

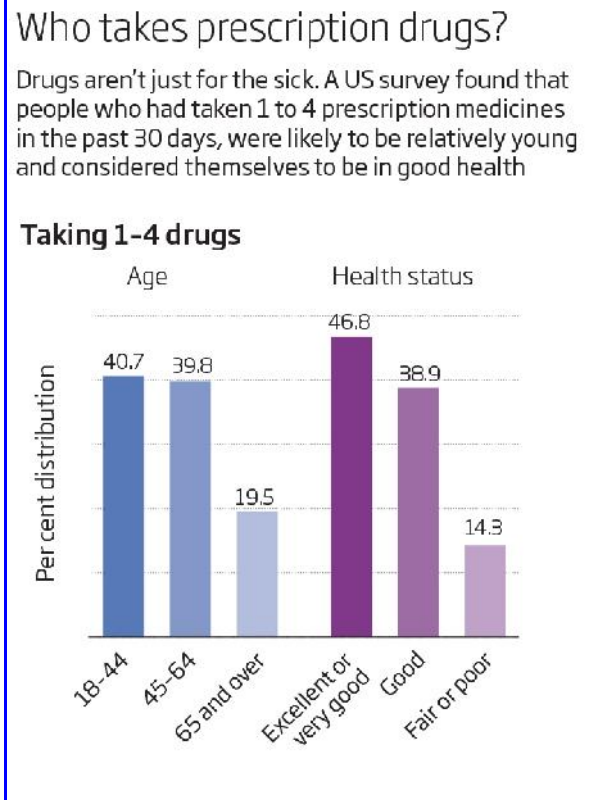
# Everyday drugs: Are we taking too many preventive pills?

By Chloe Lambert

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*As lifespans stretch, many of us are popping at least one pill a day. But all this medicine could be harming rather than helping your health.*

WHEN did you last pop a pill? The chances are it was recently, no matter how healthy you are. A growing number of us are taking medicines as part of our daily routine, not because of illness, but to prevent it (see graph). A recent survey found that 43 per cent of men in England and 50 per cent of women had taken a prescribed drug within the past week, and half of those had taken three.



“What we’ve seen is a massive rise in reliance on medicines as a panacea for all our woes,” says Clare Gerada, former chair of the UK’s Royal College of General Practitioners. “There’s been a big rise in screening to look for diseases before they happen, and we have begun treating people ‘just in case.’”

With life expectancies stretching, many of us have come to see prevention as a sensible route to living a greater number of disease-free years (see graph). And the evidence shows this strategy can work, for us and for health services. “There’s a very strong argument for saying that screening allows us to intervene to reduce the risks and consequences of developing the illness,” says Nick Finer, who studies obesity medicine at University College Hospital in London.

But there is reason to be cautious, too, and take stock of how medicalised our society is becoming. “Preventive drugs can be of huge benefit to people at

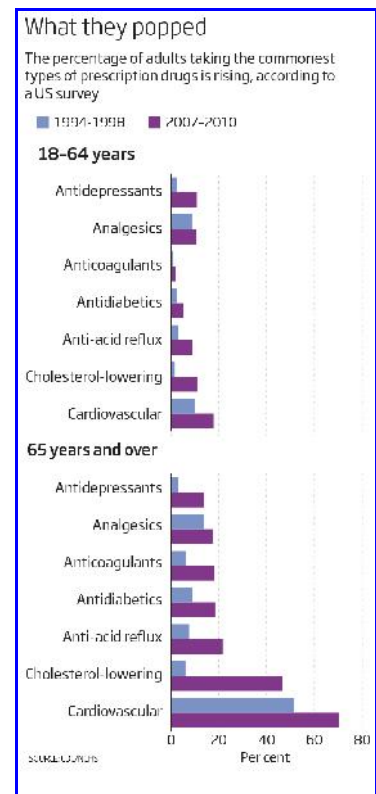
high risk of disease, but we’ve gone too far,” says Gerada. As a doctor, she says it’s not unusual to see patients on 15 different medications.

Doctors and decision-makers can become so focused on a drug’s benefits that they overlook the wider effects on patients, says Klim McPherson, an epidemiologist at the University of Oxford. “It’s a benign arm of paternalism. They don’t think about what it’s like to take a drug every day for the rest of your life.”

## “Doctors don’t think about what it’s like to take a drug every day for the rest of your life”

For some people it may feel comforting to be taking pre-emptive action. But at times that can be an illusion, as the examples on the following pages show. What is more, it can distract us from the wider social causes of disease, like alcohol, obesity and loneliness, Gerada says, none of which can be treated with a pill.

Taking several medicines at once can be risky, too. “We might know what will happen if someone takes a statin, but we don’t know what



happens if they're on a statin, and a vitamin D pill, an aspirin and a proton pump inhibitor to stop the side effect of stomach bleeds," Gerada says. One British study found that 6.5 per cent of hospital admissions were due to drug side effects.

Central to the debate is how the evidence for preventive medication is established. Many are prescribed to prevent conditions they were not developed to treat, for example. "We invent a drug which has an effect on people's complaints, test it to see what it does and end up using it not for therapeutic reasons but for prophylactic reasons, where the benefits are much less and where the possible harms may be much greater," says McPherson.

Preventing illness should save money in the long term, but channelling limited resources into treating healthy people could come at a cost to those who are sick right now, leaving clinicians tied up with patients who aren't even ill. What is more, doctors and patients alike can be bamboozled by evidence, often apparently contradictory, which frequently makes headline news.

Understanding the risks and statistics surrounding health can be puzzling for even the most mathematically literate. But as our society becomes increasingly medicalised, we need to arm ourselves with the information to help us decide whether we should be swallowing those pills. "I am surprised at how few people now complain about the number of medications they are on," says Gerada. "Even a decade ago, people would come and question whether they needed them all."

So should we embrace a drug regimen to promote better health, or accept treatments only when we need them? Over the following pages, we assess the evidence for the five most common – and controversial – everyday medicines.

## **Everyday drugs: The great statins debate**

*They're one of the most widely prescribed medicines in the world and save many thousands of lives each year – but the worries about side effects won't go away.*

One of the most widely prescribed medicines in the world, statins are thought to reduce the risk of heart attack and stroke by lowering blood cholesterol levels, and are now taken by one in four adult Americans over 45. However, once hailed as wonder drugs, they have hit the headlines in recent years over safety concerns and their use in healthy people.

The guidance used to be that statins should be prescribed to anyone who has had a heart attack or stroke. But, increasingly, people with no history of heart problems are offered them too.

In the UK, anyone deemed to have a 20 per cent risk of developing cardiovascular disease in the next decade would have qualified for a daily dose of statins – until last year. Then, following an analysis of 27 trials, the National Institute for Health and Care Excellence (NICE) lowered the threshold to a 10 per cent risk. The risk is calculated using factors like smoking, age, ethnicity and BMI (body mass index – an indicator of being under or overweight), as well as blood pressure and cholesterol levels.

That equates to an extra 5 million people on top of the estimated 7 million already taking statins in England and Wales alone. In the US, the threshold is even lower: the drugs are recommended to those with a 7.5 per cent risk of heart attack, after new guidelines came out in 2013.

NICE estimates that its strategy could prevent 28,000 heart attacks and 16,000 strokes every year. And statins are cheaper than treatment after the event.

But their increased use has met with strong resistance from doctors and patients suspicious of the notion of treating people who are not unwell.

For one thing, it means that for every heart attack prevented, more people will be taking the drug for no benefit. "For low-risk people, with a risk of, say, 10 per cent, taking statins will reduce it to about 8 per cent. A 2 or 3 per cent difference in risk of having a cardiac event is not very big," says

Klim McPherson of the University of Oxford. “If you’re expected to take a drug every day, you’ve got to wonder whether it’s worth the gamble.”

### **“For every heart attack prevented, more people will be taking statins for no benefit”**

For many that gamble is the possibility of side effects. A study and subsequent article in the BMJ questioned the data behind the NICE recommendations, warning that some trials included in the analysis were funded by statin manufacturers and that data on side effects was lacking.

Patients taking statins often anecdotally report muscle pain, although this has not been seen in the major, placebo-controlled trials. The BMJ article said that one in five people on statins experiences a side effect of some kind, although it later withdrew this claim after Rory Collins at the University of Oxford, a leading statin researcher, spoke out against the accuracy of the statistics.

Yet the anecdotal reports continue to surface. “Some doctors say they keep seeing patients with the same complaint and they feel it’s due to the statin,” says David Preiss of the University of Glasgow. “It doesn’t look that way from the trials, but we need a better answer.”

There does seem to be a link to diabetes. Preiss has studied the connection between statins and type 2 diabetes. He says taking a medium-dose statin raises your risk by 10 per cent, and the risk continues to rise in line with dosage. “These are modest changes – people who are probably already on the trajectory to diabetes, and the statin pushes them over the threshold.”

In light of all the concerns, Collins is undertaking a major review of the data on side effects, which he hopes will reassure people. That’s important, he says, because fears over statins are discouraging people from taking them, to the detriment of their health.

The results should be out later this year. In the meantime, if you’ve ever had a heart attack or stroke, you should be on a statin if possible, says Preiss. “And if you haven’t, but you’ve been shown to be moderately or markedly at risk of having a heart attack, the benefits of a statin considerably outweigh any risks.”

No one should pin all their hopes on a pill in any case. Taking statins should be accompanied by lifestyle changes such as taking exercise and giving up smoking.

## **Everyday drugs: The truth about testosterone**

*Millions of men take testosterone supplements. But is this the right way to regain youthful strength, vigour and libido?*

If the adverts are to be believed, testosterone supplements are a cure-all for men facing the unfortunate effects of middle age. The hormone is claimed to improve muscle strength, energy and sex drive. However, not only is there little evidence for this, several studies have found a link with heart disease.

Traditionally, testosterone was prescribed to men with abnormally low levels due to a congenital condition or damage to the testes from chemotherapy. Now, though, middle-aged men are being prescribed “testosterone replacement therapy” (TRT) to make up for the natural decline that often comes with age.

In the US, the number of men being prescribed testosterone rose from 1.3 million to 2.3 million in the five years up to 2013, and the UK has seen a similar trend, although the numbers are far lower (see graph).

But in March, the US Food and Drug Administration cautioned that testosterone should only be prescribed to men with low levels caused by medical conditions, rather than general ageing, and confirmed by a lab test. The European Medicines Agency has issued a similar statement.

The health bodies also asked manufacturers and prescribers of testosterone products to warn users about a possible risk of heart attacks and strokes after a number of studies showed an association. One trial was even terminated early due to an “excess of cardiovascular events” among participants. Worryingly, a 2013 analysis found that the level of cardiovascular risk reported varied, depending on whether the study was funded by the pharmaceutical industry.

One possible mechanism for testosterone’s effect on the heart could be through raising the number of red blood cells, which thickens the blood and can lead to dangerous clotting.

Another worry is prostate cancer, which feeds on testosterone; drugs blocking testosterone are sometimes used to stop the cancer spreading. A meta-analysis published in 2014 found no link with TRT in the short term, but called for more long-term data.

“There’s an absence of data on the use of testosterone outside its key clinical application and yet some clinician enthusiasts, particularly private practitioners in the US, have just exploded testosterone prescribing to the point where it’s almost become mainstream,” says Richard Quinton, an endocrinologist at Newcastle University, UK.

Part of the problem, at least in the US, is that men are not being properly tested before starting treatment, says Sander Greenland an epidemiologist at the University of California, Los Angeles, who recently found that some clinics were even failing to use blood tests, and instead diagnosed men on the basis of a questionnaire about symptoms. Others relied on a single test, which is unreliable because levels vary dramatically throughout the day.

Low testosterone can be a result of health problems such as obesity and diabetes, and some researchers are examining whether TRT could help. But in these cases, says Quinton, it would often be more appropriate to treat the primary condition – for example, by losing weight. He questions whether age-related low testosterone – or “low T” – is even a genuine condition. “Slim, healthy older men have similar levels of testosterone to healthy young men,” he says. “So probably 90 per cent of the fall in testosterone with age relates to just accumulating chronic diseases.”

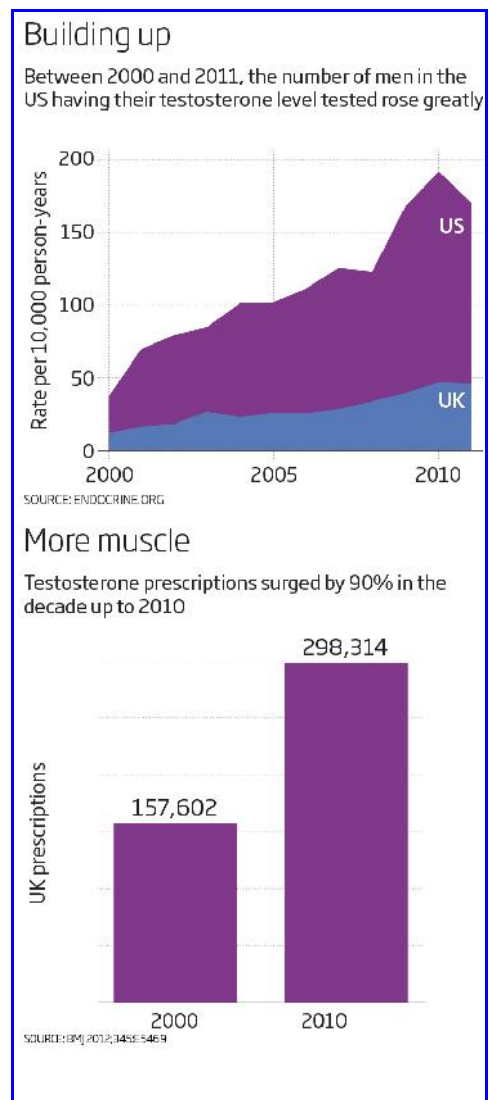
“It’s a personal choice,” says Greenland, but “if I was somebody with any cardiovascular risk, I wouldn’t go there. Most of all, get tested – and not just once – before you embark on this.”

## Everyday drugs: The rise and fall of HRT

*Hormone replacement therapy surged in the 1980s and 90s – then its reputation for disease prevention and safety crashed. So what's the safest way to take it?*

Few treatments have been the subject of such confusing and conflicting findings as hormone replacement therapy, which surged in popularity in the West in the 1980s and 90s.

Back then, enthusiasts suggested that, as well as relieving menopausal symptoms such as hot flushes and night sweats, its benefits extended to protecting the heart and bones, and boosting libido.



That all changed when, in 2002, the Women’s Health Initiative, one of the biggest studies on the safety of HRT, showed that the treatment was not protective and might actually raise the risk of heart disease and breast cancer. The number of women using it dropped dramatically as a result (see graph). Around 6 million women take HRT in the UK and US at present.

In recent months, HRT has again made the news. A review, published in March, confirmed that HRT had no protective effect on the heart, and found it increased the risk of stroke in post-menopausal women.

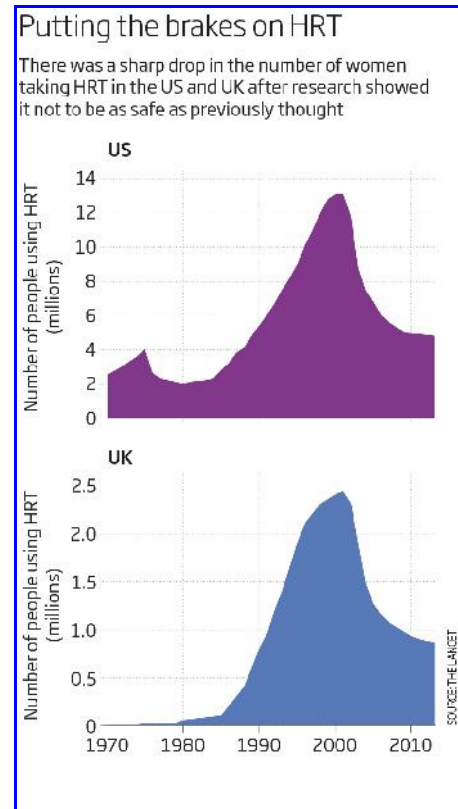
It also slightly raises the risk of ovarian cancer, even if taken for just a few years, as is now the most common approach. For every 1000 women taking HRT for five years from around age 50, there would be one extra case of ovarian cancer.

“HRT is important and very effective against menopausal symptoms for many women,” says Phil Hannaford at the University of Aberdeen, UK. “However, the current advice is to use the smallest dose possible for the minimum period of time” – usually no more than two to four years.

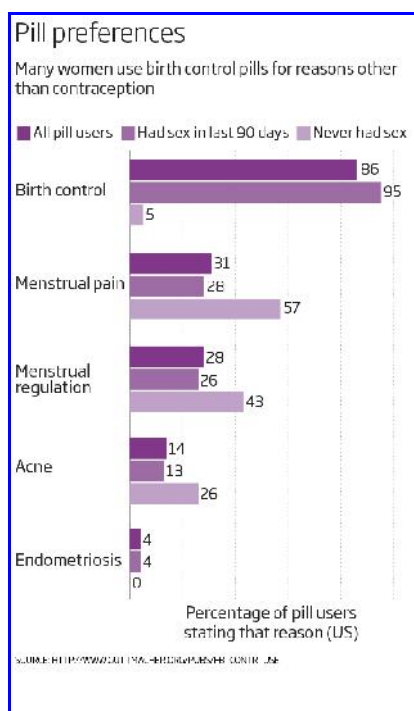
Rod Baber, an obstetrician at Sydney Medical School and president of the International Menopause Society, says women who have had breast cancer should not take HRT, and those with heart disease should be treated “with great caution”. Timing is important, too – the earlier a woman starts using it, the safer and more beneficial it is, Baber says.

**“The earlier a woman starts using HRT, the safer and more beneficial it is.”**

“Women should not start HRT over the age of 60 without consulting their doctor – but that is very different from a woman who started early and finds she needs to continue beyond 60, which is quite OK,” he says.



## Everyday drugs: Problems with the pill



*Cancer risks, cancer protection, mood swings, easier periods – the pros and cons of the revolutionary contraceptive are hard to disentangle.*

It’s one of the most efficient forms of contraception and has revolutionised reproductive control for women. One in four women of childbearing age in the UK and the US takes the contraceptive pill as a routine part of their daily schedule, often for reasons other than contraception (see graph).

The pill has drawbacks though. Last year, a review by the European Medicines Agency concluded that some of the bestselling combined contraceptive pills raise the risk of deep-vein thrombosis more than previously thought.

The packaging on these third-generation pills, so called because they contain new types of progestogen, has since been updated, and doctors were reminded to consider patients’ individual risk factors before issuing a prescription. These include being overweight, smoking and high blood pressure. The risk of blood

clots is still small so, on balance, it is deemed to be outweighed by the benefits of preventing unplanned pregnancies.

In March, it was reported that the pill may raise the risk of Crohn's disease, an inflammatory bowel condition, in women with a genetic susceptibility. And evidence also shows women on the pill have a higher risk of breast cancer.

There are hints that the pill might affect behaviour too, for instance, skewing what people find attractive in a partner. Perhaps ironically, some evidence shows that it can reduce libido.

The pill might also affect the way the brain functions. In April, a brain-scanning study found that two regions involved in emotion regulation, decision-making and reward response were thinner in women taking the pill, although the research gave no indication of whether this caused a real change in behaviour.

Confusingly, though, the pill has also recently gained attention for its health benefits. Data from 46,000 women observed for up to 39 years showed those who took the pill had a lower mortality risk. Lead author Phil Hannaford at the University of Aberdeen, UK, thinks this is because the pill protects against some cancers.

Although it does raise a woman's risk of breast cancer while she is taking it, Hannaford says most women take the pill during their 20s and early 30s, when the background risk is still low, so their chances of getting it are still very slim.

Other protective effects are longer lasting in women who take or have taken the pill. "They have a reduced risk of endometrial, ovarian and colorectal cancer and that effect seems to persist for many years after stopping – well into the age when those cancers become more common," Hannaford says.

On balance, he says, the benefits outweigh the disadvantages, but women should make their choices based on contraception, rather than possible long-term health benefits.

What is becoming clear now, though, is that not everyone responds to the various contraceptive pills available in the same way. "The pill is certainly not for every woman," says Rod Baber, at Sydney Medical School, who is studying its safety.

### **“People respond to the pill in different ways. It is certainly not for every woman”**

One of the hardest areas to pick apart is the effect on mood. Many women anecdotally report mood swings or low mood, but the evidence is woolly at best. One recent analysis actually found pill users were less likely to be depressed than non-users.

Ellen Wiebe, medical director of the Willow Women's Clinic in Vancouver, Canada, says around 30 per cent of women using hormonal contraceptives will experience emotional and sexual side effects. But it's hard to compare women on the pill with those who are not, because anyone who has experienced problems may just stop taking it without reporting this to their doctor, says Wiebe, which means the groups are self-selecting.

And often, she says, the studies are funded by the manufacturers themselves. They tend to look for symptoms of mental illness, such as suicidal thoughts, so subtler mood changes go unreported.

It's also easy to assume that mood changes are down to relationship issues or life issues. "Women sometimes tell me that they've been on the pill since they were a teenager, and then went off it for some reason and discovered they were a different person. Only then did they realise they'd been having emotional side effects," Wiebe says.



## Everyday drugs: What's the latest on aspirin?

*First they said everyone should take it. Then they said healthy people shouldn't. Now it seems to protect against cancer. Here's how to weigh up the risks.*

It's hard to keep up with the latest advice on aspirin. Known for its powerful blood-thinning properties, it is routinely prescribed in low doses to people who have had a heart attack or stroke to protect them from having another.

This has prompted some to argue that it could have a preventive effect in people who have no history of heart problems too. In the US, an estimated 40 million adults now take aspirin every day.

But last year, the US Food and Drug Administration warned against this practice, saying there was not enough evidence to warrant healthy people taking aspirin to help prevent heart disease, even those with a family history.

The key concern is a small but unquestionable risk of gastrointestinal bleeding and haemorrhagic stroke, caused by bleeding in the brain.

A study published in January found that out of 68,000 people in the US who had been prescribed aspirin for primary prevention – meaning they had a history of heart disease – one in 10 were inappropriately given the drug because their chances of heart attack or stroke were not high enough to warrant the risks.

Now the humble painkiller is attracting attention for a different reason – its apparently remarkable effects on cancer prevention. Last year, a review of the evidence led by Jack Cuzick at Queen Mary University of London found that more than 130,000 deaths from cancer would be prevented in the UK alone if all people aged 50 to 64 took a low-dose aspirin every day. Cuzick found that aspirin use led to a 30 per cent reduction in both the incidence and mortality of bowel, stomach and oesophageal cancer, with smaller effects on prostate, breast and lung cancer. The benefits took five years to kick in, but continued after stopping aspirin.

“The second most important thing you can do to prevent cancer, after not smoking, is to take a low-dose aspirin,” says Cuzick. He expects NICE, the UK health advisory body, to review the data on aspirin and begin recommending it to the over-50s within two years.

The effect seems to be down to aspirin's anti-inflammatory properties. Inflammation is part of the body's natural reaction to an invader, but cancerous cells hijack it and use it to divide and spread.

Aspirin may also help because it reduces the number of platelets in the blood – platelets can shield cancerous cells in the bloodstream so they are not recognised by the immune system.

So how do you weigh up the risks?

“We estimate that there would be one serious bleeding event for every 300 people that took aspirin for 10 years,” says Cuzick. “But aspirin would reduce eight deaths for every one that might be caused, so it's a pretty strong case.”

Cuzick found that to reap the benefits, adults would need to take a low dose-aspirin daily for five years – probably 10 – between the ages of 50 and 65. However, after the age of 70, the risk of side effects increases, so at this point aspirin would be likely to do more harm than good.

Peter Elwood at Cardiff University School of Medicine, UK, says the risk of bleeds has been “grossly exaggerated”. His research suggests they tend to occur when patients begin taking aspirin without being properly assessed for risk factors, such as high blood pressure or a history of stomach ulcers, so anyone thinking of taking aspirin regularly should consult their doctor first. And because ulcers are often caused by the common bacterium *Helicobacter pylori*, treating that first could protect against the side effects.

## **Everyday drugs: Three you should know about**

*Anticoagulants, ACE inhibitors and antidepressants... lots of people take them, but should you?*

### **Anticoagulants**

Eleven million prescriptions of warfarin were dispensed in England in 2013. It helps stop the blood from clotting, and is recommended for conditions in which dangerous clots can occur, including atrial fibrillation, deep-vein thrombosis, pulmonary embolism and heart attack. There is a small risk of internal bleeding and excessive bleeding from cuts, and side effects include nausea and diarrhoea. Those taking it must have the dose checked frequently, usually once or twice a week. Recently, alternatives that don't require monitoring have been approved for atrial fibrillation but these are expensive, and don't have such a long safety record. Bleeding episodes caused by warfarin can be stopped with vitamin K; for newer anticoagulants, there is currently no antidote.

### **Ace inhibitors**

Routinely given to people with high blood pressure, ACE inhibitors help lower their readings and prevent stroke, heart attack and kidney failure. Many people with mild hypertension are also on this medication – as many as 50 per cent are prescribed the drug in the US. Doctors are divided. Some believe that the lower your blood pressure the better, but research last year found mild hypertension to have little effect on mortality and morbidity. The US spends \$32 billion every year treating high blood pressure. Critics say those with borderline readings should make lifestyle changes before starting on medication.

### **Antidepressants**

Antidepressants are big business: 10 per cent of Americans aged 12 and over are estimated to be taking them. That doesn't necessarily mean depression is on the rise – they are also given for other mental health conditions such as anxiety, eating disorders and post-traumatic stress disorder, and a significant proportion of prescriptions are now for physical problems. Antidepressants have become a mainstay in the treatment of painful long-term conditions, and can help with migraine, arthritis and even bedwetting in children. Side effects range from sleeping problems to erectile dysfunction. And long-term use has been linked to a raised risk of type 2 diabetes.