# education

## ART OF MEDICINE

### "Well tolerated" is intolerable

"Tolerance" to a drug can be acquired or natural.

But the term is now often used in therapeutics to mean "the power or capacity of enduring."

New drugs are often described as "well tolerated" in study titles or abstracts, but this is often not reflected by the adverse effects described in the papers themselves.

Here is a typical example: of 181 patients with breast cancer and bone metastases given intravenous bisphosphonates, 13 developed "renal impairment" or "renal toxicity," one had osteonecrosis of the jaw, and 29 had hypocalcaemia, in two cases severe enough to require hospital admission. The title of the paper? "Prolonged administration of bisphosphonates is well-tolerated . . ."

A drug that is described as being well tolerated today may not be, or it may turn out to be not so harmless tomorrow. A PubMed search found about 70 000 hits for "well tolerated" and 400 for "not well tolerated." Pairing "well tolerated" with "rosiglitazone" or "rofecoxib" yielded 125 and 85 hits, respectively.

The concept of drug tolerability is poorly defined. The term does not guarantee freedom from important adverse reactions. At best it means "causing adverse reactions that participants put up with, willy nilly." Referees and editors should insist on having "well tolerated" expunged from papers about medicinal products. Authors should instead say exactly what the adverse effects and reactions were, how often they occurred, and with what intensity.

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We welcome contributions to this column via our online editorial office: https://mc.manuscriptcentral.com/bmj.

## CLINICAL UPDATES

### TNF-α inhibitors in severe ankylosing spondylitis

NICE recommends offering a tumour necrosis factor α (TNF-α) inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) to adults with severe ankylosing spondylitis who have not responded to, or tolerated, initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs).If infliximab is offered, the least expensive infliximab product should be offered first. For patients with non-radiographic axial spondyloarthritis, adalimumab, certolizumab pegol, or etanercept (but not infliximab) is recommended.

http://bit.ly/1mChnWB

### Nintedanib recommended for idiopathic pulmonary fibrosis

Nintedanib targets three growth factor receptors and is thought to block the signalling pathways involved in fibrosis. It may reduce disease progression by slowing the decline in lung function. NICE recommends offering oral nintedanib (through the patient access scheme) to people with a forced vital capacity (FVC) of 50-80% of predicted and stopping treatment if the disease progresses.

http://bit.ly/1KkzR9Q

### Use of biological agents in rheumatoid arthritis

NICE has updated guidance for the use of biological agents (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, and abatacept) in rheumatoid arthritis. These agents can be used in combination with methotrexate for severe disease (disease activity score >5.1) when a combination of conventional disease modifying antirheumatic drugs (DMARDS) has failed. Treatment should be continued beyond six months only if there is moderate improvement in the European League against Rheumatism (EULAR) score.

http://bit.ly/20yEijd

## FAST FACT—ACNE VULGARIS

Acne is not a minor problem of adolescence but a disease that can cause long lasting psychological effects and permanent scarring, so it should be treated early and aggressively. Options for treatment in primary care, guided by acne severity, include:

- Non-prescription topical treatments, such as benzoyl peroxide
- Topical prescription drugs, such as azelaic acid or retinoid
- Oral contraceptives
- Oral antibiotics, such as clindamycin and erythromycin, which should always be used in combination with benzoyl peroxide or a topical retinoid.

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10-MINUTE CONSULTATION

# Stopping antidepressants following depression

Tamara Pringsheim,[1] Martina Kelly,[2] Corrado Barbui[3]


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**WHAT YOU NEED TO KNOW**

- After successful treatment and remission of depression with antidepressant medication, treatment should be continued for up to 12 months to reduce the risk of relapse
- Treatment with antidepressants beyond a year after remission should be based on evaluation of risk factors for, and the potential consequences of, relapse.
- Individuals with two or more episodes of depression with significant functional impairment, residual depressive symptoms, functionally impairing physical health problems, or psychosocial difficulties are at higher risk of relapse

**Jocelyn started taking citalopram one year ago for her first recorded episode of depression. Her symptoms improved six weeks later. Now that she feels well, she asks if she can stop taking the pills.**

CPD/CME
0.5 CREDITS

### What you should cover

Explain to Jocelyn that, before making a decision about her medication, you should review her symptoms, response to treatment, and history of depression. Explain that there is guidance for doctors and patients on medication for depression, and that a discussion to tailor that guidance to her case would be useful.

Review the extent to which symptoms of depression persist (see box). For example, ask Jocelyn if she is enjoying life and if she is feeling confident? Use of structured tools such as the Patient Health Questionnaire-9 (PHQ9) can provide a useful guide. Ask about and document Jocelyn's attitude to the future, and whether she has thoughts of suicide. If you judge that there is a risk of suicide the focus of the consultation may alter.

Review how Jocelyn is functioning. Find out how she is getting on at home, at work, and with relationships with family and friends.

What are the chances of relapse off treatment? Ask Jocelyn how many times she has experienced depression and how long the episodes lasted. Were there triggers for her recent illness? Would she know if she were becoming unwell again?

Explore how she uses her antidepressant medication. Ask her what role the medication has played in her recovery. What makes her ask about stopping medication now? Explore how often she takes her medication. Does she experience side effects, such as somnolence, nausea, dry mouth, or sexual dysfunction? How bothersome does she find any side effects? Does she have concerns about continuing to take the medication—for example, worries about long term safety or a desire to get pregnant? Was it difficult to find a medication that worked for her? Has she taken antidepressants before, and if so which ones, for how long, and with what degree of success?

During your consultation, observe what Jocelyn looks and sounds like, and how she behaves. These observations form an important part of a mental health

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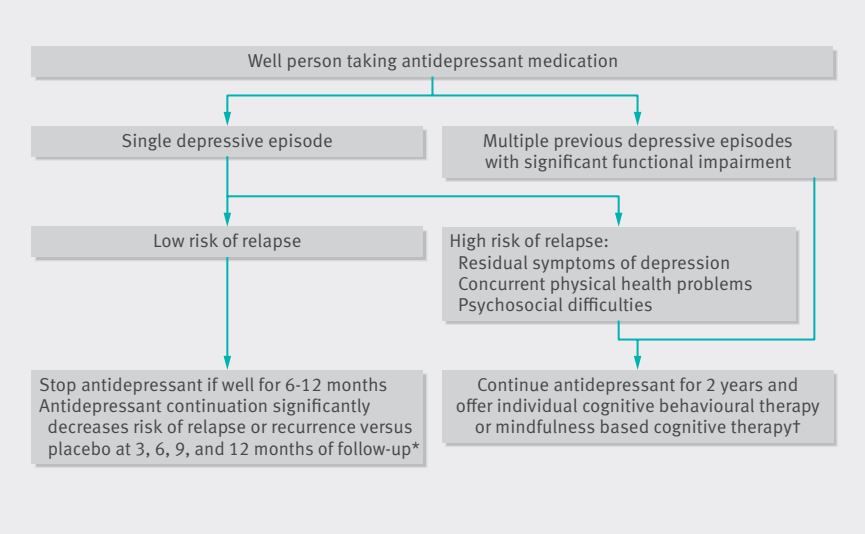
This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.




**Decision tree for stopping antidepressants after depression. *Based on meta-analysis of 30 studies including 4890 patients[5]: overall odds ratio at study endpoint was 0.30 (95% CI 0.25 to 0.35), suggesting that continuing antidepressant treatment more than halves risk of relapse. †Based on meta-analysis of six studies[6]: at 24 months of follow-up, antidepressant continuation decreases risk of relapse by 50%**

### FURTHER INFORMATION RESOURCES

**Resources for clinicians**

Patient Health Questionnaire (PHQ) Screeners, www.phqscreeners.com—Provides access to the Patient Health Questionnaire-9 in several languages, with no permission required to reproduce, translate, display, or distribute

**Resources for patients**

Depression UK, www.depressionuk.org—A national self help organisation to help people cope with their depression

### QUESTIONS FOR PRACTICE

Have you discussed continuation and discontinuation of antidepressants with patients with a history of depression?

### SYMPTOMS OF DEPRESSION

A review of symptoms, their severity, and associated functional impairment should be performed. Specifically, inquire about:

- Persistent sadness or low mood
- Marked loss of interest or pleasure
- Sleep disturbances
- Change in appetite
- Fatigue
- Poor concentration
- Feelings of worthlessness or excessive guilt
- Agitation or irritability
- Suicidal thoughts or acts

assessment. Is Jocelyn a healthy weight? Does she look clean and tidy? What is her manner? For example, does she seem depressed, anxious, or upbeat? What does her speech sound like? Is the pace and volume as you would expect? Is the content of her speech appropriate? Is Jocelyn thinking clearly? Document your observations.

**What you should do**

After successful treatment with antidepressant medication, if it is the first depressive episode and there are no risk factors for relapse, discontinuation should be discussed with Jocelyn if she has been well for six to 12 months.[1-4] The dose should be reduced over four or more weeks.[1] If discontinuation symptoms such as dizziness, headache, nausea, and lethargy emerge, Jocelyn should taper the medication over a longer period.

If Jocelyn is at higher risk of relapse, or if the consequences of relapse are likely to be severe, discuss that it may be better to continue her medication for two years.[1] People at high risk of relapse include those with two or more episodes of depression with significant functional impairment, residual depressive symptoms, physical health problems, or psychosocial difficulties (see figure). If Jocelyn continues her medication, she should continue at the dose that got her well.

Jocelyn should have been offered advice on non-pharmacological measures to improve her depression when she was unwell. These include high intensity psychological interventions such as cognitive behavioural therapy or interpersonal therapy.[1] At this stage, if residual symptoms of depression are present, individual cognitive behavioural therapy or mindfulness based cognitive therapy should be offered.[1]

Ensure Jocelyn has an appointment for follow up and phone her should she fail to attend.

**If residual symptoms of depression are present, individual cognitive behavioural therapy or mindfulness based cognitive therapy should be offered**

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PRACTICE POINTER

# Treating hypertension in patients with medical comorbidities

Lucinda Kennard, Kevin M O'Shaughnessy

## WHAT YOU NEED TO KNOW

- Two out of three people with hypertension have a comorbidity
- There is NICE guidance on blood pressure targets and drug therapy for patients with hypertension and comorbidities such as chronic kidney disease, diabetes, atrial fibrillation, and heart failure
- There remains uncertainty regarding which agents to choose for patients with multiple comorbidities

**Hypertension affects more than one in four adults in the UK[1] and prevalence is rising as the population ages. One British study found that around two in every three patients with hypertension has a comorbidity.[2] Hypertension is a public health priority but may not be the individual patient's priority. This mismatch may help to explain why in one study a quarter of all hypertensive patients did not fill out their first prescription,[3] and in another, patients did not take their prescribed medication 50% of the time.[4]**

**EDUCATION INTO PRACTICE**

Do you review and adjust treatment of hypertension in light of co-morbidities?

Advice offered here to rationalise prescribing in patients with hypertension and comorbidities is taken from several guidelines from the National Institute for Health and Care Excellence (NICE): CG127, CG182 (chronic kidney disease), CG108 (chronic heart failure), CG87 (type 2 diabetes), NG17 (type 1 diabetes), CG180 (atrial fibrillation).[5-10] When collating evidence, patients with multiple comorbidities or extremes of age are poorly represented in these datasets. These same patients are likely to have a substantial tablet burden already, so the emphasis here has been to suggest drugs that are most likely to benefit the patient's blood pressure and comorbidity. By avoiding drugs with less clear benefits it is hoped drug side effects can be reduced and compliance increased.

With all hypertensive patients who would like to lower their blood pressure, discuss lifestyle modification including regular exercise, a low salt diet (<6 g/day), low alcohol and caffeine consumption, smoking cessation, and a healthy body weight.

Figure 1 outlines the standard NICE guidance for drug treatment of hypertension.[11] The guidance below suggests how this might be modified in various circumstances. Box 1 summarises the major variations.

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| | |
|---|---|
| **Step 1** | **A** (for patients aged <55 years) or **C*** (for patients aged ≥55 years and all black people of African or Caribbean descent) |
| **Step 2** | **A + C*** |
| **Step 3** | **A + C + D** |
| **Step 4** | **Resistant hypertension** **A + C + D + further diuretic†** (or α blocker or β blocker if further diuretic treatment is not tolerated or is contraindicated or ineffective)<br><br>Consider seeking specialist advice |

**Key**
**A** = Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker
**C** = Calcium channel blocker
**D** = Thiazide-like diuretic
* Calcium channel blocker preferred, but consider thiazide-like diuretics in people with oedema or high risk of heart failure
† Consider low dose spironolactone or higher doses of thiazide-like diuretic

Fig 1 | NICE algorithm for drug treatment of hypertension (from BMJ NICE summary[11])

### Chronic kidney disease

A meta-analysis of randomised controlled trials in patients with chronic kidney disease showed reduced risk of end stage renal failure (hazard ratio 0.79 (0.67 to 0.93)) with more intensive blood pressure control. Over a 5-10 year period, for every 100 patients with poor control who progress to end stage renal failure, only 80 patients with good control will progress. This protective effect is clearest in patients who have proteinuria.[12]

Based on NICE guidance,[6] the clinic blood pressure target in patients with chronic kidney disease is <140/90 mm Hg and in those with chronic kidney disease and diabetes is <130/80 mm Hg.

### Subgroups of patients with chronic kidney disease

NICE guidance recommends that choice of treatment should be guided by the patient's urinary albumin:creatinine ratio (ACR) and diabetes status.[6] Antihypertensive treatments recommended are

- For patients **without** diabetes and blood pressure ≥140/90 mm Hg:
  - If ACR is <30 mg/mmol, treat according to the standard hypertension algorithm (fig 1)
  - If ACR is ≥30 mg/mmol, offer a renin-angiotensin system antagonist (such as lisinopril or losartan)

**Box 1 | Summary of first line treatment in patients with hypertension and comorbidities**

**Chronic kidney disease**

Diabetes status and urinary albumin:creatinine ratio (ACR) guide appropriate treatment for hypertension: use an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as first line treatment if a non-diabetic patient has ACR >30 mg/mmol or if a diabetic patient has ACR >3 mg/mmol

**Type 1 diabetes**

Treat hypertension with an ACEI (such as lisinopril) or ARB (such as losartan), followed by a low dose thiazide diuretic or a thiazide-like diuretic (such as chlortalidone) or a long acting calcium channel blocker (such as amlodipine) as second line

**Type 2 diabetes**

Treat hypertension with an ACEI as first line, except for black patients, for whom an ACEI plus a long acting calcium channel blocker or thiazide or thiazide-like diuretic should be first line

**Heart failure**

Hypertensive patients already taking an ACEI or ARB plus a β blocker, and whose blood pressure is not controlled, should also be given a thiazide or thiazide-like diuretic

**Elderly patients treated for hypertension**

Monitor for postural hypotension, especially if they are taking α blockers and after starting any new antihypertensive drug

**Asthma or chronic obstructive pulmonary disease (COPD)**

β blockers are no longer first line treatment for hypertension and should not be used routinely; if they are necessary in COPD, consider a low dose cardioselective β blocker (such as bisoprolol) with close monitoring of respiratory function

**Hypertensive women of child bearing age**

Avoid use of ACEI and ARB and use a dihydropyridine calcium channel blocker as first line treatment (or a β blocker such as labetalol if they are pregnant)

**Box 2 | Diagnosis of hypertension[11]**

*Stage 1 hypertension*—Clinic blood pressure ≥140/90 mm Hg *and* ambulatory or home blood pressure monitoring with a daytime average of ≥135/85 mm Hg

*Stage 2 hypertension*—Clinic blood pressure of ≥160/100 mm Hg *and* daytime ambulatory or home blood pressure monitoring of ≥150/95 mm Hg

*Severe hypertension*—>180 mm Hg systolic or >110 mm Hg diastolic[5]

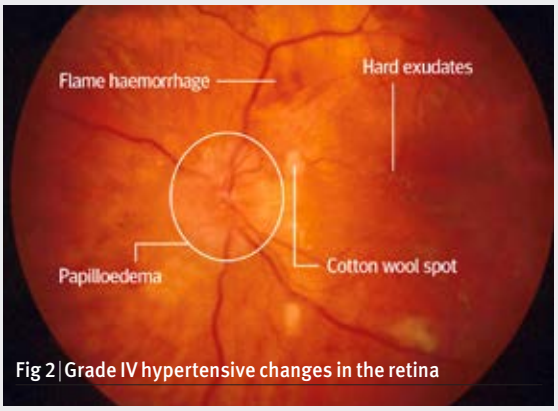


**Fig 2 | Grade IV hypertensive changes in the retina**

**Box 3 | When to offer drug treatment and which drugs to choose**

**For stage 1 hypertension**

For patients <80 years old, offer treatment if they have any of the following:

- End organ damage (such as hypertensive retinopathy (fig 2) or left ventricular hypertrophy)
- Established cardiovascular disease
- Renal disease (chronic kidney disease stage 3 to 5)
- Diabetes
- 10 year cardiovascular risk of ≥20% (use QRISK2 calculator, www.qrisk.org/)

For patients <40 years old, seek specialist evaluation if they

- Do not meet the above treatment criteria (as 10 year cardiovascular risk can be underestimated)
- Have accelerated hypertension (blood pressure >180/110 mm Hg and retinal haemorrhages or exudates (fig 2))
- Have suspected phaeochromocytoma (sweating, palpitations, headache, labile blood pressure)[5]

**For stage 2 hypertension**

Offer treatment to all patients (see fig 1 for details)

- For patients **with** diabetes and blood pressure ≥130/80 mm Hg:
  - If ACR is >3 mg/mmol, offer a renin-angiotensin system antagonist
- All patients with ACR ≥70 mg/mmol, irrespective of blood pressure, diabetes, or cardiovascular disease status, offer a renin-angiotensin system antagonist.

A systematic review comparing angiotensin converting enzyme inhibitors (ACEIs) with angiotensin receptor blockers (ARBs) found both drug classes had similar effects on blood pressure control.[13]

Diuretics are key second line drugs, as salt retention is a major driver for hypertension in chronic kidney disease[14]:

- If estimated glomerular filtration rate (eGFR) is ≥30 ml/min/1.73 $m^2$, use a thiazide or thiazide-like diuretic.[14] Higher doses are needed with chronic kidney disease (also consider twice daily dosing).
- If eGFR is <30 ml/min/1.73 $m^2$, use a loop diuretic.[14] Again, higher doses or twice daily dosing may be required.

*Cautions* Start at a low dose and check electrolytes a week later due to the increased risk of hyperkalaemia with potassium-sparing diuretics such as spironolactone in chronic kidney disease. Recheck after a week following dose adjustment. Thereafter consider monitoring every three months.

| Notes on safer prescribing of antihypertensive agents | | |
|---|---|---|
| Drug type | Caution | Monitoring |
| ACEI and ARB | Do not co-prescribe an ACEI and ARB[7 24]—this does not increase cardiovascular protection but increases hyperkalaemia and acute kidney injury<br>Avoid in women of child bearing potential<br>Contraindicated in pregnancy<br>Do not initiate routinely if pretreatment serum potassium concentration is >5.0 mmol/L[6]<br>Patients taking an ACEI or ARB and regularly taking NSAIDs are at increased risk of acute kidney injury, especially if taking diuretics as well.[25] The risk seems highest in the first month of starting an NSAID and when using NSAIDs with long half lives (such as naproxen). | Measure baseline creatinine and electrolyte levels<br>Repeat creatinine measurements 1-2 weeks after starting and after each dose adjustment (if eGFR decreases >25% or serum creatinine concentration rises by >30%, review the prescription if no other cause is likely[6])<br>Check serum potassium if co-prescribing with a potassium sparing diuretic such as spironolactone or amiloride<br>Check renal function after 2 weeks in those co-prescribed NSAIDs, and every 3 months thereafter |
| Diuretics | Avoid thiazide (or thiazide-like) and loop diuretics if there is a history of gout. If gout develops on a thiazide or loop diuretic, consider switching to an aldosterone receptor antagonist such as spironolactone | |
| β blockers | Caution in COPD<br>Avoid in asthma | Monitor symptoms and lung function tests in those with COPD |

In one study a quarter of all hypertensive patients did not fill out their first prescription, and in another, patients did not take their prescribed medication 50% of the time

### Heart failure

Patients with heart failure will probably already be taking an ACEI or ARB and a β blocker. β blockers such as carvedilol, bisoprolol, and nebivolol have the clearest evidence base in people with established heart failure and hypertension. Where blood pressure remains poorly controlled, offer a thiazide-like diuretic, chlortalidone or indapamide. If blood pressure is well controlled with other agents such as bendroflumethiazide, NICE does not recommend swapping to a thiazide-like diuretic.[5]

If a patient requires three or more antihypertensive agents, seek specialist advice. Further treatment options such as aldosterone receptor antagonists eplerenone and spironolactone are supported by randomised trials.[15-17] However, with coexisting chronic kidney disease, such treatment requires monitoring for hyperkalaemia, especially with concomitant use of ACEI or ARB.[18] Eplerenone is less likely to cause gynaecomastia than spironolactone.

### Type 2 diabetes

NICE recommends a target blood pressure of <140/80 mm Hg; but if the patient has eye, kidney, or cerebrovascular complications of diabetes, the target is lowered to <130/80 mm Hg.[8]

NICE[8] recommends:

- In non-black patients, once daily ACEI (such as lisinopril) is the first line treatment. If an ACEI is not tolerated an ARB can be used (such as losartan). Add a thiazide (or thiazide-like) diuretic and long acting calcium channel blocker (such as amlodipine) as second and third line treatments.
- In black patients, once daily ACEI should be combined with either a diuretic or a long acting calcium channel blocker as first line treatment.[8] The next step is to combine all three drugs.
- If triple therapy fails, options include an α blocker, β blocker, or aldosterone receptor antagonist (such as spironolactone, monitoring for hyperkalaemia with ACEI or ARB use).[8]
- In women of childbearing age, a calcium channel blocker is first line treatment (not an ACEI or ARB).[8] In pregnancy, nifedipine (as long acting, not instant release, formulation) is the recommended calcium channel blocker.[19]

### Type 1 diabetes

NICE recommends a target blood pressure of <135/85 mm Hg; or <130/80 mm Hg if the urinary albumin:creatinine ratio (ACR) is abnormal (>3 mg/mmol), chronic kidney disease has reached stage 3-5, or there are two or more features of metabolic syndrome.[6 9]

First line drug therapy is with an ACEI or ARB.[9] A low dose thiazide diuretic (such as bendroflumethiazide) or a long acting calcium channel blocker are effective second line drugs.[9]

### Chronic obstructive pulmonary disease (COPD) or asthma

Bronchospasm with a non-selective β blocker such as propranolol or oxprenolol (attributed to blockade of airway $\beta_2$ adrenoreceptors) has led to their avoidance in patients with COPD or asthma. This is less of an issue

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because β blockers are no longer considered first line therapy for hypertension for most groups of patients.[5] However, the exceptions are: women of childbearing age in whom ACE or ARB is contraindicated, people with increased sympathetic drive, and those intolerant of ACEIs or ARBs.[5]

In a Cochrane meta-analysis of 22 randomised trials comparing cardioselective β blockers with placebo in patients with hypertension and COPD, there was no statistically significant difference in respiratory symptoms, forced expiratory volume in one second ($FEV_1$), or $FEV_1$ response to $\beta_2$ agonists.[20] Therefore, if a β blocker is required we recommend cardioselective agents. Start at a low dose (such as 1.25 mg bisoprolol) and monitor respiratory function and symptoms.

The British Hypertension Society does not recommend the use of β blockers in hypertensive patients with asthma. However, the risk is difficult to quantify. For example, a meta-analysis of asthma patients exposed to β blockers in randomised controlled trials found that the absolute $FEV_1$ decreased by 6.9% (P≤0.001) with acute use of a cardioselective β blocker compared with 10.2% (P≤0.001) with a non-selective β blocker.[21] An increase in symptoms only occurred in those taking a non-selective β blocker.

### Older people

The optimum blood pressure target in older people, including nursing home residents is unclear and requires further evaluation. NICE advises a clinic blood pressure target of <150/90 mm Hg in people aged ≥80 years with ambulatory or home blood pressure monitoring <145/85 mm Hg during waking hours.[5] Use the same algorithm as for younger patients (box 2, fig 1), adjusted for comorbidities.[5]

In any patient with presyncopal symptoms or a history of falling, check for postural hypotension when reviewing or changing antihypertensive medication, especially α blockers. In a randomised trial in relatively well patients >80 years old, treating hypertension decreased all cause mortality.[22] However, this was not confirmed in a subsequent meta-analysis. It did report a reduced risk of stroke (35%, P<0.001), cardiovascular events (27%, P<0.001), and heart failure (50%, P=0.001), although the absolute numbers were not stated.[23]

### In hypertensive patients with atrial fibrillation

If heart rate needs to be controlled and there are no contraindications, consider adding either a β blocker (not sotalol) or a rate limiting calcium channel blocker (such as diltiazem) to any existing antihypertensive therapy.[10]

If the patient is already taking a dihydropyridine calcium channel blocker (such as amlodipine) then consider switching to a rate limiting one such as diltiazem.[10]

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**UNCERTAINTIES**

# How effective are platelet rich plasma injections for soft tissue injuries?

David J Keene,[1] Joseph Alsousou,[2] Keith Willett[1]

**WHAT YOU NEED TO KNOW**

- Autologous platelet-rich plasma (PRP) is increasingly used to treat musculoskeletal soft tissue injuries, either on its own or as an adjunct to surgery
- Routine use is not recommended as there is insufficient evidence of clinical efficacy; instead, its use should be restricted to research settings
- Ensure patients receiving PRP are aware of the limited evidence of efficacy, so that they can make an informed decision about their care
- Clinicians should be aware of the concentration of PRP, and yield of bioactive proteins, produced by their selected preparation device

Platelet-rich plasma (PRP) has become increasingly popular in sports medicine and orthopaedic practice as treatment for muscle, tendon, and ligament injuries, and has received media attention because of its promise as a regenerative therapy.[1 2] PRP is an autologous preparation of a patient's whole blood, which is centrifuged or filtered, allowing separation of a fraction containing a supraphysiological concentration of platelets (figure). PRP can be applied on its own, or as an adjunct to surgery, allowing a high "dose" of growth factors and other bioactive proteins such as cytokines and chemokines to be delivered to the target tissue. This has the potential to improve repair and regeneration, although evidence from in vitro and animal studies has been conflicting.[3-5]

As an autologous preparation, PRP has been introduced into clinical practice without being subject to the stringent development required of new drugs. Many commercially available PRP preparation devices have US Food and Drug Administration (FDA) approval, although this is based on device performance and safety, not on a requirement for evidence of clinical efficacy.[6]

### What is the evidence of uncertainty?

#### Lack of evidence of effectiveness

A 2014 Cochrane review identified 19 single centre randomised trials (1088 participants) that compared

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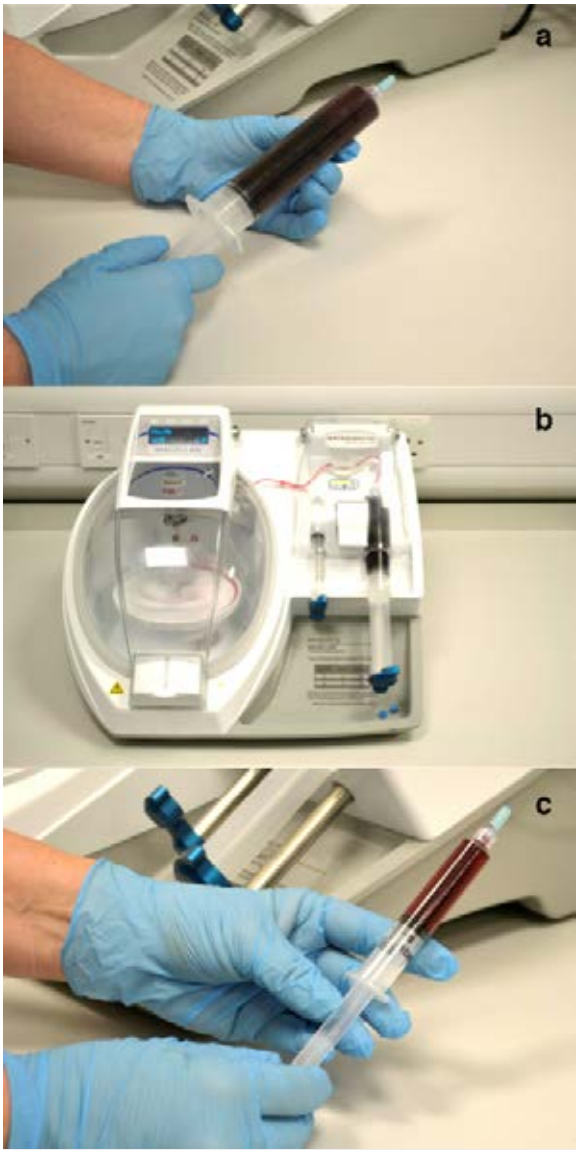


Making autologous platelet-rich plasma (PRP): a whole blood sample is taken (a) then a specialised centrifuge (such as the Magellan Autologous Platelet Separator System from Arteriocyte (b)) or filtration system is used to concentrate the platelets, and the resulting PRP is collected in a syringe for injection into the target tissue (c)

PRP has been introduced into clinical practice without being subject to the stringent development required of new drugs

PRP with placebo, whole blood, dry needling, or no treatment for eight different soft tissue injuries, either as a direct treatment (for elbow lateral epicondylitis, patellar tendinopathy, and Achilles tendon tendinopathy) or as an adjunct to surgery (anterior cruciate ligament reconstruction grafts and donor sites, rotator cuff repair, subacromial decompression, and Achilles rupture repair).[7] Comparisons with other active treatments were not included. Most trials were judged to be at high risk of bias, with lack of standardisation of PRP preparation. Overall, there was no clinically significant improvement in pain and function with PRP. The authors of the Cochrane review concluded that there was insufficient evidence to support the use of PRP.

In our review of a further 10 randomised controlled trials (476 participants), we too had difficulty drawing clear conclusions about the efficacy of PRP, because of heterogeneous musculoskeletal conditions and outcome measures, underpowered studies, and poor reporting. Only half of these trials included analyses of PRP content and quality, and these showed marked differences in platelet concentration and white cell content; this is problematic, as different PRP preparations and application techniques could affect effectiveness.[2]

### Possible harms

Autologous PRP is generally considered to carry a low risk of harm, but there are no high quality large scale clinical studies evaluating safety.[8] Pooled data from the Cochrane review did not show a significant difference between PRP and comparator groups.[7] Use of PRP may risk introducing infection, reported as an adverse event in two surgical randomised controlled trials.[9 10] A recent PRP randomised controlled trial found that 2/160 (1%) of PRP samples were positive for microbial growth, although no clinical indicators of infection developed.[11] Infection risk may also vary with different PRP preparations as some have been shown to have antimicrobial properties in vitro.[12]

### What should we do in the light of the uncertainty?

Routine use of PRP in clinical practice for musculoskeletal soft tissue injuries cannot be recommended given the lack of high quality clinical evidence supporting its efficacy. Thus the UK's National Institute for Health and Care Excellence (NICE) guidance for autologous blood injections, including PRP, for plantar fasciitis and tendinopathy states that it should "only be used with special arrangements for clinical governance, consent and audit or research," even if there are no major safety concerns with use for these conditions.[13 14]

We argue that patients should only be offered PRP for musculoskeletal soft tissue injuries within the context of well designed clinical trials, with informed consent, high quality verbal explanations, and supporting written information. Advise patients that there is currently insufficient evidence to show that it is effective treatment for musculoskeletal soft tissue injuries. Clinicians offering PRP should ask manufacturers for the evidence of the platelet and growth factor concentrations, the constitution, and the viability of their PRP product (platelet activation levels).

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**HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE**

A patient who previously had a tendon rupture and received PRP or a control treatment in a pilot randomised controlled trial gave feedback on the manuscript, which we incorporated in the revised paper. She highlighted the value of differentiating between clinical outcomes and outcomes important to patients, and the provision of clear verbal and written information to support patients.

## CASE REVIEW **Headaches and hormones: a potentially lethal combination**

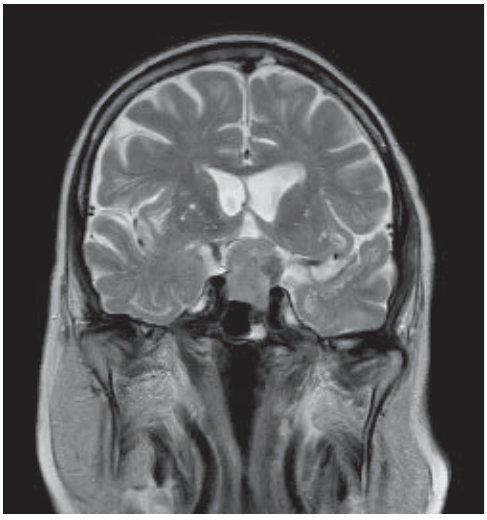
An 85 year old man presented to the emergency department with a five day history of headache, vomiting, and progressive visual loss in both eyes. He had no history of weight loss, seizures, or limb or facial weakness. He had hypertension, abdominal aortic aneurysm (under surveillance), hypothyroidism, and benign prostatic hypertrophy.

His blood pressure was 110/75 mm Hg, pulse 80 beats/min and regular, Glasgow coma score (GCS) 15. Peripheral neurological examination was normal. Cranial nerve examination showed bitemporal hemianopia with normal fundoscopy.

Initial investigations showed deranged biochemistry: sodium 126 mmol/L (reference range 135-145), potassium 3.6 mmol/L (3.5-5), urea 5.6 mmol/L (2.5-6.7), creatinine 101 µmol/L (70-150), C reactive protein 66 mg/L (‹10). Full blood count and liver function tests were normal.

He was admitted to the acute medical unit after computed tomography of the head showed a mass arising from the pituitary fossa. Magnetic resonance imaging (MRI) showed a sellar mass compressing the optic chiasm and signal changes suggestive of haemorrhagic regions within the mass (figure).

1 What are the differential diagnoses for patients presenting with bitemporal hemianopia?
2 Given the biochemical and radiological abnormalities, how would you immediately manage this patient?
3 Will he need pituitary surgery?
4 What long term follow-up would you arrange?



Submitted by Ramdeep Bajwa, Paven Preet Kaur, and Alessandro Paluzzi Patient consent obtained.

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## SPOT DIAGNOSIS

### Anatomical conundrum

Which common congenital anomaly does this coronal section of an abdominopelvic computed tomogram depict (figure)?

Submitted by Martin Raymond Hossack and Marius Paraoan
Patient consent obtained.

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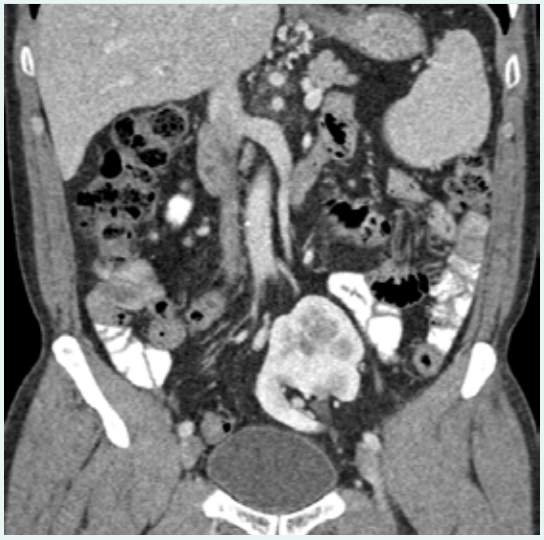
Find this at: http://dx.doi.org/10.1136/bmj.i192



We welcome contributions that would help doctors with postgraduate examinations. We also welcome submissions relevant to primary care. **See thebmj.com/endgames**

## answers

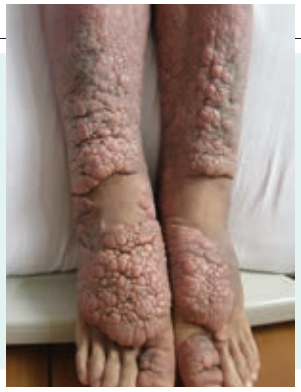
**Case Review Headaches and hormones: a potentially lethal combination**

1 Pituitary adenomas, pituitary apoplexy, craniopharyngiomas, meningiomas, gliomas, and rarely intracranial aneurysms.
2 These abnormalities suggest pituitary tumour apoplexy. This medical emergency causes hypopituitarism, particularly cortisol insufficiency, which requires steroid replacement with careful fluid and electrolyte balance.
3 Pituitary apoplexy with deteriorating neuro-ophthalmic signs or reduced GCS is a surgical emergency and the tumour is commonly resected. Stable patients can be managed conservatively but surgery may be needed if they do not improve.
4 Guidelines recommend reviewing all patients four to eight weeks after initial presentation and then annually in an endocrinology clinic. MRI of the head is recommended three to six months after initial presentation, yearly for five years, and then biennially.

SPOT DIAGNOSIS **Anatomical conundrum**

Left pelvic (ectopic) kidney.

## Localised myxoedema complicating Graves' disease



A 48 year old man diagnosed as having Graves' disease (ophthalmopathy and thyrotoxicosis) eight years earlier presented with progressive, non-pitting thickening of the skin in both feet and the pretibial and lateral area of each leg. His primary drug history was methimazole 15 mg daily. The lesions were pale red to yellow waxy plaques and nodules of different size, sharply demarcated from adjacent normal appearance skin. Localised myxoedema was not diagnosed until he presented with these classic lesions. This complication occurs in 4% of patients with Graves' disease. It is usually associated with previous surgery, trauma, or radioiodine treatment.

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Patient consent obtained.

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## Mayo germ ticks the Lyme box

Until Mayo Clinic microbiologists tested DNA in over 100 000 blood samples from people with Lyme disease during 2003 to 2014, it was thought that only one bacterium causes Lyme disease—*Borrelia burgdorferi* sensu lato. But it's now apparent that a Lyme-like disease can be caused by a second, rarer spirochaete, which they loyally named *Borrelia mayoni* after their institution. It was also found in the vector tick *Ixodes scapularis*, and their report (*Lancet Infect Dis* doi:10.1016/S1473-3099(15)00464-8) describes five clinical cases.

## Cough your lungs clear

"Our data lend support to the notion that strong cough protects from aspiration-related pneumonia" say investigators who examined the four week incidence of pneumonia in 72 patients after acute stroke (*Thorax* doi:10.1136/thoraxjnl-2015-207810). This exploratory secondary analysis of data from a trial of muscle training after stroke compared respiratory infection with measurements of peak cough flow using a pneumotachograph with full face mask. A well preserved cough reflex definitely matters

## Dangerous drugs: who's in charge?

A few drugs disappear noisily, like thalidomide, but most slip away unnoticed once their harms become known. A literature search identified 462 medicinal products that were withdrawn from the market between 1953 and 2013, mostly because of hepatotoxicity (*BMC Med* doi:10.1186/s12916-016-0553-2). Fewer than 10% of these were withdrawn worldwide—the process remains patchy and is mostly based on anecdotal reporting. Many drugs considered too dangerous elsewhere are still sold in Africa.

## Bundle of bugs

Surgical site infection can be reduced by at least five interventions, according to the research literature. Colorectal surgeons in Texas decided to see how much they could reduce site infections by bundling all five together and randomising 210 patients to the bundle or standard care (*Arch Surg* doi:10.1001/archsurg.2010.249). All patients received prophylactic antibiotics. But to their chagrin the rate of superficial wound infection in the bundle group turned out to be 36% compared with 19% in the standard care group.

## Are EBM messages getting through?

Every clinician reads drug trial reports now and again, and 549 clinicians and trainees in two US centres responded to a simple questionnaire that asked them to rate four scenarios describing the benefits of a new drug for stroke (*J Graduate Med Educ* doi:10.4300/JGME-D-15-00137.1). Responses varied widely, with composite outcomes including surrogates rated as important by many, while only 21% rated all cause mortality as more valuable than a surrogate enriched composite outcome.

## Chronic thromboembolic pulmonary hypertension

Unlike many kinds of pulmonary arterial hypertension, that caused by pulmonary embolism now carries an excellent prognosis, according to a Europe-wide registry of 679 newly diagnosed patients (*Circulation* doi:10.1161/CIRCULATIONAHA.115.016522). This is particularly true for those treated surgically, who have an 89% estimated three year survival.

## Handy way to test rotator cuffs

"Come sir, let us clasp hands and forget our quarrel" declares many a hero of historical fiction. This is also sound advice for anyone wishing to assess the function of the rotator cuff, although there is no need to pick a quarrel first. Just measure hand grip strength in any position and it will strongly correlate with shoulder lateral rotation strength, according to a study of healthy volunteers in a Manchester sports clinic (*Shoulder Elbow* doi:10.1177/1758573215626103).

## Safety: chat to a patient

Lying in hospital beds, patients are ideally placed to make observations about safety. But most have other things on their mind, so asking them to use a safety hotline or fill in a form is not likely to yield as much as talking to them by the bedside. This is borne out by a cluster randomised study in a large Leeds hospital (*BMJ Qual Saf* doi:10.1136/bmjqs-2015-004260). Interviews provided significantly more safety concerns per patient (1.91) than a paper based approach (0.92) and telephone hotline (0.43).

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