RATIONAL IMAGING

Investigating focal liver lesions

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Cite this as: *BMJ* 2012;344:e657
doi: 10.1136/bmj.e657

This series provides an update on the best use of different imaging methods for common or important clinical presentations. The series advisers are Fergus Gleeson, consultant radiologist, Churchill Hospital, Oxford, and Kamini Patel, consultant radiologist, Homerton University Hospital, London. To suggest a topic for this series, please email us at practice@bmj.com.

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Previous articles in this series

- Suspected early dementia (*BMJ* 2011;343:d5568)
- Investigating suspected subarachnoid haemorrhage in adults (*BMJ* 2011;342:d2644)
- Role of brain imaging in early parkinsonism (*BMJ* 2011;342:d638)
- Imaging transient ischaemic attack with diffusion weighted magnetic resonance imaging (*BMJ* 2010;340:c2215)

The authors discuss the commoner focal liver lesions encountered and the methods available for further investigation

A 31 year old Anglo-Indian man presented to his general practitioner for a discussion of cardiovascular risk factors because of a strong family history of ischaemic heart disease. He had no medical history of note. The patient denied excessive consumption of alcohol, although he admitted to a relatively unhealthy, high fat diet. Routine liver function tests showed raised alanine aminotransferase and aspartate aminotransferase. The patient was subsequently referred for abdominal ultrasonography, which showed moderate fatty change throughout the liver and an incidental 2.4 cm focal mass of mixed reflectivity in segment VII (fig 1).

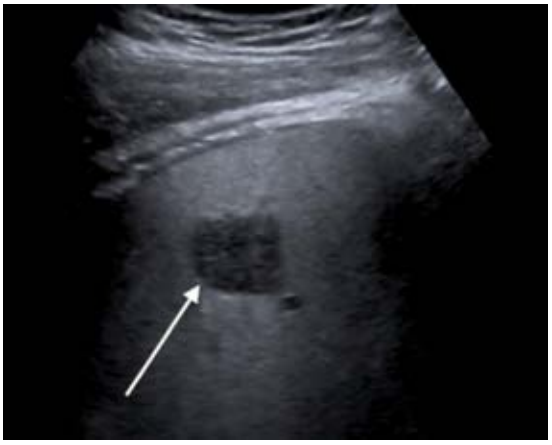

Fig 1 | Conventional ultrasound image showing focal hyporeflective lesion (white arrow) in segment VII of the liver with background increased reflectivity consistent with fatty infiltration

What is the next investigation?

Various imaging methods incidentally show focal liver lesions. The primary function of investigating a focal liver lesion is to characterise it with confidence as either needing no or only routine follow-up, or needing further, more rigorous exploration (including biopsy). The exclusion of malignancy is paramount, and most benign lesions can be characterised on non-invasive imaging grounds alone.

Conventional ultrasonography is often used as the first line imaging investigation for assessment of the liver and focal liver lesions as it is non-invasive, readily available, safe, and inexpensive. Conventional ultrasonography, however, is limited in that many focal lesions display overlapping and similar morphological features such as reflectivity, size, and shape. Further imaging of these focal lesions with computed tomography or magnetic resonance is common and is based predominantly on the administration of intravenous contrast agents. As different liver lesions vary in their blood supply, administration of a contrast agent allows evaluation and characterisation of the enhancement pattern of the lesion with respect to the background liver. In the diagnosis of the focal liver lesion, magnetic resonance imaging has higher sensitivity and specificity (82.1% and 93.4% respectively)[1] than computed tomography (71.0% and 64.5%).

Contrast enhanced ultrasonography, which has been used increasingly in recent years, has been shown to perform as effectively as contrast enhanced computed tomography or magnetic resonance imaging.[2 3]

In this patient, non-alcoholic fatty liver disease is likely to account for the diffuse background changes seen in the liver and the derangement of the liver function enzymes. However, the underlying nature of the incidental focal hepatic lesion needs to be established.

The differential diagnosis for a focal liver lesion includes simple hepatic cyst, haemangioma, focal nodular hyperplasia, focal fatty infiltration or sparing, and hepatic adenoma and malignancy, either primary or secondary. The table summarises the common features of these lesions.

It is good standard radiological practice when reporting any notable incidental lesion for the radiologist to recommend or arrange any further necessary imaging. Figure 2 shows a simplified protocol that our centre uses for investigating an incidental liver lesion. We emphasise the need always to consider further investigation in conjunction with other general factors, such as the patient's age, preferred investigation, and comorbidity and the local availability of imaging methods and expertise.

Computed tomography

Computed tomography allows for the assessment of the internal composition of focal hepatic lesions. When combined with contrast enhancement, computed tomography can show the enhancement characteristics of a lesion via a triple phase technique. The liver is initially imaged before the administration of intravenous contrast, (that is, unenhanced). The next series of images (the arterial phase) is obtained about 20 to 30 seconds after the injection of the contrast agent, as it enters the liver via the hepatic artery. The next series (the portal venous phase) is done 60 to 70 seconds later, with the images showing contrast returning from the mesenteric veins via the portal vein to the liver. Delayed images may be

LEARNING POINTS

- Incidental liver lesions on medical imaging are relatively common and the vast majority are benign
- Fatty infiltration is increasing in prevalence and can make the detection and characterisation of focal liver lesions difficult
- The choice of and need for further investigation when a focal liver lesion is identified depends on several patient factors and ideally should be recommended by the reporting radiologist
- Contrast enhanced ultrasonography, computed tomography, and magnetic resonance imaging of focal liver lesions rely on the recognition of characteristic enhancement patterns
- Biopsy may be needed where imaging fails to characterise a lesion adequately

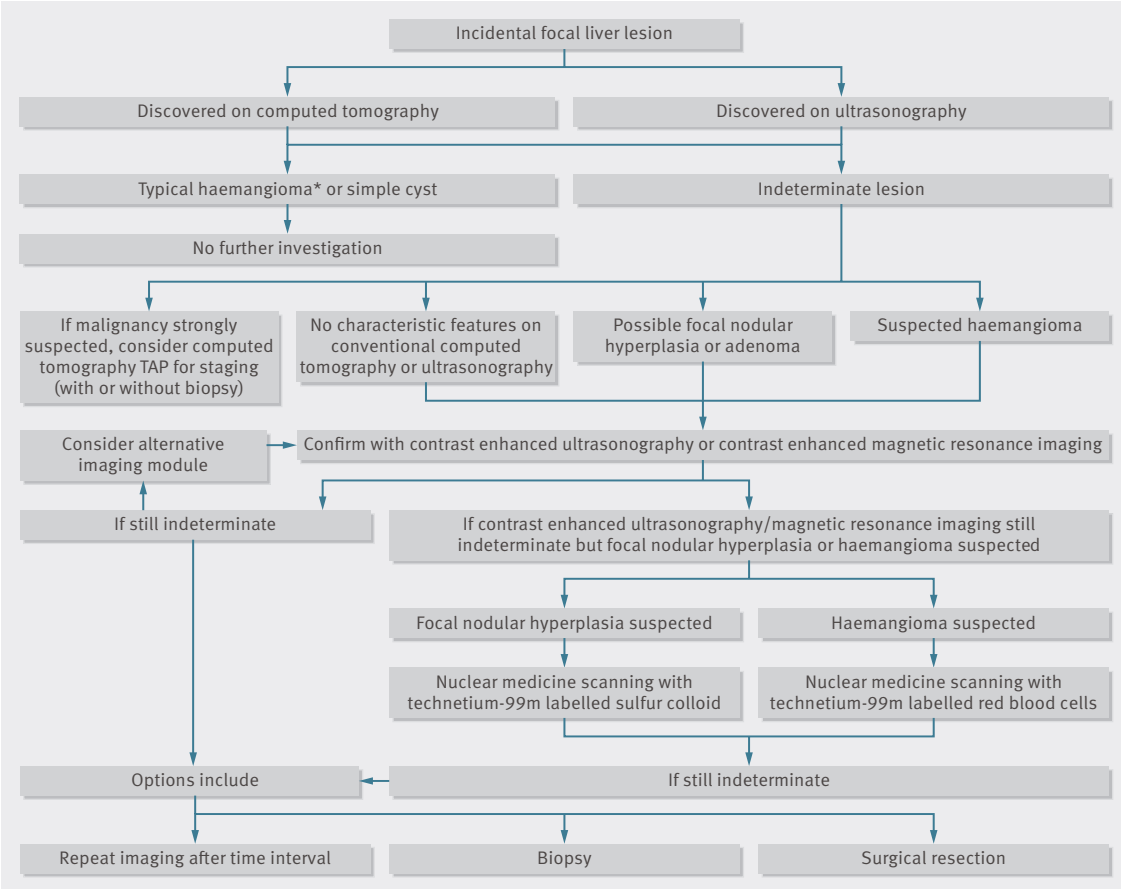

Fig 2| Protocol for the investigation of an incidentally discovered focal liver lesion

optionally obtained at 10-15 minutes after injection of the contrast agent (equilibrium phase). The observed features can then be examined and correlated with the typical features of several lesions, both benign and malignant.

Unfortunately the triple phase technique has the drawback of a substantial radiation dose (10-20 mSv[12]) and requires the use of iodinated contrast. The use of contrast material in patients with impaired renal function is contraindicated as there is an increased risk that the contrast will induce nephropathy. The exact threshold of serum creatinine concentration or of estimated glomerular filtration rate that precludes the administration of contrast agent varies between institutions, but typically the agent would not be administered if the creatinine concentration was >150-200 µmol/L or the estimated glomerular filtration rate <30 mL/min/1.73 m^2[13]; in this situation, alternative imaging modalities should be considered.

In addition, for small lesions (typically <1 cm in diameter), computed tomography may not have the capacity to produce images with optimal resolution as it cannot resolve or visualise objects below a certain size ("partial volume" artefact).

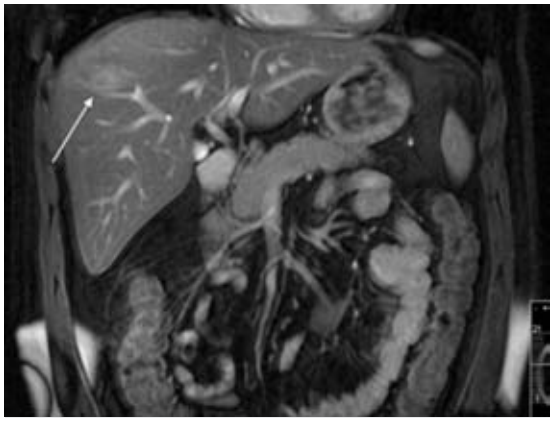

Fig 3 | T2 weighted, fat saturated magnetic resonance image showing segment VII abnormality (arrow) as hyperintense with background fatty liver

Magnetic resonance imaging

Magnetic resonance imaging can evaluate the internal chemical composition of a lesion and is especially useful for evaluating cystic hepatic abnormalities. It does not use ionising radiation but is time consuming and relatively expensive and requires the patient to lie extremely still. In combination with contrast agents, magnetic resonance imaging (like computed tomography) can examine the enhancement features of a lesion but again may suffer from partial volume artefact when dealing with smaller abnormalities.

Claustrophobic patients are unsuitable for magnetic resonance imaging, and gadolinium based contrast is contraindicated in patients with renal impairment owing to the risks of systemic nephrogenic fibrosis associated with that contrast.[14] Liver specific contrast media can be used, often as second line "problem solving" agents to distinguish between focal liver lesions of hepatocellular origin and those of non-hepatocellular origin.

Liver biopsy

Biopsy of a focal lesion under image guidance, either computed tomography or more commonly ultrasonography, enables histological analysis and in the vast majority of

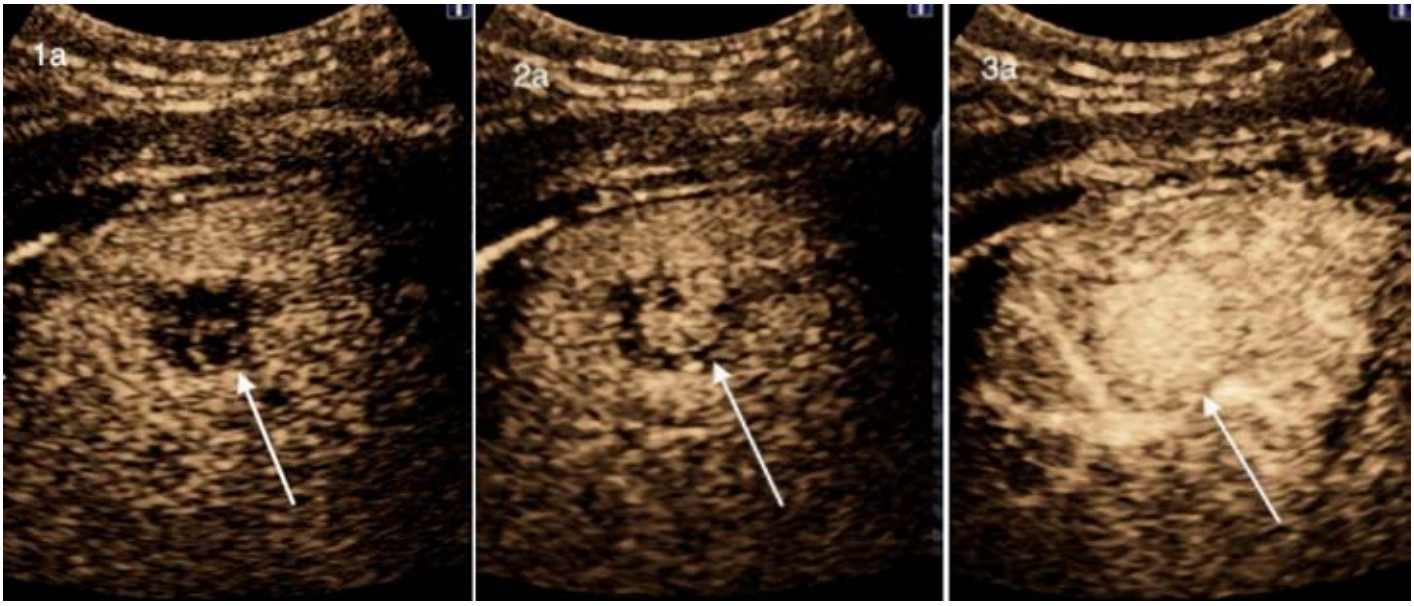

Fig 4 | Sequential contrast enhanced ultrasound images acquired at 7 (left), 12 (centre), and 20 (right) seconds after contrast injection. They show intense initial central and subsequent radial enhancement (arrows) consistent with focal nodular hyperplasia

patients is a safe and accurate procedure.[15] However, this is typically considered only when imaging has failed to characterise an abnormality with certainty. It carries the inherent risks of percutaneous biopsy; a recent study of 539 image guided liver biopsies recorded a complication rate of 2%,[15] predominantly relating to post-procedural pain and symptomatic haemorrhage. Biopsy of a focal lesion under image guidance is also time consuming, with the patient requiring preprocedural coagulation testing and most centres advocating a period of bed rest after the biopsy.[16]

Nuclear medicine

Isotope radiolabelled scanning is perhaps most useful in those patients for whom pre-existing renal dysfunction precludes contrast enhancement in computed tomography or magnetic resonance imaging. It can allow for lesion characterisation by displaying uptake by differing cell type. For example, Kupffer cell activity seen in cases of focal nodular hyperplasia and less often within hepatic adenomas can result in focal increased and persistent tracer uptake on technetium sulfur colloid scans. Radiolabelled red cell scanning is also useful in diagnosing haemangiomas. In cases of known or suspected malignancy, positron emission tomography-computed tomography (PET-CT) may also be of value. Such examinations, however, carry an inherent radiation dose and have relatively poor spatial resolution. In addition, many causes of false positive results for uptake exist, and availability of radiotracer can be a problem.

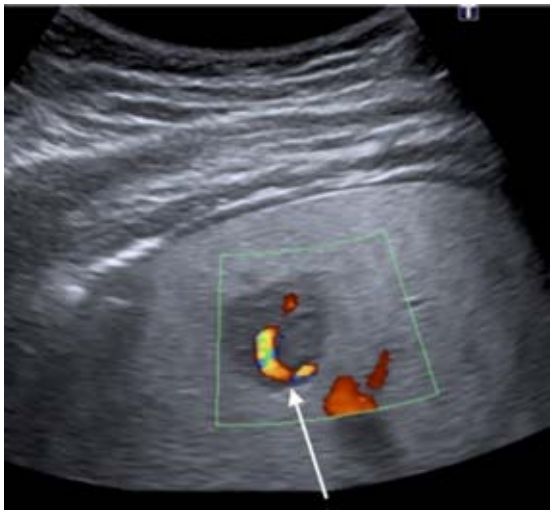

Fig 5 | Colour Doppler ultrasound image displaying central feeding artery (white arrow) in the focal nodular hyperplasia lesion

Contrast enhanced ultrasonography

Contrast enhanced ultrasonography is a fairly recent tool in the detection and characterisation of focal liver lesions, including those <1 cm in diameter. It can often obviate the need for further cross sectional imaging in investigating focal liver lesions,[17 18] with the potential for substantial cost savings.[19 20] A recent multicentre study found that for diagnosing focal liver lesions, contrast enhanced ultrasonography was more sensitive and specific (95.5% and 70.5% respectively) than contrast enhanced magnetic resonance imaging (81.8% and 42.9%) or contrast enhanced computed tomography (72.2% and 37.5%).[17]

The microbubble contrast agents used with ultrasonography consist of an inert gas or air surrounded by a protein or phospolipid shell; unlike other contrast agents, they act as pure blood-pool enhancement agents. Contrast enhanced ultrasonography is a relatively rapid procedure requiring placement of an intravenous cannula. It does not use radiation and is a suitable technique in patients with renal dysfunction, no matter how severe. Its use is limited, however, in those with end stage cardiac failure, and its safety and efficacy is untested in pregnant patients and children. Its availability is currently limited by local expertise but is expected to expand as experience and confidence in the technique increase. Its use also requires additional software on ultrasound scanners.

Outcome

Our patient initially had gadolinium enhanced magnetic resonance imaging, as recommended by the radiologist's report on the initial ultrasound scan. The gadolinium enhanced magnetic resonance scan confirmed the segment VII abnormality (fig 3). The lesion showed isointensity to the liver on

standard T1 and T2 weighted images but was hyperintense on fat saturated images, reflecting the diffuse background fatty change of the liver. After contrast injection, persistent hyperenhancement of the lesion was visible. The differential diagnosis as a result of magnetic resonance imaging was between focal nodular hyperplasia and hepatic adenoma. Contrast enhanced ultrasonography was then recommended, and this showed a well defined mass with enhancement of a central feeding vessel and spoke-wheel radial branches, consistent with focal nodular hyperplasia (fig 4). Repeat contrast enhanced ultrasonography six months later was entirely stable (fig 5), although the fatty infiltration had improved slightly after dietary modification. In this case, after the initial conventional ultrasound scan, either contrast enhanced ultrasonography or magnetic resonance imaging would have been an appropriate next investigation.

Contributors: DVP prepared the manuscript and selected the patient and images; VS and JP contributed to the editing. DVP is the guarantor.

Competing interests: None declared

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

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The *BMJ* on the death of Charles Dickens

How true to Nature, even to their most trivial details, almost every character and every incident in the works of the great novelist whose dust has just been laid to rest, really were, is best known to those whose tastes or whose duties led them to frequent the paths of life from which Dickens delighted to draw. But none, except medical men, can judge of the rare fidelity with which he followed the great Mother through the devious paths of disease and death. In reading *Oliver Twist* and *Dombey and Son*, or *The Chimes*, or even *No Thoroughfare*, the physician often felt tempted to say, "What a gain it would have been to physic if one so keen to observe and so facile to describe had devoted his powers to the medical art." It must not be forgotten that his description of hectic (in *Oliver Twist*) has found its way into more than one standard work, in both medicine and surgery (Miller's *Principles of Surgery*, second edition, p. 46; also, Dr. Aitken's *Practice of Medicine*, third edition, vol. i, p. III; also several American and French books); that he anticipated the clinical researches of M. Dax, Broca, and Hughlings Jackson, on the connection of right hemiplegia with asphasia (*vide Dombey and Son*, for the last illness of Mrs. Skewton); and that his descriptions of epilepsy in Walter Wilding, and of moral and mental insanity in characters too numerous to mention, show the hand of a master. It is feeble praise to add that he was always just, and generally generous, to our profession. Even his descriptions of our Bob Sawyers, and their less reputable friends, always wanted the coarseness, and, let us add, the *unreality*, of Albert Smith's; so that we ourselves could well afford

to laugh with the man who sometimes laughed at us, but laughed only as one who loved us. One of the later efforts of his pen was to advance the interests of the East London Hospital for Children; and his sympathies were never absent from the sick and suffering of every age. [*BMJ* 1870;i:636]

The *BMJ* is grateful to Professor Meir Kryger for bringing this article to our attention.

Cite this as: *BMJ* 2012;344:e630

10-MINUTE CONSULTATION

Varicose veins

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Cite this as: *BMJ* 2012;344:e667
doi: 10.1136/bmj.e667

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

A 55 year old woman presents with a history of tortuous veins on both legs and a related ache towards the end of the day. She finds these veins unsightly and would like to know whether she can have them treated.

What you should cover

- Varicose veins are very common: 40% of men and 32% of women aged 18-64 years have this condition.[1]
- Common presenting complaints are "heavy legs," swelling, restless legs, cramps, itching, and tingling,[2] but these symptoms are often unrelated to the presence of varicose veins.[2]
- Document risk factors such as increasing age, family history, obesity, and occupational history associated with prolonged standing.[3] Varicose veins may first become apparent during pregnancy, and the risk increases with parity.[1 3]
- Ask about red flag symptoms such as weight loss and rectal bleeding where varicose veins may be due to a pelvic or abdominal mass.
- Ask about previous treatment of varicose veins and outcome. Document a history of deep vein thrombosis or thrombophlebitis, where varicose veins could be acting as collaterals in the presence of deep vein obstruction.[3] Document symptoms of arterial insufficiency in patients with ulcers, as this situation is a contraindication to compression.

What you should do

- Document skin changes, including pigmentation and lipodermatosclerosis, and complications such as ulceration, thrombophlebitis, or haemorrhage, and refer patients with these features to a specialist.[4] Clinical examination to determine the site of venous incompetence is unreliable. The gold standard for determining this site is duplex scanning, which should be done in secondary care.[1 3]
- Reassure patients with uncomplicated varicose veins that no treatment is needed.[1 4] Because most people will not develop complications, treatment is usually not provided on the NHS. Surgery does not prevent long term complications, particularly leg ulceration, in patients with no history of ulcers. Varicose veins rarely "burst" spontaneously but are at risk of bleeding from direct trauma. Bleeding will stop with firm pressure.
- Emphasise to patients with venous ulcers that the mainstay of treatment for ulcers is compression bandaging. Varicose vein surgery will not improve healing, but will reduce the risk of recurrence.[5]
- Conservative measures include weight loss, regular exercise, prevention of constipation, elevation of limbs, and support hosiery. Compression classes vary between each country. We recommend below knee European class 2 or British class 3 stockings depending on local availability. These stockings should be worn all day and must be fitted correctly.
- Interventional options range from open surgery, such as high tie and stripping with avulsions, to less invasive procedures, such as radiofrequency ablation, endovenous laser therapy, and foam sclerotherapy. All these interventions are effective with similar recurrence rates (13-30% at five years) and are routinely performed as day cases. Treatment options will depend on local availability. Patients undergoing surgery will usually attend a pre-operative assessment clinic. On the day of surgery, the surgeon will outline the varicosities with a marker pen. Although varicose vein surgery is safe, patients need to be aware of the risks of scarring, pain, bruising, sensory symptoms, infection, deep vein thrombosis, and recurrence. Inform patients that surgery will not alter skin changes (such as thread veins) and may not improve symptoms such as aching.
- Open surgery is usually done under general or regional anaesthetic, such as spinal anaesthesia. Patients can go home the same day, and they may be advised to wear bandages or compression stockings postoperatively. They are advised to walk, but time off work may be needed, depending on occupation. Instructions on driving are similar to those for other operative procedures.

CHECKLIST: WHAT TO INCLUDE IN REFERRAL LETTER TO VASCULAR SURGEON

Background information—symptoms, duration, risk factors including occupation, thromboembolic disease, other relevant medical history
Any treatment received so far and outcome (for example, trial of support hosiery, previous surgery)
Details of any complications
Most recent examination findings, how findings have evolved over time
Patient's concerns and expectations

USEFUL RESOURCES

For patients

PatientUK (www.patient.co.uk/health/Varicose-Veins.htm)
NHS Choices (www.nhs.uk/conditions/varicose-veins/Pages/Whatarevaricoseveins.aspx)
Circulation Foundation (www.circulationfoundation.org.uk/vascular_disease/varicose_veins)

For healthcare professionals

Tisi P. Varicose veins. *Clinical Evidence* 2007;10:212 (http://clinicalevidence.bmj.com/ceweb/conditions/cvd/0212/0212-2007-10.pdf)
Medscape: Pathogenesis of varicose veins and implications for clinical management (www.medscape.com/viewarticle/567029)
NHS Clinical Knowledge Summaries (www.cks.nhs.uk/varicose_veins#-341100)

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Previous articles in this series

- Reviewing a patient with coeliac disease (*BMJ* 2012;344:d8152)
- Dyspepsia (*BMJ* 2011;343:d6234)
- The Hajj (*BMJ* 2011;343:d5593)
- Measles, mumps, and rubella vaccination in a child with suspected egg allergy (*BMJ* 2011;343:d4536)

- Radiofrequency ablation and laser therapy do not remove the vein, but seal it off by use of localised high thermal energy. They are usually done under ultrasound guidance. Similar postoperative instructions apply here, but these procedures can be done under local anaesthetic and usually result in quicker recovery.
- Foam sclerotherapy can be done in the outpatient setting and several cycles of injection may be required.
- There is no nationally agreed policy on NHS treatment of varicose veins and primary care trust policy for funding is variable. Some healthcare providers judge that uncomplicated varicose veins are of low priority and are treated in primary care, whereas others still fund surgical treatment. Surgery is funded if the varicose veins are associated with the complications mentioned above.

We thank Dr Emma Holland (GP trainee) and the general practitioners at School Lane Surgery in Thetford for advice and guidance during the preparation of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 3 October 2011

UNCERTAINTIES PAGE

Should we use individual cognitive stimulation therapy to improve cognitive function in people with dementia?

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Cite this as: *BMJ* 2012;344:e633
doi: 10.1136/bmj.e633

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

Interest is growing in the potential for mental exercises and activities to maintain and improve cognitive function, especially for patients attending memory clinics. However, a recent six week study of online brain training[1]—using cognitive tasks designed to improve reasoning, memory, planning, visuospatial skills, and attention—found that although specific improvements occurred in each domain, these effects did not transfer to untrained tasks.

Psychological therapies targeting cognitive function in dementia have been in widespread use for several decades. These approaches may involve personalised interventions, such as cognitive rehabilitation (which focuses on coping with deficits and enhancing remaining cognitive skills)[2] or cognitive training (which aims to enhance cognitive skills such as memory and attention through practice). More generic approaches include reminiscence, reality orientation, and cognitive stimulation therapy (box).[3] Reality orientation, which involved re-teaching information related to orientation to everyday life (such as date, location, and current events), has now been superseded by cognitive stimulation, which uses more implicit methods, with activities including categorisation and word association. Group based cognitive stimulation therapy is now a well established, evidence based, and cost effective approach that can improve cognition and quality of life in people with dementia.[3 4]

A systematic review in the 2011 *World Alzheimer Report* concluded that cognitive stimulation had the "strongest evidence by far" for cognitive benefits,[5] although more research is needed on longer term outcomes, including whether this approach reduces admission to care homes. In the UK, around a third of community mental health services for older people use group cognitive stimulation therapy. However, many people with dementia may be unable to take part in group therapy because they are unsuitable (for example, owing to severe sensory impairments), unwilling to participate, or unable to get to groups, or because they have no access to local groups. Evidence for the ability of other individual psychological interventions (such as cognitive training and cognitive rehabilitation) to improve cognition in dementia is weak. One small single centre randomised controlled trial found that cognitive rehabilitation improved attainment of individually relevant goals in early Alzheimer's disease.[6] An updated Cochrane review of cognitive training[2] found a lack of evidence of benefit, and the *World Alzheimer Report*[5] concluded that structured cognitive training was ineffective. The recent updated Cochrane review of cognitive stimulation[7] found robust evidence for improved cognition, but this finding mostly applied to group treatment,

Description of cognitive stimulation therapy

Cognitive stimulation therapy (www.cstdementia.com) is an intervention for people with mild to moderate dementia that is usually delivered by specifically trained staff, who may include occupational therapists and mental health nurses

It can be conducted individually or (more usually) in groups of five to eight people, in settings including care homes, memory clinics, and day centres

Sessions include structured discussions about topics such as current affairs, word associations, and money

The technique does not aim to test factual answers but to encourage participants to give their opinions, and thus to actively stimulate and engage them in an optimal learning environment, usually with the social benefits of a group

Evidence relating to cognitive stimulation therapy

Study design and number of participants	Characteristics of study participants	Intervention	Control	Cognition outcome
Systematic review[7] of 15 RCTs (n=718)	Dementia	Cognitive stimulation	Usual care or control activity	Improved cognition, effect size 0.41 (95% CI 0.25 to 0.57)
Systematic review[5] of 11 RCTs (n=743)	Mild to moderate dementia	Cognitive stimulation	Usual care or control activity	Improved cognition, no meta-analysis
Systematic review[9] of 20 RCTs (n=541)	Dementia and mild cognitive impairment	Cognitive stimulation, reminiscence, computer tasks, activity planning	Usual care or control activity	Improved cognition, effect size 0.30 (95% CI 0.13 to 0.48)
Systematic review[8] of 10 RCTs (n=270)	Dementia	Cognitive stimulation	Usual care or control activity	Improved cognition, effect size 0.44 (95% CI 0.20 to 0.69)
1 RCT[10](n=156)*	Dementia	Individual cognitive stimulation plus donepezil	Donepezil only	Improved cognition effect size 0.44 (95% CI 0.10 to 0.77)

RCT=randomised controlled trial.
*Also included in systematic reviews.[5 7-9]

since the review only included one study of individual treatment. Since around 70% of people with dementia living at home also have a family carer, this suggests that individual cognitive simulation training (delivered with the help of a family carer), if found to be effective, should be made widely available.

What is the evidence of the uncertainty?

We searched PubMed for systematic reviews of psychological interventions in dementia using the search terms systematic review, dementia or Alzheimer's, cognition, psychological, psychosocial, and interventions, from 2004 onwards. We also carried out a search through the Cochrane Collaboration for randomised controlled clinical trials. The search terms cognitive stimulation, reality orientation, memory therapy, memory support, and memory stimulation were used to search the Cochrane Dementia and Cognitive Improvement Group's specialised register. Four recent systematic reviews[5 7-9] were identified (table), but only one review looked at individual and group approaches separately.[9] The recently updated Cochrane Review [7] included only one randomised controlled trial of individual cognitive stimulation (described as reality orientation in the paper) that was of sufficient quality to be included[10] (table). The participants in this trial were people with Alzheimer's disease on cholinesterase inhibitors who were living at home. The intervention was a standardised programme delivered in the participant's own home by trained family carers for 30 minutes three times a week over 25 weeks, compared with usual care, and the principal outcome was cognition. Carers were given manual and specific schedules for each session. The study was well designed and multicentre, but follow-up was limited to only six months, and the family carers' adherence to the intervention was not measured, making it difficult to assess a possible dose effect based on the number of sessions actually received.

RECOMMENDATION FOR FURTHER RESEARCH

Population: patients with dementia living in the community supported by a family carer

Intervention and comparison: family carer delivered individual cognitive stimulation therapy sessions compared with usual care

Outcome: cognition, quality of life, and costs

Is ongoing research likely to provide relevant evidence?

We searched the European Clinical Trials Database (Eudract), the Clinical Trials database (clinicaltrials.gov), the Current Controlled Trials Database (ISRCTN Register), and the Cochrane Central Register of Controlled Trials. One trial for people with dementia in an acute hospital setting looked at the effects of individual cognitive stimulation on the severity and duration of episodes of delirium, compared with usual care. However, we found no randomised controlled trials of community based individual cognitive stimulation to improve cognition (compared with usual care) except for our own multicentre, pragmatic, single blind, 26 week study (www.controlled-trials.com/ISRCTN65945963). This trial will investigate whether individual home based cognitive stimulation delivered by a family carer to people with dementia improves cognitive function and quality of life, compared with usual treatment. Although it will provide evidence on the potential benefits of individual cognitive stimulation therapy, a longer follow-up than the initial six months would be worthwhile to better understand the longer term effects on cognition, care home admissions, and cost effectiveness. Future studies should also look at the potential for people other than family members to deliver individual cognitive stimulation therapy, including home care staff and the voluntary sector.

What should we do in the light of the uncertainty?

The NICE/Social Care Institute for Excellence guidance on dementia[11] recommends that "people with mild-to-moderate dementia of all types should be given the opportunity to participate in a structured group cognitive stimulation programme . . . irrespective of any drug prescribed for the treatment of cognitive symptoms of dementia." However, participation may be difficult for people with severe sensory problems. Developing evidence suggests that individual cognitive stimulation therapy (usually carer led) may be promising, but it may be premature to recommend this treatment routinely in dementia care until better evidence from large scale multicentre randomised controlled trials is available.

Contributors: MO devised and drafted the article. MO and AS completed the searches of literature and trials. MO, AS, and BW were all involved in editing and revising the article. MO is guarantor.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; MO, BW, and AS receive royalties (departmentally) from the sale of the cognitive stimulation therapy manual *Making a Difference* (Hawker Publications) and are grantholders for the Health Technology Association funded study "Individual Cognitive Stimulation Therapy for dementia (iCST Trial) 08/116/06"; AS runs regular training courses for staff on how to deliver cognitive stimulation therapy.

Provenance and peer review: Commissioned, externally peer reviewed.

References are in the version on bmj.com.

Accepted: 29 November 2011.

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