Death by tricyclic: the real antidepressant scandal?

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What does the general public and media know about the risks of antidepressants? Judging by the questions I regularly get asked by both constituencies many believe that there has been a scandal over the selective serotonin reuptake inhibitors (SSRIs). They often tell me that these drugs cause suicide, especially in young people and that these data were known to the pharmaceutical industry for years but kept hidden. They often believe that psychotherapy or counselling alone is all that is required and the provision of more of this will cure the problem.

In reality no young person has committed suicide on an SSRI in any of the clinical studies that revealed the increase in suicidal acts which now amounts to over 400 patient years on these drugs. Moreover, the effect of the SSRIs on reducing suicidal ideation was very profound – with rates of about 25% at entry reducing to about 3% on completion (see FDA website). In addition, the latest FDA analysis suggests that SSRIs are less likely than placebo to be associated with the emergence of suicidal ideation during treatment. The suicidal acts reported in the controlled trials, though distressing, were mostly minor and much less dangerous than the risks of untreated depression. In particular, there is no evidence that other classes of antidepressant are effective. One SSRI, fluoxetine, has proven efficacy in young people with depression (TADS, 2004), whereas the tricyclics may be worse than placebo (Hazell, 2002) and they are very much more dangerous, particularly in overdose. Psychotherapy is also unproven in this age group and one recent study found CBT to be significantly less efficacious than fluoxetine (TADS, 2004). Psychotherapy is hard to come by, difficult to quality control and not as free of unwanted effects as is commonly assumed – dependence on and withdrawal from the therapeutic process are common and abuse (both sexual and emotional) by therapists are rare but real harms.

After meeting monthly or more for one and a half years, a large expert group acting for the Committee on Safety of Medicines (CSM) has examined the safety of the SSRIs. In December 2004 it concluded that there is no evidence that SSRIs as a class increase suicide risk over placebo or other antidepressant drugs (DOH, 2004). The warnings of a possible worsening of suicidal ideation along with anxiety and agitation early in treatment have been strengthened and the safety and benefits of these drugs restated. The refutation that the SSRIs are addictive that we published (Nutt, 2003) has been supported (DOH, 2004). In light of their safety NICE (2004) recommend the SSRIs as first line treatment for moderate to severe depression. In spite of this, it is likely to take years to overturn the current misconceptions.

In the media furore over the SSRIs fuelled by Panorama programmes and many newspaper articles, including several front pages, one unarguable fact has consistently been ignored. This is that the SSRIs are exceptionally safe drugs in overdose especially compared with the older agents they have partially supplanted – the tricyclics. This was one of the main reasons the SSRIs were welcomed by psychiatrists in the early 1990s, as it was possible to prescribe these to severely depressed patients with marked suicidal ideation, confident that they could not kill themselves by taking the whole lot at once. Previously, patients prescribed tricyclics had to suffer the inconvenience and extra expense of weekly or even every third day pick-ups from a pharmacy or impose upon relatives or friends to act as custodians of their medication.

Despite the huge safety benefits of the SSRIs the tricyclics continued to be prescribed and the latest data from the Office of National Statistics (ONS, 2004a) shows that over the past decade nearly 4000 people have died from tricyclic overdose whereas 390 have died from SSRI overdose (see Table 1). Given that, other than nocturnal enuresis in children, there are no indications for the tricyclics that are not shared by the SSRIs, it would appear that nearly 3500 people have died unnecessarily from tricyclics – a real scandal about which the medical and popular press have been peculiarly silent! Although there has been a reduction in tricyclic related suicides over the past decade they are still the commonest drugs implicated in suicide. In the last data year (2002) tricyclics killed 290 people – similar to co-proxamol (287) and more than paracetamol (126) (ONS, 2004b).1

Amazingly the latest (2003) prescription data show that amitriptyline is still the most commonly prescribed antidepressant, with about 5 million scripts compared with 2.5 million for dothiepin and just over 4 million each for fluoxetine and citalopram. Most of these amitriptyline scripts are at doses of 10 and 25 mg for which the only licensed indication is nocturnal enuresis in children! (BNF, 48). Half the dothiepin scripts are for a 25 mg dose, which is sub therapeutic for depression – its only licensed indication. It may be that paradoxically the prescribing of low doses of tricyclics compounds the problem as patients with depression are inadequately treated, and so linger with suicidal ideation for much longer than they would if given a therapeutic dose of either a tricyclic or another antidepressant. One other advantage of the SSRIs is that it is almost impossible NOT to prescribe a clinically effective dose.
Why have these deaths occurred? Why have the tricyclics continued to be used since the SSRIs and other safer antidepressants such as venlafaxine, mirtazapine and reboxetine become available? One reason is almost certainly cost. At the onset of the SSRIs, many argued that the benefits of these new drugs were not worth the extra cost given that they were not more efficacious in clinical trials – the SSRIs originally cost about £30 per month compared with about £10 for the tricyclics. Interestingly, a more detailed analysis of this issue revealed that the greater drug costs did not translate into greater health care costs due to the savings in other areas of medicine, e.g. intensive care units where many people are admitted following tricyclic overdose (Jonsson and Bebbington, 1994). However, many were not persuaded, and national guidelines, e.g. Scottish Intercollegiate Guidelines Network (SIGN), encouraged tricyclic use as first-line for depression. Sadly, the personal costs of death by overdose were never overtly considered in these recommendations, even though in parallel, we were all working towards a government target of a 15% reduction in suicide deaths within the decade.

Another reason why safety in overdose was ignored or played down was the false but very common belief that individuals contemplating suicide will ‘do it anyway’ so using a less toxic drug is irrelevant. This prejudice has been proved incorrect by many papers. For example, Contemplating suicide will ‘do it anyway’ so using a less toxic drug is irrelevant. This prejudice has been proved incorrect by many papers. For example, it is hard to imagine that if another drug class had killed so many people it would still be so readily available without even a specific warning of harm in overdose. The recent recommendations from the CSM that bars GPs from initiating venlafaxine on the grounds of safety in overdose seems odd when they can still start patients on the much more toxic tricyclics. Do we still need tricyclics at all given their negative risk-benefit ratio and the presence of safer, better-tolerated alternatives? Will the worries about the SSRIs and venlafaxine lead to more prescribing of tricyclics in the misplaced belief that they are safe? Previous experience shows drug warnings can lead to perverse consequences such as the unforeseen upsurge of prescriptions of older more toxic alternatives. A good recent example has been the increase in choral hydrate and barbiturate prescriptions after the benzodiazepines were targeted by the media. In the light of historical precedents and relative risk ratios it is important that the regulatory authorities and NICE now turn their attention from the SSRI antidepressants and put into place actions to reduce deaths from the tricyclics.

### References

British National Formulary (BNF) 48, September 2004


FDA (Jan 2005) www.fda.gov


SIGN (Jan 2005) www.sign.ac.uk


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1 Since this article went to press, the CSM have given notice that co-proxamol and all related products will be withdrawn later this year on account of their association with successful suicide attempts.

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### Table 1  Deaths linked to antidepressants

<table>
<thead>
<tr>
<th>Drugs</th>
<th>All deaths where drug mentioned</th>
<th>Deaths where drug is sole one mentioned</th>
<th>Relative risk: deaths per million prescriptions (sole mention)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td>3987</td>
<td>2787</td>
<td>30.1</td>
</tr>
<tr>
<td>Of which:</td>
<td>2088</td>
<td>1558</td>
<td>48.5</td>
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<tr>
<td>Dothiepin</td>
<td>1437</td>
<td>932</td>
<td>28</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>310</td>
<td>71</td>
<td>1</td>
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<tr>
<td><strong>SSRIs</strong></td>
<td>115</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Of which:</td>
<td>67</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>74</td>
<td>20</td>
<td>1.9</td>
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<tr>
<td>Citalopram</td>
<td></td>
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