stable over the 1994 to 2004 period, while the percentage of non-Irish homicide victims has risen by 15%. Dublin was the county with the most homicides in both 1994 and 2004. The primary mode of homicide changed from gunshot in 1994 to lone blunt force trauma *and* lone stab wound(s) in 2004.

INTRODUCTION
Modes of homicide can be broadly divided into a number of categories: gun shot, stab wound, blunt force trauma (BFT), road traffic accident and asphyxiation. "Murder" includes the intent to kill or cause harm, while "manslaughter" defines death which follows an unlawful act, provocation or gross negligence without intent to cause harm.

The severity of wounds caused by gunshots varies with type of weapon used, as well as the distance between the victim and the discharging weapon. Entry wound, internal injury and exit wound all contribute to the morbidity associated with gunshot deaths. Stab wounds may be caused by any object that penetrates the skin, with knives being the most common cause of these wounds. Death may be caused by a single fatal wound or by a multitude of smaller wounds and wounds may be 'perforating' or 'penetrating'. Blunt force trauma can cause death in a number of ways, for example by fracturing bones. The cause of death in these cases is also dependent on the site of the trauma. For example, trauma to the head can fracture the skull and cause brain injury while trauma to the chest can fracture ribs, tear the aorta, directly damage the heart or cause lung injury, such as pneumothorax or contusions to the lung tissue.

METHODOLOGY
Data was sourced for this study from post-mortem files held by the Office of the State Pathologist of cases of culpable homicides for the years 1994 and 2004. All victims of murder and manslaughter in the years 1994 and 2004 were included. Those who died by suicide or by accidental and natural causes were excluded. Data collected included victim's gender, age, time of death, time of body discovery, nationality, mode of homicide, place of death, medical interventions, toxicology results and file number. Additional data from the Technical Bureau of An Garda Siochána was collected in cases when the post-mortem was not carried out by the State Pathologist or the Deputy. This process was supervised and assisted by the State Pathologist and the Deputy State Pathologist.

RESULTS

Gender & Nationality of Victims

A total of twenty-seven homicides were committed in 1994, of which twenty (74%) of the victims were male and seven (26%) were female. In 2004, there were forty-five homicides, of which thirty-four victims (76%) were male and eleven (24%) of the victims were female (Figure 1).

(A) **(B)**

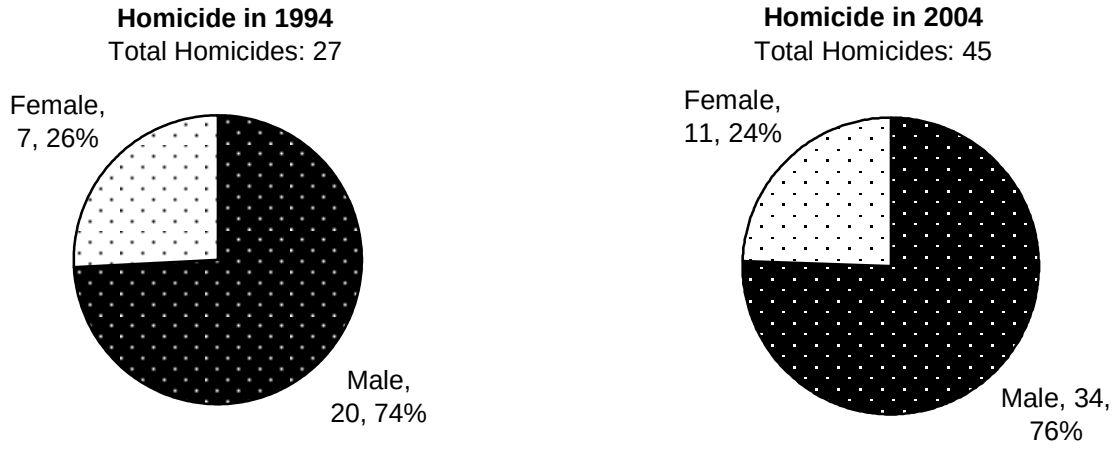

Figure 1: Ratio of male to female homicides in (A) 1994 and (B) 2004

It is clear that while the overall number of homicides has increased by two-thirds during the ten-year period, the proportion of male to female victims has remained similar. The first and most striking disparity between the two years must be the nationality of the victims. In 1994, all twenty-seven victims were Irish but in 2004, four of the forty-five victims were Lithuanian and the remaining three victims Malawian, Croatian and Slovakian. As yet there are no official figures on the changing demographics in Ireland or the increased number of foreign nationals in the country for comparison with the ethnic origin of victims.

Geographical Distribution of Homicides in Ireland

A larger proportion of homicides took place outside Dublin in 2004; using figures from the Central Statistics Office, incidence of homicide by region was compared with regional population

Table 1: Breakdown of homicide in 2004 by region.

	Total	Border	Dublin	Mid-East	Midland	Mid-West	South-East	South-West	West
POPULATION	4,043,800	448,100 11%	1,144,400 27%	437,300 11%	236,800 6%	345,400 9%	440,400 11%	597,100 15%	394,300 10%

HOMICIDE	45	7 16%	21 46%	3 7%	0 0%	7 16%	6 13%	0 0%	1 2%

46% of total homicides were committed in Dublin in 2004. The remaining 54% were spread over twelve counties. However, this does not take population density into account. The population of Dublin in 2004 was 1,144,400, or 27% of the total population of Ireland. This figure is comparable with the population of 1,037,500, or 26%, in the south of the country which comprises Cork, Kerry, Carlow, Kilkenny, Waterford, Wexford and Tipperary South. 6 homicides, or 13% of the total, were committed in this much larger region. In spite of the overall increase in the homicide rate in the rest of the country since 1994, almost half of the homicides that took place in Ireland in 2004 occurred in the capital city.

Statistics from An Garda Siochána from 2002, showed that the murder rate in North Central Dublin was 79/million population.[1] As seen in the figure below, many counties end most years homicide free.

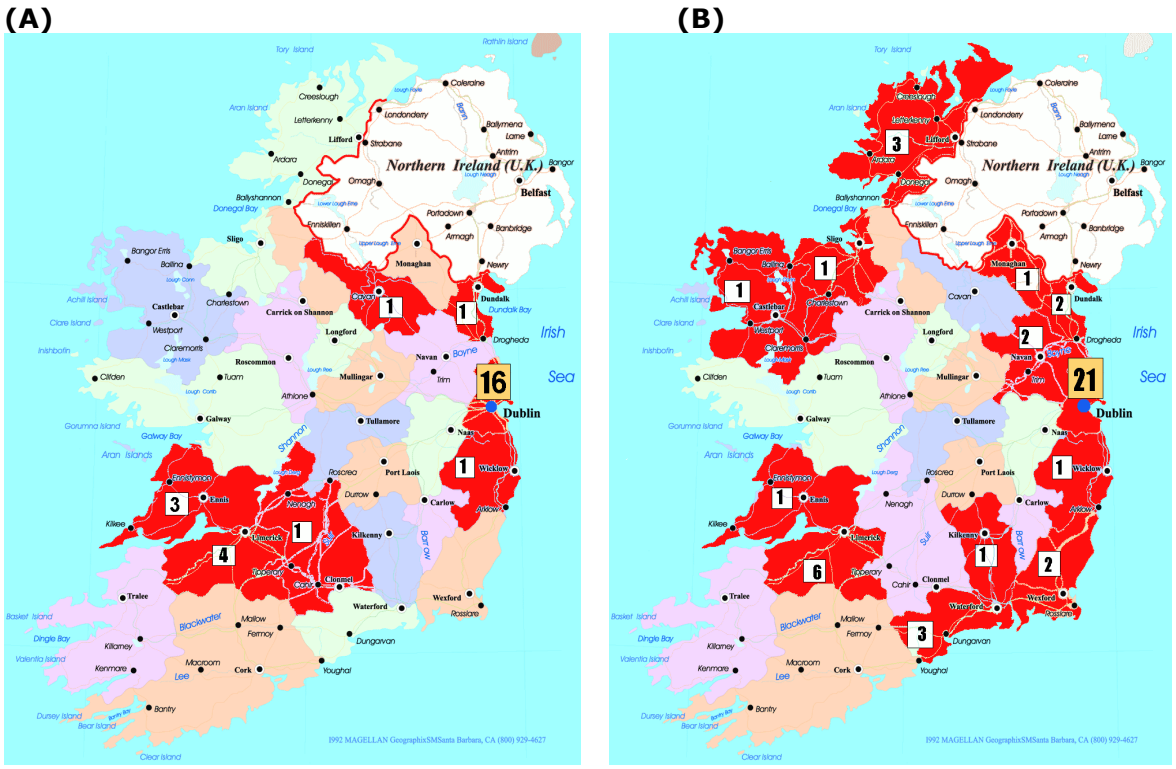

Figure 2: Geographical distribution of homicides in the Republic of Ireland[2] in (A) 1994 and (B) 2004

Circumstances of Homicide

In 1994, 29% of the cases studied were caused solely by gunshot wounds, 26% due to stab wounds and 15% due to blunt force trauma. Two deaths (7% of total) were caused by road traffic incidents (i.e. 'hit and run' type incidents) and one death involved asphyxiation. One death was caused by a combination of stabbing and blunt force trauma and one death was due to stabbing and asphyxiation. Two of the homicides in 1994 fell under the category of 'other', one from a myocardial infarction induced by an altercation and the other due to an explosive device.

20% of homicides in 2004 were caused solely by gunshot wounds while 23% were due to stab wounds and 24% to blunt force trauma. 11% of deaths studied were caused by road traffic incidents. 4% of deaths were caused by asphyxiation (i.e. strangulation) and one death from decapitation fell under the category of 'other.'

A number of the cases studied shared two contributing causes of death; one death was caused by both gunshot and blunt force trauma while another was due to both a stab wound and asphyxiation. Three deaths were caused by a combination of stabbing and blunt force trauma and a further three deaths were due to blunt force trauma together with asphyxiation.

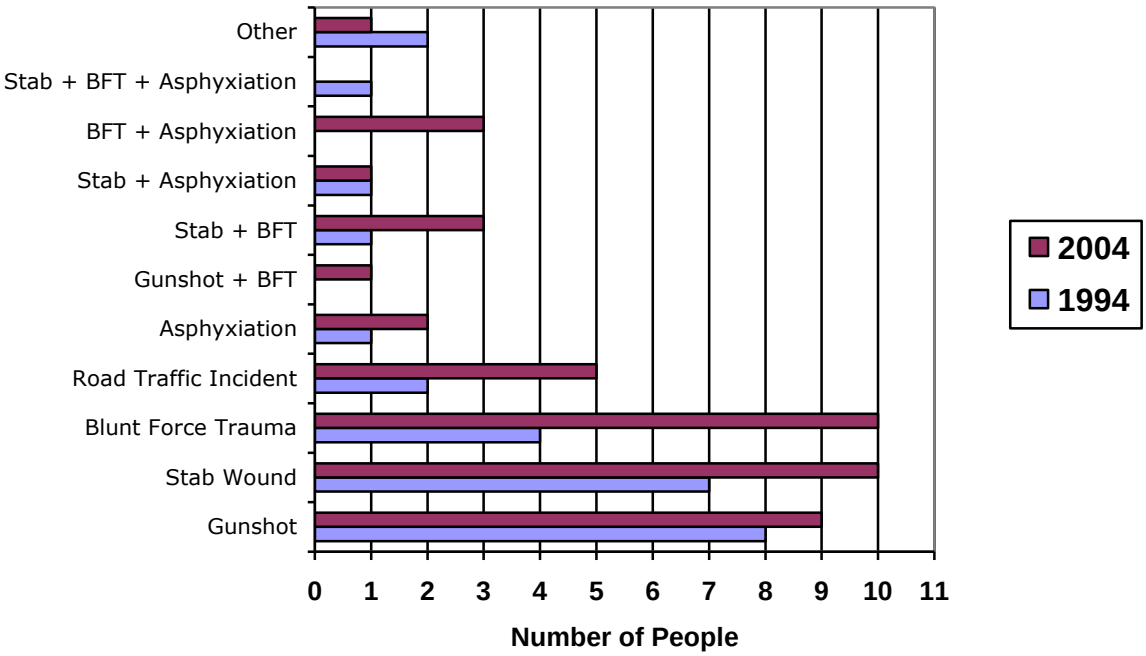

Figure 3: Comparision of modes of homicide in 1994 and 2004

DISCUSSION

The estimated population in Ireland in July 1994 was 3,539,296, while it was 4,043,800 in April 2004, an increase of 14%.[3] This indicates that the overall rate of homicide, having increased by 66%, shows a far greater growth in proportion to the rate of population growth. While the incidence of female homicide has remained relatively constant at 25% during this ten-year period, it should be noted that the proportion of female homicide victims has, in fact, fallen over the last half-century. In the 1950s, about one in three homicide victims was female; in the early twenty-first century, this figure has dropped to one in four.[1]

Also of interest is the role of alcohol in violent crimes. Evidence would suggest that alcohol now plays a substantial role in the increasing numbers of homicides in Ireland.[1] This study revealed that alcohol was found in the bloodstream of 55% of the homicide victims of 1994 and 37% of victims in 2004 but the amounts varied from victim to victim and the influence of alcohol in each individual case is

difficult to quantify without medical evidence and witness reports. It must be noted that blood samples taken for toxicology screening are not always suitable and, in those instances when the victim survives in hospital after the initial attack, blood results would not be accurate due to medical treatment such as blood transfusions and pharmacological interventions.

It is suggested that the new affluence of the Irish community has contributed to the formation of a more violent community. Contributing factors to the increase in violent crimes include: changes in reporting and recording crimes, the rise in alcohol consumption, drug trade, increasing *anomie*, relative economic success and migration patterns. These factors do not carry equal weight, are not independent of one another, and do not constitute a complete list. "For example, the improved economic situation has generated substantial inward migration and allowed increased levels of alcohol consumption. These in turn have impacted on routine activities and opportunities for violence."[1]

In the light of current concerns over the possession of fire-arms, it is interesting to note that the proportion of gun-involved homicides has actually decreased from 29% to 22% but, in keeping with the overall increase in total number of homicides, the actual number of gun-shot homicides has increased. The proportion of stabbings has also decreased but the proportion of blunt force trauma deaths has increased by 9%.

Stab-related homicides are notably high in the southwest, specifically Limerick. In 1994, 4 homicides took place in Limerick city and county, of which 3 (75%) were stabbings. The country-wide proportion of homicide due to stab wounds is markedly less at 26%. In 2004, this proportion has fallen to 43% (3 stabbings in 7 homicides). This is still far greater than the number of stabbings in the country as a whole (23%). However, in order to put these findings into perspective, a wider audit of violent crime would need to be performed to assess the incidence of non-fatal stabbings in the country.

CONCLUSIONS

This study clearly demonstrates that violent crime is increasing in Ireland. Dublin remains the area with the highest rate of homicide, and examination of homicide method shows a higher rate of blunt force trauma and asphyxiation. The proportion of male to female homicide victims has remained much the same over the past ten years but there has been a shift in the nationality of victims, with an increase in the number of foreign nationals being unlawfully killed in the Republic of Ireland.

Acknowledgement

With thanks to Dr. AN Other, Office of the State Pathologist.

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The Extent and Implications of Poly-drug Use in Ireland

Diana Hogan-Murphy
4th year Pharmacy

Abstract

The phenomenon of poly-drug use is prevalent in Ireland. Statistics from the National Drug Treatment Reporting System show that this behaviour is increasing, from 5590 cases treated in 1998 to 7845 cases treated in 2002. The most frequent combinations include: heroin and cannabis when two drugs are implicated; heroin, methadone and benzodiazepines when three drugs are involved; and heroin, methadone, benzodiazepines and cannabis when four drugs are consumed. Opiate-related deaths account for the largest proportion of fatalities amongst drug users, with most of the deaths attributable to consumption of heroin in combination with benzodiazepines, alcohol, methadone and cocaine. There is a significant problem of driving under the influence of drugs in Ireland. Results of a nationwide survey carried out by the Medical Bureau of Road Safety demonstrates that there is a strong trend of increasing positive drug tests with decreasing levels of alcohol, 68% of drivers with blood alcohol concentrations below the legal limit were positive for one or more drugs. There is a need for treatment services dealing with poly-drug use as services in Ireland remain focussed on individual drugs of abuse.

Introduction

The World Health Organisation (WHO) defines poly-drug or multiple drug use as,
"The use of more than one drug or type of drug by an individual, often at the same time or sequentially, and usually with the intention of enhancing, potentiating, or counteracting the effects of another drug. The term is also used more loosely, to include the unconnected use of two or more drugs by the same person. It carries the connotation of illicit use, although alcohol, nicotine, and caffeine are the substances most frequently taken simultaneously in developed societies." [1]

The phenomenon of poly-drug use in Ireland has been severely under-investigated, despite increased attention on drug misuse issues, and no report has been published which deals specifically with poly-drug consumption at a national level. Compared to their exclusive drug or alcohol using counterparts, poly-drug users are more likely to consume greater quantities of drugs, exhibit more symptoms of psychopathology, and are more prone to act aggressively, to engage in acts of domestic violence or other criminal conduct.[2] Poly-drug use in Ireland is not an emerging practice. It was demonstrated in the earliest prevalence studies of opiate use in Ireland in the early 1980's, and as illustrated in Table 1, continues to be a significant problem amongst individuals in drug treatment programmes.

Table 1: Studies of Poly-drug use in Ireland

Author	Sample Source	Data Collection	Definition of Poly-drug Use	Evidence of Poly-drug Use
Carr et al (1980)[3]	Treatment centre (n=100)	Interviews	Use of ≥2 drugs in last month excluding opiates	25% reported poly-drug use in the last month
Bradshaw (1983)[4]	Opiate users in the community (n=82)	Interviews	Lifetime usage	Almost 75% use heroin & other drugs
Dean et al (1984)[5]	Opiate users in the community (n=36)	Interviews	Drug usage in 12 months prior to interview	92% using heroin, cannabis & others
Lavelle (1985)[6]	Opiate users in the community (n=74)	Interviews	Lifetime usage	33% report daily use of heroin & methadone
Keogh (1997)[2]	Garda records (n=352)	Garda interviews	Lifetime usage	96% report heroin use: 35% use methadone,33% use cannabis, 20% use ecstasy & 13% use cocaine in addition to heroin
Cassin et al (1998)[7]	Health Promotion Unit (n=770)	Self report questionnaire	Drug use in previous month	67.4% < 25 years & 63.5% > 25 years reported poly-drug use (individual drugs not specified)
Centre for Health	Irish prisons	Self report	Drug use in previous 3	63% of males & 83% of females used cannabis plus other

Promotion Studies (2000)[8]	(n=777)	questionnaire	months Drug use in previous 12 months	drugs 47% of males & 52% of females used amphetamines plus heroin

Prevalence & Combinational Poly-drug Use

Drug treatment data is observed as an indicator of drug misuse and of demand for treatment services. The prevalence of poly-drug use in Ireland can be identified using The National Drug Treatment Reporting System (NDTRS), an epidemiological database monitoring treated problem drug use. This data is used at national and European levels to provide information about the features of clients entering treatment and patterns of drug misuse; formulations of drugs used and consumption behaviours. Information about the types of drugs consumed is central to developing individualised treatment plans for drug detoxification.

Statistics from the NDTRS shows that poly-drug use in Ireland is increasing, 5590 cases were treated in 1998 compared with 7845 cases in 2002.[9] Between 1998 and 2002, 33,391 cases of drug misuse were treated in Ireland. Of these, 28% reported problem use of one drug, 32% reported problem use of two drugs, 26% reported problems with three drugs and 15% reported problems with four or more drugs. Where an opiate was the main problem drug, the most common additional problem drug was cannabis, followed by benzodiazepines, other opiates and then cocaine; whereas when cannabis was the main drug of abuse, the most common additional drug were ecstasy, followed by alcohol and then amphetamines.[9]

Where two drugs only were reported as being used on a daily basis (Table 2), heroin and cannabis, and heroin and benzodiazepines were the most common combinations, accounting for 45% of all two drug combinations. A further 15% used a daily methadone and benzodiazepine combination.

Table 2: *The combinations of drugs used by all treatment contacts reporting daily use of two drugs only in the month prior to treatment, reported to the NDTRS (1999)[9]*

Drug Combination (2 drugs only)	N (%)
Heroin + Cannabis	174 (23.5)
Heroin + BZN's	159 (21.5)
Methadone + BZN's	108 (14.6)
Heroin + Methadone	85 (11.5)
Heroin + Cocaine	34 (4.6)
Other Combinations	180 (24.3)
Total	740 (100)

BZN = Benzodiazepine

Where three drugs only were reported as being used on a daily basis (Table 3), heroin, methadone and benzodiazepines was the most common combination, accounting for over 31% of reports. A daily heroin, benzodiazepine and cannabis combination was used by a further 16.5 %.

Table 3: *The combinations of drugs used by all treatment contacts reporting daily use of three drugs only in the month prior to treatment, reported to the NDTRS[9]*

Drug Combination (3 drugs only)	N(%)
Heroin + Methadone + BZN's	59 (31.4)
Heroin + BZN's + Cannabis	31 (16.5)
Heroin+Methadone + Cannabis	13 (6.9)
Methadone + BZN's + Cocaine	9 (4.8)
Methadone+ BZN's + Cannabis	6 (3.2)
Other Combinations	70 (37.2)
Total	188 (100)

BZN = Benzodiazepine

Where four drugs only were being taken on a daily basis the most common combination of drugs used was heroin, methadone, benzodiazepine and cannabis. A total of 7 (25%) of the 28 treatment contacts using four drugs daily used this combination.[9]

Of the treated cases reporting problem use of more than one drug in addition to heroin, the order of additional drugs ranked from most to least common remained similar between 1998 and 2000, namely: benzodiazepines, cannabis, opiates, ecstasy, cocaine and alcohol.[9] In 2001 and 2002, the status changed, with cannabis replacing benzodiazepines as the most common drug, while cocaine moved from fifth most common to third most common in 2002.[9]

Concurrent opiate and benzodiazepine use is a common practice amongst drug-users (Table 5). The combination of these two drugs may have implications for the efficacy of opiate treatment programmes. If opiate dependence is treated in isolation, while co-existing benzodiazepine dependence is neglected, the potential exists for drug specific treatment programmes, such as methadone maintenance, to be undermined. It is important that all aspects of poly-drug abuse are targeted to maximise benefit to the individual.

Table 4: *The combination of heroin and benzodiazepines amongst drug using individuals in Ireland*

Author	Sample Source	Data Collection	Definition of poly-drug use	Combination
Rooney et al (1998)[10]	Treatment Centre (n=63)	Interviews and urine analysis	Lifetime usage	34% of sample tested positive for opiate and benzodiazepine use
Browne et al (1998)[11]	Treatment Centre (n=107)	Urine/analysis	Drug use in 30 days prior to test	45% tested positive for using benzodiazepines while using methadone
Farrell (2000)[12]	Treatment Centres (n=18142)	Urine/analysis	Drug use in 30 days prior to test	65% tested positive for benzodiazepine use while taking methadone

Drug-related Fatalities

Drug-related deaths and deaths among drug users are indicators of the consequences of problem drug use in Ireland. Mortality trends facilitate monitoring of the impact of drug treatment programmes and drug prevention and harm reduction strategies. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) identified drug-related deaths and deaths among drug users as one of the five key indicators of drug misuse in Europe.[13] At present, it is difficult to ascertain the exact number of deaths among drug users in Ireland, the best estimate for Dublin ranges between 60 and 90 fatalities per annum.[14] However, it has been suggested that these figures may underestimate the extent of the problem.[14]
Opiate-related deaths account for the largest proportion of deaths among drug users in Ireland. Results of toxicological analyses of fatal and non-fatal overdoses associated with illegal drug use are not widely available, but those that are, consistently reveal that the majority of deaths are associated with heroin use in combination with other drugs.[14] The probable mode of death is respiratory depression. Opiates depress the respiratory control centre, reducing its sensitivity to carbon dioxide and oxygen, resulting in hypoxia and subsequent cardiac arrest. Benzodiazepines, alcohol, methadone and cocaine are the substances most frequently found in combination with opiates.[15] These centrally-acting agents enhance the respiratory depressant effects of opiates, thereby increasing the likelihood of an adverse outcome.

A review by Byrne of the files on drug and alcohol related deaths investigated by the Dublin City coroner in 1998[16] revealed that of the 520 inquests held in that year, drugs or alcohol were implicated in 108 of these. After exclusion of cases which were deemed to be primarily alcohol related (28), and suicides or possible suicides (10), a cohort of 70 remained that were believed to be exclusively drug related deaths. The majority of these deaths occurred in males aged less than 44 years. A single drug was implicated in only 7 (10%) of these fatalities. Twenty four cases (34.2%) were positive for two drugs, 25 (35.7%) for three drugs, 13 (18.6%) for four drugs and 1 case (1.4%) was positive for 5 drugs. Benzodiazepines were implicated in 69% of cases, methadone in 53%, heroin in 51% and alcohol in 43%. Between 1st January 1998 and the 31st December 2000, the Dublin City and County Coroners conducted 2063 inquests into deaths due to unnatural causes within their jurisdictions, 254 (12%) of which were related to the use of opiates.[16] A single drug was

implicated in only 6.7% of drug related deaths. Table 6 characterises the number of drugs implicated in death due to unnatural causes:

Table 6: *Number of drugs implicated in deaths due to unnatural causes from 1998 to 2000, Byrne (2001)*[16]

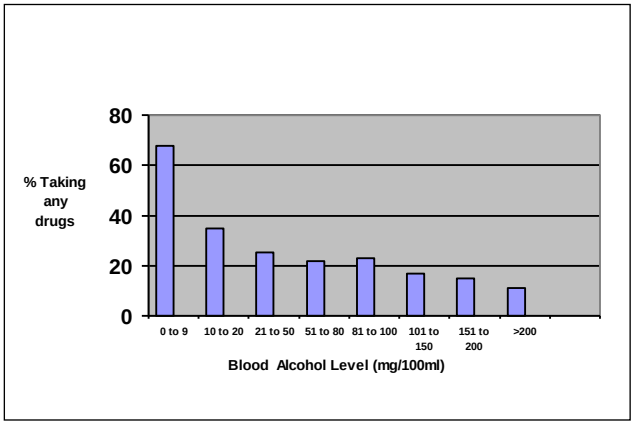
Number of Drugs	Frequency	Percentage %
0	5	2.0
1	17	6.7
2	53	20.9
3	70	27.6
4	60	23.6
5	36	14.2
6	9	3.5
7	3	1.2
10	1	0.4
Total	254	100

Benzodiazepines were implicated in the highest number of fatalities (71%), with diazepam the drug most cited (68%) in this regard. Heroin was implicated in 62% of fatalities and methadone was involved in 57% of fatalities. There were 6 ecstasy-related deaths during the three-year period.[16]

Driving Under the Influence of Drugs

The number of injuries and deaths due to road traffic accidents in Ireland is a cause for serious concern. The Government Strategy for Road Safety has identified four major factors as contributory causes in road traffic accidents: speeding, non-use of safety belts, careless and dangerous driving and intoxication.[17] Alcohol intoxication has long been recognised as a major contributor to road traffic collisions, and it remains the major intoxicant in drivers. The Road Traffic Act 1994 set the legal limits of alcohol at 80 mg/100ml in blood and 107mg/100ml in urine. Increasingly, intoxication with drugs other than alcohol has been recognised, even though driving under the influence of drugs has been illegal under statute since the 1961 Road Traffic Act. The significant effect of drugs on motor performance is evident from the number of drivers apprehended for dangerous or careless driving, while under the alcohol limit or with no alcohol present at all. Results of a nationwide survey carried out between 2000 and 2001 on drivers who were detained for dangerous driving by the Medical Bureau of Road Safety demonstrates that there is a strong trend of increasing positive drug tests with decreasing levels of alcohol. Sixty eight per cent of tested drivers with undetectable levels of alcohol were positive for one or more drugs. However, 23% of tested drivers had a combination of positive drug tests and alcohol levels above the legal limit. The classes of drugs found were similar in those who were over the legal alcohol limit and those who were under, with cannabis being the most common drug found.[17]

Figure 1: *Prevalence of Drug Taking by Blood Alcohol Level in Tested Drivers, reported by MBRS, 2003*[17]



Clearly, there is a significant problem of driving under the influence of drugs in Ireland. This is a troubling finding, as the combination of alcohol and other drugs could markedly impair driving performance, contributing significantly to the morbidity and mortality associated with road traffic accidents.

The combined effects of alcohol and drugs on individuals

Concurrent poly-drug use is a style of ingestion where multiple drugs are consumed on separate occasions. The use of multiple drugs simultaneously may have a greater influence on individuals than concurrent poly-drug consumption, by producing greater intoxication and increasing the risk of damage to health. Simultaneous poly-drug use increases psychological distress, as measured by depression, anxiety and phobic anxiety scales, compared with concurrent use.[18] In addition, unique pharmacokinetic interactions may occur, resulting in the formation of metabolites of greater toxicity than those present when drugs are used individually.[19]

The most common drug taken in combination with illegal drugs is alcohol. The risks of a fatal overdose or toxic effects on major organs, such as the heart and liver, are greatly increased when drugs and alcohol are mixed. The use of alcohol in combination with benzodiazepines has been shown to produce greater psychomotor impairment than that produced by each substance separately.[20] Doses of benzodiazepines that are excessively sedating may cause severe drowsiness in the presence of alcohol, increasing the risk of household and automotive accidents.[21] This may be especially significant in older people, who demonstrate an increased pharmacodynamic susceptibility to these drugs. Similar super-additive effects have been found for alcohol and marijuana with regard to driving performance.[22] Use of alcohol and marijuana in combination has also been shown to produce foetal damage at levels of alcohol consumption not normally associated with foetotoxicity.[23]

The simultaneous use of alcohol and cocaine is popular amongst drug users. A number of theories have been proposed to account for this: a more intense feeling of a 'high' beyond that perceived with either drug alone, to minimise alcohol-induced inebriation, and to assuage sensations associated with coming down from cocaine intoxication. Cocaine and alcohol metabolites combine to form cocaethylene, an active metabolite which is more toxic than either drug alone. Cocaethylene is the ethyl ester of benzoylecgonine, and is only formed following simultaneous ingestion of alcohol and cocaine. It has been associated with enhanced subjective euphoria, increased heart rate and increased plasma cocaine concentration.[24] Cocaethylene affects normal cardiac function and has been a contributory factor in many cocaine related deaths.[25] It can also potentiate the tendency towards violent thoughts and threats, which may lead to an increase in violent behaviour.[26]

Combined heroin and cocaine use has also been reported.[9] It has been suggested that heroin enhances the rewarding effects of cocaine by reducing the anxiolytic side effects that occur after the positive euphoric reaction of cocaine diminishes.[27] Both cocaine and μ opioid agonists activate reward pathways, the former by blocking dopamine uptake, the latter by enhancing mesolimbic dopamine release. Furthermore, there is evidence to suggest that morphine and opiates may enhance the toxic potential of cocaine, and that cocaine can induce respiratory depression, possibly contributing to the ultimate mechanism of death in narcotic overdose cases.[28]

Conclusions and Recommendations

Poly-drug use is a common practice amongst drug users, and is associated with considerable morbidity and mortality. More evidence-based research is needed to ascertain the best possible care for poly-drug users and especially for problem drug users. In recent years, much emphasis has been placed on expanding treatment services, and this has to a large extent been achieved. The challenge now is to widen the spectrum of treatment services, and refine the interventions themselves, thereby increasing their success rates. Treatment for users of several drugs in the recreational scene is virtually non-existent, as most drug services are only equipped to deal with opiate and severe dependence problems and not stimulant poly-drug use. Targeted initiatives to tackle the social origins of poly-drug problems should be addressed with inter-agency co-operation and community participation. Furthermore, there is a need to include legal drugs as part of the poly-drug treatment policy, since experience has shown that an exclusive focus on illegal drugs has limited effectiveness. Policy makers must have a clear vision of what they wish to achieve within the context of poly-drug use in Ireland if they hope to combat this escalating crisis.

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The Obesity Epidemic

Ann-Marie Mongan

Abstract

Hippocrates believed that the goal of "protecting and developing health must rank even above that of restoring it when it is impaired." This aspiration is particularly relevant at present as escalating obesity levels challenge our health service. Obesity, defined as a body mass index (BMI) higher than 30 kg/m^2, is the commonest nutritional disorder worldwide. Its medical, psychological, social and economic effects have major consequences for health, yet an effective treatment remains elusive. Genetic, environmental and behavioural factors have all been implicated in the pathophysiology of obesity, but the individual contribution of each factor is as yet unknown. This review aims to elucidate the underlying factors influencing the obesity pandemic.

Introduction

According to the World Health Organisation (WHO), there are at least 300 million obese individuals worldwide. This number is considerably higher than the 1995 estimate of 200 million, indicating that we are currently facing an acceleration of the problem.[1] Even in the developing world, obesity is escalating wildly, inflicting the paradoxical double burden of obesity and malnutrition on poorer nations. The obesity epidemic now merits pandemic status.[2] Eighteen percent of Irish adults are obese and 39% are overweight.[3] The crisis has also filtered down to paediatrics – 20% of five to twelve year old children are overweight or obese, and these figures are estimated to be rising by over 3% each year.[4,5] Obesity imposes a substantial burden on our health services. The lifetime medical costs of adults with a BMI of 32.5, is estimated to be 42% to 56% greater than those with a BMI of 22.5.[6] The cost of treating obesity and its complications is set to increase hugely as the obesity crisis comes of age.

Obesity is a chronic disease with important consequences on health, psychosocial well-being and quality of life. Extremes of BMI are related to mortality and can be illustrated by a J-shaped curve.[7]

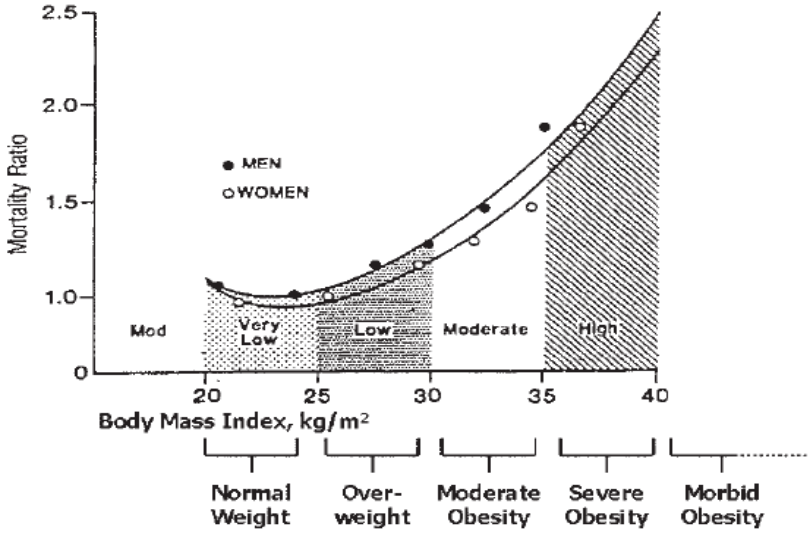

Figure 1: J-shaped curve[7]

Annually, at least 2000 people in Ireland die prematurely from obesity and related illnesses. In addition to having an increased risk of premature death, overweight and obese individuals are more likely to suffer from other adverse health effects.[9] While obesity affects almost every body system it most commonly and detrimentally affects the cardiovascular system. Obese individuals are at an increased risk of coronary heart disease, stroke, venous thromboembolism, cardiomyopathy and congestive heart failure. These effects are mediated partly by increasing cardiovascular risk factors including hypertension, dyslipidaemia, insulin resistance and inflammatory and thrombotic markers, and partly by an unknown mechanism independent of these factors. Additionally, there is a direct association between BMI and the development of type 2 diabetes mellitus.[10] The risk of developing diabetes mellitus increases as weight increases; the relative risk of diabetes increases by 25% for every extra unit of BMI greater than 22.[9] Cardiovascular and diabetes risks start to increase below the threshold of obesity. In the Nurses Health Study, each kilogram of weight gained from the age of 18 years was associated with a 3.1% increased risk of cardiovascular disease.[11]

Other potentially life-threatening complications associated with obesity include gallstones, cholecystitis and some cancers (including endometrial, prostate, breast and colon)[9]. A recent meta-analysis concluded that 3.4% of cancers in males and 6.4% cancers in females could be attributed to being overweight.[10] Furthermore, overweight people have an increased incidence of chronic incapacitating disorders such as osteoarthritis, obstructive sleep apnoea, gout, complications in pregnancy, poor female reproductive health, bladder control problems and skin conditions.[1]

While most of the medical and social burden of obesity is borne by the adult population, obese children also endure significant morbidity. Studies have shown that overweight children demonstrate cardiovascular risk factors such as dyslipidaemia, insulin resistance and hypertension. The incidence of type 2 diabetes in children has risen in recent years and this appears to be associated with the increasing levels of overweight and obesity in children.[9] They are also at risk of long term sequelae – obesity in childhood predicts risk factors and morbidity for coronary heart disease.[9] In addition, evidence suggests that childhood obesity tends to persist; overweight children grow into overweight adults. Reilly and colleagues reported that 70% of obese prepubescent children became obese adults, whereas 80% of obese adolescents remained obese in adulthood.[12]

Obesity is associated with a diminished quality of life. Obese people face discrimination in education, work, healthcare and social relationships and tend to earn lower incomes and have lower marriage rates.[13] Children as young as 3 years old display a negative attitude towards obese people, which intensifies with age.[14] A British study of 180 predominantly lean 4-11 year olds describes how professionally drawn pictures of overweight children, compared with those of normal or under-weight children, attracted many more negative attributes. Overweight children were thought of as ugly, lazy, stupid, and selfish.[9]

Pathophysiology

Obesity develops when energy intake exceeds energy output, leading to accumulation of adipose tissue. Energy balance is maintained through the control of appetite and metabolism. Appetite regulation is a complex process, influenced by peripheral and central signals. In the gastrointestinal tract, ghrelin and decreasing concentrations of nutrients such as glucose, fatty acids and amino acids stimulate hunger.[15] Ghrelin is an endogenous ligand of growth hormone secretagogue receptor (GHSR).[16] It is believed to stimulate food intake, carbohydrate utilisation and growth hormone secretion from the pituitary gland, and its administration has been shown to increase adiposity in rodents.[17] Following a meal, gastric and duodenal distension produce the feeling of satiety, aided by release of gastrointestinal peptides such as cholecystokinin, glucagon-like peptide 1 and peptide YY 3-36.[15] Cholecystokinin acts rapidly to increase satiety and decrease food intake. Peptide YY is released after the ingestion of food by endocrine L cells in the small and large intestines and it decreases food intake. Glucagon-like peptide is also secreted in response to nutrients in the intestines and increases satiety.[16] Signals regarding appetite regulation are received centrally by the brainstem and hypothalamus; these central control centres are linked by projections from brain stem neurons to the paraventricular nucleus and lateral hypothalamus. The brainstem receives information concerned with satiety via afferent vagal fibres shortly after meals, whereas the hypothalamus integrates short term and long term signals from the brain, gastrointestinal tract and peripheral circulation.[16]

The size of energy stores and the hormone leptin control appetite over a longer period of time.[15] Leptin is a hormone produced by adipose tissue which acts chiefly at the hypothalamus by binding to the leptin receptor[10]. Leptin is involved in regulating energy intake by mediating between adipose stores and the hypothalamus, and it regulates energy expenditure by stimulating the sympathetic nervous system.[18] Leptin inhibits pathways which stimulate food intake and promote weight gain by inhibiting orexins such as melanin-concentrating hormone (MCH) in the paraventricular nucleus, neuropeptide Y (NPY) and agouti-related protein (AgRP) in the arcuate nucleus.[15] It stimulates pathways which promote anorexia and weight loss, by stimulating anorexigenic signals, such as alpha melanocyte-stimulating hormone (αMSH), which affects the melanocortin-4 receptors (MC4R), corticotrophin-releasing factor in the paraventricular nucleus, preopiomelanocortin precursor polypeptide (POMC) and cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus.[15]

Leptin levels are directly proportional to levels of adipose tissue.[16] In severely obese individuals, subcutaneous adipose tissue concentrations of leptin mRNA are 80% higher than in controls, and plasma levels are also high. Plasma concentrations of leptin are reduced when weight loss occurs due to diet restriction.[15] Insulin-induced alterations in adipocyte metabolism are thought to stimulate production of leptin.[19] A diminution of adipose tissue results in reduced leptin release which stimulates appetite and restores the energy deficit.[15] The central nervous system responds to a lack of leptin as it would to an absence of adipose tissue stores, by increasing food intake and decreasing energy expenditure. Conversely, an increase in adipose tissue stimulates leptin release, thus reducing appetite and promoting weight gain.[15] Physiologic responses to decreased leptin are more pronounced than responses to increased levels of leptin, leading to speculation that the primary role of leptin is to adapt to a negative energy balance rather than to prevent obesity.[19] The feedback mechanism is not

completely understood. Adipose tissue mass may not be the sole determinant of leptin release and it has been suggested that leptin resistance may occur.[10] Many other signals such as ghrelin and cholecystokinin may have a role in long term regulation of appetite and energy, thus increasing the complexity of the feedback mechanism.[16]

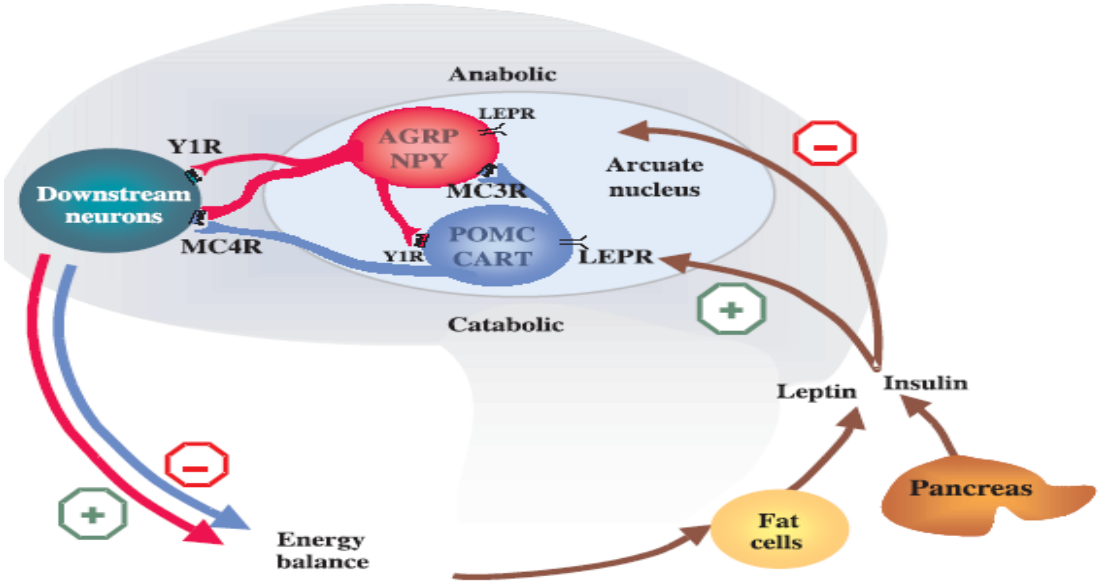

Figure 3: Central Pathways regulating Energy Balance[20]

The other side of the energy balance equation – total energy expenditure, is chiefly determined by the basal metabolic rate (BMR) thermogenesis and physical activity.[15] Metabolic rate contributes 60-70% of total energy expenditure and depends on lean body mass, energy intake, physical fitness and other factors such as age, height, stress and environmental temperature.[21] Fat-free mass is responsible for 60-80% of inter-individual variability in BMR.[21] Contrary to popular opinion, metabolic rate is generally higher in the obese than in lean individuals. This is because obese people have a correspondingly large lean body mass and tend to use a greater magnitude of energy than lean individuals when doing the same amount of activity.[13] Subject variability is also attributable to traits such as muscle fibre type, muscle tone and thyroid function.[21] Dietary thermogenesis is the energy required to digest and store food, and is greatest for protein rich meals, midway for carbohydrates and lowest for fat.[13] Physical activity is influenced by behavioural and environmental factors.

Aetiology of Obesity

Obesity is a multifaceted chronic disease with a complex aetiology, which has yet to be fully elucidated. It is an associated feature of many conditions including hypothyroidism, Cushings' syndrome, Stein-Leventhal syndrome, hypothalamic disease and drug-induced obesity, but these only account for a minority of cases.[15] Although the obesity crisis has been dominating headlines for many years, there is no consensus regarding its precise aetiology, much less the most appropriate treatment.

Genetics

The genetic contribution to obesity is substantial, but in most cases its expression is influenced by other factors, although it is known that genetic factors predict the success rates of weight loss programmes.[22] The obesity gene map shows putative loci

on all chromosomes except the Y chromosome. There are more than six hundred genes, markers and chromosomal regions associated with obese phenotypes, either rare gene variants with a strong influence or common gene variants with a weak influence.[23] Key genes are located on chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17p and 20q.[20] Segregation analyses have suggested a role for a major recessive gene, but other studies have contradicted this research.[20,23] Whether the mode of inheritance is polygenic, oligogenic, or a mixture of the two is still under dispute.

Single gene defects comprise a less common cause of obesity (approximately 5%) but provide an insight into the pathophysiology of obesity. Disorders such as Prader-Willi syndrome, Albright Hereditary Osteodystrophy and Bardet-Biedl syndrome are inherited in Mendelian fashion and feature obesity as a clinical manifestation but not as the dominant characteristic.[20] Prader-Willi syndrome is the commonest form of syndromic obesity with a prevalence of 1/25,000. Causal genes have not yet been identified for Prader-Willi syndrome, but candidate genes are expressed in regions of the hypothalamus concerned with energy balance.[24] The genes affected in Albright Hereditary Osteodystrophy and Bardet-Biedl syndrome (BBS) are GNAS1 (Guanine nucleotide-binding protein, α-stimulating activity polypeptide 1) and BBS 1,2,4,6,8 respectively.[24] While these syndromes provide us with an important means of delineating the complex genetic and metabolic pathways involved in regulating appetite and energy balance, they are an infrequent cause of obesity.

Rare mutations in humans and model organisms where obesity is the dominant feature have also provided insights into these pathways. The putative obesity gene *ob* was first identified in the naturally occurring mutant *ob/ob* mouse in 1994. The *ob* gene is found on chromosome 7 and produces leptin. A mutation in the *ob* gene leads to production of a non-functioning protein. The *ob/ob* mouse demonstrated hyperphagia, hyperinsulinaemia and obesity. The leptin receptor deficient *db/db* mouse had a similar phenotype.[10] Administration of leptin to the *ob/ob* mouse resulted in a reduction in body weight, but did not alter body weight in the *db/db* mouse.[16] In humans, mutations in leptin or its receptor produce an obese phenotype that is not normalised by dietary restriction or exercise.[10] Treatment with recombinant leptin in leptin-deficient individuals results in a significant decrease in body weight.[16] However, most obese people produce structurally normal leptin, and due to their high adipose tissue mass, have high levels of circulating leptin. Other monogenic defects of interest include those affecting pro-opiomelanocortin, the melanocortin-4 receptor, adrenergic receptor, carboxypeptidase E, peroxyisome proliferator-activated receptor γ and prohormone convertase 1.[10]

Twin, adoption and family studies have shown that genetic factors play a significant role in the pathogenesis of obesity, although there is still doubt regarding the magnitude of the genetic contribution to obesity. Twin studies have shown that genetics are responsible for 50-90% of inter-individual variation in BMI, while family studies put this number at 20-80%.[20,25] The risk of obesity when a first-degree relative is obese is increased by a factor of five if the relative is extremely obese (BMI>40), but the risk is only elevated two-fold if the relative is moderately obese (BMI>30).[10] This data has led to the development of the 'major gene hypothesis', which asserts that the genetic mechanisms underlying extreme obesity differ from those leading to more common, moderate forms of obesity.[10]

In positive energy balance experiments, it has been shown that some individuals are more prone to weight gain than others. In one experiment, sets of monozygotic twins ate a surplus of calories, resulting in an average weight gain of 8.1kg. At the start of the experiment virtually all of the excess calories were converted to weight gain. After one hundred days only 60% of the surplus energy was being stored.[10] Among the participants, there were differences in the amount of weight gained and the distribution of the adipose tissue stored. This variance was greatest between pairs of monozygotic twins rather than within pairs, suggesting that the discrepancies in response to surplus calories were attributable to differences in genotypes. Similarly, in negative energy balance experiments where monozygotic twins were exposed to energy deficient environments, alterations in body mass and body fat were greater between twins than within twin pairs.[10]

In their review of the genetic causes of obesity, Loos and Bouchard divided genetic susceptibility into four main categories: genetically obese, strong predisposition to obesity, slight predisposition to obesity and genetically resistant. According to this classification, individuals in the genetically obese and genetically resistant groups are resistant to changes in their environments. Those who are genetically obese maintain their obese phenotype in a wide range of environments, while genetically resistant people remain lean, even in obesogenic circumstances. Those who are susceptible to obesity may be slightly overweight in a restrictive environment, but are at a high risk of developing extreme obesity in an obesogenic environment. Those who are slightly predisposed to obesity may maintain a normal weight with a healthy lifestyle, but a significant proportion will become obese in an obesogenic environment. This susceptibility stems from alleles at a number of loci, and accounts for the common forms of obesity.[20]

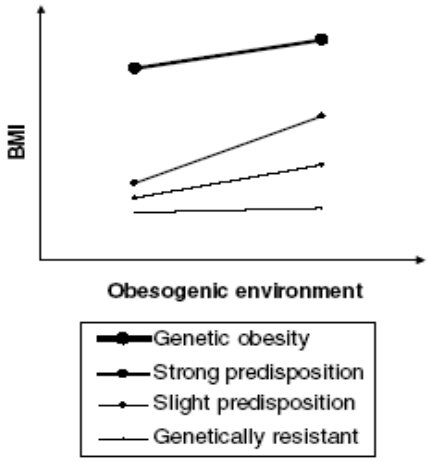

Figure 4: Genetic predisposition to obesity[20]

The "Thrifty Genotype" hypothesis first put forward by James Neel in 1962 suggests that the evolution of Homo Sapiens selected for genes that predispose to obesity.[26] Following the last glaciation, hunting decreased, while the culture of cereals rose. Protein intake, as well as that of other essential meat nutrients (iron and vitamins), decreased, producing dietary deficiencies mirrored by the reduction of body size and induction of important adaptations in the molecular processes regulating nutrient metabolism. This enabled humans to maintain glucose homeostasis and to guard

against food restrictions and deprivations. As a consequence of surviving in times of food scarcity, genes that predisposed to metabolic efficiency and increased energy stores conferred a survival advantage to the possessor. The advent of agriculture and breeding (10,000 years ago) marked a fundamental step in the human nutritional system, introducing new foods and transforming this selective metabolic advantage into a susceptibility to obesity. Humans have had little evolutional contact with diets high in fat and carbohydrate, so no mechanisms to mitigate against their over-consumption have developed.[9,20,28] Feedback regulation of fat and carbohydrate is not as efficient as for protein.[27,28] Our limited experience of energy dense, fatty foods has resulted in these foods being perceived as more palatable. Compared to animals, we store a large proportion of excess energy – rodents metabolize and eliminate 90% of their excess energy, while humans store 75% of their energy surplus.[27] In addition, the systems that regulate the body's energy balance evolved at a time of high energy expenditure. In today's obesogenic environment these conditions no longer apply and this has led to a decrease in our energy intake requirements.[29] These regulatory systems respond to increased energy expenditure by increasing intake accordingly; however, they are less efficient at lowering our energy intake in response to less physical activity.[27] Ample supplies of heavily marketed, palatable, energy-dense foods, along with labour-saving machinery and reliance on cars have combined to create an obesogenic environment to which our 'thrifty genotype' is ill-suited.

Even though genetic factors are important in the pathogenesis of obesity, the fact remains that obesity levels have escalated far too quickly to be a purely genetic phenomenon. Rather, these trends implicate environmental and behavioural changes capable of affecting large populations. The current obesity epidemic is thought to be the result of the interaction between individual genetic susceptibility and a toxic, obesogenic environment.

Nutrition

Philip James, chairman of the International Obesity Task Force, claimed that *"it's a miracle that anybody stays even moderately thin"* when meals such as a cheeseburger, a large portion of fries, and a 450 ml fizzy drink can add up to 1166 kcal (4900 kJ).[30] Surprisingly however, the National Nutrition Surveillance Centre's annual report revealed that on average, Irish people in 2002 ate less than their counterparts in 1948.[5] While energy intake may be decreasing, the energy density of the foods we eat is rising. The proportion of dietary fat consumed has increased in recent years. Recommendations from the Eurodiet Core report state that no more than 30% of the total energy intake should comprise fats, while figures show that 37% of Irish energy intake consists of fat and most people consume too much saturated fat.[3,31] Studies show an association between obesity and high fat diets, while low fat diets are a successful means of achieving weight loss (although some studies have shown that simultaneous reduction in total energy intake is necessary).[9,32] Given that fat is less satiating and more energy dense, (fat provides 9 kilocalories per gram, compared to 4 kilocalories for carbohydrates and for protein), it follows that a high fat diet predisposes to passive over-consumption of energy.[9,29]

Dietary patterns

Dietary patterns have changed enormously. Globally, the availability of calories per capita has risen by 450 kilocalories per day.[28] A SLAN survey revealed that in Ireland, 22% of 18-34 year olds consume food prepared outside the home every day.[5]

Children who dine at home with their families eat more fruit and vegetables, consume fewer fizzy drinks and eat less fat overall.[33] The 2002 HSBC survey revealed that 51% of Irish children consume sweets and 27% consume crisps. Increased consumption of sweetened drinks has been linked to the obesity epidemic and in Ireland, 37% of children drink at least one such sugary beverage every day.[34] It has been shown that each additional can per day increases the risk of obesity by 60%.[9] The recent surge in the consumption of sweetened drinks and fast food may be due to their aggressive promotion in the media, especially on television. On average, children watch 100,000 television advertisements a year, the vast majority of these promoting fast food, sweets and sweetened drinks. Hastings and colleagues have demonstrated a link between the number and content of ads and being overweight, while Gortmander and others found a dose-response relationship between TV watching and weight gain.[2,35]

Physical Activity

Physical activity is defined as 'bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level.'[9] Reductions in physical activity contribute to the positive energy balance associated with weight gain.[37] A low level of physical activity is linked with a low daily energy requirement as well as changes in metabolic activity, and will cause obesity unless energy intake is restricted accordingly.[2,36] The metabolic activity of muscle has a key role in maintaining fat balance. Reduced muscle activity leads to reduced fat oxidation favouring fat imbalance.[37] On the other hand, high levels of physical activity, especially regular exercise, stimulate fat oxidation.[43] A high fat oxidation rate plays a protective role in the risk of weight gain.[37]

The largest available prospective study, which followed 12,000 Finnish adults over five years verified that low levels of physical activity are as important as dietary factors in the aetiology of obesity.[29] A large proportion of the Western population lives a sedentary life, facilitated by advances in technology and transport. While it is recommended that adults spend a total of one hour per day on most days of the week doing moderate-intensity activity, the average Irish adult spends less than one hour per week on physical exercise, and up to 46% of Irish adults report that they engage in no physical exercise at all.[3,9] Physical activity levels decrease with age and there is normally a significant decline after adolescence. Nevertheless, Irish adolescents already exhibit nominal levels of physical exercise. The Mid-Western Region Heart Rate Monitoring Study found that none of the adolescents studied were active for 30 minutes of moderate intensity cumulative exercise on all four days.[9] Socioeconomic factors, availability of amenities and facilities, peer influence, and activity level of parents all impact on the amount of exercise children receive.[37] Obesity itself can be a deterrent to physical activity due to the physical discomfort experienced, and while overweight people expend more energy when they partake in exercise, they tend to do less vigorous physical activity.[38,39] These reductions in levels of physical activity are most apparent in people who are substantially overweight.[40] Obesity also predisposes to conditions such as arthritis, which limit the capacity for physical activity.[41] Reducing levels of physical activity then promotes further weight gain, thereby perpetuating a vicious cycle of weight gain and debilitating sequelae.[40]

Conclusion
Current modern lifestyles are creating a generation of overweight children and adults. Childhood obesity is the most prevalent paediatric disease in Europe and some experts forecast that this generation of children may have a lower life expectancy than their parents because of diseases resulting from obesity. In economic terms, the cost of treating obesity in Ireland exceeds €0.4 billion annually.[9] Clearly, the problem of obesity is very costly to society in both human and financial terms, prompting governments, health professionals and non-governmental organizations around the world to search for approaches to its control. There is compelling evidence to support the effectiveness of low calorie (1,000-1,500 kcal/day) and low fat (where 30% or less of total daily energy is derived from fat) diets combined with energy restriction, or even low-fat diets alone.[9] Unfortunately, weight loss is usually temporary, with 90% to 95% of people regaining the weight following a clinical management programme. This suggests that while traditional weight control measures are necessary, they are insufficient to reverse the incidence of obesity.[43]

The National Taskforce on Obesity recommended that policies must be introduced at a national level which support individuals in their efforts to lose weight and prevent weight gain by addressing the underlying environmental, social and cultural factors acting as barriers to change. It is obvious that society would benefit by modifying diet and fat intake, as well as increasing activity levels in accordance with literature recommendations.

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The Pharmacoeconomics of Proton Pump Inhibitors Prescribing in Ireland

Dara Grennan, Robert F. Cornell, Christopher Crush and Dania Alsammarae
5th Year Medicine

Abstract

Objectives: The purpose of this study was to determine cost-saving measures in the treatment of patients with conditions requiring proton pump inhibitor (PPI) maintenance therapy, and to examine factors that contribute to inappropriate PPI prescribing. **Methods:** Cost-Minimisation Analysis was used as the method of pharmacoeconomic evaluation for this study, an appropriate method given the National Institute for Clinical Excellence guidelines from July 2000, which concluded that all five PPIs on the market have equal efficacy. **Results:** Despite its higher cost, the original PPI omeprazole (Losec®) is still the most frequently prescribed PPI. In PPI maintenance therapy, substitution with any generic form of omeprazole (Losamel, Ulcid, Lopraz, or Losepine) is more cost-effective than using the brand-name omeprazole. Furthermore, in prescribing maintenance therapy for specific indications such as GORD, duodenal ulcer, and NSAID-induced peptic ulcer, rabeprazole (Pariet), lansoprazole (Zoton), or pantoprazole (Protium), respectively, are more cost-effective options compared with brand-name omeprazole. **Conclusion:** Substitution with these PPIs would be expected to produce savings of over six million euro per year.

Introduction

The secretion of hydrochloric acid (HCl), or gastric acid, into the stomach lumen is influenced by various physiological and neuroendocrine mechanisms. Physiologically, there are three overlapping phases of gastric acid secretion: cephalic, gastric, and intestinal. The cephalic phase is mediated by acetylcholinergic and vagal mechanisms and is stimulated by anticipation, taste and smell chemoreceptor activation, and swallowing. The gastric phase is primarily characterized by the release of gastrin from G cells found in the antrum of the stomach. The intestinal phase accounts for a minimal proportion of gastric acid secretion. The function of gastrin is to increase gastric acid secretion, and its release is stimulated by stomach distension and by the chemical effects of food products, including amino acids and peptides. In particular, phenylalanine and tryptophan are potent stimulators of gastrin secretion.

Stimulation of parietal cells in the gastric mucosa results in gastric acid secretion via up-regulation of the hydrogen-potassium adenosine triphosphotase enzyme system (H^+/K^+ ATPase), also known as the proton pump.[1] The three major stimuli of parietal cells are acetylcholine (ACh), gastrin and histamine, as shown in Figure 1.[2]

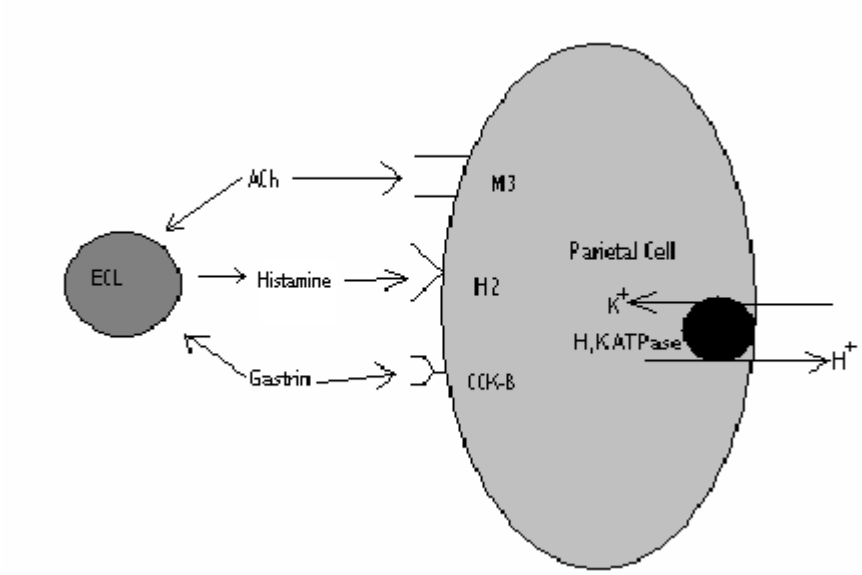

Figure 1: The regulation of acid secretion[3]

ACh released from parasympathetic neurons directly stimulates parietal cells through muscarinic subtype 3 (M3) receptors, and indirectly through activation of enterochromaffin-like cells (ECLs). ECLs release histamine, which activates histamine 2 (H_2) receptors, resulting in parietal cell stimulation. Gastrin primarily acts via stimulation of ECLs, but it can also directly stimulate parietal cells by binding to cholecystokinin-B (CCK_B) receptors. M3 and CCKb are G-protein coupled receptors (Gq), and their stimulation results in activation of phospholipase C, formation of inositol triphosphate and intracellular calcium release.[4] The majority of H_2 receptors couple with G_s, leading to activation of adenylate cyclase, resulting in elevated cyclical adenosine monophosphate concentrations.[5]

Stimulation of parietal cells induces structural and morphological changes. Parietal cells contain intracellular membrane regions called tubulovesicles, which retain H^+/K^+ ATPase pumps beneath the apical surface of the parietal cell in the unactivated state. Following activation, the tubulovesicles bind to the cell surface, resulting in translocation and insertion of the H^+/K^+ ATPase into the apical region of the parietal cell through a fusion-based mechanism, thereby creating a pathway through which acid secretion can take place.[6,7,8] Electron micrographs reveal dilated canalicular spaces, expanded apical membrane surfaces, and reduction of cytoplasmic tubulovesicles when parietal cells become activated.[8,9,10]

Structurally, PPIs contain a pyridine moiety, making them protonatable weak bases, with pKas of between 4.0-5.0.[11] In the unprotonated state, they are prodrugs and accumulate in regions where the pH is less than 4; the only area where this occurs is the canaliculi of active gastric parietal cells. PPIs are enteric-coated to protect them from premature activation by gastric acid.[12] After absorption in the duodenum, the PPI is transported to the parietal cell canaliculus, where it is protonated and converted to the active form of the drug, which forms a covalent disulphide bond with a cysteine residue in the H^+/K^+ ATPase proton pump. This irreversibly inhibits the terminal step in the acid secretory pathway, thereby reducing gastric acid secretion.[12,13]

PPIs are used to inhibit gastric acid secretion in a number of conditions: gastro-oesophageal reflux disease (GORD), duodenal ulcer, gastric ulcer, NSAID-induced ulcer, erosive esophagitis, hypersecretory syndromes including Zollinger-Ellison syndrome, and in combination therapy for the eradication of *Helicobacter pylori*. Each year approximately 40% of the population will suffer from symptoms of dyspepsia, including abdominal distension, early satiety, fullness, epigastric or retrosternal burning, anorexia, vomiting and nausea.[14] The goal of treatment is to maintain control of symptoms using the minimum effective dose of acid suppression. The standard method of treating dyspepsia is known as the 'step-up' approach, which begins with lifestyle modification and antacids. If this step fails, H_2 antagonists or motility drugs are started, followed by PPIs if necessary. The initial treatment dose of a PPI is used to bring the symptoms of dyspepsia under control, but once control has been achieved, the PPI dose is lowered in a 'step-down' approach. The majority of patients requiring long-term PPI therapy can achieve symptom control using the maintenance dosage. Long-term therapeutic dosages are only indicated in severe oesophagitis.[15]

This study examines expenditure on long-term PPI maintenance therapy in community drug schemes from 2000 to 2004. The three main community schemes, which account for about 95% of government drug expenditure, are the General Medical Services scheme (GMS), the Drugs Payment scheme (DP), and the Long Term Illness scheme (LTI), each responsible for expenditures of €550.89 million, €192.37 million, and €61.64 million, respectively, over the period from 2000 to 2003.[16]

PPIs accounted for 10.5% of total expenditure under the General Medical Services and Drugs Payment schemes in 2002, and the original PPI Losec (omeprazole) was the number-one selling drug in that year.[16] The four other PPIs on the market are lansoprazole (Zoton), rabeprazole (Pariet), esomeprazole (Nexium), and pantoprazole (Protium).[17] Branded generic forms of omeprazole are also available: Losamel, Ulcid, Lopraz and Losepine. Late in 2005, lansoprazole went off patent and generic brands Lansiop and Lanzol have recently been marketed.

In July 2000, the U.K.'s National Institute for Clinical Excellence (NICE) issued guidelines on PPI use.[18] These guidelines state that all five PPIs are of equal efficacy, so the least expensive PPI licensed for a given indication should be prescribed. Furthermore, PPIs should be prescribed in a 'step down' manner; that is, the dose should be lowered to a maintenance level after healing has been achieved, to control symptoms or prevent reoccurrence, depending on the condition. The guidelines also specify that patients diagnosed with non-ulcer dyspepsia (e.g. gastritis, duodenitis, hiatus hernia) should not be prescribed PPIs, and that long-term PPI therapy should only be implemented when a confirmed clinical diagnosis has been established.

Methodology

There are four main types of pharmacoeconomic evaluation: Cost Minimisation Analysis, Cost Effectiveness Analysis, Cost Utility Analysis, and Cost Benefit Analysis.[19,20] Cost Minimisation Analysis is used to define the most economical treatment among different alternatives already shown to have equal efficacy. It is a relatively straightforward and simple method; in practice, however, it is very difficult to find a situation where true equality in efficacy and safety exist, and consequently, this method is rarely applicable. However, since there is no difference in efficacy between the PPIs licensed for a given indication per NICE guidelines, all PPIs for an indication can be considered equal and the least expensive PPI should be used. Therefore, CMA is a suitable method of economic evaluation to identify the most appropriate PPI.

Data analyzed for this project was obtained from GMS Payment Board annual reports, 2000 to 2004, and from the GMS prescription files, which contain the following information for each prescription reimbursed:

- Date dispensed, dosage and expenditure
- ATCG Code (Anatomical Therapeutic Code Guideline; identifies drug, including therapeutic class, anatomical area, therapeutic indication)
- Patient number
- Patient gender
- GP number
- Pharmacy code

To limit the analysis to patients on maintenance therapy, only data from patients receiving PPI therapy for three consecutive months was used.

A table was compiled illustrating the different licensed indications and doses for each PPI. The cost per tablet for four weeks therapy at maintenance and treatment doses was then calculated using current retail prices. The most frequently prescribed drug was substituted using CMA with each of the other PPIs to determine potential cost savings. The percentage of prescriptions for each PPI at the higher treatment dose was determined, which prevented overestimation of potential savings for each drug. The potential savings by substitution was then calculated. Using this data, each PPI was ranked according to cost for each indication.

Results

The data collected from the GMS annual reports and prescription files shows that spending on PPIs in Ireland is increasing annually, more than doubling between 2000 and 2004[16]. Figure 2 demonstrates the overall increase in PPI expenditure, while Figure 3 compares the relative increases among the five different PPIs. The number of prescriptions mirrors the upward trend in expenditure, but the differences between Figure 3 and Figure 4 reflect the difference in price of each PPI. For example, use of the relatively inexpensive lansoprazole is increasing, as indicated by the growing number of prescriptions, but it does not contribute to the increase in expenditure to a similar degree. Overall, omeprazole is still the most frequently prescribed PPI. While its contribution to the total number of prescriptions is decreasing, it maintains a fairly consistent lead in its share of expenditure.

Figure 2: Total PPI expenditure on the GMS 2001-2004

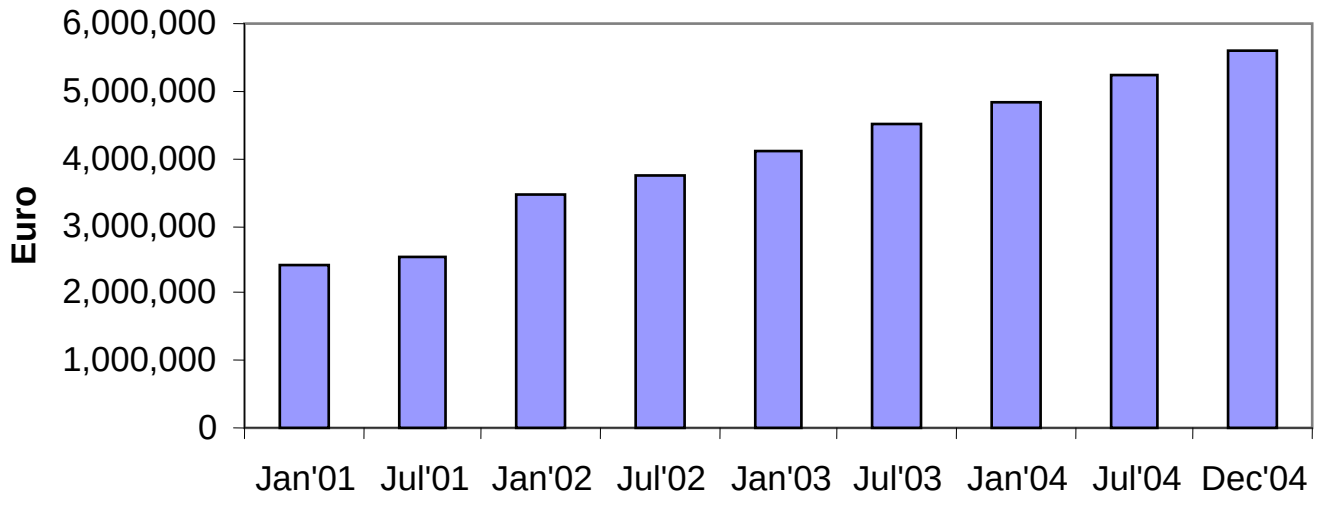

Figure 3: PPI expenditure on the GMS 2001- 2004

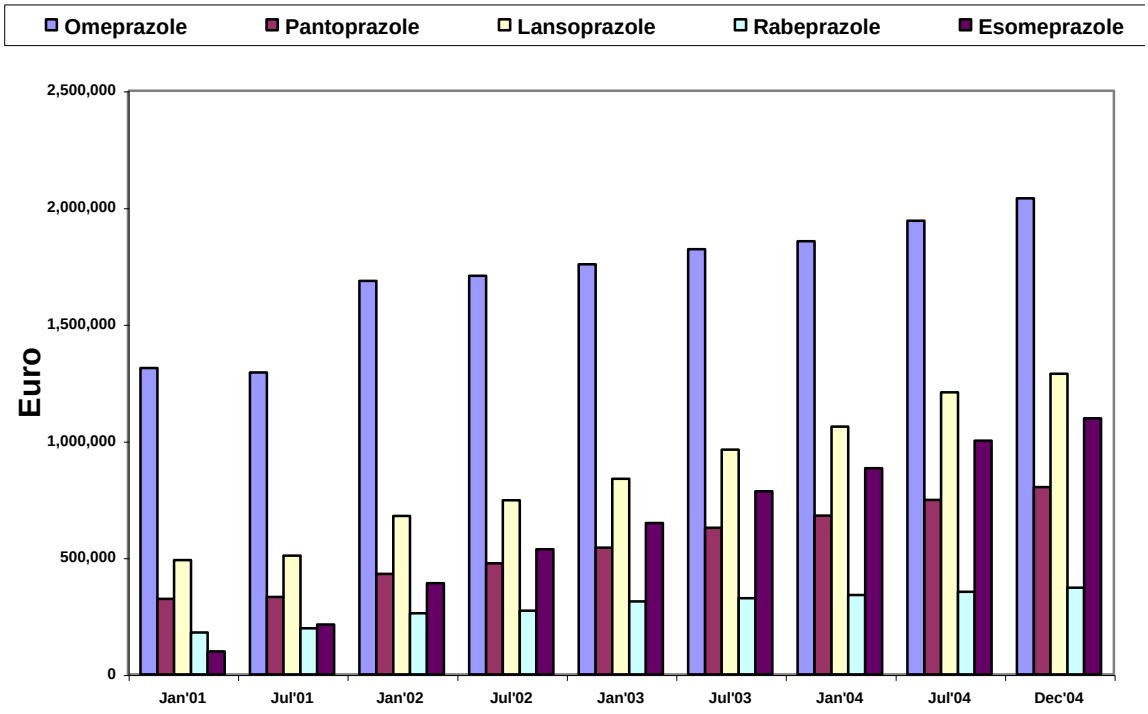

Figure 4: Total number of PPI prescriptions on the GMS between 2001-2004

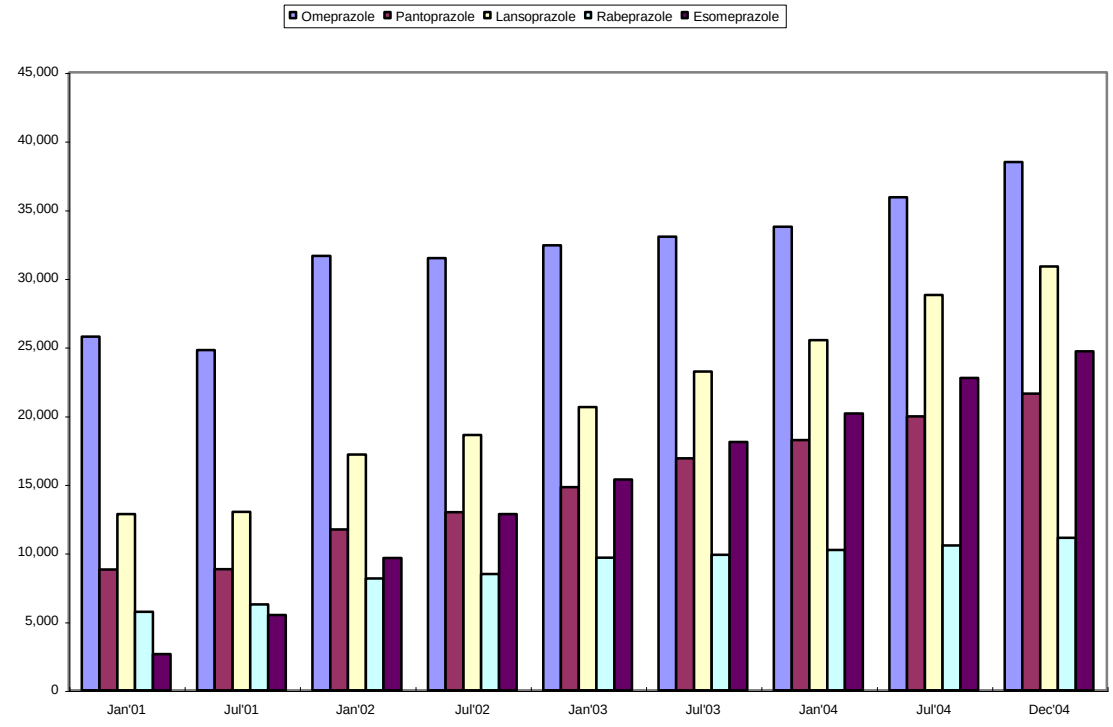

Table 1 displays the conditions for which each PPI is licensed, and whether it is licensed for treatment or for maintenance therapy. Omeprazole and lansoprazole are licensed for treatment and long-term maintenance for all three indications, while esomeprazole is only indicated for treatment and maintenance therapy of GORD. The doses for each drug and condition, for both treatment and maintenance, are compiled in Table 2, while the cost per tablet for four weeks therapy at maintenance and treatment doses using current retail prices is detailed in Table 3.

Drug	Indication				
	GORD		Duodenal Ulcer		NSAID PU
	Tx	Maintenance	Tx	Maintenance	Tx
Omeprazole (Losec, Losamel,Losepine Ulcid & Lopraz)	√	√	√	√	√
Lansoprazole	√	√	√	√	√
Rabeprazole	√	√	√	X	X
Pantoprazole	√	√	√	X	√
Esomeprazole	√	√	X	X	X

Table 1: Indication for each PPI for treatment and maintenance[17]

Drug	Dosage				
	GORD		Duodenal Ulcer		NSAID PU
	Tx	Maintenance	Tx	Maintenance	Tx
Omeprazole (Losec, Losamel,Losepine Ulcid & Lopraz)	20 mg/d	10-20 mg/d	20 mg/d 40 mg/d	10-20 mg/d	20 mg/d
Lansoprazole	30 mg/d	15-30 mg/d	30 mg/d	15 mg/d	15-30 mg/d
Rabeprazole	20 mg/d	10-20 mg/d	20 mg/d	X	X
Pantoprazole	40 mg/d	20 mg/d	40 mg/d	X	20 mg/d
Esomeprazole	20-40 mg/d	20 mg/d	X	X	X

Table 2: Dosage of each PPI for treatment and maintenance[17]

Omeprazole				
Losec	10 mg/d	10 mg x 28 =	€ 26.35	€ 0.94 / tab
	20 mg/d	20 mg x 28 =	€ 49.61	€ 1.77 / tab
	40 mg/d	40 mg x 14 =	€ 49.57	€ 3.54 / tab
Losamel	20 mg/d	20 mg x 30 =	€ 41.46	€ 1.38 / tab
Losepine	10 mg/d	10 mg x 28 =	€ 19.00	€ 0.68 / tab
	20 mg/d	20 mg x 28 =	€ 37.98	€ 1.36 / tab
Lopraz	10 mg/d	10 mg x 28 =	€ 18.95	€ 0.68 / tab
	20 mg/d	20 mg x 28 =	€ 28.95	€ 1.03 / tab
	40 mg/d	40 mg x 14 =	€ 35.50	€ 2.54 / tab
Lansoprazole				
Zoton	15 mg/d	15 mg x 28 =	€ 21.48	€ 0.77 / tab
	30 mg/d	30 mg x 28 =	€ 42.69	€ 1.52 / tab
Rabeprazole				
Pariet	10 mg/d	10 mg x 28 =	€ 20.68	€ 0.74 / tab
	20 mg/d	20 mg x 28 =	€ 32.42	€ 1.16 / tab
Pantoprazole				
Protium	20 mg/d	20 mg x 28 =	€ 21.22	€ 0.76 /tab
	40 mg/d	40 mg x 28 =	€ 39.30	€ 1.40 / tab
Esomeprazole				
Nexium	20 mg/d	20 mg x 28 =	€ 31.43	€ 1.12 / tab
	40 mg/d	40 mg x 28 =	€ 48.50	€ 1.73 / tab

Table 3: Cost of individual PPIs as per MIMS Ireland (December 2005 Edition)[21]

Given that omeprazole was shown to be the most commonly prescribed PPI, it was substituted with each of the other PPIs to determine potential cost savings using the prices calculated in Table 3. The percentage of prescriptions for each PPI at the higher treatment dose was determined, which prevented overestimation of potential savings for

each drug, and is shown in the first column of Table 4. The second column of Table 4 shows that by substituting the generic Lopraz for brand-name Losec in maintenance therapy, savings of over 6 millions euros per year would be expected. In fact, substitution with any of the generic forms of omeprazole is more cost-effective than using Losec. Furthermore, substitution of Losec with any other PPI would produce significant savings. In addition, substituting more cost-effective drugs based on indication, including rabeprazole (Pariet) for GORD, lansoprazole (Zoton) for duodenal ulcer, and pantoprazole (Protium) for NSAID-induced peptic ulcer will produce additional savings, as shown in the cost-effectiveness ranking in Table 5.

Drug	**Percentage of prescriptions at maintenance dose**	**Total savings when substituted for Losec (in euro)**
Generic omeprazole (Lopraz)	100%	6,843,000
Rabeprazole	19%	6,829,000
Generic omeprazole (Ulcid)	100%	6,419,000
Pantoprazole	34%	5,728,000
Lansoprazole	28%	4,233,000
Esomeprazole	52%	3,356,000
Generic omeprazole (Losamel)	100%	3,136,000

Table 4: Potential annual savings through substitution of alternative PPIs for brand-name omeprazole in maintenance therapy

	GORD		Duodenal Ulcer		NSAID PU
1	Losepine/Lopraz	1	Losepine/Lopraz	1	Losepine/Lopraz
2	Rabeprazole	2	Lansoprazole	2	Pantoprazole
3	Pantoprazole	3	Losamel	3	Lansoprazole
4	Lansoprazole	4	Losec	4	Losamel
5	Losamel			5	Losec
6	Esomeprazole				
7	Losec				

Table 5: Cost-effective drug list based on indication

Discussion

The objective of this study was to apply pharmacoeconomic evaluation to PPI prescribing in Ireland to ascertain whether any potential savings could be made.

The findings from this study demonstrate that omeprazole is the most frequently prescribed PPI. However, it remains the most expensive PPI, despite many licensed generic brands. Losepine and Lopraz, generic brands of omeprazole, are the most cost-effective PPI's for all indications. Substitution of Losec with these brands would produce savings in excess of 6.8 million euro (Table 5). Generic prescribing of drugs has long been advocated as good practice for all clinicians, not just to minimize expenditure but also to prevent medication errors. However, as demonstrated in Tables 3 and 5, it does not always optimize savings, as the generic brand of omeprazole, Losamel, is still more expensive than some of the other branded PPIs. Currently, legislation in Ireland restricts pharmacists from generic substitution without approval from the clinician. The council of the Pharmaceutical Society of Ireland issued the following statement in reference to generic substitution in pharmacies, "The community pharmacist has a complete responsibility for dispensing a prescription accurately and in accordance with the prescriber's instructions. In normal circumstances, where a doctor specifies a particular brand, the pharmacist is not entitled to substitute a generic 'equivalent', or even another branded product deemed to be equivalent, without the doctor's approval. In an emergency, where the prescriber is not readily contactable, the pharmacist may exercise his professional judgment in the best interest of the patient"[22]. While this issue may be addressed in the upcoming Pharmacy Act, at present the responsibility for generic prescribing lies with the doctor.

Following Losepine and Lopraz, the next most cost-effective PPI's were rabeprazole, lansoprazole, and pantoprazole for GORD, duodenal ulcer disease, and NSAID-induced ulcer respectively. Substitution of these PPIs in place of Losec in the treatment of the aforementioned conditions could result in savings of four to six million euro. A number of factors have been identified by GPs as important considerations when prescribing PPIs. These include guidelines, clinical investigations, marketing, prescribing behaviour and cost. The influence of aggressive marketing by pharmaceutical companies has been postulated as a significant cause of increased PPI prescribing.[23]

Another important finding from this study relates to the sizeable proportion of prescriptions for PPI maintenance therapy which were written at a treatment dose. All prescriptions for omeprazole were written at the correct maintenance dose, perhaps reflecting greater compliance of prescribers with its dosing schedule. However, for the remaining PPIs a great variation in the percentage of prescriptions at maintenance dose was observed: 52% for esomeprazole, 34% for pantoprazole, 28% for lansoprazole and 19% for rabeprazole. Thus, patients initially prescribed the higher, treatment dose are not

being prescribed the less expensive, maintenance dose once symptomatic control has been attained. There are two possible explanations which may account for this. Firstly, the lower dose may not be effective for symptom control in a proportion of patients and secondly, GPs may not be routinely reviewing treatment and decreasing doses as appropriate.

Conclusions

Expenditure on community drug schemes in Ireland is increasing rapidly, as illustrated in figures 2 and 3, with PPIs accounting for a considerable portion. A dramatic decrease in drug expenditure could be achieved through changes in PPI prescribing practices. As PPIs are equally effective, costs can be lowered without compromising clinical efficacy, through generic prescribing and prescribing the more cost-effective drug for certain indications. Use of the generic brands of omeprazole Losepine and Lopraz for all indications would achieve maximum savings. Expenditure could also be minimised by using rabeprazole for GORD, lansoprazole for duodenal ulcer, and pantoprazole for NSAID-induced ulcers. Generic prescribing is a simple and safe way to combat costs and all prescribers should be strongly urged to examine their prescribing practices.

According to the NICE guidelines, 70 to 80% of patients taking PPIs should be prescribed a maintenance dose.[18] Doctors should be informed of these guidelines and encouraged to periodically review the patient's symptoms and 'step down' treatment when appropriate. The results of this study highlight the potential for cost savings to be made by generic substitution, facilitating the most efficient use of the limited drugs budget.

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Colorectal Cancer Screening: mainstay of prevention

Manisha Namah
5th Year Medicine

ABSTRACT

Screening for colorectal cancer clearly reduces colorectal cancer mortality. Effective, safe, and relatively inexpensive methods for screening for the disease have been available for decades. Screening is recommended by a number of professional organizations, including the Multidisciplinary Expert Panel, the US Preventive Services Task Force and the American Cancer Society. However, no consensus has been reached on which screening modality to use. This article aims to critically assess the evidence for use of available colorectal cancer screening tests, including fecal occult blood tests, sigmoidoscopy, colonoscopy, double-contrast barium enema, and newer tests such as virtual colonoscopy and stool-based molecular screening.

INTRODUCTION

Epidemiology

Colorectal cancer (CRC) is the third most common cancer in both men and women and the second most frequent cause of death from cancer worldwide.[1] CRC is more common in developed countries with a lifetime incidence of 5%. 90% of cases occur after the age of 50.[1] Over the last 20 years, the mortality from colorectal cancer has been steadily decreasing (Figure 1). In Ireland, approximately 1488 men (15.3% of total cancer incidence in males) and 1232 women (12.8% of total cancer incidence in women) are diagnosed with CRC annually. The average mortality rate in Ireland from CRC is 840 deaths in men (14.4% of cancer deaths in males) and 716 deaths in females (13.7% of cancer deaths in females).[2]

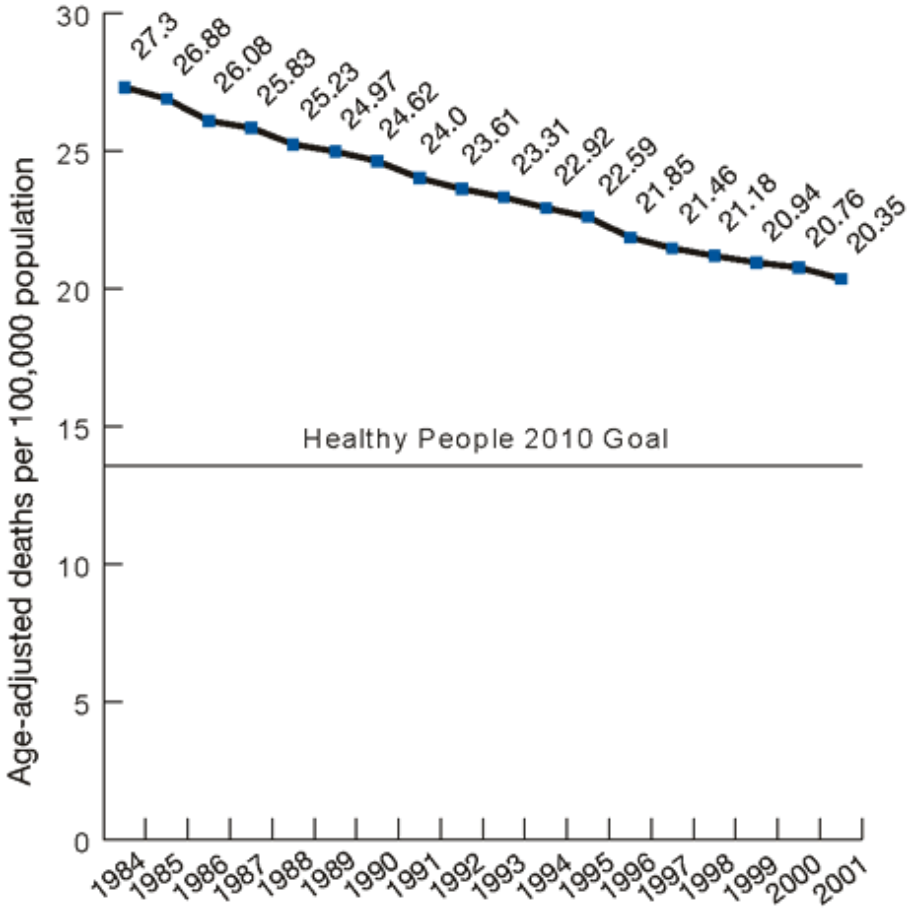

Figure 1: Mortality from colorectal cancer (Centers for Disease Control and Prevention National Center for Health Statistics data National Vital Statistics System-Mortality, analyzed by National Cancer Institute)

Pathology of colorectal cancer

Most CRCs result from malignant changes in polyps (adenomas) which develop in the lining of the bowel 10-15 years earlier.[3] A schematic of the morphologic and molecular changes in the adenoma-carcinoma sequence is shown in Figure 2. Individuals may be born with one mutant allele of the tumour suppressor gene *APC* or one normal copy is lost early in the sequence. This is the "first hit" according to Knudson's hypothesis. The loss of the remaining normal copy of *APC* follows ("second hit"). Mutations of the oncogene *k-ras* occur next and additional mutations inactivate the tumour suppressor genes *DCC* and *p53*, leading to the emergence of carcinoma. Although there seems to be a temporal sequence of changes as shown, the accumulation of mutations, rather than their occurrence in a specific order, is more important. A second pathway is characterised by genetic defects in DNA mismatch repair genes: *MSH2, MSH6, MLH1, PMS1* and *PMS2* giving rise to Hereditary Non Polyposis Colorectal Cancer (HNPCC). There is

accumulation of mutations but unlike the adenoma-carcinoma sequence, there are no clearly identifiable morphologic correlations.[4]

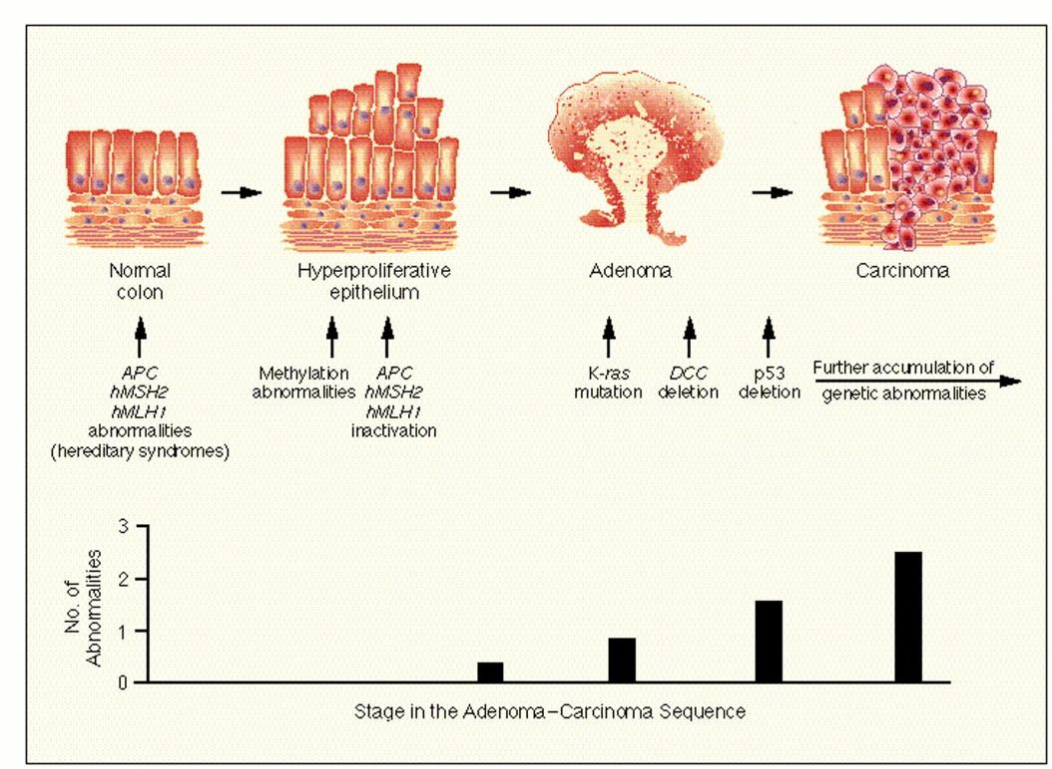

Figure 2. Adenoma-Carcinoma Sequence: molecular and morphological changes. [5]

Screening Rationale

Evidence suggests that only 10% of 1cm adenomas become malignant after 10 years.[6] The incidence of adenomatous polyps in the colon increases with age and although adenomatous polyps can be identified in 20% of the population, most of these are small and unlikely to undergo malignant change. As it takes a relatively long time for malignant transformation from adenoma to carcinoma to occur and outcomes are markedly improved by early detection of adenomas and early cancers, the potential exists to reduce disease mortality through screening asymptomatic individuals.[6]

There is a consensus that people who have no additional risk factor other than their age (i.e. of average risk) should begin regular screening at age 50 [7,8,9]. Between the ages of 40 and 49, there is a low yield for screening colonoscopy[10] and there is no evidence for capping the upper age limit of screening.[8]

SCREENING TESTS

Faecal occult blood test (FOBT)

Blood vessels at the surface of colorectal polyps, adenomas or carcinomas are often fragile and easily damaged by the passage of faeces. The damaged vessels usually release a small amount of blood in the faeces. FOBT is the only non invasive screening test for CRC with proven effectiveness, reducing both incidence and mortality when used systematically. In a randomised control trial evaluating the effectiveness of FOBT in reducing death rate from CRC, the use of annual FOBT was found to significantly reduce the incidence of CRC. A positive FOBT was followed by sigmoidoscopy and double contrast barium enema (DCBE) or by colonoscopy. The ratios of the cumulative incidence rates in the screening groups to that in the control were 0.80 (95% CI: 0.70 to 0.90; $p< 0.001$) for the annual screening group and 0.83 (95% CI: 0.73 to 0.94; $p= 0.002$) in the biennial screening group. The significant reduction in the incidence of CRC was due to the identification and removal of precursor lesions for CRC. It was argued that the high colonoscopy rate could account for the reduction in incidence rather than the effectiveness of FOBT since the former would enable detection of non bleeding lesions which FOBT would miss.[11]

FOBT on its own has a sensitivity of 23.9% as found in a study by Liebermann and colleagues with a positive predictive value (PPV) of 39.7% and negative predictive value (NPV) of 87.8%. When followed by sigmoidoscopy, the sensitivity of combined testing improves to 75.8% compared to sigmoidoscopy alone (70.3%). These statistics refer to detection of advanced neoplasia when a positive FOBT is followed by sigmoidoscopy alone compared to follow up by colonoscopy. It was also found that this combination of FOBT followed by sigmoidoscopy failed to detect a quarter of all distal advanced neoplasia and half of all advanced proximal neoplasia.[12]

The Minnesota Colon Cancer Study found that annual FOBT followed by colonoscopy and DCBE results in reduced mortality from CRC by 33% (Rate ratio=0.67; 95% CI: 0.50-0.87). Of note the incidence of Dukes D (distant metastases) CRC in the control group (no screening) was twice as many as that in the screening group. The study also recorded a greater incidence of Dukes A (confined to the bowel wall) CRCs most likely due to increased detection by screening. Survival was better in the annually screened group compared to control group. The 13 year cumulative mortality per 1000 from CRCs was 5.88 for the annual FOBT group (95% CI: 4.61-7.15): 8.33 for the biennial screening group (95% CI: 6.82-9.84) and 8.83 for the control group (95% CI: 7.26-10.40).[13] As the biennial group showed a cumulative CRC mortality rate greater than control group, it was decided to extend the follow up to 18 years. A 21% reduction (rate ratio=0.79; 95% CI: 0.62-0.97) in mortality was then found compared to 6% for the 13-year follow-up. There were 32% fewer Dukes D CRCs in the biennially screened group. Little screening was offered between years 13 and 18.[14]

In the Nottingham Study, patients selected from general practices were randomly assigned to biennial screening or to no screening. This study showed a 15% reduction (OR=0.85; 95%CI: 0.74-0.98) in CRC mortality in the biennial screened group. 4.3% more CRCs were detected in the screened group and the proportion of Dukes A tumours was significantly higher in the screening group than in the control (20 vs 11%; $p<0.001$). Incidence of Dukes C (involvement of regional nodes) and D stage CRC was lower in the screening group than in controls (ratio= 0.91; 95% CI: 0.80-1.04). Overall CRC incidence was higher in the screening group than in the control group (1.49 vs 1.44 per 1000 person years). There was a significant survival advantage for individuals in the screening group over those in the control group ($p<0.0001$). All cause mortality was similar in the screening and control groups. Sensitivity was calculated as 53.6%. Follow up was for an average of 7.8 years.[15]

Faecal DNA testing

A new non-invasive test, the faecal DNA test detects *k-ras*, *APC* and *p53* mutations; *MSI* marker *BAT-26* and a marker of long DNA thought to reflect disordered apoptosis of cancer cells sloughed in the colonic lumen. This was compared to FOBT for CRC screening in an average risk population. Faecal DNA detected 18.2% of samples with advanced neoplasia whereas Haemoccult II FOBT detected 10.8%. The sensitivity of the DNA panel for advanced adenomas was lower than previously reported, although CI overlapped. A decrease in exfoliation of cells owing to smaller adenoma size could be responsible. Specificity of Haemoccult II FOBT was 95.2% whereas that of faecal DNA was 94.4%.[16] Faecal DNA testing is not part of any published screening guidelines.

Sigmoidoscopy

Sigmoidoscopy has been acknowledged as an effective screening tool in CRC, however, data from randomized control trials are lacking. In a case-control study to determine whether sigmoidoscopy is associated with a reduction in CRC mortality, a single examination with sigmoidoscopy was found to lower the mortality rate by 80%. Individuals were found to be at lower risk compared to those who had not had any screening (OR =0.21, 95% CI: 0.08-0.52).[17]

In a population-based case-control study to evaluate the effectiveness of sigmoidoscopy in relation to screening interval, sigmoidoscopy was associated with a statistically significant and sustained reduction in the incidence of distal CRC. Compared with individuals who never had a screening sigmoidoscopy and those who had, the OR for distal CRC was 0.24 (95% CI: 0.17-0.33). The OR was similar to the OR for distal CRC among those who had a single screening sigmoidoscopy (OR: 0.30; 95% CI: 0.20-0.43). This association between screening sigmoidoscopy (whether single or multiple) and reduced incidence of distal CRC was observed for individuals who reported having

a screening sigmoidoscopy during the past 16 years relative to diagnosis or interview. Results from studies showed that optimal screening interval for sigmoidoscopy was longer than the 5-year interval recommended by the American Cancer Society.[18]

Sensitivity for the detection of potential lesions using sigmoidoscopy can be limited by a number of factors including poor bowel preparation and length of the endoscope. Prospective studies reveal that poor preparation precludes adequate rectosigmoid evaluation in 20% of examinations. Confinement of the scope to the rectum and sigmoid colon in 75-80% of attempts only leads to identification of 30-40% of lesions with a risk of perforation of 1 in 10,000. A 60cm sigmoidoscope is available, but even when passed to the splenic flexure, this can reach only 40-50% of neoplasms.[18]

Double-contrast barium enema (DCBE)

The strongest support for DCBE is based on the observation that treatment of early cancer in asymptomatic individuals lowers disease specific mortality and removal of adenomatous polyps reduces cancer incidence. Expense of DCBE is slightly higher than that of sigmoidoscopy. However DCBE is safer. No studies use DCBE as primary procedure and other studies have weak statistical power.[19] There is also considerable inter-observer error for the diagnosis of neoplasia on DCBE.[20]

In one study, 190 patients who underwent DCBE were randomly selected for colonoscopy. The sensitivity was 81% and specificity 96% for adenomas larger than 1cm.[21] In another study in which colonoscopy and DCBE were used for surveillance in patients with previous adenomas, the sensitivity for lesions larger than 7mm was 71% and the specificity was 98%. Most overlooked lesions measured between 7 and 10 mm.[22]

Therefore DCBE can probably detect at least three quarters of adenomas larger than 1cm, and possibly an even higher percentage of patients with such lesions. The cumulative benefits of periodic screening and the influence of the long natural history should also be considered.[19]
For polyps larger than 1cm sensitivity of DCBE and colonoscopy are highly comparable. For polyps smaller than 1cm colonoscopy has better test performance than DCBE, but the clinical significance of small polyps remains controversial.[23]

Colonoscopy

Colonoscopy is considered the ‘gold standard’ for CRC screening. A negative finding on colonoscopy can preclude the need for further screening for at least a further 5 years. The sensitivity of colonoscopy is influenced by the operator’s experience. In most published articles, a

highly experienced endoscopist performs the colonoscopy but in many centres, availability of such expertise may be a limiting factor to successful screening.

There is dispute that colonoscopy can avert CRC and deaths; it can find most polyps and nearly all large polyps and cancers. It also has the further advantage that lesions can be removed simultaneously. Furthermore, colonoscopy finds a significant amount of proximal lesions that would otherwise be missed by performing sigmoidscopy [24, 25, 26]

To date there are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from CRC in people at average risk by means of a randomised control trial.[8] The National Cancer Institute is currently sponsoring a pilot study of colonoscopy screening but the results from a large randomised control trial, if undertaken, will not be available for many years.

Colonoscopy has been shown to reduce the incidence of CRC in two cohort studies of individuals who had adenomatous polyps removed at colonoscopy: the US National Polyp Study and the Italian Multicentre Study. The US National Polyp Study estimated that 76 percent to 90 percent of CRC could be prevented by regular colonoscopy screening, based on comparison with historic controls.[27] However, these results should be interpreted with some caution. The comparison groups were not from the same underlying population, which could introduce bias. All participants in the study had polyps detected and removed, thereby limiting the applicability of the results to the average screening population. The Italian Multicentre Study Group found that intervention in the adenoma-carcinoma sequence through conventional colonoscopic screening and polypectomy has the potential to reduce the incidence of CRC. During a mean follow up of 10.5 years, 6 CRCs were ascertained while the expected number was 17.7 (Expected number was calculated from the reference general population). Also a significant reduction OR of 0.34 (95% CI: 0.23-0.63 $p<0.01$) in the incidence of CRC was observed in the cohort with respect to the general population.[28]

It is difficult to calculate the sensitivity of colonoscopy as a screening tool, as it is commonly used as the ‘gold standard’ examination. In a study that assessed the sensitivity of colonoscopy for detection of polyps by performing colonoscopy twice in one day by different but experienced endoscopists in 183 patients, the initial procedure missed 27 percent of adenomas <5 mm in size, 13 percent of adenomas 6 to 9 mm in size, but only 6 percent of adenomas >10 mm in size.[29]

The specificity for colonoscopy with biopsy is generally reported to be 99% to 100%. However, this assumes all detected adenomas represent true-positive results and develop into cancer. If detection of an adenoma that will not become cancer is considered a false-positive result that subjects a patient to risk without benefit, then the actual specificity of colonoscopy would be much lower.[8]

The caecum is reached in 85-95% of attempts, depending on the experience of the operator. Suboptimal preparation, incomplete examination and faster rate of progression to carcinoma compared to the usual estimates have implications for the 10-year interval recommended between screenings. The superiority of colonoscopy is demonstrated by its ability to detect right sided neoplasms. If screening colonoscopy is performed only in patients with distal polyps detected by sigmoidoscopy, about half the cases of advanced proximal neoplasms will not be detected. The data in this study suggest that a substantial proportion of advanced proximal neoplasms are not associated with any distal sentinel lesion thus limiting screening with flexible sigmoidoscopy.[24]

The Veterans Affairs Cooperative Study Group found that the majority of advanced lesions occurred in the colon distal to the splenic flexure (7.3% of study population compared to 4.1%in the proximal colon). This shows that sigmoidoscopy would pick up almost half of total colon lesions. But since 48.4% of proximal neoplasia is associated with distal colon lesion, examination of the distal colon to the splenic flexure followed by colonoscopy would identify 79.9% of patients with advanced neoplasia. Of note, prevalence of advanced proximal neoplasia in patients with no polyps of any kind in the rectum and sigmoid or descending colon was 2.7% of study population compared to 3.7% when distal colon was defined as the sigmoid colon and rectum. Patients with large adenomas (≥10mm) or small adenomas (<10mm) in the distal colon were more likely to have advanced proximal neoplasia than were patients with no distal adenomas (OR= 3.4, 95% CI= 1.8-6.5, OR=2.6 95% CI= 1.7-4.1). So an adenoma increases the risk of advanced proximal lesion, regardless of its size. Patients with distal hyperplastic polyps had a risk of advanced proximal neoplasia that was similar to patients without any polyps. Of note, the prevalence of advanced proximal lesion increases with age.[25]

Colonoscopy, which uses sedation and requires skilled support personnel, is more expensive and has a higher risk for procedural complications than other screening tests, particularly when polypectomy is performed. Two recent studies examined the incidence of complications from colonoscopy performed in screening populations. The Veterans Affairs Cooperative Study Group found that 10 out of 3121 patients (0.3%) had major complications during or immediately after the procedures. Of these 10 patients, 6 had bleeding that required hospitalisation and the others had a stroke, myocardial infarction, Fournier gangrene and thrombophlebitis respectively. Three other patients died within 1 month, probably of causes unrelated to the procedure.[25] In a study of employees of a large corporation, Imperiale and colleagues found that among 1994 persons 50 years of age and older who underwent colonoscopy, 1 (0.05%) had a perforation that did not require surgery and 3 (0.15%) had bleeding that required A&E visits but not admission or surgery.[24]

Virtual colonoscopy (VC)

This is a new method of imaging the colon in which thin section, helical computed tomography is used to generate high resolution, two-dimensional axial images. Three-dimensional images of the colon simulating those obtained with conventional colonoscopy are then reconstructed offline. Virtual colonoscopy (VC) is relatively safe, minimally invasive and does not require intravenous sedation but still requires the normal bowel preparation but no intravenous sedative is needed. In a study by Fenlon and colleages,[30] 82 of the 115 polyps (71%) in a high risk population seen on conventional colonoscopy were correctly identified on the basis of location and size. The sensitivity of VC was related to the size of the polyp. Only 29 of the 53 polyps between 1 and 5mm in diameter (55%) were correctly identified on virtual colonoscopy. The sensitivity for detection of polyps that were 6 to 9mm and those 10mm or larger was significantly higher (82 and 91% respectively, p= 0.001). The performance of VC was also related to histologic type: detection of hyperplastic polyps 1-5mm in diameter was significantly lower than detection of adenomatous polyps of the same size (48 against 67%, p=0.003). The sensitivity of VC was 71% for hyperplastic polyps 6 to 9mm in diameter and 90% for adenomatous polyps. Including polyps of all sizes, per patient sensitivity of VC was 82% and specificity was 84%. False positive findings were due to inadequate bowel preparation, poor distention and diverticular disease (other bowel pathologies). However, caution must be taken when reporting false positives, although colonoscopy is used as the ‘gold standard’, between 10-20% of colonic polyps and up to 5% of CRC may be missed on colonoscopy. Hence it is possible that the true specificity and PPV of VC are higher than reported in that study.

Adequate expertise in VC interpretation is important in evaluating the competence of this test. With CT colonography, scanning can be performed at peripheral sites and interpretation done at

central sites by experienced radiologists with electronically sent data, implying expertise in interpreting need not be a limiting factor if CT colonography were to be used for screening.

One of the limitations of this study is that the performance of VC in high risk patients may be overestimated and that VC might not do as well in average risk patients. Hence the validity of this technique for screening is not established.[30]

CONCLUSION

Guidelines for CRC screening in an average risk population are available from several professional organisations including the US Preventative Services Task Force, Multidisciplinary Expert Panel and the American Cancer Society (Table 1). All organisations recommend commencing screening a population of average risk at 50 years.

Screening tool	**US Preventative Services Task Force[8]**	**Multidisciplinary Expert Panel[9]**	**American Cancer Society[7]**
FOBT	Annually	Annually	Annually
Sigmoidoscopy	Recommeded, "periodicity unspecified"	Every 5 years	Every 5 years
FOBT + sigmoidoscopy	Recommended as an option	Annual FOBT with sigmoidoscopy every 5 years	Recommended over FOBT alone
Double-contrast barium enema	"Insufficient evidence to recommend either for or against"	An option every 5-10 years	Every 5 years
Colonoscopy	"Insufficient evidence to recommend either for or against"	Every 10 years	Recommended as an option every 10 years

Table 1: Current Colorectal Cancer Screening Guidelines

The mortality from CRC can be reduced by the detection of asymptomatic early-stage disease. Secondary prevention can be achieved by detection and removal of colorectal adenomas, from which more than 95 percent of CRC arise.

Several factors must be accounted for when recommending screening for CRC. These include the effectiveness, sensitivity, false-positive rate, safety and convenience of the test, on top of the cost and cost-effectiveness of the programme. Consideration must also be given to what is best for the individual patient, in addition to clinical policy in general.

Faecal DNA testing and virtual colonoscopy are in their infancy as screening tools. In the future our growing understanding of the pathogenesis of CRC will hopefully lead to more sensitive and specific methods of screening.

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Diabetes: is patient knowledge the key to self-management?

Claire Fitzsimmons and Brid Hollywood

ABSTRACT

Type 2 diabetes is a chronic metabolic disorder and community-based management poses many challenges to both healthcare professionals and patients. This article explores the attitudes of two different diabetic patients towards their condition by means of informal interviews. The relationship between patient knowledge and compliance with treatment regimes is also investigated through the two case studies. Current strategies for managing Type 2 diabetes in the primary-care setting are also reviewed.

INTRODUCTION

According to the World Health Organisation the incidence of diabetes is increasing rapidly, potentially reaching an estimated 221 million by 2010, and placing a substantial strain on healthcare systems worldwide.[1] Type 2 diabetes is a chronic metabolic disorder associated with significant morbidity and mortality. In Ireland, approximately 2% of the population are affected by Type 2 diabetes with 65% of these patients receiving all their diabetes care from a General Practitioner (GP).[2] Early diagnosis, good glycaemic control and screening for complications are essential for effective management of Type 2 diabetes.[3] Hyperglycaemia is the principle diagnostic feature of Type 2 diabetes. The classic diagnostic signs and symptoms include polydipsia, polyuria, lethargy, unexplained weight loss and blurred vision.[1] The increase in blood sugar levels occurs insidiously and often precedes clinical onset of the disease by many years. At diagnosis, 20-25% of patients have evidence of one or more microvascular complications of the disease (i.e. retinopathy, nephropathy, and neuropathy).[4] Therefore, regular primary-care screening of high-risk groups is essential for early diagnosis of the disease. Risk factors for Type 2 diabetes include: family history of the disease, family history of cardiovascular disease, obesity (especially central), age (> 65 years), sedentary lifestyle, high fat diet, hypertension, impaired glucose tolerance, dyslipidaemia, and the use of certain medications, e.g. steroids.[5] Diagnostic criteria are outlined in Table 1 below.

Fasting Glucose		2 Hour Glucose	Interpretation	Response
< 6.1	**AND**	< 7.8	Normal	Review as indicated
6.1 – 6.9	**AND**	< 7.8	Impaired fasting glucose	Manage CVD risk aggressively; control weight, increase exercise. Re-test annually
< 7.0	**AND**	7.8 – 11.0	Impaired glucose tolerance	
7.0 or above	**OR**	>11.0	Diabetes	Treat

Table 1: Diagnostic Criteria for Type 2 diabetes[2]

STUDY APPROACH

Two patients with Type 2 diabetes were informally interviewed about their condition. The patients selected currently have differing disease status and were interviewed

individually outside the GP surgery setting. Both patients gave informed consent for the interview.
T.S., a 37 year-old female was diagnosed 2 years ago and rarely attends her GP.
P.F., a 55 year-old male, was diagnosed 5 years ago and attends regular GP appointments.

INTERVIEWS

What is diabetes?

T.S.: I don't know. It was probably explained to me, but I didn't understand. ***Have you heard of blood glucose?*** No, I've never heard of it.

P.F.: It's a problem in the body where the pancreas doesn't produce enough insulin, therefore the blood glucose levels rise.

Why take your prescribed medication and what would happen if you didn't?

T.S.: I would be afraid of what would happen if I didn't take them; I might have a stroke or heart attack, but I don't really understand what they're for.

P.F.: Glucose levels in the blood would build up, affecting my vessels. Blood wouldn't circulate to my extremities and the functions of my vital organs would be affected; my heart, eyes, and kidneys. When I found out how serious this was I didn't want to take any risks. I don't want to face the ramifications of not looking after myself.

What medication do you take and what are they for?

T.S.: I don't know.
Glucophage 500mg: I've been on this for 2 years, for my diabetes.
Aldactone 25mg: Taking it for 2 years now, for my facial hair growth.
Aspirin 75mg: I was given this just yesterday; I think it stops heart disease.
Rosuvastatin: I was put on this yesterday, too. The doctor explained why, but my head was a million miles away and I didn't hear any of it.

P.F.: Amaryl 4mg once a day, I've been on this for 5 years. It increases my insulin production.
Metformin 850mg twice a day, I've been on this for 4 months. It increases the effectiveness of Amaryl.
Simvastatin 10mg, I've been on this for 8 months and it lowers cholesterol.
My cholesterol was 6.6 when they put me on it but I've since heard there's evidence of benefits for putting every diabetic on statins, not just if they're over 50 or have high cholesterol.

What else can you do to manage your diabetes?

T.S.: Don't eat any sugar and cut out junk food. I've done that, but I can't stop drinking Coke. I drink up to 2 litres a day. I couldn't go on a strict diet.
Do you exercise? No, but I was told I should. I'm not able to run or do sit-ups.

P.F.: Watch my diet, exercise, don't drink alcohol and keep my weight down.

How do you watch your diet? I can eat low GI foods, and slow releasing carbohydrates, like porridge and fruit - but not too much fruit. I was advised not to eat more than 5 grapes in one serving as they can make my blood sugars go high, so I don't buy them anymore. Who eats 5 grapes and stops?

I can't eat foods with high sugar content, excess carbohydrates, or too much cheese. I stopped drinking alcohol when I was diagnosed diabetic, but over the last year I've occasionally had the odd glass of red wine. I've recently heard that the best drink for a diabetic is gin and slimline tonic.

How do you measure your diabetic control and what should you aim for?

T.S.: I'm supposed to prick my finger 3 times a day with a special pen, but if I do it twice a week that would be the most. My sugars should be between 4 and 7. I don't write the values down although I should.

It goes above 7 a lot, it's usually 13 or 14. It also goes below 4 sometimes, and I get very tired and don't feel well.

P.F.: I do a pin-prick glucose test usually 3 times a day, and never less than twice.

The range should be between 4 and 7. My values range from about 3.8 to around 7. It's usually below 7. I know if it goes as low as 3.8 as I get tired.

I keep a record of my readings, and the average over the past 14 days is 6.6, and over the past 30 days is 6.8.

Why do you think you have diabetes?

T.S.: I don't know why I have it.

Do you have any family history? I have a niece who went on insulin during her recent pregnancy.

P.F.: It's familial, 3 of my 5 siblings have also found out they have diabetes since my diagnosis.

Do you attend a diabetic clinic and why?

T.S.: No, I went once but didn't go back. I tried to eat the foods they told me to, but I ended up eating more than I normally would and put on weight. The foods were expensive too.

P.F.: Yes, I visit a diabetic nurse every 3 months and see the doctor every so often. It's very important to monitor my diabetes and keep it under control.

They check my blood pressure, glucose levels, HbA_{1C}, and my feet. I also get my eyes checked once a year by a hospital specialist.

At the beginning I went through a lot of tests; ECG, renal tests, blood pressure, and eye tests. They told me that we caught the disease early, but having to go for all the tests and waiting for results really hit home with me how serious this condition was.

Has having diabetes changed your lifestyle, and if so, in what way?

T.S.: Not really. I just take the tablets and try not to eat too much junk food.

P.F.: Yes. The biggest change is my diet. It was difficult but I had to do it. It affects my social life as I don't go to the pub for a drink any more. I have to monitor and keep on top of the blood sugars every day. But the changes I make to my life now are nothing compared to changes I'd have to make if I lost my eyesight.

What are your hopes for the future with regards to your diabetes?

T.S.: I want to lose the extra weight I have on, and I would be prepared to go on insulin injections to do this, even though I hate needles.

P.F.: To control my diabetes with diet and tablets alone. I don't want to progress to using insulin, as I don't want the hassle of using needles and I don't like them.
I realise this may be inevitable, but I want to avoid it for as long as possible.

DISCUSSION

Self-Management

These cases illustrate two patients with different attitudes towards diabetes. Ultimately, the diabetic patient is in control of their disease and the role of the healthcare professional is to help the individual make informed choices about self-management.[6] Optimal management of diabetes requires significant lifestyle changes for many patients, which can be difficult to achieve and maintain.[7] A number of factors are thought to influence patient compliance with treatment plans, such as education, gender, age, socio-economic status, family history of Type 2 diabetes, current lifestyle, and patient knowledge of their condition. Just as the two patients interviewed displayed different attitudes towards diabetes, it is important to realise that no two patients are alike. The initial diagnosis of a chronic disease such as diabetes can bring with it fear and denial. At this crucial time it is essential to listen to the patient and meet their needs, avoiding information overload and maximising patient cooperation. Cooperation between the patient and healthcare professional is fundamental to the successful long-term management of diabetes.[2]

Disease progression and complications

A common misconception of patients is that Type 2 diabetes is a "mild" disease.[3,8] Research highlights the importance of in-depth exploration of patients' views during each consultation to identify service delivery failures and gaps in patient knowledge, such as a lack of awareness of macrovascular risk.[7] The incidence of macrovascular (cardiovascular disease) and microvascular (retinopathy, nephropathy and neuropathy) complications are well documented. Alarmingly, the presence of diabetes as a cardiovascular disease risk factor is equivalent to having pre-existing coronary heart disease.[2,9] Studies have shown that diabetes to now the most common single cause of end-stage renal disease[10] and adult blindness[9] in Europe and the United States. With the well-described nature of disease progression, patient awareness and cooperation with health care professionals is of paramount importance.

Lifestyle Modifications

The aims of Type 2 diabetes management are to relieve acute symptoms, improve quality of life and prevent long-term complications without precipitating hypoglycaemia.[5] It is generally accepted that aggressive management of diabetes, including a self-care regime of tight gylcaemic control, medication, diet control, and exercise promotes a better quality of life and fewer long-term complications.[11] The most common therapeutic error in Type 2 diabetes management is prescribing medication too soon. First-line therapy for diabetes, aimed at reducing insulin resistance, should be diet modification and weight loss.[3] This aspect of treatment should not be underestimated, as greater than 90% of diabetics are obese at the time of diagnosis.[12] Moderate weight loss improves glycaemic control, reduces cardiovascular disease risk and can prevent the development of Type 2 diabetes in those with impaired glucose tolerance.[13] Therefore, weight loss is an important therapeutic strategy in overweight patients who have Type 2 diabetes or are at risk of developing the disease.

All Type 2 diabetes patients should ideally be referred to a dietician.[2] Dietary guidelines are outlined in Table 2.[2,10] It is recommended that consumption of refined sugars be restricted, and that intake of complex carbohydrates should comprise 60-70% of the daily total energy intake. Protein should contribute 10-20% of total energy intake and less than 10% where renal disease or albuminuria is present. Fat should account for less than 35% of the total energy intake, with less than 10% being saturated fat. The normal weekly alcohol allowances are permitted: 21 units for males, and 14 units for females.[5] Regular physical exercise, tailored to the patient's medical condition, should be encouraged.[8] Smoking cessation should also be advised, in an effort to further decrease cardiovascular disease risk. Adoption of these lifestyle changes will reduce insulin resistance, improve glycaemic control, and have positive effects on blood pressure and lipid profile, lowering the patient's cardiovascular disease risk.[5]

Risk Factor	**Target Monitoring**	**Non-Pharmacological Action**
Hyperglycaemia	Fasting glucose < 7.0mmol/l HbA1c < 6.5%	Set reasonable achievable targets Restrict refined sugar intake
Dyslipidaemia	Total cholesterol < 4.5mmol/l LDL cholesterol < 2.5mmol/l HDL cholesterol > 1.0 (male) > 1.3 (female) Triglyceride < 1.7mmol/l	Review dietary intake Total fat < 35% TE Saturated fat < 10%
Hypertension	< 130/85	Salt restriction < 6g/day Weight reduction
Obesity	BMI 20-25kg/m^2	Reduce dietary intake Carbohydrate 60-70% TE Protein 10-20% TE (not exceeding 1g/kg) Encourage fibre, vitamin & antioxidant intake

Sedentary lifestyle	Physical activity review	Increase aerobic activity

Table 2: Management Targets for Type 2 diabetes[2,10]

Pharmacological treatments

Where treatment goals are not achieved after an adequate trial of dietary and lifestyle changes, an oral hypoglycaemic agent should be prescribed. The UK Prospective Diabetes Study found that only 23% of patients attained fasting plasma glucose levels below 7.8mmol/L when managed by dietary modification alone.[12] Oral hypoglycaemics available include the sulphonylureas, metformin and acarbose.

Sulphonylureas are first-line agents, unless the patient is obese, where metformin is the drug of choice.[3] Sulphonylureas augment endogenous insulin production by stimulating its release from pancreatic beta-cells. Many patients do not respond to the action of sulphonylureas (primary failure) and of those who respond a further 5-10% per year later become resistant (secondary failure).[3] Weight gain and hypoglycaemia are common adverse effects of sulphonylureas. Hypoglycaemia can be severe and occasionally fatal. Patients must be counselled on the warning signs of hypoglycaemia and its management.[5] Occasionally sulphonylureas can cause a disturbance in liver function, which rarely progresses to cholestatic jaundice, hepatitis and hepatic failure. Hypersensitivity reactions have also been reported.

Metformin increases insulin sensitivity by reducing hepatic glucose production and increasing peripheral glucose uptake. Insulin production is not affected, therefore hypoglycaemia does not occur as a side-effect.[8] Metformin does not cause weight gain, and is the treatment of choice in obese patients; however, it is equally effective in the non-obese. Adverse effects mainly involve gastrointestinal upset: anorexia, nausea, vomiting and diarrhoea, which may persist, particularly if high doses are used. Rarely, metformin can cause lactic acidosis, a potentially fatal complication. It is associated with renal dysfunction and consequently, metformin is contra-indicated in renal disease.

The thiazolidinediones, pioglitazone and rosiglitazone reduce peripheral insulin resistance through activation of nuclear peroxisome proliferator activated receptor γ (PPARγ), leading to a reduction of blood-glucose concentration.[14] They can be used alone or in combination with metformin or with a sulphonylurea. As weight gain is a common side effect, they preferably should be combined with metformin, particularly for obese patients. Other side effects include nausea, vomiting, headache and rarely pulmonary oedema and angiooedema. The original thiazolidinedione, troglitazone, was withdrawn from the market following reports of severe and unpredictable hepatotoxicity; consequently, liver function should be closely monitored in patients receiving thiazolidinedione therapy. They are contraindicated in patients with hepatic impairment, or if pre-treatment concentrations of alanine aminotransferase are raised more than 2.5 times the upper limit of normal. Cardiac failure of any degree is a further contraindication.

Nateglinide and repaglinide are oral insulin secretagogues with a rapid onset of action and short duration of activity. They are administered shortly before each main meal.

Repaglinide may be given as monotherapy for patients who are not overweight or for those in whom metformin is contra-indicated or not tolerated, or it may be given in combination with metformin. Nateglinide is licensed only for use with metformin. Adverse effects include abdominal pain, nausea, vomiting, hypoglycemia and rarely hypersensitivity reactions.

Acarbose may be used in patients who do not respond to diet alone, those who cannot tolerate conventional hypoglycaemics, or as an adjunct to other drugs.[5] Taken at the beginning of a meal, acarbose reduces post-prandial hyperglycaemia by reducing polysaccharide digestion in the small intestine, therefore reducing glucose absorption. The major adverse effect is GI intolerance.

Combination therapy is indicated when patients become refractory to monotherapy.[3,4] The most common combination used is metformin and a sulphonylurea. Up to 50% of patients uncontrolled with high dose sulphonylureas will achieve good glycaemic control with the addition of metformin.[8]

When both dietary and oral combination therapy fails, insulin is indicated, and the patient should be referred to a specialised service for initiation of therapy, education and monitoring. In Ireland it is estimated that 20% of Type 2 diabetes patients eventually require insulin therapy.[2]

Statins, a class of lipid-lowering drugs, have proven benefits in primary prevention of cardiovascular disease in Type 2 diabetes patients. The recent Collaborative Atorvastatin Diabetes Study (CARDS) demonstrated significant cardiovascular disease risk reduction in Type 2 diabetic patients irrespective of pre-treatment LDL-cholesterol levels.[15] Therefore, all diabetic patients should be considered for statin therapy irrespective of their lipid level unless contraindicated.[9] Evidence from the West of Scotland Coronary Prevention Study (WOSCOPS) suggest statins have a protective role in the primary prevention of Type 2 diabetes development.[16]

The American Diabetes Association recommends enteric-coated aspirin as primary prevention of cardiovascular disease in Type 2 diabetes patients aged over 30 years who are at high risk of vascular disease.[9] This includes patients with hypertension, obesity, albuminuria, hyperlipidaemia, smokers, and those with a family history of cardiovascular disease. The risk of vascular complications in Type 2 diabetes are strongly associated with raised blood pressure, and any reduction in blood pressure is likely to reduce these risks.[17] Aggressive blood pressure management is advised in these patients.

Reaching targets

For health care professionals there is increasing emphasis on the importance of achieving diabetes management targets. However, there is evidence to suggest that patients who default from follow-up may do so due to a perception that failure to achieve their diabetic targets will be met with a negative attitude on the part of the GP. The lifestyle changes necessary to improve the prognosis of Type 2 diabetes can be difficult for any patient to implement and maintain. Individualised personal targets must be agreed with each patient and reviewed at each follow-up visit. Patient education and motivation is vital for achieving treatment goals.[4] A positive environment where patients are not criticised for difficulty in complying with

recommendations, but supported and encouraged, may help to ensure repeated return for regular review and monitoring.[2]

Conclusion

The future of diabetes care will see patients managed in an appropriately resourced primary care setting, with access to a dietician, podiatrist, ophthalmologist, and diabetic nurse on a regular basis with additional specialist referrals as necessary. Shared care initiatives should be developed between GPs and local hospital-based specialist medical teams to provide high quality care for diabetic patients. There is a need for health care professionals to explore the attitudes and beliefs of Type 2 diabetes patients in order to optimise patient management. Empowering a diabetic patient requires offering accurate and up-to-date information that meets the individual's needs.[6] Providing the patient with sufficient knowledge to make informed choices gives them the independence and responsibility required for successful control of their disease.

P.F. summed up much of this in a final statement at the end of his interview. He provided an insightful analogy which may be worth remembering:

"I think learning to manage diabetes should be likened to learning to drive a car. Just as the driving instructor doesn't go into unnecessary detail on the mechanics of the car engine, but explains how to change gear and manoeuvre; I believe health carers shouldn't get too involved in explaining the detailed physiology of diabetes, but focus on teaching how to manage and control the condition, skilfully and with confidence."

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