


Reply to Associate Professor Norman

P. Ken Gillman, Consultant and Director, Department of Clinical Neuropharmacology (DCNP) Pioneer Valley Private Hospital and Honorary Senior Lecturer, Clinical Neuropharmacology, James Cook University, Queensland, Australia:

I will clarify for readers the lack of evidence for serotonergic effects in humans, because no amount of experiments on rats can prove effects in humans. When I wrote ‘whatever the supposed mechanism of action’ that statement emphasized the consideration of effect. The introduction of a distinction between ‘dual action or dual effect’ represents a side issue and stating ‘the distinction is probably more semantic than scientific’ between a classification as either a dual action or a dual effect drug’ may be as unclear to other readers as it is to me. Clinicians and patients need effects; a drug, like amitriptyline, that has some serotonin reuptake inhibitor potency (actions), but no clinical serotonergic effects, is quite different from clomipramine. One is good for OCD, the other is not. Effect matters [1].

The scientific process places the onus on those proposing that mirtazapine might have serotonergic action in humans to adduce evidence in support of that. The cliché ‘unfortunately absence of proof is not proof of absence’ is misused, because burden of provision of evidence is on the proponents of an idea; it is not up to others to demonstrate its absence.

I argue that ‘mirtazapine is not significantly serotonergic (i.e. has no clinical effect) in humans at any dose level’ for six reasons given earlier (see also [1]) which together form an integrated thesis. Not one of these six reasons has been effectively contradicted in Professor Norman’s commentary.

The greater volume of data (more than 100 cases) on serotonergic effects of overdoses carries greater weight than case reports, which constitute the lowest grade of evidence. This systematic data indicates an absence of serotonergic signs (e.g. hyperreflexia, clonus), and no serotonin toxicity [2]. The cited case reports (except one) are of mirtazapine combined with other serotonergic drugs and did not exhibit the features of serotonin toxicity. Those who wish to understand the usefulness of the spectrum concept of serotonin toxicity may read the cited reviews and the updated information at http://www.psychotropical.com/SerotoninToxicity.doc

The study from Professor Cowen at Oxford, that I quoted concerning 5-HT1A effects, used 30 mg of mirtazapine for 28 days in patients with depression. The relevance of the studies cited using a single dose of 15 mg may be judged by readers after noting other studies, again with single doses of 15 mg, have indeed demonstrated effects on both cortisol and prolactin, but reduction, not elevation [3]. This is complex data; but however one chooses to view it, there is inconsistent support for the proposal that mirtazapine increases 5-HT1A transmission in humans.

References


Guilt and PTSD

David Stratton, private practice, Burleigh Heads, Queensland, Australia:

The recent report on mental illness among NSW prisoners [1] includes statistics about the prevalence of Post-traumatic stress disorder (PTSD) among prisoners
on reception at a correctional facility. The prevalence for men was 21.7% and for women 43.6%.

Winston Churchill’s book *A history of the English-speaking peoples* [2] contains a marvellous description which might have been of PTSD.

Churchill quotes Sir Thomas More (1478–1535) describing Richard III in about 1483, after the princes were murdered in the Tower.

After this abominable deed done he never had quiet in his mind, he never thought himself sure. Where he went abroad, his eyes whirled about, his body privily fenced, his hand ever on his dagger, his countenance and manner like one always ready to strike again. He took ill rest at nights, lay long waking and musing; sore wearied with care and watch, he rather slumbered than slept. Troubled with fearful dreams, suddenly sometimes started he up, leapt out of his bed and ran about the chamber. So was his restless heart continually tossed and tumbled with the tedious impression and stormy remembrance of his most abominable deed.

That description would surely earn Richard a hit on DSM-IV 309.81. He would easily have passed the ‘A’ criteria.

There is continuing argument about whether Richard really did murder the princes, details of which enlivened the screens of members of the Auspsych email list recently. Churchill himself dryly remarked that: ‘It will take many ingenious books to raise this issue to the dignity of a historical controversy.’

The diagnosis of PTSD includes the ‘A’ criteria (a traumatic experience of a specified severity) and a series of phenomenological criteria including one out of five re-experiencing symptoms, three out seven avoidance symptoms, and two out of five arousal symptoms. The diagnosis has been criticized elsewhere [3].

The implicit assumption is that the trauma caused the symptoms. But if these symptoms may also occur in other circumstances such as guilt, is it not possible that some diagnoses of PTSD, which meet all the criteria, might actually be ‘false positives’? Prevalence rates in recently sentenced prisoners might be particularly prone to such distortion.

My impression, after assessing many Vietnam veterans, is that those with some guilty dimension of their wartime experience suffer worse and more intransigent PTSD symptoms than those who were merely ‘traumatized’. Possibly two separate processes exist with similar consequences, which might compound each other.

References