

# Pharmacological treatment to prevent and treat post-traumatic stress disorder

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## Abstract

Pharmacological treatments do have a role to play in the treatment of PTSD. Several agents have been shown to be superior to a placebo and many PTSD sufferers do appear to benefit from medication. The overall effect sizes are relatively small. It is to be hoped that in the future better pharmacological agents will be developed.

*Introduction:* In recent years there has been a large increase in the amount of research looking at the neurobiology of post-traumatic stress disorder (PTSD). We now know that certain areas of the brain become active at the time of trauma, resulting in emotional and behavioural responses, and changes in neurochemicals and hormones. The amygdala, for example, is involved in the normal fear response, determines the significance of external stimuli and triggers responses such as fight, flight and freezing. These responses lead to alterations in stress hormones, neurochemicals and activity in other parts of the brain, such as the hippocampus and medial prefrontal cortex. One hypothesis is that in PTSD there is a failure of other networks to regulate amygdala reactivity, resulting in hyper reactivity to threat commonly seen in PTSD sufferers.<sup>1</sup> Some, but not all studies have suggested that cortisol levels are lower in PTSD sufferers than in individuals without PTSD,<sup>2</sup> and that there is adrenergic overactivity shortly after traumatic events.

Our current knowledge of the neurobiology of PTSD, although not complete, suggests that certain drugs should be able to prevent its development and reduce its symptoms.

*Keywords:* Neurobiology, PTSD, controller trials, guidelines

## Pharmacological prevention

Few studies have considered administration of pharmacological treatments shortly after a traumatic event. Schelling et al<sup>3</sup> compared intravenous hydrocortisone with a placebo in 20 septic shock victims on an intensive care unit. They found evidence that those who received hydrocortisone were less likely to suffer from PTSD at 31 month follow-up than those who did not. Pitman et al<sup>4</sup> randomised individuals to receive a short course of Propranolol, a drug that reduces adrenergic activity, starting within six hours of a traumatic event, or a placebo. They found no significant difference in the rates of PTSD at follow up. However, there was some evidence that individuals who received Propranolol showed less physiological reactivity on being reminded of what had happened. Melman et al<sup>5</sup> conducted a randomised controlled trial of Temazepam, a hypnotic benzodiazepine, an average of 14 days after attendance at an emergency unit following a traumatic event. At six weeks follow up there was no significant difference between the

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groups but there was a trend for those in the Temazepam group to be more likely to have PTSD than the placebo group despite the Temazepam group reporting improved initial sleep. Another study by Stein et al<sup>6</sup> found no difference between Propranolol, Gabapentin and the placebo when started 24 to 48 hours after a traumatic event.

With the evidence available at present there is no evidence that any pharmacological agent can prevent PTSD. Therefore, routine administration is not indicated. The United Kingdom's National Institute of Clinical and Health Excellence's (NICE) guidelines<sup>7</sup> recommend that, given the absence of evidence, pharmacological treatment should only be offered, if at all, for acute phase symptomatic management, for example if an individual has marked insomnia.

### Pharmacological treatment

The published randomised controlled trials to date have considered treatment of chronic PTSD. Research suggests that around 80% of individuals attending mental health services for treatment of PTSD are currently being prescribed medication.<sup>8</sup> Antidepressants, in particular selective serotonin reuptake inhibitors, are the most commonly prescribed drugs but other medications such as atypical antipsychotics and benzodiazepines are also widely used. A large number of randomised controlled trials have now been conducted with drugs, the majority with antidepressants but the atypical antipsychotics Olanzapine and Risperidone have also been subjected to randomised controlled trials. Overall the effect sizes are relatively small although the placebo response rates have been very high. For example, in randomised controlled trials of the serotonin and noradrenaline reuptake inhibitor Venlafaxine the placebo group have reported experiencing symptom reductions

of around 50%.<sup>9</sup> This means that individuals who take medication, be it placebo or Venlafaxine, reported significant symptom reductions but those in the Venlafaxine group only did slightly better than those in the placebo group.

Paroxetine is the drug that has been most researched and shows a highly statistically significant small positive effect on symptoms of PTSD overall.<sup>7</sup> The NICE guidelines' meta-analysis of drug treatment found that Mirtazapine, Amitriptyline and Phenelzine were the only other three drugs that fared statistically significantly better than a placebo, although the number of individuals included in those studies was relatively low, particularly in the case of Mirtazapine.<sup>7</sup>

As a result of a priori determined rules regarding effect sizes, the NICE guidelines recommended drug treatment as a second line treatment for PTSD. The Australian Guidelines also recommended that drug treatments for PTSD should not be used as a routine first line treatment.<sup>10</sup> Given the current evidence, the NICE guidelines recommend a limited role for Paroxetine and Mirtazapine to be prescribed by non-specialists and Amitriptyline and Phenelzine by mental health specialists. They are likely to be indicated when a patient has a clear preference for a pharmacological rather than a psychological approach, when there is serious ongoing threat that will prevent an individual fully engaging with evidence psychological treatment, and to augment psychological treatment that has not been effective on its own. In many countries the limited availability of psychological therapists who are able to provide evidence psychological treatments means long waits to access such treatments. It is therefore likely that many individuals will be prescribed medication because of the lack of availability of psychological treatment.

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