

Post-traumatic stress disorder: new directions in pharmacotherapy

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ARTICLE

SUMMARY

As many as 10% of the population experience post-traumatic stress disorder (PTSD) at some time in their lives. It often runs a severe, chronic and treatment-resistant course. This article reviews the evidence base for typically recommended treatments such as cognitive-behavioural therapy (CBT), eye movement desensitisation and reprocessing and selective serotonin reuptake inhibitors (SSRIs). It tabulates the major randomised controlled trials of SSRIs and trauma-focused CBT and reviews research on novel treatments such as ketamine, MDMA, quetiapine, propranolol and prazosin.

DECLARATION OF INTEREST

None.

management for treatments other than first-line antidepressants or CBT. I then ran a second search, using suggestions for pharmacological management of severe, chronic or treatment-resistant PTSD as search terms. Treatments backed by research papers are incorporated in this article.

Psychopharmacology for PTSD

Although NICE guidance on PTSD states that ‘the evidence base for drug treatments in PTSD is very limited’ (National Collaborating Centre for Mental Health 2005: p. 19), there are numerous trials indicating that antidepressants are more effective than placebo and at least 18 clinical trials (10 double-blind placebo-controlled, 8 open-label)

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TABLE 1 Frequencies of symptoms in 103 trauma survivors with post-traumatic stress disorder

Symptom	Symptom frequency, %
Anxiety at reminders of the trauma	96
Insomnia	94
Intrusive thoughts, memories and sensory phenomena (e.g. visual flashbacks)	94
Poor concentration	94
Irritability	94
Diminished interest in activities or social life	87
Avoidance behaviour related to the trauma	80
Recurrent nightmares	77
Avoidance of thinking about the trauma	74
Detachment	74
Foreshortening of expectations of life	74
Poor appetite	70
Hypervigilance	51
More intense startle reaction	41
Acting as if the trauma were recurring	41
Restricted affect	25
Low libido	24
Low mood	23
Inability to recall parts of the trauma (not secondary to loss of consciousness or organic trauma)	16
Increased use of alcohol	13
Increased use of tobacco/other substances	9

Source: Green 2003.

Post-traumatic stress disorder (PTSD) is relatively common, affecting 6–10% of all individuals at some time in their lives (Kessler 2005). Key symptoms include nightmares, intrusive memories and sensory impressions (flashbacks) and avoidance behaviour. There is a considerable risk of comorbid problems (e.g. depression or alcohol misuse), and PTSD is a source of disability and increased suicide risk. Table 1 shows the relative frequencies of different symptoms in people with PTSD.

Despite the prevalence of PTSD, traditional treatments are relatively limited in their success. In 1999, the World Health Organization’s *Management of Mental Disorders* concluded that ‘PTSD is a severe disorder that is very difficult to treat’ (Andrews 1999). Various authors report treatment resistance in about 33% of sufferers. The non-response rate to cognitive-behavioural therapy (CBT) in PTSD is as high as 50% (Kar 2011) and yet this treatment is purported to have the evidence to justify it as the initial management choice for PTSD by agencies such as the National Institute for Health and Clinical Excellence (NICE; National Collaborating Centre for Mental Health 2005). For comparison, the response rate for selective serotonin reuptake inhibitors (SSRIs) is about 60–80%.

I conducted this review of recent developments in the psychopharmacology of PTSD by searching MEDLINE (from 1946 to 2013) using ‘PTSD’ as a search term and then scanning reviews on its

of atypical antipsychotics for PTSD (Ahearn 2011). I will return to the antipsychotic trials later.

Antidepressants

Looking at antidepressants, Marshall *et al* (2001) found statistically significant improvements with paroxetine (20–40 mg/day) compared with placebo on all three PTSD symptom clusters (re-experiencing, avoidance/numbing and hyperarousal) in a study involving 551 patients. In a later study involving 70 people with chronic PTSD, Marshall *et al* (2007) found significantly different response rates of 67% for paroxetine *v.* 27% for placebo after 10 weeks. Exposure therapy (a form of CBT) plus paroxetine has been found superior in producing remission compared with exposure therapy plus placebo (Schneier 2012).

Sertraline has been found to be superior to placebo in studies by Davidson *et al* (2001) and Brady *et al* (2000), which involved 208 and 187 patients respectively.

Fluoxetine has been found superior to placebo in studies by Connor *et al* (1999) involving 53 patients and van der Kolk *et al* (1994) including 64 patients.

Is trauma-focused psychotherapy the last word in PTSD treatment?

The NICE guidelines gave us a simple message in 2005: ‘All PTSD sufferers should be offered a course of trauma-focused psychological treatment (trauma-focused cognitive behavioural therapy or eye movement desensitisation and reprocessing)’ (National Collaborating Centre for Mental Health 2005: p. 17). The guidelines suggest 8–12 sessions of trauma-focused CBT, but if CBT can begin in the first month after the event, as few as 5 sessions may be needed.

Trauma-focused CBT

Most psychiatrists would be familiar with the therapeutic uses of CBT and with the concepts behind it, derived from the work of the psychiatrist Aaron T. Beck and others (Beck 1963, 2011). Trauma-focused CBT, however, is qualitatively different. It uses additional components such as stimulus confrontation, in which the patient confronts the trauma by reliving it in the imagination or in real life (Seidler 2006). Daily homework thereafter may consist of repeatedly listening to a recording of a verbal narrative of the trauma, with the aim of producing desensitisation.

Eye movement desensitisation and reprocessing

Another trauma-focused psychotherapy is eye movement desensitisation and reprocessing (EMDR). Based on work by Shapiro (2001),

EMDR is predicated on the theory that traumatic events which overwhelm the cognitive functions of the brain are not processed properly, creating dysfunctional memory systems that reveal themselves as symptoms of PTSD. Therapy involves bilateral brain stimulation using eye movements, sounds or touching while the patient evokes the traumatic visual images or memories and is encouraged to shift between the traumatic past and the safer present. No definitive explanation of how EMDR works is available.

Is EMDR supported by the evidence?

A wealth of controlled trials using EMDR demonstrate a degree of efficacy, but it is probably fair to say that there are no double-blind randomised controlled trials of the intervention, and that EMDR has not shown superior efficacy to other trauma-focused therapies (Lohr 1998). There is also not enough convincing evidence to suggest that the bilateral stimulation techniques are of any use, and some research suggests that EMDR may actually be less effective than CBT (Rothbaum 2005).

In comparative studies, a 50% reduction in PTSD symptoms can be achieved in 32–53% of patients receiving 10 sessions of CBT (Hembree 2000), but among the rest at least 14% drop out of therapy. For exposure models such as trauma-focused CBT, the drop-out rate may be as high as 50%, as many patients have difficulty re-experiencing the trauma involved in stimulus confrontation.

Nevertheless, many patients prefer a non-drug treatment and find interventions such as CBT and EMDR acceptable because they believe that it is not possible to become ‘hooked’ on psychotherapy. Certainly, there is evidence for the efficacy of trauma-focused CBT and EMDR (Hembree 2000; Ponniah 2009), but can they work for severe, chronic illness and provide a ‘once and for all’ resolution?

The evidence base for trauma-focused CBT and SSRIs

Research on both psychotherapeutic and pharmacological treatments suffers from short-termism. My MEDLINE searches revealed that randomised controlled trials (RCTs) of SSRIs ran for only 5–12 weeks (Table 2), and RCTs of trauma-focused CBT ran for 5–14 weeks (Table 3). Furthermore, such studies often neglect to include patients with chronic, treatment-resistant PTSD, who frequent more naturalistic settings than the research laboratory or university psychology department. Nor can guidelines or research adequately replicate the real world, where supply and demand dictate the non-availability of psychotherapies to the masses of people with PTSD, or provide solutions for patients

TABLE 2 Randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) for post-traumatic stress disorder^a

Study (participants, n)	Participants on SSRI, n	Participants on comparator, n	Dose, mg/day	Duration of treatment, weeks	Response measurement	Response rate	NNT (95% CI)
van der Kolk <i>et al.</i> , 1994 (64)	Fluoxetine: 33	Placebo: 31	20–60	5	BDHI, CAPS, DES, DESI, HRSD,		
Connor <i>et al.</i> , 1999 (54)	Fluoxetine: 27	Placebo: 27	20–60	12	DGRP, DTS, SDS, SIP, VS	Fluoxetine: 59% Placebo: 27%	3 (2–12)
Brady <i>et al.</i> , 2000 (187)	Sertraline: 94	Placebo: 93	50–200	12	CAPS, CGI	Sertraline: 53% Placebo: 32%	6 (8–35)
Davidson <i>et al.</i> , 2001 (208)	Sertraline: 100	Placebo: 108	25–200	12	CAPS, CGI, DTS, HAM-A, HRSD, IES, PSQI	Fluoxetine: 60% Placebo: 38%	5 (3–12)
Marshall <i>et al.</i> , 2001 (551)	Paroxetine: 365	Placebo: 186	25–50	12	CAPS, CGI, DTS, MADRS, SDS, TOP-8,	Paroxetine: 60% Placebo: 38%	5 (4–8)
Tucker <i>et al.</i> , 2001 (307)	Paroxetine: 151	Placebo: 156	20–50	12	CAPS, CGI, DTS, MADRS, SDS, TOP-8,	Paroxetine: 58% Placebo: 38%	5 (4–11)
Martenyi <i>et al.</i> , 2002 (301)	Fluoxetine: 226	Placebo: 75	20–80	12	CAPS, CGI, DES, DTS, HAM-A, MADRS, SCL-90, TOP-8	Fluoxetine: 58% Placebo: 41%	7 (4–27)
Zohar <i>et al.</i> , 2002 (42)	Sertraline: 23	Placebo: 19	50–200	10	CAPS, CGI		6 (3–12)
Chung 2004 (113)	Sertraline: 51 (completed)	Mirtazapine: 49 (completed)	Sertraline 5–100 Mirtazapine 15–30	6	CAPS, CGI, HRSD	Mirtazapine: 88% Sertraline: 69%	
Davidson <i>et al.</i> , 2006 (538)	Sertraline: 209 Venlafaxine: 161	Placebo: 168	Sertraline 25–200 Venlafaxine 37.5–300	12	CAPS, CGI, DTS, GAF	Remission rate: Sertraline 24% Venlafaxine: 30.2% Placebo: 19.6%	Sertraline: 19 (8–34)
Martenyi <i>et al.</i> , 2007 (411)	Fluoxetine: 323 Drop-out rate 4–13% (dose related)	Placebo: 88	20–40	12	CAPS, CGI, DES, DTS, HAM-A, MADRS, SCL-90, TOP-8	No significant fall in CAPS	
van der Kolk <i>et al.</i> , 2007 (88)	Fluoxetine: 30	Placebo: 29 EMDR: 29	10–60	8	BDI, CAPS	Fluoxetine: 81% EMDR: 88% Placebo: 65%	Fluoxetine v placebo: 7 (3–12)

BDHI, Buss-Durkee Hostility Inventory; BDI, Beck Depression Inventory; CAPS, Clinician-Administered PTSD Scale; CGI, Clinical Global Impression; DES, Dissociative Experiences Scale; DESI, Disorders of Extreme Stress Inventory; DGRP, Duke Global Rating for PTSD; DTS, Davidson Trauma Scale; EMDR, eye movement desensitisation and reprocessing; GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Scale; HRSD, Hamilton Rating Scale for Depression; IES, Impact of Event Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NNT, number needed to treat; PSQI, Pittsburgh Sleep Quality Index; SCL-90, Symptom Checklist 90; SDS, Sheehan Disability Scale; SIP, Short Index of Problems; TOP-8, Treatment Outcome PTSD Scale; VS, Vulnerability to Effects of Stress Scale.

Study information partially drawn from Stein DJ *et al.* (2009), from original papers and from MEDLINE.

a. Over 1600 patients with PTSD on SSRIs have been studied in randomised controlled trials against placebo, roughly 5 times the number of PTSD patients studied in trials of cognitive-behavioural therapy. Where data or details are missing, it is because they were not available.

TABLE 3 Randomised controlled trials of trauma-focused cognitive-behavioural therapy (CBT) for post-traumatic stress disorder^a

Study (participants, <i>n</i>)	Participants having CBT, <i>n</i>	Participants on comparator, ^b <i>n</i>	Sessions, <i>n</i>	Duration of treatment, weeks	Response measurement	Response rates	NNT (95% CI)
Brom <i>et al.</i> , 1989 (54)	31 Drop-out: 12%	23	15		SCL-90, STAI	Significant reduction in intrusion and avoidance	
Fecteau <i>et al.</i> , 1999 (20)	10	10	4 x 2h sessions		AFQ, BAI, BDI, CAPS, IES	CBT: 25% Waiting list: 0%	2 (2–6)
Foa 1999 (40)	25	15	9		BDI, PSS-I, SCID, STAI	CBT: 60% Waiting list: 0%	2 (2–3)
Blanchard <i>et al.</i> , 2003 (98)	30	27	8–12		APS, IES, STAI	CBT: 23% Control group: 13%	4 (2–23)
Kubany <i>et al.</i> , 2003 (37)	19 Drop-out: 14%	18	8–11		BDI, CAPS		
Kubany <i>et al.</i> , 2004 (125)	59 Drop-out: 23%	66	11		BDI, CAPS	42/59 responded (71%)	
Ehlers <i>et al.</i> , 2005 (28)	14	14	12	12	BAI, BDI, CAPS	CBT: 78% Waiting list: 0%	2 (1–2)
Foa, 2005 (171)	79 Drop-out: 34%	26 Drop-out: 4%	9–12	9	BDI, PSS-I, PSS-SR, SAS		
McDonagh <i>et al.</i> , 2005 (74)	29 Drop-out: 41% (to <i>n</i> = 17)	23 Drop-out: 13% (to <i>n</i> = 20)	14	14	CAPS	CBT: 27.6% Waiting list: 17.4%	7 (3–9)
Rothbaum <i>et al.</i> , 2005 (74)	20 Drop-out: 16%	20	8	5	AI, BDI, CAPS, DES, IES, SCID-I, STAI	CBT: 95% Waiting list: 10%	2 (1–2)
Duffy, 2007 (58)	29 Drop-out: 31%	29 Drop-out: 10%	6–12	12	DSM-IV diagnostic scale for PTSD		

AFQ, Accident Fear Questionnaire; AI, Assault Information Interview; APS, Attenuated Psychotic Symptoms; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CAPS, Clinician-Administered PTSD Scale; DES, Dissociative Experiences Scale; IES, Impact of Event Scale; NNT, number needed to treat; PSS-I, PTSD Symptom Scale interview version; PSS-SR, PTSD Symptom Scale Self-Report version; SAS, Social Adjustment Scale; SCID-I, Structured Clinical Interview for Axis I Disorders; SCL-90, Symptom Checklist 90; STAI, Spielberger State-Trait Anxiety Inventory.

a. Study information partially drawn from Bisson & Andrew (2009), from original papers and from MEDLINE.

b. Over 340 PTSD patients have received CBT in RCTs. Where data or details are missing, it is because they were not available.

c. All the chosen studies had waiting-list controls. Control groups vary greatly in some other studies.

who have graduated from their second course of CBT and relapsed yet again some months later.

NICE recommendations

The NICE guidelines favour the evidence base for CBT rather than antidepressants. Indeed, the numbers needed to treat (NNTs) in individual trials of CBT are generally more favourable (Tables 2 and 3). Certainly CBT seems more efficacious than alternatives such as psychological debriefing. However, the numbers of patients treated with SSRIs in RCTs far exceed the numbers treated with CBT and the numbers of participants in individual trials are low. Over 1600 people with PTSD have been studied in RCTs comparing SSRIs against placebo, roughly 5 times the number studied in trials of trauma-focused CBT. A further point to consider is that, where it is reported, the drop-out rate for trauma-focused CBT is high (12–41%), indicating that it is clearly not tolerated by all. The National Health Service (NHS) Health Technology Assessment Programme (Durham 2005) recommends that those espousing psychotherapies need to develop an evidence base involving ‘longitudinal research designs over extended periods of time (2–5 years), with large numbers of participants (500+)’ before cost-effectiveness could be demonstrated. On the studies that my literature search revealed (Table 3), we are still far from providing such a solid research base for CBT.

The promise of neuroimaging

We now have evidence of consistent structural and functional neuroimaging changes associated with PTSD (Bremner 2008). Structural changes include volume reduction of the hippocampus by 12%. Reduced hippocampal volume is associated with verbal memory deficits and dissociative experiences. These structural changes can reverse with treatment, as demonstrated in separate studies using paroxetine and valproate (Bremner 2008). Functional changes include hypo-responsivity in medial prefrontal cortical areas during reminder cues. Such changes have been demonstrated in studies involving war veterans with PTSD and also in PTSD suffered by survivors of prolonged childhood sexual abuse. Reminder cues included slides of combat or guided memories of childhood abuse. The medial prefrontal cortex is involved in the inhibition of fear responses in the amygdala, and hypo-responsivity therefore leads to greater activation of the amygdala and consequent PTSD symptoms such as an enhanced startle response.

The promise of neuroimaging is to find treatments that can reverse such structural and functional changes.

Novel treatments

Of the recently proposed novel treatments for PTSD, it must be said that none has a body of evidence that approaches the evidence base supporting the use of antidepressants and CBT.

Propranolol

Propranolol is a beta-adrenergic blocker. It blocks the action of adrenaline and noradrenaline on β_1 and β_2 adrenergic receptors, which also results in indirect α_1 agonism. Various studies have implied that effects of propranolol on the central nervous system may be of relevance to models of PTSD. For instance, propranolol has been shown to reduce the reactivity of the amygdala (Hurlemann 2010) and it may impair memory formation in animal neocortices by reducing synaptic potentiation (Flores 2010). Propranolol may also impair memory formation by attenuating neuropeptide S-induced memory enhancement (Okamura 2011).

Propranolol is licensed in the UK for various conditions, including hypertension and migraine. It is less often prescribed for anxiety disorders in settings such as primary care, the literature on its efficacy as an anxiolytic is very limited. Furthermore, the drug has very real side-effects, which include bradycardia, hypotension and falls, and so certain baseline investigations (electrocardiogram and blood pressure, among others) must be performed before, and monitored during, prescription.

The propranolol protection theory

There has been media interest over the past decade in a potential protective effect conferred by propranolol against the development of PTSD. The level of media interest could be argued to have been disproportionate, as it was triggered by relatively small-scale studies (e.g. Pitman 2002; Vaiva 2003) that showed a lower incidence of PTSD in people who had been treated with propranolol in the aftermath of trauma. The general concept was that propranolol, as a beta-adrenergic blocker, might prevent the excess activation of the central nucleus of the amygdala and the locus ceruleus after trauma, thought at the time to provide the neurological basis for PTSD.

This promising theory has not been confirmed by larger studies. For instance, research involving 29 children randomised to receive propranolol or placebo within 12 hours of physical trauma showed no significant between-group difference in scores on the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) at 6 weeks (Nugent 2010).

In another trial, physically injured patients were randomised to receive 14 days of propranolol

($n = 17$), gabapentin ($n = 14$) or placebo ($n = 17$) within 48 hours of injury. None of the interventions showed any effect at follow-up (Stein 2007).

Similarly, McGhee *et al* (2009) found no reduction in PTSD in US soldiers injured in Iraq who had been given propranolol. They reviewed 603 patients at a military burns centre, 226 of whom completed a PTSD checklist. Thirty-one soldiers had received propranolol and 34 matched soldiers had not. The prevalence of PTSD in the propranolol group was 32.3%, against 26.5% in the comparison group ($P = 0.785$).

The most recent study, a randomised placebo-controlled trial by Hoge *et al* (2012), evaluated the proactive use of propranolol in a clinical sample of 41 emergency department patients who had just experienced psychological trauma. Participants received either up to 240 mg/day of propranolol or placebo for 19 days. The drug did not significantly affect rates of PTSD diagnosis or severity of symptoms between the groups.

Animal research reports that propranolol given 1 hour after trauma was ineffective in preventing PTSD-like behavioural responses (e.g the startle response or freezing response on reminder cues) (Cohen 2011).

Ketamine

Ketamine is a glutamatergic *N*-methyl-D-aspartate receptor antagonist which can, very rarely nowadays, be used as an anaesthetic agent. There has been recent interest in the use of intravenous ketamine for depression. A small-scale study of intravenous ketamine in 17 patients with treatment-resistant unipolar depression showed positive effects on mood lasting for a week after a dose of the drug (Zarate 2006). Suicidal ideation was found to reduce in the hours following intravenous administration of ketamine in a study of people with treatment-resistant major depressive disorder (Diazgranados 2010a). There is also research on the use of ketamine in depression associated with chronic regional pain syndrome (Romero-Sandoval 2011) and treatment-resistant bipolar depression (Diazgranados 2010b).

The notion that ketamine might have an off-label part to play in the treatment of PTSD is perhaps less easy to understand, as the drug is associated with side-effects such as tachycardia, nightmares and hallucinations. Nevertheless, interest in ketamine arose from the observation that glutamate, which is released in stress, is important in the generation of dissociative symptoms (Chambers 1999). The Mount Sinai School of Medicine has been conducting a trial (NCT00749203) to see whether ketamine infusions may be a treatment for PTSD. It

should be noted that the role ketamine might play in long-term treatment of PTSD would be limited by the need for intravenous administration.

Of three studies of accident and burns victims given ketamine during emergency treatment or surgery, two reported negative effects. In 2005, Schöenberg *et al* studied injured accident victims who had received either (S)-ketamine or opioids as analgesia in hospital a year previously. They found that retrospectively assessed dissociation, re-experiencing and avoidance behaviour and current PTSD were higher in the (S)-ketamine group.

Further work by Schöenberg *et al* (2008) found that ketamine aggravated PTSD in burns victims, producing early acute stress disorder, dissociative states, re-experiencing, hyperarousal and avoidance behaviours. The study looked at patients who had received a dose of either ketamine ($n = 13$), opioids ($n = 24$) or non-opioid analgesics ($n = 13$) during initial emergency treatment.

McGhee *et al* (2008), however, reported reduced levels of PTSD among 119 soldiers with burns who had received ketamine during surgery compared with 28 patients who had not. The PTSD prevalence in the ketamine group was 27%, compared with 46% in the non-ketamine group ($P = 0.044$).

If ketamine's future in PTSD is not as a treatment, its potential role in stimulating PTSD symptoms may guide further research. One area of interest might be *N*-methyl-D-aspartate receptor agonists (rather than antagonists) such as D-cycloserine, which facilitates learning and hippocampal activity.

MDMA (3,4-methylenedioxymethamphetamine)

Before its use as a recreational drug ('ecstasy') in the 1990s, MDMA was used as an adjunctive agent to psychotherapy in the 1970s and 1980s. The use of stimulants in psychotherapy for PTSD has a long history. William Sargant used nikethamide and amphetamines in a therapy akin to flooding (exposure therapy) in cases of battle shock during the Second World War (Sargant 1957). Sargant called his technique abreaction, but rather than using sedation, he used stimulants to provoke a sudden and profound emotional crisis or collapse to produce a cure.

The hypothesis behind the use of MDMA in the psychotherapy of PTSD is that MDMA ameliorates fear activation during therapy and increases trust in the therapist, making exposure therapy easier. The drug may also increase blood flow in ventromedial prefrontal and occipital cortex and reduce it in the left amygdala, reversing known PTSD abnormalities (Mithoefer *et al*, 2011).

The MDMA dose used in therapy is typically between 50 and 125 mg. The drug is given when the

patient is relaxed on a couch, possibly listening to music through headphones. Patients can alternate between the inner experience and talking to the therapist. Sessions are non-directive and patients are encouraged to fully experience and express whatever arises, rather than avoiding or suppressing thoughts. The format for the psychotherapy mimics that used in past decades with lysergic acid diethylamide (LSD) (Pahnke 1971).

Precautions are usually taken to monitor for tachycardia and raised blood pressure. Small-scale studies have also monitored anxiety, depression and neurocognitive abilities. Participants often report tightness of the jaw, nausea, headache, dizziness and anxiety.

Bouso *et al* (2008) studied six individuals with PTSD who had been treated with 50–75 mg MDMA. The small number reflects the fact that the study was closed down through what the authors termed ‘political pressure’. The authors concluded that, as far as their study was concerned, MDMA was ‘safe’ with ‘promising signs of efficacy’ and suggested studies with larger samples and higher doses.

Mithoefer *et al* (2011) studied 20 individuals with PTSD, 12 of whom were allocated to psychotherapy with MDMA and 8 to psychotherapy with placebo. The outcomes measured through the Clinician-Administered PTSD Scale (CAPS) and Impact of Events Scale (IES) were significantly improved in the MDMA group ($P < 0.015$ and $P < 0.027$). At 1 year, 82% (14/17) of the MDMA group still did not meet criteria for PTSD.

Quetiapine

Antipsychotics are often prescribed off-label for treatment-resistant PTSD (Leslie 2009). A review by Ahearn *et al* (2011) identified 18 clinical trials (10 double-blind placebo-controlled, 8 open-label) of atypical antipsychotics for PTSD. The authors reported that the double-blind placebo-controlled trials showed only modest effect sizes, but these were positive for risperidone and quetiapine. The greatest improvement was seen on intrusive thoughts and hypervigilance symptom subscales. A 6-month randomised double-blind placebo-controlled multicentre study of adjunctive risperidone published after Ahearn *et al*'s review (Krystal 2011) did not find it to be of significant help in reducing PTSD symptoms.

The evidence indicates a potential role for quetiapine, which is an antagonist at the D₁, D₃ and D₄ dopamine receptors and the 5-HT serotonin receptor. An 8-week open-label trial of adjunctive quetiapine (at a mean dose of 216 mg/day) in 15 adults with severe PTSD reported a 42%

improvement in CAPS score, a 45% improvement on the Davidson Trauma Scale and a 44% improvement on the Sheehan Disability Scale (Ahearn 2006).

Another open-label trial, this time involving 6 adolescents, saw improvement in symptom checklist scores with flexibly dosed quetiapine (50–200 mg/day) over 6 weeks (Stathis 2005).

Kozaric-Kovacic & Pivac (2007) conducted an open-label study of quetiapine (25–400 mg/day) for 53 war veterans with PTSD and psychotic symptoms. Quetiapine treatment led to significant reductions in scores on the CAPS, the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression – Severity (CGI-S) scale at 2, 6 and 8 weeks.

Two short-term open-label trials (Hamner 2003; Sokolski 2003) showed improvement with low-dose quetiapine (25–300 mg/day) as an adjunct to SSRIs for chronic PTSD. Sokolski *et al* reported improvements on the DSM-IV PTSD criterion of re-experiencing in 35% of participants, on avoidance/numbing in 28% and on arousal in 65%. Hamner *et al* reported significant improvement in CAPS and improvement in depression scores.

It is worth noting that several US soldiers and veterans have died while taking high-dose quetiapine (>1600 mg) for PTSD. It is not known whether the drug contributed to the deaths, but the situation has resulted in some controversy in the USA regarding off-label prescribing for the disorder (Perrone 2010).

Quetiapine has various side-effects, including somnolence and postural hypotension (Green 1999).

Prazosin

Prazosin is an alpha-adrenergic blocker currently licensed for hypertension, cardiac failure, Raynaud's phenomenon and benign prostatic hyperplasia. The drug is also used in the management of scorpion stings. Any potential use for PTSD would be off-label, but there is now a research base to justify its further study for the disorder (Table 4) – arguably a much more substantial base than that for some other treatments considered above. There are important side-effects to be aware of, such as hypotension (especially with the first dose, which should be given in surroundings where monitoring can be done). Other adverse effects include gastrointestinal disturbance, oedema, palpitations, dyspnoea, depression, anxiety and nasal stuffiness.

At least eight studies indicate a role for prazosin in treating PTSD and, given the nature of chronic PTSD and its notable treatment resistance, these are of considerable interest and larger-scale RCTs would be welcome.

TABLE 4 Studies involving prazosin as a treatment for post-traumatic stress disorder

Study	Type	Prazosin dose, mg/day	Participants	Main findings
Peskind <i>et al</i> , 2003	Case series	2–4	9 older males with Holocaust or military trauma	Improvement in nightmares and severity of PTSD
Raskind <i>et al</i> , 2003	Double-blind cross-over study comparing prazosin with placebo, over 20 weeks	9.5(mean, at night)	10 military veterans	Improvement in nightmares, sleep quality and hyperarousal symptoms
Taylor <i>et al</i> , 2006	Case series, from 2004 to 2005	2–6	11 patients with chronic PTSD	Reduced startle response
Raskind <i>et al</i> , 2007	Randomised placebo-controlled trial lasting 8 weeks	13 (mean)	17 patients given prazosin, 17 given placebo	50% reduction in nightmares, improved sleep quality, overall improvement in global clinical status
Thompson <i>et al</i> , 2008	Case series	9.6(mean, at night)	22 veterans with chronic PTSD	Improvements in nightmares, non-nightmare awakenings and sleep quality
Taylor <i>et al</i> , 2008	Randomised placebo-controlled, cross-over trial	2–6	13 patients with chronic PTSD	Increase in sleep quantity, increased REM sleep, reduced nightmares
Boynton <i>et al</i> , 2009	Case series receiving 8 weeks of prazosin	1–6	23 refugees with chronic PTSD	Marked improvement in PTSD severity in 6, moderate improvement in 11 and minimal improvement in 6
Byers <i>et al</i> , 2010	Randomised controlled trial comparing prazosin with quetiapine, over 6 months	1–25	62 patients with treatment-resistant PTSD given prazosin and 175 given quetiapine	About 61% response rate for both prazosin and quetiapine; fewer side-effects in prazosin group
Germain <i>et al</i> , 2012	8-week randomised placebo-controlled study comparing prazosin with behavioural sleep intervention targeting nightmares and sleep disturbances, and placebo	8.9 (mean, at night; range 1–15)	50 US military veterans with chronic sleep disturbances; 18 received prazosin, 17 a behavioural sleep intervention, 15 placebo	Treatment groups showed reduction in daytime PTSD symptoms and insomnia, with a 62% in the treatment groups showing sleep improvements v. 25% in placebo group

Conclusions

Traditional PTSD treatments recommended by agencies such as NICE (e.g. CBT, EMDR and SSRIs) do have an evidence base, but they are of limited efficacy and trauma-focused CBT in particular has a high drop-out rate. Developments in neuroimaging could lead to new pharmacological treatments. Although current research has not demonstrated a significant role for either ketamine or propranolol, studies of prazosin for the treatment of severe, chronic PTSD suggest anti-nightmare efficacy and long-term tolerability. Larger-scale RCTs on prazosin are now justified.

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MCQ answers

1 a 2 b 3 d 4 e 5 d

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*An asterisk denotes studies listed in Tables 2, 3 and 4.

MCQs

Select the single best option for each question stem

1 Prazosin is:

- a an alpha-adrenergic blocker
- b a beta-adrenergic antagonist
- c an antagonist at D₁, D₃ and D₄ receptors
- d a glutamatergic drug
- e a selective serotonin reuptake inhibitor.

2 Trauma-focused CBT:

- a has efficacy rates of 80% within 10 weeks of starting therapy
- b should be offered to all sufferers of PTSD, according to the 2005 NICE guidelines
- c is demonstrably superior to EMDR for PTSD
- d has a negligible drop-out rate of less than 5%
- e has less efficacy than psychological debriefing in the treatment of PTSD.

3 Propranolol:

- a is licensed in the UK for the treatment of anxiety
- b prevents PTSD if given immediately after trauma, according to substantial, replicated double-blind randomised trials
- c can be prescribed for anxiety without first performing any physical examination or investigations
- d can cause bradycardia
- e is a specific alpha-adrenergic blocker.

4 Quetiapine:

- a is superior to prazosin in treating chronic PTSD
- b is licensed in the UK for the treatment of PTSD
- c is an agonist at D₁, D₃ and D₄ receptors
- d has been associated with fatalities at low doses in US military personnel
- e can cause postural hypotension.

5 PTSD:

- a has a lifetime prevalence of 4%
- b responds to SSRIs within 2 months in 90% of cases
- c occurs in less than 10% of people involved in road traffic accidents
- d is associated with increased alcohol consumption
- e is associated with irritability in less than 50% of cases.