

COMMENT

We Were Soldiers: MDMA-Assisted Psychotherapy for Post-Traumatic Stress
Disorder in Military Veterans

Andrea Cipriani and Philip J Cowen¹

University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

¹Corresponding author. Prof PJ Cowen, Neurosciences Building, Warneford Hospital, Oxford OX3 7JX,
Tel: 44-1865-618311; email: phil.cowen@psych.ox.ac.uk

'In thy faint slumbers I by thee have watch'd, And heard thee murmur tales of iron wars' (Henry IV Part One, Act 2, Scene 3).

As described by his wife, Kate, Hotspur's behaviour convincingly meets criteria for post-traumatic stress disorder (PTSD),¹ not unexpectedly in someone whose life is characterised by relentless martial activity. Indeed the diagnosis of PTSD was first formalised in DSM-III in 1980, in the context of persistent trauma-related symptomatology in veterans of the Vietnam War. Of course, traumatic events are widespread in civilian life but prevalence rates of PTSD are higher in military veterans and members of the emergency services ('first responders') than in the general population.^{2,3} Also, in the former groups, evidence based treatments (pharmacotherapy and trauma-focused psychotherapies) seem less effective, with approximately two thirds of patients retaining the diagnosis of PTSD after treatment and many failing to complete courses of therapy.^{2,3} The psychosocial consequences of persistent symptoms are serious and include substance misuse, aggressive behaviour, unemployment, family disruption and suicide.^{2,3,4,5}

Might it be possible to enhance the effectiveness of psychotherapy in PTSD through pharmacological augmentation of psychological treatment sessions? Perhaps the most studied approach has involved the partial NMDA receptor agonist, d-cycloserine, which in animal experimental work facilitates extinction of conditioned behaviour through glutamatergic mechanisms; however, its benefits in patients with PTSD are equivocal.⁶ In *The Lancet Psychiatry*, Mithoefer and colleagues⁷ report the effect of a different pharmacological intervention in which two extended (eight hour) sessions of non-directive psychotherapy are coupled with administration of the serotonin and dopamine releasing agent, 3,4-methylenedioxy-methamphetamine (MDMA). MDMA is a stimulant which elevates mood and activity; however, it also engenders powerful feelings of insight, relatedness and empathy, leading it to be sometimes termed an 'entactogen' or 'empathogen'. The latter properties have encouraged proposals that MDMA-assisted psychotherapy might facilitate recovery in PTSD by

allowing compassionate reappraisal of the trauma as well as promoting longer-term positive psychological development, in particular, increased openness and self-awareness.⁸

Finding the appropriate control condition for psychoactive drugs with obvious and profound subjective effects is challenging. Mithoefer et al, employed a 'low-dose' strategy (30mg of MDMA), though acknowledge that differences in the subjective effect of this dose and the two active doses might have compromised blinding for the participants. Nevertheless, in 26 participants (the majority, military veterans) both active doses of MDMA (75mg and 125mg) were substantially more effective than the 30mg dose in lowering scores on the Clinician Administered PTSD Scale (CAPS-IV) at the primary endpoint, one month after the second MDMA session. The fall in CAPS scores with the 75mg, and 125mg doses (58.3 and 44.3 respectively) were significantly greater ($p < 0.001$) than those seen with 30mg (11.4) and considerably more than the changes reported in studies employing trauma-related psychotherapies in veteran groups.² However, the lack of dose-response of the two active treatments and the wide confidence intervals for the 125mg dose (lower limit 0.04) raise some doubts about the robustness of the MDMA effect.

Nevertheless, at the primary end point, the majority of participants in the active treatment groups (68%) no longer met diagnostic criteria for PTSD while this was the case with only 29% of the low-dose group. At a year follow-up (and open label MDMA treatment for the low dose group) most participants continued to do well suggesting that the beneficial effect of treatment was not simply a temporary response to an intense psychological experience or the high level of psychotherapeutic care received by participants. It is worth noting, though, of the 26 patients, 22 were recruited via internet advertisement or word of mouth, which is likely to have "enriched" the sample with participants keen to use psychostimulants with resultant expectancy effects; this may limit the external validity of the findings.

MDMA is legally proscribed and there have been numerous safety concerns attached to its recreational use in the form of 'ecstasy' (which may not contain pure MDMA) including acute fatal toxicity as well as the possibility of longer-term cognitive impairment and damage to serotonin neurons.⁹ Recreational users can also experience a 'rebound' lowering of mood a few days after MDMA ingestion,¹⁰ a particular concern in individuals vulnerable to depression and suicidal feelings. However, Mithoefer et al show that with careful sourcing of MDMA and close medical and psychological supervision, its short-term use in carefully selected subjects with PTSD seems safe. Moreover, it does not appear that those naïve to MDMA prior to the study became 'ecstasy' users over the following year.

The current study describes the therapeutic use of MDMA by committed experts in a specialised setting in a small group of participants, most of whom self-referred for the trial. The unmet need for better PTSD treatment, particularly in veterans and first responders, is undoubted.^{2,3,11} However, the generalisability of the benefit of MDMA-assisted psychotherapy to more mainstream psychiatry remains to be established,¹² recalling perhaps the famous American watchword- 'Will it play in Peoria?'.

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