The truth about antidepressant side-effects — an expert's guide

Professor Philip Cowen demystifies new research, which ranks the drugs that eight million people in Britain take for their health

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About eight million people in the UK take some sort of antidepressant for mental health conditions such as depression and anxiety. Sometimes these can have problematic side-effects, from rapid changes in weight to rises in blood pressure or cholesterol.

This week, these side-effects were ranked for the first time by researchers from King's College London and Oxford University, who collated "league tables'' of sorts for the drugs based on each physical health outcome they may produce. To do this, they gathered data from more than 58,500 patients, analysing 151 studies and 17 Food and Drug Administration reports relating to 30 drugs commonly used for depression.

Their analysis, published in The Lancet, found a big variation between treatments, but SSRIs — or selective serotonin reuptake inhibitors — which work by increasing serotonin levels in the brain and are the most popular type of antidepressant, tended to have fewer physical side-effects.
The drugs reviewed included SSRIs like sertraline (Zoloft) and fluoxetine (Prozac); serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine (Cymbalta) and tricyclics such as amitriptyline.

Professor Andrea Cipriani from the University of Oxford, one of the study's authors, told the BBC that there had been a push for "generic, cheap medications" that meant 85 per cent of antidepressant prescriptions in the UK were for just three SSRI drugs: citalopram, sertraline and fluoxetine.

The findings of the report, he said, could result in that figure being “dramatically” reduced, with “more people accessing better treatments”.

In terms of the study’s limitations, it is worth noting that some of the fluctuations recorded were small, and not necessarily clinically significant. The trials evaluated in the analysis were also relatively short — and side-effects such as sexual dysfunction were not monitored.

Philip Cowen, professor of psychopharmacology at the University of Oxford, explains how this new data could affect prescribing — and what patients can learn from it.

Of course, every person is different so any decision must be made in consultation with your GP.

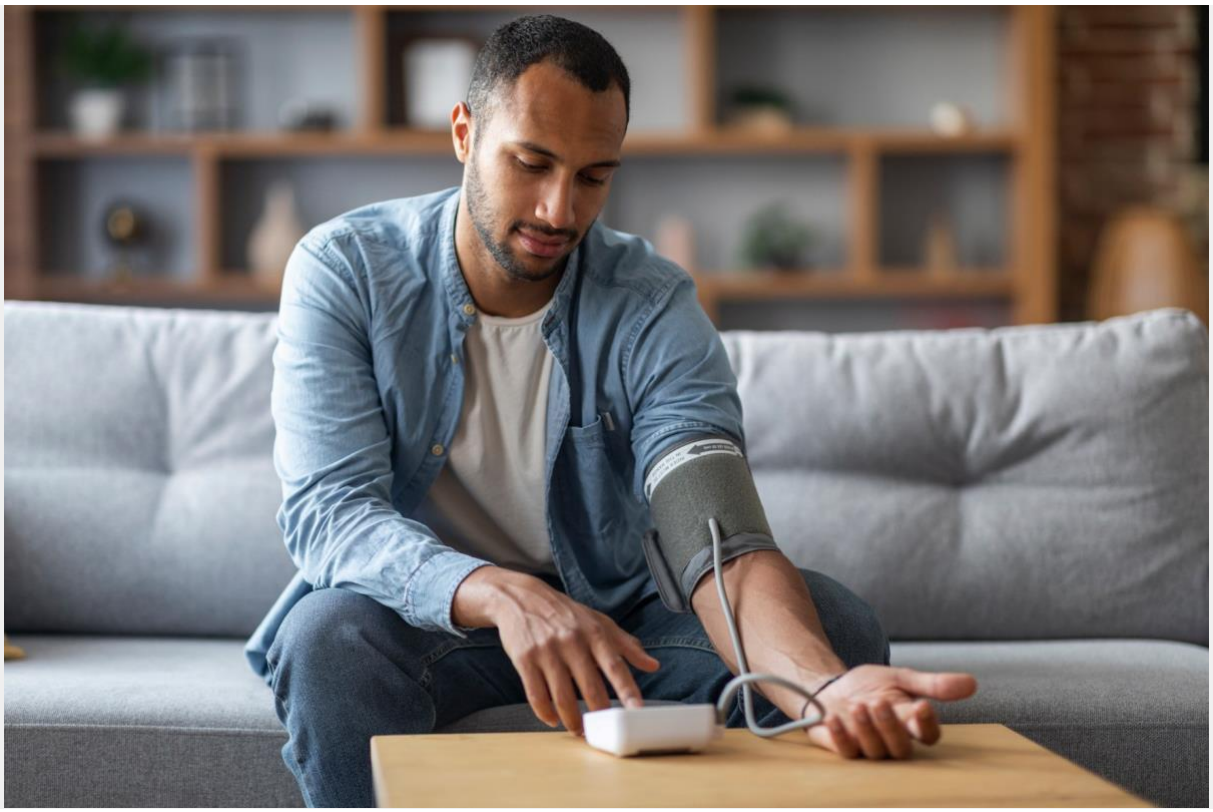
What do I need to know about SSRIs?

“Most antidepressant prescribing is done in primary care by GPs and they would usually prescribe SSRI drugs such as sertraline or fluoxetine, first-line,” Cowen says. “Citalopram and escitalopram are also used frequently but the drug data sheets carry warnings that they can increase the QTc interval in the electrocardiogram [ECG].” This is a measure of the time it takes for the heart’s ventricles to contract and relax, corrected for heart rate, and significant increases in it elevate the risk of cardiac arrhythmias, says Cowen.

He points out that this effect was not demonstrated in the meta-analysis, but it is worth noting because it’s part of the reason citalopram and escitalopram are prescribed less than other SSRIs by GPs. The primary dangers of cardiac arrhythmias include stroke, heart failure and sudden cardiac arrest.

On the plus side, citalopram was not associated with a rise in systolic blood pressure and resulted in a moderate drop in weight in the study. Fluoxetine was

also associated with participants shedding some pounds but was linked to higher systolic blood pressure. Of the other SSRIs, “Fluvoxamine is very little used in primary care because it is less tolerated than other SSRIs,” according to Cowen. The study found that it tended to increase systolic blood pressure and cause weight gain. Paroxetine is also used less because it has been associated with worse withdrawal symptoms than other SSRIs.



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I’m choosing between sertraline and fluoxetine — what should I consider?

In the study both drugs resulted in a moderate amount of weight loss. However, fluoxetine increased systolic blood pressure, unlike sertraline —– but the researchers’ confidence in the evidence for this comparison was recorded as “very low’’. Meanwhile, alkaline phosphatase (ALP) levels, which can indicate a problem with the liver or bones, were elevated in those who took sertraline but not in those on fluoxetine. Bottom line? “Any hint of liver problems, you might want to avoid sertraline.”

NHS guidance warns that “sertraline can cause liver damage in rare cases but is generally considered safe for patients with pre-existing liver disease if a lower dose is used. Patients with liver disease have increased sensitivity to sertraline.”

Fluoxetine also has one of the longest half-lives among SSRIs, which is the time it takes for the amount of the drug in the body to be reduced by 50 per cent. This is a significant factor in its clinical use because it enables a smoother reduction in antidepressant blood levels when discontinued.

“Fluoxetine has got a very long duration of action in the body — longer than sertraline. That means that you’re less likely to get unpleasant withdrawal symptoms and that’s the advantage,” Cowen says.

“Equally, the long half-life means that if you want to swap to another antidepressant, that can create problems because you have to wait for it to fully leave your system.” Whereas with sertraline, “after a few days, it’s all gone”, Cowen says. Fluoxetine may still cause medicine interactions about five or six weeks after stopping, according to research.

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I’m on an SSRI but I can’t sleep, then what?

In a case like this, GPs may use mirtazapine, Cowen explains. “Some people can’t tolerate an SSRI. They can make you sleep less well. You can be more anxious. Due to its antihistaminic effects mirtazapine provides sedation — and also has some anti-anxiety effects.”

However, because of the antihistaminic properties, it can make people hungry and therefore cause weight gain, which was apparent in the Lancet study. So if there are concerns around weight or over-sedation, mirtazapine is best avoided.

How about sexual function?

While this was not monitored as part of the study, Cowen notes that SSRIs have quite high rates of sexual dysfunction. “That’s a significant problem, particularly in longer-term use. In contrast, mirtazapine has a lower risk of causing sexual problems, which is why a GP may switch someone to mirtazapine who was struggling in that respect.” SNRIs are also associated with sexual dysfunction, says Cowen.

What do I need to know about tricyclic drugs?

The first specific antidepressant drugs, the tricyclic antidepressants (TCAs), were introduced in the late 1950s about three decades before SSRIs were developed, with the first widely marketed SSRI, Prozac (fluoxetine), being approved in 1987. SSRIs had fewer serious adverse effects.

“The older tricyclics tend to have lots of other pharmacological actions,” Cowen says, adding that they have “anticholinergic” side-effects such as dry mouth, blurred vision and constipation. They also have antihistaminic properties, which results in sedation and weight gain. The Lancet study found that amitriptyline increases weight, heart rate and blood pressure.

“Most importantly with tricyclics,” Cowen says, “is that they’re dangerous in overdose, and that’s a real problem if we’re using them for seriously depressed people.” Tricyclics are highly toxic in overdose, the most severe effects being cardiovascular and neurological instability.

“When amitriptyline and other TCAs were first line drugs to treat depression, there were about 400 deaths a year from overdoses associated with them,” Cowen says. SSRIs, meanwhile, are relatively safe in overdose and are rarely fatal when taken alone.

So when is amitriptyline used?

Amitriptyline is used to treat neuropathic pain at a low dose of 20mg daily, which means the side-effects are also reduced. The antidepressant dose, for comparison, is 150mg daily.

What do I need to know about SNRIs?

While SSRIs work by blocking the reuptake of only serotonin, SNRIs block the reuptake of both serotonin and norepinephrine. This dual action can make SNRIs more effective for some people with more severe depression or anxiety. Common examples of SNRIs include venlafaxine (Effexor) and duloxetine (Cymbalta). "Generally, SNRIs are used in people who haven't been helped sufficiently by SSRIs," Cowen says, "and that's because, though they can be more effective, they are less well tolerated. That is reflected in this Lancet study — for example, both duloxetine and venlafaxine increase blood pressure and total cholesterol."

High levels of AST and ALT (liver enzymes) indicate liver damage or stress, and in the study duloxetine resulted in increases of both enzymes. More generally, SNRIs increase blood pressure and heart rate, which is also reflected in the study's data.

This would make one cautious of using it in people taking other medications that might affect the liver or in those who have underlying liver disease, Cowen says.