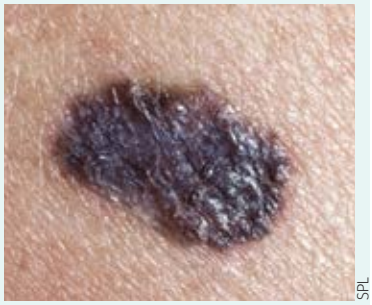
education

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman


SPL

Dissecting nodes in melanoma

Read carefully now, because what I am about to tell you might seem odd. Say you are diagnosed with malignant melanoma, and the sentinel node is positive for cancer. What's your first thought? Perhaps "Help, I'm going to die. Take my other nodes out while I draw up my will." But all that is completely wrong. In a recently published randomised trial, disease-specific survival in such patients at 3 years was 86% if they underwent immediate lymph node dissection and 86% if they did not. Those who had all their nodes removed had a 24% rate of lymphoedema compared with 6% in the observation group. For further enlightenment, read the editorial, which begins: "Because of an incomplete understanding of regional lymph nodes, they have been characterised either as active filters or barriers to the distant spread of disease or as passive indicators of the risk of distant spread. The truth almost certainly resides in a hybrid model that embraces aspects of both theories. This lack of understanding has frequently led to a 'more is better' philosophy in the surgical management of regional lymph nodes. Yet in melanoma, as in so many other cancers, the elective removal of clinically negative nodes has rarely, if ever, been shown to increase disease-specific survival."

N Engl J Med doi:10.1056/NEJMoa1613210

N Engl J Med doi: 10.1056/NEJMe17042 90

Lithium in pregnancy and cardiac malformations

Lithium taken in pregnancy has been associated with cardiac abnormalities in offspring, especially right ventricular outflow tract obstruction defects. In a massive study of more than a million American births covered by Medicaid, the rate of these defects was 0.60% among infants exposed to lithium, compared with 0.18% in unexposed infants (adjusted risk ratio 2.66; 95% confidence interval 1.00 to 7.06). So there almost certainly is an added risk, but notice how the 95% confidence interval includes unity.

N Engl J Med doi:10.1056/NEJMoa1612222

Persistent pain and cognitive decline

Here's a sad study of 10 067 Americans aged between 67 and 78, of whom 11% suffered from persistent pain. These people showed lower baseline score for activity and higher scores for depression at baseline. And after 10 years, they also showed a higher rate of dementia.

JAMA Intern Med doi:10.1001/jamainternmed.2017.1622

Small breast cancers and over diagnosis

"Are Small Breast Cancers Good because They Are Small or Small because They Are Good?" Did this paper get into *NEJM* because it has such a good title, or was the paper so good that the *NEJM* came up with the cool title? Or did the *NEJM* come up with the cool title and then commission the Special Article? You can see the problem. It's the same with cancers. We know that mammographic screening detects mostly lesions that would never grow and spread, but we also know that breast cancer can be considered as a systemic disease from the start. It's becoming clear that there are at least a dozen kinds of breast cancer (or is it a hundred?) with different biological and prognostic features. This paper gives a few clues from present knowledge of the relationship between cancer genotypes and size.

N Engl J Med doi:10.1056/NEJMsr1613680

Salt in American food

I don't really care how much sodium there is in food, provided it doesn't taste too salty. American food always tastes too salty. This article tells us that packaged American food is less salty now than in 2000, which still can't possibly bring American packaged food to the level of edible. For that they would need to tackle the real problem both for taste and health: corn syrup. And most of the other stuff in American packaged food.

JAMA Intern Med doi:10.1001/jamainternmed.2017.140

Desirable weight in pregnancy

A survey of 1.3 million American pregnancies gives me the opportunity to tell you belatedly that the US Institute of Medicine is now called the National Academy of Medicine, and has been for more than two years. When it was still the Institute of Medicine, the luminaries who sat there decided on the desirable range of weight gain for women during pregnancy. Roughly speaking, they seem to have got it right. Women who put on too much weight (47% of the sample) have bigger babies and more caesarean sections, while women who put on too little tend to have smaller babies and a higher risk of premature birth.

JAMA doi:10.1001/jama.2017.3635

Glucose strips in orally treated type 2 diabetes: America catches up

To celebrate the tenth anniversary of Andrew Farmer's landmark *BMJ* paper showing that self monitoring of blood glucose is a waste of time for Britons with type 2 diabetes who are not on insulin, *JAMA IM* publishes a North Carolina study which shows that the same is true for Americans.

BMJ doi:10.1136/bmj.39247.447431.BE

JAMA Intern Med doi:10.1001/jamainternmed.2017.1233

10-MINUTE CONSULTATION

Stress at work

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A 55 year old executive presents with low back pain. He appears anxious. A reorganisation within his company has increased his workload and he has been working more hours but receiving no recognition from management. Last week he felt humiliated by a colleague. Since then he has not been able to sleep for more than a couple of hours each night.

WHAT YOU NEED TO KNOW

- Long working hours and strain at work contribute to stress, ill health, and increased risk of cardiovascular diseases, diabetes, and mental illnesses
- Explore occupational factors such as an imbalance between effort and reward, work overload, bullying, and job insecurity
- Workplace interventions, a short period of leave from work, and psychological treatment can be considered, alongside regular follow-up to assess how the patient is coping

Stress accounts for more than a third of all cases of work related ill health and almost half of all working days lost due to illness.[1] Internationally, systematic reviews and meta-analysis of observational data suggest that job strain and poorly functioning work environments are associated with the development of depressive symptoms.[2-4] A longitudinal cohort study from Norway found workplace bullying to be associated with subsequent suicidal ideation.[5] Long working hours are also associated with increased risk of stroke, heart disease,[6] and diabetes,[7] and poor lifestyle including inactivity,[7] smoking,[7] and risky alcohol use.[8]

Patients might present with unexplained somatic symptoms, such as odd aches and pains, palpitations, loss of appetite, and loss of sleep.[9 10] Explore their symptoms and discuss any contributing factors in their work and personal life. The consultation can be long and difficult, as the patient might not volunteer all the information or draw the association with work stress. The objective of this first consultation is to perform a quick risk assessment and explore factors in the patient's job that are contributing to stress.

What you should cover

The following questions are based on systematic reviews, and the experiences of clinicians and patients.

OCCUPATIONAL FACTORS FOR STRESS[2-13]

- Conflict of values (being asked to do a poor quality job or cut costs for a person who likes to keep high standards in their work)
- Feeling insufficiently rewarded compared with the person's assessment of their efforts ("effort-reward imbalance")
- Inability to make decisions about when or how to stop work
- Lack of support from colleagues and management
- Isolation at work (no cooperation between teams)
- Work overload (working after hours) or insufficient workload (nothing to do)
- Discrimination, humiliation, violence, bullying, and harassment at work
- Cases of work related stress in the same company
- Company situation in terms of finances, organisational changes, and employee turnover
- Job insecurity, temporary employment status

Ask about

- the nature and duration of the patient's presenting symptoms
- associated depressive symptoms, such as
  - feeling down, low, or sad
  - loss of interest in activities
  - tiring easily
  - lack of concentration
  - changes in sleep and appetite
- feelings of hopelessness, (eg, a belief that the situation cannot improve)[11]
- occupation, working environment, and stressors at work (box)
- the chronology of events, how the patient has coped so far, and if things have changed recently in their workplace. Typically, three phases are described[13]:
  - an initial ("serene") phase, where the patient reports no particular difficulty
  - a "problem" phase, when obstacles and conflicts gradually appear and the patient tries to deal with the situation
  - a "crisis" phase, where the patient comes to see you
- protective factors for severity of outcome include a supportive family environment and financial wellbeing. Aggravating factors are familial isolation, being a single parent with young children, having financial difficulties, or being bound by a particular type of employment contract that forces the patient to stay in the same job. The latter can delay diagnosis, and limit the range of remedial options available.
- thoughts of ending their life or causing harm to themselves or others
- other medical illnesses, including diabetes, hypertension, cardiovascular events, or psychiatric disorders
- smoking, alcohol, and drug abuse
- family history of depression or mental disorders, which could increase the risk of depression and suicide

Patients come to their doctor primarily to address their symptoms, but some will also want assistance and advice on how to cope with the situation at work.

CPD READING

0.5 HOURS

Examination

Assess general appearance and look for signs of psychomotor agitation such as restlessness, rapid talking, and racing thoughts, or of psychomotor retardation such as apparent exhaustion and visible slowing of physical activity. These might indicate a mental illness or organic cause, such as a thyroid disorder.

Perform a quick general examination to look for fever, tachycardia, hypertension, and signs of thyroid disorder (which can be a differential diagnosis). Examine thoroughly for reported pain, though somatisation is likely.

GETTY IMAGES

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients in our practice reported a need to rethink what they had experienced at work and to share this in writing. This helped them identify and clearly communicate the chronology of events. Based on their feedback we recommend encouraging patients to write about their work environment and factors contributing to stress, though this need not be mandatory.

A patient reviewed this article and attested that writing a two page memorandum would have been enormously helpful to identify problems at work and how they had escalated over time, and to come to terms with the situation.

What you should do

Investigation and management of physical and mental health diagnoses—Offer usual management of conditions such as depression. Consider immediate referral to psychiatry if the patient describes suicidal or aggressive thoughts or intentions.

Make the connection between the patient's experience and work stress—For patients with work related stress and a variety of symptoms, acknowledge their situation and validate their feelings with a phrase such as, "I understand that you are suffering and that this feeling is arising from a stressful work environment."

Offer a supportive setting to discuss and make progress in dealing with work stress—High quality evidence and guidelines for interventions to manage work related adjustment issues and stress are lacking.[14] Cognitive therapy, stepwise reintegration planning, and relaxation training can all be considered.[15 16] Therapy needs to be supportive, active, flexible, goal directed, and time bound.[10-14]

Consider offering a second appointment—for example, if there is too much to cover. You might suggest that the patient brings a family member to the next appointment for support.

In the interim, you might ask the patient to reflect on their job and personal situation, and possibly to write a short description of their problems at work, the chronology of these problems, and their relationship to the patient's symptoms. In our experience, some patients find this helps them reflect on the events, and it can help you understand their situation better. This will help to initiate discussion on strategies that the patient might employ to navigate their workspace going forward.

Making contact with the workplace to modify work or reduce workload in collaboration with the employer can be helpful. Discuss whether the occupational health services or human resources division at the patient's company could be involved.

Consider whether the patient wants or might benefit from time away from work including a "sick note."

Schedule a follow-up visit to assess how the patient is coping with symptoms and workplace issues, and modify the approach accordingly.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j2489

EDUCATION INTO PRACTICE

- What factors would you typically explore in the patient's history to understand their working environment and stress? Does this article offer you ideas on how to do so differently?
- Sometimes, asking the patient to write down their problems at work, the times at which the problems occurred, and the patient's symptoms, is helpful. Are there ways in which you might consider using this or other techniques to help patients better organise their thoughts or understand them yourself?
- Do you offer a second appointment, if there is too much to cover, or if the patient wishes to include a friend or family member?
- In difficult cases, do you work in collaboration with mental health professionals as well as occupational health professionals?

RATIONAL TESTING

Interpreting iron studies

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This is an edited version; the full version is on bmj.com

CPD READING
0.5 HOURS

LEARNING MODULE
See http://learning.bmj.com for linked learning module

A 63 year old woman visits her doctor with a three month history of fatigue and generalised joint pains. Her medical history is unremarkable and she reports no recent stress, infection, or weight loss. There are no abnormalities on clinical examination. Haemoglobin, creatinine, and electrolytes, liver enzymes, glucose, inflammatory markers, and thyroid function tests are normal. Ferritin, iron, transferrin, and transferrin saturation are also requested.

This article discusses some situations in which ferritin and iron studies might be helpful and how to avoid common pitfalls in their interpretation.

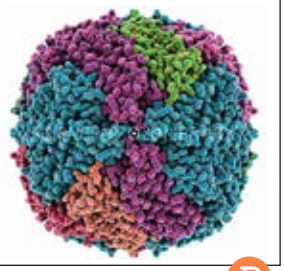
What are the next investigations?

The doctor in this case requested iron studies to investigate the possibility of iron overload and to screen for haemochromatosis. Iron studies are also commonly indicated in clinical practice to investigate iron deficiency, or to monitor response to treatment for these conditions (box 1).

Conventional laboratory tests of iron status are often referred to as "iron studies." They include tests for serum ferritin, iron, transferrin, or total iron binding capacity (TIBC), and transferrin saturation. Normal iron metabolism and regulation are outlined in the figure.

WHAT YOU NEED TO KNOW

- Iron overload typically results in a high ferritin and transferrin saturation
- Iron deficiency is best assessed using serum ferritin, which is low in the absence of inflammation
- Ferritin levels can be elevated by inflammatory processes and can mask iron deficiency



LAGUNA DESIGN/SPL

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients with iron related disorders were informally interviewed about their experiences with iron related blood tests during investigation and diagnosis. Some expressed the view that they would have valued more detailed explanation of their test results, which helped inspire the content of this article

What is included in iron studies?

Ferritin—is the intracellular storage form of iron. A very small amount is found in serum. In inflammation, liver disease, and malignancy, ferritin levels can rise because ferritin is an acute phase protein.[4] In these patients, ferritin can appear either falsely high or normal, when in reality stores are low.

Serum iron—refers to ferric ions (Fe^{3+}) bound to serum transferrin. Serum iron concentration is highly variable and is affected by dietary iron intake, inflammation, and infection.[5]

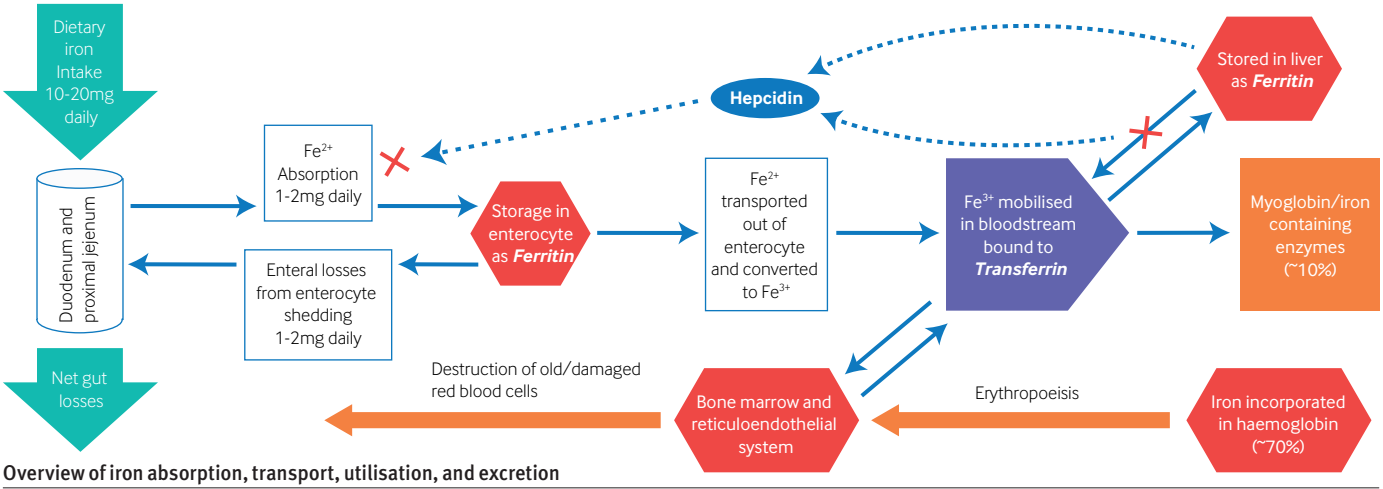
Transferrin—is the principal iron transport protein in plasma. It increases in iron deficiency to maximise utilisation of available iron.[4] Total iron binding capacity is an alternative test to transferrin. TIBC reflects the availability of iron binding sites on transferrin. Values increase in iron deficiency and decrease in iron overload.

Transferrin saturation—is calculated from serum iron and either TIBC or transferrin measurements. Typically, transferrin is 30% saturated with iron.[5] Transferrin saturation rises in iron overload and falls in iron deficiency, but does not quantitatively reflect iron stores.[1] A rise in serum iron due to dietary iron intake can cause raised transferrin saturation.

Box 1 | Suggested indications for iron studies

Investigation of

- iron overload (haemochromatosis)[1]
  - at early stages can be asymptomatic or present with vague symptoms such as fatigue, weakness, or generalised joint pains
  - later manifestations might include deranged liver enzymes, cirrhosis, erectile dysfunction, arthritis, or cardiomyopathy
  - suspected iron overdose/toxicity
- iron deficiency[2]
  - investigating aetiology of low haemoglobin
  - symptoms of anaemia—such as lethargy, shortness of breath, palpitations, pallor, headache, atrophic glossitis, angular cheilosis. Suspected occult blood loss in males and post menopausal females—eg, peptic ulcer disease
  - menorrhagia
  - iron malabsorption—eg, investigation of unintentional weight loss or chronic diarrhoea, or secondary to existing conditions such as coeliac disease
  - Anaemia in pregnancy (increased iron demands)
  - investigation of poor growth in infants
  - distinguishing low iron stores from functional iron deficiency—eg, in chronic kidney disease
- response to medical treatment
  - monitoring patients who require repeated transfusions or venesection
  - monitoring response to iron chelators
  - assessing response to iron therapy



Overview of iron absorption, transport, utilisation, and excretion

Serum measures of iron status in states of deficiency and overload

	Serum ferritin	Serum iron	Transferrin/total iron binding capacity (TIBC)	Unsaturated iron binding capacity	% transferrin saturation
Normal values	15-200 µg/L(premenopausal women) 20-300 µg/L(men and postmenopausal women)	10-30 nmol/L	Transferrin 2.0-3.5 g/LTIBC45-81 µmol/L	12-43 µmol/L (men) 13-56 µmol/L (women)	25%-45%
Haemochromatosis with iron overload	↑	↑	↓	↓	↑
Secondary iron overload (eg, repeated transfusion)	↑	↑	↓/↔	↓/↔	↑
Iron poisoning	↔	↑	↔	↓	↔/↑
Iron deficiency	↓	↓	↔/↑	↑	↓
Anaemia of chronic disease/ inflammatory response	↑	↓	↓	↓/↔	↓

Interpretation

Interpretation of iron studies can be challenging because the difficulties listed above affect almost all markers of iron status. Nevertheless, iron studies play an important role in clinical assessment (table above). Reference intervals can vary by laboratory.

Iron overload

Testing for iron overload (increased total body iron stores with or without organ dysfunction) can be triggered by clinical features such as those listed in box 1. Primary iron overload includes inherited mutations in iron regulatory genes (causing iron loading syndromes such as haemochromatosis). Secondary iron overload is associated with other conditions or iatrogenic factors (box 2).

Hereditary haemochromatosis (an autosomal recessive genetic condition caused by mutation of the HFE gene) is the most common inherited cause of iron overload. Homozygosity for the C282Y polymorphism affects 1 in 200 people of northern European descent and accounts for more than 80% of clinically recognised cases. Clinical penetrance varies widely (1%-28% of C282Y homozygotes in population studies).[7] In an unselected population, raised serum ferritin (>200 µg/L for premenopausal women or >300 µg/L for men and postmenopausal women) and transferrin saturation >50% diagnosed C282Y homozygosity with a sensitivity of 90% in men and 75% in women.[8] An approach to hyperferritinaemia has previously been discussed.[6]

Box 2 | Causes of iron overload[6]

Primary

- Inherited mutations in iron regulatory genes (eg, haemochromatosis)

Secondary to other conditions/iatrogenic

- Repeated blood transfusion (eg, beta thalassaemia, sickle cell anaemia)
- Iron loading anaemias (eg, beta thalassaemia, sideroblastic anaemias, chronic haemolytic anaemia, aplastic anaemia)
- Iron and iron containing supplements
- Porphyria cutanea tarda

Tips on requests and interpretation

- Request serum ferritin and transferrin saturation together to assess for iron overload, alongside haemoglobin to identify anaemia and aid treatment decisions (eg, venesection).
- If elevated transferrin saturation is the only biochemical abnormality or the result is borderline, repeat the test on a fasting sample to eliminate a rise caused by dietary iron.
- If transferrin saturation is persistently raised, offer HFE gene analysis with pre-test counselling.
- In C282Y homozygotes, transferrin saturation is the first biochemical parameter to rise. Serum ferritin might be normal in the early stages of the disease, however some patients later develop clinically significant iron overload[7] (organ dysfunction with or without symptoms). Annual monitoring of serum ferritin is proposed in established guidelines.[1] In the absence of local defined protocols, consider referral for further assessment if hyperferritinaemia develops or ferritin is progressively rising.
- Ingestion of therapeutic iron (including iron containing multivitamins) can raise transferrin saturation to levels reaching 100%,[5] and based on our clinical experience we recommend waiting four weeks after cessation of treatment before requesting serum iron, transferrin/TIBC, and transferrin saturation.
- High iron, transferrin, transferrin saturation, and serum ferritin can be seen in acute hepatic injury due to leakage of intracellular contents, and can incorrectly give the impression of iron overload.[5]

Box 3 | World Health Organization definitions of iron deficiency (2001)[9]

- Ferritin ‹15 µg/L
- OR transferrin saturation ‹16%
- OR haemoglobin increase of 1 g/dL after two months of iron supplementation (values vary with ethnicity and pregnancy)

Anaemia is defined as haemoglobin ‹120 g/L in women and ‹130 g/L in men (15 years of age and above).

TEK IMAGE/SPL

Investigating iron deficiency

Biochemical definitions are listed in box 3.[9] Low serum ferritin (<15 µg/L) provides absolute evidence of iron deficiency.[10]

Iron deficiency can result from inadequate intake of iron, inadequate absorption or loss (through bleeding, whether frank or occult), or a combination of both. Prevalence varies by region and is often estimated using anaemia as an indirect indicator.[9] It is quoted as 4.5%-18% in US based population studies.[2]

A fourth form of iron deficiency is functional. In such patients there are sufficient iron stores but they are inadequately utilised. Functional iron deficiency can occur in patients with acute and chronic infectious, inflammatory, or malignant conditions.[11] In certain patients—eg, those with chronic kidney disease, ferritin below the reference interval indicates deficient iron stores; however normal or high values cannot exclude functional iron deficiency.

Diagnosis of functional iron deficiency in patients with an inflammatory condition can be useful in guiding further investigations and treatment (eg, iron supplementation), particularly when the patient has symptomatic anaemia or there is suspected occult blood loss. This is problematic, however, as there is no single reliable and widely available biochemical marker for functional iron deficiency. The British Committee for Standards in Haematology recommends percentage of hypochromic red cells (% HRC) as the best established variable for the diagnosis of functional iron deficiency.[11] %HRC (>6%) is recommended for diagnosis of iron deficiency in chronic kidney disease if the sample can be processed within six hours. Reticulocyte haemoglobin content (<29 pg) is an alternative.[14]

Important points to consider when interpreting iron studies in the context of iron deficiency

- Suspected iron deficiency anaemia is best investigated using serum ferritin. Iron deficiency is confirmed by a level below the reference interval.
- Low serum iron cannot be interpreted in isolation because it might be seen in infection, inflammation, and malignancy as well as iron deficiency.[5] We recommend measuring C reactive protein if serum ferritin is normal or high with serum iron or transferrin saturation below their respective reference intervals.
- Transferrin saturation <16% is poorly specific, as pregnancy, oral contraceptive use, and chronic illness can result in low transferrin saturation without iron deficiency.[15]
- In general, avoid checking iron studies in those with acute inflammatory illness or when C reactive protein is known to be >10 mg/L. For patients with chronic inflammatory conditions, interpretation should be performed cautiously and results discussed with a specialist where there is doubt.

Monitoring response to treatment

Serial measurements of serum ferritin are commonly requested to monitor iron status in patients who are receiving interventions to treat deficiency or prevent iron loading—eg, venesection and iron chelation. Which iron measure is chosen depends on the clinical situation.

Monitor ferritin in those with haemochromatosis undergoing venesection to deplete iron until ferritin is less than 50 µg/L, and maintain ferritin 50-100 µg/L thereafter.[1] Iron studies might be requested to guide treatment with intravenous iron. In chronic kidney disease, serum ferritin concentration <100 µg/L in non-dialysed patients or <200 µg/L in chronic haemodialysis patients is associated with a high likelihood of iron deficiency and a potentially good response to intravenous iron treatment.[14] Response to oral iron therapy in iron deficiency anaemia can usually be confirmed by monitoring the rise in haemoglobin,[2] and re-checking iron studies is not routinely required.

Patient outcome

Results in this patient showed ferritin 682 µg/L (normal range 15-200), iron 34 nmol/L (10-30), transferrin 2.0 mg/L (2-3.5), and transferrin saturation 68% (25-45), in keeping with iron overload. After discussing genetic testing, the patient consented to HFE gene analysis. She was found to be homozygous for the C282Y mutation, confirming the diagnosis of hereditary haemochromatosis. She was referred to a specialist for assessment and venesection therapy.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j2513

EDUCATION INTO PRACTICE

- How might your approach to testing for iron abnormalities in the presence of infection or inflammation change as a result of reading this article?
- Is serum ferritin used routinely in your place of work as an investigation for iron deficiency?
- When and how might you contact specialist teams for assistance with interpreting iron studies results?

STATE OF THE ART REVIEW

Management of chronic pain using complementary and integrative medicine

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This article summarises the State of the Art Review published on bmj.com http://www.bmj.com/content/356/bmj.j1284

WHAT YOU NEED TO KNOW

- Complementary and integrative medicine (CIM) combines Western-style medicine and complementary health approaches
- Chronic pain is the leading indication for the use of CIM, and about a third of adults have used it in this context
- Despite the increased use of acupuncture, research data remain inconclusive about its effectiveness in the management of chronic pain
- Mind-body interventions support active self care, and in doing so can be useful in managing chronic pain
- Overall, the evidence on CIM is inconclusive, resulting in a mixed picture of recommendations for clinicians in guidelines

Complementary and integrative medicine (CIM) combines Western-style medicine and complementary health approaches to treat a variety of conditions. Chronic pain is the leading indication for the use of CIM and about a third of adults have tried CIM. This review (full version on bmj.com) covers the use of CIM in chronic back pain, neck pain, and rheumatoid arthritis.

What is CIM?

CIM includes a variety of practices, which can largely be grouped into traditional medicines, mind-body interventions, physical treatments, and nutrition and natural products (fig 1).

EDUCATION INTO PRACTICE

Up to a third of people with chronic pain will try complementary and integrative medicine (CIM). To what extent do you routinely explore its use with patients?

Can you discuss the evidence base for different types of CIM in people with chronic pain?

What one thing would you do differently as a result of reading this article?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The creation of the full version of this article did not involve patients.

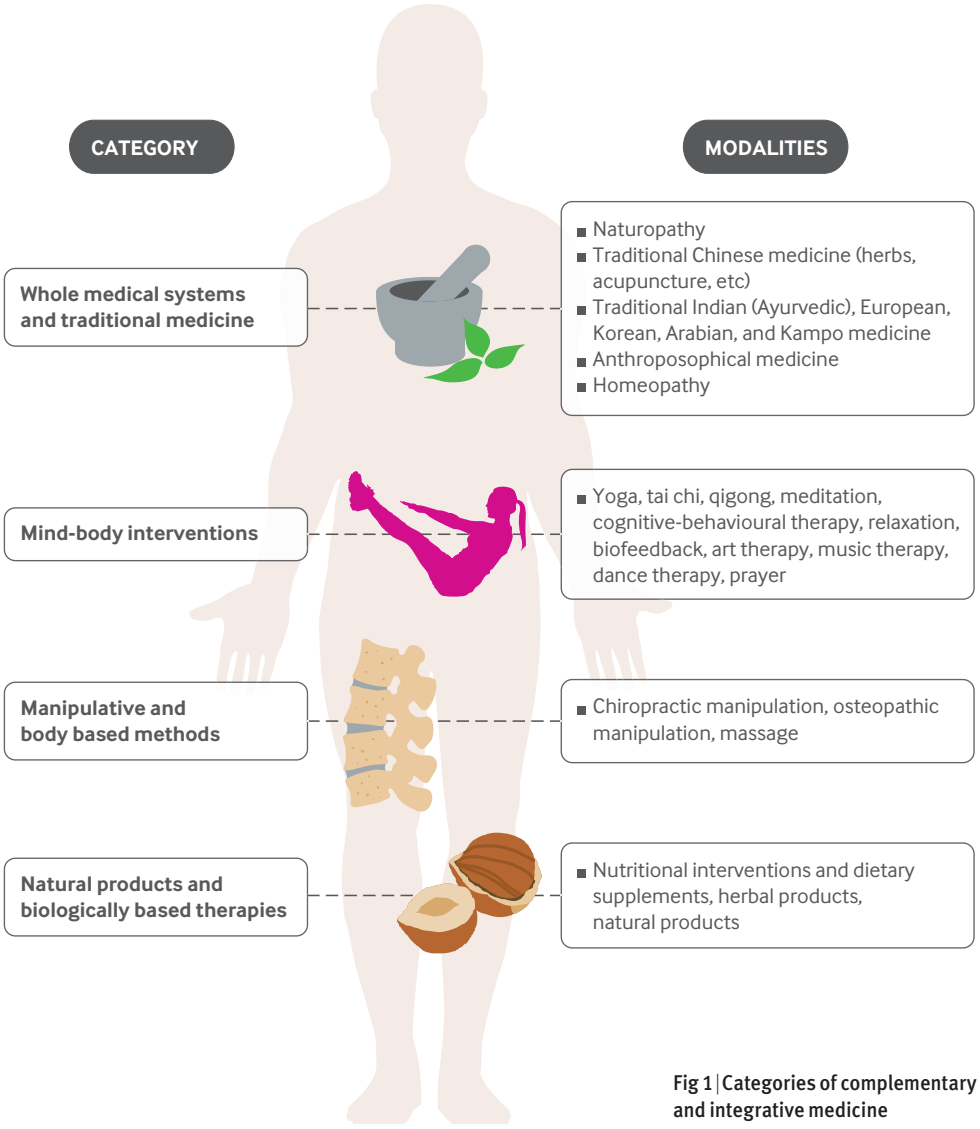

Fig 1 | Categories of complementary and integrative medicine

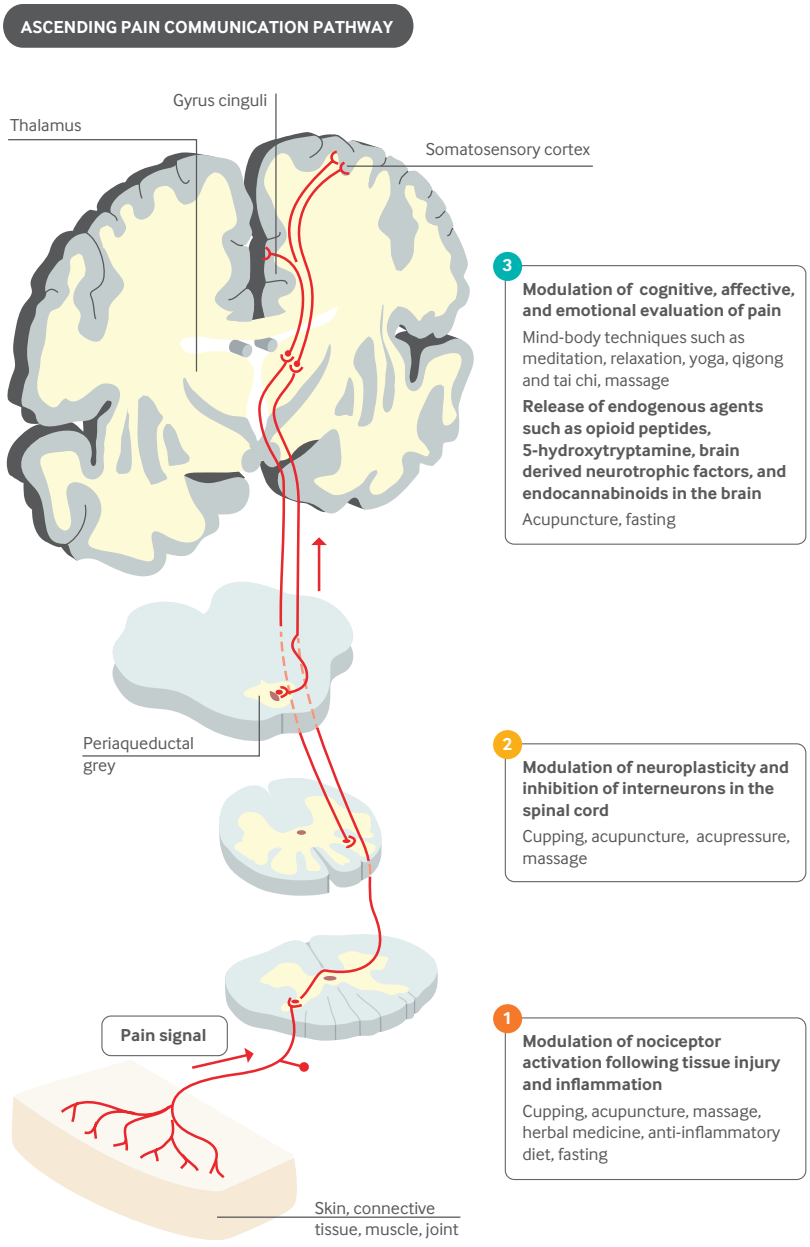

Fig 2 | Mechanisms of action of various complementary and integrative medicine methods

How do CIM practices work?

The mechanisms of action vary and are illustrated in figure 2. Examples include nociceptor activation, changes in neuroplasticity, release of endogenous substances such as opioids, and changes in cognitive responses to pain.

How effective are these practices?

Acupuncture

Systematic reviews and meta-analyses suggest that acupuncture is significantly statistically better than both sham acupuncture and standard care for some but not all types of chronic pain. Evidence is strongest for chronic low back pain but is inconsistent for rheumatoid arthritis. The effect of a course of acupuncture can last 6-12 months. However, studies of acupuncture are often limited by methodological problems so it is not possible to draw firm conclusions.

Mind-body interventions

These practices focus on altering interactions between the brain, mind, body, and behaviour. They are intended to induce relaxation and counterbalance negative, uncontrolled emotion or stress related to disease or symptoms such as pain. Most of these interventions complement active self care and they seem to be useful for comprehensive management of chronic pain. For example, in rheumatoid arthritis, mind-body interventions may improve quality of life and psychological wellbeing.

Nutrition and fasting

The effect of specific diets on chronic back and neck pain is yet to be tested in clinical trials.

Patients with rheumatoid arthritis may benefit and experience pain relief from fasting, a plant based diet, a Mediterranean diet, and possibly an elimination diet. However, much of the evidence was produced before the introduction of disease modifying anti-rheumatic drugs (DMARDs), including biological drugs, so the effects of diet need to be tested alongside these newer drug treatments.

Natural products and herbal medicine

Herbal medicine is popular in Europe and is a cornerstone of most traditional medical systems worldwide. Overall, no strong evidence shows that herbal medicine reduces pain in rheumatoid arthritis. However, small randomised controlled trials suggest that borage seed oil and curcumin (turmeric) may reduce pain in people with rheumatoid arthritis. Evidence that herbal medicine reduces pain in chronic back and neck pain is weak.

Herbal medicine and nutritional supplements generally have minimal adverse effects. However, some herbal preparations such as *Tripterygium Wilfordii* Hook F (TWH; thunder god vine) can increase the risk of serious adverse effects and have important pharmacological interactions with standard drugs. The safety of herbal medicine requires further research.

When do guidelines recommend the use of CIM?

For back pain, the National Institute for Health and Care Excellence's guidelines recommend self management without specifying modalities. Acupuncture should not be offered. The American College of Physicians and the American Pain Society published guidelines on back pain in 2007. Self care options were strongly recommended; for patients who do not improve, the addition of acupuncture, yoga, and some relaxation methods received a weak recommendation.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j1284

CASE REVIEW **Purpura in a 5 year old girl**

A 5 year old girl presented with a one day history of fever, coryzal symptoms, and multiple skin lesions. She also reported abdominal pain and had vomited once. Physical examination revealed hypotension and multiple petechial bruises and purpura-like lesions over the four limbs and the face (fig 1). Over 12 hours, the skin lesions evolved into irregular gangrenous purpura with a central dusky necrosis surrounded by fading redness (fig 2). Blood tests revealed anaemia, thrombocytopenia, high C reactive protein, acute renal failure, and coagulopathy.

1 What is the most likely diagnosis?
2 How would you manage the most likely diagnosis?
3 What are the preventive measures?

Submitted by Chi-Hone Lien, Ming-Dar Lee, and Chien-Yu Lin

Parental consent obtained.

Cite this as: *BMJ* 2017;357:j2530

Fig 1 | Multiple petechial and purpuric lesions

Fig 2 | Irregular gangrenous purpura with a central dusky necrosis surrounded by fading redness

SPOT DIAGNOSIS
An unusual pelvis radiograph

A 95 year old woman was admitted to hospital after a fall. She had sustained a hip fracture. She had Alzheimer's disease, hypertension, and type 2 diabetes mellitus, for which she was taking metformin. A radiograph of the pelvis was obtained (figure). Other than the hip fracture, what is the likely diagnosis?

Submitted by Yu Xi Terence Law, Welras Long, and King Chien Joe Lee

Patient consent obtained.

Cite this as: *BMJ* 2017;357:j2593

If you would like to write a Case Review for Endgames, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

answers

CASE REVIEW
Purpura in a 5 year old girl

1 Purpura fulminans caused by Neisseria meningitidis.
2 Immediate broad spectrum antimicrobial treatment, supportive care in an intensive care environment, and correction of the coagulopathy.
3 Initiate chemoprophylaxis of close contacts and vaccination groups who are at risk.

SPOT DIAGNOSIS
An unusual pelvis radiograph

Right femoral neck fracture (blue arrow) and incidental finding of emphysematous cystitis (red arrow).

CPD READING
0.5 HOURS

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Phytophotodermatitis triggered by parsnips

A 43 year old woman presented to the dermatology on-call service with a burning rash affecting her forearms. Two days before she had been trimming parsnips in her allotment on a sunny day. Examination revealed erythematous streaks in unusual configuration with tense blisters on both forearms (figure). The linearity of several lesions suggested exposure to an external force that had contributed to the process. The woman was diagnosed as having phytophotodermatitis triggered by contact with parsnips and exposure to sunlight. The rash improved with topical dermovate. Phytophotodermatitis is a phototoxic reaction. It occurs after contact with plants containing furocoumarins and concomitant or subsequent UVA from sunlight. Common plants that might cause the reaction include parsnips, lime, parsley, celery, fig, and carrot. The initial blistering and erythema resolve with marked hyperpigmentation and without scarring.

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Patient consent obtained.

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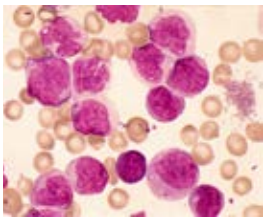
Less is more for responsive chronic myeloid leukaemia



Like so many cancer treatments, tyrosine kinase inhibitors for chronic myeloid leukaemia are both toxic and extremely expensive. Imatinib, dasatinib, and nilotinib typically cost between £20 000 and £30 000 (€22 800–€35 000; $25 500–$38 300) per year, but in a trial of patients with the condition who had been taking a TK inhibitor for three years or more with a stable molecular response, it proved possible to halve the dose and maintain the response (*Lancet Haematol* doi:10.1016/S2352-3026(17)30066-2). Previous trials have shown that it is possible to discontinue them entirely if there is a deep molecular response.

Numbers needed to treat

The concept of numbers needed to treat is nearly 30 years old, but behind their seemingly simple digits, NNTs often hide complexity and uncertainty about treatment effects. An analysis of 51 meta-analyses and study reports in leading general medical journals (*BMC Med* doi:10.1186/s12916-017-0875-8) concludes that authors frequently fall short of basic methodological recommendations in reporting NNTs. As a result, clinicians already struggling to explain benefits (and harms) to patients might be working with figures that are unreliable, as well as poorly matched to the individuals they are talking to.

Lithium and severe unipolar depression

Depression serious enough to cause hospital admission affected 123 712 people in Finland over a period of nearly eight years. In a nationwide cohort study, those who were given lithium for unipolar depression had half the rate of readmission compared with those given standard antidepressants or antipsychotics (*Lancet Psychiatry* doi:/10.1016/S2215-0366(17)30134-7).

Biphasic blood pressure response

When the massive ALLHAT trial was reported in 2002, one striking finding was that the thiazide-like diuretic chlortalidone was more effective than other blood pressure lowering agents in preventing cardiovascular events. Oddly, this has been mostly ignored since. It re-emerges in a new analysis of the trial data (*Hypertension* doi:10.1161/HYPERTENSIONAHA.117.09221), which also for the first time detects a surprising difference in responses to the drug combination used in ALLHAT. Most of the nearly 40 000 participants showed an immediate drop in systolic blood pressure, but about 15% took more than 30 days to respond. Over the following 6-24 months, these delayed responders showed a higher incidence of stroke and heart failure.

Conformal radiotherapy

"A rare and laudable clinical trial" is how *JAMA Oncology* describes a long term prospective trial evaluating the efficacy of stereotactic conformal radiotherapy compared with conventional radiotherapy in 200 young patients with benign or low-grade brain tumours (*JAMA Oncol* doi: 10.1001/jamaoncol.2017.0997). Over five years, it is clear that stereotactic conformal radiotherapy achieves better neurocognitive and neuroendocrine functional outcomes without compromising survival. Trials like this that address important clinical questions simply and over the right period of time are indeed laudable, and sadly rare.

Keep your money, I'm a woman

In the USA, the CMS Open Payment Database reveals industry payments to doctors, and an article (*JAMA Otolaryngol Head Neck Surg* doi:10.1001/jamaoto.2017.0276) looked specifically at 1514 academic otolaryngologists. Of these, 79.4% were men, and they received 88.5% of the $4.3m (£3.3m; €3.8m) that industry lavished on these specialists. Overall, a greater proportion of men received industry contributions than women (68.0% *v* 56.1%). Minerva likes to think that this is due to the superior integrity of women, and not just because they don't happen to belong to the right old boy networks.

Cite this as: *BMJ* 2017;357:j2820