BAP Statement on Antidepressants and Suicide for Health Select Committee’s inquiry into suicide prevention.

Thank you for asking for particular advice regarding antidepressants and suicide. We note that our recent BAP Guideline (Cleare et al, J Psychopharmacol. 2015 May;29(5):459-525) reviewed the clinical use of antidepressants comprehensively. A full copy of these guidelines is attached and we suggest that close reading of these will inform the reader. We also quote the most relevant passage of these guidelines below:

“Suicidality. There has been considerable concern as to whether antidepressants, particularly SSRIs, may be associated with an increase in suicidal ideation or acts. Two meta-analyses (Fergusson et al., 2005; Gunnell et al., 2005) with 477 and 702 studies, respectively, and a large nested case-control study comparing new prescriptions of SSRIs and TCAs (Martinez et al., 2005) found no evidence of an increase in completed suicide with SSRIs but possible evidence of increased suicidal/selfharm behaviour with SSRIs compared with placebo (NNH 754 and 684 in the two meta-analyses). There was no overall difference between SSRIs and TCAs (Fergusson et al., 2005; Martinez et al., 2005) but Martinez et al. (2005) found some evidence for increased self-harm behaviour on SSRIs compared with TCAs in those under 19 years. A meta-analysis of 27 RCTs of SSRIs in children and adolescents with depression, OCD and other anxiety disorders (Bridge et al., 2007) found no completed suicides but a small significant increase in suicidal ideation/self-harm attempts with SSRIs compared with placebo (NNH 143), not significant for each indication separately. However the inferential and retrospective nature of the ascertainment of ‘suicidality’ in these studies has been criticised (Klein, 2006). An analysis of 61 placebo-controlled trials of paroxetine in adults showed that for all disorders combined there were no significant differences in the incidence of overall suicidality (i.e. suicidal behaviour plus suicidal ideation) between paroxetine and placebo (Carpenter et al., 2011). A higher incidence of suicidal behaviour was seen with paroxetine compared with placebo in all indications in those aged 18–24 years (2.19% vs. 0.92%). In contrast, no increase in suicidality was seen in older age groups. A higher incidence of suicidality was seen with paroxetine versus placebo in an analysis restricted to major depression, though this was largely explained by the higher incidence in young adults. In order to assess the risk of suicidal behaviour in clinical practice, database linkage methods have been used. The risk of clinically significant suicidal behaviour was found to be highest in the month before starting antidepressants and declined thereafter, with significantly higher rates seen in adolescents compared with adults (Jick et al., 2004; Simon et al., 2006b). No temporal pattern of completed suicide was evident in the 6 months after starting an antidepressant (Simon et al., 2006b) and there was no increase in suicide/suicide attempt seen with SSRIs compared with other antidepressants in adolescents or adults (Jick et al., 2004; Simon et al., 2006b). The highest rates of suicidal behaviour were seen in patients treated by psychiatrists, but the same pattern was also seen with psychological treatments and in primary care (Simon and Savarino, 2007). Ecological data have also failed to find any link between SSRI use and higher completed suicide rates in adults and children/adolescents (Gibbons et al., 2005, 2006; Hall and Lucke, 2006); in fact, the association is generally for increased SSRI use to be linked to lower suicide rates, and recent data from the Netherlands and United States show an inverse relationship between decreases in SSRI use and increase in suicide in adolescents since warnings about SSRI use have been issued (Gibbons et al., 2007); however this inverse relationship was not reported in the UK. Several naturalistic studies have shown that overall suicide rates have decreased as antidepressant prescriptions have increased (e.g. Gusmão et al., 2013), although these ‘association’ studies are not able to make causal links.
Taken together, the evidence indicates a lack of a specific link between antidepressant/SSRI use and suicide/suicidal behaviour in adults. There is some evidence for a small increase in non-fatal suicidal ideation/self-harm behaviour in adolescents treated with SSRIs but not for completed suicide; indeed, indirect evidence suggests that SSRI use may reduce suicide rates. The risk–benefit analysis therefore needs to take into account the reality that suicidal behaviour is relatively high in depressed adolescents before treatment, and that the increased chance of successful treatment following an SSRI (NNT 10) outweighs the increased risk of non-fatal self-harm (NNH >100) by more than 10 times. Suicidality requires careful monitoring during antidepressant therapy, particularly early on in treatment in younger adults.”

Since the publication of the BAP guidelines a number of relevant papers have been published. Although we have not systematically reviewed the relevant literature we highlight two papers of note.

Bschor et al (Psychother Psychosom 2016;85:171–179) recently published a paper entitled “Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder” (please see the attached PDF).

Again we quote directly from the text: “Out of 807 studies screened 29 were included, covering 6,934 patients (5,529 patient-years). In total, 1.45 suicides and 2.76 suicide attempts per 1,000 patient-years were reported. Seven out of 8 suicides and 13 out of 14 suicide attempts occurred in antidepressant arms, resulting in incidence rate ratios of 5.03 (0.78–114.1; p = 0.102) for suicides and of 9.02 (1.58–193.6; p = 0.007) for suicide attempts. Peto ORs were 2.6 (0.6–11.2; nonsignificant) and 3.4 (1.1–11.0; p = 0.04), respectively. Dropouts due to unknown reasons were similar in the anti-depressant and placebo arms (9.6 vs. 9.9%). The majority of suicides and suicide attempts originated from 1 study, accounting for a fifth of all patient-years in this meta-analysis. Leaving out this study resulted in a nonsignificant incidence rate ratio for suicide attempts of 3.83 (0.53–91.01). Conclusions: Therapists should be aware of the lack of proof from RCTs that antidepressants prevent suicides and suicide attempts. We cannot conclude with certainty whether antidepressants increase the risk for suicide or suicide attempts. Researchers must report all suicides and suicide attempts in RCTs.”

Another recent paper on this topic has attracted some attention (Bielefeldt AØ, Danborg PB, Gøtzsche PC. J R Soc Med. 2016 Oct;109(10):381-392. Precursors to suicidality and violence on antidepressants: systematic review of trials in adult healthy volunteers. However, it should be noted that academics have suggested that the data do not support the conclusions drawn by the authors. Professor Phil Cowen, a professor of psychopharmacology at the University of Oxford, contends, for instance, that the results show no direct reports of violence or suicidal behaviour.

"What one sees are known adverse effects of serotonergic antidepressants such as anxiety, nervousness, tremor and abnormal dreams," Cowen writes. "These side-effects are clinically significant, frequently distressing and an important topic for discussion between patient and clinician. However, the notion that they are necessarily indicative of violence and suicide seems to me rather like arguing that transient annoyance with a colleague is much the same thing as attempted murder."
For any consideration of suicide to be complete it should be noted that there is very good evidence that lithium (widely used to treat Mood Disorders, including depression) has evidence of benefits. A recent review of the literature (Cipriani A, Hawton K, Stockton S, Geddes JR. BMJ. 2013 Jun 27;346:f3646. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis). This review concludes: “Lithium is an effective treatment for reducing the risk of suicide in people with mood disorders.” We note that this evidence was included in our BAP Guidelines for Bipolar Disorders (J Psychopharmacol. 2016 Jun;30(6):495-553) a copy of which is attached. Furthermore, the role of SSRIs in reducing suicide has been advocated strongly (see Nutt, 2005).

Answers to specific questions:

Q: How good is the evidence base on the use of these medicines and the increased risk of suicidal ideation, both in adults, young people, and children?

A: As described above the current evidence base across all age ranges is in favour of offering patients the choice of treating depression (particularly moderate to severe depression), a condition associated with high levels of mortality (including by suicide) using appropriate psychopharmacological agents.

Q: Are there clear guidelines for health professionals explaining the risks and benefits of these medicines and their association with increased risk of suicidal ideation? If so, are health professionals who prescribe these medicines aware of the guidelines, and are they following them?

A: We have cited BAP guidelines above that are recent. Health professionals should be aware of them. We cannot answer whether they are following the guidelines and this should be studied.

Q: Are medicines which have an association with increased risk of suicidal ideation being prescribed appropriately? Are patients taking these medicines being adequately monitored?

A: More often than not, medications prescribed are done so appropriately and potential risks explained to the patient and/or carer (particularly when the patient is under 18 years). The need for adequate monitoring is important and whether this is being done adequately, requires evaluation.

Q: Is there a need for further research and/or enhanced monitoring of ADRs in relation to suicide prevention?

A: Yes.