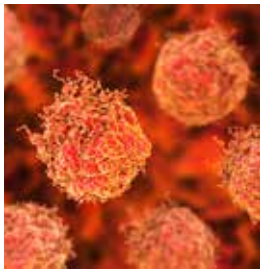
education

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

Refining radiotherapy for prostate cancer



A large Scandinavian randomised controlled trial compared ultra-hypofractionated radiotherapy for prostate cancer with conventional fractionation.

The ultra-hypofractionated group received the total dose over a much shorter time period, but the overall dose was lower. As expected the early side effects were worse in the ultra-hypofractionated group, while late side effects were similar. The trial was "positive" in that non-inferiority of ultra-hypofractionation was shown. This study is important not only for reducing the burden to patients of repeated hospital visits to receive radiotherapy, but also for resource management as it reduces the workload of the radiotherapy department. However, patients were only followed up for five years, so longer term inferiority is still possible.

Lancet doi:10.1016/S0140-6736(19)31131-6

Tenosynovial giant cell tumours

The ENLIVEN trial randomised 120 people with a tenosynovial giant cell tumour not amenable to surgery to pexidartinib or placebo for six months. This tumour can impact on physical function and become too big to operate on without the surgery causing functional impairment. Pexidartinib is a tyrosine kinase inhibitor targeting CSF1, which is a protein with a key role in this non-malignant but locally aggressive and clinically troublesome tumour.

There was no treatment response in the placebo group, but a response was seen in 39% of people in the pexidartinib group. While effective, the drug did, however, display alarming adverse effects including hepatotoxicity.

Lancet doi:10.1016/S0140-6736(19)30764-0

A nod for nose surgery?

In this randomised controlled trial, septoplasty for correcting septal deviation was compared with non-surgical management. After one year, the surgical group had higher disease specific quality of life scores and better airflow. However, staff and patients knew which treatment the patient had been randomised to, so there is potential for bias. While it is a step in the right direction to be establishing evidence for a procedure, this was not a placebo controlled trial. No matter how well conducted and reported this study was, the design means the investigators have measured the effect of surgery, but not how much of this effect was placebo effect and how much actual effect.

Lancet doi:10.1016/S0140-6736(19)30354-X

Cardiac testing in stable coronary artery disease

The MR-INFORM study compared two strategies for investigation and treatment of stable coronary artery disease. It was designed to demonstrate that a procedure guided by magnetic resonance imaging (MRI) was non-inferior in terms of rates of death, non-fatal myocardial infarction, and target vessel revascularisation at one year compared with invasive angiography with measurement of fractional flow reserve (FFR).

Event rates were 3.7% in the FFR guided group versus 3.6% in the MRI guided group—that is, no different. This result was somewhat a given. Revascularisation for stable coronary artery disease doesn't convincingly reduce death or myocardial infarction in previous studies, so why would a strategy that allows some deferral of revascularisation result in worse outcomes? Nevertheless, this provides evidence to support the use of MRI first with no detriment to patient's cardiovascular outcomes or symptoms. The real benefit of the MRI guided strategy was reducing rates of invasive angiography and less revascularisation.

N Engl J Med doi:10.1056/NEJMoa1716734

Hip fracture in older women

How strong is the mandate for treatment to prevent fractures in women over 80 years old with osteoporosis? Ensrud and colleagues investigated this in a large prospective cohort study. They followed 1528 treatment naive, community dwelling women with either osteoporosis or a high fracture risk without osteoporosis.

Over five years, 8.8% of women had a hip fracture and 18.8% had died before experiencing a hip fracture. The risk of hip fracture was 18.1% in women with osteoporosis who also had more than three comorbidities and 46.7% in those with a poorer prognosis. Those without osteoporosis had far lower fracture rates in the five year period even though they were deemed to be at high risk of fracture. If the treatment benefits over age 80 are similar to those seen in randomised controlled trials in younger women, there is clearly a group of women (those with more comorbidities or poorer prognosis) who had a lot to gain.

JAMA Intern Med doi:10.1001/jamainternmed.2019.0682

Alex Nowbar is a clinical research fellow at Imperial College London

RATIONAL TESTING

Investigating acute kidney injury in primary care

Indre K Semogas,[1] Amy Davis,[2] Imran Rafi,[3] Christopher Anderson,[3 4] Nicholas M P Annear[1 3 5]

[1]Department of Acute Medicine, St George's University Hospitals NHS Foundation Trust, London
[2]Department of Radiology, Epsom & St Helier Hospital NHS Trust, London
[3]Institute of Medical and Biomedical Education, St George's University of London
[4]Department of Urology, St George's University Hospitals NHS Foundation Trust
[5]Department of Renal & Transplantation Medicine, St George's University Hospitals NHS Foundation Trust

Correspondence to: N M P Annear nickannear@doctors.org.uk

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

CPD READING
0.5 HOURS

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

A 65 year old obese man with diabetes, hypertension, osteoarthritis, and a two month history of persistent lower urinary tract symptoms attended his general practice with general malaise. Regular medications included metformin, gliclazide, ramipril, and ibuprofen. On examination, his blood pressure was 150/96 mm Hg. Digital rectal examination revealed a smooth enlarged prostate. Urine analysis showed 2+ proteinuria. Blood tests revealed a serum creatinine concentration of 160 µmol/L, compared with 78 µmol/L three weeks earlier; his prostate specific antigen (PSA) level had been 6 µg/L.

The problem

Acute kidney injury (AKI) is a syndrome characterised by a sudden decline in renal function. Population incidence of AKI is as high as 0.2%,[2] and between 8.4% and 17.6% among hospital inpatients.[3 4] Around two thirds of AKI cases identified in hospital develop in the community before hospitalisation.[5] AKI is associated with longer inpatient admissions, increased risk of progression to chronic kidney disease (CKD), and higher mortality (in hospital[6] and long term).[3 7] Prompt identification of AKI and early management initiated in primary care is central to improving outcomes.

Identifying AKI in primary care

AKI in the community is most commonly due to infections such as influenza or gastroenteritis, with associated fluid depletion.[8] Patients generally present with non-specific symptoms; instead patients are identified as being at enhanced risk of developing AKI (box 1).[9] AKI may be confirmed either incidentally or through targeted screening showing an elevated serum creatinine level above baseline (table 1).[1] To support early identification, in the UK, electronic AKI alerts should accompany all blood tests from primary and secondary care, notifying responsible clinicians of an AKI episode.[10] A common problem is that it is impossible to discriminate between AKI and CKD from a single blood test result without baseline values, although other blood and imaging results may strongly suggest underlying CKD (box 2).[10 11]

Box 1 | Factors warranting investigation for acute kidney injury (AKI) in acutely ill patients*

- Age >65 years
- Medical history of
  - Chronic kidney disease
  - Prior AKI
  - Heart failure
  - Liver failure
- Exposure to nephrotoxic drugs within previous week
- Exposure to contrast agent within previous week
- Factors predisposing to hypovolaemia (such as reliance on carer)
- Clinical evidence of hypovolaemia
- Sepsis
- History of, predisposing factors for, or symptoms of urological obstruction

*Recommended by National Institute for Health and Care Excellence (NICE)[9]

WHAT YOU NEED TO KNOW

- Acute kidney injury (AKI) in the community is most commonly due to infections such as influenza or gastroenteritis, with associated fluid depletion, but 10% of community cases are due to obstructive uropathy
- AKI is associated with longer inpatient admissions, increased risk of progression to chronic kidney disease (CKD), and higher in-hospital and long term mortality
- After an episode of AKI, review patients in primary care to advise on appropriate management and reintroduction of any medications withheld during an AKI episode and to screen for CKD

Table 1 | KDIGO classification of acute kidney injury (AKI)[1]

AKI stage	Serum creatinine	Urine output
Stage 1	1.5-1.9 × baseline creatinine* *or* >26 µmol/L within 24 hours	<0.5 mL/kg/hour for 6 hours
Stage 2	2.0-2.9 × baseline creatinine*	<0.5 mL/kg/hour for 12 hours
Stage 3	3.0 × baseline creatinine* *or* >353.6 µmol/L* *or* Initiation of renal replacement therapy *or* Decrease of eGFR to <35 mL/min in patients <18 years old	<0.3 mL/kg/hour for 24 hours *or* Anuria for 12 hours

KDIGO=Kidney Disease: Improving Global Outcomes. eGFR=estimated glomerular filtration rate.
*Applicable when creatinine change presumed to have occurred in previous 7 days

What is the next investigation?

Early clinical assessment involves reviewing blood parameters to exclude severe complications (hyperkalaemia, uraemia, and hypovolaemia or hypervolaemia[12 13]). Further investigations will be indicated to determine the cause of AKI (table 2).[10 14] Factors warranting earlier review include hyperkalaemia, suspected urinary tract obstruction, suspected intrinsic renal disease, history of CKD or renal transplant, frailty, history of AKI.

Urine analysis

Perform dipstick urine analysis in all cases of AKI as a rapid screen for treatable pathology.[9] Presence of leucocytes and/or nitrites may indicate bacteriuria, urinary tract infection, or pyelonephritis; haematuria and proteinuria alone may suggest glomerulonephritis; leucocytes alone may indicate interstitial nephritis.[9]

Blood tests

Blood tests confirming AKI may reveal abnormalities requiring urgent intervention (such as hyperkalaemia).[13] Full blood count, C reactive protein assay, and bone profile must be undertaken to screen for infection, inflammation, or electrolyte abnormalities. If there is no clear cause, or intrinsic renal disease is suspected, additional blood tests may be undertaken, accompanying urgent nephrological referral (box 2). Repeat serum creatinine levels should be taken alongside clinical review after an AKI episode (box 2). This will help identify refractory AKI and guide management.[1 10]

Ultrasound scan

Urinary tract ultrasound scan is the investigation of choice when obstructive uropathy is suspected.[9] About 10% of AKI cases in the community are due to obstructive uropathy[15]; of these, 95% will demonstrate hydronephrosis.[16] Causes for false negative results include early obstruction or extrinsic compression preventing ureteric dilatation. False positive results may occur in pregnancy or vesicoureteric reflux.[11] Other common non-obstructive pathologies found on ultrasound include nephrolithiasis, anatomical variants, and altered renal parenchymal echogenicity.[11] Ultrasound may help distinguish between AKI and CKD: reduced kidney size and cortical and parenchymal thickness suggest underlying CKD.[11]

Referral for urgent renal ultrasound

If available, a post-micturition bladder scan can expedite investigation. However, if obstructive uropathy or pyelonephritis is suspected in relation to AKI, an urgent renal ultrasound scan is needed. A history of abdominal or pelvic malignancy, benign prostatic hyperplasia, neurogenic bladder, nephrolithiasis, and treatments associated with retroperitoneal fibrosis all raise suspicion for obstructive uropathy.[19] Further suggestive features include a history of lower urinary tract symptoms, oligouria or anuria, and a palpable bladder, abdominal mass, or prostate on examination.

Current UK guidelines advise ultrasound be performed within 24 hours if obstruction is suspected or there is no identifiable cause.[9] Features suggestive of pyonephrosis (fever, flank pain, and/or dysuria associated with leucocyturia, nitrite-positive urine analysis, and raised inflammatory blood markers) necessitate ultrasound within six hours, probably through emergency referral to secondary care.[9]

Box 2 | Blood and urine tests to consider when investigating acute kidney injury (AKI)

In all cases

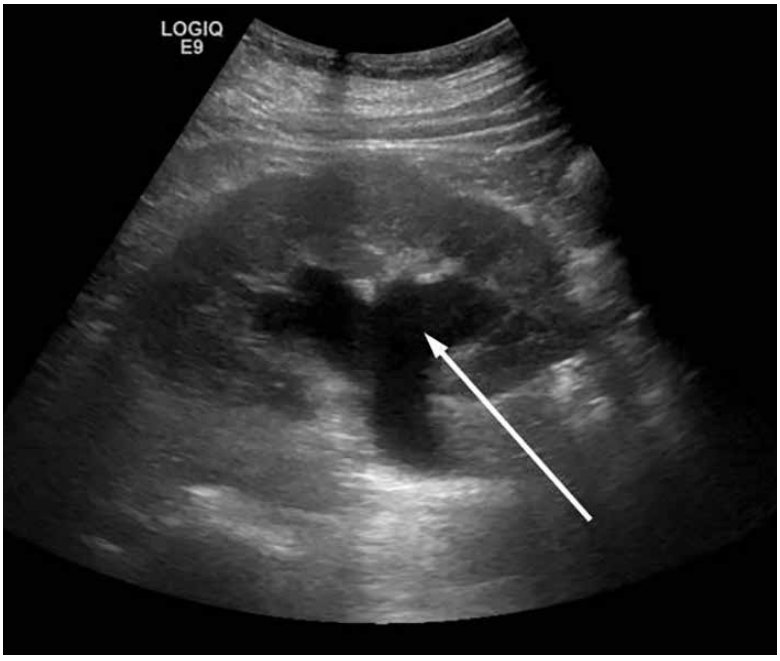
- Urine analysis
  - Microscopy, culture, and sensitivity if clinical suspicion or urine analysis is positive for nitrites or leucocytes
  - Protein:creatinine ratio if urine analysis is positive for proteinuria or haematuria
- Blood tests
  - Full blood count (normocytic anaemia may suggest underlying chronic kidney disease (CKD))
  - Urea and electrolytes (particularly screen for hyperkalaemia in AKI and CKD)
  - Bone profile (raised serum phosphate levels may suggest underlying CKD)
  - C reactive protein (raised in infection or inflammation)

Suspected intrinsic renal disease*

- Further blood tests
  - Serum bicarbonate and chloride (screen for metabolic acidosis in AKI and CKD)
  - Creatine kinase (may indicate muscle injury, such as rhabdomyolysis)
  - Erythrocyte sedimentation rate (raised in infection or inflammation)
- Immunological tests
  - Antinuclear antibody (raised in many autoimmune conditions)
  - Double stranded DNA antibody (raised in systemic lupus erythematosus (SLE))
  - Antinuclear cytoplasmic antibodies (raised in vasculitis, but also in infection)
  - Antiglomerular basement membrane antibody (raised in anti-GBM disease)
  - Rheumatoid factor (raised in rheumatoid arthritis and cryoglobulinaemia)
  - Complement levels (C3 and C4) (low in active SLE and cryoglobulinaemia)
  - Immunoglobulins/Serum and urine protein electrophoresis (screen for multiple myeloma)
- Serological tests
  - Antistreptolysin O titre (raised after streptococcal infection)
  - Hepatitis B and C serology (hepatitis B surface antigen, hepatitis C antibody)
  - HIV serology (HIV-1 and HIV-2 antibodies)

*May be undertaken in primary care after urgent specialist referral

GETTY IMAGES



Transverse ultrasound scan of right kidney showing dilatation of pelvicalyceal system (arrow) consistent with hydronephrosis

EDUCATION INTO PRACTICE

- Consider your last patient diagnosed with AKI. How were they managed?
- After reading this article, how would you alter your approach towards investigating and managing AKI?
- Consider the next patient due in clinic. Are they at risk of developing AKI?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The article was reviewed and endorsed by a small cohort of patients at our AKI clinic who had recovered from AKI.

Table 2 | Causes of acute kidney injury (AKI) (adapted from Think Kidneys[10 14])

	Specific causes	History	Examination
Sepsis, hypoperfusion, hypovolaemia	• Sepsis • Organ failure • Dehydration • Haemorrhage	• Infective symptoms • Oral fluid intake • History of heart failure, renal failure, liver failure	• Blood volume status (capillary refill, jugular venous pressure, pulse, blood pressure) • Source of infection
Medication/ Toxicity	• Medication contributing to hypovolaemia or hypotension • Nephrotoxic medications • Recent exposure to contrast agent	• Medication history: - NSAIDs, diuretics, antihypertensive agents - Drugs that accumulate, causing harm in AKI - New drugs that may cause AKI, such as PPIs	
Obstruction	• Benign prostatic hypertrophy • Prostatic, pelvic, or abdominal malignancy • Kidney or bladder stones • Retroperitoneal fibrosis	• Lower urinary tract symptoms • History of: - Malignancy - Kidney stones - Pelvic radiotherapy • Family history of malignancy	• Palpable abdominal or pelvic mass • Palpable bladder • Enlarged prostate
Primary or intrinsic renal disease	• Glomerulonephritis • Interstitial nephritis • Myeloma	• Medication history • History of: - Shortness of breath or haemoptysis - Rash - Back or bone pain - Weight loss	• Urine analysis • Skin rashes

NSAIDs = non-steroidal anti-inflammatory drugs. PPIs = proton pump inhibitors.

Management of AKI

Appropriate management of clinically stable patients with AKI stages 1-2 can be undertaken in primary care or in outpatient clinics, depending on local AKI service availability. It is recommended that patients with AKI are hydrated, infections treated, nephrotoxic medications discontinued, and diuretic and angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are temporarily withheld.[1 21]

For particular situations, such as concurrent heart failure, a more nuanced approach may be required, recognising a necessary trade-off between cardiac and renal function. While there remains an insufficient evidence in this setting, an important approach is to treat the patient, and not the blood result.[10] Further management depends on aetiology: specialist urology referral will be required for obstructive uropathy.[9] If AKI stage 3 is identified, urgent nephrological referral is indicated. Such referral is also indicated if there is suspected intrinsic renal disease, no clear cause for AKI identified, refractory AKI, or AKI in renal transplant patients. If a patient is unwell with AKI they may, depending on clinical context, be best managed on an acute medical unit.[9]

To ensure patients are adequately informed, provide patient information leaflets (such as *Understanding Acute Kidney Injury*[22]) alongside discussions about AKI.

Management after recovery from AKI

After resolution of AKI, review patients in primary care to advise on appropriate management and reintroduction of drugs withheld during an AKI episode.[8 23] Regardless of aetiology and management, review all patients with AKI at three months to screen for evolving CKD.[1]

Patient outcome

AKI stage 2 was diagnosed; the patient was re-assessed as clinically stable with no severe complications. An urgent outpatient ultrasound scan revealed bilateral hydronephrosis (figure) and an enlarged prostate compressing the bladder (fig 2, see bmj.com). The patient was catheterised and commenced α blockade and finasteride. His serum creatinine level returned to baseline at 80 µmol/L. Definitive urological management of his prostatic outflow obstruction was then arranged.

Competing interests: None declared.

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STATE OF THE ART REVIEW

Depression in primary care: diagnosis and management

Parashar Ramanuj,[1 2] Erin K Ferenchick,[3] Harold Alan Pincus[4 5 6]

Full author details on bmj.com

Correspondence to: E K Ferenchick ef2015@columbia.edu

Series explanation: State of the Art reviews are written with academic or specialist international and US readers in mind. This summary for non-specialists was created by *The BMJ* with input from the authors and appears as a summary for non-specialists.

CPD READING

0.5 HOURS

Introduction

About 90% of people in the UK with depression are treated in the primary care setting. Primary care providers play a central role in managing depression and have a distinct role and skill set that complement but are not substitutes for specialist mental health input. Most primary care providers screen for, diagnose, and treat depression and ensure routine follow-up.

Even when specialist mental health input is needed, primary care providers maintain an important role in managing chronic physical comorbidities, tackling social vulnerabilities, and monitoring psychiatric risk.

Although this review focuses on major depressive disorder, depression is a broad and heterogeneous condition. DSM-5 (the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition) draws a distinction between a range of eight depressive conditions including major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and substance/medication induced depressive disorder, among others. Similarly, the ICD-11 (*International Statistical Classification of Diseases and Related Health Problems*, 11th revision) classification includes a range of depressive disorders.

The common feature shared by these depressive disorders across both classification systems is the presence of sad or empty mood accompanied by somatic and cognitive changes that affect a person's ability to function, but they are distinct in their duration, timing, and cause.

Epidemiology

The World Health Organization (WHO) estimates that more than 300 million people, or 4.4% of the world's population, have depression. The total number of people living with depression increased by 18.4% between 2005 and 2015. In England, about 4-10% of people will experience depression in their lifetime.

Risk factors

Depression is associated with a combination of genetic, environmental, biological, cultural, and psychological factors. The heritability of depression is much lower than for other mental disorders (about 37%), suggesting that most depression at a population level can be explained by environmental factors.

Depression can occur at any age, although it often begins in the second or third decade of life. Prevalence rates vary by age, peaking in older adulthood, with an estimated prevalence of 7.5% among women and 5.5% among men aged 55-74 years. Major depression is about twice as common in women as in men. Different patterns of depression exist within racial and ethnic minorities and are attributable to nativity/ethnicity, socioeconomic status, and the interplay between other protective effects and risk factors.

Depression has an important bidirectional relation with other chronic physical diseases. These conditions are more prevalent and often worse when depression is present, and depression and chronic conditions have a joint effect on functional disability. A large population based study among 245 404 people in 60 countries found that 9-23% of people with one or more chronic physical conditions experienced comorbid depression, compared with 3.2% (95% confidence interval 3.0% to 3.5%) of people who experienced depression in the absence of other physical conditions. In addition, prescription drugs taken for common chronic medical conditions may cause side effects that contribute to depression.

Natural course of depression in primary care

The PREDICT-NL study, a prospective cohort study from 2012, examined the natural course and outcome of depression in primary care (from now on called depression).[5] At baseline, 174 (13%) of 1338 consecutive attendees had depression, of which 17% had a chronic course, defined as still having symptoms after 39 months, and 40% had a fluctuating course; 43% remitted. Patients with chronic depression were noted to have more depressive and somatic symptoms and greater mental dysfunction at baseline, independent of age, sex, level of education, presence of a chronic disease, and lifetime depression, compared with those who remitted from baseline.

Other studies have found a similar range of factors to be associated with chronic or recurrent depression. These factors include a previous history of recurrent depression, a history of dysthymia, psychiatric comorbidities, comorbid chronic medical illness, younger age at onset, family history of mood disorders, greater severity of depressive symptoms at baseline, and incomplete recovery following acute treatments. Low levels of social integration and/or negative social interactions also seem to appear concurrently with chronic depression.

Diagnosis

Two classification systems are widely used to diagnose depression—DSM-5, developed by the American Psychiatric Association, and ICD-11, developed and recently updated by WHO (see fig 1 in first review on bmj.com). To date, no research has compared the effectiveness of DSM-5 and ICD-11 in diagnosing depression. In the absence of overwhelming evidence supporting one system over another, we suggest that either may be used for diagnosing depression in the primary care setting.

Formal diagnosis and assessment of severity

A formal diagnosis of major depressive disorder using the DSM-5 criteria requires at least one key symptom (low mood, loss of interest and pleasure, or loss of energy) to be present, whereas the ICD-11 criteria require depressed mood or diminished interest in activities to diagnose a depressive episode. In both, symptoms should be present for at least two weeks and each symptom should be present at sufficient severity for most of every day. DSM-5 requires at least five out of nine symptoms for a diagnosis of depression, whereas the updated ICD-11 classification system does not quantify the number of symptoms needed.

The severity of a patient's depression should be primarily assessed on the basis of the degree of functional impairment, taking symptom severity into account, rather than being based solely on symptom count. Although this approach makes the grading of severity more subjective, highlighting the distinction is important as evidence based treatment is guided by severity. Both systems classify depressive episodes as mild, moderate, or severe on the basis of the number, type, and severity of symptoms present and degree of functional impairment.

Alternative and comorbid psychiatric diagnoses

Depressive symptoms that do not meet the criteria for major depressive disorder in DSM-5 or for a single episode or recurrent depressive disorder in ICD-11 may arise from other depressive disorders. For example, patients with bipolar disorder are often misdiagnosed as having major depressive disorder, particularly at initial presentation in the primary care setting. Therefore, patients who present with symptoms of depression should also be evaluated for possible bipolar disorder.

Patients with depression may also have comorbid psychiatric conditions, particularly anxiety disorders and substance use disorders, and the presence of one disorder significantly increases the likelihood of another being present. Therefore, screening for these conditions, using instruments such as the Generalized Anxiety Disorder scale or the SBIRT (screening, brief intervention, referral, and treatment) for substance use disorders, is important.

Depression and suicide risk

Depression is a major risk factor for both attempted and completed suicide, and a history of self harm attempts, in combination with a history of well developed suicide plans, place the patient at a greater eventual risk of completing a suicide attempt. Once the diagnosis of depression has been made, primary care providers should assess patients for risk of suicide.

They should specifically ask about suicide with a focus on suicidal thoughts, plans for suicide and intent, and assess the level of risk to define the level of care needed. If any uncertainty exists about either of these levels, consultation with a psychiatrist should be considered.

Management

Effective management of depression in primary care requires strategies at the individual and organisational level. The table shows our overall recommendations. Individual interventions are discussed below.

Psychological interventions

This review focuses on therapies that can be feasibly delivered in primary care settings, defined as those that are time limited, require fewer resources, and lend themselves to being put into practice (see table 1 on bmj.com). Several systematic reviews have found little or no difference in the effectiveness of different modalities of brief, time limited therapies—either low or high intensity—compared with longer term interventions such as long term psychoanalytic or psychodynamic approaches.

Cognitive behavioural therapy (CBT) is the most studied psychological intervention. Evidence suggests that CBT has efficacy over treatment as usual, particularly for the treatment of depression with comorbid physical conditions, but effectiveness over other psychological or pharmacological interventions for depression has not been established.

Evidence suggests that non-specific factors such as the therapeutic relationship and the client's expectations are very important for the outcome of most therapies, particularly in low intensity, unstructured interventions such as generic counselling or self help, and that this therapeutic relationship can be maintained through remote technologies.

Summary of management recommendations

Point of care	Recommendations	Elaboration/caveats
General principles	The aim of treatment should be remission from depression for ≥2 months. Emphasis should be placed on return to functioning over reduction in symptoms. However, where this is not possible, symptom reduction should be sought as it is associated with reduced relapse and increased likelihood of recovery over time [B]	Patients themselves may value improvements in features such as self confidence and optimism above symptom reduction [C]
	Treatment choice should ideally be made using an SDM approach taking into consideration the patient's circumstances and preferences [B]	The use of decision aids to support an SDM approach takes time (one study suggested a median of 40 min), so this may not be practicable in primary care. Facilitating the SDM approach may require changes at the organisational level or expanding the roles of other health professionals such as physician associates or prescribing pharmacists [C]
	Management should follow a stepped care approach, in which treatment is guided by the severity of depression, requiring active monitoring of symptoms and functioning [A]	
Treatment of mild depression	Consider active monitoring for patients who do not want psychological or pharmacological interventions [C]	
	A programme to increase physical activity, either in group or individual settings, may be more effective than no treatment or treatment as usual in reducing severity of symptoms [D]	Evidence supports physical activity as a strategy for primary prevention of depression at a population level, although "moderate to vigorous exercise" may be needed to produce results [B]
	Low intensity psychological interventions are more effective than control: (1) psychological counselling that adheres to a psychological modality [B]; (2) self help guided by a psychologically trained professional [B]; (3) computerized CBT [A]. Many of these therapies may be offered remotely through digital technology and have efficacy over treatment as usual or wait list control [B]	Non-specific interpersonal factors, especially the therapeutic relationship between therapist and client, client expectation, and suitability for psychological intervention as judged by a clinician, may be more important than the type of therapy offered [B]
Treatment of moderate to severe depression	Specific high intensity psychological interventions and pharmacological interventions have comparative effectiveness above control [A]	
	High intensity psychological interventions with effectiveness above control include CBT [A], PST [B], and (IPT) [B]	
	If considering drug treatment, recommendations should be made on the basis of the patient's preference and circumstances, especially considering the relative side effect profile of the different antidepressants [B]	SSRIs should be prescribed with great caution in older adults because of increased risk of falls [B], fractures [B], hyponatremia [B], upper gastrointestinal bleeding [B], and cerebrovascular bleeding [C]
Management of non-response to initial treatment	Change to other drug—either within class or from a different class—may prove effective if the first intervention has failed [A]	According to the STAR*D trial, the effectiveness of interventions decreases and attrition increases with each failed intervention [A]
	Change from psychological therapy to pharmacological intervention may prove effective if the first intervention has failed [A]	
	Combination of pharmacological and psychological treatments may be more effective than either alone [A]	
Prevention of relapse	Antidepressants continued for ≥6 months after remission reduce risk of relapse [A]	
	Certain psychological treatments, provided as maintenance interventions during remission, are effective at preventing relapse above control. These are CBT [B], IPT [B], and MBCT [C]	
Referral to specialist services	There is low level evidence to guide decisions to refer patients for specialist services. Of these, high risk of suicide, treatment resistance, and severity of depression are the most commonly cited reasons [C]; patient preference and co-occurring mental or physical disorders are also commonly cited [D]	Most primary care physicians use clinical judgment to refer patients to specialist services, based on their perceived competencies and confidence in managing the patient [C]
		When guidelines advocating a stepped care approach are followed, referral rates increase [C]
	In addition, several guidelines recommend referral to specialist services when two interventions, which the patient has adhered to for an adequate length of time, have failed (this is often taken to mean treatment resistance) [C]	
Organizational changes	Simple educational strategies aimed at helping primary care professionals to better detect and treat depression may not be effective at improving diagnosis of depression or reducing severity of depression, unless combined with organizational strategies such as revision of professional roles (eg, introduction of nurse led case management) or formal integration of services [C]	
	MBC—a practice that bases clinical care on routine and systematically collected outcome data throughout treatment—may be more effective than usual care at achieving response and remission and reducing time to both [B]	MBC should be used to complement clinical judgment, in a patient centred manner, in collaboration with patients, their families, or caregivers [D]
	The CCM is more effective than usual care at reducing severity of depression, achieving remission, and improving satisfaction and quality of life for older adults with depression and in those with co-occurring long term physical conditions treated in primary care [A]	The CCM is a complex intervention that requires changes to multiple processes at multiple levels of a system and should be considered a transformative change in primary care [C]
	The CCM is probably cost effective (at a health system level) at treating depression in primary care when targeted to specific subgroups (eg, older adults and those with co-occurring chronic physical conditions) [B]	

CBT=cognitive behavioural therapy; CCM=Collaborative Care Model; IPT=interpersonal therapy; MBC=measurement based care; MBCT=mindfulness based cognitive therapy; PST=problem solving therapy; SDM=shared decision making.

Evidence for each recommendation was graded using the Oxford Centre for Evidence-Based Medicine (CEBM)'s levels of evidence. A=consistent level 1 studies; B=consistent level 2 or 3 studies or extrapolations from level 1 studies; C=level 4 studies or extrapolations from level 2 or 3 studies; D=level 5 evidence or troublingly inconsistent or inconclusive studies of any level. Level 1=systematic reviews (with homogeneity) of randomized controlled trials (RCTs) or individual RCTs (with narrow confidence interval); level 2=systematic reviews (with homogeneity) of cohort studies, individual cohort study (or low quality RCT—eg, <80% follow-up), "outcomes" research, or ecological studies; level 3=systematic review (with homogeneity) of case-control studies or individual case-control study; level 4=case series (and poor quality cohort and case-control studies); level 5=expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

Adverse effects

Research on the possible harms of psychological interventions is sparse, but a recent survey reported that the most common harms were resurfacing of unpleasant memories (38%), increased lasting stress (38%), and increase in anxiety (37%). Primary care providers should make patients aware that anxiety may increase on starting therapy before improvement in depressive symptoms is achieved.

Pharmacological interventions

Antidepressants are often considered the cornerstone of treatment. However, several guidelines, including those from the National Institute for Health and Care Excellence (NICE), reserve the use of antidepressants for moderate to severe forms of depression, where severity is defined by impact on everyday functioning.

First line agents

Selective serotonin reuptake inhibitors (SSRIs) are recommended as first line agents because of their tolerability and costs. In UK primary care, SSRIs are the most commonly prescribed antidepressants followed by tricyclic antidepressants and serotonin-noradrenaline (norepinephrine) reuptake inhibitors (bupropion is not licensed for the treatment of depression in the UK).

Comparative data

Until recently, systematic reviews had not been able to establish firm conclusions on the efficacy or tolerability of one antidepressant (any SSRI, duloxetine, mirtazapine, venlafaxine) over another. However, in 2018, a large network meta-analysis comparing 21 antidepressants with placebo or another antidepressant in adults with major depressive disorder found comparative differences. The review included 522 double blind randomised controlled trials (RCTs) (116 477 participants) and additional unpublished data. All antidepressants were more effective than placebo for both remission and response, with amitriptyline, mirtazapine, duloxetine, venlafaxine, and paroxetine being the most efficacious (range of odds ratios 1.75-2.13 for response) and clomipramine, trazadone, citalopram, fluoxetine, and bupropion being least effective (1.49-1.58 for response). Agomelatine, fluoxetine, and escitalopram were better tolerated than other antidepressants (range of odds ratios 0.43-0.77), whereas amitriptyline, duloxetine, trazadone, and venlafaxine had the highest dropout rates (1.30-2.32).

This analysis focused only on the acute treatment of depression (eight weeks), and most participants had moderate to severe depression. As primary care populations have a higher prevalence of mild to moderate depression compared with those in specialist settings, the results may not be generalisable. A subsequent recent meta-analysis concluded that no comparative differences exist between the different classes of antidepressants for moderate to severe depression. Drug selection, therefore, still often depends on the relative side effect profile of the various antidepressants (see table 2 in second review on bmj.com) and the patient's preference.

Adverse effects

Tricyclic antidepressants have adverse cardiovascular and anticholinergic effects and are particularly toxic in overdose, limiting their use. SSRIs tend to have a more benign side effect profile (the most common side effects are headache and gastrointestinal symptoms) except in older adults. In 2012 the American Geriatric Society categorised SSRIs as potentially inappropriate drugs for older adults with a history of falls or fractures. SSRIs also significantly increase the risk of gastrointestinal, and possibly cerebrovascular, bleeds in older adults, although the odds are modest (odds ratio 1.66, 1.44 to 1.92, for upper gastrointestinal bleeding) except when combined with other high risk drugs (for example, non-steroidal anti-inflammatory drugs: odds ratio 4.25, 2.82 to 6.42). These findings suggest that primary care providers should use antidepressants, and particularly the SSRIs, with caution in older adults and possibly at lower doses and with more active monitoring for side effects.

Starting antidepressants

All antidepressants exert maximal effects within the first two weeks of treatment. If no response has occurred by three weeks, the drug should be changed or the dose increased. However, as slow responders have also been described, even minimal improvement at three weeks could suggest eventual response. About half of all people who stop their antidepressants immediately on remission will have a relapse within three to six months. Evidence supports continuing treatment for at least six months after remission, as this has been shown to reduce the three year odds of relapse by 65%.

Ongoing management

Referral to specialist services

Several international studies have shown that only about 20-25% of patients with depression are referred for specialist mental healthcare. The decision to refer patients for specialist input is complex, involving clinician, patient, and practice related factors. Considerable variation exists in individual referral rates, as primary care providers tend to use clinical judgment rather than recommended guidance on when to refer patients. Therapeutic confidence in managing an individual patient's depression and perceived severity of depression seem to play a strong part. When guidelines are strictly followed, the proportion of people referred increases to about 60%, suggesting that family physicians manage a significant burden of disease.

English, European, and Australian guidelines recommend referral to specialist services for severe depression, particularly if mood congruent psychotic features are present and if considerable suicidal risk exists. NICE suggests that earlier referral should be considered when depression co-occurs with other psychiatric disorders (particularly anxiety disorders and personality disorders) or complicates physical illness, or if multiple somatic concerns exist. Most guidelines advocate referral for treatment resistant depression.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l835

SPOT DIAGNOSIS

Post-traumatic toe deformity in a child

A 5 year old boy experienced pain in the little toe of his right foot after falling down the last two steps of a flight of stairs.

Initially the diagnosis was a "sprained toe." No radiograph was taken at that time.

Five days later he was referred to orthopaedics because the pain was persisting. On examination, the toe was tender and swollen with subtle lateral deviation, but circulation and sensation were intact. Radiography was requested (fig 1).

What does the radiograph show?

Submitted by Tun Hing Lui

Parental consent obtained.

Cite this as: *BMJ* 2019;365:l2224

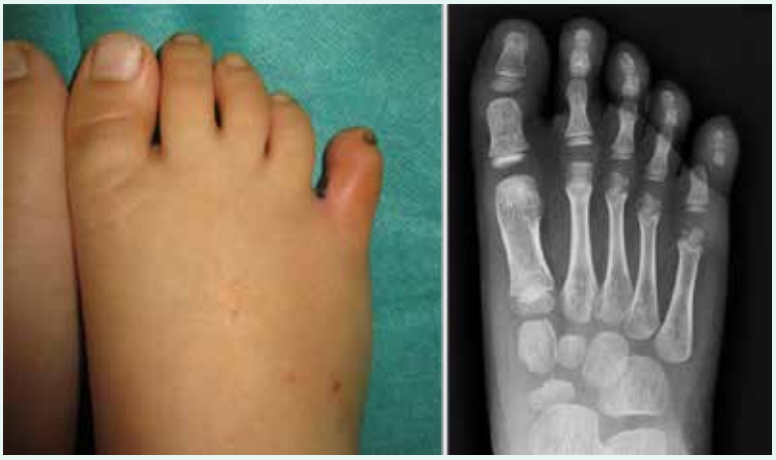

Fig 1 | (Left) Photograph of the right foot; (right) dorsolateral radiograph

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answers

SPOT DIAGNOSIS

Post-traumatic toe deformity in a child

What does the radiograph show?

The radiograph shows dislocation of the proximal interphalangeal joint (fig 2).

Differential diagnoses of a clinically deformed little toe include dislocation or subluxation of the metatarsophalangeal or proximal interphalangeal joint, fracture of the proximal phalanx, or physeal injury of the proximal phalanx or metatarsal. However, diagnosis cannot be based solely on the clinical appearance of the deformity. Early confirmation with radiography is required.

Most dislocations can be reduced with closed techniques, but non-reducible dislocations can occur as a result of interposition of the ruptured plantar plate or collateral ligament in the joint space. Irreducible dislocation of the proximal interphalangeal joint of the little toe can also occur without interposed soft tissue and can be a result of delayed presentation.

Dislocation of interphalangeal joints accounts for 7.6% of all dislocations in adults. It is less common in children.

LEARNING POINTS

- Any type of limb deformity associated with injury requires radiographic assessment at the first presentation
- Open reduction of the dislocated joint may be required if presentation/diagnosis is delayed.

PATIENT OUTCOME

Attempts at closed reduction under sedation and under general anaesthesia were unsuccessful. Open reduction of the dislocated joint was performed. The joint was stabilised by a K-wire which was removed four weeks after the operation. The joint remained reduced and stable six months after removal of the wire.

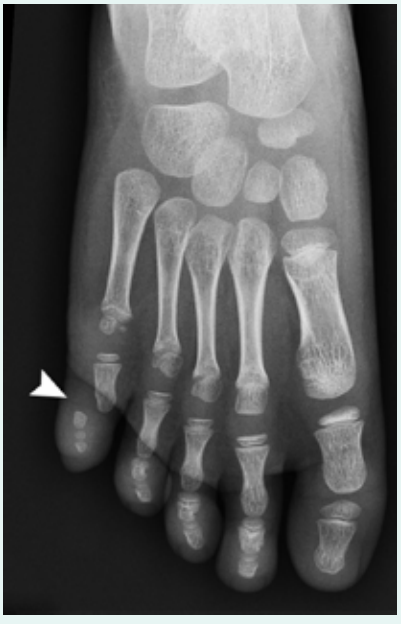


Fig 2 | Dorsolateral radiograph showing dislocation of the proximal interphalangeal joint (arrow)

CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

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

Phototoxic reaction to ciprofloxacin

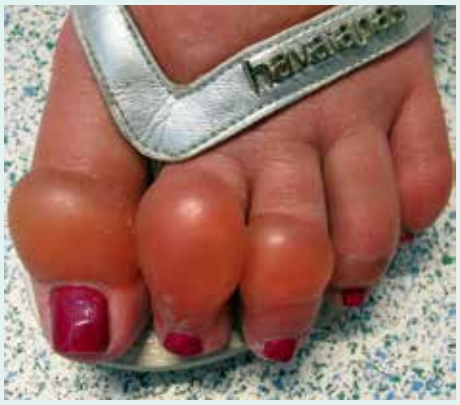
A 66 year old woman presented with a three week history of a blistering eruption on sun exposed toes of both feet (figure, right). She had taken ciprofloxacin 750 mg twice a day for nearly five months for a wound infection following spinal surgery. She was also taking naproxen.

Abrupt onset of severe bullous change in a sun exposed site suggests phototoxicity. She stopped both drugs and successfully restarted naproxen without further problems, making pseudoporphyria unlikely. Phototoxic reactions to ciprofloxacin and other macrolide antibiotics occur more frequently with higher dosage and greater sunlight intensity.

Alice Manley; Jane Sansom (Jane.Sansom@uhbristol.nhs.uk), Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust

Patient consent obtained.

Cite this as: *BMJ* 2019;365:l2413



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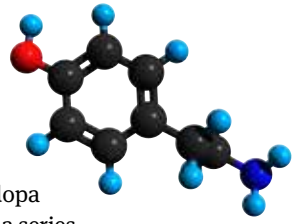
Gut microbes inactivate L-dopa



Tyrosine decarboxylase and dopamine dehydroxylase are two enzymes produced by two different species of gut microorganisms. They can sequentially metabolise L-dopa into tyramine, according to a series of laboratory experiments reported in *Science*. The investigators wonder if this explains why people with Parkinson's disease vary in their response to L-dopa preparations and in the doses that they need. However, as L-dopa is mainly absorbed from the jejunum and proximal ileum where the contents are usually sterile, Minerva isn't yet convinced that these biochemical findings are relevant clinically.

Disease progression in people with multiple sclerosis

It's generally thought that multiple sclerosis has two stages. The first is characterised by relapses and remissions. Disability accumulates because of incomplete recovery from the relapses. The second is a secondary progressive stage in which there is a gradual decline in function caused by axonal degeneration and gliosis.

The findings of a large longitudinal study question this view. Progressive deterioration was common in people with the relapsing and remitting form of the disease and was largely independent of clinical relapses or evidence on magnetic resonance imaging of new lesion formation (*Ann Neurol*).

Topical steroid use and type 2 diabetes

Treatment with glucocorticosteroids is well known to precipitate type 2 diabetes. A series of population based studies from the UK and Denmark finds that this is true even for topical preparations used to treat inflammatory skin conditions such as eczema and psoriasis (*Diabetes Care*).

People who had been prescribed topical corticosteroids had a roughly 25% increased risk of developing type 2 diabetes, and the risk was higher if they received more potent preparations. But in absolute terms the hazard is small—the equivalent of two extra cases of diabetes for every 1000 people exposed.

Treating adolescents for sexually transmitted infections

In a retrospective study of adolescents, almost all female, who attended an emergency department in the US with a sexually transmitted infection, more than 200 were given outpatient prescriptions for antimicrobial treatment for urethritis, cervicitis, or pelvic inflammatory disease (*JAMA Pediatr*). Follow-up revealed that almost half of these prescriptions remained unfilled.

In a group of people whose symptoms were severe enough to take them to hospital, such a high rate of non-adherence seems hardly credible—except that other studies have reported similar results.

Confessions of a serial killer

Sture Bergwall (below) was once considered Sweden's most prolific serial killer. He was tried and convicted for the murders of eight people and confessed to killing many more. In the end, it all turned out to have been a macabre hoax and a lot of lawyers, police, and psychiatrists were left with egg on their faces.

An essay in the *Postgraduate Medical Journal* ponders some of the lessons. One is being too ready to believe in someone else's insanity. Another is the peril of groupthink. When a large number of people subscribe to an idea, it becomes almost impossible to step back and take a fresh view (*Postgrad Med J*).

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