THERAPEUTICS

Cholinesterase inhibitors and memantine for symptomatic treatment of dementia

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com

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Previous articles in this series

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- Hormone replacement therapy (*BMJ* 2012;344:e763)
- Newer drugs for focal epilepsy in adults (*BMJ* 2012;344:e345)
- Newer antidepressants for the treatment of depression in adults (*BMJ* 2012;344:d8300)

A 78 year old woman is assessed in the memory clinic. Her family feel that she has become increasingly forgetful over the past two years, misplacing objects around the house and forgetting her drugs. Her speech is repetitive, and she struggles with day to day activities such as cooking. Routine blood tests are normal, and she scores 21/30 on the mini-mental state examination (MMSE) with deficits in orientation, attention and concentration, and recall. Magnetic resonance imaging, performed to exclude other pathology, reveals global cerebral atrophy consistent with Alzheimer's disease. In discussion with her and her family, a management plan is formulated that includes referral to the local dementia advisor and social services for day opportunities as well as prescription of a cholinesterase inhibitor.

What are cholinesterase inhibitors and memantine?

The most common types of dementia are Alzheimer's disease, vascular dementia, mixed dementia, dementia with Lewy bodies, and frontotemporal dementia. At present, four drugs are licensed in the UK for the management of Alzheimer's disease, the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine, a partial antagonist of NMDA receptors (table 1). The use of these drugs in other types of dementia has been investigated, with the most convincing evidence coming from studies of dementia with Lewy bodies and Parkinson's disease dementia. There is currently no evidence to support the use of cholinesterase inhibitors or memantine in frontotemporal dementia or mild cognitive impairment.

Cholinesterase inhibitors increase the availability of acetylcholine at the synaptic cleft by preventing its breakdown by the enzyme acetylcholinesterase. Galantamine also modulates nicotinic acetylcholine receptors, and rivastigmine inhibits butylcholinesterase, but the importance of these additional properties is unknown. Memantine is believed to act by reducing glutamate mediated excitotoxicity.

In this review we summarise the evidence and current guidance related to the use of cholinesterase inhibitors and memantine in Alzheimer's disease and other types of dementia in terms of cognition and global outcomes.

How well do they work?

Cholinesterase inhibitors in mild to moderate Alzheimer's disease

A 2008 systematic review and meta-analysis of placebo controlled and comparative studies of donepezil, galantamine, and rivastigmine in Alzheimer's disease included 22 trials of good or fair quality. On a commonly used measure of cognition, the Alzheimer's disease assessment scale cognitive section (ADAS-cog), 14 studies showed that all three cholinesterase inhibitors showed a modest mean benefit of about 2.7 points (95% confidence interval 2.3 to 3.0) on the 70 point ADAS-cog compared with placebo after three to six months of treatment. Most studies reporting measures of function such as the Alzheimer's Disease Cooperative Study's activities of daily living inventory (ADCS/ADL), also significantly favoured active treatment.[1] There is currently no evidence to support the use of one cholinesterase over another.

The clinical meaningfulness of the reported small changes on clinical scales is the subject of considerable controversy; one group suggests that a four point change over six months on the ADAS-cog scale is clinically important.[2] It has also been suggested that the apparent small mean improvements on clinical scales may be driven by a small percentage of patients deriving substantial benefit while the remainder do not benefit at all. Attempts to more accurately define characteristics of this group of potential responders are currently under way.

However, recent studies have considered response to treatment as "reduced worsening than expected if left untreated." A pooled data analysis from three randomised controlled trials using a definition of "clinical worsening" incorporating cognition, global outcome, and function reported that more placebo patients showed clinical worsening from baseline over the six month trial period compared with those taking donepezil (30% *v* 14%, giving a number needed to treat of six),[3]

Table 1 | Licensed indications for cholinesterase inhibitors and memantine in the UK

	Donepezil	Rivastigmine	Galantamine	Memantine
Mild Alzheimer's disease	Yes	Yes	Yes	No
Moderate Alzheimer's disease	Yes	Yes	Yes	Yes
Severe Alzheimer's disease:				
UK	No	No	No	Yes
(US)	(Yes)	(No)	(No)	(Yes)
Mild to moderate Parkinson's disease dementia	No	Yes	No	No
Vascular dementia	No	No	No	No
Mild cognitive impairment	No	No	No	No
Dementia with Lewy bodies	No	Yes	No	No
Frontotemporal dementia	No	No	No	No

Current NICE guidance relating to cholinesterase inhibitors and memantine[8 9]

- Donepezil, galantamine, and rivastigmine are recommended as options for management of mild to moderate Alzheimer's disease and for people with dementia with Lewy bodies who have non-cognitive symptoms that cause significant distress to the individual
- Memantine is recommended as an option for severe Alzheimer's disease and for people with moderate Alzheimer's disease who are unable to take cholinesterase inhibitors
- Cholinesterase inhibitors and memantine are not recommended for use in patients with vascular dementia or mild cognitive impairment except as part of properly constructed clinical studies
- Treatment should be initiated by a specialist in the care of patients with dementia, and carers' views should be sought
- Treatment should continue only if thought to be having a worthwhile effect on cognitive, functional, or behavioural symptoms
- Patients continuing with treatment should be reviewed regularly either by a specialist or according to local shared care protocols
- Assessment of the severity of Alzheimer's disease should not rely purely on cognitive measures (such as the mini-mental state examination (MMSE))

highlighting the possibility that apparent "non-responders" are still able to derive benefit from treatment. Assessing multiple domains in this manner is, arguably, a more clinically meaningful outcome measure since it helps determine whether the patient's condition as a whole is deteriorating.

Cholinesterase inhibitors in severe Alzheimer's disease

Donepezil is licensed in the US, but not the UK, for severe Alzheimer's disease. However, two separate randomised controlled trials in patients with severe Alzheimer's disease in community or nursing home settings found that donepezil significantly improved cognitive function and, in the nursing home study, preserved general function.[4 5] A more recent 2010 post hoc pooled analysis included three multinational randomised controlled trials of donepezil and reported significant benefits for patients with severe Alzheimer's disease on the severe impairment battery (SIB), a tool for assessing cognition in patients for whom floor effects (when everyone scores at the bottom of the scale) limit the use of the MMSE.[6] Similar findings have been published in a double blind, placebo controlled study in 10 European countries for galantamine in severe Alzheimer's disease.[7] These data suggest that there are untreated patients with severe disease in the community and nursing home settings who could benefit from treatment. In the UK, however, use of cholinesterase inhibitors in severe disease remains outside current licence indications and guidance from the National Institute for Health and Clinical Excellence (NICE) (see box).

Memantine in Alzheimer's disease

Contrary to a manufacturer sponsored analysis recommending memantine for mild Alzheimer's disease, a 2006 Cochrane review[10] and a 2011 independent meta-analysis[11] found no difference between memantine and placebo on any cognitive measure.

In moderate to severe Alzheimer's disease, for which memantine is licensed in the UK, a Cochrane review of data from three pooled randomised controlled trials supported a beneficial effect at six months on cognition (2.97 points on the 100 point severe impairment battery (95% confidence interval 1.68 to 4.26), P<0.0001), activities of daily living, and behaviour which was detectable clinically.[10]

The available randomised controlled trials examining the effect of adding memantine for patients whose Alzheimer's disease was already stabilised with cholinesterase inhibitors provide conflicting evidence. In a study of 404 patients who had been stabilised for six months with donepezil, the addition of memantine for six months produced a statistically significant improvement over placebo on cognition, global measures, and activities of daily living.[12] In a subsequent study of patients with mild or moderate Alzheimer's disease stabilised with any cholinesterase inhibitor, addition of memantine was no better than placebo on various assessments.[13] More recently, the DOMINO study—a 12 month, double blind, randomised controlled trial of people with moderate to severe Alzheimer's disease already taking donepezil—reported no significant benefit of the combination of donepezil and memantine compared with donepezil alone in terms of cognitive or functional measures.[14]

Long term treatment

It is difficult to draw firm conclusions about long term treatment as most controlled treatment trials average six months. Generalisability of data from the longest running placebo controlled trial published[15] was limited by the multiple washout design and high drop-out rate (70%) and was excluded from the Cochrane review. However, the DOMINO study reported that continuation of donepezil was associated with greater cognitive and functional benefit over 12 months compared with discontinuation (1.9 points (1.3 to 2.5), P<0.001) on the standardised MMSE.[14]

Vascular dementia

A meta-analysis of eight large randomised controlled trials of antidementia drugs (three of donepezil, two of galantamine, one of rivastigmine, and two of memantine; trial duration 24–28 weeks; including both published and unpublished data) in patients with vascular dementia reported modest but significant cognitive effects in favour of cholinesterase inhibitors based on the ADAS-cog (or VaDAS-cog) measure in all trials, ranging from −1.10 (−2.15 to −0.05) points for rivastigmine to −2.17 (−2.98 to −1.35) points for donepezil, similar to that reported in trials in Alzheimer's disease.[16] However, there was no consistent benefit in terms of global measures or activities of daily living, and patients in the cholinesterase inhibitor (but not memantine) treatment arms had a significantly increased risk of adverse events compared with placebo groups.

Although current evidence has led to the approval of antidementia drugs for use in Alzheimer's disease but not in vascular dementia, many patients in clinical practice have both Alzheimer's disease and cerebrovascular

pathology; several population based studies of autopsy results have identified the most common pathological substrate for dementia is combined Alzheimer's pathology and cerebrovascular disease.[17] Most industry sponsored trials of cholinesterase inhibitors have concentrated on rigid diagnoses of either Alzheimer's disease or vascular dementia to the exclusion of many "real life" patients who have overlapping pathology and multiple comorbidities. Subanalyses of patients with mixed dementia suggest that those with Alzheimer's disease plus cerebrovascular disease benefit from treatment with cholinesterase inhibitors: for example, a large randomised controlled trial of galantamine included 592 patients with mild to moderate vascular dementia or Alzheimer's disease plus cerebrovascular disease and reported improvements in cognitive and global functioning over six months in the latter group of a similar magnitude to that reported in the trials of Alzheimer's disease.[18] Clinicians should thus not be dissuaded from treating patients with Alzheimer's disease who also have vascular risk factors or pathology.

Dementia with Lewy bodies and Parkinson's disease dementia

Dementia with Lewy bodies and Parkinson's disease dementia are overlapping clinicopathological conditions existing within a spectrum of Lewy body disorders and are both associated with marked cholinergic deficits. A randomised controlled trial of rivastigmine in dementia with Lewy bodies included 120 participants with an MMSE score ≥10 and reported significant treatment benefits on measures of neuropsychiatric symptoms, but not on cognitive or global measures, over 20 weeks.[19] In a subsequent 24 week trial of 541 participants with mild to moderate Parkinson's disease dementia, the number needed to treat for significant improvement or avoidance of clinically significant worsening on global measures was seven.[20] Trials of memantine in patients with either Parkinson's disease dementia or dementia with Lewy bodies have reported similar results: one study of a combined group of patients with dementia with Lewy bodies or with Parkinson's disease dementia reported improvements in global outcomes (mean difference of 0.7 points on the Alzheimer's disease assessment scale clinicians' global impression of change (ADAS-CGIC), P=0.03),[21] while a second study reported improved global outcomes in dementia with Lewy bodies but not Parkinson's disease dementia.[22]

At present, only rivastigmine is licensed for use in Parkinson's disease dementia, and neither cholinesterase inhibitors nor memantine are licensed for use in dementia with Lewy bodies. NICE guidance does not refer to dementia with Lewy bodies or Parkinson's disease dementia with respect to treatment of cognitive symptoms with cholinesterase inhibitors or memantine, but recommends use of cholinesterase inhibitors for treatment of non-cognitive symptoms in dementia with Lewy bodies and suggests that the recommendations may be useful when considering treatments for Parkinson's disease dementia. The evidence suggests that it is appropriate to offer patients with dementia with Lewy bodies or with Parkinson's disease dementia a trial of a cholinesterase inhibitor. It is also worth noting that many patients with dementia with Lewy bodies or Parkinson's disease dementia also have noticeable Alzheimer's disease pathology,[23] and many patients in the clinical setting will have mixed pathology.

How safe are they?

Cholinesterase inhibitors

The meta-analysis from the 2006 Cochrane review of cholinesterase inhibitors in Alzheimer's disease showed that patients in treatment arms were more likely than those in placebo arms to report a single adverse event (number need to harm of seven) and that donepezil was associated with fewer adverse events than the other cholinesterase inhibitors.[24] A meta-analysis of trials of cholinesterase inhibitors and memantine showed that cholinesterase inhibitors were associated with an increased risk of syncope (odds ratio 1.53 (95% confidence interval 1.02 to 2.30), number needed to harm=143) but not falls.[25]

Memantine

Overall, memantine is associated with fewer and less serious side effects than the cholinesterase inhibitors. Meta-analysis shows similar rates of withdrawal due to adverse events in memantine and placebo arms.[10]

What are the precautions?

Cholinesterase inhibitors

Most adverse effects of cholinesterase inhibitors arise from direct cholinergic effects or via increased vagal tone. Importantly, this necessitates caution in the presence of sick sinus syndrome and atrioventricular block. Caution is advised in patients with chronic obstructive pulmonary disease or asthma, urinary retention, and those with a history of peptic ulcer, although these are not absolute contraindications and many patients with these conditions can be successfully prescribed cholinesterase inhibitors. Depending on the nature and severity of the condition, it may be necessary to request relevant specialist advice, and memantine is an alternative option in many cases.

Table 2 | Cholinesterase inhibitor and memantine preparations

	Tablet	Capsule	Orodispersible tablet	Oral solution	Transdermal patch
Donepezil	Yes 23 mg in US	—	Yes	—	—
Galantamine	Yes*	Yes	—	Yes*	—
Rivastigmine	—	Yes*	—	Yes*	Yes
Memantine†	Yes	—	—	Yes	—

*Twice daily dosing required; all other preparations are administered once daily
†Previously 10 mg twice daily, now 20 mg once daily

TIPS FOR PATIENTS

Your doctor has prescribed this drug to help you with the symptoms of dementia, which may include memory problems. You will need to take it every day and you will not necessarily see a benefit straight away. Some people benefit more than others from this type of drug, and, while some people will experience a period of improved symptoms, for many people the main benefit may be that their symptoms do not worsen as quickly as they would without treatment. The drug acts by affecting chemicals within the brain, although it does not change the disease process itself.

When taking donepezil (Aricept), rivastigmine (Exelon), or galantamine (Reminyl) it is not uncommon to experience side effects such as nausea, diarrhoea, headache, and dizziness. These are usually mild and usually subside after a few days of treatment as your body gets used to the drug. For this reason, you will be prescribed a low dose at first, which will be increased unless there are side effects. If the drug doesn't suit you, there are other similar drugs that you can take. Your doctor will want to see you regularly to assess how you are responding to the treatment.

You can find more information about these drugs at http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=147.

The most common adverse effects of the cholinesterase inhibitors are nausea, vomiting, diarrhoea, abdominal pain, anorexia, and dizziness, and these can generally be reduced by dose titration. The rivastigmine transdermal patch is associated with reduced gastrointestinal adverse events compared with the capsule formulation.[26]

Although there are potential synergistic or additive interactions between cholinesterase inhibitors and other drugs that may slow heart rate, there is no indication to routinely stop digoxin or atenolol before a cholinesterase inhibitor can be prescribed. All cholinesterase inhibitors will interfere with the effects of anticholinergic drugs and may exaggerate the effects of muscle relaxants used during anaesthesia.

A comprehensive review of the available data on cardiovascular adverse events concluded that serious events were rare and outlined a clinical protocol that included screening and monitoring using pulse rate in asymptomatic, non-bradycardic patients.[27]

Memantine

Other than hypersensitivity to the drug or its excipients, there are no absolute contraindications to memantine. Although caution is advised when there is a history of seizure, the effect of memantine on seizure activity has not been systematically evaluated, and animal studies suggest that it may have both pro-convulsant and anticonvulsant effects mediated via the NMDA receptor system.

The most common side effects of memantine are constipation, dizziness, headache, hypertension, and somnolence.

How are they taken and monitored?

Memantine and cholinesterase inhibitors are available in a variety of preparations (table 2). Start these drugs at low doses and gradually titrate up to minimise the risk of adverse events. Individualise treatment plans according to comorbidities (see section on precautions). Patients taking cholinesterase inhibitors should have their pulse checked regularly, although there are no clear data on which to base the frequency of monitoring. One clinical protocol suggests that this should be monthly during dose titration and then six monthly.[27] There are no data to support routine use of electrocardiography before starting treatment.

How cost effective are they?

The 2011 NICE technology appraisal[8] concluded that all cholinesterase inhibitors produce cost savings for mild to moderate Alzheimer's disease compared with best supportive care. However, figures varied between the analyses considered: for example, the manufacturer of donepezil calculated total cost savings per patient of £3379 (€4100; $5450) and £1889 in mild and moderate Alzheimer's disease respectively, whereas the NICE assessment group calculated savings of £551 and £621 in patients with mild and moderate disease. The key driver of cost effectiveness in all current economic analyses is delay to full time care, although this is a late stage event.

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A PATIENT'S JOURNEY

At either end of the tube

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The BMJ welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

RESOURCES FOR PATIENTS

Patient.co.uk provides a comprehensive information service for patients with a wide range of conditions, including infective endocarditis—www.patient.co.uk/health/Endocarditis-Infective.htm

This patient, who was a junior doctor when he was faced with open heart surgery, recounts his experience of postoperative intensive care, with help from his friend Robin Kerr to distinguish between hallucination and reality

We are often told that experiencing illness will make us better doctors. Perhaps one of the more extreme examples of this is being intubated and sedated in the intensive care unit five weeks before starting work there.

I was in the second month of my foundation year 1. I had been sent home on two consecutive days for vomiting on the ward, and when I returned colleagues mentioned that I had lost weight. As I struggled to clerk a patient for an elective finger operation, he commented, "I think that you are more unwell than I am, doctor." The rigors continued through that day, and I was sent home again in blissful ignorance of the severity of my condition.

I continued to feel dreadful, became anuric, and was admitted to our hospital's medical assessment unit. A medical student took my history, performed an examination with an incredibly detailed neurological component, and presented a diagnosis of viral gastroenteritis. I was beginning to become concerned, but the medical team reassured me that my high C reactive protein and thrombocytopenia were not significant. I was aware that I was due to rotate through this unit and did not question that no qualified clinician had examined me. These doctors were my seniors, and I did not want a reputation as a paranoid hypochondriac before my first ward round there. I was discharged the next morning.

The fever got worse. I had not eaten in days, continued to rigor, and was beginning to hallucinate. I was due to fly to India for my brother's wedding when I saw my general practitioner again. She commented that I looked "awful," which I found strangely reassuring—I was not wasting another senior clinician's time. She expertly discovered a new murmur and the splinter haemorrhages that I had missed.

The diagnosis of endocarditis was devastating and terrifying, but an excellent cardiology team ensured I was on my feet and back to work. Unfortunately I had not escaped complications; severe mitral regurgitation meant I was to face open heart surgery the next spring.

The six months between diagnosis and surgery rolled by, and I convinced myself that I was neither anxious nor unwell. At work I wanted no special treatment and undertook all my responsibilities as a junior doctor. I rotated through the medical assessment unit and even worked under the consultant who had dismissed me so quickly. He seemed to have no memory of me or my admission, and I did not ever mention it.

As surgery approached, I became very particular about planning every small detail I could—such as specific music for the hospital and which T shirt I would wear. I even reconciled with an old girlfriend when I discovered she would be the foundation year 1 doctor covering my postoperative ward. In retrospect, I realise that this was my way of hiding from the fear of it all. While I regarded the surgery itself as a matter of routine, what worried me was the outcome. The decision about whether to repair

A DOCTOR'S PERSPECTIVE

This 27 year old man attended the emergency department with symptoms of a sore throat, vomiting, and rigors. His temperature was 38.5°C, but all other vital parameters were normal. No abnormal findings were noted on physical examination. Blood tests were in the normal range except for an elevated C reactive protein at 218 mg/L and a depressed platelet count at 64×10^9/L. He was admitted to the medical assessment unit with the diagnosis of viral gastroenteritis and was assessed by the general medical consultant. A further physical examination by a doctor was not undertaken, and he was discharged after intravenous fluid therapy.

The patient was readmitted to hospital four days later, after his general practitioner, having noted splinter haemorrhages and a pansystolic murmur radiating to the axilla, raised the possibility of infective endocarditis. His C reactive protein remained elevated at 194 mg/L. Three sets of blood cultures were taken.

A transthoracic echocardiogram suggested a vegetation attached to the anterior mitral valve (figure). A diagnosis of infective endocarditis was made, and he was started on a course of benzylpenicillin and gentamicin. A second transoesophageal echocardiogram revealed the anterior valve leaflet was normal, but the posterior mitral valve leaflet was partially destroyed, had a perforation, and was prolapsing with a resultant jet of severe mitral regurgitation (figure). There were two vegetations seen oscillating on the posterior valve leaflet. This shows the limited ability of transthoracic scans in this scenario.

Blood cultures taken during the second admission grew a Gram negative bacillus. This was identified as *Haemophilus parainfluenzae* type b, and the antibiotic regimen was rationalised to ceftriaxone. There was an excellent clinical response, with the C reactive protein falling to below 10 mg/L.

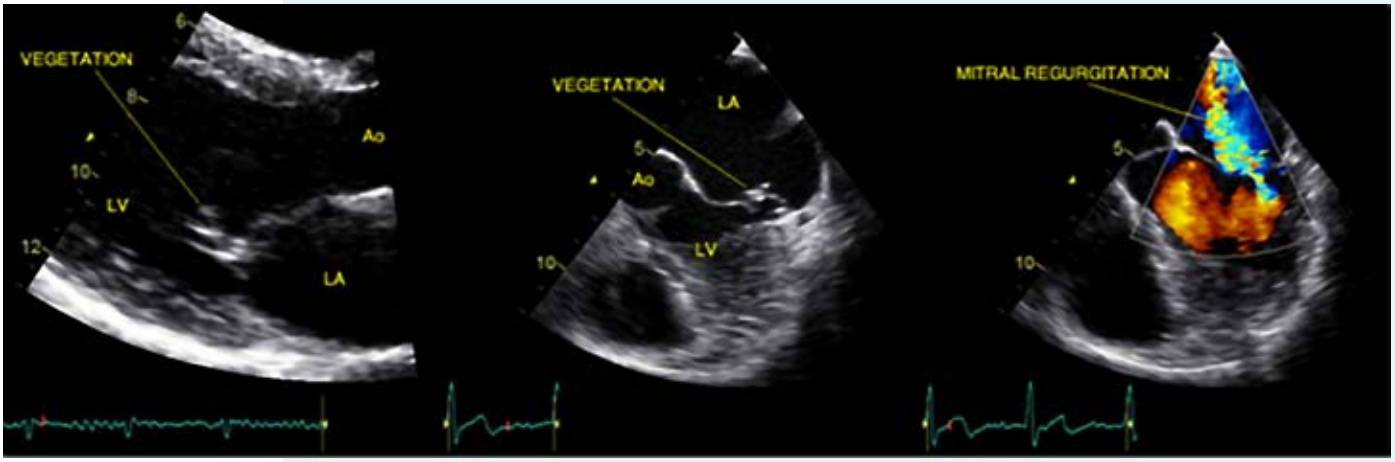
The patient was discharged home. Although his infective parameters remained in the normal range, he became breathless on exertion. Repeat transoesophageal echocardiography revealed a flail segment on the posterior mitral valve leaflet with a ruptured chord and a healed vegetation. The severe mitral regurgitation was still evident, and the case was discussed with the cardiothoracic surgery team, who offered a repair operation.

The repair was carried out successfully with subsequent echocardiography revealing a fully competent mitral valve. In the weeks after surgery the patient improved clinically with an enhanced exercise tolerance. He has remained under clinical follow-up and has been in excellent health.

The patient would almost certainly have had signs of endocarditis on his first hospital admission, but he was examined only once in a busy emergency department and the splinter haemorrhages and murmur were not appreciated. The opportunity to take blood cultures in a feverish and ill young man with a high C reactive protein was not taken. I also note he was working within a tertiary referral hospital for three days with unrecognised Gram negative sepsis.

The patient was clearly worried about the prospect of a mitral valve replacement as opposed to repair. The discussion between the cardiology and cardiothoracic team in this regard was very much routine. It is interesting to be reminded how much these decisions affect a patient's anxiety and long term wellbeing.

Shirjel Alam



Transthoracic echocardiograms of patient. Initial echocardiogram (left) seemed to show vegetation on the anterior mitral leaflet. A second echocardiogram showed vegetation on the posterior mitral valve leaflet (middle) and jet of mitral regurgitation (right). LV=left ventricle, LA=left atrium, Ao=aortic outflow

or replace the valve was to be made intraoperatively, the latter ensuring a limited valve life and ongoing warfarin treatment. I was wheeled into theatre with my future uncertain.

My memory of events in the intensive care unit after surgery, intubated and sedated, feels unshakably real. However, these memories proved to be inaccurate in both sequence and content when I recounted them to those present.

All I can recollect from those 18 hours are events that had an association with the people and world I knew. A friendly visitor or piece of medical jargon would punctuate the fog of my stay with momentary clarity. My thought process at the time was totally devoid of both insight and emotion. Even being told that the valve repair had been successful, and the replacement I feared had been avoided, was processed purely as a fact. There was no elation, no relief. Being sedated was like living a synchronous yet separate life from reality.

My first visitor was Robin, a good friend from medical school. I clearly remember him leaning over my bed with the same sympathetic smile and manner he has always

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used with patients. I later learnt this was fiction; he was actually teasing me for squeezing his hand with uncharacteristic affection. I could only salivate in response. I can't explain my clear visualisation, as he assures me I did not open my eyes. I wonder if all sedated patients are like me, apparently using past experiences to make sense of current events.

Unconscious and intubated, I was relying on my instincts. My training certainly influenced how I behaved, although this was not necessarily appreciated by the nursing staff. We are drilled in the benefits of patient controlled analgesia as medical students, and this was reiterated preoperatively by my anaesthetist. My brain told me I had had an operation and therefore I must push the button. So I did—excessively. I was pain-free throughout, yet I could overhear the staff discussing increasing my analgesia in response to my unrelenting use of the analgesia button.

Experience had also taught me that a poor arterial trace can be the result of suboptimal positioning of an arterial line. When I overheard a visiting colleague discuss my low blood pressure reading my right arm became completely disinhibited, and I started waving it around like an elated dog's tail, perhaps in a subconscious attempt to improve the trace. Thereafter, only physical restraint from my nurse came close to achieving optimal positioning.

Before surgery I was concerned that delirium would be a feature of my stay, and I feared being sectioned. It seems that a visitor could act as a trigger to my vulnerable mind, precipitating florid auditory and visual hallucinations. A colleague jokingly commented on the height of my "ST segments." Consequently, a fictional registrar requested a fictional troponin level. A fictional group of nurses then refused to carry out the request, arguing their case by sketching a fictional graph of cardiac enzymes on the wall in permanent black marker. When I was lucid the following day, this sketch was notably absent.

My first conscious thought process was my desire to be extubated, which seemed to go on for hours. I could hear the nurses saying that I was not yet awake enough to be extubated, but I was thinking, "Yes I am, I just can't tell you." Despite the sensation of choking, I was not distressed; rather I was frustrated as I struggled to get my point across. I found that biting the tube led to more sedation, so I eventually gave up and then somehow got my wish. I had completed my adventure through fiction and delirium to conscious thought and extubation.

My journey concluded five weeks later, back in the intensive care unit, but this time as a foundation year 2 doctor. I was concerned that my return to the same environment might trigger suppressed emotions. Thankfully this fear was unjustified. My only apprehension was of being singled out from my new colleagues, so I hid my sternotomy scar with a T shirt under my scrubs.

Could things have been different had I insisted on a further examination on my initial presentation? Could I have avoided surgery and a sternotomy scar? These questions will remain unanswered, but I have been fortunate that my journey has had a positive ending. Having been a patient in the intensive care unit, I then discovered a love for intensive care as a doctor and, one year later, began training in anaesthesia and critical care. My experience has given me a greater insight into life as a patient than I ever would have wanted, but it has equipped me with a great deal of empathy and understanding for patients as I now play my role in their similar journeys.

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ANSWERS TO ENDGAMES, p 50

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ANATOMY QUIZ **Facial view II**

A: Right coronoid process
B: Odontoid peg
C: Left infraorbital margin
D: Left zygomatic arch
E: Left body of mandible

STATISTICAL QUESTION

Confidence intervals: predicting uncertainty

Statement *c* best describes the information provided by the 95% confidence interval for mean weight loss at four months for the standardised consultation group.

PICTURE QUIZ

A returning traveller with fever, facial swelling, and skin lesions

1 Differential diagnoses specific to his recent travel history include malaria, dengue fever and other arboviral infections, enteric fever, leptospirosis, meningitis, visceral leishmaniasis, African trypanosomiasis, and acute schistosomiasis. Endocarditis must also be considered in view of his prosthetic heart valve.
2 The well defined structures have a reproducible morphology and a central nucleus with trypanosoma trypomastigotes. The diagnosis is human African trypanosomiasis (HAT), otherwise known as sleeping sickness.
3 HAT is characterised by a haemolymphatic stage and a subsequent meningoencephalitic stage. Death can occur at either stage if the disease is left untreated.
4 Refer patients to a specialist unit for intravenous treatment with suramin or an alternative (pentamidine, eflornithine, nifurtimox, or melarsoprol) and supportive treatment guided by the organism isolated and condition of the patient.