education

FROM THE JOURNALS Edited highlights of weekly research reviews

Predicting sudden death

My dad died of a sudden cardiac arrest when he was 48 years old. His death, like many similar cases, was never really explained. One recently discovered cause of sudden death is a genetic arrhythmia syndrome called calcium release deficiency syndrome (CRDS). Could a new test identify CRDS before it presents as a sudden death?

This multicentre case-control study found a unique repolarisation response on electrocardiography (T wave amplitude) to brief tachycardia and a pause in 10 patients with CRDS compared with controls, which could form the basis of a predictive test. The human findings were replicated in genetic mouse models and were caused by abnormally high release of calcium from the sarcoplasmic reticulum during systole. This was a small preliminary report from an ongoing DIAGNOSE CRDS study that will take years to complete. It offers the prospect of a clinical diagnostic test for CRDS in families who have been devastated by multiple and early sudden deaths.

JAMA doi:10.1001/jama.2024.8599

No smoke without fire

What works best if you want to quit smoking; electronic cigarettes containing nicotine or varenicline?

In this Finnish randomised, placebo controlled trial of 458 adults with moderate to heavy dependence on nicotine who were motivated to quit smoking traditional cigarettes, 12 weeks of nicotine-containing electronic cigarettes and varenicline were both effective in helping people to stop smoking for up to six months compared with placebo (40.4% *v* 43.8% *v* 19.7%) with no serious side effects.

As both are equally effective, it may be better to recommend varenicline over electronic cigarettes because it weans people off the habit of smoking and doesn't contain nicotine.

JAMA Intern Med doi:10.1001/jamainternmed.2024.1822

Shedding light on dementia

In the department of Antioquia in north west Colombia there is a large family of 6000 blood relatives that include more than 1000 carriers of the autosomal dominant E280A variant of the *PSEN1* gene (encoding the protein presenilin 1). Almost 100% of these carriers develop Alzheimer's disease with mild cognitive impairment starting in their mid-40s and dementia by the time they're 50 years old.

This study found 27 of the family members carrying the E280A variant who were also heterozygous for the *APOE3Ch* gene variant (encoding apolipoprotein E) and who had later onset of symptoms compared with 1050 family E280A carriers who didn't have the *APOE3Ch* variant (onset of cognitive decline 5 years later and dementia 4 years later) as well as a different pattern on brain imaging (positron emission tomography).

The hypothesis is that the variant prevents the accumulation of tau tangles and associated cell death, and researchers are working on treatments for Alzheimer's disease that could replicate its apparent protective effects.

N Engl J Med doi:10.1056/NEJMoa2308583

Safety of metformin in early pregnancy

Is metformin safe to use in early pregnancy? This US observational cohort study of over 12 000 pregnant women with pregestational type 2 diabetes who were taking metformin monotherapy before their last menstrual period (LMP) compared insulin monotherapy (discontinue metformin and initiate insulin monotherapy within 90 days of LMP) with insulin plus metformin (continue metformin and initiate insulin within 90 days of LMP).

Taking metformin in addition to insulin was as safe as insulin alone (risk ratio estimated non-live births and congenital malformation 1.02 and 0.72 respectively). There was some risk of confounding based on glycaemic control and body mass index, but results were reassuring.

Ann Intern Med doi:10.7326/M23-2038

But what about the dads?

Metformin has known antiandrogenic and epigenetic modifying effects. So, if men take metformin during the period of spermatogenesis before conception, does it increase the risk of genomic changes and major congenital malformations in the newborn?

This nationally representative cohort study from Israel of nearly 400 000 live births (1999-2020) found that paternal use of metformin monotherapy did not increase the risk of major congenital malformations. However, paternal use of metformin in polytherapy was associated with an increased risk of major congenital malformations (adjusted odds ratio 1.36), which was possibly because these men had more poorly controlled diabetes and worse cardiometabolic health. One limitation of the study was that results for haemoglobin A1c weren't available in all subsets.

Ann Intern Med doi:10.7326/M23-1405

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GUIDELINES

Vitamin B12 deficiency: NICE guideline summary

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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

Vitamin B_{12} deficiency is associated with a range of symptoms and signs, resulting in substantial variation in patient presentation. While epidemiological data are limited, cross sectional studies from the UK and US suggest a prevalence of 3% in people aged 20-39, increasing with age up to about 20% in people aged 85 and over.[1 2] Complications of vitamin B_{12} deficiency include visual changes, paraesthesia, and ataxia.

In March 2024, the National Institute for Health and Care Excellence (NICE) published new guidance on the diagnosis and management of B_{12} deficiency.[3] This summary aims to raise awareness of the symptoms and signs, assessment, and management of vitamin B_{12} deficiency, with particular focus on what is most relevant to general practice and primary care. Readers are directed to the full guideline for a comprehensive review of all recommendations.

Recommendations

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

WHAT YOU NEED TO KNOW

- Offer an initial diagnostic test (total or active B_{12}) for suspected deficiency to people who have at least one common symptom or sign and at least one common risk factor for the condition
- Consider a further test to measure serum methylmalonic acid concentrations in people who have symptoms or signs of vitamin B_{12} deficiency and an indeterminate total or active B_{12} test result
- When offering oral vitamin B_{12} replacement to people with vitamin B_{12} deficiency caused, or suspected to be caused, by malabsorption, prescribe a dosage of at least 1 mg a day

When to test

Vitamin B_{12} deficiency is a complex condition with significant variability in the type and severity of symptoms that people experience. Following extensive discussion as to which features on presentation and risk factors should be emphasised, the guideline committee prioritised the importance of timely testing while not increasing the volume of testing unnecessarily in people who are unlikely to be deficient. Therefore, the guideline focuses on symptoms and signs commonly attributed to vitamin B_{12} deficiency when testing is likely to identify people with a clinical deficiency and a diagnosis is most likely to be achieved.

The presence of at least one risk factor and one symptom or sign increases the likelihood of vitamin B_{12} deficiency. People with symptoms and signs but no risk factors may still have a deficiency, and some people may be unaware of any risk factors they have. Currently, evidence establishing a direct correlation between symptoms, signs, and clinical outcomes is lacking.

- Offer an initial diagnostic test for vitamin B_{12} deficiency to people who have
  - At least one common symptom or sign (box 1) and
  - At least one common risk factor for the condition (box 2).
- Use clinical judgment when deciding whether to test people who have at least one common symptom or sign (box 1) but no common risk factors (box 2).

Diagnosis

First line testing

Based on the experience of the guideline committee, active B_{12} (serum holotranscobalamin) is a more accurate test than total B_{12} (serum cobalamin) for vitamin B_{12} deficiency because active B_{12} measures the biologically active form of vitamin B_{12} that is available for use by cells. Testing active B_{12} is more expensive than testing total B_{12}, (active B_{12} is £18 per test versus total B_{12} which is £2 per test, mean costs reported by guideline committee members at the time of analysis). This is in part due to active B_{12} testing mainly being performed by external referral laboratories rather than local hospital laboratories, and increases the turnaround time to receive a result for an active B_{12} test compared with a total B_{12} test. Despite the suggestion that active B_{12} is a more accurate test than total B_{12}, evidence is lacking to support a recommendation that would signal a significant and expensive change in practice. Either test is preferrable to not testing when suspicion of deficiency arises from symptoms or signs and risk factors.

This recommendation should not be applied to people who are pregnant or suspected of vitamin B_{12} deficiency that results from recreational use of nitrous oxide, and guidance on testing for these groups is available in the full guideline.

Box 1 | Common symptoms and signs of vitamin B_{12} deficiency

- Abnormal findings, such as anaemia or macrocytosis, on a blood count
- Cognitive difficulties, such as difficulty concentrating or short term memory loss (sometimes described as "brain fog"), which can also be symptoms of delirium or dementia
- Eyesight problems related to optic nerve dysfunction:
  - Blurred vision
  - Optic atrophy
  - Visual field loss (scotoma)
- Glossitis
- Neurological or mobility problems related to peripheral neuropathy, or to central nervous system disease including myelopathy (spinal cord disease):
  - Balance issues and falls caused by impaired proprioception (the ability to sense movement, action, and location) and linked to sensory ataxia (which may have been caused by spinal cord damage)
  - Impaired gait
  - Pins and needles or numbness (paraesthesia)
- Symptoms or signs of anaemia that suggest iron treatment is not working properly during pregnancy or breastfeeding
- Unexplained fatigue

Box 2 | Common risk factors for vitamin B_{12} deficiency

- Diet low in vitamin B_{12} (without regular use of over-the-counter preparations), for example, in people who:
  - Follow a diet that excludes, or is low in, animal source foods (such as a vegan diet or diets that exclude meat for religious beliefs)
  - Do not consume food or drinks fortified with vitamin B_{12}
  - Have an allergy to some foods such as eggs, milk, or fish
  - Find it difficult to buy or prepare food (for example, people who have dementia or frailty, or those with mental health conditions)
  - Find it difficult to obtain or afford foods rich in vitamin B_{12} (for example, people on low income)
  - Have a restricted diet (for example, because of an eating disorder)
- Family history of vitamin B_{12} deficiency or an autoimmune condition
- Health conditions:
  - Atrophic gastritis affecting the gastric body
  - Coeliac disease or another autoimmune condition (such as thyroid disease, Sjögren syndrome, or type 1 diabetes)
- Medicines:
  - Colchicine
  - H_2 receptor antagonists
  - Metformin (see the MHRA safety advice on metformin and reduced vitamin B_{12}[4])
  - Phenobarbital
  - Pregabalin
  - Primidone
  - Proton pump inhibitors
  - Topiramate
- Previous abdominal or pelvic radiotherapy
- Previous gastrointestinal surgery:
  - Many bariatric operations (for example, Roux-en-Y gastric bypass or sleeve gastrectomy)
  - Gastrectomy or terminal ileal resection
- Recreational nitrous oxide use

Further testing

Interpretation and follow-up are dependent on the initial total or active B_{12} test result. This was based on the experience of the guideline committee and limited, poor quality evidence. The committee recommended considering measuring methylmalonic acid (MMA) as a confirmatory test when initial test results were in an indeterminate range (table). Although MMA provides a more reliable diagnosis that reflects the functional status of vitamin B_{12}, it is unsuitable as a first line test. Testing for MMA is expensive (£11-80, range of costs reported by guideline committee members at the time of analysis), requires specialist analytical equipment, and often requires analysis in external laboratories, resulting in an increased time to receive a result.

A cost utility analysis was performed to evaluate the cost effectiveness of second line MMA testing if the initial B_{12} test results were indeterminate. MMA testing before treatment is the most cost effective strategy compared with not testing MMA, with an incremental cost effectiveness ratio of £3946 per quality adjusted life year. Importantly, the model did not account for testing for other underlying causes and assumed that people who had not been diagnosed correctly as B_{12} deficient on their first visit would attend primary care once more to gain the correct diagnosis. The model was not able to incorporate multiple assumptions stemming from the lack of evidence for the model parameters, including accuracy of MMA testing, prevalence of elevated MMA in the population, variation in quality of life (utility) experienced by people who are B_{12} deficient, and potential impact on resources because of testing, thereby potentially overestimating savings (owing to uncertainty).

- Use either total B_{12} (serum cobalamin) or active B_{12} (serum holotranscobalamin) as the initial test for suspected vitamin B_{12} deficiency.
- Consider a further test to measure serum MMA concentrations in people who have symptoms or signs of vitamin B_{12} deficiency and an indeterminate total or active B_{12} test result.

Replacement therapy

Management of vitamin B_{12} deficiency is dependent on the underlying cause. Selection of management options underscored the guideline committee's efforts to balance efficacy, cost effectiveness, and patient preferences in the absence of robust evidence. In this summary, we focus on people with malabsorption conditions specifically. For information and recommendations relating to dietary deficiency, and deficiency caused by medicines or recreational nitrous oxide use, refer to the full guideline.

Malabsorption as the suspected or confirmed cause of vitamin B_{12} deficiency

All evidence identified for vitamin B_{12} replacement was in patient populations in which the cause of deficiency was unspecified. This was a major limitation in application of the evidence, and was

reflected in downgrading of all the evidence because of indirectness. Recommendations were based on seven randomised controlled trials and two observational studies reporting the effect of vitamin B_{12} replacement on haematological values and experience of the guideline committee.

We identified three economic evaluations that compared oral and parenteral vitamin B_{12} treatments, all of which assumed equivalent effectiveness between the two modalities.[5-7] Studies ranged in patient selection, setting, and duration of follow-up. Two studies, including a short term cost utility analysis of patients with unexplained fatigue in an Australian primary care setting, concluded that oral treatment was the most cost effective strategy.[5 6] Conversely, one study found that parenteral administration was cheaper unless accounting for the long term savings from avoiding additional GP appointments and blood tests costs.[7] However, none of the studies reflect current treatment costs, and if the models were updated, then parenteral treatment would be the more cost effective option.

In our cost comparison, 50 µg tablets were priced at £0.43 compared with 1 mg tablets at £0.33 at the time of analysis. The guideline committee agreed that it is reasonable to assume that the higher dosage would be at least as effective as the lower strength tablet, and recommended considering the 1 mg tablet as the preferred oral treatment. If people are prescribed a higher dose than 50 µg daily, ie, 100-150 µg daily, then it would be appropriate to use 1 mg, which is the most commonly used dose in current practice. Prescribing a higher dose may be more effective and provide greater health benefit as a larger amount of B_{12} is being delivered to the bloodstream, and therefore absorbed, while also being convenient to patients by reducing tablet burden.

In the short term, intramuscular treatment is more expensive than oral treatment. For individuals who require long term treatment, such as those with autoimmune gastritis, intramuscular treatment is preferred as it is more cost effective. This recommendation is based on its superior efficacy in the experience of the guideline committee and the economic evidence, as well as the rationale that oral replacement would not be effective if malabsorption were present.

For other malabsorptive states, excluding autoimmune gastritis, in which absorption is reduced but not eradicated altogether, some members of the guideline committee suggested that oral replacement may be effective. During the covid-19 pandemic, many people were moved from in-person intramuscular to self-administered oral treatments, but the guideline committee agreed that the evidence to support this as an effective route of administration for this group of patients was inadequate. This view was reiterated by some lay members of the guideline committee, who had experienced a significant worsening of symptoms when switched to oral replacement.

Primary care teams and patients may prefer trialling oral treatment at diagnosis, as prescriptions can be issued directly to people and may be more convenient. No data were identified that support the effectiveness and safety of self-administration of intramuscular replacement.

- Offer lifelong intramuscular vitamin B_{12} replacement to people if:
  - Autoimmune gastritis is the cause, or suspected cause, of vitamin B_{12} deficiency or
  - They have had a total gastrectomy or a complete terminal ileal resection.
- If the person has a vitamin B_{12} deficiency because of malabsorption that is not caused by autoimmune gastritis, or a total gastrectomy or complete terminal ileal resection (for example, malabsorption caused by coeliac disease, partial gastrectomy, or some forms of bariatric surgery):
  - Offer vitamin B12 replacement and
  - Consider intramuscular instead of oral vitamin B12 replacement.
- When offering oral vitamin B_{12} replacement to people with vitamin B_{12} deficiency caused, or suspected to be caused, by malabsorption, prescribe a dosage of at least 1 mg a day.

Despite efforts to identify symptoms, signs, and risk factors that may increase the likelihood of diagnosing vitamin B_{12} deficiency, it is likely that the volume of testing will increase compared with current practice. This may be justified by the prospect of earlier diagnosis and subsequent management of vitamin B_{12} deficiency, thereby mitigating the risk of unnecessary appointments and investigations, while simultaneously enhancing the quality of life for people with vitamin B_{12} deficiency.

Interpreting test results for total or active B_{12}

Results if testing total B_{12} concentrations	Results if testing active B_{12} concentrations	Likelihood of vitamin B_{12} deficiency
Less than 180 ng (133 pmol) per litre	Less than 25 pmol per litre	Confirmed vitamin B_{12} deficiency
180-350 ng (133-258 pmol) per litre	25-70 pmol per litre	Indeterminate test result – possible vitamin B_{12} deficiency
More than 350 ng (258 pmol) per litre	More than 70 pmol per litre	Test result suggests vitamin B_{12} deficiency is unlikely

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Maddie Smith is a patient with vitamin B_{12} deficiency and contributed to the preparation of this manuscript. Guideline committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

GUIDELINES INTO PRACTICE

- What do you ask patients about when deciding whether to test for potential vitamin B_{12} deficiency?
- How do you determine whether a person with B_{12} deficiency should be started on oral or intramuscular vitamin B_{12} replacement?

Competing interests: See bmj.com.
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EDITORIAL

Vitamin B12 deficiency: a persistent challenge

New guidelines from NICE should help physicians and patients navigate uncertainty

The presentation of vitamin B_{12} deficiency can be frustratingly vague, non-specific, and variable both within and between individual patients.

While the incidence of laboratory defined vitamin B_{12} deficiency is approximately 6% in younger adults and 20% in those over 60 in the US and UK,[1] the incidence may be as high as 40% to 60% in developing countries.[2] Risk factors include chronic use of metformin and proton pump inhibitors, malabsorption disorders, and a strict vegan diet, although deficiency may occur in the absence of obvious risk factors.[3]

So called classic findings of vitamin B_{12} deficiency, such as macrocytosis and glossitis, are often absent in clinical practice,[4] and it is unclear whether common haematological, cognitive and neurological, and mental health symptoms associated with vitamin B_{12} deficiency are truly caused by it. New guidelines from the National Institute for Health and Care Excellence (NICE),[5] summarised in a linked *BMJ* article (doi:10.1136/bmj.q1019),[6] propose a standardised approach in primary care to vitamin B_{12} deficiency, and review the challenges that persist in identification and treatment.

No gold standards

No gold standard test exists for diagnosing vitamin B_{12} deficiency.[7] Current testing strategies, including measurement of total serum B_{12}, its active form (holotranscobalamin), and/or a product of its metabolic activity (methylmalonic acid), are based on very low certainty evidence.[3]

Levels of all three measurements can fluctuate substantially in the short term,[3] which can be clinically challenging when borderline deficient values occur in individuals who are asymptomatic or report non-specific symptoms. One well recognised source of this variability is the lack of standardisation among different assays for measuring vitamin B_{12}, which may have implications for diagnosis and for monitoring response to treatment.[8] The optimal strategy for monitoring clinical and laboratory response to treatment is unknown.

The guideline is an aide, not a policy, to help provide safe and effective care

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While intramuscular replacement is preferred for selected patients (such as those with atrophic gastritis),[3] oral replacement is effective for many patients in primary care settings.[9] The safest and most effective way to transition patients from acute replacement to maintenance therapy is also unknown.

The NICE guidelines recommend offering an initial diagnostic test for vitamin B_{12} deficiency to people who have at least one common symptom or sign and one risk factor, allowing for clinical judgment in patients who do not strictly meet these criteria. While the identified potential presentations and risk factors for the conditions are not exhaustive, guideline authors have created an initial shared mental model to help physicians and patients communicate more effectively with each other.

Initial screening with either total vitamin B_{12} or holotranscobalamin is recommended. Confirmatory testing with methylmalonic acid should be considered for indeterminate results (180-350 ng/L) only if a compelling reason to start treatment is absent. Despite a lack of strong supporting evidence, this recommendation presents a reasonable evaluation approach.

Recommendations on timing and route of treatment delivery depend on severity of symptoms and suspected cause, and most recommendations were based on very low to moderate certainty evidence and on the consensus and opinion of the guideline committee only. For most patients, improvement of symptoms may take weeks to months, but lifelong replacement is usually required.

Intramuscular injections

Immediate treatment is recommended in the presence of megaloblastic anaemia or focal neurological symptoms even before testing results are known. Intramuscular B_{12} injection is preferred for patients with autoimmune gastritis and surgically induced malabsorption, and may be offered for other causes of malabsorption, medicine induced deficiency, or if there are concerns about adherence to oral treatments.

Self-administered injections are effective and may be more acceptable to some patients. When used for cases of malabsorption, oral therapy should be given at a dose of 1 mg daily.

Questions that require further study include identification of at-risk asymptomatic individuals who would benefit from screening, the optimal testing strategy for suspected vitamin B_{12} deficiency, the preferred length of treatment, and the best method to gauge response to therapy.

Although welcome, the new NICE guideline is only an aide, not a policy, to help physicians provide safe and effective care using a model of shared decision making. It aims to provide a framework for more meaningful clinical conversations about the nuances of identifying and treating vitamin B_{12} deficiency and ultimately, to improve patient outcomes.

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CLINICAL UPDATE

Analgesia for low back pain

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CPD READING

0.5 HOURS

Low back pain is the world's leading cause of disability.[1] At any time, half a billion (9%) adults are affected.[1] Many are prescribed, or use, analgesics for pain relief.[2] In this article, we review what is known about common analgesics for treating non-specific low back pain (defined as pain without an identifiable structural or disease cause). We focus on adults aged 18-60 years.

What is low back pain?

Low back pain (synonymous with "primary" low back pain) is pain felt between the lower ribs and the buttocks.[5] This differs from radicular low back pain, which is when a spinal nerve root is affected, resulting in pain that extends down the legs.[6] Approximately 90% of cases are non-specific, meaning a specific cause has not been identified. The causes of the remaining 10%, affecting around <1 in 100 in primary care[7] and about 5 in 100 in emergency departments,[8] include fractures, infections, malignancies, inflammatory disorders such as spondylarthritis, spinal stenosis, or non-spinal problems such as kidney problems or menstrual related pain.[9]

The prognosis for a new episode of non-specific low back pain is good. Most people recover from acute low back pain within a few weeks irrespective of any treatment.[5] Some people, however, develop chronic low back pain (typically defined as symptoms lasting for over three months), either as a fluctuating/recurring or continuous problem.[10] Of those who present to primary care with acute low back pain, a quarter will have some ongoing pain or functional impairment at three months (chronic pain), although the estimates from individual studies range widely from 2% to 48%.[11]

WHAT YOU NEED TO KNOW

- Analgesics have limited effect on low back pain and some, such as opioids and benzodiazepines, have substantial risks
- Oral and, less certainly, topical non-steroidal anti-inflammatory drugs have small benefits that may not be outweighed by risks (particularly gastrointestinal) for short-term use for low back pain
- Acute low back pain typically improves within a few weeks without treatment; for chronic low back pain, the focus of management should be on non-pharmacological treatments to improve function and address the broader determinates of pain

Who is affected?

Low back pain affects all people of all ages, genders, and ethnic or racial groups, although the point prevalence is slightly higher in women than men (~10% absolute difference consistently across age groups).[12] Prevalence peaks in the 40-69 years age group.[12] Disability resulting from low back pain is similar in high, middle, and lower income countries[1 13] and in urban and rural areas.[12]
A 2018 umbrella review identified 54 risk factors associated with low back pain.[14] Examples of potentially modifiable ones include current smoking (odds ratio (OR) 1.8 (95% confidence interval 1.3 to 2.7)), sleep problems (OR 3.2 (1.9 to 5.5)), >2 hours daily spent driving (OR 4.9 (1.4 to 16.4)), prolonged standing or walking (OR 2.9 (1.5 to 5.5)), and mental distress (OR 2.2 (1.3 to 3.7)).[14]

How is low back pain managed?

Most international guidelines advise non-drug treatment and limited, careful use of some analgesic treatments.[15-18] People with non-specific low back pain should be advised to keep active (continue usual physical activities as much as possible), avoid bed rest (as it does not aid recovery),[19] and use self management strategies such as heat packs.[15] About one in five people with chronic low back pain will experience major life or work limitations and may benefit from further treatment.[20 21] For people with chronic non-specific low back pain, optimal approaches use physical and psychological therapies that improve function and address psychosocial contributors to low back pain (table).[15]

Both prescription and over-the-counter analgesics are easily accessible and widely used as an alternative or addition to non-drug treatments. Across primary care services in high income countries Australia,[2] Portugal,[23] US,[24] and Switzerland,[25] 66-89% of consultations for low back pain result in a prescription for analgesia. There are limited prescribing data from low and middle income countries. Herbal medicines and homoeopathy are prescribed for low back pain in some settings, but the type of agents used varies between regions and is influenced by cultural practices.[26 27]

Efficacy of analgesia

Most commonly used analgesics used to treat low back pain offer no to small benefit versus placebo, and all have a risk of harm (to varying degrees). In this article, we focus primarily on reporting pain intensity, as this is the outcome most consistently reported in literature and a recommended core outcome across acute and chronic pain studies[28] (see table 2 in full article on bmj.com for details of the evidence).

Paracetamol (acetaminophen)

There is moderate to high certainty evidence of no effect over placebo for both acute and chronic low back pain. A systematic review of 13 randomised controlled trials (RCTs) in Australian and Austrian cohorts of patients with low back pain found a mean difference in pain score of −0.5 (95% confidence interval −2.9 to 1.9).[29] In trials of patients with low back pain, there was no increased risk of harms. However, in RCTs assessing people with osteoarthritis or low back pain, using paracetamol was more likely to cause abnormal liver function tests (although the clinical importance remains unknown).[29]

Observational data and trials in broader populations using paracetamol for any reason (such as other pain, fever) at standard therapeutic doses show a dose-dependent increase in risk of harms (cardiovascular, gastrointestinal, and renal).[44] We observe in practice that paracetamol is typically safe when taken as directed in people without contraindications and is generally safer than anti-inflammatories.[45 46]

Summary of current guideline recommendations for non-specific low back pain

Treatment	Recommendation (certainty of evidence)
Acute	
Certain analgesics (non-steroidal ani-inflammatory drugs (NSAIDs) and muscle relaxants)	Effective (moderate)
Superficial heat	Effective (moderate)
Acupuncture or needling therapies	Effective (low)
Massage	Effective (low)
Spinal manipulation therapy	Effective (low)
Exercise	Not effective (low)
Orthotics	Not effective (low)
Other analgesics	Not effective (low)
Chronic	
Multicomponent biopsychosocial care	Effective (moderate)
Structured exercise programmes	Effective (moderate)
Certain analgesics (NSAIDs and topical cayenne pepper)	Effective (moderate to low)
Acupuncture/needling therapies	Effective (low)
Structured exercise advice	Effective (low)
Cognitive behavioural therapy	Effective (very low)
Massage	Effective (very low)
Operant therapy	Effective (very low)
Spinal manipulation therapy	Effective (very low)
Mobility assistive products	No evidence, good practice recommendation only
Other analgesics	Not effective (moderate to low)
Therapeutic ultrasound	Not effective (low)
Orthotics (braces, supports)	Not effective (very low)
Pharmacological weight loss	Not effective (very low)
Traction	Not effective (very low)
Transcutaneous electrical stimulation	Not effective (very low)

Certainty of evidence as measured by GRADE approach.

Acute treatment as recommended by 2017 American College of Physicians guideline.[18] Chronic treatment as recommended by 2023 WHO guidelines.[16]

NICE guidance[22] broadly agrees with the above except it recommends against acupuncture and makes recommendations on invasive/surgical procedures (consider radiofrequency denervation or spinal decompression for chronic low back pain in limited circumstances).

SPECIAL CONSIDERATIONS FOR PATIENTS WITH LOW BACK PAIN

- The evidence presented here should be used to guide clinical practice around starting new medicines for patients who are not already long term users
- Despite the lack of evidence for efficacy, many people with chronic low back pain are already using long term analgesics
- Rapid or forced tapering of analgesics with risk of withdrawal (such as opioids, anticonvulsants, and benzodiazepines) can cause serious harm
- Long term users of medicines should be assessed individually to determine the benefit-harm balance of reducing their use of pain medicines
- Some patients may require supportive treatments while undergoing tapering, and appropriate treatment for substance use disorders if they are identified[58]
- Some of the medicines used for low back pain carry the risk of drug interactions. For example, combining opioids with other sedatives or respiratory depressants, such as benzodiazepines, increases the risk of mortality and serious adverse events[59]

Non-steroidal anti-inflammatories (NSAIDs)

NSAIDs include ibuprofen, diclofenac, naproxen, and celecoxib. For acute low back pain, there is moderate certainty evidence of small benefit above placebo (mean difference in pain intensity −0.9 (95% CI −1.1 to −0.7) from six RCTs conducted in Norway, Belgium, France, Australia, and Germany)[30] and a risk ratio of 2.5 (1.2 to 5.2) of gastrointestinal harms (28/702 participants taking NSAIDs compared with 9/465 in the placebo groups).[30] For chronic low back pain, there is low certainty evidence of small average benefits (mean difference −0.7 (−1.1 to −0.3, from six RCTs conducted in Italy, UK, and US).[31]

The available data from RCTs of chronic low back pain do not report increased risk of harm compared with placebo.[31] However, RCTs and observational studies of populations taking NSAIDs for any reason (such as osteoarthritis or rheumatoid arthritis) showed increased NSAID related adverse events (such as gastrointestinal, cardiovascular, and renal) which escalate with increasing doses and long term use.[47]

Antidepressants

There are no data on antidepressants for treating acute low back pain. For chronic low back pain, there is moderate certainty evidence that serotonin-norepinephrine reuptake inhibitors (such as duloxetine) may have a small effect (mean difference −3.67 (−5.91 to −1.42) from three RCTs conducted in the US and Japan) and low certainty evidence that tricyclic antidepressants are ineffective (mean difference −0.9 (−5.4 to 3.7) from three RCTs conducted in the US and Switzerland).[32] Harms when used specifically for low back pain are unclear, although in broader populations (such as mood disorders) antidepressants are associated with nausea, weight gain, sexual dysfunction, and sleep problems.[48]

Opioids

A 2023 trial conducted in Australia in 347 patients with acute low back pain found strong evidence of no effect of oxycodone (mean difference 0.5 (0.0 to 1.1)), and worse long term outcomes (such as worse pain and a higher risk of opioid misuse) compared with placebo.[49] For chronic low back pain, there is moderate certainty evidence that opioids (numerous single or combination opioid formulations including morphine, tramadol alone or with paracetamol, tapentadol, oxycodone, and fentanyl) probably have a small average effect (mean difference −1.0 (−1.3 to −0.7) from 13 RCTs conducted in Germany, US, Canada, and Australia).[33] Despite this, opioids are

not recommended to treat chronic pain because of risks of harms with long term use, including dependence, misuse, overdose, and tolerance.[33 50]

Anticonvulsants

There are no data on efficacy for acute low back pain. However, there is high certainty evidence of no effect above placebo of gabapentin or pregabalin for chronic low back pain (mean difference 0.0 (−0.8 to 0.7) from 14 RCTs conducted in Australia, US, and Ireland).[34] The use of anticonvulsants causes increased risk of harms including drowsiness, somnolence, dizziness, and nausea.[34 51]

Benzodiazepines

Small trials conducted in the 1970s to 1990s report some effect on acute or chronic low back pain (effect size and level of certainty not reported).[35] Other studies indicate that benzodiazepines do not possess meaningful analgesic properties separate from their sedative properties.[52] A 2017 RCT of 114 patients conducted in the US did not find that that adding diazepam to diclofenac in people attending an emergency department improved functional outcomes or pain at one week.[53] Benzodiazepines are associated with increased falls, cognitive impairment, and risk of addiction.[54]

Non-benzodiazepine muscle relaxants

This category of medicine is broad and includes a variety of pharmacologically unrelated medications such as cyclobenzaprine, tolperisone, baclofen, and orphenadrine with similar indications. In both acute and chronic low back pain, there is low and very low certainty evidence that non-benzodiazepine muscle relaxants might offer small benefits (mean difference −0.8 (−1.2 to −0.3) from 14 RCTs from the US, Finland, UK, Turkey, and India) but increase the risk of harms, primarily sedation.[36]

Oral corticosteroids

Limited evidence suggests they may be not effective for acute or chronic low back pain (mean difference 0.6 (−2.2 to 1.0) from one RCT conducted in the US), and may not cause harm in short courses.[37]

Cannabinoids

A single RCT of oral cannabidiol in 100 patients conducted in Australia found no effect on low back pain compared with placebo (mean difference −0.3 (−1.3 to 0.6)) and no increase in short term harms in a hyperacute, emergency department setting.[55] There are no data for chronic low back pain, and no data on harms associated with long term use in other chronic conditions.[38]

Oral combination medicines

There is low certainty evidence that combining medicines does not produce superior effect sizes and may increase the risk of harms.[56]

Topical preparations

There is some indirect evidence (level of certainty not assessed) that some formulations of NSAIDs and rubefacients may reduce back pain attributed to muscle strains or sprains more than placebo (effect size not reported),[39] which may apply to some cases of acute low back pain, with no increased risk of harms.[39] There are no data on efficacy for chronic low back pain, but indirect evidence from other chronic pain conditions such as knee osteoarthritis has shown limited effect.[39]

Homoeopathy

There is no reliable evidence of efficacy of homoeopathy for acute or chronic low back pain.[57] While many may consider homoeopathy harmless, some indirect risks may apply, including the risk of harm to patient's trust and delaying use of treatments that may be more effective.[57]

Herbal medicines

Some herbal remedies have reported efficacy compared with placebo (with low to moderate certainty) for both acute and chronic low back pain, such as cayenne or capsaicin plasters, devil's claw, willow bark, and topical lavender oil.[41] However, the size of the effects is unclear due to critical heterogeneity across trials. Most available trials are limited by authors' conflicts of interest.[41] Harms are uncertain, with suboptimal reporting in trials.[41]

Dissonance between evidence and practice

Analgesics are still commonly used for low back pain.[2 12] In our experience, reasons for this include a real or perceived lack of alternatives, pressure from patients, a strong desire to help, and the lower cost and better accessibility of medicines compared with physical and psychological therapies.

If an analgesic is to be recommended for management of low back pain, oral NSAIDs (or topical NSAIDs if there are contraindications to oral formulations) probably have the most favourable benefit-harm balance. There is high to moderate certainty evidence that paracetamol, opioids, antidepressants, and anticonvulsants are not effective. These medicines have associated harms, many of which are serious. The box outlines special considerations when managing patients with low back pain.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two authors of this article are patients. MS had severe chronic disabling back pain and has now recovered. He is a consumer representative at Cochrane Back and Neck since 2000. JC has ongoing chronic disabling back pain that came on after a workplace injury that prevented him working. He has been prescribed various pharmaceutical and non-pharmaceutical strategies. Both authors reviewed multiple drafts of the article.

Other authors CMPJ, MU, and CWCL have all had episodes of acute low back pain.

EDUCATION INTO PRACTICE

- Think about the last time you reviewed a patient who presented with low back pain. What factors led to your decision whether to prescribe an analgesic or not?
- How might you explain effectiveness and risks of oxycodone to a patient who requests it for low back pain?

Competing interests: None declared.

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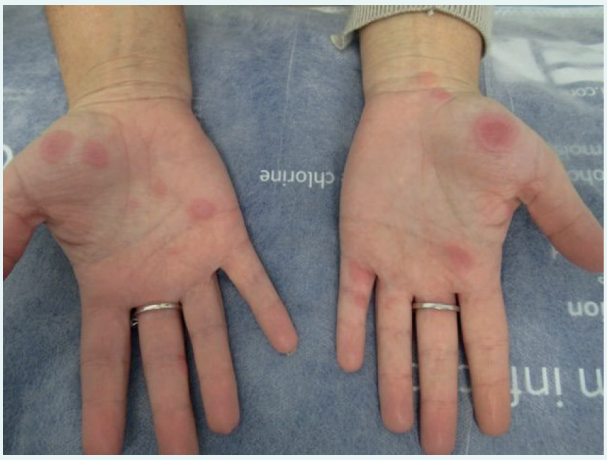
CASE REVIEW

Recurrent rash and orogenital ulcers

A woman in her 30s presented with a one year history of a recurrent rash on her hands in association with oral and genital ulcers. She was otherwise well and took no regular medication but described recurrent episodes of dysuria and frequency, followed 1-3 days later by the development of oral and genital ulcers and painful dermal plaques. She had been treated several times during these episodes for presumed recurrent urinary tract infections but received no other treatment and the rash had resolved spontaneously after a few weeks. No systemic symptoms such as fever or arthralgias were experienced.

Examination during an acute episode showed dusky pink targetoid plaques on the palms (figure). Similar lesions surrounded the genital skin and two superficial ulcers were present on the labia minora. She had no oral lesions. Blood test results were unremarkable. A swab from a vulval ulcer was positive for herpes simplex virus type 2.

1 **What are the differential diagnoses?**
2 **What is the most likely diagnosis?**
3 **How should this condition be managed?**



Dusky pink targetoid plaques on the palms

Submitted by Maeve Herlihy and Muriel Sadlier

Patient consent obtained.

Cite this as: *BMJ* 2024;385:e079717

answers

CASE REVIEW **Recurrent rash and orogenital ulcers**

1 What are the differential diagnoses?

Differential diagnoses include erythema multiforme, Behçet's disease, autoimmune blistering disorders, connective tissue disorders such as lupus or Sjögren syndrome, recurrent aphthous ulceration, and Crohn's disease.

2 What is the most likely diagnosis?

Erythema multiforme—a mucocutaneous immune mediated reaction, most common in young adults. About 20% of cases occur in children. Typical clinical features include target-like or bullseye-like lesions consisting of three concentric rings of colour variation—a central, dusky area of epidermal necrosis surrounded by a lighter oedematous area with a peripheral erythematous margin. Lesions typically develop symmetrically at the periphery, with a predilection for extensor surfaces. The lesions are often asymptomatic but may be painful or itchy. Mucosal lesions develop as blisters and shallow erosions. Patients might experience prodromal symptoms such as fever or fatigue before the onset of the rash. Mucosal involvement distinguishes erythema multiforme major from the more common erythema multiforme minor. Erythema multiforme major mainly affects oral membranes, with urogenital mucosa less commonly involved. Rarely, ocular lesions can occur. Mucous membrane involvement can be painful, and lesions might occur before or after cutaneous lesions. Systemic symptoms such as arthralgia, fever, and malaise are more common with erythema multiforme major. Additionally, lesions associated with erythema multiforme major are usually larger and might blister. Episodes are usually isolated and self-limiting. Lesions typically heal within four weeks, and treatment is rarely indicated in acute disease. Recurrent episodes can occasionally occur, most frequently related to herpes simplex virus infection. Treatment for recurrent erythema multiforme is more challenging. In the first instance, the cause should be determined. Any recent infections should be treated, and if evidence suggests that the erythema multiforme is drug related, treatment should be discontinued. In both herpes simplex virus associated erythema multiforme and idiopathic multiforme, antiviral prophylaxis is the first line treatment. For those who do not respond to aciclovir, dapsone has been used with some success. In case reports and small case series, remission has been reported with azathioprine, adalimumab, rituximab, and thalidomide. Erythema multiforme major is also self-limiting, and treatment depends on identification and treatment of potential triggers.

3 How should this condition be managed?

LEARNING POINTS

- Erythema multiforme is an uncommon mucocutaneous hypersensitivity reaction that results in a characteristic rash with target lesions.
- Erythema multiforme is typically self-limiting but can be recurrent or persistent.
- Herpesvirus infection is the most common trigger. Other causes include drugs, other infections, inflammatory bowel disease, and malignancy.

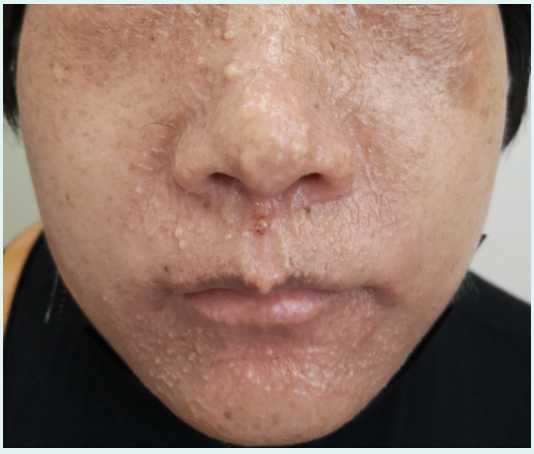
PATIENT OUTCOME

See bmj.com.

Widespread papules and skin tightening

This woman in her late 40s presented with widespread papules and tightening of the skin that had progressed over the past seven years. Physical examination showed numerous 1-3 mm asymptomatic waxy, skin coloured papules on the face and neck, dorsal aspect of the hands, forearms, trunk, and legs, along with hyperpigmentation and reduced joint mobility in the hands and larger extremities. She had no history of Raynaud's phenomenon or dysphagia, and results for thyroid function and autoantibody screening were normal, excluding myxoedema and systemic sclerosis as likely diagnoses. Protein electrophoresis showed a monoclonal gammopathy of the IgG lambda component, and a skin biopsy sample showed fibroblast proliferation with increased mucin and collagen deposition.

This is a case of scleromyxoedema, a generalised form of lichen myxoedematosus. It is a rare cutaneous mucinosis usually manifesting in middle age and characterised by small, waxy, skin coloured papules in linear, symmetrical patterns, favouring the upper body. The scalp, palms, and mucous membranes commonly remain unaffected. The clinical course of scleromyxoedema is unpredictable and the prognosis poor because of the associated systemic effects. Treatment is challenging but typically consists of intravenous immunoglobulin and systemic glucocorticoids alone or in combination.



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Patient consent obtained.

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Sweet drinks tax

Seattle is one of seven US cities that have implemented taxes on sweetened beverages. Sales have fallen and a complicated analysis of longitudinal data on 6000 children finds evidence of a reduction in adiposity. The primary outcome was children's BMIp95, which is body mass index expressed as a percentage of the 95th percentile for an age and sex-matched reference population—a measure of adiposity thought to be better at capturing change than a BMI z score. Children living in the city showed a greater change in BMIp95 than those living in a nearby non-taxed comparison area (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.13644).

Mothers of low birthweight babies

For the fetus, low birthweight is associated with increased perinatal mortality and morbidity, poorer growth and cognitive development, and a higher risk of several non-communicable diseases later in life. For the mother, having a low birthweight offspring may reflect underlying vascular or metabolic dysfunction. Among participants in a large longitudinal investigation of female nurses, scores on tests of cognitive and psychomotor function at the age of 62 were lower in those with a history of low birthweight delivery than those of parous women whose offspring were of normal birthweight (*Neurology* doi:10.1212/WNL.0000000000209504).

Long term implications of cancer in young people

Several investigations have found that, even after successful treatment, young cancer patients are not only more likely to develop a second malignancy but also experience an increased risk of cardiovascular and other diseases. A nationwide, retrospective study of people living in Sweden, all diagnosed with cancer under 25 confirms these findings. Compared with controls matched for age, sex, and area of residence, young cancer patients had a threefold higher risk for subsequent cancer and a roughly 30% increase in risk of cardiovascular, pulmonary, endocrine, and neurological disease (*Lancet Reg Health* doi:10.1016/j.lanepe.2024.100925).

Remission and recovery in psychotic disorders

Twenty five year follow-up of 600 people who presented with a first episode of psychosis shows that the prognosis is highly dependent on the underlying diagnosis. The most common trajectory for patients with schizophrenic disorders was no remission and no recovery. The outlook for people with other psychotic disorders was less bleak, with multiple transitions into and out of remission. One in five experienced a sustained recovery (*Am J Psychiatr* doi:10.1176/appi.ajp.20230189).

Plastic eating fungus

The *Tremella purgare* fungus was released into the Gulf of Mexico after a major oil spill. Intended as a bioremediation strategy, the intervention ran out of control. Spores from the fungi spread from sea to land and, once airborne, latched on to any oil based synthetic material which they rapidly digested. It wasn't long before the planet was in deep trouble. Although this is only a piece of science fiction in *Nature*'s Futures series, it contains a moral. Confronted with a problem, it's better to deal with the root cause than implement an untested quick fix (*Nature* doi: 10.1038/d41586-024-01723-z).

Animal research

The Australian philosopher Peter Singer argues that it's morally indefensible to favour human interests over animal interests. But you don't have to go that far to be dismayed by the findings of an umbrella review of translational biomedical research which reveals that only one in 20 treatments tested in animals ever achieve regulatory approval for use in humans. Apart from the waste of animal life, the low rate of approval suggests that the design of many animal and early clinical studies is defective (*PLoS Biol* doi:10.1371/journal.pbio.3002667).

Cite this as: *BMJ* 2024;385:q1354