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Editorial

HBsAg carriers with normal ALT levels: Healthy carriers or true patients?

Claudio Puoti

It is well documented that many HBsAg-positive / HBeAg-negative patients show normal alanine aminotransferase (ALT) levels. However, two different scenarios have been proven to exist: inactive Hepatitis B Virus (HBV) carriers (previously defined as "healthy" HBV carriers) and patients with chronic hepatitis B (CHB) with transient virological and biochemical remission. These subsets of patients share HBsAg positivity and normal ALT levels; however, progression of disease, outcome, HBV DNA levels, severity of liver damage, requirement for liver biopsy and antiviral treatment significantly differ between the two patient populations.

Thus, among HBsAg-positive / HBeAg-negative subjects with normal liver biochemistry, it is important and sometimes difficult to distinguish the '*true inactive HBV carriers*' from patients with '*active CHB*' in whom phases of spontaneous remission have occurred. The former have a good prognosis with a low risk of complications, while the latter patient population have active liver disease with a high risk of progression to liver cirrhosis and/or hepatocellular carcinoma (HCC). Therefore, prolonged biochemical and virological follow-up are mandatory for diagnosis and decision to treat.

The term '*chronic hepatitis B*' refers to a chronic necroinflammatory disease of the liver caused by persistent HBV infection [1]. The term 'necroinflammatory' describes the presence of death of periportal hepatocytes (periportal necrosis) with or without disruption of the limiting plate by inflammatory cells, intralobular necrosis, portal or intralobular inflammation, and formation of bridges between vascular structures (the so-called bridging necrosis). Chronic hepatitis B can be subdivided into HbeAg positive and HBeAg-negative chronic hepatitis B [1,2]. These two forms may have different natural histories and different response rates to antiviral treatment, although both may progress to more severe liver damage [3], such as, liver cirrhosis [4] or HCC [5].

The second subset is called the *'inactive HBsAg carrier state'*. It means a persistent HBV infection of the liver but without continual significant necroinflammatory disease. It is characterized by very low or undetectable serum HBV DNA levels and normal serum aminotransferases [1]. It has been shown that histologically significant liver damage is rare in these patients, particularly when HBV DNA is lower than 2000 IU/ml, and thus a liver biopsy is not indicated in these subjects [4]. Even among HBeAg-negative carriers with serum HBV DNA between 2000 and 20,000 IU/ml, histologically significant liver disease is also rare [6]. Thus, these subjects should be followed up closely, but biopsy and treatment are not currently indicated.

As mentioned above, it is sometimes difficult to distinguish true inactive HBV carriers from patients with active HBeAg-negative CHB in whom phases of spontaneous remission may have occurred [1]. The former patients have a good prognosis with a very low risk of complications, while the latter have active liver disease with a high risk of progression to advanced hepatic fibrosis, cirrhosis and subsequent complications such as decompensated cirrhosis and HCC [3-6]. Thus, a minimum follow-up of 1 year with ALT levels every 3–4 months and periodical measurements of serum HBV DNA levels are required before classifying a patient as an inactive HBV carrier [1]. ALT levels should remain consistently within the normal range, and HBV DNA should be below 2000 IU/ml [7]. Thereafter, the inactive HBV carrier with undetectable or very low HBV DNA levels should be followed up with ALT determinations every 6 months after the first year and periodical measurement of HBV DNA levels [6] for the rest of their lifetime. This follow-up policy usually allows detection of fluctuations of activity in patients with true HBeAg-negative CHB [8].

It is important to underline that some inactive carriers may have HBV DNA levels greater than 2000 IU/ml (usually below 20,000 IU/ml), despite their persistently normal ALT levels [1,6,9]. In these carriers the follow-up should be much more condensed, with ALT determinations every 3 months and HBV DNA measurements every 6–12 months for at least 3 years [1]. After these 3 years, these patients should be followed up for life like all inactive chronic HBV carriers [6]. After all, the inactive HBV carrier state confers a favourable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients [1,10,11]. Patients with high baseline viremia levels have higher risk of subsequent reactivation. A liver biopsy should be recommended if ALT levels become abnormal and HBV DNA increases above 20,000 IU/ml. Non-invasive evaluation of liver fibrosis [12] may be useful, although these non-invasive tools, such as transient elastography, need further evaluation [6].

HBsAg clearance and seroconversion to anti-HBs antibody may occur spontaneously only in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA [7].

On the other hand, progression to HBeAg-negative CHB may also occur [10].

Although the optimal definition of persistently normal ALT (PNALT) levels has not been established, the fluctuating nature of chronic HBV infection reasonably justifies serial ALT determinations. These should be done with a minimum of four to five tests 3–4 months apart within the first year of presentation, before determining whether an HBeAg-negative patient truly has PNALT. An initial follow-up of at least 1 year is supported by the finding of mild histological lesions in HBeAg-negative patients with true PNALT during the first year [6]. The risk of developing abnormal ALT levels in HBeAg-negative patients with a normal baseline ALT have been reported to be higher during the first year (15–20%) and decline after 3 years of follow-up, therefore frequent monitoring during the first 1–3 years is critical [6,10].

Antiviral treatment of inactive HBsAg subjects is not indicated [1]. Patients should be considered for treatment only when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal and severity of liver damage assessed by liver biopsy showing moderate to severe active necroinflammation and/or at least moderate fibrosis[1,2].

Competing Interests
None declared
Author Details
CLAUDIO PUOTI, MD, Chief, Dept. of Internal Medicine and Liver Unit, Marino General Hospital, Marino, Rome, Italy
CORRESSPONDENCE: CLAUDIO PUOTI, Chief, Dept. of Internal Medicine and Liver Unit, Marino General Hospital, Viale XXIV Maggio, 00047, Marino, Rome, Italy.
Email: puoti@epatologia.org

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Research Article

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Evidence and recovery; improving outcomes in opiate substitution treatment

James Bell, Christine Healey, Fiona Kennedy, Mohammad Faizal and Aadil Jan Shah

Abstract

Background: Based on the perception that many patients on methadone are not receiving effective treatment, drug policy in the UK is being reoriented towards the 'recovery agenda'[1].

Aim: To assess the extent to which current delivery of OST is evidence-based, and whether bringing treatment into line with evidence improves outcomes.

Method: Clinical audit in two OST services in Merseyside. Non-responding patients - those reporting regular heroin use in treatment - were identified from files, and patients in one service were referred for medical review to bring their treatment into line with current UK guidelines[2] – predominantly, ensuring adequate methadone doses. Patients in the other clinic continued to receive treatment as usual. Files were re-audited 9 months later and rates of heroin use between the clinics compared.

Results: 175 (17% of patients in treatment) reported regular heroin use; most were on less than 60mg/day of methadone. Although reporting high depression scores and low quality of life, patients resisted changes to their treatment; of 104 patients referred for medical review, only 47 attended. Medical review and changes to treatment were seen as an intrusion into patients' choices. At follow up audit, there was no difference in reductions in heroin use between the two OST services.

Conclusion: Many non-responders appeared "stuck", but resisted change. The clinical ethos was oriented towards supporting clients in their choices rather than achieving specific treatment objectives. By focusing on outcomes rather than process, the 'recovery agenda' may facilitate the implementation of evidence based care, as opposed to being a competing paradigm.

KEYWORDS : opiate substitution treatment, recovery agenda, optimisation clinic, audit, evidence-based care.

Introduction

Driven by a global rise in opioid dependence, Opioid Substitution Treatment (OST), the prescribing of opioids (usually methadone or buprenorphine) as maintenance treatment, has expanded worldwide over the last two decades[3]. Participation in OST reduces the risk of death by overdose[4], reduces the risk of HIV transmission[5] and reduces participants' involvement in property crime[6]. For these reasons, maintenance with methadone remains the major public health response to reduce the harms caused by heroin addiction.

In the United Kingdom (UK) in the late 1990s, government funding to expand access to OST was provided, with the explicit objective of reducing crime[7]. The expansion of treatment was supported with clinical guidelines[2], and targets were set to try to ensure good outcomes. Given the research evidence on the importance of retention in producing better outcomes, service providers were set a target of retaining at least 75% of people in treatment for 3 months. A tool to monitor outcomes, the Treatment Outcomes Profile (TOP)[8], was developed and service providers nationally were set a target of 80% of people in OST completing TOP at entry and after 6 months[9]. This 20-item self-report questionnaire records a set of core data for the previous 28 days, including the number of days on which heroin and cocaine have been used.

The amount of methadone prescribed in England and Scotland increased fourfold over the decade 1998 – 2008[3]. However, in 2010, Britain's newly-elected government signalled a change in the direction of drug policy[1]. The paradigm on which the new policy is based is "recovery", a concept embracing self-help, mutual support, and optimism about the possibility of positive change. The policy is in part driven by the perception that treatment services have a defeatist attitude, expecting little positive change – hence the claim that there are too many patients "parked on methadone". To counteract this perceived pessimism, the "recovery agenda" includes incentives to services to promote abstinence from all drugs including prescribed OST medication. This policy has been criticized as being inconsistent with the available evidence[10], but has been defended on the grounds that many patients on methadone were doing poorly, and needed encouragement to make positive changes in their lives.

In 2010, we decided to investigate to what extent people were responding poorly to treatment, and whether this could be improved by implementation of evidence-based treatment.

Methods

This quality improvement project was undertaken in two OST clinics in Merseyside, managing in total over 1000 patients. The services had the same senior leadership and medical staff, but

separate teams of nurses and key workers. Supervised administration was provided by local retail pharmacies.

In October 2010 key workers were provided with list of patients currently under their care and asked to identify patients they thought were using heroin regularly. A research assistant then checked case notes of identified patients, looking at self-reported heroin use as recorded in TOP monitoring forms, and at the results of previous urine toxicology tests. Those whose most recent TOP was performed at entry to treatment were excluded (since their self-reported heroin use covered a time when they were not in treatment). Among the remainder patients reporting use of heroin on at least 8 days in the 4 weeks preceding their last TOP interview were classified as "non-responding" patients. The case notes of all identified "non-responders" were reviewed using an audit tool covering age, sex, postcode, date of entry into treatment, duration of treatment, dose of medications, extent of supervised administration, dates and results of recent urine toxicology, and date and self-reported drug use from previous TOP questionnaires. This data was collected at baseline and again at re-audit (follow-up) 9 months later.

Postcodes were used to derive Index of Multiple Deprivation (IMD) scores[11]. The English index of multiple deprivation (IMD) is a measure of multiple deprivations, with domains including employment deprivation, health deprivation and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation, and crime.

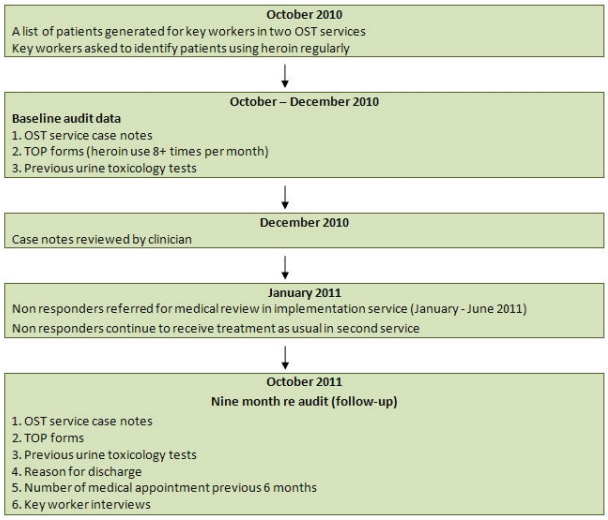
In one clinic, the "implementation clinic", beginning January 2011, key workers were asked to refer all non-responders for a medical review. Patients were also screened for comorbidity, taking advantage of a separate project running concurrently which was designed to test the psychometric properties of a new questionnaire on mental health and well-being. All service users at the implementation clinic were invited to take part. The study had National Research Ethics approval and approval from the Merseycare NHS Trust R&D Office. Quality of life was assessed with the EQD[12]which comprises 5 domains measuring health-related quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Depression was screened for with the Beck Depression Inventory[13].

UK guidelines recommend for patients doing poorly "*..ensuring medication is provided within evidence-based optimal levels, changing to another substitute medication, increasing key working or psychosocial interventions and increasing supervised consumption"*[3]. The recommended dosage for effective treatment is listed as in the range 60-120mg/day of methadone. At medical review, the plan was for the doctor to assess the non-responding patients, and propose raising methadone dose progressively until heroin use ceased, or a maximum dose of 120mg/day was reached; and requiring supervised consumption of methadone for patients persisting in heroin use.

Establishing the medical reviews in one of the two clinics was necessary for logistic reasons, but it also allowed an opportunity to assess the impact of the reviews, by comparing the outcomes of non-responders in the two clinics. If effective, it was proposed to extend this approach to the second 'treatment as usual' service. Referrals for medical review ceased in June 2011, and over the next three months staff feedback about the process was sought. In October 2011 a repeat audit of case notes including TOP results of all previously identified non-responders at both services was undertaken.

At follow-up data on the frequency of medical appointments in the preceding 6 months were also collected. In cases where people had left treatment, the TOP performed on exit from treatment was used. Those non-responders who had left treatment were identified and tabulated according to the reason for leaving treatment.

Flowchart 1: The audit and re-audit process



Ethics

The audit was approved by the local NHS Trust R&D Office. Funding was obtained to undertake the work by Mersey Care NHS Trust.

Analysis

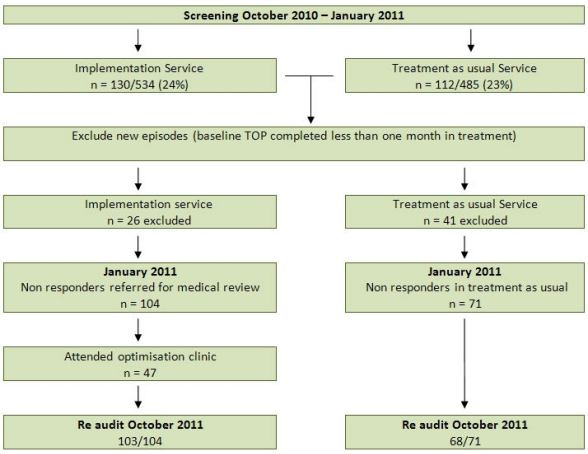
Data was entered into SPSS version 18 (for windows). Summary statistics and standard hypothesis tests compared non responders in the intervention service to non responders in treatment as usual to ensure there were no statistically significant differences between the two groups at baseline. Chi-square and t-tests compared age, sex distribution, IMD scores, methadone dose and months in treatment this episode. Mann-Whitney U tests compared the number of TOP forms completed in each group during the previous 6 and 12 months. Regression analysis explored whether there was a relationship between attendance for supervised administration, self-reported quality of life and depression for non responders in the

implementation group. Differences in baseline and at 9 month re audit methadone dose and heroin use were tabulated for each group. Mann-Whitney U-tests compared any differences between the two groups. Differences within each group were also compared using the Wilcoxon signed ranks test.

Results

The implementation service managed 534 patients, of whom 130 (24%) were initially identified as non-responders, reporting heroin use on 8 or more days in the previous month at their last TOP interview. At the TAU service there were 485 patients, of whom 112 (23%) were identified as non-responders. Of the 242 non-responders in total, 67 (28%) were new to treatment, and were excluded. This is illustrated in the flowchart 2.

Flowchart 2: Sample Algorithm



Approximately 50% of the non-responders in each group reported daily heroin use at baseline. The two groups of non-responders did not differ significantly in terms of age, sex distribution, nor on the Index of Multiple deprivation scores (mean of 62 reflecting very severe social exclusion across both groups). Non responders in the implementation service had been in treatment a median of 18 months compared to 17 months for those in treatment as usual. Urine testing was performed infrequently in both services, but a result was available from the six months prior to baseline for 133 of the remaining 175 subjects. The urine tests results were broadly consistent with the patients self-report. Aspects of treatment at the two services differed, as shown in Table 1. At baseline, doses did not differ significantly, but the treatment as usual group was significantly less likely to have their methadone administration supervised, and had less frequent TOP monitoring.

Despite almost all non-responders being booked in for an appointment and given reminders at the implementation service, only 47 (45%) of the 104 identified attended at least one medical review. Keyworkers commented that the main reason for non-attendance was that clients were quite happy continuing heroin use and did not see stopping as something they wanted to do. When patients were told they would only receive their prescription renewal after attending, some patients chose to go without methadone and make contact a few days later, rather than attend an appointment. Among those who did attend, there was frequently resistance to increasing their methadone dose, and anger at the suggestion that medication administration should be supervised. Word of mouth spread through the service that doctors were proposing dose increases and more supervision. This increased resistance among patients, and appears to have generated some resistance among keyworkers, some of whom saw their role as advocates for the patients.

Table 1 Profile of non-responders and their treatment at baseline

	Implementation	TAU	Total
N	104	71	175
Mean age in years (min, max)	42 (25,66)	43 (23,63)	42 (23,66)
Male (%)	65 (63%)	48 (68%)	113 (65%)
Mean IMD Score (SD)	62 (14.6)	62 (14.7)	62 (14.7)
Mean methadone dose in mg (SD)	60 (17.8)	60 (21.3)	60 (20.3)
Median Months in this Rx episode (IQR)	18 (20)	17 (10)	18 (14)
Any supervised doses	56 (54%)	22 (31%)*	78 (45%)
Last TOPS > 6/12 ago	15 (15%)	29 (42%)**	44 (25%)
*Pearson Chi square 9.995, df=2, p=0.007 **Mann-Whitney U =2654, p=0.002			

The attempt to implement change in one clinic appears to have had small effects in increasing average doses there, and having more patients seen by a doctor. Between baseline and 9 month re-audit (follow-up), mean methadone doses increased in the implementation group and fell in the TAU group, as shown in Table 2. There was a small and statistically significant increase in methadone dose in the implementation group compared to the TAU group. The difference in change in methadone dose between the two groups was statistically significant (Mann-Whitney U= 2745, p=0.002), but the mean dose increase (3mg) in the implementation group was small. In the 6 months prior to the collection of follow-up data, medical reviews in both services were infrequent; 36% of patients in the implementation group and 66% of patients in the TAU group had not seen a doctor in their OST service (Chi square =13.38, df=1, p=0.001).

In both groups, the reductions in heroin use over time were statistically significant (Wilcoxon signed ranks test p = <0.05), but the change in heroin use over time did not differ significantly between the two services (Mann-Whitney U 2832.5, p=0.7). The changes from baseline audit to 9 month re

audit are shown in Table 2. Among the 47 patients who attended a medical review, the mean prescribed methadone dose rose from 58 to 66mg/day, but the number receiving supervised doses actually fell, from 23 at baseline to 20 at follow-up. Mean days of reported heroin use fell from 20 to 12 (6 patients reported abstinence) – changes almost identical to what was observed in the TAU group.

Table 2 Changes in dose and heroin use between baseline (T1) and follow-up/re audit (T2)

	Implementation		**TAU**	
	Time 1	Time 2	Time 1	Time 2
N	104	103	71	68
Mean Self-report heroin days/28 (SD)	19.9 (8.6)	13.4 (10.8)	19.6 (8.3)	11.7 (10.8)
Reported daily heroin use	52 (50%)	33 (32%)	25 (42%)	17 (25%)
Heroin abstinence	-	14 (14%)	-	15 (22%)
Urine test positive morphine %	88%	76%	85%	70%
Mean daily methadone dose	59.5	62.9	60.1	57
Proportion self-report cocaine	67%	54%	53%	44%
Urine test cocaine positive	66%	57%	58%	45%

29 non responders (28%) from the implementation service, and 27 (38%) from the TAU service had left the service between baseline and 9 month re audit. Most discharges (31/56) were transfers to another service as part of a local policy to move more people into treatment in primary care. Eight patients from the Implementation service dropped out of treatment, and 4 patients from the TAU service did so. Differences in the pattern of leaving the two services did not approach significance.

Table 3 Reason for discharge

Reason	**Implementation**	**TAU**	**Total**
Transfer of Rx	13	17	30
Did not attend (DNA)	8 (28%)	4 (15%)	12
Elective Withdrawal	3	3	6
Deceased	2	0	2
Prison/drug diversion program	3	3	6
Total	29	27	56

44 non responders who attended a medical review at the implementaion service completed questionnaires on health, quality of life, and depression. Ninety-six percent were not in education, employment or training (NEET). On the Beck Depression Inventory, 50% of respondents reported depression in the moderate to severe range. Regression analysis indicated that having to attend for supervised doses was associated with less depression measured on the BDI (r=-.332, p=0.039), and with better quality of life in terms of EDQ scale of self-care (r=-.598, p<0.001) and being able to undertake usual activities (r=-.605, p<0.001).

Discussion

Many people persisting in heroin use were receiving care that was out of line with guidelines – doses below 60mg, often with no supervised doses, and seldom attending for medical reviews. However, the attempt to systematically implement guidelines was not effective. Most patients did not attend, and many of those who did attend resisted changes. Although patients who attended received slightly higher doses, changes in heroin use in the subset who actually attended for review were no different to the changes observed in the TAU group.

Higher methadone doses, and patients having control over their doses, have been shown in a meta-analysis to be independently predictive of better outcomes[14]. One possible explanation for the failure to implement guidelines is that it may have been perceived as challenging clients' control over their treatment. If so, it was a challenge easily defeated. Patients clearly had substantial control over their treatment, choosing whether to attend appointments, whether to accept higher doses, and whether to accept supervised doses. However, this degree of control over their treatment did not appear to be beneficial. "Non-responders" reported depression, disability and a poor quality of life.

Guidelines need to move beyond systematic reviews of effectiveness, to include evidence about implementing evidence in a real world setting[15]. Our conclusion is that the failure to implement guidelines was that the approach adopted was not congruent with clinic culture, which emphasised "support" rather than "structure". "Structure" refers to both cognitive and behavioural elements of treatment. The cognitive elements are defined and agreed objectives, a sense of the direction and purpose of treatment. In all areas of mental health, clinical interactions are most useful if focused on specific performance goals related to the patient's circumstances[16]. In the OST services studied, there appeared to be a focus on process and on supporting patients, rather than achieving outcomes.

Structure also includes behavioural elements - expectations and rules regarding attendance, and daily attendance for supervised administration. Interviews with UK patients in OST have indicated that they understand and value the role of supervision, not only in minimizing diversion and misuse, but in providing an activity for many people without social roles[17]. Consistent with the benefits of supervision, in the current audit more supervision was associated with less depression and less-poor quality of life.

This audit had several limitations. It did not attempt to measure the proportion of patients responding poorly to long-term methadone treatment, and it is possible that the true

proportion may be higher than the 17% identified by key workers. Documentation of treatment outcomes, using TOP reports and UDS results, was unsystematic, limiting the number of patients in whom complete data was available. "Non-responders" self-reported heroin use to keyworkers, who administered the TOP questionnaire, and there may have been under-reporting. However, while this study may not have identified all non-responding patients, this does not invalidate the observation that attempting to implement guidelines was not successful.

Most importantly, the observations from these clinics may not be generalisable to other treatment settings. However, certain key data are available suggesting the treatment and outcomes observed in this study were not atypical. A report on national TOP monitoring noted patchy availability of follow-up data, and confirmed a high rate of persisting heroin use in treatment, with 38% of participants reporting abstinence from heroin[18]. Despite this high rate of heroin use, a recent survey reported a mean dose of 56mg of methadone in a national survey[19]. In this regard, the clinics in this report thus seem representative.

Medical staff appeared to have a peripheral role in delivery of OST in these clinics. Most non-responders did not have a medical review in 6 months – despite persisting heroin use, and self-reported depression. In the 1980s in the US, methadone treatment underwent a process labelled "demedicalisation", marginalisation of the role of medical practitioners, and a loss of the sense that methadone was a medical treatment with clearly defined objectives and guidelines[20]. This contributed to a situation in which much methadone treatment in the US was out of line with research evidence[21]. The current audit suggests that a similar process of demedicalisation and deviation from evidence-based treatment has been occurring in some NHS services in the UK.

If these observations are representative of at least some treatment culture in the UK, they lend support to the criticisms made of methadone treatment in the new UK drug strategy[1]. To the extent that the recovery agenda challenges clinic culture and shifts the focus of treatment onto outcomes, it is a positive development.

However, many well-intentioned policies have unintended consequences, and there are well-based fears that the new policy promoting abstinence from OST as an objective of recovery will lead to an increase in overdose deaths[3]. This is specifically because of the risk of overdose deaths after leaving treatment. The reason for the increased risk of overdose after leaving treatment is that newly abstinent addicts who have reduced opioid tolerance, and a dose of heroin they previously used during periods of addiction becomes a potentially fatal dose once they are abstinent. This risk attaches to all forms of drug free treatment, as well as to patients who have left methadone. The critical issue is that lapses to heroin use, and relapses to dependent heroin use, are very common among newly-abstinent addicts. It is the high probability of relapse to heroin use which is the basis of long-term maintenance treatment – better to keep people safe and functioning normally, albeit while still taking a medication, than the risk of relapse and re-addiction, or relapse and fatal overdose. In the UK, implementation of the recovery agenda has included incentives to abstinence, and this is not consistent with evidence about the risk of relapse. If the recovery agenda can accommodate the evidence that indefinite maintenance as a valid option for many, perhaps most heroin users, then the evidence of this study is that far from being in contradiction, the recovery agenda may facilitate the implementation of evidence-based practice.

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Author Details
JAMES BELL, BA(Hons), MD, FRACP, FAChAM, South London and Maudsley NHS Foundation Trust, UK. CHRISTINE HEALEY BA (Hons), DipSW, MSc, MPhil, University of Liverpool, UK. FIONA KENNEDY BA (Hons), University of Liverpool, UK. MOHAMMAD FAIZAL, MBBS, MRCPsych, MBA, Clinical Director, Addictions, MerseyCare NHS Trust, UK. AADIL JAN SHAH, MBBs, MSc, MRCPsych, Consultant Psychiatrist, Cheshire and Wirral Partnership NHS Foundation Trust, UK.
CORRESSPONDENCE: DR JAMES BELL, 63-65 Denmark Hill, London SE5 8RS, UK.
Email: James.bell@kcl.ac.uk

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Review Article

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Management of Painful Peripheral Diabetic Neuropathy

Namita Arora and Dr. G Niraj

Abstract
Diabetes Mellitus is an endocrine disorder which causes metabolic disturbance producing a state of hyperglycaemia. Hyperglycaemia adversely affects cardiovascular, renal, nervous and visual systems. The importance of good glycaemic control in these patients has been emphasised in literature to reduce the end organ damage. Diabetes can cause autonomic and peripheral neuropathy. The autonomic neuropathy can affect the cardiovascular, genitourinary and gastrointestinal systems. Peripheral neuropathy can cause acute and chronic sensorimotor neuropathy, which can cause significant morbidity in these patients affecting their daily activities and quality of life. It can be challenging to treat them because the pain can be resistant to the medication and the effective medication can be associated with adverse effects which the patients may find difficult to tolerate. It is very important to increase the dose of the drugs to their highest effective dose (within the therapeutic range of that drug) for each patient with a balance of the side effects caused by that drug in that patient. These patients often need more than one drug to provide adequate pain relief. There are guidelines and recommendations available to help the clinicians to use appropriate combination of available treatment options.

Epidemiology:

The WHO estimated that 171 million people had diabetes in the year 2000 and predicted this number to increase to 366 million in the year 2030. Given the increasing prevalence of obesity it is likely that these figures provide an underestimate of future diabetes prevalence[1]. Peripheral diabetic neuropathy (PDN) may be present in 60 to 65% diabetic patients, with 11% patients of diabetic neuropathy complaining of pain. The management of this condition can be particularly challenging as these patients may not get good response to the medications used for the treatment and the medications used are associated with side effects which the patients may find difficult to tolerate.

Pathophysiology:

Pathophysiology of PDN is complex and incompletely understood. Both peripheral and central processes contribute to the chronic neuropathic pain in diabetes. Peripherally at the molecular level due to hyperglycaemia, glycosylated end products are generated, which deposit around the nerve fibres causing demyelination, axonal degeneration and reduction in nerve conduction velocity. Deposition of glycosylated end products around the capillary basement membrane causes basement membrane thickening and capillary endothelial damage, which in association with a hypercoaguable state causes peripheral arterial disease. The peripheral arterial disease leads to neuronal ischemia which worsens nerve damage. There also occurs depletion of NADPH by activation of NADPH oxidase causing increased oxidative stress and generation of oxidative free radicals which aggravate the nerve damage. Calcium and sodium channel dysfunction, changes in receptor expression are the other peripheral processes which cause further neuronal tissue injury. The nerve damage can cause neuronal hyperexcitability. Neurotropic factors are required for nerve regeneration. In diabetes there occurs a low level of both nerve growth factors and insulin-like growth factors resulting in impaired neuronal regeneration. This can lead to peripheral hyperexcitability. Central sensitization is cause by increased excitability at the synapse, which recruits several sub-threshold inputs and amplifies noxious and non-noxious stimuli. Loss of inhibitory interneurons, growth of non-damaged touch fibres into the territory of damaged pain pathways, increased concentration of neurotransmitters and wind up caused by NMDA receptors are responsible for central sensitization at the level of dorsal horn in the spinal cord[2].

Clinical Presentation:

Chronic sensorimotor distal polyneuropathy is the most common type of diabetic neuropathy. Acute sensorimotor neuropathy is rare and is usually associated with diabetic ketoacidosis and acute neuritis caused by hyperglycaemia. Autonomic neuropathy is common and often under reported. It can affect cardiovascular, gastrointestinal and genitourinary system. The other presentations can be cranial neuropathies, thoraco-abdominal neuropathies or peripheral mononeuropathies involving median, ulnar, radial, femoral, lateral cutaneous nerve of the thigh or common peritoneal nerve.

The patients usually complain of one or more of the following symptoms. They can have a chronic continuous or intermittent pain described as burning, aching, crushing, cramping or gnawing pain. The pain can be associated with numbness. They

can have brief abnormal stimulus evoked pain like allodynia or hyperalgesia. Some patients also complain of brief lancinating pains described as electrical or lightening pains which can be spontaneous or evoked. The symptoms typically start in the toes and feet and ascend in the lower limb over years and are worse at night. Diabetic distal polyneuropathy is typically described in glove and stocking distribution but the upper limb involvement is rare. On examination there can be paradoxically reduced sensation to light touch and pin prick in the area of pain. Examination can also show features of allodynia (pain caused by a stimulus that does not normally cause pain), hyperalgesia (pain of abnormal severity in response to a stimulus that normally produces pain), hyperpathia (painful reaction to a repetitive stimulus associated with increased threshold to pain), dysaesthesia (unpleasant abnormal sensation as numbness, pins and needles or burning), paraesthesia (abnormal sensation which is not unpleasant) or evoke electric shock like pains. There can be features of peripheral autonomic neuropathy including vasomotor changes like colour changes of feet which can be red, pale or cyanotic and temperature changes like warm or cold feet. With autonomic neuropathy there can also occur trophic changes which includes dry skin, callouses in pressure areas and abnormal hair and nail growth and sudomotor changes involving swollen feet with increased or decreased sweating. Mechanical allodynia is the most common type of allodynia, but there can be thermal allodynia described as cold or warmth allodynia. Patient often describes cold allodynia as the pain getting worse in cold weather and warmth allodynia can make the patient keep the effected limb cool by using fan or ice bags. There can be reduced joint position sense, reduced vibration sense, reduced temperature sensation and reduced ankle jerks.

Diagnosis:

The diagnosis of PDN can be made by clinical tests using pinprick, temperature and vibration perception (using a 128-Hz tuning fork). The feet should be examined for ulcers, calluses and deformities. Combinations of more than one test have >87% sensitivity in detecting PDN. Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy, B_{12} deficiency, hypothyroidism and uraemia, occur more frequently in diabetes and should be ruled out. If required these patients should be referred to a neurologist for specialized examination and testing[3].

Treatment Options:

US Food and Drug Administration has approved duloxetine in 2004 and pregabalin in 2005 for the treatment of painful DPN. Amitriptyline, nortriptyline and imipramine are not licenced for the treatment of neuropathic pain.

NICE clinical guidance on pharmacological management of neuropathic pain in adults in non-specialist settings as shown in Figure 1, recommends duloxetine as the first line treatment, which if contraindicated amitriptyline is suggested to be the first line. Second line treatment is amitriptyline or pregabalin. Pregabalin can be used alone or in combination with either amitriptyline or duloxetine, which if ineffective the patient should be referred to specialist pain services. While awaiting the referral tramadol can be started as the third line treatment. NICE also recommends that these patients should be reviewed to titrate the doses of the medication started, to assess the tolerability, adverse effects, pain reduction, improvement in daily activities, mood, quality of sleep and the overall improvement caused by the medication as reported by the patient[4].

The Mayo clinic recommends[5] the first tier of drugs for peripheral diabetic neuropathy are duloxetine, oxycodone CR, pregabalin and tricyclic antidepressants. The second tier of drugs iscarbamazepine, gabapentin, lamotrigine, tramadol and venlafaxine extended release. The topical agents suggested are capsaicin and lidocaine.

"Evidence Based guideline on treatment of Painful Diabetic Neuropathy", was formulated by American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. A systematic review of the literature between time period 1960 to 2008 was carried out. The review included the articles which looked at the efficacy of a given treatment either pharmacological or non-pharmacological to reduce pain and improve physical function and quality of life (QOL) in patients with PDN. They subsequently recommended that Pregabalin is established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence or the evidence is negative. Effective treatments for PDN are available, but many have side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and quality of life[6].

Non-pharmacological techniques:

Letícia et al. following their literature review on therapies used for PDN concluded that for non-pharmacological techniques like acupuncture, reiki, photic stimulation, electromagnetic stimulation of neural electrical stimulation, laser therapy, there is a lack of consensus about their effectiveness and there is scarce knowledge about them. They suggested new researches, including treatments for a longer period of time, with dosimetry control, and representative samples are necessary to discover the actual importance of these therapies for pain relief[7].Spinal Cord Stimulators have however been shown to be effective and safe in severe resistant cases[8,9].

Pharmacological Therapies:

Pregabalin: Pregabalin is a gamma aminobutyric acid analogue which binds to α2δ subunit of calcium channels and modulates them. Its starting dose is 150 mg/day with a maximum dose of 600 mg/day. As 98% of the drug is excreted unchanged in the urine, its dose is reduced in patients with renal impairment (creatinine clearance below 60 ml/min)[10]. A Cochrane Database Systematic Review in 2009 showed that Pregabalin was effective at daily doses of 300 mg, 450 mg and 600 mg, but a daily dose of 150 mg was generally ineffective. The NNT for at least 50% pain relief for 600 mg daily pregabalin dose compared with placebo was 5.0 (4.0 to 6.6) for PDN[11].

Duloxetine: Duloxetine reduces the reuptake of serotonin and noradrenaline at the level of spinal cord, thereby potentiating the descending inhibitory pain pathways to reduce pain. It is started at a dose of 30 mg/day and its dose can be increased to 120mg/day[10]. Sultan et al. in their systematic review found that pain relief achieved with daily dose of 60 mg Duloxetine was comparable with daily dose of 120 mg of Duloxetine. The number needed to treat (NNT) for at least 50% pain relief at 12 to 13 weeks with duloxetine 60 mg versus placebo was 5.8 as compared to NNT of 5.7 for daily dose of 120 mg of duloxetine. The side effects reported with Duloxetine were reduction in appetite, nausea, constipation and somnolence[12]. Systematic Reviews and cohort studies have shown that duloxetine provides overall savings in terms of better health outcomes and reduction in opioid use, in comparison to gabapentin and pregabalin, tricyclic antidepressants and venlafaxine, in pain caused by PDN[13, 14].

Gabapetin: Gabapentin is structurally related to gamma-aminobutyric acid (GABA) but acts by binding to the alpha2-delta subunit of voltage-gated calcium channels and thereby reducing the transmission of neuronal signals. Gabapentin bioavailability is non-linear and it tends to decrease with increasing dose. Gabapentin is not bound to plasma proteins and has a high volume of distribution. It is eliminated unchanged by the kidneys so in elderly patients and in patients with impaired renal function, its dose must be reduced. Gabapentin can be started froma daily dose of 300 to 900 mg and the dose can be increased to a maximum daily dose of 3600 mg over 3 weeks period[10]. Gabapentin provides good pain relief in about one third of patients when taken for neuropathic pain. Adverse events are frequent, but most of them are tolerable[15].

Tricyclic Antidepressants (TCA): Amitriptyline and nortriptyline are the commonly used TCA for PDN. They may be used if there is no benefit from pregabalin or gabapentin and duloxetine. They may be used alone or in combination with pregabalin or gabapentin. In small RCTs, amitriptyline has been found to relieve pain better than placebo in patients with diabetic neuropathy[10.] Amitriptyline is a tricyclic antidepressant with marked anticholinergic and sedative properties. It increases the synaptic concentration of noradrenaline and serotonin in the CNS by inhibiting their re-uptake by the pre-synaptic neuronal membrane. For neuropathic pain it is started at 10-25 mg orally once daily at bed time initially and increased according to response to a maximum of 150 mg/day.

TCA should be used with caution in patients with a history of epilepsy, cardiovascular disorders, deranged liver function, prostatic hypertrophy, history of urinary retention, blood dyscrasias, narrow-angle glaucoma or increased intra-ocular pressure. It's other side-effects are agitation, confusion and postural hypotension in elderly patients[10]. Amitriptyline is the most studied TCA for DPN and has been compared with placebo, imipramine, and desipramine. Amitriptyline, when compared with placebo, reduced pain to a significant degree. Pain relief was evident as early as the second week of therapy, with greater pain relief noted at higher doses (at a mean dose of 90 mg). A decrease in pain was not associated with improvement in mood. A systematic review of the TCAs, including fewer than 200 patients, found no difference in efficacy between the agents[16]. Nortriptyline is associated with fewer adverse events than amitriptyline and therefore it should be preferred in elderly patients.

Opioids: The use of opioids in chronic neuropathic pain has been a topic of debate because of uncertainty about their effectiveness, the concerns about addiction problems, the loss of efficacy with their long term use due to development of tolerance with their long term use and the development of hyperalgesia associated with their use. Cochrane review of twenty-three trials of opiates was carried out. The short-term studies showed equivocal evidence, while the intermediate-term studies showed significant efficacy of opioids over placebo, in reducing the intensity of neuropathic pain. Adverse events of opioids were reported to be common but were not life threatening. The authors recommended the need for further randomized controlled trials to establish long-term efficacy, safety (including addiction potential) and effects on quality of life[17]. In RCT Tramadol/Acetaminophen combination was shown to be associated with significantly greater improvement than placebo ($p < or = 0.05$) in reducing pain intensity, sleep interference and several measures of quality of life and mood[18]. In another RCT, controlled release (CR) oxycodone was compared with placebo, CR oxycodone resulted in significantly lower mean daily pain, steady pain, brief pain, skin pain, total pain and disability. In this study the number needed to treat to obtain one patient with at least 50% pain relief is 2.6[19]. Gabapentin and morphine combination in randomised controlled trial showed that the combination of the two drugs provided better analgesia at lower doses of each drug than either of the drugs used as a single agent[20].

Capsaicin: Capsaicin is the active component of chilli peppers. Capsaicin works by releasing the pro-inflammatory mediators like substance P from the peripheral sensory nerve endings and thereby causes its depletion from the peripheral nerve.

Pharmacological preparations of Capsaicin are available as 0.025% cream, 0.075% cream and 8% capsaicin patches[10]. Repeated application of a low dose (0.075%) cream, or a single application of a high dose (8%) patch has been shown to provide a degree of pain relief in some patients with painful neuropathy. Common side effect includes local skin irritation which causes burning and stinging. It is often mild and transient but sometimes severe and not tolerated by the patients leading to withdrawal from treatment. Capsaicin rarely causes systemic adverse effects. Capsaicin can be used either alone or in combination with other treatment to provide useful pain relief in individuals with neuropathic pain[21].

5% Lidocaine medicated plasters: A recent systematic review showed that 5% Lidocaine medicated plaster causes pain relief comparable to pain relief caused by amitriptyline, capsaicin, gabapentin and pregabalin in treatment of painful diabetic peripheral neuropathy. Lidocaine plaster being a topical agent may be associated with lesser clinically significant adverse events than the side effects of systemic agents. The need for further studies has been recommended by the reviewer as limited number and size of studies were included in the systematic review [22].

Conclusion:

The American Academy of Neurology, Mayo Clinic and NICE have both developed guidelines for treatment of peripheral diabetic neuropathic pain. There are several peripheral and central pathological mechanisms leading to the development of this condition and no single drug is available to target all these pathological mechanisms. Therefore often a combination of drugs is required for their management. Despite using a combination of medicines, managing these cases can be challenging. At the same time there is limited evidence on combination therapy in diabetic neuropathy and much work is required in this area. While using opioids for this condition the controversies over the use of opioids in non-malignant pain should be kept in mind and the advantages and disadvantages of using them should be discussed with the patients. Opioids should only be started with patient's consensus. The treatment should be modified from the guidelines on an individual basis to achieve the optimal pain relief.

Competing Interests
None
Author Details
NAMITA ARORA, FFPMRCA, FRCA, MD Anaesthesiology, Specialist Trainee 7, Cambridge University Hospitals NHS Foundation Trust, UK. G NIRAJ, FFPMRCA, FRCA, MD, Consultant in Anaesthesia & Pain Medicine, University Hospitals of Leicester NHS Trust, Honorary Clinical Lecturer Department of Health Sciences, University of Leicester, UK.
CORRESSPONDENCE: NAMITA ARORA, Specialist Trainee 7, Cambridge University Hospitals NHS Foundation Trust, UK.
Email: namitaarora@hotmail.co.uk

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Review Article

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Recent advances in the management of major obstetric haemorrhage

Rajashree Chavan and M Y Latoo

Introduction

Major Obstetric haemorrhage (MOH) remains one of the leading causes of maternal mortality & morbidity worldwide. In the 2003-2005 report of the UK Confidential Enquiries into Maternal Deaths, haemorrhage was the third highest direct cause of maternal death (6.6 deaths/million maternities) with the rate similar to the previous triennium [1, 2]. Postpartum haemorrhage (PPH) accounts for the majority of these deaths. This triennium, 2006-2008, unlike in previous reports there has been a change in the rankings of direct deaths by cause. Deaths from haemorrhage have dropped, to sixth place, following genital tract sepsis, preeclampsia, thromboembolism, amniotic fluid embolism and early pregnancy deaths[3]. A well-defined multidisciplinary approach that aims to act quickly has probably been the key to successful management of MOH. In the developing world, several countries have maternal mortality rates in excess of 1000 women per 100,000 live births, and WHO statistics suggests that 25 % of maternal deaths are due to PPH, accounting for more than 100,000 maternal deaths per year [4].The blood loss may be notoriously difficult to assess in obstetric bleeds [5, 6]. Bleeding may sometimes be concealed & presence of amniotic fluid makes accurate estimation challenging.

Definition

MOH is variably defined as blood loss from uterus or genital tract >1500 mls or a decrease in haemoglobin of >4 gm/dl or acute loss requiring transfusion of >4 units of blood. Blood loss may be:

1. Antepartum: Haemorrhage after 24th week gestation & before delivery; for example: placenta praevia, placental abruption, bleeding from vaginal or cervical lesions.
2. Postpartum: Haemorrhage after delivery
   - Primary PPH: Within 24 hours of delivery, which is >500 mls following vaginal delivery & > 1000mls following a caesarean section [7].
   - Secondary PPH: 24 hours to 6 weeks post-delivery; for example: Uterine atony, retained products of conception, genital tract trauma, uterine inversion, puerperal sepsis, uterine pathology such as fibroids [8].

PPH can be minor (500-1000 mls) or major (> 1000 mls). Major PPH could be divided to moderate (1000-2000 mls) or severe (>2000 mls).

Causes

Causes of PPH may be conveniently remembered using 4 T's as a mnemonic:

- Tone(Uterine atony)
- Tissue (retained products)
- Trauma(cervical & genital tract trauma during delivery)
- Thrombosis (coagulation disorder)

Other Risk factors include:-Prolonged labour, multiple pregnancy, polyhydramnios, large baby, obesity, previous uterine atony & coagulopathy.

Prevention

The most significant intervention shown to reduce the incidence of PPH is the active management of the third stage of labour (see below).Other measures to prevent or reduce the impact of MOH include

- Avoidance of prolonged labour
- Minimal trauma during assisted vaginal delivery
- Detection & treatment of anaemia during pregnancy
- Identification of placenta praevia by antenatal ultrasound examination.
- Where facilities exist, magnetic resonance imaging (MRI) may be a useful tool and assist in determining whether the placenta is accreta or percreta. Women with placenta accreta/percreta are at very high risk of major PPH. If placenta accreta or percreta is diagnosed antenatally, there should be consultant-led multidisciplinary planning for delivery [9].

Active management of the third stage

This represents a group of interventions including early clamping of the umbilical cord, controlled cord traction for placental delivery & prophylactic administration of uterotonic at delivery (e.g. oxytocin) [10]. Active management of the third

stage is associated with a lower incidence of PPH and need for blood transfusion [11]. A longer acting oxytocin derivative, carbetocin, is licensed in the UK specifically for the indication of prevention of PPH in context of caesarean delivery. Randomised trials suggest that a single dose (100 mcg) of carbetocin is at least as effective as oxytocin by infusion [12, 13].

Management of MOH

Pregnant women are often young, healthy & have an increased blood volume of up to 20 % at term and therefore likely to compensate well to haemorrhage until the circulating blood volume is very low [14]. MEOWS are a useful bedside tool for predicting morbidity. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS) in all obstetric inpatients to track maternal physiological parameters, and to aid early recognition and treatment of the acutely unwell parturient. In addition, blood loss may sometimes be concealed and difficult to calculate. More commonly massive haemorrhage may be obvious; signs other than revealed haemorrhage include:

- Tachycardia
- Hypotension(BP may not drop until significant blood is lost)
- Pallor
- Oliguria
- Cool peripheries
- Lower abdominal pain

Management of anticipated MOH

On some occasions, cases at high risk of MOH can be predicted; e.g. caesarean section in a lady with a low lying placenta and previous uterine scar. These cases may be at a risk of placenta accreta and massive blood loss.

- 2 large bore IV cannulae
- Rapid infusion device or pressure bags in theatre
- Blood warmer & warming blanket
- Blood cross-matched & available
- Consider preoperative invasive monitoring
- Consider cell salvage if available (see below)
- Consider interventional radiological procedures if available (see below)

Management of unanticipated MOH

Management involves four components, all of which must be undertaken SIMULTANEOUSLY: communication, resuscitation, monitoring and investigation, arresting the bleeding [9, 15]. Most maternity units in UK have CODE RED bleep system for alerting MOH.

Communication & teamwork:

Communication and teamwork are essential in cases of both anticipated & unanticipated maternal haemorrhage. This includes:

- Call for help. Alert the midwife-in-charge, senior obstetrician & anaesthetist.
- Alert Blood transfusion service & haematologist.
- Alert portering service for transport of blood samples & collection of blood products
- Check blood is available. In the UK 2-4 units of O-neg blood is kept on labour ward for emergency use.
- Allocate roles to team members.
- Ensure departmental guidelines exist for the management of MOH & regularly practice 'fire drills'.
- Alert one member of the team to record events, fluids, drugs and vital signs [9].
- The use of standard form of words (such as 'on going major obstetric haemorrhage', 'we need compatible blood now or group specific blood') [9].

Goals of management:

- Early identification of maternal bleed and institution of major haemorrhage drill
- Rapid access to infusion of fluid in first instance with rapid availability & administration of blood.
- Avoidance/limitation of complications of massive blood transfusion namely: acid/base disturbance, transfusion related acute lung injury (TRALI), hypocalcaemia, hyperkalaemia, hypothermia & thrombocytopenia.
- Efficient team working & management decision making.

Resuscitation & immediate management:

- ABC, 100% oxygen
- 2 large bore cannulae & bloods for X-match
- Fluid resuscitation; crystalloid/colloid 2000mls via rapid infuser or pressure bags e.g. Level 1 Rapid infuser (can achieve >500mls/min warmed fluid flow)
- Fluid therapy and blood product transfusion [9]
- Crystalloid Up to 2 litres Hartmann's solution
- Colloid up to 1–2 litres colloid until blood arrives
- Blood Crossmatched
- If crossmatched blood is still unavailable, give uncrossmatched group-specific blood OR give 'O RhD negative' blood
- Fresh frozen plasma 4 units for every 6 units of red cells or prothrombin time/activated partial thromboplastin time > 1.5 x normal (12–15 ml/kg or total 1litres)
- Platelets concentrates if platelet count < 50 x 10^9
- Cryoprecipitate If fibrinogen < 1 g/l
- Thromboelastography and rotational thromboelastometry coagulation tests: In most cases, medical and transfusion

therapy is not based on the actual coagulation state because conventional laboratory test results are usually not available for 45 to 60 minutes. Thromboelastography and rotational thromboelastometry are point-of-care coagulation tests. A good correlation has been shown between thromboelastometric and conventional coagulation tests, and the use of these in massive bleeding in non-obstetric patients is widely practiced and it has been proven to be cost-effective.

- A 2006 guideline from the British Committee for Standards in Haematology [1, 4]summarizes the main therapeutic goals of management of massive blood loss is to maintain:
    - Haemoglobin > 8g/dl
    - Platelet count > 75 x 10^9/l
    - Prothrombin < 1.5 x mean control
    - activated prothrombin times < 1.5 x mean control
    - Fibrinogen > 1.0 g/l.
- In addition, the Confidential Enquiry into Maternal and Child Health recommends that women with known risk factors for PPH should not be delivered in a hospital without a blood bank on site [1].
- Transfer to theatre.
- Non-surgical intervention for uterine atony.
- Bimanual uterine compression (rubbing up the fundus) to stimulate contractions.
- Ensure bladder is empty (Foley catheter, leave in place). 'Rub up 'the uterus
- Syntocinon 5 units by slow intravenous injection (may have repeat dose).
- Ergometrine 0.5 mg by slow iv/im injection (contraindicated in women with hypertension) [16].
- Syntocinon infusion (40 units over 4 hours).
- Carboprost 0.25 mg by intramuscular injection repeated at intervals of not less than 15 minutes to a maximum of 8 doses (contraindicated in women with asthma).
- Direct intramyometrial injection of carboprost 0.5 mg im (Haemobate or Prostaglandin F2a) with responsibility of the administering clinician as it is not recommended for intramyometrial use. Can be repeated up to 5 doses (contraindicated in women with asthma, may cause bronchospasm, flushing & hypertension [17]).
- Misoprostol 1000 micrograms rectally.
- If pharmacological measures fail to control the haemorrhage, initiate surgical haemostasis sooner than later.

Surgical treatment and other interventions

The most common cause of primary PPH is uterine atony. However, clinical examination must be undertaken to exclude other or additional causes:

- Retained products (placenta, membranes, clots)
- Vaginal/cervical lacerations or hematoma
- Ruptured uterus
- Broad ligament hematoma
- Extra genital bleeding (for example, subcapsular liver rupture)
- Uterine inversion.

Intrauterine balloon tamponade is an appropriate first line 'surgical' intervention for most women where uterine atony is the only or main cause of haemorrhage. If this fails to stop the bleeding, the following conservative surgical interventions may be attempted, depending on clinical circumstances and available expertise:

- Balloon tamponade (Bakri/Rusch balloon, Foley's/condom catheter, Sengstaken-Blakemore tube [18-21]
- Haemostatic brace suturing (such as B-Lynch or modified compression sutures).
- Bilateral ligation of uterine arteries.
- Bilateral ligation of internal iliac (hypogastric) arteries.
- Selective arterial embolisation or balloon occlusion radiologically.
- Compression/ clamping aorta to buy time.
- Uterine replacement if uterine inversion

It is recommended that a laminated diagram of the brace technique be kept in theatre. Resort to hysterectomy sooner rather than later (especially in cases of placenta accreta or uterine rupture). A second consultant clinician should be involved in the decision for hysterectomy.

Interventional Radiological techniques

Interventional techniques are gaining popularity if the facilities & expertise exist and are especially useful for the anticipated massive bleeds e.g. planned LSCS in a woman with anticipated placenta accrete. Though evidence of effectiveness is still limited, there are increasing case reports of its successful use. This suggests that prophylactic arterial catherisation (with a view to embolisation) could be considered where facilities permit until such time as further evidence becomes available [22-28].

- Bilateral internal iliac artery balloons may be placed electively & inflated at C. section/ should bleed occur.
- Selective pelvic artery (internal iliac arteries, anterior division of internal iliac or uterine artery) embolisation can be performed.
- Complications appear rarely & include: haematoma, false aneurysms & lower limb ischemia.

Interventional radiology may be considered in cases of placenta praevia with accreta if intra-arterial balloons can be placed in the radiology department before the woman goes to theatre for caesarean section. Follow up studies of women who had undergone arterial embolisation for control of PPH suggest that the intervention does not impair subsequent menstruation and fertility [29, 30].

Intraoperative cell salvage in obstetrics (ICSO)

Cell salvage has now been used in numerous cases of obstetric bleeds and appear safe. Concerns relate to re-infusion of foetal cells which could theoretically cause haemolytic disease in future pregnancies and also the potential for amniotic fluid embolus. If cell salvage techniques are utilised, separate suction of amniotic fluid is recommended and a leukocyte depletion filter used during re-infusion of salvaged blood. Setting up cell salvage measures should not divert staff an attention from initial resuscitation.

Intraoperative cell salvage (the process whereby bloodshed during an operation is collected, filtered and washed to produce autologous red blood cells for transfusion to the patient) is commonly being used in cardiac, orthopaedic and vascular surgery with relative reduction of blood transfusion by 39% and absolute risk reduction by 23%, with cell salvage not appearing to impact adversely on clinical outcomes [31, 32]. Although large prospective trials of cell salvage with auto transfusion in obstetrics are lacking, to date, no single serious complication leading to poor maternal outcome has been directly attributed to its use. Several bodies based on current evidence have endorsed cell salvage in obstetrics. Current evidence supports the use of cell salvage in obstetrics, which is likely to become increasingly commonplace, but more data are required concerning its clinical use [33]. A National UK survey in 2007 showed that, in 2005–2006, 38% of all UK maternity units were using cell salvage and that 28% incorporated cell salvage into their massive haemorrhage guidelines [34]. In particular, this survey showed that a lack of training was the main perceived barrier to its use: 48% of units specifically stated that their reason for not using cell salvage was lack of training and equipment, with fears about safety being expressed by only 10%. However, the potential difficulty is the effective removal of amniotic fluid and the degree of contamination with fetal red cells with potential maternal sensitization, intraoperative cell salvage may be a useful technique in women who refuse blood or blood products (Jehovah's Witnesses guideline) [9] or those where massive blood loss is anticipated (placenta percreta or accreta). For women who are Rh-negative, to prevent sensitization, the standard dose of anti-D should be given and a Kleihauer test taken 1 hour after cell salvage has finished, to determine whether further anti-D is required [35].

Recombinant activated factor VII (rFVIIa)

Recombinant activated factor VII (rFVIIa) was developed for the treatment of haemophilia. Over the past decade, it has also been used to control bleeding in other circumstances. A 2007 review identified case reports of 65 women treated with rFVIIa for PPH [36].Although the case reports suggested that rFVIIa reduced bleeding, 30 of the 65 women underwent peripartum hysterectomy and particular caution is required in interpreting data from uncontrolled case reports. In the face of life-threatening PPH, and in consultation with a haematologist, rFVIIa may be used as an adjuvant to standard pharmacological and surgical treatments. A suggested dose is 90 micrograms/kg, which may be repeated in the absence of clinical response within 15–30 minutes [37]. Although there is no clear evidence of thrombosis with the use of rFVIIa in obstetric practice, there have been case reports of thrombosis with the use in cardiac surgery[38-40]. Women with PPH are particularly susceptible to defibrination (severe hypofibrinogenaemia) and this is particularly relevant to the most severe cases that will be considered for rFVIIa; rFVIIa will not work if there is no fibrinogen and effectiveness may also be suboptimal with severe thrombocytopenia (less than 20 x 10^9/l).Therefore, fibrinogen should be above 1g/l and platelets greater than 20 x 10^9/l before rFVIIa is given. If there is a suboptimal clinical response to rFVIIa, these should be checked and acted on (with cryoprecipitate, fibrinogen concentrate or platelet transfusion as appropriate) before a second dose is given [36-40].

Anaesthetic management [15]:

- GA with RSI is generally advocated if actively bleeding or coagulopathy.
- Reduce dose of induction agent if severe on going bleeding.
- Regional anaesthesia is relative contraindication but may be maintained if the patient has an epidural insitu & bleeding is controlled.
- Alert Blood bank & haematologist.
- Consider arterial line, central line and urinary catheter but only after definitive treatment has commenced. Their insertion must not delay resuscitation & fluid management.
- Use fluid warmer & aim to keep the patient normothermic.
- Regular monitoring of haemoglobin level and coagulation using near patient devices if available (e.g. Haemacue). FFP, platelets transfusion & cryoprecipitate may be necessary if coagulopathy develops. Liaise early with haematology department for optimal & timely product replacement.
- Perioperative monitoring as per AAGBI guidelines.
- Recording of parameters on a flow chart such as the modified obstetric early warning system charts.
- Consider systemic haemostatic agents such as Aprotonin, Vit K, Tranexemic acid, Recombinant factor VII a (Novo seven R). Although evidence is conflicting, there is a consensus view that fibrinolytic inhibitors seldom, if ever, have a place in the management of obstetric haemorrhage [41, 42].
- Postoperative management includes transfer to ITU/HDU.
- Anticipate coagulopathy & treat clinically until coagulation results available.
- It is also important that, once the bleeding is arrested and any coagulopathy is corrected, thromboprophylaxis is administered, as there is a high risk of thrombosis. Alternatively, pneumatic compression devices can be used, if thromboprophylaxis is contraindicated in cases of thrombocytopenia.

Conclusion

Globally, postpartum haemorrhage (PPH) is the leading cause of maternal morbidity and mortality. Major obstetric haemorrhage is managed by multidisciplinary approach. In the current treatment of severe PPH, first-line therapy includes transfusion of packed cells and fresh-frozen plasma in addition to uterotonic medical management and surgical interventions. In persistent PPH, tranexamic acid, fibrinogen, and coagulation factors are often administered. Secondary coagulopathy due to PPH or its treatment is often underestimated and therefore remains untreated, potentially causing progression to even more severe PPH. The most postnatal haemorrhage is due to uterine atony and can be temporarily controlled with firm bimanual pressure while waiting for definitive treatment.

Competing Interests

None declared

Author Details

RAJASHREE CHAVAN, MBBS, MD, DA, FRCA; Cambridge University Hospital Foundation Trust, UK. M Y LATOO, FRCA(London) Consultant Anaesthetist, Bedford Hospital, UK.

CORRESSPONDENCE: DR RAJASHREE CHAVAN, Cambridge University Hospital Foundation Trust, UK.

Email: vidula77@doctors.net.uk

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Review Article

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Often overlooked neuropsychiatric syndromes in Parkinson's disease

Javed Latoo, Minal Mistry, and Francis J Dunne

Abstract
Parkinson's disease (PD) is a subcortical disorder that eventually spreads to the cortex. There is a wide variation in the global incidence and prevalence of PD. The disease usually presents in patients over the age of 65, although 5% of cases are under the age of 40 at the time of diagnosis. PD has a high prevalence of psychiatric co-morbidity. In this article, written with general neurologists and psychiatrists in mind, the main features and pathology of PD will be briefly outlined followed by a review of the epidemiology, aetiology, clinical features, and treatment of other often overlooked neuropsychiatric syndromes associated with PD. Close liaison between neurologists and psychiatrists is recommended in order to optimize treatment.

Introduction

The global epidemiology of PD varies widely which could be partly accounted for by differences in survival rates.[1] One review paper examined the epidemiology of PD in Austria, the Czech Republic, France, Germany, Italy, The Netherlands, Portugal, Spain, Sweden and United Kingdom. It revealed that the prevalence rates range from 65.6 per 100,000 to 12,500 per 100,000 and annual incidence estimates ranged from 5 per 100,000 to 346 per 100,000.[2] The wide variation in incidence and prevalence rates of PD across Europe could be due to environmental and genetic factors. Differences in methodologies for case ascertainment, diagnostic criteria, or age distributions of the study populations, could also account for the wide variations.[2]

Described by James Parkinson in 1817, PD is the second most common neurodegenerative disorder next to Alzheimer's dementia. Depletion of dopaminergic neurones in the substantia nigra is the main pathology found in PD. Symptoms usually appear when dopamine levels are reduced by 50-80%.[3] Noradrenergic, cholinergic and serotonergic pathways are also affected. Clinically PD is characterised by rigidity, tremor (cogwheel, lead pipe, and resting), akinesia, bradykinesia (poverty and slowness of movement), and postural instability (leading to frequent falls).[4] These symptoms may also be accompanied by a range of non-motor symptoms other than well-known neuropsychiatric syndromes of depression, psychosis, and cognitive impairment.

In essence, a syndrome is a combination of signs and symptoms related to an underlying pathological process. PD may present with neuropsychiatric syndromes of depression, psychosis (usually affective in origin) and cognitive impairment.[5]These syndromes are not under discussion here as readers are likely to be familiar with them. However, PD may also present with other neuropsychiatric syndromes and for the purpose of this article we have classified them into: 1) Anxiety disorders, 2) Apathy, 3) Involuntary emotional expression disorder, 4) Sleep disorders, and 5) Impulse control disorders.

Drugs used to treat PD themselves are associated with neuropsychiatric side effects. For example, dopamine agonists are well-known to cause sleep disturbance, dizziness (usually due to postural hypotension), hallucinations, hypersexuality, and compulsive gambling. Anticholinergics may cause confusion, hallucinations and impaired memory. Surgery also may cause adverse effects including depression, confusion and cognitive impairment.[6] Table 1 illustrates the groups of drugs used in PD.

Table 1. Drugs used in Parkinson's Disease

Group	Drug
Dopamine receptor agonists	Apomorphine, pramipexole, ropinirole, rotigotine
N-Methyl-D-aspartate (NMDA) receptor antagonist	Amantadine hydrochloride
Levodopa	Co-benedopa (levodopa/benzeraside), co-careldopa (levodopa/carbidopa)
Monoamine oxidase B inhibitors (MAO-B)	Rasagiline, selegiline hydrochloride
Catechol-O-methyltransferase (COMT) inhibitors	Entacapone, tolcapone
Antimuscarinic drugs	Benztropine mesylate, orphenadrine, procyclidine, trihexyphenidyl

Overlooked neuropsychiatric syndromes in Parkinson's disease

The prevalence of overlooked neuropsychiatric syndromes found in PD, summarised in Table 2, is generally less common than PD syndromes of depression (up to 50%),psychosis (up to 60%) and dementia (ultimately develops in 80%).[7, 8, 9]

Table 2. Overlooked neuropsychiatric syndromes found in Parkinson's Disease.	
Neuropsychiatric syndrome	Prevalence
Anxiety disorders	Up to 40%
Apathy	16-42%
Involuntary emotional expression disorder	Up to 16.8%
Sleep disorders	60-98%
Impulse control disorders	Up to 13.6%

Anxiety Disorders

Epidemiology

There is a wide range in the reporting of the prevalence of anxiety in patients with PD. Anxiety is significantly more prevalent in PD sufferers compared with age and sex matched non-sufferers. Prevalence is quite high with estimates indicating that up to 40% of PD patients suffer significant anxiety.[10] However, clinicians' recognition and awareness of anxiety in PD need to be raised because it is likely to be under-diagnosed and untreated.[11, 12] Consequently the prevalence of anxiety may be even higher. Severity of anxiety is not correlated with severity of parkinsonian symptoms, duration of levodopa use, or current dose of levodopa.

Aetiology and risk factors

Anxiety is an understandable psychological response to the physical symptoms, to the neurochemical changes of the disease itself, or as a side effect of the various medications used to treat the condition.[10] Sleep disturbances and cognitive impairment have been proposed as possible aetiological factors for anxiety in PD.[11, 12] Depression in PD may manifest in two clinical phenotypes, one 'anxious-depressed' and the other 'depressed'. However, a further large proportion of patients can have relatively isolated anxiety.[13]

Anxiety frequently precedes the development of motor symptoms, suggesting specific neurobiological processes are involved, not merely social and psychological reactions in learning to adapt to PD.[14]

Patients with postural instability and gait dysfunction have a higher incidence of anxiety compared with tremor-dominant patients. Younger-onset PD patients are also more likely to experience anxiety. The pathogenesis of anxiety involves noradrenergic, serotonin and dopamine neurotransmitters. GABAergic pathways may also be involved.[14] Right hemisphere disturbances have also been implicated, particularly with panic disorder. Symptom variation in PD may be due to medication, as well as motor fluctuations.[11] One study revealed that although the dose of levodopa was not associated with anxiety, the experience of dyskinesia or on-off fluctuations increased the risk of anxiety.[12, 14, 15]

Presentation and diagnosis

The commonest disorders found in PD are generalised anxiety, panic disorder, and social phobia. Anxiety contributes to the complexity of PD and lowers quality of life. [14, 15] The degree of comorbidity between anxiety and depression in PD patients is in excess of that found in patients without PD. While anxiety is significantly associated with depression, some patients show anxiety without depression.[10]

The main features of anxiety are inappropriate feelings of apprehension as well as mood, cognitive, and somatic changes. Some symptoms may be common to PD, such as autonomic symptoms, fatigue, muscle tension, insomnia and attention problems. Psychologically, anxiety in PD is understandable because being diagnosed with a chronic disease with no known cure and an inexorable course, would be difficult for anyone to contemplate. Motor signs and changes in appearance could explain social anxiety. However, the frequency of anxiety in PD seems to be higher than in other chronic diseases and unrelated to the severity of motor signs. Even in social phobia the phobic symptoms do not correlate with disease severity and are not restricted to performance situations. Furthermore, anxiety can precede motor signs by several years, suggesting that the neurobiological substrate of PD is responsible for anxiety at least in part.

Treatment

Treatment comprises the use of selective serotonin reuptake inhibitors (SSRIs) such as sertraline, fluoxetine and citalopram as well as other newer antidepressants - serotonin and noradrenaline reuptake inhibitor (SNRIs) for example, venlafaxine, cognitive behavioural therapy (CBT), exercise, the occasional use of atypical neuroleptics, and benzodiazepines.[14] However, benzodiazepines have a tendency to cause sedation, unsteadiness of gait, and even confusion. Antidepressants are useful because they treat both anxiety and depression that often overlap: depression coexists with anxiety in 14% of cases.[15] Low dose tricyclic antidepressants with minimal anticholinergic effects may be useful in those patients who do not respond to benzodiazepines.

Apathy

Epidemiology

Apathy, a state of lethargic indifference and loss of motivation, and fatigue are prominent non-motor symptom in PD with a prevalence of between 16-42%.[16, 17] Fatigue is a sense of tiredness or exhaustion, due to mental or physical causes. Apathy and fatigue are important because they have significant repercussions for the quality of life in PD.[18, 19] Apathy can exist without depression but, by definition, patients themselves do not complain of apathy, though are found to be unmotivated to engage in activities. Apathy and fatigue are often difficult to

distinguish from low mood and daytime sleepiness, both of which are common to depression.

A four-year prospective longitudinal study of 79 patients found that 13.9% of those with PD had persistent apathy and 49.4% had developed apathy at follow up. The study showed apathy to be a frequent and persistent behavioural feature in PD with a high incidence and prevalence over time, and associated with neurotransmitter deficits.[20]

Aetiology and risk factors

The dorsolateral, medial and orbital frontal cortices, as well as subcortical structures such as the basal ganglia, thalamus and internal capsule are implicated in the pathogenesis of apathy. The independent risk factors for apathy are dementia at baseline, a more rapid decline in speech, and axial impairment (e.g. poor ability to turn in bed) during follow up.[20, 21] A more recent study showed that male gender, higher depressive scores, and severe motor symptoms, were significantly associated with apathy, but not with greater cognitive impairment.[22] It has been observed that deep brain stimulation (DBS) may contribute to the development of apathy[23] but other studies show conflicting results.[24]

Presentation and diagnosis

There is a higher incidence of depression and dementia in PD patients with apathy. Therefore differential diagnosis between apathy and cognitive deficits and depression is essential because the therapeutic approaches are different.[19, 20] It is equally important to differentiate between apathy and depression that are different clinical entities although both may coexist. The crucial difference is that people with apathy lack serious self-reproach or feelings of guilt. [21, 25] The Lille Apathy Rating Scale (LARS), administered as a structured interview, can be a useful tool to distinguish them both[26]though further research is needed to differentiate the neurological and neurochemical basis for depression and apathy.

Treatment

Treatment options for apathy are limited. The use of methylphenidate, a stimulant drug related to amphetamine, has been suggested but evidence is scarce and side effects may outweigh its clinical benefit.[27] Methylphenidate has been described as effective for both apathy and fatigue[28] but more studies are necessary. Antidepressants are not effective, can cause unnecessary side effects and can even aggravate apathy, demonstrating that these syndromes are really independent.[29] The association between cognition and apathy, along with the potential benefit of cholinesterase inhibitors on both cognition and apathy, suggests that cholinergic mechanisms take part in the pathophysiology of apathy.[30, 31] 'Off-time' refers to periods of the day when the medication is not working well, causing worsening symptoms of fatigue and apathy. 'Wearing-off' episodes may occur predictably and gradually, or they may emerge suddenly and unexpectedly. Wearing-off periods may be improved with appropriate changes in the medication regimen. This would mean optimizing dopaminergic agents or using a long-acting levodopa or a catechol-*O*-methyltransferase (COMT) inhibitor. Wearing off may be also better controlled by shortening the time between medication doses. In a study of 23 PD patients in both the 'on' and 'off' states compared to 28 controls, L-dopa had a positive effect on motivation suggesting striatofrontal loops are involved.[32]

Involuntary emotional expression disorder

Epidemiology

Involuntary emotional expression disorder (IEED) has been found to occur in 16.8% of PD patients, and in 15.3% if comorbid depressive disorder was excluded.[33] However, other studies suggest that the *symptoms* of IEED are present in up 15% of PD patients but the actual IEED disorder occurs in half of these cases.[34] This implies that IEED symptoms occur in PD but the condition of IEED is not present although this may depend on the criteria used for the diagnosis. If IEED does develop in PD it is particularly common in the later stages of PD and is likely to be distinct from depressive disorder which remains an important differential diagnosis.[33, 35]

Aetiology and risk factors

IEED can occur in neurological conditions such as stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, seizure disorders, multiple system atrophy, corticobasal degeneration, and Alzheimer's disease.[35] Injury to the neurological pathways that control the expression of emotion have been implicated in its pathogenesis. Emotional expression involves various pathways within the frontal lobe, limbic system, brainstem and cerebellum, with disruption of regulatory and inhibitory mechanisms in this network implicated.[36, 37]

Presentation and diagnosis

IEED is described as sudden episodes of laughing or crying that may be spontaneous or disproportionate to the triggering stimuli. The emotional outbursts of IEED may involve laughter, crying or anger. The episodes all share common features in that they are involuntary, uncontrollable, and excessive, not sustained, and usually last from seconds to minutes. Outbursts are often stereotyped though single individuals may have episodes of both laughing and crying. IEED is also known as pseudobulbar affect, pathological laughter and crying, emotional lability, emotionalism, and emotional dysregulation. Despite the various terms used to describe the disorder, IEED is often missed and even sometimes mistaken for depression.[33, 35] Symptoms of IEED are important because they are associated with an impairment of social and occupational functioning.[38] It is hypothesized that neurological disease and injuries affect the excitatory action of glutamate,

leading to excessive glutaminergic signalling and increased electrical activity in neurons. As glutamate is the primary excitatory neurotransmitter of the central nervous system, stabilizing or reducing glutaminergic activity could prove useful in the treatment of IEED.[39]

Treatment

Medication options include the use of SSRIs, tricyclic antidepressants (TCAs) for example, amitriptyline, and less frequently dopaminergic agents.A combination of dextromethorphan and quinidine has also been suggested. [35 38]

Sleep disorders

Epidemiology

Sleep disorders have been known to affect 60-98% of patients with PD.[40]

Aetiology and risk factors

The aetiology of sleep disorders includes PD itself or other comorbid conditions such as depression, and cognitive impairment.[41] Nocturnal pain from rigidity or dystonia, restless legs syndrome, and autonomic disturbance leading to nocturnal frequency and urgency, also contribute to insomnia. Degeneration of sleep regulatory centres in the brainstem and thalamocortical pathways, side effects of drugs, motor impairment, and incontinence may affect sleep. Sleep disorders may precede the onset of motor symptoms. Rapid Eye Movement (REM) sleep behaviour disorder (RBD), which occurs in almost a third of PD patients, is often associated with cognitive impairment and hallucinations. This disorder is directly related to the degenerative process of the pedunculopontine nucleus, the locus subceruleus and the retrorubral nucleus. A sudden onset of the disorder is almost always due to the introduction or the withdrawal of drugs, especially antidepressants. Curiously, parkinsonism can disappear during the RBD.[42]

Sleep fragmentation is the earliest and most common sleep disorder in PD, and gradually worsens as the disease progresses. Vivid dreaming, nightmares and night terrors are common and occur in up to 30% of patients using levodopa for long periods. Dream content is probably altered in PD and many patients vocalize during sleep. Vocalization may vary from incomprehensible sounds to detailed conversations, laughing, cursing or screaming. Excessive daytime sleepiness and 'sleep attacks' affect half of patients with PD and may precede disease onset. The causes are a combination of the disease process, the consequence of other sleep disorders and medication. A sudden onset of sleep during the day is a phenomenon in PD which resembles narcolepsy, and it is commonly associated with dopaminergic drugs. PD patients may be more prone to restless legs syndrome, periodic limb movements and obstructive sleep apnoea.

Sleep disorders in PD are seldom diagnosed and treated. Although an accurate diagnosis of a particular sleep disorder depends on polysomnography, sometimes the diagnosis can be based on clinical observation. Treatment is based on the correct diagnosis and underlying cause of the sleep disorder. Often it is difficult to decide whether excessive daytime sleepiness is cause or consequence of insomnia.[43]

Presentation and diagnosis

Sleep disorders may manifest as insomnia, excessive daytime sleepiness and sleepwalking.[44, 45] Sudden attacks of sleepiness are known to occur during stimulating activities such as walking, eating, and even driving a car. These sudden sleep episodes can be associated with medication such as dopamine agonists and levodopa.[46]

RBD is characterised by the loss of the normal atonia during dreaming. In other words, patients act out their dreams as manifested by crying out, kicking or thrashing about during their sleep. RBD can predate the development of motor symptoms by several years and a longitudinal study of a cohort of 26 patients found an association between RBD and the later development of PD. [47]

Treatment

Management involves the review of medication that may be contributing to the sleep disorder. Treatment of comorbid conditions such as depression and cognitive impairment is essential.

Sleep hygiene is the initial and basic measure applied to all patients. For instance, stimulating patients during the day can decrease the excessive naps and improve sleep at night, thus improving daytime sleepiness. Additional techniques include going to bed only when sleepy, exposure to natural and bright light during day, reduction of light and noise exposure at night as much as possible, and maintenance of a regular schedule.

Long-acting dopaminergic drugs might improve insomnia caused by worsening of motor symptoms at night. Clonazepam, a benzodiazepine, is efficacious and well tolerated by the majority of patients afflicted by RBD and should be considered as initial treatment.[48] Antidepressants with a sedative effect might be helpful in cases of insomnia with comorbid depression or anxiety. Quetiapine, an antipsychotic which has sedative properties as a side effect, may be a safe and effective treatment for insomnia in PD because it has no untoward effects on motor function.[49] Small clinical trials with Modafinil for excessive daytime sleepiness had controversial results. An additional remark concerning treatment of sleep disorder in PD is that sleep may provide a short-term benefit on motor symptoms.[28, 43]

Impulse control disorders

Epidemiology

A large multi-centre investigation (the DOMINION study) of 3,090 patients with PD revealed that impulse control disorder (ICD) was identified in 13.6% of PD patients; specifically, pathological gambling in 5%, compulsive sexual behaviour in 3.5%, compulsive buying in 5.7% and binge-eating disorder in 4.3%.[50] The prevalence of ICD rises to 14% for patients taking dopamine agonists, compared with 0.7% for patients taking levodopa alone.[51] It is not clear whether these ICD symptoms reflect a primary pathology of PD or whether dopaminergic medication is interacting with an underlying predisposition or vulnerability.[52] Possible neurobiological explanation centres around dopamine-receptor binding profiles. Dopamine D2 and D1 receptors, abundant in the dorsal striatum, may mediate the motor effects of dopamine replacement therapies, whereas D3 receptors are abundant in the ventral striatum, a brain region associated with addictive behaviour and substance misuse disorders. Second generation non-ergot dopamine agonists (e.g. pramipexole and ropinirole) demonstrate relative selectivity for D3 receptors compared with D2 and D1 receptors.[50]

Aetiology and risk factors

Addiction to dopaminergic medication used in the treatment of PD may explain behaviours such as drug-seeking, gambling, and hypersexuality. The risk of pathological gambling increases if dopamine agonists are used in those with younger age of onset, higher novelty seeking traits, and a personal and family history of alcohol misuse.[53]

Presentation and diagnosis

In addition to the above PD patients with ICD may present with compulsive shopping, compulsive eating, and compulsive medication use, all of which can have potentially devastating psychosocial consequences because they are often hidden. Complex stereotyped repetitive behaviours (punding) may also be present.[54]Punding behaviour is stereotyped and purposeless and includes hoarding, shuffling papers, sorting labels, assembling and disassembling objects, to name a few.

Treatment

Stopping dopaminergic medication should be considered in the first instance. Further treatment options are limited but one double-blind crossover study demonstrated the use of amantadine in abolishing or reducing pathological gambling.[55]In addition, one case report suggested the antipsychotic quetiapine to be effective in treating pathological gambling.[56]Whether other treatments, such as DBS, are effective for these compulsive repetitive behaviours, remains to be seen.

Management of overlooked neuropsychiatric syndromes in PD

Because of the significant disability and impact on quality of life caused by overlooked neuropsychiatric symptoms in PD, it is important for neurologists and psychiatrists to recognise them and develop their clinical skills in order to be aware of their significance. Early detection is crucial. We have shown there is a limited range of treatment strategies available to guide the clinician in treatment choices. Because neuropsychiatric diagnoses in PD are different in phenomenology it is important to remember that treatment with 'psychiatric' drugs will often be insufficient and therefore more consideration should be given to 'antiparkinsonian' medications because the underlying pathology of PD is causing the various syndromes mentioned.

Table 3 provides an overview of the medical treatment of overlooked neuropsychiatric syndromes in PD, although it should be noted that overall very few studies document the effectiveness of the solutions proposed and more controlled studies are needed. Nonetheless, the reader should find the following useful.

Table 3. Summary of the medical treatment of overlooked neuropsychiatric syndromes in Parkinson's Disease.

Psychiatric syndrome	Treatment
Anxiety	- Antidepressants - sertraline, citalopram, fluoxetine, venlafaxine- Others - antipsychotics, benzodiazepines - Cognitive Behavioural Therapy - Exercise
Apathy (diminished motivation)	- Cholinesterase inhibitors - Dopamine agonists - Possible use of methylphenidate
Involuntary emotional expressive disorder	- Antidepressants - Dopaminergic agents. - Possible combination of dextromethorphan and quinidine
Sleep disorders	- Benzodiazepine - clonazepam - Antipsychotic (sedating) – quetiapine - Sleep hygiene
Impulse control disorders	- Possible use of amantadine or quetiapine in pathological gambling - Further research required

Conclusion and implications

The management of PD is often complicated because of the diverse factors underlying its aetiology. Dopaminergic, serotonergic, noradrenergic and cholinergic pathways are involved.[57] Clinicians are generally competent in recognising the more common disorders such as depression, psychosis and cognitive impairment associated with PD though there is a tendency to focus too much on these at the expense of other nonmotor symptoms. Anxiety, apathy, involuntary emotional expression disorder, sleep disorders, and impulse control

disorders cause significant disability and impact heavily on patients and carers.

Before introducing treatment for psychiatric complications it is essential to exclude causes such as antiparkinson's medication, DBS (implicated in apathy), and underlying medical conditions. Once excluded or treated, subsequent management includes psychotropic pharmacotherapy but there are limited options. With no specific drug designed to treat the overlooked conditions, a wide range of medications (e.g. antidepressants, antipsychotics, benzodiazepines, dopaminergic agents, and psychostimulants) are available to manage the symptoms.

Neurologists and psychiatrists need to work together to manage these syndromes and they must be innovative in setting up joint research ventures into developing treatment options. Simple questionnaires may alert physicians when presenting symptoms are abstruse because many of the nonmotor symptoms predate the motor symptoms[58] (the presymptomatic phase of stages 1-2 of Braak's classification system).[59] [60] For example, anosmia, constipation and other autonomic symptoms are not considered neuropsychiatric syndromes per se, but are some of the nonmotor problems associated with PD and may give clues that PD is developing.

Despite research highlighting the presence of these disorders in PD, they generally go unrecognised by clinicians, being less common, and therefore psychiatrists in old age and adult psychiatry as well as general neurologists may lack skills to recognise them. Besides, there are no clear treatment guidelines on how to manage the conditions.

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Author Details
JAVED LATOO, Consultant Psychiatrist, 5 Boroughs Partnership NHS Foundation Trust, Hollins Lane, Warrington WA2 8WA, UK. MINAL MISTRY, Consultant Psychiatrist, Southern Health NHS Foundation Trust, Hampshire, UK. FRANCIS J DUNNE, Consultant Psychiatrist and Honorary Senior Lecturer, North East London Foundation Trust (NELFT) United Kingdom, & University College London.
CORRESSPONDENCE: JAVED LATOO, Consultant Psychiatrist, 5 Boroughs Partnership NHS Foundation Trust, Hollins Lane, Warrington WA2 8WA, UK. Email: javedlatoo@gmail.com

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Case Report

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Persistent genital arousal disorder in a male: a case report and analysis of the cause

Rajkumar Kamatchi and Andrew Ashley-Smith

A 54-year-old male presented to the psychosexual clinic with symptoms suggestive of persistent genital arousal disorder of 2years duration. Physical examination and investigations ruled out any underlying urological or neurological causes. He was treated with Diazepam and Pregabalin and his symptoms reduced in intensity.

Introduction:

Persistent genital arousal disorder (PGAD), also known as persistent sexual arousal syndrome (PSAS) or restless genital syndrome (ReGS), is recently recognised as a sexual health problem in western countries although it is not been considered as a physical or psychiatric disorder by DSM IV or ICD 10. PGAD is associated with constant, spontaneous and intrusive feelings of genital arousal in the absence of conscious sexual thoughts or stimuli.

The working definition of PGAD[1],[2] is as follows:

1) Persistent physical arousal in the genital area
2) in the absence of conscious thoughts of sexual desire or interests
3) associated with spontaneous orgasm or feelings that orgasm is imminent and
4) the symptoms not diminished by orgasm.

It may be present throughout the person's life (primary PGAD) or develop at any age (secondary PGAD). It is associated with varying degrees of distress in the patients. This new disorder has been reported in women by numerous clinicians in the last decade. However, so far, there is only one report of two males suffering with ReGS in the literature.[3] We report a case of PGAD in a male and aim to analyse the cause.

Case Report

A 54-year-old male was referred to the psychosexual clinic by an urologist with 2 years history of constant feelings of physical arousal in the genital area as if he was about to ejaculate. These feelings were associated with pain which was relieved to an extent after ejaculation. These symptoms started suddenly for the first time when he was browsing the internet and accidentally ended up in pornographic websites. But later on, the symptoms were constant without any sexual stimuli and he got some relief from attaining climax.

He described that the physical arousal in the genital area increased in intensity to a point he had to ejaculate to have some relief. He felt this "as if wanting to have climax all the time". Post- ejaculation, he felt anxious, tired and nauseated for sometime, during which the symptoms intensified again that he needed climax. Initially this cycle repeated every 2-3 days but later on the frequency increased to 2-3 times a day. He achieved climax both by masturbation and sexual intercourse. He felt these ejaculations were unpleasant and not enjoyable. He felt frenzied if he couldn't ejaculate and the post orgasmic feelings were severe if he avoided orgasm for a day or two. He described regular ejaculations led to less severe "come downs" but left him constantly drained.

His medical history included vasectomy four years ago with minor complication of painful scrotum which subsided fully with pain killers. He also had few urinary tract infections (UTI) in the past which were treated with antibiotics. He was initially seen by urologist who carried out physical examination which was noted to be normal. Then investigations including CT-KUB, CT- Abdomen, Urogram, Transrectal Ultrasound of prostate and seminal vesicles, Flexible Cystoscopy were done and no abnormalities noted. He also had MRI- Brain which was normal. He had no symptoms of hyperactive bladder and no varicocele was noted.

When he was seen in the psychosexual clinic, he was noted to be very anxious and expressed guilty feelings around the incident of watching pornography which initiated the onset of symptoms. There were no depressive or psychotic symptoms. Prior to attending this clinic he was prescribed duloxetine 30mgs by the urologist, which he took only for few weeks. He stopped it as there was no symptom relief. He was started on diazepam and pregabalin. The dose was increased to 2mgs qds of diazepam and 50mgs qds of pregabalin. His symptoms diminished gradually and now he remains mildly symptomatic although feeling "more in control". He was also referred to psychologist and had an assessment. As he was not

psychologically minded and unable to engage in sessions, he stopped attending.

Discussion

The clinical features in this man were consistent with the definition of PGAD. He had physical arousal symptoms, which were not related to sexual desire or thoughts and was causing severe distress to him. The symptoms were relieved by ejaculation to a certain extent. He was treated with diazepam and pregabalin which reduced the intensity of the symptoms.

There is an emerging literature on the pathophysiology, possible aetiological factors and the management options of PGAD. There are various associations reported including psychological[4,5] and organic[6-9] pathologies with some convincing evidence.

In this case, he suffered few UTI and a minor complication of painful scrotum following vasectomy, few years before the onset of PGAD. However he had a full urological and neurological work-up recently which didn't show any underlying organic cause for his current symptoms. He suffered no previous depressive or anxiety disorder. Hence his current symptoms may be induced by anxiety which is further worsened by the fact that he became focussed on the genital arousal and attaining climax to relieve the pain. When he was prescribed diazepam and pregabalin, his anxiety eased and his physical symptoms diminished in intensity. However the possibility of an organic cause cannot be ruled out completely as he previously suffered sensory neuropathic pain following vasectomy. Further pregabalin is useful for both generalised anxiety and neuropathic pain. Therefore we conclude that his symptoms may be a result of interaction between physical and psychological factors. This suggests that PGAD could be a psychosomatic condition, which was already proposed as a cause for PGAD in women by Goldmeier and Leiblum.[4]

Similar to the causes for PGAD, there is few treatment modalities reported in the literature. These include treatment of the underlying organic causes if any found, electro-convulsive therapy (ECT) if co-morbid with mood symptoms,[10]transcutaneous electrical nerve stimulation (TENS),[3] cognitive behavioural therapy[11] and medications like varenicline.[2]We used anti-anxiety medications (diazepam and pregabalin) and achieved adequate symptom relief. This also supports the idea that PGAD could be a psychosomatic condition related to the peripheral nerves of the genito-urinary system.

This case is reported to confirm that PGAD also occurs in males, which is quite different from priapism and it could be a psychosomatic condition. More research is needed into the pathophysiology of PGAD and its management.

Competing Interests
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Author Details
RAJKUMAR KAMATCHI, MBBS, DMH, MRCPsych, ST6- General Adult Psychiatry trainee & Honorary Associate Clinical Teacher, Warwick Medical School, The Caludon Centre, Coventry, UK. ANDREW ASHLEY-SMITH, FRCPsych (SA), MRCPsych, MMedSci, Consultant Psychiatrist & Honorary Associate Clinical Professor, Warwick Medical School, The Caludon Centre, Coventry, UK.
CORRESSPONDENCE: DR RAJKUMAR KAMATCHI, The Caludon Centre, Coventry, UK, CV2 2TE.
Email: rajkumaranjali@yahoo.com

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Case Report

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Eslicarbazepine use in Multiple Sclerosis with refractory Trigeminal Neuralgaia

Tarek A-Z K Gaber, Myint Myint Kyu and Wah Wah Oo

Abstract

When associated with Multiple Sclerosis (MS), Trigeminal Neuralgia (TN) is often bilateral and more refractory to treatment. Carbamazepine is the first line of treatment for TN, however, common side effects of carbamazepine such as hyponatremia occasionally limit its use.

We report the case of a 62 year old female patient with a well controlled MS associated TN using carbamazepine. This drug needed to be discontinued because of recurrent symptomatic hyponatremia. Several agents including topiramate, gabapentine and amitriptyline were tried but none had any beneficial effect on TN. A small dose of eslicarbazepine (400 mg daily) provided excellent control of the TN pain on one hand and did not affect the plasma sodium levels on the other hand.

Eslicarbazepine main advantage is providing the same effects of carbamazepine or oxcarbazepine but with an incidence of hyponatremia of less than 1%. It is much safer to use when the risk of hyponatremia is increased. To our knowledge, this is the first case that reports the use of eslicarbazepine in one of the several indications of carbamazepine such as pain and mental health problems. Eslicarbazepine use in epilepsy was reported extensively.

We feel that a therapeutic trial of eslicarbazepine is justified when either carbamazepine or oxcarbazepine have to be discontinued because of hyponatremia despite their efficacy.

KEYWORDS: Eslicarbazepine, Trigeminal Neuralgia, Multiple Sclerosis, hyponatremia

Trigeminal Neuralgia (TN) is relatively rare in Multiple Sclerosis (MS) affecting approximately 2% of patients[1]. The severity of the pain is indistinguishable whether TN is an isolated impairment or is associated with MS. However, when associated with MS, TN is often bilateral, affecting younger patients and is more refractory to medical treatment [2].

Several pharmacological agents are reported to be effective in TN associated with MS. Topiramate[3,4], gabapentin[5] and lamotrigine[6] were all reported to benefit patients with TN associated with MS in small uncontrolled trials. Several other drugs such as phenytoin, misoprostol and amitriptyline are routinely tried in patients with TN despite the lack of convincing evidence of their efficacy[7].

In 2008, Both the American Academy of Neurology and the European Federation of Neurological Societies launched joint Task Force general guidelines for the management of TN. After systematic review of the literature the Task Force came to a series of evidence-based recommendations [8]. Carbamazepine and oxcarbazepine had the strongest evidence of efficacy and were recommended as the first line treatment. An earlier Cochrane systematic review reached the same conclusion. [9].

Case report

A 62 year old female patient had been suffering from MS for about 20 years. The MS presented with trigeminal neuralgia from the outset and this was then followed by pyramidal lower limbs' weakness and sphincteric dysfunction. The patient started to use a wheelchair 10 years ago but she became totally wheelchair dependent about 6 years later.

Trigeminal neuralgia remained active throughout the 20 years. Carbamazepine (300 mg daily) provided the patient with a satisfactory control of TN. Despite having occasional break through TN pain; the patient declined having higher doses of carbamazepine as excessive sedation was an unacceptable side effect.

Recently; the patient was admitted to hospital in two separate occasions complaining of increasing malaise and confusion. Plasma sodium levels were found to be low in both occasions (first presentation 118 mmol/l and second admission 114 mmol/l). Clinical evaluation confirmed Syndrome of Anti Diuretic Hormone Secretion (SIADH) as the cause of the hyponatremia and in the absence of any other explanation for the SIADH; carbamazepine was thought to be the main reason and was duly discontinued.

Unfortunately, TN attacks came back with vengeance. During the following 6 months, therapeutic trials using gabapentine, topiramate and amitriptyline failed to show any beneficial effect on either the severity or the frequency of the TN attacks. All three drugs were duly discontinued.

The patient was started on eslicrbazepine 400 mg on a single daily dose. This dose lead to almost complete eradication of the TN attacks. The control of TN and the plasma sodium levels remained stable a year following the initiation of the therapy.

Comments

Hyponatremia, defined as a sodium level < 135 mmol/l is a common side effect of carbamazepine and oxcarbazepine

therapy. The incidence of hyponatremia secondary to carbamazepine therapy ranges between 4.8 and 40 % depending on the population studied[10,11]. In most cases, hyponatremia is asymptomatic and continuation of the carbamazepine use is possible whilst a close eye is kept on the plasma sodium level[10]. In rare occasions hyponatremia is symptomatic and discontinuation of carbamazepine is warranted. Administration of demeclocycline to normalise the sodium level was suggested by some authors.[12] However, the long term use of demeclocycline is associated with several complications and this approach is hardly a standard practice.

Clinicians often face a dilemma when carbamazepine is the only agent able to control a specific clinical problem. With many antiepileptics available, it is unusual to face such a problem in epileptic patients. Trigeminal neuralgia on the other hand can be extremely difficult to control and carbamazepine was found to have a unique ability to manage such unpleasant condition even before its antiepileptic effects were noticed on 1962[13].

Eslicarbazepine is promoted as an alternative to carbamazepine when side effects occurs on otherwise responsive patients to its favourable antiepileptic effects[14]. Hyponatremia is rare in eslacarbazepine users with only an incidence of less than 1% in the small populations studied[15,16]. Frequency of hyponatraemia increased with increasing eslicarbazepine dose. In patients with pre-existing renal disease leading to hyponatraemia, or in patients concomitantly treated with medicinal products which may themselves lead to hyponatraemia[17].

Our patient showed the same favourable response to eslicarbazepine as she experienced with carbamazepine. However, hyponatremia did not occur with eslicarbazepine therapy. This enabled our patient to continue with pharmacological management and avoid surgical interventions.

With the exception of epilepsy, no reports are available commenting on the use of eslicarbazepine on the wide range of conditions that carbamazepine is traditionally used for such as mental health problems and neuropathic pain. When patients are well controlled on carbamazepine whatever the indication is, the occurrence of side effects such as hyponatremia is often managed by an automatic replacement with another agent. We feel that in such patients a therapeutic trial of eslicarbazepine might be appropriate especially if the control on carbamazepine was robust or if the benefits of carbamazepine therapy were clearly superior to other pharmacological agents potentially useful for the targeted clinical condition.

Competing Interests

None declared

Author Details

TAREK A-Z K GABER, FRCP (London), Consultant in Neurological Rehabilitation, Wrightington, Wigan and Leigh NHS Foundation Trust, UK. MYINT MYINT KYU, MRCP, Specialist Registrar in Rehabilitation Medicine, North West of England Deanery, UK. WAH WAH OO, MRCP, Specialist Registrar in Rehabilitation Medicine, North West of England Deanery, UK. CORRESSPONDENCE: DR TAREK GABER, Consultant in Neurological Rehabilitation, Leigh Infirmary, Leigh, Lancs. WN7 3NF, UK.
Email: tgaber@doctors.net.uk

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Clinical Practice

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Irritable Bowel Syndrome for Primary Care Physicians

Ali Khanbhai and Daljit Singh Sura

Introduction and Epidemiology

Irritable bowel syndrome (IBS) is a chronic and often debilitating condition with a complex aetiology[1]. It is the most common diagnosis made by gastroenterologists worldwide[2]. The incidence and prevalence of IBS vary depending on the diagnostic criteria used but it is estimated that the prevalence in the UK is 17% overall, with a prevalence of 11% among men and 23% among women[3-4]. IBS can have a significant negative impact on quality of life and social functioning, although it is not known to be associated with the development of serious disease or excess mortality. However, patients with IBS are more likely to undergo specific surgical operations such as hysterectomy and cholecystectomy. IBS further represents an economic burden on society due to the high consumption of healthcare resources and the non-productivity of IBS patients[5]. It appears that 33–90% of patients do not consult a physician, and that a proportion of patients who meet the IBS criteria are not diagnosed with IBS. The frequency of IBS symptoms peaks in the third and fourth decades, and there is a female predominance of about 2:1 in the 20s and 30s, although this discrepancy is less apparent in older patients[6]. The female predominance is less apparent in the general population, which suggests that women with IBS are more likely to seek healthcare for their symptoms[7]. IBS symptoms which persist beyond middle life continue to be reported by a substantial proportion of individuals in their seventh and eighth decades.

Pathogenesis

The pathogenesis of IBS appears to be multifactorial. The following factors play a central role in the pathogenesis: heritability and genetics, dietary and intestinal microbiota, low-grade inflammation and disturbances in the neuroendocrine system of the gut[2].

IBS is known to aggregate in families and to affect multiple generations but not in a manner consistent with a major Mendelian effect. Relatives of an individual with IBS are two to three times as likely to have IBS[8].

Psychological distress is not only a common co-morbidity in IBS patients, but also a factor which is likely to play a direct role in the pathogenesis[4]. Interestingly, parental modelling and the reinforcement of illness behaviour can also contribute to IBS. Having a mother with IBS has been shown to account for as much variance as having an identical set of genes as a co-twin who has IBS. This insinuates that the contribution of social learning to IBS is at least as great as the contribution of heredity. Furthermore, the role of childhood events such as nasogastric tube placement, poor nutrition, abuse, and other stressors have been clearly associated with IBS[8].

A substantial proportion of patients with IBS report onset of their symptoms after acute gastroenteritis[9]. Post-infectious (PI)-IBS has been reported after viral, bacterial, protozoa and nematode infections, with the incidence of PI-IBS varying between 7% and 31%. In this subset of IBS patients GI symptoms appear following gastroenteritis, with approximately 10% developing persistent symptomsRecent studies suggest that some individuals are genetically predisposed to developing PI-IBS, with some people demonstrating a specific cytokine response to infection[4].

It is important to note that women appear to have more frequent and severe IBS symptoms during menses compared to other phases of the menstrual cycle and that female gender is a significant independent risk factor for the development of IBS[7].

Diagnosis and Investigations

Adult patients who present to their general practitioner (GP) with lower gastrointestinal tract disorders account for one in 20 of all general practice consultations. The possibility of sinister conditions such as colorectal cancer or inflammatory bowel disease may create diagnostic uncertainty and reluctance for the doctor to attribute the symptoms to IBS. In the United Kingdom up to 29% of patients with IBS are referred to a specialist but the majority of these will return to their GP for long term management[6].

Primary care differs from specialist care because the GP's greater familiarity with the patient, and their previous consultations, enable presenting problems to be seen in context rather than in isolation. Furthermore, it involves the first contact for care of problems at a stage when they are likely to be poorly defined. Lastly, primary care is characterised by a biopsychosocial model of care that takes into account the context of the person's

problem. These characteristics are especially important when managing chronic disorders, such as IBS, where there is a high priority on continuity of care[6].

There is currently no biochemical, histopathological or radiological diagnostic test for IBS. The diagnosis is based principally on symptom assessment. The Rome III criteria (Figure 1) is the most recent, updated and universal diagnostic criteria for IBS. However, although the Rome III criteria are widely used in clinical studies, it is not used by most cliniciansIn fact, most primary care physicians are not aware of diagnostic criteria for IBS and about one third of secondary care doctors do not use them in practice[6].

IBS patients are grouped on the basis of the most predominant bowel symptom as diarrhoea- predominant, constipation-predominant, a mixture of both diarrhoea and constipation, and un-subtyped IBS in patients with an insufficient abnormality of stool consistency to meet the criteria for the other sub-groups. Approximately one third of patients have diarrhoea- predominant, one third have constipation-predominant, and the remainder have a mixture of both diarrhoea and constipation. The classification of IBS patients into sub-groups is useful for clinical practice, but it is common for IBS patients to switch from one subtype to another over time. More than 75% of IBS patients change to either of the other 2 subtypes at least once over a 1-year period[2,10].

Figure 1 - Rome III diagnostic criteria* for IBS [6]

Recurrent abdominal pain or discomfort** at least 3 days a month in the past 3 months, associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

*Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis

** "discomfort" means an uncomfortable sensation not described as pain

According to the National Institute for Health and Clinical Excellence (NICE), healthcare professionals should consider assessment for IBS if a patient presents with any of the following symptoms for at least six months[11]:

- abdominal pain/discomfort
- bloating
- or a change in bowel habit

NICE has also given the following guideline pertaining to "red flag" indicators. All people presenting with possible IBS symptoms should be asked if they have any of the following indicators. Referral to secondary care should be made if any are present[11]:

- unintentional and unexplained weight loss
- rectal bleeding
- family history of bowel or ovarian cancer
- change in bowel habit to looser and/or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.

Furthermore, all patients presenting with IBS symptoms should be appropriately assessed and clinically examined for the following 'red flag' indicators. A referral should be made to secondary care if any are present[11]:

- Anaemia
- Abdominal masses
- Rectal masses
- Inflammatory markers for inflammatory bowel disease
- Serum CA125 should be measured in women with symptoms that suggest ovarian cancer

In addition, NICE have stated that IBS should be considered only if the person has abdominal pain or discomfort that is either relieved by defecation or associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms[11]:

- altered stool passage (straining, urgency, incomplete evacuation)
- abdominal bloating (more common in women), distension, tension or hardness
- symptoms made worse by eating
- passage of mucus

Other features such as lethargy, nausea, backache and bladder symptoms are common in people with IBS, and may be used to support the diagnosis.

According to NICE, patients who meet the IBS diagnostic criteria should have the following tests to exclude other diagnoses (Figure 2):

Figure 2 [11] - Tests to exclude other diagnoses

Full blood count (FBC)
Erythrocyte sedimentation rate (ESR) or plasma viscosity
C-reactive protein (CRP)
Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG])

The value of serological tests for coeliac disease (EMA or TTG antibodies) in patients with IBS diarrhoea-predominant depends on the population and is generally considered cost-effective if the incidence of coeliac disease is above 1%. It is therefore likely to be beneficial in the United Kingdom, where up to 3% of cases of IBS diarrhoea-predominant in primary care have coeliac disease[6].

The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria[11]:

- Ultrasound
- Rigid/flexible sigmoidoscopy

- Colonoscopy/barium enema
- Thyroid function test
- Faecal ova and parasite test
- Faecal occult blood
- Hydrogen breath test (for lactose intolerance and bacterial overgrowth)

It is important to note that IBS is associated with several other conditions. At least half of IBS patients can be described as depressed, anxious, or hypochondriacal. In addition, between 20% and 50% of IBS patients have fibromyalgia. Furthermore, IBS is common in several chronic pain disorders, being present in 51% of patients with chronic fatigue syndrome, in 64% with temporomandibular joint disorder, and in 50% with chronic pelvic pain. The lifetime rates of IBS in patients with these syndromes are even higher. Patients with such co-morbidities generally have more severe IBS. A careful history to identify such associated disorders is helpful in identifying patients who are likely to have severe IBS and associated psychiatric disorder[6].

Management

The treatment of IBS is determined by the patient's most troublesome symptoms. Although there is overlap in the therapies offered to the different IBS sub-groups, treatment decisions are primarily based on the frequency and severity of symptomsThe management discussed in this section is largely based on the NICE guidelines[11].

Dietary and lifestyle advice

People with IBS should be given information about the importance of self-help in effectively managing their IBS. This should include information on general lifestyle, physical activity, diet and symptom-targeted medication. Healthcare professionals should assess the physical activity levels of people with IBS (ideally using the General Practice Physical Activity Questionnaire). People with low activity levels should be given advice to encourage them to increase their activity levels. Healthcare professionals should also encourage people with IBS to make the most of their available leisure time and to create time for relaxation[11].

Figure 3 summarises the general advice that should be given to patients regarding their diet and nutrition. If diet continues to be considered a major factor in a person's symptoms and they are following general lifestyle/dietary advice, they should be referred to a dietician for further advice and treatment, including single food avoidance and exclusion diets. Such advice should only be given by a dietician[11].

Probiotics are live microorganisms which when taken in sufficient quantities, confer a health benefitPeople with IBS who try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer[11].

Figure 3 - Diet and nutrition should be assessed and the following general advice given [11]

Have regular meals and take time to eat
Avoid missing meals or leaving long gaps between eating
Drink at least eight cups of fluid per day, especially water or other non-caffeinated drinks, for example herbal teas
Restrict tea and coffee to three cups per day
Reduce intake of alcohol and fizzy drinks
It may be helpful to limit intake of high-fibre food (such as wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
Reduce intake of 'resistant starch' (starch that resists digestion in the small intestine and reaches the colon intact), which is often found in processed or re-cooked foods
Limit fresh fruit to three portions per day (a portion should be approximately 80 g)
People with diarrhoea should avoid sorbitol, an artificial sweetener found in sugar-free sweets (including chewing gum) and drinks, and in some diabetic and slimming products.
People with wind and bloating may find it helpful to eat oats (such as oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).
Healthcare professionals should review the fibre intake of patients, adjusting (usually reducing) it while monitoring the effect on symptoms. People with IBS should be discouraged from eating insoluble fibre (for example, bran). If an increase in dietary fibre is advised, it should be soluble fibre such as ispaghula powder or foods high in soluble fibre (for example, oats)

Pharmacological therapy

Healthcare professionals should consider prescribing antispasmodics for patients. These should be taken as required, alongside dietary and lifestyle advice. Laxatives should be considered for the treatment of constipation, but patients should avoid taking lactulose. Patients should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4). Loperamide should be the first choice of antimotility agent for diarrhoeaOne advantage of loperamide is its peripheral site of action with little penetration of the blood brain barrier and thus, little potential for CNS side effects or habituation[4].

Psychotropics possess a variety of peripheral and central effects which make them attractive treatments for IBS. These effects include modulation of pain perception, mood stabilisation, treatment of associated psychiatric conditions, and possible direct effects on GI motility and secretion. Healthcare professionals should consider tricyclic antidepressants (TCAs) as second-line treatment for patients if laxatives, loperamide or antispasmodics have not helped. Treatment should be started at a low dose (5–10 mg equivalent of amitriptyline), which should

be taken once at night and reviewed regularly. The dose may be increased, but does not usually need to exceed 30 mg[11].

Selective serotonin reuptake inhibitors (SSRIs) should be considered only if TCAs have been ineffective. The anticholinergic effects of TCAs and their ability to prolong intestinal transit times are the reasons they are particularly preferred over SSRIs in IBS diarrhoea-predominant. Furthermore, given the propensity of SSRIs to commonly cause GI adverse events of nausea, vomiting, and diarrhoea, indicate that TCAs may have more utility in IBS diarrhoea-predominant than SSRIs[12]. Healthcare professionals should take into account the possible side effects when prescribing TCAs or SSRIs. After prescribing either of these drugs for the first time at low doses, the patient should be followed up after 4 weeks and then at 6–12 monthly intervals[11].

Psychological interventions

Anxiety and depression are common in IBS and patients report a correlation between stress and their symptoms, providing a rationale for psychological therapy. Referral for psychological interventions (cognitive behavioural therapy, hypnotherapy and/or psychological therapy) should be considered for people with IBS who do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS).[11]Hypnotherapy reduces patient anxiety and improves symptom control in the majority of patients with refractory IBS. The benefits extend well beyond symptom control and include improvements in quality of life and reduction in emotional distress[13]. Data from general practice shows that hypnotherapy is effective during the first three months, although the effect is less marked after that[6].

Prognosis of IBS depends on the length of the history, those with a long history being less likely to improve. Follow-up should be agreed between the healthcare professional and the patient based on the response of the person's symptoms to interventions. The emergence of any 'red flag' symptoms during management and follow-up should prompt further investigation and/or referral to secondary care[11].

Competing Interests
None declared
Author Details
ALI KHANBHAI, MB ChB DRCOG, GP VTS ST2 Trainee, Queen's Hospital, Rom Valley Way, Romford, Essex, RM7 0AG, United Kingdom. DALJIT SINGH SURA, MBBS BSc DRCOG DFSRH MRCGP, General Practitioner, North Street Medical Care, Romford, RM1 4QJ, United Kingdom. CORRESSPONDENCE: ALI KHANBHAI, GP VTS ST2 Trainee, Queen's Hospital, Rom Valley Way, Romford, Essex, RM7 0AG, United Kingdom. Email: ali.dh.kh@gmail.com

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Clinical Practice

Gastrointestinal bleeding in spinal injuries patient: Is prophylaxis essential?

Fahim Anwar, Ahmad Al-Khayer, Hoda El-Mahrouki and Muriell Purcell

ABSTRACT

Introduction: Acute gastrointestinal (GI) ulcerations and erosions are common in major trauma victims and in intensive care units. The reported incidence of gastrointestinal haemorrhage in acute spinal cord injuries is between 5 and 22%.

Aims: This study aims to review prophylactic management of GI bleeding after spinal cord injury at the Queen Elizabeth National Spinal Injuries Unit, Scotland and to analyse the morbidity and mortality associated with GI bleeding.

Setting: Model spinal injury centre in Sctoland. A policy of stress ulcer prophylaxis is followed in all patients admitted to this centre.

Material and Methods: Retrospective review of case notes of patients with a clnincally significant GI bleed from January 2006 to May 2008.

Results: A total of 360 new injury patients were admitted. 19 (5.2%) had a clinically significant GI bleed during the study period. There were 2 females and 17 males with a mean age of 51.2 years. Cervical spine injury was present in 12 cases 63.1%. Eight (42.1%) patients underwent endoscopic treatment and 3(15.7%) patients required a had laprotomy. One death (5.2%) was reported.

Conclusion: Gastrointestinal haemorrhage is potentially a serious complication in spinal cord injured patients. Appropriate prophylaxis, early diagnosis and prompt management may help avoiding a possible fatality.

KEYWORDS: Gastrointestinal, bleeding, spinal injuries

Introduction

Acute gastrointestinal ulcerations and erosions (stress ulcers) are common in major trauma victims and in intensive care units. In fact, 75% of all critically ill admissions may have endoscopic evidence of gastroduodenal or upper gastrointestinal bleeding[1]. The bleeding could be in mutiple forms such as haematemesis,coffee ground aspirates, melaena, or haematochezia. Clinically significant haemorrhage causes hypotension and tachycardia and requires blood transfusion. Aggressive management is required in order to improve the outcomes of this potentially fatal complication. Prevention of stress ulcers helps reduce the morbidity and mortality of major bleeding[2]. Multiple causes may be responsible for gastrointestinal ulceration in patients with spinal cord injury[1]. Furthermore, steroids, thrombophylactic agents, anticoagulants and heavy cigarette smoking may act as predisposing factors to gastrointestinal bleed.

The aim of this study was to review our practice of stress ulcer prophylaxis after spinal cord injury and analyse morbidity and mortality associated with stress ulcer bleeding.

Patients and Methods

The Queen Elizabeth National Spinal Injuries Unit is the sole spinal cord injury centre in Scotland. It serves a population of 5.1 million and admits approximately 175 acute spinal injuries patients per year.

This study is retrospective. Only cases of life threatening or massive gastrointestinal haemorrhage were included. The period studied is between January 2006 and May 2008.

The department policy is to start all patients on Ranitidine 150 mg twice daily provided they are not on alternative medications before their admission, in which case the policy is to continue with the original pre admission medication.

Clinical notes of included patients were reviewed and information on patient's demographics, cause and level of injury, past medical history, preadmission medications, clotting profile, prophylaxis, and management of bleeding were collected.

Results

A total of 360 patients were admitted. Out of them 19 (2 Female:17 Male) met the inclusion criteria as they suffered a life threatening GI bleed or major haemorrhage. The age range was 19 to 78 years with a mean age of 51.2 years. The majority of patients had a cervical spine injury (63%) followed by lumbar (21%) and thoracic (16%) spine injuries . Fall down stairs was the most common cause of injury occurring in 6 (31.5%) patients followed by road traffic accidents (26.3%) and fall from a height (21%). One patient suffered spinal injury whilst playing rugby and 1 patient suffered a cycling accident. The majority of cases (17 out 19) were admitted with acute injuries. However, 2 patients were admitted for complications of chronic injuries (one with a post surgical abscess and one with pressure sores). The various causes of spinal injuries are shown in table 1.

Table 1: Causes of Spinal Cord Injury

Cause of Injury	Number	Percentage
Fall from stairs	6	31.5%
Road traffic accidents	5	26.3%
Fall from height	4	21%
Rugby injury	1	5.2%
Cycling accident	1	5.2%
Old injury admitted with skin problem	1	5.2%
Post surgical abscess	1	5.2%

The American Spinal Injury Association (ASIA) impairment scales of all 19 patients are shown in Table 2. Associated injuries were encountered in 4 (21%) of patients. These associated injuries include sternum fracture, rib fractures, clavicle fracture, tendon injury and a calcaneum fracture. Significant past medical history was found in 14 (73.6%) patients whereas 5 (26.4%) did not have any previous medical illness. The list of all the significant past medical problems is shown in Table 3.

Table 2: American Spinal Injury Association Impairment Scale

ASIA Impairment Scale	Number	Percentage
A= Complete: No motor or sensory function is preserved in the sacral segments S4-S5.	3	15.7%
B=Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5	1	5.2%
C=Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3	10	52.6%
D=Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more	2	10.5%
E=Normal: motor and sensory function are normal	3	15.7%

4 (21%) patients were already taking Omeprazole before admission, whereas 2 (10.5%) were taking Ranitidine and 1 (5.2%) patient was taking Lansoprazole.

7 out of 19 patients (36.8%) had either one or two episodes of significant coffee ground vomiting, 6 (31.5%) patients had an episode of haematemesis and 4 (21%) patients had combined coffee ground vomiting and haematemesis. Two (10.5%) patients had positive nasogastric aspirate for bleeding.

All 19 patients were started on intravenous Omeprazole and Sucralfate was added in 13 patients. Low molecular weight heparin, Ibuprofen and Aspirin was discontinued in all patients. Six (31.5%) patients were transfused 40 units of fresh frozen plasma and packed red cells (Figure 1). Eight patients (42.1%) underwent endoscopic treatment (Table 4) and 3 (15.7%) patients underwent laparotomy. There was one (5.2%) fatality reported.

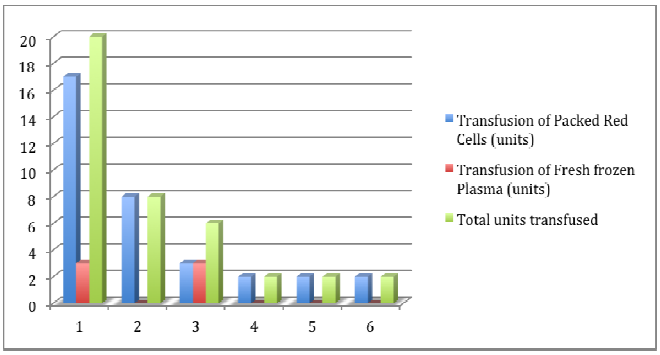
Table 3: Previous Risk Factors in Spinal Cord Injured Patients with Stress Ulcers

Adverse Factor	Number of Patients with the Problem
Smoking	13 (68.4%)
Alcohol	5 (26.3%)
Reflux Oesophagitis	4 (21%)
Hypertension	3 (15.8%)
Diabetes Mellitus	3 (15.8%)
Hiatus Hernia	2 (10.5%)
Ischemic Heart Disease	2 (10.5%)
Asthma	1 (5.3%)
Duodenal Ulcers	1 (5.3%)
Anaemia	1 (5.3%)
Pyloric Stenosis	1 (5.3%)

Table 4: Endoscopic Findings, Procedures and Outcome

Number	Endoscopic findings, Procedures and Outcome
2	Bleeding Duodenal Ulcer injected with adrenaline Bleeding stopped
1	Had Endoscopy twice and bleeding Duodenal Ulcer injected with adrenaline on both occasions Continuous bleeding Underwent Laparotomy and over Sewing of the ulcer
1	Endoscopic findings were Oesophagitis, Hiatus Hernia and superficial ulcerations No procedure performed Treated Conservatively
1	Bleeding Duodenal Ulcer injected with adrenaline Continuous bleeding Prepared for Laparotomy but could not survive
1	Bleeding Duodenal Ulcer injected with adrenaline Bleeding stopped Barrett's oesophagus was found and biopsied but biopsy results were negative
2	Bleeding Duodenal Ulcer injected with adrenaline Continuous bleeding Laparotomy and over sewing

Figure 1: Packed Red Cells and Fresh frozen Plasma Transfusion Units Patients



Discussion

The development of "stress" ulceration in the upper GI tract has been part of critical care folklore for a long time. In 1823 Curling described a series of severe duodenal ulceration associated with burns[3]; in 1832 Cushing reported ulcer disease associated with surgery and trauma[4]In the early years of intensive care, a strong association between severity of illness and the incidence of GI bleeds was established. Patients who had major bleeds had a high mortality rate and, consequently, prophylaxis against this complication has become a central issue in ICU care.

Gastrointestinal haemorrhage in patients with spinal cord disease was not reported until 1933 when Polstorff described gastric ulceration in an epileptic patient with spontaneous hematomyelia[5]. El Marsi and colleagues in 1982 reported 5.5% incidence of gastrointestinal bleeding in acute spinal cord injury patients[6]. Lesions of the spinal cord including traumatic, viral and infectious have been described with gastrointestinal bleeding[7]. It has been found mainly associated with injury to the cervical spinal cord[8].

Controversy still exists regarding the appropriate prophylaxis of stress ulcers in trauma patients. There have been numerous randomized, controlled trials and several meta-analyses evaluating the use of drug therapy for stress ulcer prophylaxis in trauma patients[9]. One meta-analysis concluded that Sucralfate is as effective as pH-altering medications in preventing stress ulcer bleeding[10]. There is currently no large study that proves the superiority of proton pump inhibitors over H2- receptor antagonists for stress ulcer prophylaxis [11, 12]. A survey of all the Level I trauma centers in the United States by Barletta et al[9] revealed that H2-receptor blockers were the preferred agents. It is important to mention that some studies have questioned the need for prophylaxis altogether but these were mainly retrospective studies that primarily evaluated medical patients as compared to trauma patients[13, 14, 15, 16]. The reported incidence of gastrointestinal haemorrhage in the medical literature in acute spinal cord injuries is between 5 and 22% [6, 17,18]. In our study 19 out of 360 patients (5.2%) suffered a major bleed from the gastrointestinal tract. This incidence is similar to lower percentage reported in the medical literature[17, 18]. The strict adherence to the department policy of early prophylaxis for all admitted patients could be the reason for this low percentage of significant bleeding.

It is interesting to note that despite the increasing use of steroids and anticoagulants in the last decade, the incidence of gastrointestinal bleeding in acute spinal cord injuries have remained the same. The possible reason for this could be the increased awareness of this condition by spinal cord injury specialists and the regular prophylaxis initiated in the early phases of the injury. Our unit aims to admit patients as soon as they are fit for transfer and approximately 50% of our patients are transferred within the 48 hours of their injury from the peripheral hospitals. The referring hospitals are advised to commence H_2 receptor antagonist at the time of referral.

Increasing use of antacids, H_2 receptor antagonists and proton pump inhibitors in primary care[19] may also contribute to the reduction of the incidence of gastrointestinal bleeding in patients with spinal cord injuries. This assumption is supported by our study as 7 (36.8%) patients in our study were already on these medications prior to their spinal cord injury.

The aetiology of gastroduodenal bleeding in spinal cord injury is multifactorial including, synergetic effects of the stress of the accident along with added effects of concomitant surgery, sepsis, unopposed reduced vagal tone and mucosal ischemia[20]. Also prolonged mechanical ventilation and coagulopathy has been shown to be associated with increased risk of stress ulcers in spinal injuries[21].Other identified risk factors include multiple injuries, acute renal failure and use of high dose steroids[22]. Croft[23] in 1977 first described the dynamics of the surface epithelium in the stomach. He reported that various agents were responsible for the damage of the gastric mucosa; stress, steroids and uraemia were causing decrease in the production of the mucosal cells; and alcohol and aspirin were causing increase in the shed of the gastric mucosal cells. This serious complication usually develops during the first four weeks after the spinal cord injury[20,24]. However, the period of greatest risk for gastrointestinal haemorrhage is reported to be between the fourth and tenth day after the injury[8]Nuseilben also reported focal ischemia of the gastric mucosa as early as 24 hours following the acute spinal cord injuries[25].

Spinal injuries seldom occur in isolation; in a study by Silver[26] in 1985 a 15% incidence of associated injuries was reported. The incidence of associated injuries in our study was 21%.

In a study by Walters and Silver[1] all patients that bled had a combination of at least 3 risk factors. In our study 73.6% of patients who developed gastroduodenal bleeding had significant history of risk factors with smoking (68.4%) and alcohol (26.3%) being the major contributors. The other risk factors in our study were reflux oesophagitis (21%), hypertension (15.8%), diabetes mellitus (15.8%), hiatus hernia (10.5%) and ischemic heart disease (10.5%). However, only 7 (36.8%) patients had a combination of three or more risk factors at the time of admission. The reason for this decreased incidence as compared to Walter and Silver[1] is difficult to explain.

In this study the majority of patients with gastrointestinal bleeding had cervical cord injuries (63.1%) as compared to thoracic and lumbar spine injuries. Kewalramani[20] also showed predominance of gastrointestinal bleeding in patients with cervical cord injuries. This favours the neurogenic hypothesis as a major cause of gastrointestinal bleeding following the spinal injury [20].

Finally, there is no consensus, in literature, over the discontinuation of stress ulcer prophylaxis. Some studies suggest the continuation of prophylaxis throughout the duration of the critical illness or intensive care unit stay[27, 28, 29].

Conclusion:

Gastrointestinal haemorrhage is a serious complication in spinal cord injured patients. Appropriate prophylaxis, early diagnosis and prompt management may help to avoid a possible fatality. Patients with spinal cord injury especially with cervical cord injury are at a high risk of gastrointestinal bleeding at all times even during period of rehabilitation[30, 31]. All acute spinal cord injured patients and patients who are undergoing rehabilitation who become critically ill may benefit from receiving chemical prophylaxis for stress ulceration. The duration of treatment is ill defined but is maybe better to continue while risk factors are present. Prevention could be the cornerstone in the overall management of this problem.

Competing Interests
None declared
Author Details
FAHIM ANWAR, MRCSEd, FEBPRM, Consultant in Rehabilitation Medicine, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK. AHMAD AL-KHAYER, MRCS, FEBPRM, Consultant in Rehabilitation Medicine, Al-Ahli Hoospital, Doha, Qatar. HODA EL-MAHROUKI, Specialist Registrar, Southern General Hospital, Glasgow, G51 4TF, UK. MURIELL PURCELL, MRCP, Consultant in Spinal Injuries, Queen Elizabeth Spinal Injuries Unit, Southern General Hospital, Glasgow, G51 4TF, UK.
CORRESSPONDENCE: DR FAHIM ANWAR, MRCSEd, FEBPRM, Consultant in Rehabilitation Medicine, Addenbrooke's Hospital, Hills Road, Box 248, Cambridge, CB2 0QQ, UK.
Email: fanwar10@gmail.com

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