



## Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: June 2015

### Risk of suicide, attempted suicide or self-harm with antidepressants

A large UK observational study using a primary care database found that the risk of suicide, attempted suicide or self-harm did not differ between adults with depression who were prescribed selective serotonin reuptake inhibitors (SSRIs) and those prescribed tricyclic antidepressants. For individual drugs, mirtazapine, venlafaxine and trazodone were associated with the highest rates of suicide and attempted suicide or self-harm. However, the results should be interpreted with caution because there were few suicide events overall and this study has several important limitations. The NICE guideline on depression in adults recommends that if an antidepressant is indicated it should normally be an SSRI in generic form. It also emphasises the importance of frequent monitoring of suicide risk when an antidepressant is initiated.

#### Overview and current advice

Suicide is the main cause of premature death in depression and is most common in people with comorbid physical and mental illness. There is evidence for a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment. However, this needs to be balanced against evidence suggesting that the risk of clinically important suicidal behaviour is highest in the month before starting antidepressants. It is not clear to what extent suicidal thoughts or behaviour can be attributable to a direct result of taking an antidepressant as opposed to the timing of when help was sought (see the [NICE Full Guideline](#) for more details).

The NICE guidelines on [depression in adults](#) and [depression in children \(5–11 years\) and young \(12–18 years\) people](#) recommend non-drug interventions (such as cognitive behavioural therapy [CBT]) as the mainstay of treatment for people with depression, with drugs generally reserved for more severe illness or when symptoms have failed to respond to non-drug interventions.

If an antidepressant is indicated, the NICE guideline on [depression in adults](#) recommends that it should normally be a selective serotonin reuptake inhibitor (SSRI) in generic form. SSRIs are equally as effective as other antidepressants and have a favourable risk–benefit ratio. Toxicity in overdose should be considered for people at significant risk of suicide. If someone started on antidepressants is considered to present an increased suicide risk or is younger than 30 years (because of the increased

prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) they should normally be seen after 1 week and frequently thereafter until the risk is no longer considered clinically important. The NICE guideline on [depression in children \(5–11 years\) and young \(12–18 years\) people](#), which was updated in March 2015, gives recommendations on antidepressant choice and monitoring for the appearance of suicidal behaviour, self-harm or hostility in this younger age-group, particularly at the beginning of treatment.

The [NICE Pathway: depression](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. NICE has also produced a [Key Therapeutic Topic on first-choice antidepressant use in adults with depression or generalised anxiety disorder](#).

## New evidence

A UK [cohort study](#) using a primary care database ([QResearch](#)) assessed the associations between different antidepressants and the rates of suicide and attempted suicide or self-harm in 238,963 people aged 20 to 64 years (mean 39.5) with a first diagnosis of depression from January 2000 to the end of July 2011<sup>1</sup>. Out of these, 209,476 people received one or more prescriptions for antidepressants. Participants were followed-up for a median of 5.2 years and the median duration of treatment with antidepressants was 221 days, with a third of patients having treatment for at least a year and 5.5% having treatment for at least 5 years. People who had schizophrenia, bipolar disorder and other psychoses, or who were prescribed lithium or other antimanic drugs were excluded. The cohort consisted of more women (61%) than men (39%) and most people (72%) were documented to have mild depression.

The most commonly prescribed drug class was SSRIs (71.3% of antidepressant prescriptions, around three-quarters of which were for citalopram or fluoxetine), then tricyclic and related antidepressants (16.0%, around three-quarters for amitriptyline and dosulepin), then 'other antidepressants' (12.7%, 90.7% for venlafaxine and mirtazapine), with monoamine oxidase inhibitors (MAOIs) being the least commonly prescribed (0.05%).

When people who took MAOIs were excluded, there were 198 suicides reported in the first 5 years (43 in men and 9 in women per 100,000 person years) and 5243 cases of attempted suicide or self-harm (737 in men and 517 in women per 100,000 person years). Compared with SSRIs, treatment with tricyclic antidepressants did not show a statistically significant difference in the risk of suicide (adjusted hazard ratio [HR] 0.84, 95% [confidence interval](#) [CI] 0.47 to 1.50;  $p=0.6$ ) or attempted suicide or self-harm (adjusted HR 0.96, 95% CI 0.87 to 1.08;  $p=0.5$ ). However, when 'other antidepressants' (which comprised mostly of venlafaxine and mirtazapine) were compared with SSRIs, the risk of suicide more than doubled (HR 2.64, 95% CI 1.74 to 3.99;  $p<0.001$ ) and the risk of attempted suicide and self-harm almost doubled (HR 1.80, 95% CI 1.61 to 2.00;  $p<0.001$ ).

For individual antidepressants, mirtazapine, venlafaxine and trazodone were associated with the highest [absolute risks](#) (ARs) of suicide and attempted suicide or self-harm over 1 year (AR of suicide: mirtazapine 0.19%, 95% CI 0.07 to 0.47%; venlafaxine 0.14% 95% CI 0.05 to 0.37%; trazodone 0.10% 95% CI 0.01 to 0.79%; SSRIs 0.05%, 95% CI 0.01 to 0.11. AR of attempted suicide or self-harm: mirtazapine 2.55%, 95% CI 2.03 to 3.21%; venlafaxine 2.96% 95% CI 2.40 to 3.64%; trazodone 2.64%, 95% CI 1.69 to 4.13%; SSRIs 1.38%, 95% CI 1.17 to 1.61).

Rates of suicide and attempted suicide were highest in the first 28 days after starting treatment and rates of suicide were also highest in the first 28 days after stopping treatment.

## Commentary

### Commentary provided by the Medicines and Prescribing Centre

[This study](#)<sup>1</sup> suggests that mirtazapine, venlafaxine and trazodone are associated with the highest rates of suicide and attempted suicide or self-harm in people with depression and there is no difference in these risks between SSRIs and tricyclic antidepressants as a group. A strength of the study is that it is large and covers a broad UK population. The results are generalisable to people aged 20 to 64 years in primary care who have a diagnosis of depression. However, as commented by the authors, these results should be interpreted with caution because the numbers of suicide events were small. In addition, this study has several other important limitations.

Being an [observational study](#), it is likely to have some [confounding](#) by indication. Depression itself is already associated with an increased risk of suicide and self-harm. Therefore, it is difficult to disentangle the effects of antidepressants from those of the disease. In addition, it is possible that mirtazapine, venlafaxine and trazodone, which were associated with the highest risk, were prescribed to people who were already at a higher risk of suicide or attempted suicide than other people. The authors attempted to adjust for several confounding factors. However, some confounding remained. For example, although they adjusted for severity of depression at baseline, changes in depression severity during follow-up were not recorded. Also, antidepressant use in this study was extrapolated from prescriptions for antidepressants and may not exactly reflect what the patients had taken.

Data on [deaths related to drug poisoning in England and Wales](#) show that deaths involving antidepressants other than SSRIs, tricyclic antidepressants and MAOIs have been increasing since 2000. However, in many cases, people were taking other drugs in addition to an antidepressant. Most of these deaths have involved venlafaxine or mirtazapine. Deaths from mirtazapine increased by 49% in 2013 to 73 deaths from 49 in 2012, the highest number on record since 1993. Venlafaxine deaths increased from 17 in 2000 to 48 in 2013, although over recent years the number of deaths has been fluctuating around a constant level. Although prescriptions for 'other antidepressant drugs' like venlafaxine and mirtazapine (BNF section 4.3.4) accounted for only 18% of all antidepressant prescriptions in 2013, this proportion has increased from 16% in 2009 and may partly explain the increase in deaths. The NICE guideline on [depression in adults](#) highlights that compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine in particular is associated with a greater risk of death from overdose. It also warns that tricyclic antidepressants, except for lofepramine, are associated with the greatest risk in overdose.

Despite its limitations, the results of this study<sup>1</sup> are consistent with the NICE guideline on [depression in adults](#), which recommends that if an antidepressant is indicated it should normally be an SSRI in generic form. Other antidepressants, such as venlafaxine, a tricyclic antidepressant or a MAOI should only be considered when symptoms have not responded adequately to initial treatment. The results of this study also emphasise the importance of following NICE recommendations on frequent monitoring of adults who are considered to have an increased suicide risk when they are started on an antidepressant.

It is interesting to note that 72% of people in this study who were taking antidepressants were documented to have mild depression. The NICE guideline on [depression in adults](#) advises healthcare professionals not to use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor, although it lists certain situations where it might be appropriate to prescribe an antidepressant for mild depression. Even so, this study looked at people with a first diagnosis of depression and we do not know if many people in the study

received antidepressants ahead of non-drug treatments for mild depression, which is outside NICE recommendations.

## Study sponsorship

This study was funded by the National Institute for Health Research School for Primary Care Research.

## References

1. Coupland C, Hill T, Morriss R et al. (2015) [Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database](#). BMJ 350:h517

## About this Medicines Evidence Commentary

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