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ABSTRACT

Aim: To study the etiology, presentation and complications of Gastrointestinal tract (GIT) perforations due to ingestion of foreign bodies.
Methods: A retrospective review of 21 patients with perforations in the GIT due to foreign body ingestion was done in the Department of General Surgery Sher-i-Kashmir Institute of Medical Sciences Srinagar (SKIMS) from January 2002 to December 2011. Data was reviewed in terms of the type and nature of the foreign objects, mode of entry into the gastrointestinal (GIT), preoperative diagnosis, perforation site, and treatment received.
Results: 66.6% of patients were males with age ranging from 7 to 82 years and a median age of 65 years. A definitive preoperative history of foreign body ingestion was obtained in 4 (19.04%) of the 21 patients. The mean time from ingestion to presentation was 9.3 days. The various foreign bodies recovered were chicken bones in 10 (47%), fish bones in 7 (33.33%), toothpick in 2 (9.5%) and metallic staple in 2 (9.5%) patients. A preoperative diagnosis of acute abdomen of uncertain origin was given in 12 (57.14%) of the 21 patients. Site of involvement in decreasing order of frequency was ileum in 14 (66.6%), colon in 5 (23.8%) and jejunum in 2 (9.5%) patients. Commonest surgery done on these patients was emergency laparotomy with primary repair of the foreign objects, mode of entry into the gastrointestinal (GIT), preoperative diagnosis, perforation site, and treatment received. Complication in terms of surgical site infection was seen in 3 (14.28%) patients and 2 (9.5%) deaths were recorded.
Conclusion: Dietary foreign body is the most commonly ingested object giving rise to GIT perforation. Treatment consists of surgery and antibiotics. Patients are rarely aware of foreign body ingestion and a high index of suspicion is required to make a diagnosis of ingested foreign body in all acute abdomen conditions particularly at extremes of age as seen in the results.
KEYWORDS: foreign body, perforation, peritonitis, ileostomy

Introduction:

Foreign body ingestion is a common occurrence, especially in children, alcoholics, mentally handicapped and edentulous people wearing dentures. However, majority of the individuals pass these objects without any complications. Most foreign bodies pass readily into the stomach and travel the remainder of the gastrointestinal tract without difficulty; nevertheless, the experience is traumatic for the patient, the parents, and the physician, who must await the removal or the ultimate passage of the foreign body. The alimentary canal is remarkably resistant to perforation: 80% of ingested objects pass through the gastrointestinal tract without complications. About 20% of ingested foreign bodies fail to pass through the entire gastrointestinal tract. Any foreign body that remains in the tract may cause obstruction, perforation or hemorrhage, and fistula formation. Less than 1% result in perforations from the mouth to the anus and those are mostly caused by sharp objects and erosions. Of these sharp objects, chicken bones and fish bones account for half of the reported perforations. The most common sites of perforation are the ileo-cecal junction and sigmoid colon.

Materials and Methods

This study, "Gastrointestinal tract perforations due to foreign bodies; a review of 21 cases over a ten year period" was carried out in the Department of General Surgery at the Sher-i-Kashmir Institute of Medical Sciences Srinagar (SKIMS), a tertiary care hospital in North India, from January 2002 to December 2011. A total of 21 consecutive patients who underwent surgery for an ingested foreign body perforation of the GI tract over a period of ten years were retrospectively reviewed. Computer database and extensive case note search of patient’s personal data including age, sex, residence, presenting complaints with special stress on clinical examination findings was done. The type and nature of the foreign objects, mode of entry into the gastrointestinal tract, preoperative diagnosis, perforation site, and treatment received were recorded. The complications arising due to perforation of GIT because of the foreign body ingestion and complications arising due to specific treatment received were noted. Important findings on various laboratory tests, including a complete blood count, erythrocyte sedimentation rate, [pre-op/post-op/follow up], blood cultures, and serum chemistry, chest and abdominal X-rays were penned down. Special efforts were made to identify the predisposing factors for ingestion of foreign bodies including edentulous patients with dentures, psychosis, extremes of age and hurried eating habits. Clinical, laboratory and radiological findings, treatment modalities, operative findings and therapeutic outcomes were summarized. Data collected as such was described as mean and percentage.
<table>
<thead>
<tr>
<th>S No</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Foreign Body</th>
<th>Presentation &amp; Pre Op Diagnosis</th>
<th>Procedure Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>Male</td>
<td>40 cm from ileo-caecal valve</td>
<td>Fish bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Removal of foreign body and repair</td>
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<tr>
<td>2</td>
<td>65</td>
<td>Female</td>
<td>30 cm from ileo-caecal valve</td>
<td>Chicken bone</td>
<td>Acute abdomen, diverticulitis</td>
<td>Resection of the perforated distal ileum and ileum stoma</td>
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<tr>
<td>3</td>
<td>80</td>
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<td>30 cm from ileo-caecal valve</td>
<td>Chicken bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Resection of the perforated distal ileum and ileum stoma</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>Male</td>
<td>Jejunum</td>
<td>Tooth pick</td>
<td>Acute abdomen, appendicitis</td>
<td>Removal of foreign body and repair</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
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<td>10 cm from ileo-caecal valve</td>
<td>Metallic staple</td>
<td>Acute abdomen, diverticulitis</td>
<td>Removal of foreign body and repair</td>
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<tr>
<td>6</td>
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<td>Female</td>
<td>Jejunum</td>
<td>Chicken bone</td>
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<tr>
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<td>Fish bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Resection of the perforated distal ileum and ileum stoma</td>
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<tr>
<td>8</td>
<td>59</td>
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<td>Sigmoid colon</td>
<td>Chicken bone</td>
<td>Acute abdomen, diverticulitis</td>
<td>Removal of foreign body and repair</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>Female</td>
<td>30 cm from ileo-caecal valve</td>
<td>Chicken bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Removal of foreign body and repair</td>
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<tr>
<td>10</td>
<td>49</td>
<td>Female</td>
<td>40 cm from ileo-caecal valve</td>
<td>Chicken bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Removal of foreign body and repair</td>
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<tr>
<td>11</td>
<td>7</td>
<td>Male</td>
<td>Sigmoid colon</td>
<td>Metallic staple</td>
<td>Acute abdomen, diverticulitis</td>
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<tr>
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<tr>
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<td>Acute abdomen, appendicitis</td>
<td>Resection of the perforated distal ileum and ileum stoma</td>
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<tr>
<td>14</td>
<td>56</td>
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<td>20 cm from ileo-caecal valve</td>
<td>Tooth pick</td>
<td>Acute abdomen, appendicitis</td>
<td>Resection of the perforated distal ileum and ileum stoma</td>
</tr>
<tr>
<td>15</td>
<td>65</td>
<td>Male</td>
<td>Sigmoid colon</td>
<td>Fish bone</td>
<td>Acute abdomen, diverticulitis</td>
<td>Removal of foreign body and repair</td>
</tr>
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<td>Resection of the perforated distal ileum and ileum stoma</td>
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<tr>
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<td>Chicken bone</td>
<td>Acute abdomen, appendicitis</td>
<td>Removal of foreign body and repair</td>
</tr>
<tr>
<td>18</td>
<td>55</td>
<td>Female</td>
<td>Sigmoid colon</td>
<td>Fish bone</td>
<td>Hematochizia acute abdomen, diverticulitis</td>
<td>Removal of foreign body and repair</td>
</tr>
<tr>
<td>19</td>
<td>56</td>
<td>Male</td>
<td>20 cm from ileo-caecal valve</td>
<td>Chicken bone</td>
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<td>Resection of the perforated distal ileum and ileum stoma</td>
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</table>
I/V Antibiotics ( Ceftriaxone + Metronidazole ) were given in the emergency room and changed to specific therapy as per the culture sensitivity postoperatively.

Results

The average follow up duration was 13 months (range 7 – 19 months). There were 14 male(66.66%) and 7 female (33.33%) patients ranging in age from 7 years to 82 years with a median age of 65 yrs at the time of diagnosis. The most frequently ingested objects were dietary foreign body (n = 17). Four patients had ingested objects like toothpicks (n =2) and metallic staples (n=2) [as shown in figure 1]. Among the dietary foreign bodies fish bone was found in 7(33.3%) and chicken bone in 10(47%) [as shown in figure 2] . All the patients described their ingestion as accidental and involuntary. A definitive preoperative history of foreign body ingestion was obtained in 4(19.04%) patients and an additional 9(42.8%) patients admitted ingestion of foreign body in the post operative period. Of these 13 patients the average duration between ingestion of foreign body and presentation was 9.3 days. Remaining 8 (38.09%) patients did not recall any history of foreign body ingestion; dietary or otherwise. In terms of impaction and perforation of ingested foreign body, ileum was the commonest site with 14(66.66%) patients showing perforation near the distal portions of the ileum followed by sigmoid colon in 5(23.8%). Jejunal perforation was seen in 2(9.5%) patients.

Fig 1: X-ray abdomen AP view showing ingested metallic pin

All our patients presented with acute abdomen and were admitted first in emergency department. Since majority of patients did not give any specific history of foreign body ingestion, they were managed as cases of acute abdomen with urgency and level of care varying according to the condition of patients. Eight patients presented with free air in the peritoneum and air under the right side of diaphragm. The most common preoperative diagnoses were acute abdomen of uncertain origin: 12 (57.14%); acute diverticulitis:5 (23.8%) and acute appendicitis: 4 (19.04%).

Fig 2: Intra operative picture showing perforation of small gut due to chicken bone

All the patients underwent an emergency celiotomy and confirmation of foreign body induced perforation was possible in all the 21 patients .Patients with a suspected appendicitis were explored via classical grid iron incision and rest via midline incision. Varying degrees of abdominal contamination was present in all the patients. Out of the 21 patients 11(52.38%) underwent removal of foreign body and primary repair of their perforations after minimal debridement. Intestinal resection with stoma formation (resection of the perforated ileum and ileum stoma) was done in 10 (47.6%) of the 21 patients as shown in Table 1. Take down of stoma was done at a later date. Three (14.28%) patients developed incisional superficial surgical site infection which responded to local treatment. Two (9.5%) patients died in the postoperative period due to sepsis. One patient (Patient no. 3 in table 1) who was a diabetic on Insulin, Chronic obstructive pulmonary disease and Hypertension died on 3rd postoperative day in surgical Intensive care unit due to severe sepsis. Another patient, (Patient no. 12 in table 1 ) an elderly female with no co-morbid illness developed severe sepsis due to Pseudomonas aeruginosa, died on 4th postoperative day. She was managed at a peripheral primary care center for first 3 days for her vague abdominal pain with minimal signs. All the other patients had an uneventful recovery and were discharged home between 6-14th postoperative day.

Discussion:

Foreign bodies such as dentures, fish bones, chicken bones, toothpicks and cocktail sticks have been known to cause bowel perforation6. Perforation commonly occurs at the point of acute angulation and narrowing.7, 8 The risk of perforation is related to the length and the sharpness of the object.7 The length of the foreign body is also a risk factor for obstruction, particularly in children under 2 years of age because they have considerable difficulty in passing objects longer than 5 cm through the duodenal loop into the jejunum. In infants, foreign bodies 2 or
3 cm in length may also become impacted in the duodenum. The most common sites of perforation are the ileo-cecal junction and sigmoid colon. Other potential sites are the duodeno-jejunal flexure, appendix, colonic flexure, diverticulae and the anal sphincter. Colonic diverticulitis or previously unsuspected colon carcinoma have been reported as secondary findings in cases of sigmoid perforation caused by chicken bones. Even colovesical or colorectal fistulas have been reported as being caused by ingested chicken bones. In our study ileum was the most common site with 14 patients showing perforation near the distal portions of the ileum followed by sigmoid colon. Jejunal perforation was seen in 2 patients.

The predisposing factors for ingestion and subsequent impaction are dentures causing defective tactile sensation of the palate, sensory defects due to cerebro-vascular accident, previous gastric surgery facilitating the passage of foreign bodies, achlorhydria where the foreign body passes unaltered from the stomach, previous bowel surgery causing stenosis and adhesions and diverticula predisposing to impaction. Overeating, rapid eating, or a voracious appetite may be contributing factors for ingesting chicken bones. The mean time from ingestion to perforation is 10.4 days. In cases when objects fail to pass the tract in 3 to 4 weeks, reactive fibrinous exudates due to the foreign body may cause adherence to the mucosa, and objects may migrate outside the intestinal lumen to unusual locations such as the hip joint, bladder, liver, and peritoneal cavity. The length of time between ingestion and presentation may vary from hours to months and in unusual cases to years, as in the case reported by Yamamoto of an 18 cm chopstick removed from the duodenum of a 71-year-old man, 60 years after ingestion. In our study the average duration between ingestion of foreign body and presentation was 9.3 days.

In a proportion of cases, definitive preoperative history of foreign body ingestion is uncertain. Small bowel perforations are rarely diagnosed preoperatively because clinical symptoms are usually non-specific and mimic other surgical conditions, such as appendicitis and caecal diverticulitis. In our study the most common preoperative diagnoses were acute abdomen of uncertain origin (n =12), acute diverticulitis (n = 5) and acute appendicitis (n = 4). Patients with foreign body perforations in the stomach, duodenum, and large intestine are significantly more likely to be febrile with chronic symptoms with a normal total white blood cell count compared to those with foreign body perforations in the jejunum and ileum. Plain radiographs of neck and chest in both anteroposterior and lateral views are required in all cases of suspect foreign body ingestion and perforations in addition to abdominal films. CT scans are more informative especially if radiographs are inconclusive. Computerised tomography (CT) scanning and ultrasonography can recognise radiolucent foreign bodies. An ultrasound scan can directly visualize foreign bodies and abscesses due to perforation. The ability to detect a foreign body depends on its constituent materials, dimensions, shape and position. Contrast studies with Gastrografin may be required in excluding or locating the site of impaction of the foreign body as well as determining the level of a perforation. Using contrast is important in identifying and locating foreign bodies if intrinsically non-radiopaque substances, such as wooden checkers or fish and chicken bones are ingested. The high performance of computed tomography (CT) or multidetector-row computed tomography (MDCT) scan of the abdomen in identifying intestinal perforation caused by foreign bodies has been well described by Coulier et al. Although, in some cases imaging findings can be nonspecific, however, the identification of a foreign body with an associated mass or extraluminal collection of gas in patients with clinical signs of peritonitis, mechanical bowel obstruction, or pneumoperitoneum strongly suggests the diagnosis. Finally, endoscopic examination, especially in the upper gastrointestinal tract, can be useful in diagnosis and management of ingested foreign bodies.

Whenever a diagnosis of peritonitis subsequent to foreign body ingestion is made, an exploratory laparotomy is performed. However, laparoscopically assisted, or complete, laparoscopic approaches have been reported. The treatment usually involves resection of the bowel, although occasionally repair has been described. The most common treatment was simple suture of the defect. Once the foreign body passes the esophagogastric junction into the stomach, it will usually pass through the pylorus; however, surgical removal is indicated if the foreign body has sharp points or if it remains in one location for more than 4 to 5 days especially in the presence of symptoms. A decision should be based on the nature of the foreign body in those cases, as to whether a corrosive or toxic metal in ingested. Occasionally, objects that reach the colon may be expelled after enema administration. However, stool softeners, cathartics and special diets are of no proven benefit in the management of foreign bodies.

Competing Interests
None declared

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REFERENCES
Landing on the MARS!!!

Sohail Abrar , Ahmed Shoka , Noman Arain and Candice Widuch-Mert

ABSTRACT

Background: Inadequate adherence to prescribed medication severely affects the efficacy of the treatment and acts as an important modifier of health system effectiveness. It has significant negative economic and clinical effects which are manifested by frequent relapses and re-hospitalisations.

Aims: By using a validated and reliable tool to assess medication adherence, we were aiming to identify the compliance level among our Psychiatric group of patients, and explore the reasons and possible causes of non-adherence. We also aim to identify the diagnoses and medicines which are mostly linked to non-adherence.

Method: We used the Medication Adherence Rating Scale (MARS) and a patient questionnaire to obtain information about client's adherence and their attitude towards psychotropic medications. We used prospective consecutive sampling and included all clients seen in the outpatient clinic during the 2 months duration of the study. The sample included clients aged 16 years and above.

Results & Clinical Implications: Results indicate a significant gap between subjective and objective rates of adherence. They also indicate that patients' attitudes towards their psychotropic medications are quite negative. Taking into account and addressing issues pertaining to side effects are very important to improve the level of adherence. Results also show that most of our clients are only partially adherent to psychotropic medication.

Introduction:

Non adherence to medication is a significant problem for client group in Psychiatry. Between a third and half of medicines that are prescribed for long term conditions are not used as recommended. In the case of Schizophrenia, studies reveal that almost 76% of the sufferers become non-compliant to the medication within the first 18 months of treatment.

Non-adherence has consequences for both clients and the Health Care System. If the issues of non-adherence are better identified and addressed actively, it has the potential of improving the mental health of our clients which will reduce the burden of cost to mental health resources. It is estimated that unused or unwanted medications cost the NHS about £300 million every year. This does not include indirect costs which result from the increased likelihood of hospitalization and complications associated with non-adherence.

The WHO identified non-adherence as "a worldwide problem of striking magnitude". This problem is not only just linked with our psychiatric client groups, but also is prevalent with most chronic physical conditions. It has been reported that adherence to medications significantly drop after six months of treatment.

In broad term compliance is defined as the extent to which the patient is following the medical advice. Adherence on the other hand is defined as the behavior of the clients towards medical advice and their concordance with the treatment plan. Adherence appears to be a more active process in which patients accept and understand the need of their treatment through their own free will and portray their understanding with either a positive or negative attitude towards their medications.

Unfortunately there is no agreed consensual standard to define non adherence. Trials suggest a rate of >50% compliance as adequate adherence while other researchers believe it should be at least >95%. As per White Paper of DOH (2010), it has been recommended that clinicians have the responsibility to identify such issues and improve collaborative relationships among multidisciplinary teams to deliver a better clinical and cost effective service.

Methods:

Sampling:

Our cohort included a prospective consecutive sample of 179 patients. The study was conducted in North Essex Partnership NHS Trust which provides general adult services for a catchment area of approximately 147,000 in Tendring area. All these clients were seen at the out patient's clinic at Clacton & District Hospital. Informed consent was taken as per recommendation of local clinical governance team. The study was conducted during a 2 month period from October to November in 2010. No patient was excluded from the study. Sample consists of clients who were aged 16 years and above.

Tools Used:

All the clients were asked questions using a standard questionnaire and MARS (Medication Adherence Rating Scale). MARS was developed by Thompson et al in 1999 as a quick self-reported measure of adherence mainly around psychiatric
clients. It was mainly devised from a 30 item Drug Attitude Inventory (DAI) and a 4 item Morisky Medication Adherence Questionnaire (MAQ). The validity and reliability of MARS has been established by Thompson et al and then Fialko et al in 2008 in a large study and has been reported to be adequate.

The patient questionnaire directly asked clients about their current medications and dosage regimens. It also enquired about various factors leading to non-compliance. It included factors like whether the medication makes them feeling suicidal, causes weight gain, makes them aggressive, causes sleep disturbances, causes sexual side effects, the form and size of tablets, stigma and family pressure, their personal belief about medication or do they feel that they become non adherent because as a direct effect and consequence of the illness.

Medication Adherence Rating Scale focuses both on adherence as well as the patient’s attitudes towards medications. It includes questions about how frequently they forget to take medications or are they careless about taking their medications. It also asks them if they stop taking their medication do they feel well or more unwell. Other aspects include whether they only take medicines when they are sick and do they believe that it is unnatural for their thoughts to be controlled by medications. It also asks about the effect of medication on them, such as; are they able to think clearly, or do they feel like a zombie on them?, or are they tired all the time?. It also checks their belief that if they remain compliant to medication, will it prevent them from getting sick again.

Results:

In total 179 clients were seen in the outpatient clinic during the period of two months. Out of those (54%, n=97) were females whereas nearly half (46%, n=82) were males. Age of the clients ranged from 18 years to 93 years. The mean age of the client group was 55; mode 41 and median was 69.5.

The diagnosis profile was quite varied. As far as the primary diagnosis is concerned, the majority (n=144) of service users were given a primary diagnosis using the ICD 10 criteria. Mood disorders were the most common primary diagnosis whereas personality disorder and anxiety were the most common secondary diagnosis. Table 1 show the number and percentage of the service users who presented with the most common diagnosed conditions.

Subjectively 160 (89%) patients reported that they were compliant with medications whereas 19(11%) patients admitted that they have not been adherent to medications. Out of those who said that they were non-adherent, 8 were suffering from Mood disorders, 2 had schizoaffective disorder, 3 had psychotic illness, 3 had organic brain disorder, 2 clients had personality disorder, whereas 1 client had anxiety and 1 had neurological illness.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Disorders</td>
<td>72 (50%)</td>
<td>07 (26.92%)</td>
</tr>
<tr>
<td>Psychotic illness</td>
<td>25 (17.36%)</td>
<td>01 (3.85%)</td>
</tr>
<tr>
<td>Anxiety and PD</td>
<td>13 (9%)</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>24 (16.7%)</td>
<td>02 (7.69%)</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>07 (4.86%)</td>
<td>01 (3.85%)</td>
</tr>
<tr>
<td>Drugs related illness</td>
<td>02 (1.39%)</td>
<td>02 (7.69%)</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>01 (0.69%)</td>
<td>00 (0.0%)</td>
</tr>
</tbody>
</table>

Prescription rate varied between different types of psychotrope medications. Antipsychotics were the most prescribed medication in our cohort. Table 2 shows data of each individual category.

<table>
<thead>
<tr>
<th>Medication category</th>
<th>N-number of prescribed meds</th>
<th>% of total prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>100</td>
<td>44%</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>72</td>
<td>31%</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>21</td>
<td>09%</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>21</td>
<td>09%</td>
</tr>
<tr>
<td>ACH Inhibitors</td>
<td>12</td>
<td>05%</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>04</td>
<td>02%</td>
</tr>
</tbody>
</table>

Less than half (39%, n=69) of service users had only one type of psychotropic medication whereas the majority (58%, n=104) of patients were on more than one psychotropic medication. A very small number of clients (3%, n=6) were not using any medications at all. When explored further it was revealed that almost two third of the antidepressant prescriptions comprised of SSRI’s (67%, n=55), about one fourth of SNRI (24%, n=21), a small proportion (6%, n=5) of NARI’s and very few (3%, n=3) were given tricyclic antidepressants. Similarly in antipsychotics, 75% of patients were on atypical and 25% were prescribed typical antipsychotics.

Factors leading to non-adherence:

Below is the graphical representation of what clients perceived as the major factors leading to the non adherence to the medication. Weight gain, illness effect, stigma and personal belief appear to be the major factors as displayed in Chart 1.

Attitude towards Medications:

The overall Service users’ attitude towards medication did not appear to be particularly good. They mainly complained of getting tired and forgetting to take medication. Below in Chart 2 is the graphical representation of what overall attitude they had expressed towards psychotropic medications.
As far as overall MARS score is concerned, the majority of patients (63%, n=110) scored >6 and about one third of patients (37%, n=63) scored <6. A score of less than 6 is generally considered as a poor level of adherence which means that almost one third of our client group does not comply with medications.

**Discussion:**

The aim of our study was to highlight the importance of the factors which often lead to non-adherence to medications and to explore patients’ attitudes towards medications. Results are indicating that the problem of non-adherence is much wider and deeper in our clients group. There is a significant gap in between subjective and objective rate of adherence. However we should be mindful that adherence appears to be more of a continuum rather than a fixed entity e.g. some patients can be more adherent than others but still have inadequate adherence and hence arises the concept of partial adherence. It is evident from the results that patients’ attitudes were not encouragingly positive towards psychotropic medications.

Human beings are born potentially non-compliant. It is our tendency to crave and indulge in things which we know might not be good for our health e.g. eating non healthy food, alcohol and substance misuse. We have better compliance to issues which give us the immediate reward like pain relief or euphoria from illicit drugs where as because of lack of this immediate reward, our compliance gradually becomes erratic. Compliance and adherence appears to be a learnt phenomenon which needs to be nurtured throughout our life.

**Manifestations of non-adherence:**

The consequences of non-adherence are mainly manifested and expressed through clinical and economic indicators. Clinically it means an increase in the rate of relapse and re-hospitalisation. As per one study non-adherent patients have about a 3.7 times high risk of relapse within 6 months to 2 years as compared to patients who are adherent. In US it was estimated that at least 23% of admissions to nursing homes were happening due to non adherence which meant a cost of $31.3 billion/380,000 admissions per year. Similarly 10% of admissions happened for the same reason costing the economy an amount of $15.2
billion/3.5 million patients\textsuperscript{13,14}. Figures in UK are also not much different where the cost of prescriptions issued in 2007-08 was estimated to be £8.1 billion and it was highlighted that £4.0 billion out of that amount was not used properly\textsuperscript{15}. Similarly in terms of hospitalization, about 4% admissions happen every year happen because of non-adherence. The total cost of hospitalization in 2007 was estimated to be £16.4 billion and it was suggested that non-adherence had a burden of costs in the region of £36-196 million\textsuperscript{17}.

From a clinical aspect it has been suggested that non-adherence causes about 125,000 deaths just in the US every year. Meta-analysis has suggested significant statistical association between non-adherence and causing depression in certain chronic physical conditions e.g. Diabetes\textsuperscript{19}.

**Dimensional Phenomenon?**

We need to be aware that adherence is a multidimensional and a multifaceted phenomenon and is better understood in dimensional rather than categorical terms. It has been widely accepted that if concordance is the process, then adherence will be the ultimate outcome. This was highlighted by WHO guidelines using following diagram:

**Chart 3: WHO diagram of the five dimension of adherence:**

Therefore any strategy developed to address the issue of non-adherence should be able to consider all these five dimensions; otherwise it will be less likely to have any chance of success.

**Measures to improve Compliance:**

All the known as clinical and economic indicators suggest that non-adherence issue needs significant attention and special measures which ought to be taken in order to avoid complications. There are already some running campaigns in other countries in order to improve adherence and we need to learn from their experiences such as the National Medication Adherence Campaign in US (March 2011). The campaign is basically a research-based public education effort targeting patients with chronic conditions, their family caregivers, and health care professionals\textsuperscript{20}.

Levine (1998) demonstrated that the following steps may help in increasing adherence:

- To appropriately assess the patient’s knowledge and understanding about the disease process and the need for treatment and to address those issues if there is some dysfunctional belief.
- To link the taking of medication with other daily routines of the life.
- To use aids to assist medication adherence e.g. MEMS, ePills, Calendar or Dossette box
- To simplify the dosage regimen
- Flexible Health care team who is willing to support
- Addressing current Psychosocial and environmental issues which might hinder the adherence\textsuperscript{21}.

It is extremely important for the clinician to take time to discuss in detail with their patients all the possible side effects and indications of the prescribed medications. Unfortunately clinicians may not be able to predict the possibility of having side effects but can certainly educate patients about their psychopathology, indication and rationale for the medication and make them realise how important it is for them to remain adherent to medication. Health education is considered equally effective as compared to any sophisticated adherence therapy and should be used routinely\textsuperscript{22}.

Clinicians also have very important role to play in simplifying the dosage regimen and emphasise to the patients that “Medications don’t work in patients who don’t take them”\textsuperscript{23}.

Various studies have tried to estimate the efficacy of a single factor and the multi factor approaches to improve adherence\textsuperscript{24}. Studies have showed proven efficacy for education in self management\textsuperscript{25,26}, pharmacy management programmes\textsuperscript{27,28}, nursing, pharmacy and other non medical health professional intervention protocols\textsuperscript{29,30}, counselling\textsuperscript{31,32}, behavioural interventions\textsuperscript{33,34} and follow up\textsuperscript{35,36}. However multi factor approaches have been found to be more effective than single factor approaches\textsuperscript{38}. Therefore it has been suggested that we need to address all the five dimensions of adherence (Chart 3) with multiple interventions to improve the adherence in our patients.

One factor potentially of concern leading to non-adherence is the possibility of the current overt or covert misuse of alcohol, illicit substances and over the counter available medications. This issue understandably can lead to partial or complete non adherence as well as worsening of existing psychiatric conditions. Therefore it needs to be explored further in future research projects.
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Management of alopecia areata: an update

Imran Majid and Abid Keen

Abstract
Alopecia areata is a common, non-scarring, autoimmune disorder affecting any hair-bearing area. It is often psychologically devastating. This disorder occurs in both the sexes, in all age groups, and is characterized by the sudden appearance of circumscribed areas of hair loss on the scalp or other parts of the body. Various therapeutic approaches are presently available for managing alopecia areata including corticosteroids, contact sensitizers and immunosuppressants, but none have been shown to alter the course of the disease on a consistent basis.

Keywords
Alopecia areata, treatment, autoimmune, corticosteroids, recent advances, contact sensitizers

Introduction
Alopecia areata is a non-scarring autoimmune, inflammatory hair loss affecting the scalp and/or body. Although the etiopathogenesis of alopecia areata is still unknown, the most widely accepted hypothesis is that it is a T-cell mediated autoimmune condition that occurs in genetically predisposed individuals. The term ‘alopecia areata’ was first used for this disorder by Savages. Alopecia areata has a reported incidence of 0.1-0.2%, with a life-time risk of 1.7%. The disease can begin at any age, but the peak incidence is between 20 and 50 years of age. Both the sexes are equally affected and there is no racial variation reported. Clinical symptoms of alopecia areata may present as a single well demarcated patch of hair loss, multiple patches, or extensive hair loss in the form of total loss of scalp hair (alopecia totalis) or loss of entire scalp and body hair (alopecia universalis). Histopathologically, alopecia areata is characterized by an increase in the number of catagen and telogen follicles and the presence of perifollicular lymphocytic infiltrate around the anagen phase hair follicles. The condition is thought to be self-limited in majority of cases, but in some the disease has a progressive course and needs active treatment in the form of oral or topical therapeutic options. Progressive alopecia areata is associated with severe social and emotional impact.

Clinical features
Alopecia areata mostly presents as a sudden loss of hair in well demarcated localized areas. The lesion is usually a round or oval flat patch of alopecia with normal skin colour and texture involving the scalp or any other region of the body. The patch of alopecia may be isolated or there may be numerous patches. It usually has a distinctive border where normal hair demarcates the periphery of the lesion. In acute phases, the lesions can be slightly erythematous and oedematous. The patches of alopecia areata are usually asymptomatic, although several patients may sometimes complain of local paraesthesia, pruritus or pain. The affected hairs undergo an abrupt conversion from anagen to telogen, clinically seen as localized shedding. Characteristic hairs, known as ‘exclamation point hairs’ may be seen within or around the areas of alopecia. The hairs are tapered towards the scalp end with thickening at the distal end. These hairs may also demonstrate deposition of melanin pigment in the distal extremity, also known as Wildy’s sign. Although not absolutely pathognomonic, it strongly suggests the diagnosis of alopecia areata. Hair pull test conducted at the periphery of the lesion may be positively correlated (six or more) with disease activity. In the chronic phases, the test is negative, since the hair is not plucked as easily as in the acute phases.

Another important clinical sign that can aid in the diagnosis is the presence of ‘cadaverous hair’. These are the hairs in which there occurs a fracture of the shaft inside the hair follicle, producing blackened points inside the follicular ostia resembling comedones. In alopecia areata, the hair loss progresses in a circumferential pattern. Often, distinct patches merge to form large patches. Upon regrowth, hairs will often initially lack pigment resulting in blonde or white hairs.

Extrafollicular involvement in alopecia areata:

a) Nail changes: Nail changes are more frequent in children (12%) than in adults (3.3%). The prevalence of nail changes is greater in the more severe forms of alopecia areata such as alopecia universalis and alopecia totalis. Finger nails are more commonly involved than the toe nails. Pitting is the most common finding. Other nail changes include koilonychias, onycholysis, onychomadesis, punctuate leukonychia, trachyonychia, Beau’s lines and red lunulae.
b) Ocular changes: Various ocular changes have been reported to occur in alopecia areata. These include focal hypopigmentation of the retina, lens opacities, posterior subcapsular cataracts, decrease in visual acuity, Horner’s syndrome, heterochromia of the iris, miosis and palpebral ptosis.

Treatment of alopecia areata

Treatment of alopecia areata is not mandatory in every affected patient because the condition is benign in majority and spontaneous remission is common. Treatment is mainly directed towards halting the disease activity as there is no evidence that the treatment modalities influence the ultimate natural course of the disease. Treatment modalities are usually tailored as per the extent of hair loss and the patient’s age. Addressing the impressive inflammatory process occurring in alopecia areata, corticosteroids have by far been the most commonly used treatment modality. Few treatments have been subjected to randomized control trials and except for contact immunotherapy, there is a paucity of published data on their long term outcomes. Currently, new treatments targeting the immune system are being explored for the use in alopecia areata.

<table>
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<th>Topical treatments</th>
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<td>Topical steroids</td>
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<tr>
<td>Intralesional steroid injections</td>
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<tr>
<td>Topical contact sensitizers</td>
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<tr>
<td>Anthralin</td>
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<tr>
<td>Minoxidil</td>
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<tr>
<td>Topical retinoids</td>
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<td>Tacrolimus</td>
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<td>Systemic treatments</td>
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<tr>
<td>Systemic corticosteroids</td>
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<tr>
<td>Sulfasalazine</td>
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<td>Azathioprine</td>
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<td>Methotrexate</td>
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<td>Oral zinc sulphate</td>
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<td>Photo-and photochemotherapy</td>
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<td>PUVA</td>
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<td>NBUVB</td>
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<td>Excimer laser</td>
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<tr>
<td>Miscellaneous and Non-pharmacological treatment</td>
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<tr>
<td>Dermatography, wigs</td>
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<td>Hypnotherapy etc.</td>
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</table>

Topical treatment options

Topical corticosteroids:

Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata. These include fluocinolone acetonide cream, fluocinolone scalp gel, betamethasone valerate lotion, cloprostenol propionate ointment, dexamethasone in a penetration-enhancing vehicle and halcinonide cream. They are a good option in children because of their painless application and wide safety margin. Topical corticosteroids are ineffective in alopecia totalis/universalis. Folliculitis is a common side effect of corticosteroid treatment, appearing after a few weeks of treatment. Telangiectasia and local atrophy have also been reported. Treatment must be continued for a minimum of 3 months before regrowth can be expected and maintenance therapy often is sometimes necessary.

Intralesional corticosteroids:

Intralesional corticosteroids are widely used in the treatment of alopecia areata. In fact, they are the first-line treatment in localized conditions involving <50% of the scalp. Hydrocortisone acetate (25mg/ml) and Triamcinolone acetonide (5-10mg/ml) are commonly used. Triamcinolone acetonide is administered usually in the concentration of 5mg/ml using a 0.5 inch long 30-gauge needle in multiple 0.1 ml injections approximately 1 cm apart. The solution is injected in or just beneath the dermis and a maximum of 3 ml on the scalp in one visit is recommended. Lower concentrations of 2.5mg/ml are used for eyebrows and face. Regrowth usually is seen within 4-6 weeks in responsive patients. Treatments are repeated every 3-6 weeks. Skin atrophy at the sites of injection is a common side effect, particularly if triamcinolone is used, but this usually resolves after a few months. Repeated injections at the same site or the use of higher concentrations of triamcinolone should be avoided as this may lead to prolonged skin atrophy. Pain limits the practicality of this treatment method in children who are less than 10 years of age. Severe cases of alopecia areata, alopecia totalis, alopecia universalis as well as rapidly progressive alopecia areata respond poorly to this form of treatment.

Anthralin:

Dithranol (anthralin) or other irritants have been used in the treatment of alopecia areata. The exact mechanism of action is unknown, but it is believed to be through immunosuppressant and anti-inflammatory properties with the generation of free radicals. It is used at concentrations ranging from 0.5 to 1% for 20-30 minutes after which the scalp should be washed with shampoos in order to avoid excessive irritant effects. The applications are made initially every other day and later on daily. Adverse effects include pruritus, erythema, scaling, staining of treated skin and fabrics, folliculitis, and regional lymphadenopathy. In an open study, 25% patients with severe alopecia areata were shown to respond positively to local applications of 0.5-1% anthralin. More placebo control studies are needed to justify the use of anthralin in alopecia areata.

Minoxidil:

Minoxidil appears to be effective in the treatment of alopecia areata. It’s mechanism of action has yet to be determined, but it is known to stimulate DNA synthesis in hair follicles and has a direct action on the proliferation and differentiation of the...
keratinocytes. In one clinical study, hair growth was demonstrated in 38% and 81% of patients treated with 1% and 5% minoxidil respectively. Thus 5% minoxidil solution is usually recommended as a treatment option in alopecia areata.

No more than 25 drops are applied twice per day regardless of the extent of the affected area. Initial regrowth can be seen within 3 months, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil has also been studied in combination with anthralin, which is usually recommended as a treatment option in alopecia areata. A recent study showed that 1% minoxidil has been used to treat extensive hair loss, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil has also been studied in combination with anthralin, which is usually recommended as a treatment option in alopecia areata.

Topical immunotherapy:

Topical immunotherapy is the best documented treatment so far for severe and refractory cases of alopecia areata. Topical immunotherapy is defined as the induction and periodic elicitation of allergic contact dermatitis by applying a potent contact allergen. In 1965, the alkylating agent triethyleneimino benzoquinone was the first topical sensitizer used to treat cutaneous disease, but it was abandoned on account of its mutagenic potential. Later nitrogen mustard, poison ivy, nickel, formalin, and primin were tried, mainly as topical immunotherapy, for alopecia areata and warts. Contact immunotherapy was introduced in 1976, by Rosenbeige and Drake. Later, potent contact allergens namely dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DPCP) replaced the allergens that were used earlier. DNCB is mutagenic against Salmonella typhimurium in the Ames test and is no longer used. Neither SADBE, nor DPCP are mutagenic. DPCP is more stable in solution and is usually the agent of choice.

Mechanism of action: Topical immunotherapy acts by varied mechanisms of action. The most important mechanism is a decrease in CD4 to CD8 lymphocyte ratio which changes from 4:1 to 1:1 after contact immunotherapy. A decrease in the intrafollicular CD6 lymphocytes and Langerhan cells is also noted. Happle et al., proposed the concept of 'antigenic competition', where an allergic reaction generates suppressor T cells that nonspecifically inhibit the autoimmune reaction against a hair follicle constituent. Expression of class I and III MHC molecules, which are normally increased in areas affected by alopecia areata disappear after topical immunotherapy treatment. A 'cytokine inhibitor' theory has also been postulated.

Method of sensitization: The protocol for contact immunotherapy was first described by Happle et al in 1983. The scalp is the usual sensitization site. For the initial sensitization a cotton-tipped applicator saturated with 2% DPCP in acetone is applied to a small area. Patients are advised to avoid washing the area and protect it from sunlight for 48 hours. After 2 weeks 0.001% solution of DPCP is applied on the scalp and then the application of contact allergen is repeated weekly with increasing concentrations. The usual concentration of DPCP that ultimately causes mild contact eczema is 0.01-0.1% and this is repeated weekly till a response is seen. An eczematous response indicates that sensitization has taken place. Only 1-2% of the patients fail to sensitize. It is important to remember that DPCP is degraded by light and should thus be stored in the dark and the patient should also wear a wig or hat during the day after application of DPCP. DPCP immunotherapy has even been combined with oral fexofenadine treatment with good effect.

Evaluation of efficacy: The clinical response after six months of treatment is rated as per the grading system proposed by Mcdonald Hull and Norris.

- Grade 1- Regrowth of vellus hair.
- Grade 2- Regrowth of sparse pigmented terminal hair.
- Grade 3- Regrowth of terminal hair with patches of alopecia.
- Grade 4- Regrowth of terminal hair on scalp.

If no regrowth is observed within six months of treatment, the patient is considered to be a non-responder. Evaluation of plucked hair is done using light microscopy, for evaluation of anagen/telogen ratio.

A review of most of the published studies of contact immunotherapy concluded that 50-60% of patients achieve a worthwhile response but the range of response rates was very wide (9-87%). Patients with extensive hair loss are less likely to respond. Other reported poor prognostic factors include the presence of nail changes, early onset disease and a positive family history.

Topical immunotherapy can lead to certain side effects such as persistent dermatitis, painful central lymphadenopathy, generalized eczema, blistering, contact leukoderma, and urticarial reaction. Systemic manifestations such as fever, arthralgia and yellowish discoloration of hair are noted more often with DNCB.

In poor responders to DPCP, squaric acid dibutylester (SADBE) can be tried as a contact sensitizer. The method of application is the same as with DPCP but the applications are done once or twice weekly.

Good care should be taken to avoid contact with the allergen by handlers, including pharmacy and nursing staff. Those applying the antigen should wear gloves and aprons. There is no available data on the safety of contact immunotherapy during pregnancy and it should not be used in pregnant women or in women intending to become pregnant.
Tacrolimus:

Tacrolimus is a topical calcineurin inhibitor that inhibits transcription following T-cell activation of several cytokines including IL-2, IFN-gamma and TNF-α. Yamamoto et al reported in their findings that tacrolimus stimulated hair growth in mice, although subsequent studies have shown conflicting results. Recently, Price et al reported an 11-patient study in which none of the patients had terminal hair growth in response to tacrolimus ointment 0.1% applied twice daily for 24 weeks.

Topical garlic

Garlic is a very commonly used home remedy in the treatment of alopecia areata in India and even in the rest of the world. One study analyzed the effect of a combination of topical garlic gel and betamethasone valerate ointment in alopecia areata in a double-blind study. The study found the combination useful in the treatment and control groups.

Topical retinoids:

Among topical retinoids, tretinoin and bexarotene have been tried in alopecia areata with mixed results. Irritation of the skin is a very common side effect and the efficacy is doubtful in the absence of double-blind randomized trials.

Prostaglandin analogs:

The propensity of certain prostaglandin analogues used as anti-glaucoma eye drops to cause hypertrichosis has been employed in the treatment of alopecia areata. These prostaglandin analogues include Latanoprost and Bimatoprost and they are used in the treatment of alopecia areata involving the eyelashes. However, the results obtained with these drugs have not been really encouraging.

Systemic treatments

Systemic treatments, as a rule, are used only in progressive forms of alopecia areata and going by the immune nature of the disease, majority of these treatment options are immunosuppressants or immunomodulators in nature.

Systemic corticosteroids:

The use of systemic corticosteroids for the treatment of alopecia areata is under much debate. Some authors support a beneficial role of systemic steroids on halting the progression of alopecia areata, but many others have had poor results with this form of therapy. The suggested dosages are 0.5-1mg/kg/day for adults and 0.1-1 mg/kg/day for children. Treatment course ranges from 1-6 months, but prolonged courses should be avoided to prevent the side effects of corticosteroids. Side effects profile of corticosteroids in conjunction with the long-term treatment requirements and high relapse rates make systemic corticosteroids a more limited option. In addition to the daily oral administration of corticosteroids, there are several reports of high-dose pulsed corticosteroid treatments employing different oral and intravenous regimens. Many of these regimens have been tried in alopecia areata with encouraging results but the majority of these studies have been non-blind open studies. One such pulsed administration employs a high dose oral corticosteroid on two consecutive days every week with a gap of 5 days between the two pulses. This modality of treatment is known as oral minipulse therapy (OMP) and it has been tried in many skin diseases in addition to alopecia areata like vitiligo and lichen planus. Some open label studies on corticosteroid OMP therapy have reported encouraging results in alopecia areata.

Sulfasalazine:

Because of its immunomodulatory and immunosuppressive actions, sulfasalazine has shown good hair regrowth in the treatment of alopecia areata. The drug is administered orally usually as enteric coated tablets to minimize the gastrointestinal side effects. The treatment is started at a lower dose, usually in the range of 500 mg twice daily and then the dose is gradually increased to 1 g three times a day. Adverse effects include gastrointestinal distress, liver toxicity and haematological side effects. Sulfasalazine helps in alopecia areata because it causes inhibition of T cell proliferation, and natural killer cell activity and also inhibits antibody production. It also inhibits the secretion of interleukin (IL)-2, IL-1, TNF- and IFN-gamma and even IL-6.

A number of clinical studies have documented a positive effect of sulfasalazine in alopecia areata. In one clinical study, 23% patients showed a really good response with satisfactory hair growth after sulfasalazine therapy. Other studies have also shown a beneficial effect of this treatment option in resistant cases of alopecia areata.

Azathioprine:

Azathioprine, being an immunosuppressive agent has also been tried in alopecia areata. The drug is used in many cutaneous disorders owing to its effect on circulating lymphocytes as well as Langerhan cells. In a limited study on 20 patients hair regrowth was demonstrated in about half of the patients with a dosage regimen of 2g/day.

Cyclosporine:

This drug has proven effective in the treatment of alopecia areata because of its immunosuppressive and hypertrichotic properties. The side effect profile and high rate of recurrence render the drug a poor choice for the use in alopecia areata. So the drug is to be attempted only in severe forms of alopecia areata not responding to treatment.
Methotrexate:
Methotrexate either alone or in combination with prednisolone has been used in the treatment of alopecia areata in various studies with variable success rates.

Oral zinc sulphate
Serum zinc levels have been found to be lower in patients with alopecia areata than in control populations. In a study on 15 patients, hair regrowth was observed in 9 patients (67%) after oral zinc gluconate administration.

Biological agents:
Tumor necrosis factor inhibitors such as Adalimumab, Infliximab and Etanercept have been tried in alopecia areata, but the results have not been encouraging. Clinical trials conducted till now have failed to demonstrate the efficacy of any biological agent in alopecia areata.

Photo-and photochemotherapy
Photochemotherapy:
Several uncontrolled studies regarding PUVA therapy for the treatment of alopecia areata exist. All types of PUVA (oral PUVA, topical PUVA, local or whole body UVA irradiation) have been used with success rates of up to 60-65%.

Phototherapy
Although narrowband UVB is among the most effective treatment options in a number of immune mediated skin diseases, the same efficacy has not been found in alopecia areata. Properly designed randomized trials are needed to elucidate whether NBUVB has any role in the management of alopecia areata.

Excimer laser and excimer light
Excimer laser and excimer light are two more recent additions to the phototherapeutic armamentarium for many skin and hair disorders. While the main use of these phototherapeutic modalities remains to be psoriasis and vitiligo, their immunomodulatory effect can be made use of in many other skin disorders. Some clinical studies have documented the efficacy of excimer laser and excimer light in alopecia areata.

Miscellaneous therapies
Various non-conventional therapeutic agents have been used in alopecia areata with some degrees of success. These include fractional Er-Glass laser, topical azelaic acid, topical onion juice, topical 5-fluorouracil ointment and photodynamic therapy. The efficacy and safety of these therapeutic agents need to be confirmed in large-scale, double-blind, placebo-controlled trials before they can be recommended for treatment of alopecia areata.

Non-pharmacological methods
Cosmetic treatments for patients with alopecia areata include the following:

a) Dermatography: It has been used to camouflage eyebrows of patients with alopecia areata. In this treatment tiny pigment dots of pigment are used on the skin on the region of the eyebrows to mask the underlying alopecia.

b) Wigs or Hair pieces: These are useful for patients with extensive disease and allow them to carry on their usual social life.

Conclusion:
Alopecia areata is now regarded as an autoimmune disease involving the cellular immunity through the CD8 lymphocytes that act on follicular antigens. The pathogenesis of alopecia areata is being unravelled with various animal and human studies.

The localized forms often heal spontaneously or respond to simple treatments such as topical or intralesional corticosteroids. The severe forms have a reserved prognosis and are difficult to treat. In these cases the best results are achieved by topical immunotherapy technique.
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Integrative model of chronically activated immune-hormonal pathways important in the generation of fibromyalgia

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ABSTRACT
Clinicians are often challenged by patients presenting with a syndrome of chronic and diffuse full body pain with long standing fatigue and a cluster of related symptoms. Fibromyalgia has become the commonly accepted term for this syndrome. Diagnosis is established through recognized subjective symptoms, such as tender points and other indicators of chronic full body pain and fatigue. Suspected triggers have included bacterial and viral infections, toxins, allergens, and emotional and physical trauma. Unknown causes limit the prescription of effective treatments; however, neuropathic pain and fatigue have been identified as key components so dual reuptake inhibitors and anti-convulsants have shown some effectiveness for some patients. Based upon laboratory and clinical studies of the last decade, this article proposes a model for a subset of fibromyalgia patients who have prolonged immune activation with related oxidative and nitrogenous stress leading to multiple hormonal repression, disrupted collagen physiology, neuropathic pain and fatigue. This integrative model of fibromyalgia is based on chronic up-regulation of the immune system with subsequent hormonal, connective tissue and nervous system implications.

Introduction

Fibromyalgia (FM) is a challenging set of chronic, overlapping and debilitating syndromes with widespread pain, abnormal pain processing, sleep disturbance, fatigue and psychological distress. The American College of Rheumatology (ACR) 1990 diagnostic guidelines were based primarily on tender point examination findings at 11 of 18 potential tender points; however, lack of consistent application of these guidelines in clinical settings led the ACR in 2010 to develop new diagnostic criteria based on a Widespread Pain Index (WPI) and symptom severity (SS) scale with no requirement of a tender point examination. Symptoms must have been present for at least three months with the absence of any other disorder that would otherwise explain the pain and other signs and symptoms.

Type of pain and other symptoms vary widely in FM, complicating diagnosis and treatment. A cross-sectional survey of 3,035 patients in Germany utilized cluster analysis to evaluate daily records of symptoms noted by patients on handheld computers. Five subgroups were described: four with pain evoked by thermal stimuli, spontaneous burning pain, pressure pain, and pressure pain combined with spontaneous pain; the fifth subgroup had moderate sensory disturbances, but greater sleep disturbances and the highest depression scores.

Estimates of the prevalence of FM have varied based on case definitions and survey methods. Using 1990 ACR guidelines, it was estimated to affect between 0.1 to 3.3% of populations in western countries and 2.0% in the United States. Greater prevalence occurs among females, with estimates ranging from 1.0 to 4.9%. Reasons for the gender difference have not been determined.

Fibromyalgia Risk Factors

Identification of risk factors for FM has been complicated by the array of seemingly unrelated signs and symptoms. The United States Centers for Disease Control (CDC) notes loose association with genetic predisposition, bacterial and viral infections, toxins, allergies, autoimmunity, obesity and both physical and emotional trauma.

Chronic fatigue syndrome and infection

Although chronic fatigue syndrome (CFS) has been defined as a separate syndrome, up to 70% of patients with FM are also diagnosed with CFS and 35-70% of patients with CFS have also been diagnosed with FM. Thus studies of patients with CFS may have clinical relevance to FM. Several case controlled studies of CFS and one of CFS/FM have been associated with chronic bacterial infections due to Chlamydia (Chlamydophila p.), Mycoplasma, Brucella, and Borrelia. The most prevalent chronic infection found has been that of the various Mycoplasma species.

Mycoplasmas are commonly found in the mucosa of the oral cavity, intestinal and urogenital tracts, but risk of systemic illness occurs with invasion into the blood vascular system and subsequent colonization of organs and other tissues. Mycoplasmal infections have been identified in 52 – 70% of CFS patients compared with 5 to 10% of healthy subjects in North America and Europe (Belgium). For example,
the odds ratio (OR) of finding Mycoplasma species in CFS was 13.8 (95% Cl. 5.8-32.9, p< 0.001) in North America. A review by Endresen concluded that mycoplasmal blood infection could be detected in about 50% of patients with CFS and/or FM. A CDC case-control study attempted to replicate these findings based on the hypothesis that intracellular bacteria would leave some evidence of cellular debris in cell-free plasma samples. Results were that the healthy subjects actually had evidence of more bacteria although the difference was not significant. The authors noted the complexity and limitations of this type of analysis and also postulated that since the CFS patients were years past the onset of illness, they might have previously cleared the triggering agent. However, most studies found Mycoplasma DNA in intracellular but not extracellular compartments in CFS patients, and this could explain the discrepancy. Other studies have found that 10.8% of CFS patients were positive for Brucella species (OR=8.2, 95% Cl. 1-66, p<0.01) and 8% were positive for Chlamydia pn. (OR= 8.6; 95% Cl 1-71.1, p< 0.01).

The presence of multiple co-infections may be an especially critical factor associated with either initiation or progression of CFS. Multiple infections have been found in about one-half of Mycoplasma-positive CFS patients (OR = 18.0, 95% Cl 8.5-37.9, p< 0.001), compared with single infections in the few control subjects with any evidence of infection. A North American study identified chronic infections in 142 of 200 patients (71%) with 22% of all patients having multiple mycoplasmal infections while just 12 of the 100 control subjects (12%) had infections (p<0.01) and none had multiple infections. Similarly, a European study reported chronic mycoplasmal infections in 68.6% of CFS and 5.6% of controls. Multiple infections were found in 17.2% of the CFS patients compared with none in the controls (p<0.001). Multiple co-infections were also associated with significantly increased severity of symptoms (p<0.01).

Viral infections associated with CFS have included Epstein Barr virus, human herpes virus-6, cytomegalovirus, enteroviruses and several other viruses. Despite indications of single or multiple bacterial and/or viral infections in most patients with CFS, antibiotic or antiviral treatments have yielded inconsistent results. Slow growing intracellular bacteria are relatively insensitive to most antibiotics and have inactive phases when they would be completely insensitive to any antibiotics. Some treatments may actually have resolved the infections, but not the immune pathways that may remain in an activated state capable of producing symptoms.

**Fibromyalgia and infection**

Bacterial infections associated with FM as a separate syndrome have included small intestinal bacterial overgrowth (SIBO) and helicobacter pylori (HP). Utilizing the lactulose hydrogen breath test (LHBT), investigators found SIBO in 100% of 42 patients with FM. They noted that 30-75% of patients with FM have also been found to have irritable bowel syndrome (IBS). A confounding factor is that medications prescribed for FM often have gastrointestinal side effects. HP diagnosed by positive immunoglobulin gamma (IgG) serum antibody was significantly higher in women with FM (44/65 or 67.7%) compared with controls (18/41 or 43.9%) (p=0.025) in Turkey.

Viral infections associated with FM have included hepatitis C, in which two studies found an association, and two studies found no association. Associations with FM have also been found with hepatitis B, human immunodeficiency virus (HIV), and human T cell lymphotropic virus type I (HTLV-1).

**Fibromyalgia and non-infectious associations**

Non-infectious triggers associated with FM have included toxins, allergens, and physical or emotional trauma. These triggers may not have been strictly “non-infectious” as allergens and toxins may also be produced by infections, and physical or emotional trauma may lead to the reactivation of previously controlled infections. Respondents to an internet survey of people with FM (n=2,596) also identified triggers as chronic stress (41.9%), emotional trauma (31.3%), acute illness (26.7%) and accidents (motor vehicle 16.1%, non-motor vehicle 17.1%). Physical trauma associated with FM has included cervical spine injuries as well as motor vehicle and other accidents.

**Fibromyalgia and autoimmunity**

Three studies have found thyroid autoantibodies to be in greater percentages in subjects with FM compared with controls, in spite of normal thyroid hormone levels. One study reported autoantibodies in 41% of FM patients versus 15% of controls. The second study reported 16% in FM versus 7.3% in controls, p<0.01. The third study reported 34.4% in FM versus 18.8% in controls (p=0.025) and OR =3.87, 95% Cl. 1.54-10.13. This could also have been the result of thyroiditis, because infections like Mycoplasma are often found in thyroiditis patients.

Autoantibodies to serotonin were identified in 74% of 50 patients with FM compared with 6% of 32 healthy (blood donor) controls. Notably, serotonin levels were normal in 90% of the FM patients indicating serotonin receptor involvement.

**Fibromyalgia and Metabolic Syndrome**

Metabolic Syndrome consisting of abdominal obesity, high triglycerides, high blood pressure, elevated fasting glucose and decreased high-density lipids, was associated with FM in a U.S. study in which cases were 5.6 times as likely to have Metabolic
syndrome as controls ($\chi^2_{\text{MH}} = 3.84$, $p = .047$, 95% CL 1.25 – 24.74).

Fibromyalgia and emotional trauma

Although emotional trauma has been acknowledged as a contributing factor, most studies of CFS/FM have used recognized tests such as Beck’s Depression Index, Beck’s Anxiety Index and Minnesota Multi Personality Index (MMPI) to exclude potential subjects with actual psychiatric illnesses.\(^{51}\)

Psychological and physiological subsets of fibromyalgia

A Wisconsin cross sectional survey of 107 women with confirmed diagnoses of FM used validated psychological and physiological measures followed by cluster analysis. Four distinct subsets were identified: (I) history of childhood maltreatment and hypocortisolism with the most pain and disability; (II) “physiological dysregulation” described as “distinctive on nearly every biological index measured” with high levels of pain, fatigue and disability; (III) normal biomarkers with intermediate pain severity and higher global functioning; and (IV) psychological well-being with less disability and pain.\(^{52}\)

The “physiological dysregulation” of FM subset II consisted of the highest antinuclear antibody (ANA) titers ($t=4.06$, $p=0.001$), highest total cholesterol levels ($t=3.96$, $p<0.001$), larger body mass index (BMI) values ($t=2.21$, $p<0.05$), lowest Natural Killer (NK) cell numbers ($t=3.95$, $p<0.001$), lowest growth hormone ($t=3.20$, $p<0.002$), and lowest testosterone levels ($t=3.80$, $p<0.001$). Trends were also indicated toward the highest erythrocyte sedimentation rate (ESR) ($t=2.02$, $p=0.056$), lowest creatinine clearance ($t=1.85$, $p=0.067$) and lowest cortisol ($t=2.78$, $p<0.007$).\(^{53}\)

Proposed Model of Fibromyalgia

The authors’ proposed model of FM develops a rationale for the “physiological dysregulation” indicated in subset II of the Wisconsin study. In this model, various triggers are followed by prolonged immune activation with subsequent multiple hormonal repression, disrupted collagen physiology and neuropathic pain.

Activation of immune response pathways

Innate immune responses begin with anatomical barriers, such as the epithelium and mucosal layers of the gastrointestinal, urogenital and respiratory tracts, and physiological barriers, such as the low pH of stomach acid and hydrolytic enzymes in bodily secretions.\(^{54}\) Breaching of these barriers activates cell-mediated immunity launched by leucocytes with pattern recognition receptors: neutrophils, macrophages and dendritic cells (DCs).\(^{55}\) Insufficient or damaged anatomical or physiological barriers would necessarily keep this cell mediated level of innate defense in a constant state of alert and activity.

In contrast to the innate immune response, adaptive immunity has highly specific recognition and response activities resulting in lasting changes produced by leukocytes known as lymphocytes. B lymphocytes (B cells) secrete plasma cells producing antibodies to specific pathogens. T lymphocytes (T cells), the other major cells of adaptive immunity, can be either cytotoxic (Tc) or helper cells (Th). Tc cells produce progeny that are toxic to non-self peptides and Th lymphocytes secrete small proteins (cytokines) that mediate signaling between leukocytes and other cell types. All types of lymphocytes retain memory so that subsequent invasions provoke faster and more rapid differentiation into effector cells.\(^{56, 57}\) Some Th cells respond to intracellular pathogens (Th1) and some to extracellular pathogens (Th2). A third type (Th17) appears to respond to certain bacterial and fungal infections, tumor cells and are also involved in autoimmune diseases.\(^{58}\)

In the presence of environmental stressors, cells may release stress proteins to alert the organism to potentially damaging conditions. These proteins can bind to peptides and other proteins to facilitate surveillance of both the intracellular and extracellular protein environment. One form of stress proteins, heat shock proteins (HSP), can mimic the effects of inflammation and can be microbicidal.\(^{59, 60}\)

One of the earliest responses to intracellular viral or bacterial infections involves production of three types of interferon (IFNα, IFNβ and IFNγ). Any of these can initiate a series of metabolic events in uninfected host cells that produce an antiviral or anti-bacterial state.\(^{61, 62}\) When IFN-γ targets genes in uninfected cells, the targeted genes become microbicidal by encoding enzymes generating oxygen (O$_3$) and nitric oxide (NO) radicals.\(^{58}\) Activation of O$_3$ or NO radicals triggers another cascade involving IL-6, IL-1β, the cytokine Tumor Necrosis Factor-α (TNF-α) and the transcription nuclear factor κB (IKKB–NF-κB). NF-κB can be activated by a variety of inflammatory stimuli, such as cytokines, growth factors, hormones, oncogenes, viruses and their products, bacteria and fungi and their products, eukaryotic parasites, oxidative and chemical stresses, therapeutic and recreational drugs, additional chemical agents, natural products, and physical and psychological stresses.\(^{63, 64}\) Activation of NF-κB releases its subunits; the p50 subunit has been associated with autoimmunity and the RelA/p65 unit with transcriptional activity involving cell adhesion molecules, cytokines, hematopoietic growth factors, acute phase proteins, transcription factors and viral genes.\(^{61}\) The authors propose that chronic infection or other stress would be a sustaining trigger of an immune cascade that includes NF-κB and resultant cell signaling processes that drive many of the symptoms of fibromyalgia.

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The cytokine interleukin-6 (IL-6) can either activate or repress NF-κB through a switching mechanism involving IL-1α and Interleukin 1β (IL-1β). IL-6 first activates Interleukin 1β (IL-1β), which then activates TNF-α, leading to the subsequent activation of NF-κB. Specifically, the release of the RelA/p65 subunit of activated NF-κB switches on an inhibitory signaling protein gene (Smad 7) that blocks phosphorylation of Transforming Growth Factor Beta (TGF-β) resulting in the repression of multiple genes. Alternatively, IL-6 activates IL-1α, which allows TGF-β to phosphorylate and induce the expression of activating signaling protein genes Smad2 and Smad3, resulting in the full expression of multiple genes.

NF-κB plays a key role in the development and maintenance of intra- (Th1) and inter- (Th2) cellular immunity through the regulation of developing B and T lymphocytes. The p50 dimer of NF-κB has been shown to block B Cell Receptor (BCR) editing in macrophages, resulting in loss of recognition and tolerance of host cells (autoimmunity). T cells that are strongly auto-reactive are normally eliminated in the thymus, but weakly reactive ones are allowed to survive to be subsequently regulated by regulatory T-cells and macrophages. Acquired defects in peripheral T-regulatory cells may lead to failure to recognize and eliminate weakly reactive ones. The IL-17 cytokine associated with autoimmunity can activate NF-κB through a pathway that does not require TNF-α. NF-κB activity can also be activated or repressed by the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) in the early phases (3 days) of nerve injury through its main effector enzyme, protein kinase A (PKA). PKA decreases during later stages as the enzyme protein kinase C (PKC) increases. PKC then plays important roles in several cell type specific signal transduction cascades. An isoform of PKC within primary afferent nociceptive nerve fibers signals through IL-1β and prostaglandins E2 (PGE2) as demonstrated in animal studies. This process has been called “hyperalgesic priming,” and it has been described as responsible for the switch from acute to long-lasting hypersensitivity to inflammatory cytokines.

Figure 1 depicts key immune pathways leading to expression or repression of multiple genes proposed to be important in FM and neuropathic pain.

Fibromyalgia and immune - hormonal interactions

Reciprocity exists between the immune system and the hypothalamic-pituitary-adrenal (HPA) axis through its production of glucocorticoid signal transduction cascades. Hormones such as cortisol (hydrocortisone) produced by the adrenal cortex, affect metabolism of glucose, fat and protein. The glucocorticoid receptor (GR), a member of the steroid/thyroid/retinoid super family of nuclear receptors is expressed in “virtually all cells”. When the GR in the cytoplasm binds a glucocorticoid, it migrates to the nucleus where it modulates gene transcription resulting in either expression or repression of TNF-α, IL-1β and the NF-κB p65/Rel A subunit. However, the RelA/p65 protein can also repress the Glucocorticoid Receptor.

Growth hormone (GH), an activator of NF-κB, is usually secreted by the anterior pituitary, but changes found in FM may be hypothalamic in origin. GH is needed for normal childhood growth and adult recovery from physical stresses. Although low levels of GH were found in subset II of the Wisconsin study, functional deficiency may be expressed as low insulin-like growth factor 1 (IGF-1) combined with elevated GH, suggesting GH resistance. Defective GH response to exercise has been associated with increased pain and elevated levels of IL-1β, IL-6, and IL-8.

The hormones serotonin and norepinephrine modulate the movement of pain signals within the brain. Serotonin has been found to suppress inflammatory cytokine generation by human monocytes through inhibition of the NF-κB cytokine pathway in vitro; however, NF-κB promotion of antibodies can repress serotonin. Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), such as duloxetine and milnacipran, are key treatment options for fibromyalgia and have been approved by the U.S. Food and Drug Administration (FDA). Although serotonin has been best measured in cerebral spinal fluid (CSF), recently improved methods of collection were utilized (using rats and in 18 women) that yielded a high degree of correlation (r=0.97) between CSF and plasma, platelet, and urine measurements.

NF-κB activation has also been documented to interfere with thyroid hormone action through impairment of Triiodothyronine (T3) gene expression in hepatic cells. However, T3 administration has induced oxidative stress and activated NF-κB in rats.

Metabolic Syndrome, a confounding factor in Fibromyalgia

Leptin and insulin hormones interact to regulate appetite and energy metabolism. Leptin, produced by adipose cells, circulates in the blood eventually crossing the blood-brain barrier to bond with a network of receptors within the hypothalamus. Insulin, produced by beta cells in the pancreas, similarly crosses the blood brain barrier to interact with its own network of hypothalamic receptors. Leptin and its receptors share structural and functional similarities to long-chain helical cytokines, such as IL-6, and it has been suggested that leptin be classified as a cytokine.

Metabolic syndrome can be a confounding factor in FM due to peripheral accumulation of fatty acids, acylglycerols and lipid intermediates in liver, bone, skeletal muscle and endothelial cells. This promotes oxidative endoplasmic reticulum (ER)
stress and the activation of inflammatory pathways involving PKC and hypothalamic NF-κB, leading to central insulin and leptin repression. 85-87 Hyperinsulinemia further stimulates adipose cells to secrete and attract cytokines such as TNFα and IL-6 that trigger NF-κB in a positive feedback loop, which can be complicated by chronic over nutrition that increases the generation of reactive oxygen intermediates and monocyte chemoattractant protein-1 (MCP-1). 87, 88 When exposed to a chronic high fat diet, hypothalamic NF-κB was activated two fold in normal mice and six times in mice with the obese (OB) gene. 89

**Fibromyalgia and indicators of immune-hormonal activity**

Although most components of either innate or adaptive cell mediated immune responses exist for only fractions of seconds, some of their effects and products can be detected long after in the skin, muscle, blood, saliva or sweat. 82-83 One component, nitric oxide (NO), can suppress bacteria; however, endothelial damage causes dysfunction with impaired release of NO and loss of its protective properties. 86 The enzyme transaldolase acts as a counterbalance by limiting NO damage to normal cells. Thus, high levels of transaldolase indicate elevated reactive oxygen species, reactive nitrogen species (ROS/RNS) and cellular stress. The “exclusive and significant over-expression of transaldolase” in the saliva samples of 22 women with FM compared with 26 healthy controls (77.3% sensitivity and 84.6% specificity, p<0.0001; 3 times greater than controls; p=0.02) was “the most relevant observation”; although there was no correlation between transaldolase expression and the severity of FM symptoms. 82

High levels of NO have been associated with high levels of insulin, and insulin itself is a vasodilator that, in turn, can stimulate NO production. Beta cells of the pancreas are quite susceptible to ROS/NOS damage. 84 When free radical damage of beta cells reaches critical mass, insulin production plummets with an associated decline in NO levels. Thus, patients with FM who have high NO levels would likely be suffering from associated metabolic syndrome, and patients with low NO levels would likely be suffering from Type II diabetes. 85, 88

Figure 2 illustrates the relationship of NF-κB to various hormone systems.

**Fibromyalgia and immune-hormonal influences on connective tissue**

Inflammation of muscles, tendons, and/or fascia is generally followed by proliferative and remodeling phases of healing initiated by fibroblasts which lay down an extracellular matrix (ECM) composed of collagen and elastin fibers. “Fibroblasts respond to mechanical strain by altering shape and alignment, undergoing hyperplasia and secreting inflammatory cytokines including IL-6.” The extra cellular matrix is initially laid down in a disorganized pattern that is subsequently matured and aligned. Chronic and excessive mechanical tension from postural imbalance, hormonal disruption or other factors may interfere with collagen maturation. 91 Remodeling of the extracellular matrix and collagen deposition around terminal nerve fibers may be compressive and contribute to neuropathic pain. 95

Oxidative stress in muscles accelerates the generation of advanced glucose (glycation) end products (AGEs). AGE-mediated cross-linked proteins have decreased solubility and are highly resistant to proteolytic digestion. Interaction of AGEs with their receptors leads to activation of NF-κB resulting in an increased expression of cytokines, chemokines, growth factors, and adhesion molecules. 96-97

Two AGE products have been reported at significantly elevated levels in the serum of patients with FM: N-carboxymethyllysine (CML) (2386.56 ± 73.48 pmol/mL; CL 61.36-2611.76 versus controls 2121.97 ± 459.41 pmol/mL; CL 2020.39-2223.560; p<0.05) and pentosidine (mean 190 ± 120 SD and median 164 versus controls mean 128 ± 37 SD and median 124; p<0.05). 87 Comparison of muscle biopsies showed “clear differences in the intensity and distribution of the immunohistochemical staining”. CML was seen primarily in the interstitial tissue between the muscle fibers where collagens were localized and in the endothelium of small vessels of patients. Activated NF-κB was seen in cells of the interstitial tissue especially around the vessels of patients, but almost no activated NF-κB was seen in the control biopsies. AGE activation of NF-κB has been shown to be significantly more prolonged than the activation of NF-κB by cytokines. 96-97

**Fibromyalgia, the nervous system and pain**

Sensory transmission in humans occurs through three primary afferent nerve fiber types: heavily myelinated mechanical afferent pathways (A Beta fibers) that transmit non-noxious tactile sensations, small-diameter myelinated fibers (A Delta fibers) that transmit sharp pain, and small diameter unmyelinated fibers (C fibers) that transmit dull aching pain. The heavily myelinated non-pain Aβ fiber type has been shown to sprout axons that terminate on pain lamina in the posterior horn of the spinal cord resulting in the conversion of mechanical stimuli to pain. Within the brain, sensitization of the N-methyl D-aspartate (NMDA) receptors can amplify pain signals between the thalamus and the sensory cortex. 67-68

Chronic damage or excitation of nociceptive afferent fibers from compressive collagen deposition may develop into spontaneous (ectopic) firing oscillating at frequencies sufficient to initiate cross (ephaptic) excitation of sympathetic and sensory fibers (myelinated A-delta and non-myelinated C fibers) within the dorsal root ganglia (DRG) of the central nervous system.
Figure 1. Key immune pathways leading to multiple gene repression or expression

Infectious & Non-infectious Triggers

Inflammation & oxidative stress

Immune cellular responses

Immune effectors:
- Nitric Oxide
- Cyclic AMP, Protein Kinase A (early)
- Protein Kinase C (late, chronic)

Transaldolase modulates

Neuropathic Pain – Substance P

Prostaglandin E2 → IL-1β

IL-6 Switching Process

TNF-α

NF-κB

p56/RoA pathway

Smad7 inhibitory gene protein

Multiple gene repression

Autoantibodies → NF-κB p50

IL-17

Figure 2. Relationship of NFκb to various hormone systems

Glucocorticoid system

Serotonin system (NFκb repression through autoantibodies)

Thyroid system with normal hormone levels, but symptoms of hypothyroidism

Hyperthyroidism

Growth hormone system

Leptin appetite system

Insulin glucose system

Key: Activation: → Repression
Normally, the DRG has little sympathetic innervation, but trauma can trigger sympathetic sprouting that forms basket-like structures within the DRG. Neurotrophins, in particular nerve growth factor (NGF), play an important role in sympathetic fiber sprouting of sensory ganglia in murine models. DRG can be reservoirs for latent viral infections such as Herpes Zoster, HIV and enteroviruses. In addition, the Borrelia species has been identified in a non-human primate model of Lyme disease. NGF also facilitates expression of Substance P (SP), a peptide neurotransmitter involved in the induction of the IL-6 - NF-κB pathway and in the transmission of neuropathic pain.

Summary and Conclusions

Chronic unresolved infection, trauma, and/or emotional stresses that trigger immune pathways with subsequent chronic hormonal and nervous system responses is proposed to perpetuate chronic neuropathic pain. Figure 3 provides a summary model of immune-hormonal contributions to neuropathic pain in fibromyalgia.

The ACR criteria and severity scales have defined fibromyalgia and The Wisconsin study has identified psychological and physiological subsets that are critical steps in its characterization. This type of testing could be further strengthened through the use of specific biomarkers. Potential markers of FM status include the RelA/p65 and p50 subunits of NF-κB, which are currently the focus of several clinical trials of other chronic painful conditions. Additional potential markers include: IL-6, IL-1β, TNF-α, PKC, transaldolase, CML, pentosidine and NGF. Substance P has been previously identified as a marker of pain, but is problematic as a marker for FM, since it has only been measured in the CSF. The search for markers that are truly specific to FM may continue to be a difficult task due to their overlap with other metabolic conditions, such as CFS, metabolic syndrome, type II diabetes, and IBS. Nonetheless, these markers remain important as they can indicate oxidative stress, cytokine activation, hormonal dysregulation and neuropathic pain. These potential FM markers need to be evaluated in clinical trials where they can be measured over time and correlated with patient symptoms.

Currently, family and general medical practice physicians are uniquely positioned to establish the FM diagnosis, determine subsets of FM patients, investigate potential triggers of chronic immune activation, advise patients, prescribe medications and refer patients to appropriate specialists or pain centers. Establishment of the FM diagnosis requires use of the ACR Widespread Pain Index (WPI) and symptom severity (SS) scale, but no longer requires the tender point examination.

Determination of FM subsets can be accomplished using the approach used in the Wisconsin cross sectional survey. Investigation of potential triggers of chronic immune activation needs to include sources of underlying infection, unresolved
physical or emotional trauma, toxins and food sensitivities. These investigations may be accomplished through careful interviewing and well-designed questionnaires. Advising the patient should acknowledge the reality of their pain and other symptoms and provide rational approaches to resolution of those symptoms. Prescribing of medications needs to be sensitive to current and previous patient experience with medications, in addition to following current guidelines for stabilizing FM symptoms. Referral to appropriate specialists and centers would include those with expertise in physical medicine, psychology and nutrition. Physical medicine can address pain and functional deficits; psychology can address underlying emotional issues and trauma; and nutrition can focus on resolution of chronic inflammation, oxidative stress, and intestinal dysbiosis.

Where do we go from here for additional FM treatment options? Immune modulators have been used successfully in other painful conditions, such as rheumatoid arthritis. Immune modulators acting on the IL-6 - NF-κB cascade have considerable potential for FM, but only after ruling out or successfully treating any underlying infections. Numerous pharmaceutical blockers of NF-κB exist, but most are associated with serious side effects. Natural products may provide additional options as some are able to mediate pathways leading to NF-κB without the same side effects.¹⁰ Medications that elevate individual hormone levels have been included in accepted treatment protocols in the case of serotonin and norepinephrine. However, elevations of other hormones, such as cortisol and thyroid hormones, are under investigation and remain controversial. Elevation of individual hormones may be problematic because of the number of different hormones influenced by the IL-6 - NF-κB pathway.

References


Case Presentation: Reflex Anoxic Seizures and Anaesthesia

Nicholas Port and Asquad Sultan

Reflex anoxic seizures (‘RAS’) may present, as potentially life threatening events, but these are often preventable. They are most common in preschool children (but can occur in any age) and more so in females. As a cause of seizures they are not rare; one study estimated a frequency of 8 in 1000 preschool children, but they are often misdiagnosed. The pathophysiology of RAS is vagally mediated – a noxious stimulus causes a supranormal vagal discharge resulting in bradycardia and then asystole. This then results in cerebral under perfusion and hypoxia. During this time the patient is often noted to become very pale with dusky lips, initially flaccid and then tonic with rigid extension and clenched jaws. They may then have a generalised convulsion, often with rolling eyes and urinary incontinence. The patient spontaneously recovers (the whole episode lasting around 30 to 60 seconds) and will feel somnolent, often remaining pale for a while.

From this description it can be easily understood how such an event can be misdiagnosed as epilepsy; however it is not associated with the uncontrolled neuronal discharge of epilepsy and if monitored by EEG this is absent. It may also be mistaken as breath-holding attacks (where intra-thoracic pressure restricts cerebral perfusion) or Stokes-Adams attacks (where there is abnormal electrical function of the heart).

The noxious stimuli responsible can be many different things. Ocular pressure, venepuncture, accidental trauma and fear have all been implicated. If these stimuli cannot be prevented, management is normally just supportive (positioning, protection from trauma, oxygen) and allowing the fit to self-resolve. Further management can involve atropine (either acutely or preventatively), maintenance anticonvulsants (though these often just stop the fitting but not the syncope) and even pacemaker insertion.

The case we encountered was that of a 20 year old female student, presenting for a planned day case removal of a molar tooth. She was otherwise fit and well with no other past medical history, only taking the combined oral contraceptive pill. Her history with RAS started at age 1, when she was admitted to hospital following two seizures. The seizures occurred every few months and she was provisionally diagnosed as suffering from epilepsy, with prophylactic treatment started. However, as she grew older she was able to describe how the attacks were not associated with a preceding aura, but rather an unpleasant stimulus (such as accidental injury). A new diagnosis of RAS was made and the antiepileptics were stopped without the seizures becoming more frequent. As she entered late childhood and adolescence the frequency of the seizures became less, but (atypically) they did not stop entirely. On preassessment she reported being seizure free for just over a year and was anxious that today could precipitate another.

After consideration, we decided to proceed with anaesthesia with the following measures. The patient was kept calm by having a clear explanation of what to expect before coming to theatre, and then was reassured by an affable theatre team (who had been informed of her condition). Atropine was drawn up and available if vagal over stimulation occurred, as was suxamethonium in case of emergency airway intervention. For cannulation, cold spray was used along with distraction. Induction was with propofol (under full monitoring) and anaesthesia was maintained with sevoflurane/nitrous oxide via LMA. To prevent pain as a potential trigger, fentanyl (at induction) and paracetamol (after induction) were given and local anaesthetic (lidocaine) was administered before any surgery. Emergence was kept as smooth as possible by removing the LMA prior to any gagging and coughing and manually supporting the airway until she was awake.

With these measures the procedure was uneventful and the patient could be discharged home as planned. We hope this case report will help improve awareness and understanding of RAS, and the steps that can be taken peri-operatively to help ensure safe anaesthesia.

Competing Interests
None declared

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Case Report: Sleep wake cycle disorder and agitation associated with Levetiracetam in an elderly patient with traumatic brain injury

Nair CV and Kadies MA

ABSTRACT
Rehabilitation following traumatic brain injury (TBI) in the elderly is challenging. They tend to have poorer functional outcomes and often have associated cognitive decline. Rehabilitation interventions directed towards functional recovery are often hampered by agitation, confusion and fatigue. Identifying and correcting all possible causes is imperative in aiding rehabilitation. We present a 76 year old man who was admitted to an intermediate neurorehabilitation unit for cognitive rehabilitation following TBI. He was on multiple antiepileptic drugs (AED) for post TBI seizures. He was noted to have persistent sleep wake cycle disorder and agitation which were attributed to his TBI and consequent cognitive decline. However following withdrawal of Levetiracetam from his AED drug regimen, there was a marked decrease in his agitation with gradual normalization of his sleep wake cycle. This in turn led to his better participation in the rehabilitation program.

KEYWORDS
Traumatic brain injury, Levetiracetam, Sleep wake cycle disorder, Agitation

Introduction:
In traumatic brain injury (TBI) the primary insult to the brain and the secondary insults as a result of systemic complications may result in a multitude of sequelae ranging from subtle neurological deficits to significant morbidity and mortality. As the brain recovers by repair and adaptation, changes become apparent and may result in physical, cognitive and psychosocial dysfunction. Rehabilitation is usually structured to recover physical ability, cognitive and social retraining with the aim of gaining independence in activities of daily living.

Case Report:
A 76 year old male patient was admitted to an intermediate neurorehabilitation unit following a traumatic brain injury (TBI). He had fallen from a height of 11 feet resulting in intracerebral haemorrhage in the left parietal lobe and a left parietotemporal subarachnoid hemorrhage which was managed conservatively in the neurosurgical unit. He developed recurrent post traumatic seizures in the form of myoclonic jerks for which he was started on antiepileptic drugs (AEDs) sodium valproate, clobazam and levetiracetam. During his stay in the acute neurorehabilitation unit, he was noted to be confused and wandering with a disrupted sleep wake cycle. Cognitive assessment showed global impairment across all cognitive domains suggesting that cognitive impairment was secondary to TBI with the chaotic sleeping pattern and fatigue having a significant effect on his cognition. He was then transferred to an intermediate neurorehabilitation unit four months post head injury for rehabilitation prior to discharge.

On admission he was confused, and disorientated. His neurological examination was normal except for mild expressive dysphasia. On the first night of his stay in the unit, he did not sleep at all, was restless, agitated and aggressive towards the staff. His initial agitation was attributed to the change of surroundings and general disorientation. However during his first week at the rehabilitation unit it was noted that his sleep wake cycle was completely disrupted. He would have short fragmented naps through the day and would regularly get agitated at night with threatening behaviour towards staff. On admission the Rancho Los Amigos scale† was 4(confused-agitated) and he needed specialized supervision. Despite environmental modification and optimal pharmacotherapy to improve sleep and decrease agitation, the patient still continued to have aggressive outbursts and no identifiable sleep wake pattern. It was noted by the nursing staff that occasionally when very agitated, the patient refused to have his night time medications including all AEDs. On such occasions he was reported to have slept better at night and did not have any daytime naps. All blood investigations were within normal limits except for mild hyponatremia with a normal creatinine clearance and CT head showed changes consistent with previous TBI with no new pathology. A neurology opinion was sought and with a Naranjo adverse drug reaction probability score†† of 7/10, a decision was taken to slowly decrease levetiracetam and wean it to stop, while continuing all other regular AEDs. The levetiracetam was reduced from an original dose of 750mg twice daily by 500mg every week with an aim to stop. This resulted in a considerable improvement in the patient’s agitation with a complete halt in the nighttime aggressiveness. His sleep wake cycle normalized and he started...
Discussion:

TBI particularly in elderly aged over 64 years has a worse functional outcome as compared to non elderly.1 Closed head injury in older adults produces considerable cognitive deficits in the early stages of recovery2 and there have been studies suggesting TBI to be a risk factor for developing Alzheimer’s disease.3 Memory deficits, attention problems, loss of executive function and confusion are common after TBI.4 This impaired cognitive function reduces the patient’s ability to recognize environmental stimuli often resulting in agitation and aggression towards perceived threats. TBI by itself may result in a variety of sleep disorders ranging from hypersomnia, narcolepsy, alteration of sleep wake cycle, insomnia to movement disorders.5 Sleep wake schedule disorders following TBI are relatively rare and may clinically present as insomnia.6 Often these sleep disorders result in additional neurocognitive deficits and functional impairment, which might often be attributed to the original brain injury itself and thus be left without specific treatment.

While dealing with disrupted sleep pattern and agitation in the elderly following TBI, treatable causes such as neurological, infectious, metabolic, and medications should be ruled out. This is imperative as they disrupt rehabilitation and achievement of functional goals. Long duration of agitation post TBI has been associated with longer duration of rehabilitation stay and persisting limitations in functional independence.7 After ruling out all the treatable causes the first focus is on environmental management with provision of a safe, quiet, familiar, structured environment while reducing stimulation and providing emotional support. The next step is introduction of pharmacotherapy to reduce agitation. Though a variety of pharmacological agents are available, there is no firm evidence of efficacy of any one class and often the choice of drug is decided by monitoring its effectiveness in practice and watching for side-effects.8 In pharmacotherapy, the general principle followed is start low and go slow while developing clear goals to help decide when to wean and stop medications. Atypical antipsychotics are often used for the agitation while benzodiazepines and non benzodiazepine hypnotics such as zopiclone are recommended for treatment of insomnia.9 However atypical antipsychotics carry a FDA black box warning being associated with increased risk of stroke and death among elderly.

But what does one do when all optimal non pharmacologic and pharmacologic measures fail? That brings us back to the drawing board which in this case led the team to rethink Levetiracetam, a novel new antiepileptic that has been used as monotherapy for partial seizures and adjunctive therapy for generalized tonic clonic and myoclonic seizures. Levetiracetam treated patients have been reported to have psychiatric adverse effects10 including agitation, hostility, anxiety, apathy, emotional lability, depersonalization, and depression with few case reports of frank psychosis.11 While in healthy volunteers levetiracetam is noted to consolidate sleep,12 in patients with complex partial seizures, levetiracetam has been noted to cause drowsiness decreasing day time motor activity and increasing naps without any major effects on total sleep time and sleep efficiency during night.13 There has been an isolated report of psychic disturbances following administration of levetiracetam and valproate in a patient with epilepsy which resolved following withdrawal of valproate.14 However in practice it is used for recurrent post TBI seizures as it is a potent AED with a relatively mild adverse effect profile and no clinically significant interactions with commonly prescribed AEDs.15

Any adverse drug reaction (ADR) should be evaluated while keeping the patients clinical state in mind. This was, indeed, difficult in our case. With a history of TBI and cognitive decline, it became difficult to ascertain whether the neurocognitive issues were purely due to the nature of TBI or due to an ADR. Assigning causality to a single agent is difficult and fraught with errors. Using the Naranjo algorithm, with a score of 7/10 (probable ADR) and a notable response on withdrawal of the offending drug as in this case helps establish possible causality.

This is a rare instance where sleep wake cycle disorder and agitation resolved following withdrawal of Levetiracetam in an elderly patient with TBI. This in turn led to the patient having a stable mood so that therapists could communicate and interact with him in order to improve basic cognitive functions such as attention, memory, thinking and executive control. This case illustrates the constant need to systematically and frequently reassess patients as they recover from TBI.

Appendix: Ranchos Los Amigos Levels of cognitive functioning.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No response: Total assistance</td>
</tr>
<tr>
<td>II</td>
<td>Generalized response: Total assistance</td>
</tr>
<tr>
<td>III</td>
<td>Localized response: Total assistance</td>
</tr>
<tr>
<td>IV</td>
<td>Confused-agitated: Maximal assistance</td>
</tr>
<tr>
<td>V</td>
<td>Confused-inappropriate, non-agitated: Maximal assistance</td>
</tr>
<tr>
<td>VI</td>
<td>Confused-appropriate: Moderate assistance</td>
</tr>
<tr>
<td>VII</td>
<td>Automatic-appropriate: Minimal assistance for daily living skills</td>
</tr>
<tr>
<td>VIII</td>
<td>Purposeful-appropriate: Stand-by assistance</td>
</tr>
<tr>
<td>IX</td>
<td>Purposeful-appropriate: Stand-by assistance on request</td>
</tr>
<tr>
<td>X</td>
<td>Purposeful-appropriate: Modified independent</td>
</tr>
</tbody>
</table>
Naranjo Adverse Drug Reaction Probability Score:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Score

<0 = Doubtful ADR
1-4 = Possible ADR
5-8 = Probable ADR
>9 = Definite ADR

Competing Interests
None declared

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An analysis of time and money spent on investigating painful Total Knee Replacements

AM Kassam, Professor P Dieppe and AD Toms

ABSTRACT
Painful Total Knee Replacements (TKR) occur in 10-20% of patients according to current literature. Considerable expense is incurred investigating and managing patients presenting with a painful TKR. We studied 41 patients with painful TKRs who were referred to one of the authors, a knee surgeon with a specialist interest in revision surgery. We calculated the number of appointments, investigations (serological, radiological and microbiological) along with the different managements (both surgical and medical) performed by both the originating surgeon and the specialist knee surgeon. We estimate that an average of £5136 is spent on each patient. Many of these investigations were repetitive and unnecessary. There is also a considerable difference in the cost of medical and surgical management of painful TKR patients, suggesting that early pain management would be beneficial. We conclude that early referral of patients with a painful TKR to a knee surgeon with specialist interest in revision knee surgery is beneficial and allows to reduced incurred cost to the NHS and also improved patient assessment, investigation and management.

Introduction:

Total knee replacement (TKR) is an effective and cost-effective intervention for advanced osteoarthritis (OA). Pain is the main indication for the procedure, and the majority of patients undergoing a TKR gain significant pain relief.

However, an important minority of those who undergo a TKR have persistent pain in the operated knee. Baker showed that 19.8% of patients with data in the National Joint Registry had persistent knee pain, and 18.2% were dissatisfied with the procedure. Anderson, in a study of 98 patients, found that 8.1% claimed that the operated knee was worse at follow-up (2-3 years after surgery) than prior to surgery and 9.2% were dissatisfied. Wylde et al reviewed the available literature in 2009, and found that 10-20% of patients report significant pain in the operated knee, and that the patient centred outcomes of TKR appear to be considerably worse than those of total hip replacement, where as implant survivorship figures are fairly similar.

There are numerous possible causes of pain after a TKR, including anterior knee pain arising from the patello-femoral joint and extensor apparatus, prosthesis loosening, or infection. Other likely causes include soft-tissue periarticular problems, referred pain, pain sensitisation, or neuropathic pain. Because of the risk of infection, and the possible need for further surgery, orthopaedic surgeons are generally keen to investigate these patients thoroughly and exclude surgical causes of the problem. However, there seems to be background pain vulnerability in the knee causing this high incidence of post-operative pain. The pain itself clearly needs appropriate management but patients also need surgical evaluation to exclude important reversible causes.

In spite of this being a sizeable and worrying problem in orthopaedics, very little has been written about the assessment or management of these patients. No protocols or guidelines are available and the costs of management have not been explored.

In this paper we describe the first case series of patients with chronic knee pain after a TKR, and document the investigations and treatment undertaken, and the direct financial costs of their care to the NHS Trust in which they were seen.

RD&E provides an Arthroplasty tertiary referral service for a large area but is a large District General Hospital and as such the costs and results we report should be representative of most trusts within the UK.

Methods:

A specialist service for revision knee surgery is available at the Royal Devon and Exeter Hospital, resulting in the referral of patients with problems in a knee after a TKR. A registry of such patients has been established at the hospital. The data presented here is based on examination of the records of 41 of these patients. These were patients with a painful TKR who had been referred to one of the authors from Orthopaedic specialists in various institutions including the resident hospital.

The notes of these patients were analysed to ascertain the number of appointments patients’ had attended to address the TKR problem, and what investigations and treatments had
been undertaken for that problem both by the originating surgeon and by the revision knee specialist.

In addition data was obtained from the Trust on the current costs of the clinic appointments, investigations and any treatment or interventions undertaken.

Results:

The 41 patients studied included 27 women and 14 men, with a mean age of 63.9 years (range 49-81) at time of initial TKR. In the year 2009, 536 TKR’s were performed in the trust with an average age of 70.5 years (range 37-94) with 298 females and 238 males.

Investigations were commenced for abnormal pain post total knee replacement on average 15 months (range 1-84) after their knee replacement. Appointments and investigations were undertaken over a mean time of 20 months from initial investigation (range 7-45).

Neuropathic pain was diagnosed in 6 patients and instability was identified as a cause in 5 patients. 4 patients suffered aseptic loosening and no diagnosis was made in 26 patients (63%).

Table 1 shows the average number of appointments attended and investigations undertaken on these 41 patients.

Data on the costs of these appointments, investigations and treatments to the local NHS Trust are presented in Table 2.

The outcomes of these 41 patients included medical management alone in 19 (14 of whom reported significant improvement) and further surgical interventions in 22 (14 of whom reported improvement). The calculated direct costs of investigation and management of those treated solely medically (i.e. non-surgically) was £190/patient, while the cost of those treated surgically was £5,051/patient. This is shown in table 3.

Discussion:

We have analysed the management of a case series of patients with persistent pain in the knee after TKR. The results show that most of the 41 people studied attended numerous appointments with different specialists, and had the same investigations (serology and x-rays) repeated on many occasions over a relatively short period of time (less than 2 years), often before referral to a surgeon with a specific revision knee interest. We have also shown that the investigations and treatment undertaken were costly to the NHS, particularly if specialist imaging investigations (CT or MRI) or further surgical procedures (including aspiration or arthroscopy) were undertaken. The costs to the patients of the numerous appointments and repeated investigations have not been included, but are likely to have been considerable.

The fact that many different appointments were offered, and many investigations repeated, along with the wide range of different approaches to the different patients, are indicative of the absence of clear patient pathways or of a co-ordinated clinical service for these patients. Patients were seen by orthopaedic surgeons, pain specialists and physiotherapists, but definitive diagnoses or management plans did not often result from these appointments, and investigations were often repeated unnecessarily. We do not believe that this situation is unique to our area, as there are no clear guidelines or protocols.

Table 1 - Number of appointments and investigations per patient with a painful TKR

<table>
<thead>
<tr>
<th></th>
<th>Ave aptt/pt</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopaedic appointment</td>
<td>4.37</td>
<td>2 – 11</td>
</tr>
<tr>
<td>Pain team appointment</td>
<td>2.05</td>
<td>0 – 6</td>
</tr>
<tr>
<td>Physiotherapy appointment</td>
<td>3.05</td>
<td>0 – 12</td>
</tr>
<tr>
<td>Hydrotherapy appointment</td>
<td>0.8</td>
<td>0 – 8</td>
</tr>
<tr>
<td>ESR/CRP/WCC/PV</td>
<td>7.75</td>
<td>2 – 38</td>
</tr>
<tr>
<td>X-rays</td>
<td>7.92</td>
<td>2 – 35</td>
</tr>
<tr>
<td>MRI/CT/Bone scan</td>
<td>0.41</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Aspiration/Arthroscopies</td>
<td>0.51</td>
<td>0 – 3</td>
</tr>
</tbody>
</table>

Table 2 – Costs of appointments, investigations and treatments per patient

<table>
<thead>
<tr>
<th></th>
<th>Ave cost/pt (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopaedic appointment</td>
<td>370</td>
</tr>
<tr>
<td>Pain team appointment</td>
<td>235</td>
</tr>
<tr>
<td>Physiotherapy appointment</td>
<td>45</td>
</tr>
<tr>
<td>Hydrotherapy appointment</td>
<td>68</td>
</tr>
<tr>
<td>ESR/CRP/WCC/PV</td>
<td>21</td>
</tr>
<tr>
<td>X-rays</td>
<td>*</td>
</tr>
<tr>
<td>MRI/CT/Bone scan</td>
<td>70</td>
</tr>
<tr>
<td>Aspiration/Arthroscopies</td>
<td>1529</td>
</tr>
<tr>
<td>Operative Costs</td>
<td>2624</td>
</tr>
<tr>
<td>Drug Costs</td>
<td>174</td>
</tr>
<tr>
<td>Average cost/patient</td>
<td>5136</td>
</tr>
</tbody>
</table>

* = X-ray radiographs costs were insignificant and not charged to the NHS Trust

Table 3 – Comparison of operative versus non-operative costs

<table>
<thead>
<tr>
<th></th>
<th>Average Surgical intervention cost/pt</th>
<th>Average drug therapy cost/pt</th>
<th>Total cost/pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative patients (22)</td>
<td>4891.09</td>
<td>160.22</td>
<td>5051.31</td>
</tr>
<tr>
<td>Non-operative patients (19)</td>
<td>N/A</td>
<td>190.63</td>
<td>190.63</td>
</tr>
</tbody>
</table>
to help us know how best to investigate or manage these patients before referral and the natural history of the condition is unknown.

The investigations carried out most frequently were serological tests (ESR and CRP) to try to exclude infection, and x-rays to look for prosthesis loosening or other bony problems. Previous work has shown that a single test of ESR greater than 22.5 or CRP greater than 13.5, in this situation, has a sensitivity of 0.77 and a specificity of 0.93 for the diagnosis of infection. Repeating these tests offers little help, and if these were positive it would seem more appropriate to proceed to joint aspiration.13,12-15

Similarly, there is little point in doing more than one x-ray study a year, as the rate of change in radiographic findings is slow. If a bone problem is suspected, other more sophisticated imaging modalities can be used16-18.

The cost data obtained from our Trust show that high costs are incurred from new clinic referrals and visits, sophisticated imaging procedures (CT, MRI and bone scans), and surgical procedures – in particular revision surgery. These high costs of investigations would indicate that patients with a painful TKR would be more appropriately investigated and managed by specialist centres with early and meticulous evaluation by surgeons with a special interest in revision knee surgery.

The surgical costs of management of painful TKR's dwarf the amount of money spent on medical (i.e. non-surgical) approaches. This considerable difference suggests that it is of paramount importance to manage the pain early, irrespective of whether surgery is required. Good pain management will allow the surgeon, and particularly the patient, to evaluate the problem in a clearer manner, weighing up the treatment options and making a decision from a more balanced position.

According to data from the National Joint Registry, over 53,000 TKRs were performed in NHS hospitals in England and Wales in 2009.19 Using the estimates of Baker, and Wylde and others on the numbers of these patients who are in pain or dissatisfied, we calculate that over 10,000 patients each year, in this country alone, are acquiring the problem of persistent pain in a TKR. This represents a huge public health problem, and one that, if our Trust's cost figures are representative, is probably costing the NHS over £10 Million/annum. In view of that, we believe that this issue needs urgent attention from the research community and health care providers.

Our recommendation is that research is undertaken to document the natural history of pain in a TKR knee, differentiate the main causes of this pain, and develop simple algorithms to help clinicians make the correct diagnosis. We suggest a protocol that can be utilised by healthcare professionals to investigate painful TKR’s to allow correct assessment and diagnosis (Figure 1). We believe that health care providers in major orthopaedic centres should set up interdisciplinary clinics in which surgeons, pain specialists and physiotherapists can work together to help investigate and manage these patients.

Competing Interests
None declared

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Figure 1 – Algorithm for assessment of a patient with a painful TKR
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Managing Change

Kathryn Critchley

Isaac Asimov famously said: ‘The only constant is change.’ (Cited in Hartung, 2004).

So why is it so difficult for most of us to understand, manage, or embrace change?

Coping with change can be challenging for many and, depending on the change and what the impact or outcome of the change means to the individual, will depend upon how well they embrace and accept it. Should a person be fearful of change then it is natural that they will attempt to resist it which in turn can cause high levels of stress and anxiety.

Understanding how we typically react to change also helps us to cope better and manage change. The Kubler-Ross (2009) Model of Change is perhaps one of the best known and most applied models within clinical environments (her original work being around the five stages of grief) which is now also applied to businesses and organisations when looking at changes in the workplace such as loss or change of job.

The five stages she refers to are:

1. Denial
2. Anger
3. Bargaining
4. Depression
5. Acceptance

Applying the Kubler Ross Model to this situation, this is how a person may typically react:

Denial - This cannot be happening! Try again. And again! Check the other things in the car are working such as the lights and radio. Try again but still nothing.

Anger - Arrrrgh you stupid car!!! I’m sick of this car!! Why is this happening today of all days!! Slamming a hand against the steering wheel.

Bargaining - (realising that it really isn’t going to start and that you’re going to be late for work),..., Oh please car, if you will just start one more time I promise I’ll buy you a brand new battery and keep you clean and tidy. Please just start this one time.

Depression - Oh no! What am I going to do? I’m going to be late for work. I give up. I don’t really care any more. What’s the use?

Acceptance - Right I need to do something. It is not going to start. I need to call the breakdown service and ring into work.

The above example is a simple example yet I’m sure most of us have experienced it or something similar quite often. If you apply this to a situation where the stakes are far higher such as a sudden loss or change of a job, bereavement, house, relationship etc which may impact upon so many things including stability of finances, family, health and other forms of security, then you may be able to see the harsh effect this could have on an individual during this time.

Often individuals add to their stress by expecting themselves to be able to cope with such events. It is important to understand it is not about strength or weakness but about human nature to react by demonstrating the signs of loss and grief. Organisations, managers and individuals need to be understanding and supportive when situations like this happen.

Another way of understanding and coping with change is to consider what goes on in the mind of the individual at the time of the change and what it ‘means’ to them. Some people see risk and uncertainty as exciting and embrace change (depending on the change), whereas others can be fearful of any change, even...
those perceived to be minor changes, as for them any change is seen as a risk and takes them out of their comfort zone.

The comfort zone

Your comfort zone is where you are fully able, competent and comfortable. The job that you can do with your eyes shut or routines of life where you know exactly what you are doing. You may feel slightly challenged now and then, but there’s nothing you cannot easily handle.

When invited to step outside their comfort zone – or if they’re pushed outside of it - many people react with resistance. This is because of the human fear of failure which, when you look into it more deeply, comes from a desire to be accepted, liked and even loved. When most people ‘fail’ they feel embarrassed, ashamed, silly or stupid because they feel they can’t or couldn’t do whatever it was they tried.

So it’s understandable if at work, or any area of life where there is change, people react with resistance. Change is the unknown, and if you don’t know whether you can do something – especially if you have a ‘Be Perfect’ driver – you could have fears over whether you can do it, can be a success or even cope. Everyday changes such as new computers or telephone systems, new staff, new jobs, new routines and procedures, new management, merging of departments, sections or whole companies or, on a personal level, exams, weddings, divorce, births, deaths, moving house and so on, are all high on the list of stressors due to change.

How big is your zone?

Are you resistant to change? If you are, you’re causing yourself stress. Imagine what size a child’s comfort zone would be compared to an adult’s. Children do not have inhibitions and fears; it’s only as we grow older that we learn to feel fear, that we learn what embarrassment is and how to feel silly or stupid – that is, we learn to have an ego. This restricts our ability to have the freedom to learn, grow and be open to change, as we are nervous about asking questions for fear of looking silly, or trying new things for fear of failure, and we avoid doing anything that may cause us to feel embarrassed.

By being more fluid and open to change, accepting any fear and dealing with it effectively, you would not only grow your confidence and self-esteem, but you will be free to develop your life with more happiness and less stress.

By looking at change differently (for example, recognising that change can also be a good thing; focusing on the possible positives from a situation rather than being quick to look at the negatives from a point of fear and therefore resistance) stress can be greatly reduced.

Choose to flow with change rather than resist; choose to step out of your comfort zone and grow the size of your comfort zone daily. Aim to have a comfort zone the size of a child’s where nothing can faze or worry you, and you will notice a huge difference to the amount of stress you have in your life.

‘The greatest discovery of my generation is that a human being can change their life by altering their attitude of mind.’ William James (cited in Maxwell, 2007).

Remember – the only failure is not trying again. If we fail at something at least we know what NOT to do next time!

Identifying your zones and being rational

Following are three simple exercises you can complete to help you to gain a rational perspective on understanding how you cope with change and also being solution focused when embracing change.

The zones of change help us to understand the different levels of comfort or ‘risk’ and where changes may sit in terms of their perceived meanings to the individual.

Zones of change

Exercise 1

Think back to a significant change in your life or work (something from the past).

What were your perceived risks at the time?

………………………………………………………………

………………………………………………………………

What did you lose?

………………………………………………………………

………………………………………………………………

What did you gain?

………………………………………………………………

………………………………………………………………
This exercise demonstrates that our ‘perceived risks’ at the time of a change were often far different than the reality of how the change occurred. It is also common for an individual to notice that their ‘gains’ can be larger than their ‘losses’ (time can play a factor in this too, often a change can seem a disaster at the time but over time a person can look back and be glad it happened in comparison to how their life is now.)

Exercise 2

Think of a change that you are currently undergoing.

What aspects of the change are in your ‘comfort zone’?

What aspects are in your ‘risk zone’?

What aspects are in your ‘high risk zone’?

What do you need to make the ‘high risk’ into ‘risk’ and the ‘risk’ into ‘comfort’?

This exercise is excellent for considering a current change and how it may affect a person.

Actually listing in categories the level of ‘risk,’ or even drawing the zones on a piece of paper and writing in each change in the place on the zone where the person believes it sits, will give a rational perspective.

Once all the ‘risks’ are highlighted then that is the time to minimize ‘risk’ and find solutions for the individual to cope or manage that change. This is good for action planning and allowing a person to take control to embrace a change rather than being reactive once the change has occurred.

Exercise 3

Think of a life or work change which is going to occur in the future.

Blockers

What I’d be sorry to lose.

My fears and concerns.

Drivers

Benefits of the change.

What I’d be glad to leave behind.

Answering these questions assists a person to determine how much resistance they may feel/have towards a change. Listing potential blockers will identify fears and concerns of the change as well as the levels of risk and loss. Listing drivers will encourage the individual to consider the benefits of the change, the gains, and that change can also be a good thing.

Typically, whichever list is the longest or has the most meaning/impact will be the strongest for that person. If this is the blockers they will resist the change and cause themselves pressure and stress. Therefore addressing the zones of change and looking for ways to reduce risk would be a good strategy in action planning to manage the change well. Should the drivers be the strongest for the person then they are likely to embrace the change more readily although they may still need to address their thoughts and rationale for any blockers listed.

Change tips:

• Embrace change, as if you don’t accept it someone will push you into it.
• Take every opportunity to grow your comfort zone.
• Have the attitude that there is no failure and only learning and development – when we ‘fail’ we know what NOT to do next time.
• The worst rarely happens, so why waste energy focusing on it and enforcing irrational fears?
• Change CAN be a good thing.
• There is always a solution, it may take time for you to see it, but if you look, you will find it.
Competing Interests
None declared

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Are Psychiatrists Paying Attention to Sleep?

Adeel Meraj

ABSTRACT
Sleep medicine is a relatively new medical discipline since the 1970’s. It has developed tremendously and has come across as an independent discipline in the United States over the last thirty years. The US has a well-developed and respected sleep medicine training structure which allows specialists from various disciplines, including psychiatry, to acquire specialty training in sleep and become certified sleep specialists. This is not the case in Europe and the United Kingdom where there is no structured training and the practice of sleep medicine is limited to respiratory physicians (such as pulmonologists). In the last decade there has been an increased interest among US psychiatry residents in pursuing further training in sleep medicine. This article gives a brief overview of the development of sleep medicine in the US in the past 30 years and the current structure of training in the US compared to several European countries. It highlights the value of sleep medicine as a career choice for psychiatrists and the advantage psychiatrists have in treating sleep disorders.

Introduction:
Sleep is a fundamental part of our lives and about one-third of it is spent sleeping. Sleep deprivation has been linked with such high profile public disasters, as Chernobyl, the Challenger shuttle disaster and the nuclear meltdown at Three Mile Island. According to the US Highway Traffic Safety Administration, approx. 100,000 motor vehicle accidents are the result of driver’s drowsiness and fatigue¹. There is an association of sleep disorders with anxiety and depression which may be bidirectional. Patients with insomnia for 2 weeks or longer, without current depression are at increased risk of developing major depression. Both insomnia and hypersomnia are considered independent predictors of depression and anxiety².

Key Milestones in the Development of American Sleep Medicine:
The history of treatment of sleep disorders dates back to at least the use of opium as a hypnotic reported in ancient Egyptian text. Sleep medicine, however did not emerge as a distinct discipline until the 1970’s. Drs. Kleitman and Dement were significant early contributors to this field in the United States. In 1957 they first described Non Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep and proposed the 4 stages of NREM sleep. In 1972 Dr. Dement, a Professor of Psychiatry and Behavioural Sciences at Stanford University School of Medicine, contributed to the establishment of the first sleep disorder centre in Stanford. After Stanford, other centres in New York, Texas, Ohio and Pennsylvania started providing sleep evaluations for which patients stayed in the centre overnight. The Association of Sleep Disorders Centre (ASDC) was established in 1975 and Dr. Dement served as its first president for 12 years. In 1999 ASDC was renamed American Academy of Sleep Medicine (AASM).

The first textbook of sleep medicine “Principles and Practice of Sleep Medicine” was published in 80’s. The journal SLEEP started in 1978. In 1998 the AASM commissioned the fellowship training committee to develop guidelines for sleep medicine fellowship training. The first two programmes to be granted formal accreditation were Stanford University in California and the Centre for Sleep and Wake in Montefiore Medical Centre, New York. The American Medical Association recognized sleep medicine as a specialty in 1996. In 2004 the Accreditation Council on Graduate Medical Education (ACGME) took over the fellowship accreditation process and approved a one year training programme 1,3,4,5.

Sleep Medicine training in Europe:
Unlike United States, there are no formal sleep medicine training programmes or qualification in the United Kingdom or Europe. Sleep medicine is restricted to a small group of respiratory physicians with a special interest in sleep medicine. Psychiatry trainees are exposed to very little formal teaching in sleep medicine. However in the last 3 years the neuropsychiatry section of the Royal College of Psychiatrists of the United Kingdom has formed the “sleep working group” under the leadership of Dr. Hugh Selsick, this group is responsible for increasing awareness of sleep medicine among British psychiatrists, by emphasizing the importance of sleep medicine in psychiatric practice and encouraging psychiatrists to contribute to the field of sleep medicine. This group has developed a competency based curriculum that incorporates the training of sleep medicine into the psychiatry curriculum, to organize sleep medicine symposia at annual conferences of the Royal College and to develop professional training (CPD) modules for psychiatrists. British Sleep Society is another forum that brings together physicians from various backgrounds.
interested in sleep medicine. Royal Society of Medicine also has a sleep medicine section which organizes various conferences. There are two, weeklong courses on sleep medicine, the Edinburgh and Cambridge courses. Recently the University of Glasgow started a Master’s of Science (MSc) in behavioural sleep medicine program for healthcare providers working in Scotland, the rest of the United Kingdom and Europe. There is a trans-European move to start a formal sleep medicine certification similar to what we have in the United States. European Sleep Research Society (ESRC), a professional body of sleep scientists in Europe responsible for promoting sleep research and sleep medicine is starting its “first ESRS certification examination” in sleep medicine; this examination is scheduled to take place on September 4th, 2012 at the 21st Congress of the European Sleep Research Society in Paris. Since there are no formal training programmes this will be for those without formal training.

Psychiatry and Sleep:

Asking about the patient’s sleep is an integral part of a psychiatric consultation. Almost all the medication that psychiatrists prescribe has an effect on sleep architecture. Some psychiatric medications are used to treat sleep disorders and others can cause sleep disorders like Restless Legs Syndrome and PMLD. Understanding sleep can help us understand the mechanism of psychiatric illness. Many psychiatric disorders have comorbid sleep disorders and several behavioural therapies have been used successfully for the treatment of sleep disorders. There is a bidirectional association between sleep disorders and psychiatric disorders. With the growing population of military soldiers returning from Iraq and Afghanistan with post-traumatic stress disorder, sleep problems and depression, there is an increased need for psychiatrists who possess knowledge in both sleep disorders and comorbid psychiatric illness. Psychiatrists have a distinct advantage dealing with sleep disorders and can bring those skills to sleep medicine.

Are psychiatrists attracted towards sleep medicine? The answer is yes. In the recent years we have seen an increased interest among psychiatry trainees for a sleep fellowship in United States. In recognition of behavioural consequences of sleep problems and multidisciplinary approach in sleep disorders, fellowship programmes are increasingly taking applicants from various backgrounds and not just pulmonology and neurology. Many psychiatry trainees are choosing a sleep medicine elective earlier in residency. Currently there are more than 710 accredited sleep centres in the United States. Many major university medical centres have a one year fellowship programme accepting applications from physicians from various backgrounds including Psychiatry, Neurology, Internal Medicine, Pulmonology, Paediatrics, ENT and Anaesthesia. There are more than 24 AGME accredited sleep medicine fellowship programmes in the United States. New fellowship programmes are being opened at the University of Kansas Medical Centre and the University of Texas Health Sciences Centre, San Antonio.

Conclusion:

Sleep medicine is a new and exciting field of medicine with potential to grow in future. It’s a multidisciplinary field. American sleep medicine has evolved greatly over the last 30 years and there appears to be much to learn from the American model. There is a need for the psychiatry training programs both in the United States and the Europe to encourage and prepare their trainees to consider training in sleep medicine. Psychiatry trainees in the United States interested in sleep medicine should speak with their programme directors early in their residency training to register their interest and residents should also contact the local sleep centre for more advice. Each year American Academy of Sleep Medicine (AASM) accepts 10 international physicians for its 4 week mini-fellowship programme. Three weeks of the fellowship are spent at an AASM-accredited U.S sleep centre with their last week of the fellowship spent at the annual SLEEP conference. A certificate of training is issued at the end of the mini fellowship.

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