GUIDELINES

Shared decision-making: summary of NICE guidance

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Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

CPD READING
0.5 HOURS

Shared decision-making is widely accepted as a core feature of good healthcare. The National Institute for Health and Care Excellence (NICE) was asked to produce guidance about facilitating shared decision-making and embedding it in everyday practice. For the purposes of the guideline, shared decision-making was defined as "a collaborative process that involves a person and their healthcare professional working together to reach a joint decision about care."

This article summarises the recommendations from the NICE guideline.[2]

WHAT YOU NEED TO KNOW

- Shared decision-making requires organisational leadership and planning as well as practitioner skills
- Shared decision-making is a process requiring a collaborative relationship between patient and healthcare professional; it is not a one-off intervention that healthcare professionals can insert into the consultation
- Use patient decision aids as part of a toolkit to support shared decision-making
- Discuss risks, benefits, and consequences of different options in the context of the person's life and values
- Be aware that people interpret terms such as "risk," "rare," "unusual," and "common" in different ways

Recommendations

NICE recommendations are based on systematic reviews of best available evidence. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Embedding shared decision-making at an organisational level

Shared decision-making is more likely to become standard practice in organisations when it is led from the highest levels of the organisation. This can drive systematic planning and implementation of shared decision-making across the organisation. A dual approach is needed, promoting shared decision-making to people who use services as well as training and supporting staff to deliver it.

The first set of guideline recommendations aims to support this approach in all sizes of healthcare organisation, with recommendations about high level leadership; planning and implementing shared decision-making; sharing information between services; encouraging healthcare professionals to develop and maintain skills and competencies; and promoting shared decision-making to people who use services.

Putting shared decision-making into practice

The guideline recommends things that healthcare professionals can do before, during, and after discussions with patients and service users to facilitate shared decision-making. This includes making sure that information sources are reliable and of high quality, and that they are likely to be accessible to the people for whom they are intended.

Before an appointment

When possible, shared decision-making should begin in advance of any discussion or appointment to maximise the person's ability to participate and to reassure them that shared decision-making will be supported by the healthcare professional they see.

- Offer the person access to resources that encourage them to think about what matters to them, what they hope will happen as a result of the discussion, and what questions they would like to ask.
- Ask the person if they would like to invite a friend or relative to join the discussion, in order to help them understand the resources provided and support them to take an active part in decision-making.
- For people who do not have anyone they would like to ask to support them, and who might find it difficult to share in decision-making, offer additional support—for example, from a nurse, social worker, translator, or volunteer.

During an appointment

- Create a collaborative atmosphere: agree an agenda for the conversation; make sure patients or service users understand that they can participate as much as they want; encourage people to think about what matters to them; allow enough time to answer questions; and offer a further opportunity for discussion.
- Discuss the risks, benefits, and consequences of the possible tests, treatments, or interventions openly: clarify what the person hopes to gain from the intervention and discuss their ideas and

concerns. Explain the potential benefits and harms of each option, including doing nothing.
- Make a record of the discussion (for example, in the clinical notes or care plan) that includes any decisions made along with details of what the person said was important to them in making those decisions. Share this with the person, for example, in a post-clinic letter (letters should be written directly to patients and copied to the relevant healthcare professionals).

Following an appointment

The guideline committee also recommended actions to follow up from appointments.
- Offer people resources to help them understand what was discussed and agreed. This could be a printout summarising their diagnosis, the options and decisions or plans made, and links to high quality online resources options.
- Ensure that information provided after discussions includes details of who to contact with any further questions.
- Offer additional support to people who are likely to need extra help to engage in shared decision-making. This could include encouraging them to record the discussion, explaining in writing the decisions that have been made, or arranging follow-up by a clinical member of staff or a suitable alternative.

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Patient decision aids

The recommendations focus on the need for patient decision aids (PDAs) to be quality assured. They also stress that PDAs are a tool to support shared decision-making and that shared decision-making is not dependent on them.

The committee recommended the following actions for PDAs in shared decision-making.
- Use patient decision aids as one part of an overall "toolkit" to support shared decision-making, alongside the other skills and interventions outlined in the guideline.
- Only use a patient decision aid if it is:
  - Up to date and reflects evidence-based best practice
  - Relevant to that discussion, and the decision that needs to be made
  - Relevant to that clinical setting.
- Before using a particular decision aid, healthcare professionals should be familiar with it, including how it will help people to understand which option is best for them.

The committee also made recommendations for organisations to maintain a database of decision aids that are regularly reviewed and updated, or signpost staff to decision aids produced by national bodies such as NICE, and to ensure they are available in different ways to support people's needs (for example, in print, online, or in different languages).

Risk communication

Finally, the committee updated the section on risk communication from the NICE guideline on patient experience in adult NHS services[3] and brought it into the shared decision-making guideline. Rather than referring to risk communication, the committee agreed it was better to talk to patients about "risks, benefits, and consequences" since people often interpret the term "risk" as negative. They recommended that healthcare professionals:
- Discuss risks, benefits, and consequences in the context of each person's life and what matters to them.
- Personalise information on risks, benefits, and consequences as much as possible.
- Make it clear to people how the information they are providing applies to that person personally and how much uncertainty is associated with it.
- Have a good understanding of the information and how to apply and explain it clearly.

The committee also made a series of recommendations about the best ways to communicate numerical information to people. They agreed that this would vary according to the person but that generally it was best to:
- Use a mixture of numbers and pictures (for example, numerical rates and pictograms or icon arrays) to allow people to see both positive and negative framing at the same time.
- Use numerical data to describe risks if available (different people interpret terms such as "risk," "rare," "unusual," and "common" in different ways).
- Use absolute risk rather than relative risk and natural frequencies (for example, 10 in 100) rather than percentages (10%).
- Be consistent when using data. For example, use the same denominator when comparing risk.
- Present a risk over a defined period of time (months or years) if relevant. For example, if 100 people are treated for 1 year, 10 will experience a given side effect.
- Use both positive and negative framing. For example, treatment will be successful for 97 out of 100 people and it will be unsuccessful for 3 out of 100 people.

Competing interests: See bmj.com.

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

GUIDELINES INTO PRACTICE
- As a healthcare professional in a busy setting with limited continuity of care, how can you promote shared decision-making within your everyday practice?
- When you organise or commission clinical services, how can you ensure that practitioners' working arrangements support them to practise shared decision-making, and that they are competent to do so?

PARTNERSHIP IN PRACTICE

Access to personal electronic health records during covid-19

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0.5 HOURS

Rapid rollout of electronic personal health records for patients accessing sexual health, contraception, and abortion care at University Hospitals Plymouth NHS Trust has benefited patients and health professionals alike

Zoe Warwick, consultant in sexual and reproductive health

At a conference in 2013 I heard how providing patients with electronic personal health records (ePHR) could improve patient services. The benefits—to patients, clinicians, and the NHS—of providing people with access to and control of a full digital version of their medical records seemed obvious, and I requested to be part of a pilot project. Eight years on, access by patients to ePHR is now integral to how we deliver care for our HIV positive patients, and since the onset of the covid-19 pandemic, for those accessing sexual health, contraception, and abortion care.

In March 2020, when face-to-face communications were limited by covid-19 restrictions, the adoption of ePHR via the PatientsKnowBest platform provided a secure way of communicating with patients within established information governance protocols. The system invites patients to register with the ePHR, and creates password protected access. Clinicians log on to a professional interface to access functions such as messaging, image transfer, and patient symptom diaries. Activity is recorded and can be used for future consultations.

Using ePHR, patients and healthcare professionals can exchange messages and data, including encrypted clinical images for diagnostic purposes; and healthcare providers can carry out pre-assessments ahead of virtual consultations for abortion care, provide information about medication, and offer advice about managing health conditions tailored to people's individual needs and circumstances. Patients can also use their ePHR to track communication between the different providers involved in their care—including their GPs—keep symptom diaries, and upload relevant documents and biometric data. Real time access to test results is provided through integration with our laboratory IT system.

This use falls short of sharing all information as the ePHR is not integrated with our hospital's electronic patient record and consultation details are not available to patients. We are currently transitioning to an electronic patient record which will allow this and will also enable online appointment booking, requests for tests and services, and accessing results. We will look at integrating PatientsKnowBest with this new system.

Challenges and lessons learnt

Offering patients access to an ePHR made us realise we needed to find out what our patients understood by "confidentiality" of medical records. We learnt from our cohort of 340 patients with HIV that understanding of the extent to which information is shared varies. Around a third thought all records were widely shared within healthcare services, one third thought all records were kept within the department and not shared at all, and one third had not given the issue much thought.

This made us aware of the need to explain the status quo with respect to confidentiality of medical records and information sharing in our HIV service, where information about HIV care was recorded separately from general hospital records. As we talked to our patients and told them what the new system would involve and enable them to do, many clearly highly valued the fact that access and use of ePHR would embed a "not without my knowledge and consent" approach to sharing of information and test results. Formerly, not all results were shared with patients and they were not always copied in to all communication between clinicians.

Age, gender, and ethnic background did not predict interest in registering to get ePHR, and within nine months more than 90% of our patients signed up for them. Those without internet access at home logged on via their phones. Approximately half of those registered use the system to facilitate care—for example, to set up remote consultations and exchange messages with their health professionals. Some find this more convenient than telephone consultations. Others use their ePHR to aid communication—for example, they show their GPs their latest blood results or bring healthcare providers together for conversations through the messaging system. There is a willingness to do this more, but a lack of understanding of how to use the system and the fact that medical electronic

KEY MESSAGES

- Standards and good practice guidelines now cover ePHR, and the push for digitally integrated infrastructures that empower patients should nudge clinicians and healthcare systems to prioritise integration of ePHR into IT systems and care delivery models, to realise major advances in quality and cost efficiency[3]
- Improved user interface design is needed to enable clearer presentation of results accompanied by an explanation of what they mean
- Patient understanding and use of personal health information and data depends on access to and support to use a digital healthcare tool that works as well as the digital tools they use in other areas of their lives

patient records in primary and secondary care are not integrated with PatientsKnowBest limits patients' ability to maximise the potential of holding ePHR. Some feedback we have received includes:

"Would definitely be useful for my GP to be able to log in and look at results etc. For example, if I come to see my consultant, they always ask how you have been...they could simply log on and see what medical issues or appointments I have had with my GP between check ups."

Some find the data difficult to interpret:

"I would use it to see my results, but I can't understand them. A simple CD4/viral load graph would be better and easier to understand."

System design needs to be informed by patient experience and views of functionality. It is also essential to support patients to acquire sufficient digital literacy to use ePHR as a tool to manage their own health.[1] This can be time consuming, but if patients try to engage and fail, re-engaging them is challenging.

System design needs to be informed by patient experience and views of functionality

Professional reluctance to give patients full access and control of ePHR

When we started implementing ePHR we learnt (as others have) why some healthcare providers are reluctant to embrace them. Comments included:

"It adds no value to us as clinicians"

"Results would go directly to the patient, how would they manage with this information, what if they have the information before I do?"

How the covid-19 pandemic has changed mindsets and practice

In March 2020, staff unfamiliar with the use of ePHR by patients suddenly appreciated their value and we found that both they and our patients preferred telephone consultations supported by images taken by patients on their smartphones and shared in the ePHR, rather than video consultations.[2]

Sharing images is a two step process. Firstly, the patient registers with the system and then after the telephone consultation logs on separately, takes a photo (of a rash, for example), uploads it, and then sends it. Healthcare professionals feel comfortable with this process as the consent for sharing is in the patient's hands. The patients in turn know that the images held on their digital record are controlled by them and are more secure than if they were to share images by email. Image quality on the ePHR is better than that produced via video link, and so improves diagnostic accuracy of rashes, lumps, and ulceration, where visual diagnosis is backed up by tests sent by post where possible.

Benefits so far

Patient satisfaction with using ePHR to facilitate virtual consultations is high.[2] Patients do not misuse the system and only get in touch if they have relevant concerns. If the issues they raise aren't about something we can help with directly, the ePHR can facilitate signposting, referral, and education. Unnecessary outpatient visits can be avoided, patient understanding of how to interpret results facilitated, and self-management developed.

Fatima Joll-Elawany: patient

I'm a 54 year old woman who received a diagnosis of HIV in 1989. Over the years my consultants have always tried to be accessible in emergencies but the recent adoption of the PatientsKnowBest system has stepped up communication to a new level. I can now email my consultant any time and if the system shows she is not available, I can contact another member of the team.

I've been too ill at home for the covid-19 pandemic to have affected me a lot, but I am aware how it has changed the world; and that telephone and video consults are now common. Using the PatientsKnowBest system has improved the control I have over my medical care. For example, my GP was having no success treating a recurring infection I had. It can take over a week to get a GP appointment, so exchange is slow and interaction over weeks had not solved the problem. So I emailed one of my HIV doctors. The message was swiftly passed on to another doctor who asked me to send photos. He looked at them that day, diagnosed the nature of the infection, and put the medication in the post. Within days I was getting better. Obviously there are times when face-to-face consultations are essential, but during the pandemic it's been easier and definitely safer to use the PatientsKnowBest system.

Living with HIV can be challenging and while the disease is no longer the death threat it once was, I think some health professionals do not realise this. Messing with medication or prescribing incompatible medications can be life threatening. The PatientsKnowBest system allows me to email my medical team and ask them to communicate with other health professionals who prescribe medicines for me. If I suspect a problem, I can also use PatientsKnowBest to email questions in relation to it. When the doctors do their rounds the next day they can see my concerns and any exchanges I have had with health professionals. If a problem is identified, my HIV doctor or one of her team will phone and sort things out immediately.

Using PatientsKnowBest has also facilitated conversations across teams. I have found this to be very helpful. For example, when my care has involved the upper gastrointestinal team or mental health team, we have been able to work together to achieve the best possible outcomes. One of the problems I have found is that many professionals have never used or even heard of PatientsKnowBest, so this resource is not used to its full potential. I have lost count of the times when I have had a discussion with a doctor and refer to the results of a recent blood test, only to find that they have not seen the result. When this happens I open PatientsKnowBest and show them the results, which they find helpful and time saving.

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RATIONAL TESTING

Investigating raised creatine kinase

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages: https://www.bmj.com/about-bmj/resources-authors/article-types.

0.5 HOURS

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

A 76 year old man with hypercholesterolaemia is referred to the lipid clinic because of persistently raised creatine kinase activity of 1000 IU/L or above (reference range 40-320 IU/L) after trying multiple statins. He describes no significant myalgia but had some proximal muscle weakness, which is demonstrated when he stands up from a seated position and when walking upstairs.

Creatine kinase (known previously as creatine phosphokinase or CPK) is distinct from creatinine and is a biomarker of muscle damage. The reference range for normal creatine kinase is 40-320 IU/L for men and 25-200 IU/L for women, though this may vary across laboratories and assays. Creatine kinase levels are dependent on age, sex, and muscle mass: the upper limit of normal (ULN) for men is higher than in women, and ageing is associated with reduced muscle mass, so minor increases in creatine kinase may indicate a greater extent of muscle damage in older adults.[1]

Pathologies involving muscle include myalgia (muscle pain with no creatine kinase rise), myopathy (muscle pain with creatine kinase rise), and rhabdomyolysis (muscle pain, weakness, and/or swelling with myoglobinuria and elevated creatine kinase). Creatine kinase can also be elevated without any muscle symptoms.[2] Moreover, no clear correlation exists between creatine kinase activity and the extent of actual muscle injury. That said, creatine kinase >5000 IU/L (10-50 times the upper limit of normal) should prompt consideration of rhabdomyolysis.

WHAT YOU NEED TO KNOW

- Most elevations in creatine kinase are physiological or secondary to exercise and do not require further investigation unless likely to be secondary to newly prescribed drug therapies
- Persistent symptomatic changes in creatine kinase warrant investigation for underlying secondary causes including endocrine, autoimmune, and genetic disorders
- Measure creatine kinase if a patient on statin therapy develops muscle pain

What can cause an elevated creatine kinase?

Most cases of raised creatine kinase can be attributed to normal variants or the acute effects of exercise, especially if associated with dehydration.[3] Elevations in creatine kinase can also arise from muscle trauma induced by seizures or surgery, other injuries, or direct drug toxicity[4] (table 1). Drug interactions between pharmaceuticals metabolised through the cytochrome P_{450} 3A4 pathway, including macrolide antibiotics such as clarithromycin, antifungals such as ketoconazole, and statins (simvastatin >atorvastatin), are a common cause of elevated creatine kinase.[7]

Endocrine disorders, autoimmune or inflammatory myopathies,[8] and thiamine deficiency (often associated with excess alcohol consumption[6]) can also result in a raised creatine kinase. Elevations may be multifactorial, caused by an interaction between patient demographic factors, concomitant pathology, and/or drug therapies such as statins. Finally, a small percentage of people with creatine kinase elevations are ultimately found to have a hereditary myopathy.[9 10] By contrast, central nervous system disorders such as parkinsonism, myasthenia gravis, or multiple sclerosis do not usually cause elevations of creatine kinase unless complicated by inflammatory myositis.[11] The use of creatine supplements has no effect on creatine kinase level but does affect plasma creatinine.

Asymptomatic raised creatine kinase can occur in all ethnic groups. An enriched cohort study of 1444 Dutch adults who had creatine kinase measured after three days of rest found creatine kinase levels above quoted reference intervals in 49% of participants of African descent, compared with 13% and 23% in participants of white European and South Asian descent, respectively.[1 12] Typically, levels are 200-2500 IU/L, but 10-15% of patients can have raised creatine kinase up to 5000 IU/L .

What is statin associated myalgia and myopathy?

Statin associated myalgia is pain induced after statin treatment accompanied by no or minimal creatine kinase rise (<4×ULN). When pain is accompanied by creatine kinase >4×ULN this is defined as statin associated myopathy.[13 14] The severity of statin associated myotoxicity[13 15] is graded on clinical symptoms and creatine kinase levels (table 2).[13 14] Statin associated myalgia and/or myopathy occurs most often within one to three months of starting a statin,[16] but it can present later, such as when the statin dose is increased (and resolves with dose reduction), or be precipitated when an interacting medication is initiated.[5-14] Most statin

Table 1 | Causes of an elevated creatine kinase[5 6]

Category	Cause
Exercise, trauma, diet	Exercise related: • Resistance type training • Extreme exercise, eg, ultra-endurance sports
	Muscle trauma: • Seizures • Surgery • Other trauma including crush injuries
	Alcohol excess
	Thiamine deficiency
Drugs	Adrenergic stimulants, eg, MDMA, cocaine, amphetamines
	Lipid lowering therapies: • Statins (especially at high doses) Cytochrome CYP3A4 interactions • Fibrates • Macrolide antibiotics such as clarithromycin • Systemic antifungals, eg, ketoconazole
	Dermatological therapies • Systemic retinoids
	Oncologic drugs • BRAF inhibitors, PD-L1 antagonists
	Antiretroviral therapies for HIV • Mitochondrial effects, eg, nucleoside analogueues • Cytochrome metabolism interactions (especially with protease inhibitor-ritonavir combinations)
	Rheumatological drugs • Hydroxychloroquine, colchicine
	Neurologic or psychiatric drugs, especially if related to neuroleptic malignant syndrome • Clozapine • Antipsychotics (eg, olanzapine)
Endocrine	Severe hypothyroidism (TSH >100 m IU/L)
	Cushing's disease
	Acromegaly
	Hyperparathyroidism
	Hyperthyroidism (rare)
Autoimmune disease	Systemic lupus erythematosus Rheumatoid arthritis Polymyalgia rheumatica Coeliac disease (myopathic form) Dermatomyositis Polymyositis Immune mediated necrotising myopathy Sporadic inclusion body myositis
Hereditary myopathies	Non-metabolic myopathy (eg, myotonic dystrophy, Duchenne muscular dystrophy, Becker muscular dystrophy, inclusion-body myositis) Metabolic myopathy (eg, glycogen storage disease)

Ask patients with a raised creatine kinase above the ULN who are asymptomatic or have mild symptoms about their exercise history

adverse effects are dose dependent, but lower intensity statins that lower low density lipoprotein cholesterol to lesser degrees are not less myotoxic.[17] In a prospective cohort study of 107 835 patients taking a statin, 17.4% of patients had "a statin related event" of some kind, but only 4.7% of patients in the study had myalgia/myopathy, and only 992 patients (0.9%) had creatine kinase >3-10×ULN. Statin rechallenge occurred in 6579 of 11 124 of patients who had discontinued a statin, and 92% of these patients were still taking a statin 12 months later, suggesting minimal or tolerable side effects on re-challenge.[18] Meta-analyses show lower rates of muscle related adverse events with rosuvastatin and atorvastatin compared with pravastatin and simvastatin.[17]

Statin intolerance is defined as myalgia, raised creatine kinase, or both in response to three different statins on sequential challenge, and is associated with lean body mass, drug distribution, and drug metabolism, which vary by age and sex.[5-14] Personal or family history of muscle disease or cramps (odds ratio (OR) 4.0; 95% confidence interval (CI) 3.5 to 5.0), previous statin related muscle pain (OR 10; 95% CI 8 to 12) or an asymptomatic raised creatine kinase (OR 2.0; 95% CI 1.6 to 2.7) are associated with increased risk of statin intolerance.[5 19] Comorbidities such as untreated hypothyroidism, chronic kidney disease, liver impairment, and possibly low vitamin D levels can also exacerbate statin intolerance.[14] Autoimmune necrotising statin induced myositis is a rare cause of severe myositis and an absolute contraindication to further use of these drugs.[14]

What is the next investigation?

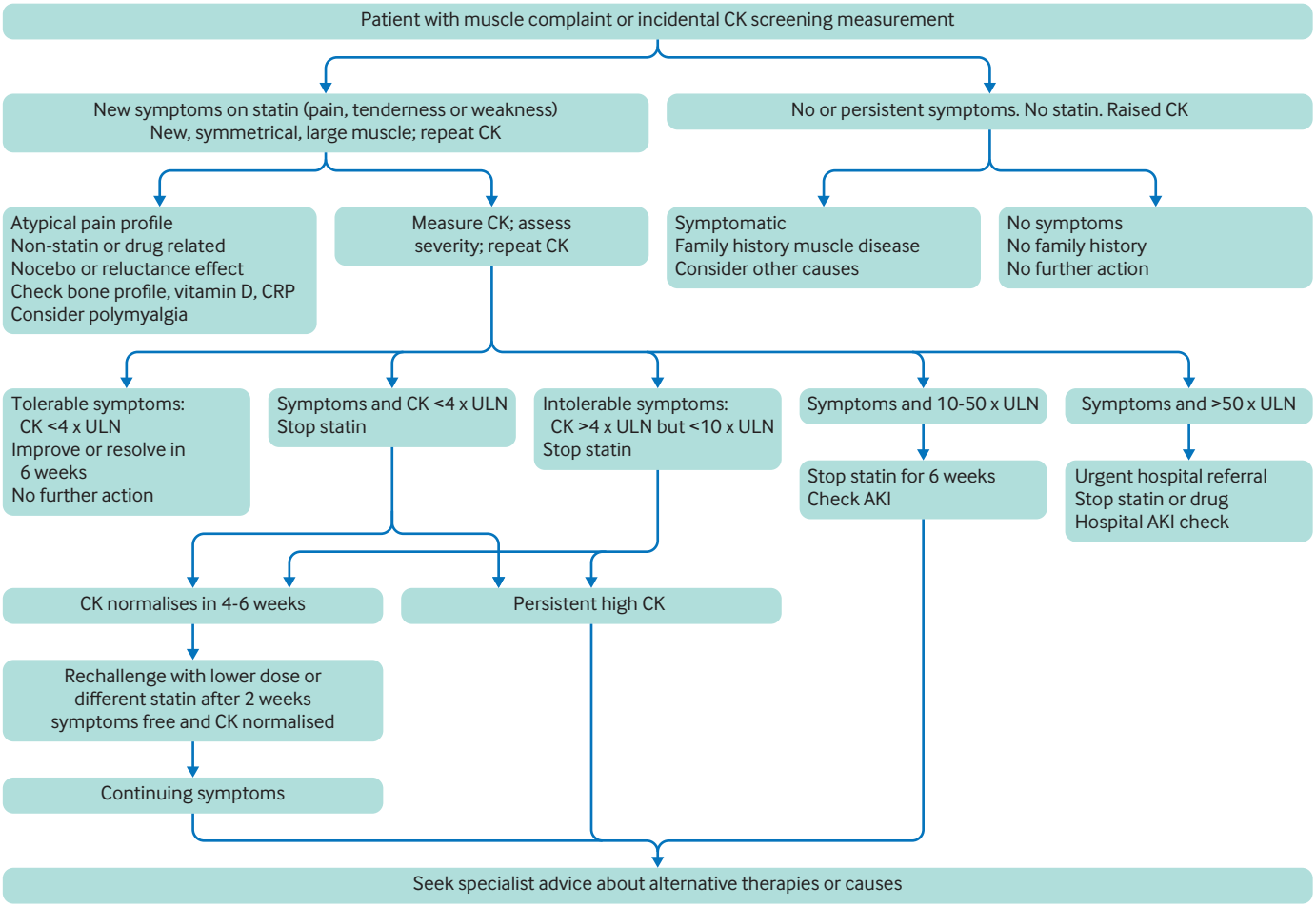
Creatine kinase <4×ULN

Most occurrences of raised creatine kinase <4×ULN (approximately <500 IU/L) are incidental to exercise or other transient causes and will resolve spontaneously.[20] A recurrent stable high creatine kinase in an asymptomatic individual needs no further investigation. Ask patients with a raised creatine kinase above the ULN who are asymptomatic or have mild symptoms about their exercise history, especially anaerobic resistance exercise. If patients with elevated creatine kinase <4×ULN have a recent history of high intensity exercise, treatment consists of rest and adequate hydration. In these patients, creatine kinase typically normalises after 3-7 days and this should be confirmed on re-testing creatine kinase after one to two weeks. Review lifestyle factors and current medications, as well as any personal or family history of muscle disease in patients with elevated creatine kinase in order to guide targeted further testing.

Table 2 | A consensus group standardised classification of statin related side effects and their frequency in patients taking statins.[14] Adapted from Alfirevic et al[2]

Statin related myopathy grade	Phenotype	Approximate incidence	Symptom	Plasma creatine kinase level	Resolves with cessation of precipitant
0	Creatine kinase rise	1-26%	Asymptomatic	<4×ULN (approx <500 IU/L)	Yes
1	Myalgia (mild)	0.2%	Muscle ache	<4×ULN (approx <500 IU/L)	Yes
2	Myalgia (severe)	0.1%	Muscle ache	<4×ULN (approx <500 IU/L)	Yes
3	Myopathy (mild)	0.05%	Muscle ache	4-10xULN (approx 500-1000 IU/L)	Yes
4	Myopathy (severe)	0.05%	Muscle ache (severe)	10-50×ULN (approx 1000-5000 IU/L)	Yes
5	Rhabdomyolysis	0.001-0.002% 1 in 50 000-100 000 patients treated	Muscle aches (severe)	>50×ULN (approx >5000 IU/L) or >10×ULN (approx >1000 IU/L) with acute kidney injury	Yes, eventually
6	Autoimmune statin related necrotising myositis	1-2 per million patients treated	Muscle ache (continuous and severe)	Creatine kinase >10×ULN (approx >1000 IU/L) HMGCR Ab(+) in plasma HMGCR staining on muscle biopsy	No

HMGCR=2-hydroxy-methyl-glutaryl CoA reductase; ULN=upper limit of normal



General principles of investigation and management of raised creatine kinase

Creatine kinase 4-10×ULN

Consider secondary causes of elevated creatine kinase in patients with a creatine kinase of 4-10×ULN and vague or mild symptoms, of which hypothyroidism or drug therapies including statins are the commonest.[3] Initial blood tests should include kidney, liver, and thyroid function tests, adjusted serum calcium, phosphate, magnesium, and 25 hydroxy-vitamin D status. Other endocrine profile and inflammatory markers could also be considered if indicated by clinical assessment. A small number of patients in this group have muscle disease with either an autoimmune, endocrine, or genetic cause, some of which are treatable (table 1).[5 11] Autoimmune causes are more frequent in symptomatic patients over 50-60 years with raised creatine kinase, and these patients might benefit from referral to rheumatology.

Creatine kinase >10×ULN

Patients with a creatine kinase >10×ULN usually present with muscle pain, weakness, and/or swelling, and warrant urgent referral for assessment if renal impairment (eg, oliguria and/or acute kidney injury) and myoglobinuria is present. Myoglobinuria is frequently seen in rhabdomyolysis but is not often directly measured; an approximate surrogate is the use of 2+haematuria on dipstick urine testing without detectable red cells on urine microscopy.[21]

Patients with rhabdomyolysis and acute kidney injury have worse outcomes[22] and require urgent assessment and consideration for admission, since dialysis may be required. If creatine kinase is >50×ULN and renal function is normal, then a referral to a metabolic/neurology clinic is appropriate to investigate a possible metabolic or genetic myopathy, such as muscular dystrophy syndromes.

Patients with a history of muscle pain

Patients with a history of muscle pain and persistently elevated creatine kinase on two or more occasions merit further investigation.[11] In any patient with a chronic history of muscle weakness or elevated creatine kinase, it is reasonable to exclude significant renal disease (renal profile, urine dipstick) and hypothyroidism in the first instance (figure). Target further investigations around any additional symptoms or family history, seeking to elicit features of endocrine disease (hypopituitarism, Cushing's disease), autoimmune disease (especially if the patient has autoimmune hypothyroidism or vitamin B_{12} deficiency), or hereditary myopathies (table 1). Some patients with a persistently raised creatine kinase, weakness, and a strong history of statin intolerance, for example, may have underlying genetic muscle disease. These patients may warrant referral to a neurology or adult inherited metabolic errors service.

Treatment of raised creatine kinase

Treatment of elevated creatine kinase depends on the underlying cause: elevated creatine kinase attributable to exercise or trauma resolves with time and rest, while any substantial metabolic abnormalities or autoimmune conditions need to be treated. As drug interactions are a common cause of raised creatine kinase, medications may need to be stopped or changed. Most cases of statin associated myalgia or myopathy with creatine kinase <4×ULN can be managed by reducing the dose of the current statin or switching to a second generation statin (atorvastatin or rosuvastatin).[13-17] However, in patients on a statin with myalgia and creatine kinase >4×ULN, it would be sensible to discontinue the statin, maintain a high fluid intake and monitor whether the symptom resolves.[5-14] If creatine kinase is >10×ULN, discontinue the statin immediately because of the possibility of rhabdomyolysis, and monitor creatine kinase before considering rechallenge.[13 14]

If patients are statin intolerant after rechallenge, very low dose statin therapy[3 15] or other lipid lowering medications (eg, ezetimibe, bempedoic acid) may be indicated. Patients with cardiovascular disease or familial hypercholesterolaemia and a contraindication to statins (eg, diagnosed muscle disease) may be candidates for a pro-protein convertase subtilisin kexin-9 inhibitor (prescription of which currently requires referral to secondary care in the UK).

When should I measure creatine kinase?

Creatine kinase was previously a routine part of statin initiation and monitoring, but this is now discouraged. In the UK, the National Institute for Health and Care Excellence (NICE) recommends measuring creatine kinase before starting a statin in people who have had "persistent generalised unexplained muscle pain" (with or without lipid lowering therapy); statins should not be started in patients with creatine kinase >5×ULN in two tests seven days apart.[19] NICE also recommends against measuring creatine kinase in asymptomatic patients taking a statin.[19] Other guidelines suggest a baseline creatine kinase level might be useful in patients at risk of statin associated myopathy (eg, personal or family history of muscle pain, prior autoimmune disease, renal disease (especially nephrotic), and patients living with human immunodeficiency virus).[5-16] Systemic illnesses such as sepsis, lung infarction, ischaemic bowel, malignancy, bacterial, or viral infection (eg, influenza) can cause myositis, and measurement of creatine kinase is of little clinical value unless acute kidney injury secondary to rhabdomyolysis is suspected.

Case outcome

In the case described at the start of this article, secondary and common autoimmune causes were excluded. The patient was referred to the neuromuscular service in light of persistent raised creatine kinase and muscle symptoms. A muscle biopsy showed an inflammatory myopathy suggesting a contribution of statin therapy to his creatine kinase rise and myopathy. The statin was discontinued, creatine kinase was monitored, and his muscle pain resolved. His hyperlipidaemia was treated with ezetimibe, which partially corrected the lipid profile (LDL-C 3.5 mmol/L). His creatine kinase stabilised at 600 IU/L.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the creation of this article

EDUCATION INTO PRACTICE

- How would you offer advice on exercise to a patient with raised creatine kinase?
- In how many patients have you measured creatine kinase in the past year and how many had levels greater than 1000 IU/L?
- Think about when you last reviewed a patient with muscle ache and a raised creatine kinase. What advice and investigations did you perform and what might you do now?

HOW THIS ARTICLE WAS MADE

A Pubmed search was performed using the terms "creatine kinase" and "review" (2455 results) and then restricted to "algorithm" (51 publications), and "Cochrane" (102 results). Relevant articles were identified after individual review.

Competing interests: See bmj.com.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.n1486

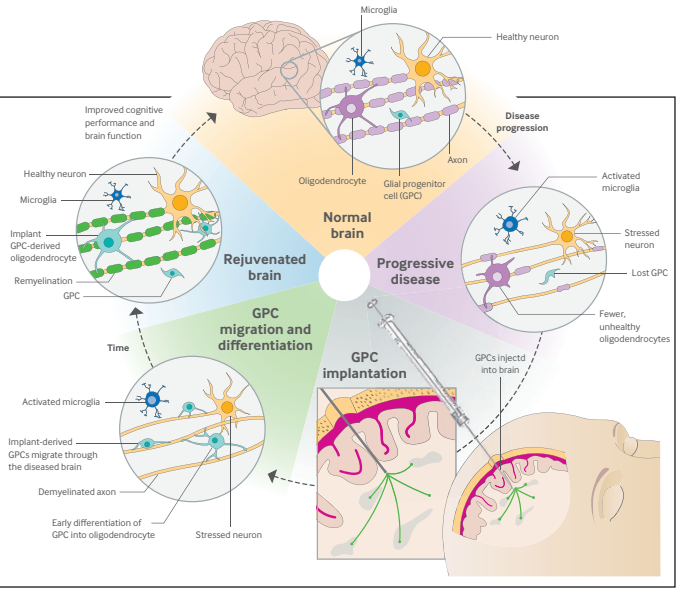
ONLINE NOW

Regenerative medicine for neurological diseases: a State of the Art Review

A State of the Art Review published this week on bmj.com (https://www.bmj.com/content/373/bmj.n955) evaluates the rationale, paradigms, and translational progress of regenerative neurosurgery.

Pioneering efforts over the past three decades have introduced cells, neurotrophins, and genes with putative regenerative capacity into the CNS to combat neurodegenerative, ischaemic, and traumatic diseases. The review looks at ongoing translational efforts in Parkinson's disease, amyotrophic lateral sclerosis, stroke, and spinal cord injury, using these to illustrate the principles, challenges, and opportunities of regenerative neurosurgery.

See all clinical reviews at https://www.bmj.com/education/clinical-review



CASE REVIEW

Why can't I see in the dark?

A man in his 70s presented with an eight month history of bilateral progressive visual loss. Initially, he could see well in bright daylight but was unable to see in the dark. He described his peripheral vision as becoming darker over time, until eventually he was unable to see in bright or dim light conditions.

He was congenitally deaf and communicated with sign language. He had no previous visual problems. Both parents and two siblings were also congenitally deaf; no family members were visually impaired.

Over the previous year the patient had lost about 13 kg in weight, despite consuming a healthy balanced diet, had chronic abdominal discomfort, and passed frequent loose, pale stools. Previous investigations showed microcytic anaemia with low ferritin levels (14 µg/L, normal range 33-490 µg/L).

On examination, the patient's visual acuity of both eyes was reduced to counting fingers and he had severely constricted visual fields (figure). His pupil reactions were normal, and his fundi appeared normal.

Blood tests showed the patient had anaemia with multiple vitamin deficiencies (table).

1 **Which vitamin deficiencies can cause visual loss?**
2 **What are the differentials of night blindness?**
3 **What is the most likely cause of this patient's visual loss?**

Submitted by Selina Khan, Sophie Beavers, Claire Rice, and Denize Atan (Denize.Atan@bristol.ac.uk)

Patient consent obtained.

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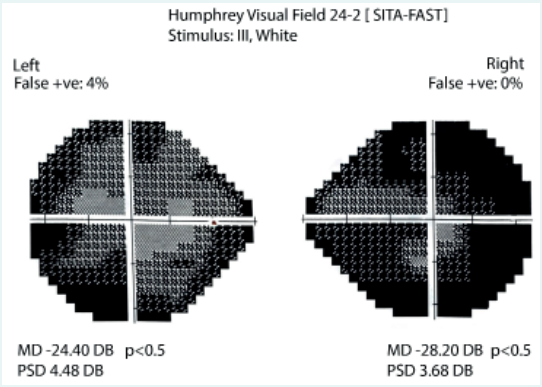

Humphrey 24-2 visual field test results of both eyes. Dark shading peripherally and lighter shading centrally indicate profound constriction of visual fields

Relevant blood test results

Test	Result	Normal range
Haemoglobin	113	130-170 g/L
Mean corpuscular volume	77.7	83-100 fL
White cell count (with normal differential)	6.16	4.0-11.0×10^9/L
Platelets	665	150-450×10^9/L
Erythrocyte sedimentation rate	6	<20 mm in first hour
C reactive protein	13	<6.0 mg/L
Vitamins:		
A	<0.1	1.1-3.4 mmol/L
B_9 (folate)	1.5	2.5-19.5 mg/L
B_{12} (cobalamin)	1778	180-900 ng/L
D	27	>50 nmol/l
E	<1.5	10.2-39 mmol/L

answers

CASE REVIEW **Why can't I see in the dark?**

1 Which vitamin deficiencies can cause visual loss?

Deficiencies in vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folate), B12 (cobalamin), and copper can affect optic nerve function.

Night blindness is not a symptom of optic neuropathy but can be caused by vitamin A deficiency.

Although vitamin D deficiency is a risk factor for optic neuritis and multiple sclerosis, it does not directly affect retinal or optic nerve function.

Vitamin E deficiency can affect retinal function, but it is a rare cause of visual loss.

2 What are the differentials of night blindness?

Inherited retinal disease

Progressive—rod-cone dystrophy—eg, retinitis pigmentosa, Usher's syndrome

Non-progressive—stationary (eg, congenital stationary night blindness, Leber's congenital amaurosis)

Nutritional deficiencies

Vitamin A

Vitamin E

Drugs

eg, Desferrioxamine and isotretinoin toxicity

Neoplasia

Cancer associated retinopathy, most commonly, lung cancer: this is rare

3 What is the most likely cause of this patient's visual loss?

Vitamin A deficiency caused by malabsorption.

The pigment rhodopsin, expressed in rod photoreceptors, is made from the vitamin A derivative, retinol; rod photoreceptors are responsible for night vision. Cone photoreceptors express other pigments in addition to rhodopsin; therefore, daytime vision only becomes affected after prolonged, severe vitamin A deficiency.

Multiple vitamin deficiencies, despite a healthy balanced diet, suggest underlying malabsorption. Weight loss might, or might not, be present. Refer to gastroenterology for specialist investigations.

LEARNING POINTS

- Nutritional deficiencies are potentially reversible causes of vision loss, if treated early.
- Investigate patients with a single micronutrient deficiency for associated deficiencies in other micronutrients and for underlying malabsorption syndromes.
- Exclude treatable causes of visual loss—for example, poor diet and malabsorption, before investigating for genetic diseases.

PATIENT OUTCOME

See bmj.com.

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0.5 HOURS

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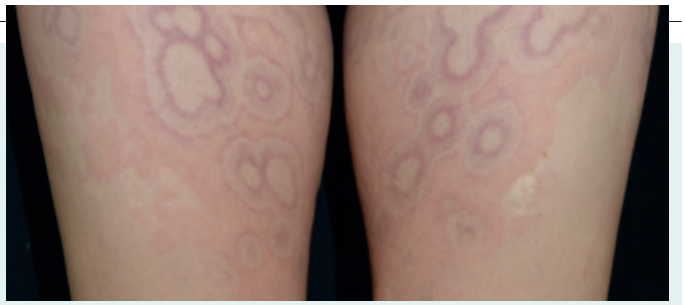
LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

MINERVA

Targetoid lesions, weals, or both?



This is normocomplementemic urticarial vasculitis on the thighs of a woman in her 50s. She presented with a two day history of rash and a tingling sensation on her thighs, but no pruritus. Examination revealed annular and targetoid-like eruptions with symmetrical rings of ecchymosis. No systemic findings were noted. Skin biopsy showed features compatible with urticarial vasculitis. No deposition of immune complexes was seen under direct immunofluorescence.

Blood test results for erythrocyte sedimentation rate, C3 and C4, cryoglobulin, autoimmune panel, and complete and differential blood count were normal. Additional investigations could have included C1q, anti-C1q, and C reactive protein if systemic signs or recurrent urticarial vasculitis episodes were present.

Urticarial vasculitis is a small vessel vasculitis with predominantly cutaneous involvement. In most cases the cause is idiopathic, but the condition can be precipitated by drugs, infections, autoimmune diseases, and, rarely, malignancy.

Consider urticarial vasculitis in patients presenting with this characteristic skin eruption who experience pain or tingling rather than pruritus, which is the common presenting symptom of urticaria.

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Patient consent obtained.

Cite this as: *BMJ* 2021;373:n1457

If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Inflammatory bowel disease in pregnancy

A study in the Netherlands followed the offspring of 600 women with inflammatory bowel disease. The most important findings were reassuringly negative (*Gut* doi:10.1136/gutjnl-2019-319129). Prenatal exposure either to anti-TNF-α drugs or to thiopurine, both of which cross the placenta, wasn't associated with adverse birth outcomes or growth failure, autoimmune diseases, malignancies, or severe infections in the first five years.

Bone and heart

Calcification in arteries and in bone show an inverse relation, according to a large study in Korean women. More than 12 000 women aged 50-80 underwent bone mineral density measurements. Over nine years of follow-up, women with lower bone mineral density were substantially more likely to suffer from atherosclerotic diseases (*Heart* doi:10.1136/heartjnl-2020-318764). Risk of myocardial infarction, ischaemic stroke, or death from cardiovascular causes increased by around 40% for each standard deviation decrease in bone mineral density.

Vitamin D and risk of early onset type 2 diabetes

Some evidence suggests that fetal vitamin D status has a long term influence on glucose homoeostasis and the risk of developing type 2 diabetes. But the idea gets no support from a Danish study that measured 25-hydroxyvitamin D3 concentrations in the dried blood spot samples obtained at neonatal screening (*Diabetologia* doi: 10.1007/s00125-021-05450-2). Vitamin D concentrations in those who subsequently developed diabetes were no lower than those of a random sample of children born in the same period.

Mice in study of Alzheimer's

An analysis of 600 scientific papers describing studies that used mouse models to investigate Alzheimer's disease found that more than a third failed to mention mice in the title (*PLoS Biol* doi:10.1371/journal.pbio.3001260). This matters because absence of information about the experimental species made it more likely that the research would be picked up by newspapers and other media and reported as if the results applied directly to humans.

Guillain-Barré syndrome after covid-19

During the first wave of the covid-19 pandemic, the incidence of Guillain-Barré syndrome in the UK fell (*Brain* doi:10.1093/brain/awaa433). It's likely that lockdown reduced transmission of the infections that commonly cause the disease. In contrast, a study from 12 hospitals in northern Italy reports that Guillain-Barré syndrome was nearly three times more frequent in March and April 2020 than in the same months of the previous year (*Neurol Neurosurg Psych* doi:10.1136/jnnp-2020-324837). The increase was attributed to a predominantly demyelinating type of the neuropathy in patients with covid-19.

Kiwifruit for constipation

Prunes are a time honoured cure for constipation. They work because prunes contain both fibre and sorbitol. But so, of course, do kiwifruit. A small trial in adults with chronic constipation finds that, judged by increase in the weekly number of spontaneous bowel movements—the primary outcome of the trial—kiwifruit (two per day) and prunes (100 g per day) are equally effective (*Am J Gastroenterol* doi:10.14309/ajg.0000000000001149).

Mental health in partners of people with diabetes

People living with a partner with diabetes are at increased risk of developing depression or anxiety. That's the finding of a longitudinal study of households in the US (*Diabetes Care* doi:10.2337/dc20-2652). Those whose partners were limited in their daily activities because of diabetes, or who suffered from other chronic conditions in addition to diabetes, were roughly twice as likely to be depressed or anxious as people whose partners didn't have diabetes.

Cite this as: *BMJ* 2021;374:n1614