education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Trial reporting not up to scratch

DeVito et al used the ClinicalTrials.gov database to assess compliance with the FDA regulation to report results within a year of trial completion in the US. Only 40.9% reported results within one year, and 63.8% of trials posted results at any time. I applaud the authors for their rigorous analysis and spotlight on a critical deficiency in clinical research, but I object to them throwing the book at regulators. The roots of failure to report clinical trials run deep in academia. Enforcement of regulation doesn't help overcome the barriers to reporting. While this study reports factors associated with better reporting rates, data on why the unreported trials remain unreported are not available. There needs to be a carrot to incentivise good practice rather than the stick of public shaming.

Lancet doi:10.1016/S0140-6736(19)33220-9

New thromboprophylactic after knee arthroplasty

The phase II FOXTROT trial randomised over 800 people undergoing knee arthroplasty to osocimab, enoxaparin, or apixaban in an open label fashion and measured incidence of venous thromboembolism. Bilateral venography was compulsory at 10-13 days after surgery, thereby allowing the detection of subclinical venous thromboembolism. Osocimab is a monoclonal antibody against factor XIa. The main finding of the trial was that osocimab was non-inferior to enoxaparin. An interesting aspect of this trial, however, was not only the testing of various doses, but also the testing of preoperative and postoperative administration of the new drug. Bleeding rates were not negligible in the highest dose, particularly in the preoperative dosing regimen.

JAMA doi:10.1001/jama.2019.20687

Lupus outcomes in the limelight

Systemic lupus erythematosus has varied clinical manifestations, making assessment of therapeutic success challenging. The TULIP-2 trial is a lesson in endpoint selection. The trial randomised 365 people with lupus to anifrolumab or placebo in a double blind fashion. The primary endpoint was the BICLA, which is a composite of seemingly patient centred outcomes. You either "responded" as measured by BICLA or you didn't: 47.8% of patients in the anifrolumab group responded compared with 31.5% in the placebo group. This could be good news for patients. The new drug comes with an added risk of herpes zoster, but otherwise appeared safe in this sample. The benefit seen here contrasts with a previous anifrolumab study (TULIP-1), in which the drug showed no benefit as measured by Systemic Lupus Erythematosus Responder Index (another composite of patient centred outcomes). So do we believe the anifrolumab is a useful drug? I'm going to go out on a limb to say, yes, I believe. That should save another fairy.

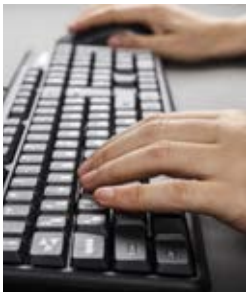
N Engl J Med doi:10.1056/NEJMoa1912196

SGLT2 inhibitors and gout protection

Fralick et al conducted a cohort study of almost 300 000 patients in the US with type 2 diabetes looking at rates of gout. To assess the risk of gout in users of sodium-glucose cotransporter 2 (SGLT2) inhibitors, they chose a comparator group of users of glucagon-like peptide-1 (GLP-1) agonists. This isn't unreasonable as both drugs are in a similar standing in the pathway of treatment escalation. However, there will be differences in characteristics between the users of one drug and the users of the other drug because this isn't randomised data. Fralick et al found that SGLT2 inhibitors were associated with lower rates of gout than GLP-1 agonists. The theory is that SGLT2 inhibitors reduce serum uric acid levels. While this protective effect is a positive finding, it is slightly misleading to consider gout in isolation. Both drugs, and indeed diabetes itself, carry various risks and benefits that can't easily be weighed up.

Ann Intern Med doi:10.7326/M19-2610

War against the machines



Overhage et al (who have declared financial ties to electronic health record provider Cerner) analysed time spent on Cerner covering 100 million patient encounters by 155 000 physicians from 417 health systems. They report that "physicians spent an average of 16 minutes and 14 seconds per encounter using [electronic health records], with chart review (33%), documentation (24%), and ordering (17%) functions accounting for most of the time." This is a lot of time but not surprising. The paper does a good job in laying the groundwork for Cerner to present us with some solutions or improvements, but I won't be holding my breath.

Ann Intern Med doi:10.7326/M18-3684

Alex Nowbar is a clinical research fellow at Imperial College London

Partial knee replacement could be first choice for some patients with osteoarthritis

The study

The clinical and cost effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial

Beard D, Davies L, Cook J, et al

Lancet 2019;394:746-56

Why was this study needed?

Knee replacement is a common operation to treat severe knee osteoarthritis that has not been adequately helped by other treatments. More than 300 000 knee replacements were carried out in the UK between 2015 and 2017.

Some people have damage to the knee joint on only one side (unicompartmental osteoarthritis) which means they could consider either a partial or total knee replacement. Evidence to suggest which operation works best for these people has, to date, been insufficient.

At present, less than 9% of knee replacements are partial. However, a study of registry data from England suggested that partial knee replacement could be more cost effective than total knee replacement.

The current trial was intended to fill the gap in the evidence and inform practice.

What did this study do?

TOPKAT (Total or Partial Knee Arthroplasty Trial) was a randomised controlled trial carried out at 27 sites across the UK, involving 68 surgeons and 528 patients.

The sites recruited people who were being considered for knee replacement, who had osteoarthritis of the medial compartment of the knee. This meant they would be suitable for either partial or total knee replacement.

People were randomly assigned to one or other operation.

Among the 528 people randomised, 44 had a knee replacement using the technique they had not been assigned to. This was either because of patient choice or surgeon decision once surgery was under way. For example, partial knee replacement was not possible if the arthritis was more widespread than expected.

Participants were followed up for five years and checked annually.

The results should be relevant to UK hospitals, assuming they have surgeons with sufficient expertise in partial knee replacement.

What did it find?

- Both groups of patients had much improved knee pain and function, assessed by the 48 point Oxford knee score. After five years, people who had total knee replacement had an 18 point improvement and people who had partial knee replacement had a 19 point improvement. A 5 point difference is considered clinically significant, so the two procedures were similar for this outcome.
- The study's cost effectiveness analysis found that partial knee replacement was more effective in terms of quality of life, resulting in 0.24 additional quality adjusted life years (QALYs) over five years. It was also less expensive, with care costing £910 less over the five years of follow-up.
- Average hospital stay was longer for total knee replacement (4.3 days) than for partial knee replacement (3.2 days).
- The proportion of people who had a re-operation was similar in both groups.

What does current guidance say on this issue?

The guideline on osteoarthritis published by the National Institute for Health and Care Excellence (NICE) in 2014 includes recommendations on referral for consideration of joint replacement. However, it does not include guidance on which type of joint replacement device or technique is recommended. This guideline is being updated, with the update due to be published in August 2021.

In addition, a NICE guideline on primary joint replacement of the hip, knee, or shoulder is in development and is expected to be published in March 2020.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies.
Further details of other interests, disclaimers, and permissions can be found on bmj.com

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CPD READING

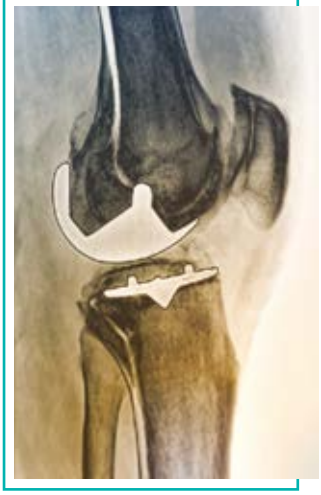
0.5 HOURS

What are the implications?

The results of the study imply that partial knee replacement can be offered with confidence for people with single compartment disease who are considering knee replacement. Offering partial knee replacement as a first choice may be better value for the NHS as it reduces costs, mainly because of shorter hospital stays.

Questions remain about the revision and re-operation rate for partial knee replacement over the longer term, and results from the planned 10 year follow-up of this trial will be of interest.

Surgeons would need to be fully trained and experienced in partial knee replacement in order to be able to replicate the results of this study.



ZEPHR/SPL

PRACTICE POINTER

The patient who reports a drug allergy

CPD READING
0.5 HOURS

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What should clinicians do when a patient gives a history of a "drug allergy"? If it really is an allergy—an immunological reaction—or a serious adverse drug reaction (ADR), then patients risk serious harm unless they avoid the drug. But often, patients and healthcare professionals use "drug allergy" to mean any suspected ADR. Accepting a "drug allergy" at face value can unnecessarily deprive the patient of a potentially useful treatment. It may directly cause harm: patients labelled "allergic to penicillin" are more likely to become infected with methicillin resistant *Staphylococcus aureus* or *Clostridioides difficile*, for instance.[1]

In some cases it may be safe for a patient to take, perhaps in a lower dose, a drug that caused an ADR. Here we offer a guide to help patients and practitioners when the issue of "drug allergy" arises.

A scheme for assessing a patient who describes a drug allergy, based on our experience, is set out in the figure. Begin by trying to establish if the harm was caused by medication, or something else. If it was an ADR, consider whether the reaction was serious, whether it was likely to be a true allergy, and whether it might have been related to the dose.

SOURCES AND SELECTION CRITERIA

We searched MEDLINE to identify any systematic reviews and meta-analyses on drug hypersensitivity. We also used NICE guidance on drug allergy and anaphylaxis and our own collection of references on adverse drug reactions.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked five expert patients from the UK, France, and Italy for their views on an early draft of our paper, and have used their extremely helpful comments and suggestions to make our article more useful for doctors and patients. Their comments led us to revise the algorithm, to adopt a cautious approach to re-exposure, and to consider the international perspective.

WHAT YOU NEED TO KNOW

- Non-immunological adverse drug reactions are often incorrectly labelled "drug allergy"
- Unnecessarily labelling patients "allergic" to a drug can be harmful and can deny them best treatment
- A detailed history can help clinicians decide if re-administration is safe, although specialist tests may be necessary

Box 1 | Definitions

Adverse drug reaction—any unintended harm that a patient suffers from a medicine, eg, oral thrush with a broad spectrum antibiotic

Adverse event—any unintended harm that a patient suffers, whether or not caused by a medicine

Allergy—a harmful immunological reaction from hypersensitivity to a foreign antigen, eg, anaphylaxis from peanuts

Drug allergy—a harmful immunological reaction directly or indirectly caused by a medicine, eg, toxic epidermal necrolysis from carbamazepine

Side effect—any unintended effect of a medicine on a patient, whether beneficial or harmful, eg, pink urine with rifampicin

Box 2 | What constitutes a serious adverse drug reaction?[4]

Serious reactions are those that

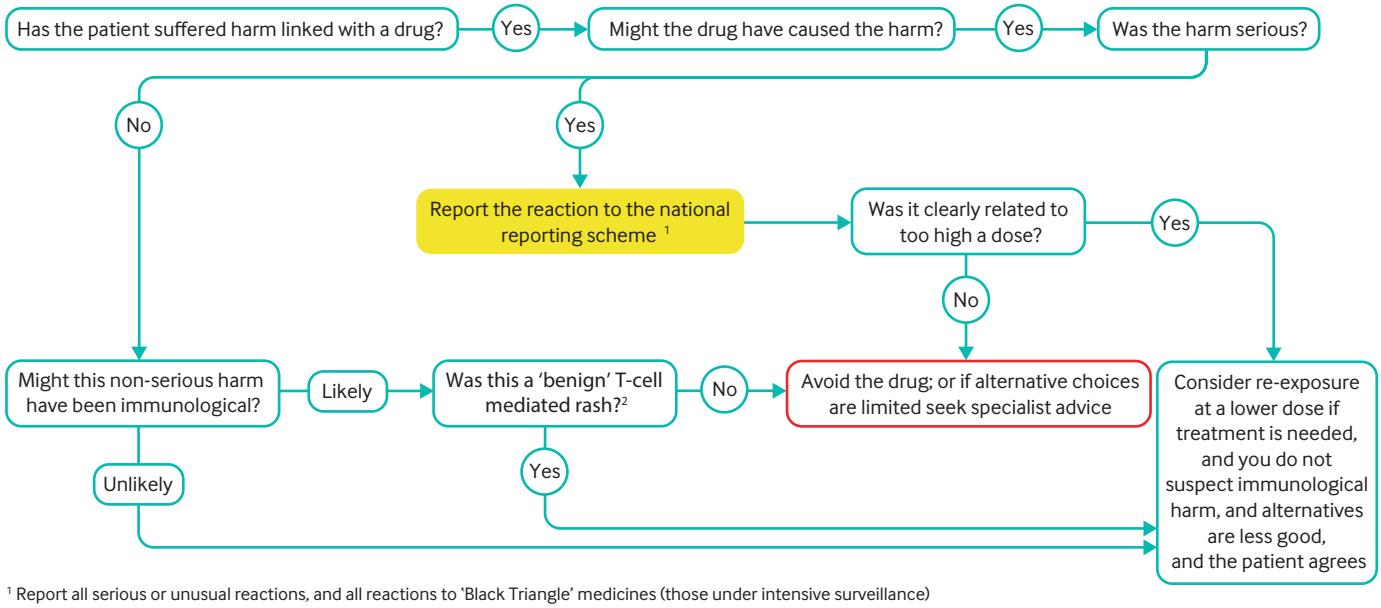
- are fatal
- are life threatening
- cause hospitalisation
- result in persistent or major disability or incapacity
- require intervention to prevent permanent damage, or
- cause congenital anomalies

Did the drug cause the harm?

When taking a drug history, it is better to ask: "Have you had a bad experience with any medicines or drugs?" rather than inquiring about drug allergy (see box 1 for definitions). If the patient volunteers a "drug allergy," a detailed history should help to establish what caused the harm, and whether any ADR was immunological.

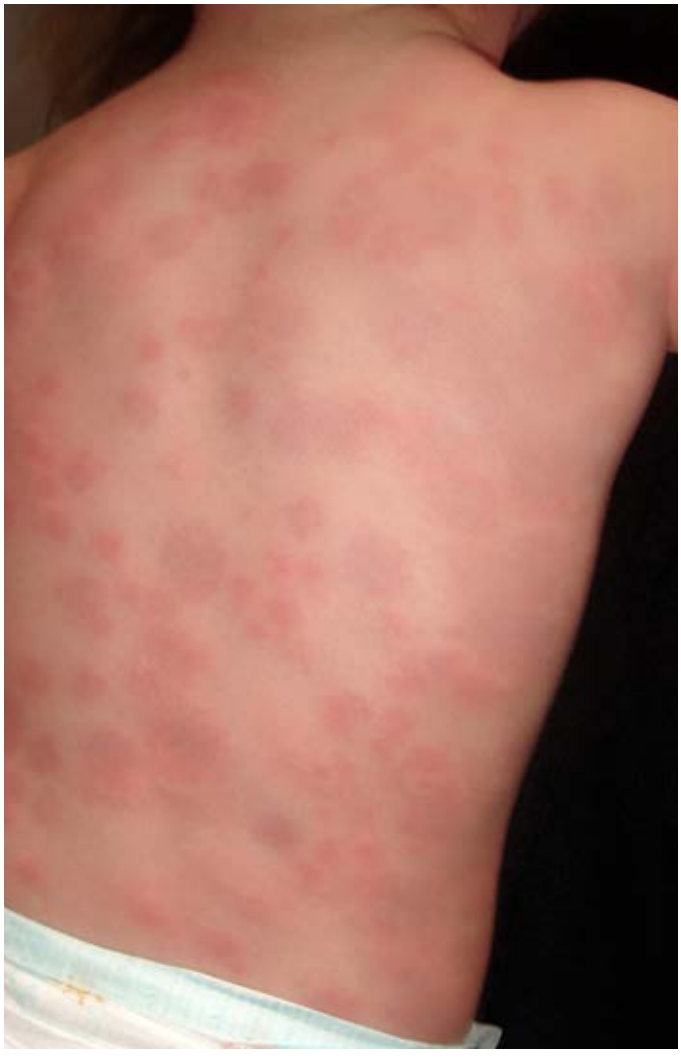
The history will sometimes indicate that the event was likely to be a consequence of the condition that was being treated. For instance, the patient may tell you: "I took clarithromycin tablets for a cough, and then I developed chest pain."

It can be hard to decide if an adverse event is an ADR. Some ADRs have characteristic relations to time of exposure, and characteristic clinical features. Fetal phocomelia after the mother has taken thalidomide in pregnancy is a clear example, but even this clinical picture is not absolutely specific.[2] Formal algorithms can help estimate the probability that a clinical event is an ADR, but they rarely give clear cut answers.[3]



[1] Report all serious or unusual reactions, and all reactions to 'Black Triangle' medicines (those under intensive surveillance)
[2] A T-cell mediated rash is typically morbilliform (it looks like measles) (See Table 2)

An algorithm to guide decisions when a patient reports a "drug allergy"



SPL

Urticaria

Was the ADR serious?

Serious ADRs cause serious harm. The internationally agreed definition of a serious ADR is set out in box 2. Document and report serious ADRs. With a few exceptions—such as bleeding from warfarin—avoid re-exposure to the causative drug.

Patients often describe a well recognised ADR that would not be classified as serious by the formal definition. Examples include oral thrush with antibiotic treatment,[3] or a throbbing headache with glyceryl trinitrate. But even these non-serious reactions can be very unpleasant for the patient, and may limit prescribing choices.

Was it a true allergic reaction?

True allergy is an immunological phenomenon. It is also uncommon: one in 10 Americans is labelled "penicillin allergic," yet only 1 in 100 Americans is reckoned to be at risk of an acute reaction.[5] The most feared form of drug allergy is anaphylaxis. If a patient develops swelling airways, wheeze, hypotension, tachycardia, and urticaria within minutes of an injection of benzylpenicillin, then anaphylaxis caused by a penicillin is the only likely diagnosis.[6] The reaction is caused by mediators released when mast cells degranulate in response to specific antigen binding to IgE on the cell surface. Serum mast cell tryptase activity is very high immediately after mast cell degranulation and falls over the next several hours, so taking a blood sample to measure tryptase activity shortly after onset can help to confirm the diagnosis. As a separate phenomenon, some treatments, such as acetylcysteine used to treat paracetamol poisoning, and the antibiotic vancomycin, can provoke the non-immunological release of mediators from mast cells, which can lead to flushing, wheeze, and hypotension.

Some life threatening immune ADRs have a delayed onset, which can make them difficult to diagnose. For example, toxic epidermal necrolysis[7] can appear after exposure to the causative drug has ceased, but can have an alternative cause, such as viral infection, that is not related to drug exposure.

Table 1 | Immunological skin reactions[8]

	IgE mediated adverse drug reactions (ADRs)	Non-serious T cell mediated ADRs	Serious T cell mediated cutaneous ADRs (SCARs*)
Onset	In minutes to hours	In a few days	In days to weeks
Skin involvement	Urticaria ("hives") Pale, itchy lumps	Morbilliform ("like measles") flat, red, blotchy rash	Blistering, pustules, or skin loss
Mucosal involvement	No	No	Yes: conjunctival, oral, and urogenital mucosae can all be involved
Organ involvement	Yes: in anaphylaxis	No	Yes
Is re-exposure safe?	Only if urticaria is the sole manifestation and skin prick test is negative	Rash may recur; unlikely to cause a serious ADR	Never

*SCARs include Stevens-Johnson syndrome and toxic epidermal necrolysis; drug rash with eosinophilia and systemic symptoms; and acute generalised exanthematous pustulosis

Are all immune reactions serious?

Although serious immune reactions such as anaphylaxis and toxic epidermal necrolysis are a major concern, they are very rare. Non-serious drug rashes are much more common: they occur in up to 5% of patients treated with penicillins and cephalosporins. A systematic review of cutaneous reactions to drugs characterised 95% to be morbilliform drug exanthems and 5% to be urticaria.[8] A simple classification of immune skin reactions can help guide practice (table 1).[9]

What about non-immune reactions?

Emphasis on allergy can distract attention from non-immune ADRs that are acute and life threatening and will recur on re-exposure. Examples include catastrophic haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, caused by exposure to oxidising drugs such as aspirin, primaquine, and sulfonamides; and malignant hyperpyrexia (malignant hyperthermia) provoked by anaesthetic agents. Serious ADRs such as renal or hepatic failure would generally contraindicate re-exposure to the suspected drug cause, whether or not they were immune reactions. Even if they are not serious, it can sometimes be hard to distinguish immunological from non-immunological reactions (table 2).

The effects of drug dose

All pharmacological effects depend on dose. Even in a patient who has had anaphylaxis, the degree of systemic response depends on the dose, which is why skin prick testing is usually possible. Sometimes, the patient will have suffered a serious ADR that depends on the dose within the therapeutic range—for example, bleeding with an anticoagulant; or above the standard therapeutic range, like seizures with intravenous or intrathecal penicillin.[19] Many cancer patients develop dose related neutropenia from drug therapy, but nonetheless resume treatment because the overall benefits outweigh the harms.

Table 2 | Examples of potentially serious adverse drug reactions. Pharmacological and immunological mechanisms can sometimes cause similar clinical features

Clinical feature	Pharmacological mechanism	Immunological mechanism (allergy)
Syncope	Torsade de pointes—eg, with newer antipsychotic agents[10]	Anaphylaxis—eg, to penicillins
Wheeze	Bronchoconstriction—eg, with β-blockers Aspirin exacerbated respiratory disease—with non-steroidal anti-inflammatory drugs[11] Non-immune mast cell degranulation—eg, with hyperosmolar radio contrast media	Anaphylaxis—eg, to penicillins
Abnormal liver function	Toxic liver damage—eg. with high dose paracetamol[12]	With halothane, on re-exposure[13] Cholestasis with flucloxacillin [14]
Renal impairment	Renal tubular damage—eg, with aminoglycoside antibiotics Impaired glomerular blood flow—eg, with angiotensin converting enzyme inhibitors in patients with renal artery stenosis	Tubulointerstitial nephritis with proton-pump inhibitors[15]
Rash	Photosensitive rash—eg, with amiodarone	Drug induced urticaria[16] Toxic epidermal necrolysis[17] Drug induced rash, eosinophilia, and systemic symptoms[18]

Table 3 | Examples of adverse drug reactions where it is reasonable to consider re-exposure

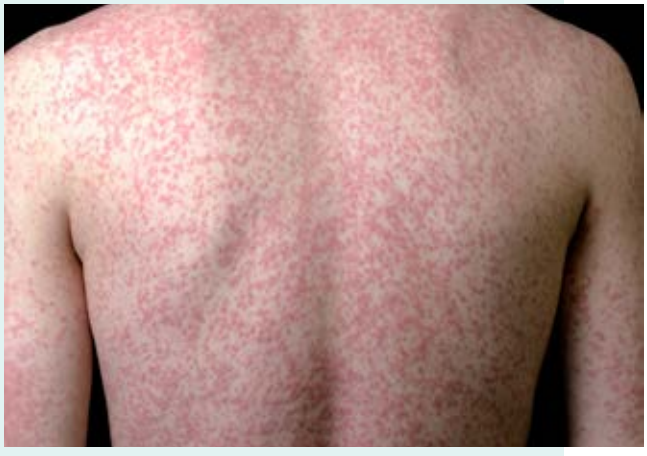
Drug	Reaction	Comments
Acetylcysteine infusion	Flushing	Slow the infusion rate
Broad spectrum antibiotics	Diarrhoea	Advise the patient to cease treatment and to report to prescriber
Corticosteroid inhalers	Oral candida	Rinse mouth after dosing; use a spacer
Antihypertensives	Hypotension	Reduce dose or split dosing during the day Consider evening dosing[20]
Nitrates	Headache	Usually diminishes with continued treatment
Opiates	Constipation	Co-prescribe stimulant laxatives (when starting treatment)
Phenytoin	Cerebellar ataxia	Reduce the dose; keep within therapeutic range
Statins	Muscle pain	If creatine kinase activity is not elevated, discuss the benefit–harm balance with the patient
Warfarin	Bleeding	Identify source; keep within therapeutic INR range

EDUCATION INTO PRACTICE

- When taking a drug history, do you only ask about allergies?
- How do you code harm from drugs on patients' electronic health records?
- How do you keep up to date with new adverse drug reactions?

A RASH WITH AMPICILLIN

A 35 year old woman presents with recurrent impetigo. You want to offer flucloxacillin but she says she is allergic to penicillin. When you ask her to tell you more about it, she says she developed a blotchy rash "like measles" when she was given ampicillin for a sore throat when she had glandular fever as a teenager. Following the algorithm in the figure (p 117), the harm was associated with the drug, but there was no evidence that it was caused by too high a dose, and it was not serious. The association could well have been causal. A little extra knowledge about this ADR is helpful here: people with Epstein-Barr virus infections are especially prone to rashes with aminopenicillins. Most such reactions are transient,[27] and if they do recur, they are unlikely to be provoked by non-aminopenicillins.[28] You explain to your patient that she may have a mild allergic reaction to ampicillin and amoxicillin, but that it should be safe to take other penicillins. She agrees to take flucloxacillin, and to stop the treatment at once and to seek medical advice if the reaction reoccurs. You clearly document the discussion and note on her records that she developed a morbilliform rash with aminopenicillins. All goes well. Your careful analysis of the patient's history of drug allergy allowed you to define the potential cause of her adverse drug reaction and come to a shared decision with the patient to prescribe optimal treatment.



SPL

Morbilliform rash

Making a decision

The prescriber needs to decide whether to prescribe or withhold the medicine or seek specialist advice. It is usually safest to avoid a medicine that may have caused serious harm. This is also prudent if a non-serious ADR was probably immune related, unless it was a morbilliform drug rash (table 1).

Taking a minute or two to consider the history and previous medical records of a reported drug allergy can help to assess the potential risks of re-exposure (table 3). For example, a patient who describes "penicillin allergy" in infancy, but has had repeated treatment with different penicillins as an adult, is at low risk. The additional information allows the prescriber and the patient to reach a shared prescribing decision that balances the risk of a possible ADR against the risk of suboptimal treatment.

When to refer

If a patient has suffered a suspected anaphylactic reaction, the National Institute for Health and Care Excellence (NICE) recommends referral to specialist drug allergy services.[21] Specific allergy tests may be needed to confirm an immunological reaction. NICE also recommends referral for patients who have suffered immune mediated severe cutaneous adverse reactions such as toxic epidermal necrolysis. Family history alone is not a reason for referral. If a drug caused a serious reaction other than anaphylaxis and is needed for the patient's treatment, then seek specialist advice. The same is true of any immunological reaction other than a non-serious "drug rash." Referral may be to a clinical pharmacologist or an allergist, or sometimes to an organ specialist for possible drug induced hepatitis or pneumonitis or after a serious cutaneous reaction.

Laboratory tests have a limited role in preventing ADRs.[22] Rarely—for example with abacavir and HLA-B*5701—genetic tests carried out before the drug is prescribed can identify patients at risk of an ADR. The use of genetic testing to predict drug responses is likely to increase as pharmacogenomics precision improves.[23]

The value of diagnostic tests for immunological drug reactions that occur more than six hours after exposure is disputed.[24]

If too high a dose offers a good explanation for a serious ADR, consider restarting treatment with a lower dose, as would happen after a haemorrhagic event in a patient with a metallic heart valve prosthesis who is treated with warfarin. Rapid increases in serum concentration of drugs such as the antibiotic vancomycin or the paracetamol antidote acetylcysteine can cause mast cell degranulation with histamine release. The resulting ADR, manifested as wheezing, flushing, and hypotension, recovers if the infusion is stopped; and does not recur if the infusion is subsequently given slowly.[25 26]

Competing interests: REF has provided medico-legal reports on adverse drug reactions.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l6791

UNCERTAINTIES

Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis?

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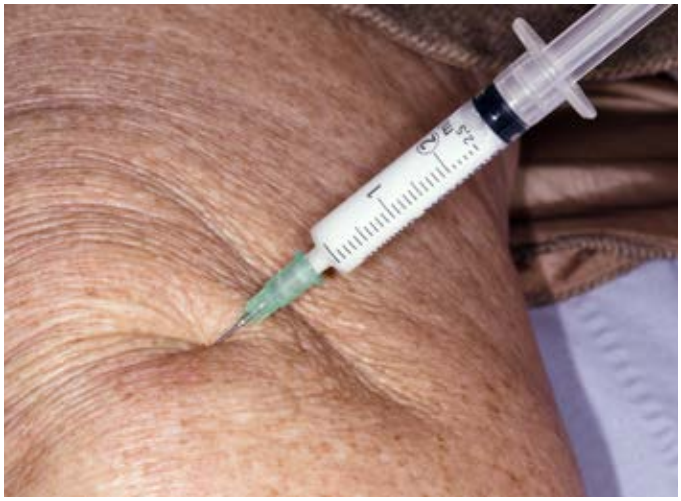
This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com

CPD READING

0.5 HOURS

The prevalence of end-stage knee osteoarthritis requiring joint replacement is increasing globally.[1] Some of this increase is due to increasing obesity and worsening lifestyle factors such as poor physical activity. It also requires us to evaluate whether standard treatments for mild to moderate osteoarthritis are effective.

Intra-articular corticosteroid, also referred to as corticosteroid injection, is widely prescribed for osteoarthritis of the knee. Guidelines, such as those produced by the National Institute for Health and Care Excellence (NICE),[2] have traditionally supported its use,[3] but reviews of efficacy indicate a high degree of uncertainty.[4 5] On average, a patient might have symptomatic knee osteoarthritis for 30 years. It is uncertain how the long term safety or harms of corticosteroid injection balance against the likelihood of short term pain improvement.



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WHAT YOU NEED TO KNOW

- Intra-articular corticosteroid injections possibly improve pain and function in the short term (<8 weeks) in patients with osteoarthritis of the knee, but the evidence is of low quality, and any benefit is not usually sustained beyond 3 months
- Emerging evidence suggests a possible small risk of joint deterioration and worsening symptoms over the long term with intra-articular corticosteroid injections
- Consider the severity of pain, feasibility of other treatment options including exercise, and the patient's preferences regarding risks and benefits when planning treatment

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l6923

What is the evidence of uncertainty?

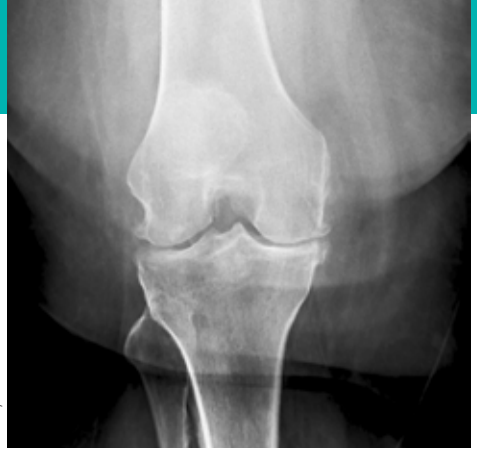
Systematic reviews indicate low quality evidence that intra-articular corticosteroid injections may provide short term pain relief and a small improvement in physical function for up to six weeks in knee osteoarthritis compared with placebo.[4 6] Patients with more severe disease are likely to experience greater improvement.[7] The benefits are not seen to last beyond three months in trials,[4] although individual patients may report longer periods of symptom relief. There is considerable heterogeneity between trials. While corticosteroid injections have been found to be safe in the short term, long term harms have not been well assessed. Recent cohort studies suggest possible risk of progression of osteoarthritis and worsening symptoms in patients prescribed intra-articular corticosteroid.[8 9]

Benefits of intra-articular corticosteroid injection

A Cochrane review of corticosteroid injection for knee osteoarthritis in 2015 (27 randomised controlled trials, 1767 patients) concluded there was low quality evidence of improvement in pain and function compared with placebo over a 1-6 week period.[4] The number of patients needed to treat to gain additional benefit was eight, and average pain improvement was one point on a 10 point scale lasting up to six weeks.[4] The quality of studies was consistently low. The single trial at low risk of bias showed no benefit.

A high quality, well powered, placebo controlled randomised trial (140 patients) published subsequently[7] found no clinical difference in pain reduction with corticosteroid injection every three months compared with placebo for knee osteoarthritis at any stage over a two year follow-up. Measurements were made three months after each injection and so could have missed short term improvements.

A recent systematic review and meta-analysis reported uncertain effect sizes beyond one year for pain improvement for all pharmacological treatments for knee osteoarthritis compared with placebo. Limited evidence from four trials suggests that intermittent corticosteroid injection was not associated with pain improvement in the long term.[5]



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EDUCATION INTO PRACTICE

- Think of a patient you have seen with knee osteoarthritis. Based on reading this article, how would you discuss the risks and benefits of intra-articular corticosteroid injections with your patient?
- Have patients with osteoarthritis at your practice been given detailed information about exercise planning under instruction of a health professional?
- For patients at your practice who were advised cortisone injection for knee osteoarthritis, is there a documented discussion of the risks and benefits before treatment?

Patients with severe pain may experience greater improvement in short term pain (for up to four weeks) with corticosteroid injection compared with placebo, as shown by a meta-analysis of individual patient data (7 randomised controlled trials, 620 patients).[6] However, this meta-analysis combined data for patients with knee osteoarthritis and hip osteoarthritis.

Risks of intra-articular corticosteroid injection

The Cochrane review did not find any evidence of harm from corticosteroid injection in the short term (<6 months). Long term harms were not assessed.

The McAlindon trial mentioned above reported a small (−0.1 mm) but statistically significant deterioration in knee cartilage depth in the corticosteroid injection group on imaging.[7] Cartilage depth and quality is a radiological indicator of worsening disease in osteoarthritis, although its association with clinical progression is not established. An earlier study[10] did not find similar disease progression in terms of joint space reduction on x ray after two years with similar corticosteroid injection regimen. This study was smaller in size (68 patients) and used a less sensitive form of imaging.

Recent cohort studies indicate worsening of pain, stiffness, and function with intra-articular corticosteroid at two year follow-up[8] as well as joint deterioration and progression to total knee replacement.[9] Repeated intra-articular injections of corticosteroids exhibited greater risk of disease progression, but this does not rule out joint deterioration with a single injection.[9] A retrospective study using a national insurance database in the United States highlights possible increased risk of infection after knee surgery in patients who had received a corticosteroid injection in the same knee within three months before surgery.[11 12] A recent case series reported adverse joint events on imaging in 8% (36/459) of patients with hip and knee osteoarthritis who had received at least one intra-articular corticosteroid injection in the preceding year.[13] This study has several limitations but warrants further investigation into risks of disease worsening.

What should we do in light of this uncertainty?

Intra-articular corticosteroid injection possibly offers a small and transient improvement in symptoms of knee osteoarthritis, which must be offset against some risk of disease worsening in the long term.

Most of the uncertainty relates to the ability of the clinician and patient to weigh up the risks and benefits and to consider whether the short term or long term outcome is more important for a particular patient. There is possibly a place for corticosteroid injections in frail elderly patients, for example, who have severe pain from knee osteoarthritis but are unsuitable for joint replacement. However, for younger and middle aged patients with an expectation of minimising disease progression, longer term risk-benefit profile is generally more important, although short term improvement may occasionally be important in younger patients, such as before an overseas holiday.

Other treatments for knee osteoarthritis

The evidence for the benefit of exercise and weight loss in osteoarthritis continues to accrue.[2 14 15] Moderate load exercise programmes are the mainstay of management of mild to moderate knee osteoarthritis. Encourage graduated increase of moderate, low impact exercise and advise the patient to refrain from high doses of high impact exercise, which can worsen symptoms. Offer referral to physiotherapy for designing a structured exercise programme. Knee replacement may be required in severe and end stage osteoarthritis in suitable patients.[16] Concerns of harms associated with opioids and the lack of efficacy of knee arthroscopy[17] make these poor options.

WHAT PATIENTS AND CARERS NEED TO KNOW

- Osteoarthritis is a lifelong condition, although symptoms of pain and stiffness can fluctuate over time
- Moderate exercise is the mainstay of treatment for mild to moderate osteoarthritis of the knee
- Cortisone injections may give a small degree of symptom relief in the short term (about 6 weeks), but symptoms are likely to return and studies have not shown benefits beyond the short term
- There is emerging evidence from individual studies of possible cartilage deterioration and worsening of symptoms with repeated injections over two years
- Ask your doctor about the treatment options to develop a shared management plan considering the severity of your symptoms and your preferences

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A patient reviewer kindly reviewed this article for *The BMJ*. She asked to clarify the risk of disease progression with injection as most patients are not aware of it. She also suggested considering the treatment advice for different age groups. I have accordingly elaborated on these in the article. I also agree with her suggestion for more research in this area so patients may be informed and opt for another treatment such as exercise over corticosteroid injections. I am grateful for her input.

CASE REVIEW **A pigmented lesion on the eye**

A 46 year old white woman was referred for ophthalmologic evaluation of a pigmented lesion on the ocular surface of her left eye. The lesion had been noted during a routine eye examination by her general practitioner. She had first noticed the lesion six years earlier, believing it to be gradually increasing in size. Slit lamp biomicroscopy of the eye is shown in fig 1. No cysts were noted within the lesion and no other lesions were evident on complete ophthalmic examination, which included eversion of the eyelids and retinal evaluation. The woman was otherwise healthy.

1 What is seen in fig 1?

2 What are the differential diagnoses?

3 What is the most likely diagnosis?

Submitted by Olivia M Bennett and Rajesh C Rao

Patient consent obtained.

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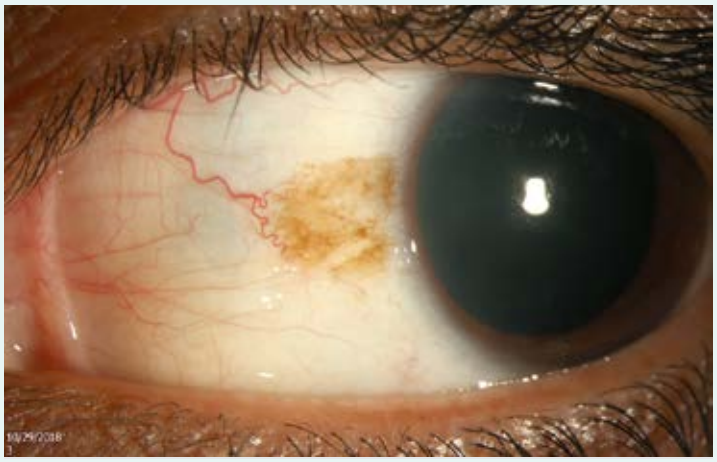


Fig 1 | Slit lamp biomicroscopy of the left eye

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

answers

CASE REVIEW **A pigmented lesion on the eye**

1 What is seen in fig 1?

A wedge shaped pigmented lesion with slight dome like thickening of the conjunctiva (fig 2 *). Dilated, corkscrew shaped feeder vessels abutted the lesion (fig 2, arrow head).

2 What are the differential diagnoses?

Differential diagnoses include benign conjunctival naevus, conjunctival complexion associated melanosis, and benign or pre-cancerous forms of primary acquired melanosis, or malignant melanoma.

A definitive diagnosis of conjunctival naevus, primary acquired melanosis, or malignant melanoma requires histopathology. Pre-cancerous primary acquired melanosis progresses into melanoma in 13% of cases. Conjunctival complexion associated melanosis is generally a clinical diagnosis associated with non-white ethnicities.

3 What is the most likely diagnosis?

Primary acquired melanosis is most likely because the lesion is flat and non-circumscribed. This condition is also more likely to attract feeder vessels (fig 2), and it typically occurs in middle aged individuals of white ethnicity. Confirmation of the diagnosis, and determining whether it is benign or pre-cancerous requires histopathological evaluation.

Benign conjunctival naevus and primary acquired melanosis can both be similarly darkly coloured (brown or black). However, naevi are often congenital or present from childhood, contain cysts, and are well demarcated.

The typical features of malignant melanoma (thickened, elevated, or nodular lesions) are absent, making that condition unlikely. Conjunctival complexion associated melanosis is also unlikely because it is uncommon in white individuals.

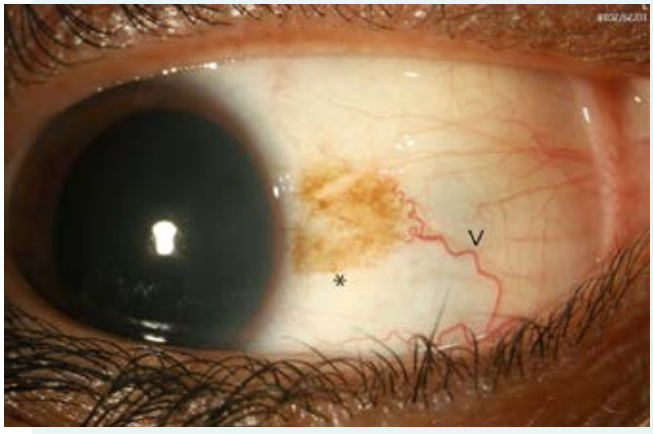


Fig 2 | Slit lamp biomicroscopy image of the left eye shows pigmented lesion (asterisk) associated with a feeder vessel (arrowhead)

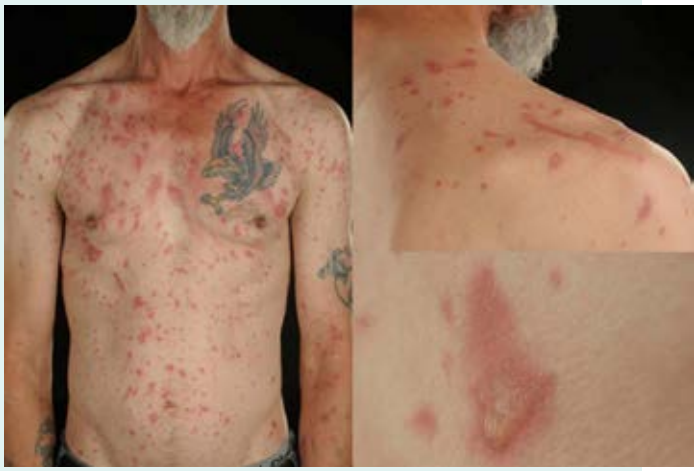
LEARNING POINTS

- Refer all patients with pigmented ocular lesion(s) to an ophthalmologist for close monitoring and consideration of biopsy.
- Primary acquired melanosis can progress to malignant melanoma.

PATIENT OUTCOME

This patient chose to defer biopsy and is instead monitored by her ophthalmologist every 6-12 months with slit lamp photography and ophthalmic examination.

An unexpected side effect of gardening



This is a picture of phytophotodermatitis.

The patient was a 50 year old man with three days of erythematous blistering across his torso after cutting grass, shirtless, in an area with a high concentration of hogweed on a hot sunny day. On examination, extensive flagellate ("whip-like" linear streaks) erythema with tense blisters was seen.

Phytophotodermatitis was diagnosed in view of a strong history of exposure to hogweed and a typical clinical presentation.

Phytophotodermatitis is a phototoxic cutaneous reaction precipitated by exposure to ultraviolet light and sensitisation to botanical substances. A class of sensitising chemical agents known as furocoumarins is commonly found in phototoxic plants such as hogweed and citrus fruits.

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Patient consent obtained.

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Scurvy

Scurvy once occurred in seafarers and long distance travellers. Currently, the most vulnerable group seems to be children with autism or developmental delay who will eat only highly selective diets. Ten children seen at a rheumatology clinic in North America had been referred because of pain and difficulty in walking and weight bearing (*J Pediatr* doi:10.1016/j.jpeds.2019.10.059). Before the correct diagnosis was made, conditions such as juvenile arthritis, osteomyelitis, and vasculitis were considered and investigated. All responded quickly to vitamin C supplements.

The obesity transition

In rich countries, obesity is commonest among poorer people, while overweight is fairly evenly distributed across the population. In low income countries, obesity and overweight are commoner among richer people. A worldwide survey of households in 103 countries predicts a transition in obesity from the wealthy to the poor as low and middle income countries develop economically (*PLoS Med* doi:10.1371/journal.pmed.1002968). When the per capita gross domestic product of a country reaches $8000 (£6150), the prevalence of obesity among poorer people begins to increase.

Retained placenta

Nitric oxide donors such as nitroglycerin relax uterine smooth muscle. Small studies have suggested that they may be an effective treatment for retained placenta. However, a large UK trial reports disappointing results (*PLoS Med* doi:10.1371/journal.pmed.1003001). Judged by a primary outcome of the need for manual removal of placenta, those receiving the active treatment did no better than those allocated to placebo. Palpitations following drug administration occurred more often in women who received nitroglycerin, but serious adverse events were no commoner in the active group than in those who received placebo.

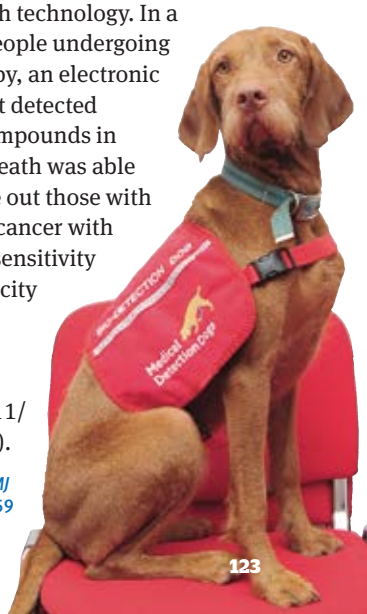
A life without pain

A 66 year old woman required no postoperative analgesia after hand surgery. She did not have a peripheral neuropathy and tests showed normal sensation apart from an inability to register pain. Genetic investigation identified mutations in the fatty-acid amide hydrolase gene that led to high circulating levels of anandamide and enhanced levels of endocannabinoid signalling. There might be a clue here for the development of new types of analgesia (*Br J Anaesthes* doi:10.1016/j.bja.2019.02.019).

Equally interesting is an essay about her in the *New Yorker* that explores what it might be like to live in a world where the experience of physical pain is absent (https://www.newyorker.com/magazine/2020/01/13/a-world-without-pain).

Sniffing out cancer

There are occasional reports of dogs that behaved in a way that led to a diagnosis of cancer in their owners. There are even studies claiming that dogs can be trained to recognise people with cancer from bodily excretions. The likely explanation is that dogs can smell volatile organic compounds characteristic of malignant tissue. It may be possible to do something similar with technology. In a series of people undergoing colonoscopy, an electronic "nose" that detected organic compounds in exhaled breath was able to separate out those with colorectal cancer with moderate sensitivity and specificity (*Aliment Pharmacol Ther* doi:10.1111/apt.15622).



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