# Newer Antidepressants - No Hint of the Controversies, Medico-legal Implications or Neuropsychiatric Difficulties with SSRIs

by

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Instant response to an article in the BMJ 28 January 2012

***Newer Antidepressants for the Treatment of Depression in Adults***
***Simon Hatcher, Bruce Arroll***
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This series of articles on therapeutics is of great help to practising doctors and of interest to clinical pharmacologists such as myself. However, I am prompted to respond for a number of reasons.

It is surprising for the article to be entitled '*Newer Antidepressants'*, for Fluoxetine was first registered in 1987 and most of the antidepressants covered are now indeed off-patent and available generically. I expected the article to be about drugs such as Agomelatine, which is truly '*newer'*.

It was also surprising to me that the article did not stress that any antidepressant is only part of the management of patients with depression, which should also include one of the many forms of psychotherapy available, self-help in the form of personal development, and probably alternative therapies such as meditation, massage and visualisation. All these help lead to changes in emotions, thought and lifestyle. If prescribed by a doctor insurers such as BUPA, who are very careful with their money, will willingly pay for the alternative therapies in depression.

Antidepressants have to be used in conjunction with frequent visits to a responsible clinician, particularly in the early stages of treatment to detect the possible unhelpful changes in behaviour that these drugs can produce. Carers, spouses, partners, parents and offspring should also be warned to observe for these changes. It does not stress that due to the time these medications take to work, that it is usual that side effects are apparent prior to therapeutic effect and it is often hard to keep patients on the medication as they see more distress than improvement. The early agitation, anxiety and other side effects are minimised by starting in small doses and increasing incrementally.

The side effects may be very distressing, particularly those around behaviour, mood, emotions and feelings, as well as sexual dysfunction. Among medications they are the most troublesome in that they often produce delayed orgasm or even anorgasmia, in addition to loss of libido and erectile dysfunction.

This adverse effect is so marked that those with an interest in sexual health have been using the SSRIs as a treatment for premature ejaculation for many years and in fact one of the newer SSRIs, Dapoxetine (brand mane in the UK, Priligy), has received a marketing authorisation for this condition, although currently I believe is only available on private prescription.

Surprisingly, the article makes little of the controversies surrounding this group of compounds in relation to increases in suicidal thinking and behaviour, as well as other behavioural changes which may precipitate forensically important behaviour such as aggression.

In relation to the former, there is a clear age related effect with a marked excess in those of and below adult age, a significant effect in those aged under 24, with variable and possible neutral effect between 25 and 64, only in those aged over 65 is there a net decrease. In all age groups the net effect is probably due to them decreasing suicidal thought content and behaviour in a significant proportion, while also increasing it in others. It being only the net effect which is different across the age structure.

The absence of any consideration of the controversies surrounding their use is, I believe, a significant omission.

The US full product information labelling and the SPC advise caution and observation of patients starting SSRIs for abnormal behaviour and increasing aggression. Although early work did not clearly show the effect of these medications, many such as Breggin[1] and Healy, Herxheimer & Menkes[2] have raised concerns.

A recent paper by Moore[3] et al entitled '*Prescription Drugs Associated with Reports of Violence Towards Others*', to my mind clearly shows that there is a high chance that they do produce, as a class, violence towards others, although the standard three-legged defence may still apply in that these events are more common in the patients who have them, there is lack of consistent proof of this effect and that the patients may have other predisposing reasons for this behaviour.

There is no doubt that in some patients they may cause behaviours associated with forensic events from shoplifting to possible homicide, including mania, psychosis, flattened emotions and psychomotor restlessness or akathesia and that if these events occur, then a thorough assessment is called for in each and every case, as detailed in many publications including my own entitled '*Could the cure really be the cause?*'[4].

The time the patient is most at risk is when the dose is increasing or decreasing, particularly if they get a withdrawal syndrome.

In the other area where caution has to particularly be applied, is in their effects on platelet aggregation and the possibility that they cause a propensity to disorders of haemostasis and bleeding. This is particularly noticeable when other drugs with serotoninergic properties are used with them such as Sumatriptan and similar compounds. There is also the difficulty that some SSRIs like Duloxetine are not only indicated in depression, but also in other conditions whereby people may not immediately consider them to be SSRIs. This will undoubtedly relate to Dapoxetine. They also interact with non steroidal anti inflammatory drugs, steroids, Clopidogrel and Warfarin.

In my extensive experience of SSRIs gained from coordinating the clinical development of them; being a hands on psychiatric investigator, a practising physician with an interest in mental health, coordinator of parental support groups in an adolescent and young adult mental health unit, it is by no means unusual for patients, or those associated with them, to phone in distress with side effects, even though they may be absent or minimal in half the patients taking them. Sleeplessness and disturbance of

sleep architecture is often a problem and although the authors recommend short term benzodiazepines for this, I have seen many patients in who this is impossible to stop due to both withdrawal symptoms and severe insomnia and many end up addicted. Alternatively, I have found more benefits from using a nocturnal dose of Trazodone.

The other experience I have is as a patient, and I have experienced Fluoxetine induced severe insomnia, sexual difficulties with Paroxetine, severe psychomotor restlessness after a single dose of Venlafaxine and Reboxetine associated mania. Luckily I have remained well for many years.

I have also worked extensively with cardiovascular drugs such as antiarrhythmic agents post myocardial infarction and despite the medical complexities and dangers with these compounds, they have caused me nowhere near the difficulties of SSRIs. Despite these difficulties, the SSRIs have been a very useful addition to the treatment of depression and although the authors should be commended on getting so much information into six pages, I have some regrets that they do not spend more time talking about the difficulties they may cause to patients and those prescribing.

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[1] Peter R Breggin. *Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis.* International Journal of Risk and Safety in Medicine 16 (2003/2004) 31-49.

[2] David Healy, Andrew Herxheimer, David B Menkes. *Antidepressants and Violence: Problems at the Interface of Medicine and Law*. PLoS Medicine. September 2006: volume 3: issue 9: e372.

[3] Thomas J Moore, Joseph Glenmullen, Curt D Furberg. Prescription Drugs Associated with Reports of Violence Towards Others. PLoS One. December 2010: volume 5: issue 12: e15337.

[4] Malcolm VandenBurg. *Could the cure really be the cause?*' Your Witness. Summer 2009. A Press Publishers Ltd. Stockport UK.