Depressing news about pharmacogenetics

How do you decide which antidepressant to prescribe for your patients? It’s usually pretty hit and miss, and with relapse rates of 30%, more precision would be welcome. Pharmacogenomic testing looks for gene variants that may predict whether an individual is likely to respond to a drug or have harmful interactions. This randomised trial of nearly 2000 people with major depressive disorder found that pharmacogenetic tests for drug interactions resulted in significantly more prescriptions with no predicted drug-gene interactions compared with people who didn’t have the testing (45% v 18%).

However, despite a small early advantage in remission of symptoms (16.5% v 11.2% at 12 weeks), there was no difference in effectiveness between the two groups by 24 weeks. Most people won’t have any predisposition to drug-gene interactions, and future studies could enrich the randomised sample for those with known potential interactions. If further studies demonstrate a more compelling benefit in terms of effectiveness and if costs come down, then we may live to see pharmacogenetic testing become the norm before any new drug is started.

*Cite this as: JAMA doi: 10.1001/jama.2022.9805*

Surviving a spell in hospital

My gran had a morbid fear of hospitals. So she would have been cheered by this positive cross sectional study of over a quarter of a million adults who were admitted to US hospitals between 2010 and 2019 and who experienced significantly fewer adverse events as the decade progressed (annual adjusted relative risk for myocardial infarction 0.94, for pneumonia 0.94, and for major surgery 0.93).

The improvements in adverse drug events and hospital acquired infections are welcome, although the absolute figures may still be some cause for alarm (218 adverse events/1000 discharges for myocardial infarction in 2010 to 139/1000 in 2019). Overall, better information technology, safer processes, and more minimally invasive surgery are likely to have contributed.

*Cite this as: JAMA doi: 10.1001/jama.2022.9600*

Hidden hypoxaemia

Covid-19 has raised the profile of pulse oximetry (SpO₂), routinely used for transcutaneous monitoring of blood oxygenation. But reliance on oximetry is a problem as it can overestimate actual oxygenation, especially in some groups. This useful retrospective cohort study of 3069 patients in a US intensive care unit found that Asian, black, and Hispanic patients had a higher adjusted time weighted average pulse oximetry reading and received significantly less supplemental oxygen for a given average haemoglobin oxygen saturation compared with white patients. In other words, people from an ethnic minority were effectively undertreated because of over-reliance on pulse oximetry readings that didn’t accurately reflect their oxygen needs.

*Cite this as: JAMA Intern Med doi: 10.1001/jamainternmed.2022.2587*

Covid vaccination in pregnancy

Babies under 6 months old are at increased risk of complications if they catch covid-19, but the present vaccines aren’t approved for newborns. Does vaccinating women with mRNA vaccines (Pfizer or Moderna) in pregnancy offer the babies protection by transplacental antibody transfer? This case-control test negative study looked at 537 infants under 6 months (median age 2 months) who were admitted to hospital with covid (around a third when the delta strain was rife, and the rest during omicron) compared with 512 control infants who were in hospital for non-covid reasons. Of the babies with covid-19, 21% were admitted to intensive care and two died.

The effectiveness of maternal vaccination against hospital admission for covid among infants was 52% overall (80% during the delta outbreak and 38% during the omicron outbreak). Vaccination was most effective in the second half of pregnancy (69% v 38%). The study lends weight to advice to pregnant women to get vaccinated.

*Cite this as: N Engl J Med doi: 10.1056/NEJMoa2204399*

Consigning hepatitis C to history

In my working lifetime, hepatitis C has become identifiable, treatable, and now curable. The WHO target of elimination by 2030 seems a possibility, but the challenge is to find and persuade people who inject drugs (PWIDs) to complete treatment. This community based longitudinal cohort study of 1323 PWIDs in Baltimore with chronic hepatitis C found elimination of hepatitis C virus (HCV) in over half of participants after treatment (detectable HCV RNA 100% in 2006 and 48% in 2019). The risk of cirrhosis and death fell significantly among those with undetectable HCV RNA.

A small caveat is that the non-invasive measures of liver stiffness used in this study as a marker for liver fibrosis haven’t been validated in people who have been cured of hepatitis C. But it seems clear that elimination of HCV reduces liver disease and saves lives.

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Investigating suspected lung cancer

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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. To suggest a topic for this series, please email us at practice@bmj.com

A 49 year old woman who has never smoked has a telephone follow-up appointment with a GP. She originally consulted one month ago with tiredness and non-exertional chest pain. Her phone call today is to receive the results of an electrocardiogram (ECG) and blood tests, which were organised following her initial presentation. She reports that her symptoms have not resolved.

Globally, an estimated 10-25% of lung cancer cases occur in people who have never smoked; additionally, if lung cancer in non-smokers were considered a separate disease, estimates suggest that it would be the seventh most prevalent cancer worldwide.1 Nonetheless, increasing age and tobacco exposure are still the most important risk factors,2 and lung cancer (irrespective of smoking status) is the leading cause of cancer death worldwide.3

Outcome is closely correlated to stage at diagnosis,4 but the high prevalence of common lung cancer symptoms (such as cough) presenting in primary care can make timely diagnosis difficult.5

WHAT YOU NEED TO KNOW

- Up to a quarter of lung cancers are diagnosed in people who have never smoked
- Consider chest radiography and urgent specialist referral or advice for unusual presentations that are not explicitly listed in local referral pathways
- Unexplained haemoptysis warrants urgent referral (within 14 days) for computed tomography imaging
- Inform patients when you anticipate that positive radiography and/or blood tests might provide insufficient reassurance to exclude lung cancer/other serious illness and advise that further investigations may be needed

How is risk assigned?

Symptoms that indicate risk of lung cancer are typically presented as positive predictive values (PPVs), which represent the risk that a patient with symptoms, or a collection of symptoms, has lung cancer (figure). In this article we consider symptom PPVs of ≥ 3% as representing a “high risk,” 1-3% as “moderate risk,” and ≤1% as “low risk.” Specific PPVs for uncommon presentations are unknown. The National Institute for Health and Care Excellence (NICE) recommends a 3% PPV threshold for urgent suspected cancer referrals.1 The presence of more than one clinical feature substantially increases the risk of lung cancer.

PPVs for individual features and combinations of two features, derived from a case-control study aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients, are reproduced in figure 1.6 Other studies and a meta-analysis have different estimates for PPVs for haemoptysis, cough, dyspnoea, and weight loss; these are summarised in the full NICE guideline.7-10
Table 1 | Percentage of patients who presented with symptoms in the year prior to lung cancer diagnosis, from a cohort of 27 795 patients^{12}

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>% of patients with each symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>26.3</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>16.3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>3.8</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.0</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Box 1 | Summary of NICE guidance on investigations for suspected lung cancer^{13}

- Refer people using a suspected cancer pathway referral (appointment within two weeks) if
  - Chest radiograph findings suggest lung cancer or
  - They are 40 or over with unexplained haemoptysis.
- Offer urgent chest radiography (within two weeks) to people aged 40 or over if they have two or more of the following unexplained symptoms, or if they have ever smoked and have one or more of the following unexplained symptoms:
  - Cough
  - Fatigue
  - Shortness of breath
  - Chest pain
  - Weight loss
  - Appetite loss
- Consider urgent chest radiography (within two weeks) in people aged 40 and over with any of the following:
  - Persistent or recurrent chest infection
  - Finger clubbing
  - Supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
  - Chest signs consistent with lung cancer
  - Thrombocytosis

Box 2 | Uncommon symptoms, signs, and syndromes associated with lung cancer

The following presentations, for which positive predictive values are not available, have been identified by the authors through their clinical practice and are intended to highlight the myriad ways in which lung cancer can present. They do not constitute a comprehensive list.

**Symptoms**
- Unilateral wheeze
- Hoarseness or stridor
- Shoulder pain

**Sign**
- Hypertrophic pulmonary osteoarthropathy (clubbing and periostitis of small hand joints, particularly distal interphalangeal joints)

** Syndromes**
- Superior vena cava obstruction
- Horner’s syndrome (miosis, partial ptosis, apparent anhidrosis)
- Paraneoplastic syndromes including Lambert Eaton myasthenic syndrome, syndrome of inappropriate anti-diuretic hormone secretion, and dermatomyositis

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High prevalence of common symptoms, such as cough, presenting in primary care can make timely diagnosis difficult

**Why is diagnosis challenging?**

In an analysis of 2362 lung cancer cases in the 2010 English National Cancer Experience Survey, about a third of patients presented three times or more before being referred onward.^{11} Haemoptysis is the single symptom that confers the highest risk of lung cancer (figure). However, a serial cross sectional observational study of primary care patients with lung cancer showed that haemoptysis is present in less than 4% of cases (table 1) and, in recent years, has become even less common.^{12} Cough and dyspnoea are more common presentations than haemoptysis (table 1), but because of their ubiquity, the respective PPVs of these symptoms are lower (figure).

**What is the next investigation?**

**Chest radiography**

Chest radiography is the first line investigation for most symptoms consistent with lung cancer, and is relatively inexpensive, widely accessible, and safe to perform. Chest radiography may also identify other causes of patients’ symptoms. Several countries’ guidelines support maintaining a low threshold for requesting chest radiography for low risk symptoms (ie, PPV ≤1% or unknown, figure).^{11-17} Ninety two per cent of 533 primary care patients in a vignette study were supportive of a liberal testing strategy, stating they would wish to have chest radiography if they had a lung cancer risk of 1%.^{18}

NICE recommends urgent chest radiography when certain symptoms are present (box 1). Box 2 includes other possible lung cancer symptoms that are not listed by NICE, and for which PPVs are not available.

A cohort study of 3398 patients diagnosed with community acquired pneumonia showed that 3% of those aged over 50 were diagnosed with a lung cancer within one year.^{19} Based on this, and on guidelines from the British Thoracic Society, we advise arranging chest radiography for patients with persistent symptoms (≥ 6 weeks) after a diagnosis of pneumonia, particularly in those aged over 50 and smokers.^{20}

**How accurate and safe is chest radiography?**

In a cohort of 8996 patients who were investigated because of possible lung cancer symptoms, chest radiography was found to have a sensitivity of 75.4% (95% confidence interval, CI, 67.5 to 83.3) and a negative predictive value of 99.7% (95% CI 99.5 to 99.8).^{21}

Radiation dose of a frontal chest radiograph is low (equivalent to a period of 2-3 days of natural background exposure) (table 2) and need not deter doctors and patients (including patients who are pregnant) from considering investigation.^{22-25}

**How to follow up negative chest radiographs**

When clinical suspicion for lung cancer is high, a negative chest radiograph provides only limited reassurance.^{26} When the radiograph is requested, explain that further assessment may be
only limited reassurance

negative chest radiograph provides

When clinical suspicion is high, a negative chest radiograph provides only limited reassurance

required as lung cancer is not always identified with radiography. NICE recommends providing individually tailored advice—eg, planning for further investigation or assessment if symptoms persist beyond an agreed anticipated timeframe for resolution. Consider inviting patients to involve a family member or friend in these discussions for support on what to do if symptoms persist. If the patient does not meet referral criteria without a positive radiograph (eg, as set out in box 1), make arrangements for follow-up, and ask patients to re-present if they have concerns in the meantime.

For patients judged as moderate or high risk of cancer despite negative radiography—eg, because of specific symptoms (eg, PPV >1%, figure), persistence of symptoms beyond the duration expected for self-limiting illness, patient concern, or doctor intuition—maintain a low threshold for considering urgent specialist referral, further direct access investigation with computed tomography, or—if local pathway criteria for these are not met—obtaining urgent specialist advice. In particular, patients with unexplained haemoptysis require urgent referral for suspected cancer, or urgent investigation with computed tomography if available (eg, within 14 days), without waiting for the results of a chest radiograph.

Non-specific lung cancer symptoms—eg, weight loss, fatigue, appetite loss—are also associated with other diagnostically challenging cancers, including ovarian cancer and myeloma. If concerned for serious disease, when requesting a chest radiograph, plan follow-up for other potential serious disease and avoid offering inappropriate reassurance if the result is negative. In some regions, multidisciplinary diagnostic centres may undertake further investigations for patients with non-specific symptoms.

When clinical suspicion for lung cancer or other serious illness is low, further investigation may not be necessary after a negative chest radiograph. We recommend trying to reach a satisfactory diagnosis for patients who have isolated, low risk symptoms (PPV <1%), such as a cough, which have persisted. Options include arranging spirometry (if asthma or chronic obstructive pulmonary disease is suspected), trial of treatment for a presumptive diagnosis such as proton pump inhibitor for reflux cough, routine (non-urgent) referral for specialist assessment, or arranging repeat chest radiography after 12 weeks, and/or (when indicated) routine investigation with computed tomography if available.

Blood tests

If concern for cancers other than lung cancer will remain if chest radiography is negative, consider blood tests, including full blood count, and inflammatory markers at the same time as imaging, although, normal results do not exclude serious illness. Renal function blood tests may also be required prior to computed tomography with contrast agents.

A cohort study of 31 261 patients with thrombocytosis suggests that thrombocytosis has a PPV for all cancers of 11.6% (95% CI 11.0 to 12.3) for men and 6.2% (95% CI 5.9 to 6.5) for women. Another cohort study showed that inflammatory markers (C reactive protein, plasma viscosity, and erythrocyte sedimentation rate) have a PPV of 3.5% (95% CI 3.4 to 3.7).

Computed tomography

NICE recommends conventional computed tomography with intravenous contrast in the evaluation of suspected lung cancer—for example, following findings on chest radiograph or presentation with haemoptysis. Computed tomography carries a higher radiation dose and a higher risk of iatrogenic harm than chest radiography, although these risks are still low (table 2). It is also more costly, carries more potential for overdiagnosis, and is frequently less accessible. Although evidence from symptomatic populations is lacking, screening studies show that computed tomography is considerably more sensitive than chest radiography in detecting lung cancer. A large screening trial in the US found that the sensitivity and specificity of computed tomography was 93.1% and 76.5%, respectively, compared with sensitivity and specificity of 73.5% and 91.3%, respectively, for chest radiography.

A recent negative computed tomography screen (eg, within the last year) does not rule out lung cancer if new symptoms develop, as rapidly advancing cancers that arise between screening rounds (“interval cancers”) have been observed.

Competing interests. See bmj.com.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The text of this article was reviewed by four patient and public representatives, including a patient who has received a diagnosis of lung cancer, a patient who has experienced lung cancer screening, and two people who have had family members with lung cancer. After their feedback, the manuscript was amended to suggest that GPs explain that chest radiography does not always detect lung cancer, that involving a family member or friend may help patients retain follow-up guidance, and that patients who require further investigations following a negative chest radiograph are advised of this when the radiograph is requested.

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Radiation dose of investigations using ionising radiation, with equivalent duration of background radiation

<table>
<thead>
<tr>
<th>Modality</th>
<th>Effective dose (mSv)</th>
<th>Equivalent duration of background radiation (3 mSv/year)</th>
<th>Lifetime additional risk of fatal cancer per examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>0.02</td>
<td>3 days</td>
<td>1 in 1 000 000</td>
</tr>
<tr>
<td>Computed tomography scan of chest</td>
<td>8</td>
<td>2 years, 1 222 days</td>
<td>1 in 2 500</td>
</tr>
</tbody>
</table>

mSv=millisieverts. Background radiation is assumed to be 3 mSv per year. These values are estimates, and actual doses vary depending on body habitus, imaging protocols, and equipment used.

Table 2: Radiation dose of investigations using ionising radiation, with equivalent duration of background radiation.
Epilepsy is one of the most common and serious neurological disorders worldwide, affecting about 50 million people, and more than 600 000 people in the UK. Epilepsy is a symptom of different underlying causes. Many different types of epilepsy and epilepsy syndromes exist, varying in terms of presentation, management, and prognosis. Epilepsy represents far more than seizures alone, and is associated with complex cognitive, developmental, psychological, and psychosocial comorbidities.

Seizures also have significant risks, including injuries and premature mortality. Epilepsy consequently has high socioeconomic costs. The holistic care of people with epilepsy could be improved through a standardised approach underpinned by a comprehensive guideline.

The National Institute for Health and Care Excellence (NICE) initially published guidance on the management of people with epilepsy in 2004, with a limited update (to pharmacological treatment) in 2012. Since then, important advances have occurred in the diagnosis, treatment, and holistic management of people with epilepsy, highlighting the need for an update to the guideline.

Epilepsy is associated with complex cognitive, developmental, psychological, and psychosocial comorbidities.

While specialist teams commonly manage epilepsy, primary care and non-specialists play a vital role in the identification, referral, early management, and provision of information and support to people with epilepsy, their families, or carers. This article summarises the most recent recommendations from the NICE guideline on epilepsies in children, young people, and adults, with an emphasis on aspects most relevant for primary and secondary care. Evidence levels for the recommendations are in the full version of this article on bmj.com.

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 development group’s experience and opinion of what constitutes good practice.

Diagnosis and assessment

People with epilepsy receive a diagnosis after two unprovoked seizures, or after a single seizure when assessment suggests a high risk of further events. A first seizure may significantly affect a person’s life. Diagnosing a paroxysmal event as a seizure is complex. People presenting with a suspected first seizure should, therefore, be referred urgently (for an appointment within two weeks) to ensure that a specialist (an adult or paediatric neurologist who undertakes continuing professional development in the investigation, diagnosis, and management of epilepsy) is involved early in diagnosis. The likelihood of having a further seizure differs between individuals, and quantifying the risk of a second seizure is challenging. The updated guideline contains recommendations aimed at minimising seizures and risks associated with them; avoiding potential provoking factors for seizures, including specific factors to consider when assessing the likelihood of a second seizure occurring; and for conducting initial investigations. It also includes updated recommendations about information and support to offer patients after a first seizure, and provides comprehensive advice on activities of daily living for people with epilepsy (box 1).
Topics to discuss with people with epilepsy and their families and carers

Activities of daily living
- Safety issues, including activities to be adapted or avoided; for example, showering rather than having baths, cooking safely, caring for babies and young children safely, and avoiding working at heights
- Safety issues for children and young people, including supervised swimming and water sports, and not climbing above their height without supervision
- Potential impact on lifestyle and social life and any experiences of social exclusion
- Driving, including Driver and Vehicle Licensing Agency regulations
- Employment and education, including concerns and rights related to employment and education

Carers
- Physical and emotional demands of caring for and supporting a person with epilepsy
- Information and support for carers, including assessing carers’ needs (see also NICE’s guideline on supporting adult carers)

Cognition
- Concerns about the impact of epilepsy and anti-seizure medication on cognitive function, including memory, attention, concentration, educational attainment, and performance in the workplace

Medication
- Adherence to anti-seizure medication and how to improve this (see also NICE’s guidelines on medicines adherence and medicines optimisation)
- Experiences of side effects from medication, and coping strategies
- Explaining changes to medication

Mental health
- Emotional health and psychological wellbeing, for example, experience of depression, anxiety, or low mood (see also NICE’s guidelines on depression in adults with a chronic physical health problem, depression in children and young people, and mental health problems in people with learning disabilities)
- Neurobehavioural disorders commonly associated with epilepsy, including autism and attention deficit/hyperactivity disorder
- Stigmatisation of epilepsy

Reproductive health and pregnancy
- Support and information on contraception and pregnancy for women and their partners to enable them to make informed decisions
- Support for changes in medications and the potential interactions with contraception
- Teratogenicity of medications
- Pre-conception planning, including the use of folic acid and reducing risk related to epilepsy during pregnancy
- Planning the birth
- Postnatal care and breastfeeding.

Sudden unexpected death in epilepsy (SUDEP)
- Concerns of people with epilepsy and their families and carers about SUDEP
- Information about SUDEP, including risk factors for SUDEP and how to reduce the risks
- Availability of SUDEP counselling

Assessing the risk of a second seizure
- When a child, young person, or adult presents with a first seizure, carry out an individualised assessment of their risk of a second seizure.
- In adults, assessment should include checking for the following modifiable factors that may increase the risk of a second seizure:
  - An underlying mental health problem (such as depression, anxiety, psychosis, and alcohol or substance misuse)
  - Vascular risk factors (for example, diabetes, hypertension, atrial fibrillation)
- Be aware that children presenting with a first afebrile seizure (seizure without a fever) are at an increased risk of further afebrile seizures, especially within six to 12 months, compared with children with a febrile seizure (seizure with a fever).
- Be aware that children presenting with complicated febrile seizures (febrile seizures that last longer than 10 minutes or febrile seizures associated with other features, such as weakness, on one side of the body) may be at higher risk of epilepsy, especially if other predisposing risk factors for epilepsy are present.
- Using a person centred approach, discuss with the person, and their family and carers if appropriate, their individualised risks for further seizures. This should include any mental, physical, and social factors identified as possible risk factors and how these may be modified.

Initial investigations

Neuroimaging
- Offer a magnetic resonance imaging (MRI) scan to children, young people, and adults diagnosed with epilepsy, unless they have idiopathic generalised epilepsy or self-limited epilepsy with centrotemporal spikes. The MRI should be carried out:
  - Within six weeks of the MRI referral and
  - Following regionally agreed epilepsy MRI protocols.
- If MRI is contraindicated, consider a computed tomography scan for children, young people, and adults with epilepsy.

Electroencephalogram (EEG)
- If the person’s history and examination suggest an epileptic seizure, and a diagnosis of epilepsy is suspected, consider a routine EEG carried out while awake to support diagnosis and provide information about seizure type and epilepsy syndrome.
- Do not use EEG to exclude a diagnosis of epilepsy.
- If an EEG is requested after a first seizure, perform it as soon as possible (ideally within 72 hours of the seizure).

Principles of treatment, safety, monitoring, and withdrawal
Anti-seizure medications are the mainstay of treatment in epilepsy. Epilepsy is a treatable condition and around 70% of people with epilepsy will become free of seizures with appropriate medication. Before starting medication, discuss with the patient an individualised strategy,
People presenting with a suspected first seizure should be referred to a specialist within two weeks

Box 2 | Monotherapy for focal seizures with or without evolution to bilateral tonic-clonic seizures

- Consider lamotrigine or levetiracetam as first line monotherapy for people with focal seizures. If the first choice is unsuccessful, consider the other of these options.

In April 2022, these were off-label uses of lamotrigine in children under 13 and levetiracetam in children and young people under 16. See NICE’s information on prescribing medicines.15
- If first line monotherapies are unsuccessful in people with focal seizures, consider one of the following second line monotherapy options:
  - Carbamazepine
  - Oxcarbazepine
  - Zonisamide.

If the first choice is unsuccessful, consider the other second line monotherapy options.

In April 2022, these were off-label uses of oxcarbazepine in children under 6 and zonisamide in children. See NICE’s information on prescribing medicines.15
- If second line monotherapies tried are unsuccessful in people with focal seizures, consider lacosamide as third line monotherapy.

In April 2022, this was an off-label use of lacosamide in children under 4. See NICE’s information on prescribing medicines.15

Box 3 | Monotherapy for generalised tonic-clonic seizures

- Offer sodium valproate as first line monotherapy for generalised tonic-clonic seizures in:
  - Boys and men
  - Girls under 10 and who are unlikely to need treatment when they are old enough to have children
  - Boys and men

- Offer lamotrigine or levetiracetam as first line monotherapy for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). If the first choice is unsuccessful, offer the other of these options.

In April 2022, these were off-label uses of lamotrigine in children under 13 and levetiracetam in adults and children. See NICE’s information on prescribing medicines.15
- If first line monotherapy with sodium valproate is unsuccessful for generalised tonic-clonic seizures, offer lamotrigine or levetiracetam as second line monotherapy treatment. If the first choice is unsuccessful, try the other of these options.

In April 2022, these were off-label uses of lamotrigine in children under 13 and levetiracetam in adults and children. See NICE’s information on prescribing medicines.15
- Do not offer sodium valproate monotherapy for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children) unless:
  - Other treatment options are unsuccessful
  - The risks and benefits have been fully discussed, including the risks to an unborn child
  - The likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.

Follow the MHRA safety advice on valproate use by women and girls.14

considering the epilepsy type, personal preferences, and the individual’s circumstances. The updated guideline stresses the importance of taking the fewest medicines possible to optimise seizure control. The guideline also includes new recommendations on safety considerations, with a focus on information, support, and individualised treatment plans. Specific recommendations for the support and monitoring of women and girls or women planning a pregnancy or who are pregnant are provided.

When to start anti-seizure medication

- Start treatment with an anti-seizure medication once the diagnosis of epilepsy is confirmed.
- Consider starting treatment after a first unprovoked seizure if any of the following apply:
  - An examination identifies signs of neurological deficit
  - The EEG shows unequivocal epileptic activity
  - After a discussion of the risk of further seizures, the person or their family or carers consider the risk unacceptable
  - Brain imaging shows a structural abnormality.

Anti-seizure medications for women and girls

- Refer women and girls with epilepsy who are planning pregnancy or are pregnant to an epilepsy specialist team for a review of their anti-seizure medication options.
- Give women and girls with epilepsy information and support that is tailored to their age-specific and developmental needs. Review regularly information provided about:
  - Contraception
  - Folic acid supplementation
  - Conception
  - Pregnancy
  - Breastfeeding
  - Caring for children
  - Menopause.

- Discuss with women and girls with epilepsy who are able to have children (including young girls who are likely to need treatment when they are able to have children), and their families or carers if appropriate, the risks to an unborn child of taking anti-seizure medications during pregnancy, such as congenital malformations, neurodevelopmental impairments, and fetal growth restriction.
- Assess the risks and benefits of treatment with individual anti-seizure medications when prescribing anti-seizure medications for women and girls who are able to have children, now or in the future. Take into account the latest data on the risks to the unborn child and be aware of important uncertainties about the risks, particularly with newer drugs. Follow the MHRA safety advice on anti-epileptic drugs in pregnancy.15
- Specifically, discuss the risks to the unborn child of using sodium valproate during pregnancy, including the increased risk with higher doses and polytherapy. Follow the MHRA safety advice on valproate use by women and girls.14
Monitoring and review

- Arrange regular (at least annual) monitoring reviews for adults with epilepsy and any of the following:
  - A learning disability
  - Drug resistant epilepsy
  - A high risk of SUDEP (see the section below "Reducing the risk of epilepsy-related death including sudden unexpected death in epilepsy")
  - A serious comorbidity, such as a complex psychosocial, cognitive, or mental health problem
  - Adults who are taking anti-seizure medications associated with long term side effects or drug interactions
  - Adults who are able to get pregnant and are taking valproate or any other high risk teratogenic anti-seizure medication (see also the MHRA safety advice on antiepileptic drugs in pregnancy). 3
- Discuss monitoring reviews with children and young people with epilepsy and their families and carers, and agree a frequency for regular reviews that is:
  - Individually tailored to the child or young person’s needs, preferences, and the nature of their epilepsy, and
  - At least every 12 months.

Discontinuing anti-seizure medication

Discontinuing anti-seizure medication is a nuanced decision that should be made based on the individual’s preferences and individualised risk of seizure recurrence. The updated guideline retains the recommendation to conduct an individualised assessment by a specialist if there are doubts or concerns of the risk of seizure recurrence in those who have been two years without seizures, and focuses on specific factors to take into consideration when agreeing on a plan for discontinuing anti-seizure medication.

Management of focal seizures with or without evolution to bilateral tonic-clonic seizures

Focal seizures originate in one part of the brain and may evolve during the clinical course of the seizure to involve a wider area of the brain resulting in tonic-clonic seizures—these are referred to as focal to bilateral tonic-clonic seizures (previously called secondarily generalised tonic-clonic seizures). New evidence was identified to provide guidance on the management of focal seizures with or without evolution to bilateral tonic-clonic seizures (box 2).

Management of generalised tonic-clonic seizures

Generalised tonic-clonic seizures are common among many different epilepsy types. These are defined as seizures that rapidly engage both sides of the brain from onset.

New evidence was identified to provide guidance on the management of generalised tonic-clonic seizures (box 3).

Referral to tertiary epilepsy services

While diagnosis should be made by specialist physicians with expertise in epilepsy and management may remain local thereafter, specific circumstances warrant referral to tertiary epilepsy services. The updated guideline strengthens previous recommendations for referral to specialist services for further advice, investigations, and management. The updated guideline includes new criteria for immediate referral; however most recommendations are in line with the previous guideline.

Introducing the risk of epilepsy-related death, including sudden unexpected death in epilepsy

Epilepsy associates with mortality from a range of causes, one of which is SUDEP. The lifetime risk of SUDEP is estimated to be between 7% and 12%. The updated guideline provides recommendations on when to discuss epilepsy related mortality, how to reduce this risk, and the co-occurring conditions that may increase it.

- Potentially modifiable risk factors for SUDEP include:
  - Non-adherence to medication
  - Alcohol and drug misuse
  - Having focal to bilateral tonic-clonic seizures or generalised tonic-clonic seizures
  - Having uncontrolled seizures
  - Living alone
  - Sleeping alone without supervision.
- The risk of epilepsy related death is increased in people with:
  - Previous brain injury
  - Previous central nervous system function
  - Metastatic cancer
  - Previous stroke
  - Abnormal neurological examination findings.
- Discuss the possibility of introducing or increasing night time supervision, for example, a parent or carer may wish to use a night monitor for people with epilepsy who have seizures during sleep and have been assessed to be at higher risk of epilepsy related death.
- Support people with epilepsy to take their medications as prescribed to reduce seizures. Explain that uncontrolled seizures increase the risk of epilepsy related death, particularly for people with generalised tonic-clonic seizures or focal to bilateral tonic-clonic seizures. Follow the recommendations in NICE’s guideline on medicines adherence.

Epilepsy specialist nurses

Epilepsy specialist nurses are embedded in practice and play a key role in assisting other healthcare providers in primary, secondary, and tertiary care settings, as well as educational and social care settings. The updated guideline puts marked emphasis on this and used the evidence to determine the common features of clinically and cost-effective epilepsy specialist nurse interventions.

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 people with epilepsy, carers and members with lived experience of epilepsy and use of relevant services, all of whom contributed to the formulation of the recommendations summarised here.
A woman in her 20s presented with a two year history of annular plaques on the neck, shoulders, chest, abdomen, back, and upper limbs (figure). The lesions started as erythematous papules and plaques, then gradually increased in number and slowly extended centrifugally. The woman attended local hospitals several times, and oral antihistamines and topical corticosteroid ointment were prescribed, but the lesions gradually expanded and some coalesced. There was no drug intake before the eruption started.

Laboratory tests revealed a fasting glucose level of 7.8 mmol/L (normal range 3.9-5.6 mmol/L), a postprandial glucose level of 16.1 mmol/L (normal value <7.8 mmol/L), and a glycated haemoglobin (HbA1c) of 57 mmol/mol (7.4%). Complete blood count, thyroid hormone levels, and blood lipid profile were all within normal limits.

A skin biopsy taken from the patient’s neck showed a palisading granulomatous infiltrate composed of lymphocytes and histiocytes around a central zone of degenerated collagen and increased amount of mucin.

What is the diagnosis?

**SPOT DIAGNOSIS**

**Generalised annular plaques on the trunk**

Well demarcated, erythematous, annular plaques with raised edges consisting of small, firm, skin coloured or erythematous papules

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**LEARNING LEVEL**

underlying diseases may contribute to lesion

- uncontrolled diabetes
- uncontrolled renal disease
- rheumatoid arthritis
- leprosy
- HIV
- hepatitis
- sarcoidosis

**PATIENT OUTCOME**

The patient began daily insulin injections and oral hydroxychloroquine 400 mg per day. The lesions gradually flattened three months later and had completely disappeared at an 18 month follow-up.

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**LEARNING POINT**

- Generalised granuloma annulare may be associated with diabetes, malignancy, lipid metabolism disorder, thyroid disease, rheumatoid arthritis, and HIV, hepatitis B, and hepatitis C infection.

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Cigarette smoking and heart failure

Almost all diseases are made worse by smoking cigarettes and heart failure is no exception. A longitudinal study from the US finds that risk of heart failure is roughly doubled in people who smoke. This is true both for heart failure with preserved ejection fraction and for heart failure with reduced ejection fraction. Although the risk fell in people who stopped smoking, it took decades to reach the level of non-smokers (The American Journal of Cardiology doi: 10.1016/j.jacc.2022.03.377).

Managing unruptured intracranial aneurysms

A microsimulation model was used to compare costs and benefits of annual surveillance, using magnetic resonance imaging (MRI), of middle aged women diagnosed with an unruptured intracranial aneurysm in the US, the UK, and the Netherlands. Only in the Netherlands did it approach cost effectiveness, at a threshold of £80 000/quality adjusted life year. Around 2000 women needed to undergo an annual MRI scan to prevent one case of subarachnoid haemorrhage per year (Neurology doi: 10.1212/WNL.00000000000200785).

Hunger influences mood

There’s a fine line between research that puts what everyone assumes to be true on a secure evidential footing and proving the blindingly obvious. Straddling this line is a study of 64 people who kept diaries of what they ate and their emotional state over three weeks. It found that greater levels of self-reported hunger were associated with feelings of anger and irritability, and with reduced pleasure (PLoS One doi: 10.1371/journal.pone.0269629).

Appetite suppressing peptides

Glucagon-like peptide-1 analogues are effective treatments for obesity but they carry the disadvantage that they have to be injected. A synthetic 9-amino acid peptide could be a step forward. Oral administration of this peptide led to a lowering of leptin resistance, up-regulation of uroguanylin expression, and a 10% reduction in body weight. So far, these effects have been observed only in mice, rats, and macaque monkeys (Gut doi: 10.1136/gutjnl-2022-328035).

Outpatient treatment of appendicitis

A secondary analysis of data from a trial of antibiotics for acute appendicitis suggests that it’s safe to discharge people within 24 hours of presentation providing they are haemodynamically stable, afebrile, able to tolerate oral fluids, and without severe pain. Over the seven days following discharge, serious adverse events occurred in less than 1%, and were no more frequent than in people treated as inpatients (JAMA Network Open doi: 10.1001/jamanetworkopen.2022.20039).

Greater levels of self-reported hunger were associated with feelings of anger and irritability

Precision treatment for rheumatoid arthritis

There is an old joke that power from controlled nuclear fusion is just 20 years away—and it always will be. Minerva sometimes thinks that a similar jibe could be made about precision medicine. Prediction of treatment responses in people with rheumatoid arthritis using molecular patterns in biopsied synovial joint tissue might be a counter example. Elevated myeloid signatures correlated with better responses to tocilizumab, while low B cell signatures signalled suboptimal results with rituximab. However, these findings emerged in a retrospective analysis, and they’ll need validation (Nature doi: 10.1038/s41591-022-01857-5).

Myocardial infarction in people with type 1 diabetes

No one needs reminding that type 1 diabetes is a risk factor for myocardial infarction. Less obviously, the presence of diabetes means that outcomes of acute cardiac events are worse. A series of 2000 cases from Finland shows that case fatality after myocardial infarction was 50% higher in patients with type 1 diabetes than in controls without diabetes at both 30 days and one year (Diabetes Care doi: 10.2337/dc22-0042). 

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