South African Family Practice 2016; 58(6):24-27

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

When past and present collide: A concise clinical review of post-traumatic stress disorder (PTSD) within the context of family practice

Sarel Brand, De Wet Wolmarans*

Centre of Excellence for Pharmaceutical Sciences, Division of Pharmacology, Faculty of Health Sciences, North-West University, Potchefstroom Campus
**Corresponding author, email: dewet.wolmarans@nwu.ac.za*

Introduction

Murdered. Murdering. Attempted murder. Armed robbery. Rape. Sexual harassment. Harassment in the work place. Hijacking. Drive-by shootings. Motor vehicle accidents. Child theft. Human trafficking. Domestic violence. Bullying. Abuse. Loss. Pain.

In South Africa, trauma has been described as a regular occurrence and more than 7 out of 10 individuals have been found to have experienced trauma during their lives. The most prevalent traumatic events experienced in this country are cited as trauma through the experiences of close others, life-threatening incidents and falling victim to crime or violence.[1] Although most people experience trauma at some stage during the course of their lives, and considering that emotional distress following such an event is natural, individual differences in pre- and post-trauma coping behaviour, described in 1979 by Aaron Antonovsky as salutogenic variance,[2] result in two broad post-traumatic trajectories: adapting, coping and continuing or befalling psychiatric illness. This diversion between post-trauma clinical progressions gradually changed perceptions that post-traumatic stress disorder (PTSD) is monocausal, resulting only from traumatic experience. Rather, PTSD can be conceptualised as a condition of memory impairment[3] that manifests only in psycho-genetically susceptible patients following exposure to severe trauma.[4]

Intrinsically, PTSD only refers to the symptomology arising after an individual has been exposed to a traumatic event. However, as initial trauma is necessary to trigger clinical PTSD and considering that the treatment of patients immediately following exposure to trauma may alter the course of disease progression, the current paper will explore core clinical aspects of both trauma and its long term sequelae.

A brief overview of the diagnosis of PTSD

Subsequent to traumatic events, defined in the context of PTSD by the DSM-5 as exposure to death, threatened death, and actual or attempted serious injury or sexual violence,[5] a host of psychological disorders may precipitate. Importantly, these can be experienced directly or indirectly by witnessing or exposure to the consequences of trauma in other individuals. As such, patients suffering from PTSD present with long-lasting anxiety coupled with fear-related symptomology, including re-experiencing, avoidance, aberrant cognition, e.g. impaired contextual memory, and hyperarousal, i.e. difficulty falling asleep, aggressive outbursts and irritability.[5-6] It has further been suggested that the clinical severity of PTSD following exposure to trauma may be determined by the type and/or intensity of the trauma.[7] While acute stress reactions following trauma and characterised by stupor, amnesia and symptoms related to anxiety, e.g. tachycardia and sweating,[8] are usually transient, they may become clinically significant when the severity and/or duration thereof become prolonged in the absence of stress and lead to impairment of day-to-day functioning.[9] Symptoms of PTSD normally transpire within 6 months following exposure to trauma,[5] and may be regarded as acute, if not being present for longer than 3 months from the time of first diagnosis.[5] Importantly, consultations with patients demonstrating symptoms of PTSD normally occur at two or more instances, the first of which is immediately following the traumatic event. Subsequently, due to the striking similarity between the re-experiencing of trauma and the actual event,[6] a need for follow-up consultations will often be triggered by distressing memories, nightmares or panic attacks.

Fundamentals of fear

When presented with visual or auditory fear-inducing stimuli, the central nervous system reacts via the thalamus which activates the fear centre in the amygdala; that in turn signals the downstream release of noradrenalin and prepares the individual for the fight-or-flight response.[10] Immediately following this response priming, the thalamus projects the fear related information to the frontal cortex that is responsible for the cognitive appraisal of the stimuli. If, following such appraisal, the frontal cortex continues the fear response, the amygdala remains activated and the fear related memory is strengthened and consolidated in the hippocampus.[11] However, if cortical appraisal results in the discontinuation of the fear response, the amygdala is inactivated, noradrenalin levels decrease and patients learn to switch immediately between fear activation and extinction upon re-exposures to a reminder of the former traumatic event.[12] Hence, it can be understood that a prolonged and severe hyperadrenergic state following trauma may contribute to an

overemphasis of fear, resulting in an inflated consolidation of the relevant memory.

Why we need targeted therapy: The complex nature of trauma and delayed re-experiencing

As alluded to above, a rapid neuronal response at the time of first exposure to trauma is a pivotal process in the contextual appraisal of fear, consolidating the memory of such context and eventually priming the central nervous system to prevent an exaggerated fear response upon future exposures to contextual reminders of the initial traumatic incident. While the exact reasons are not fully understood, it is clear that patients with PTSD fail to switch from fear consolidation to extinction.[13] Furthermore, while most individuals experience trauma to some extent during their lifetime, it is impractical to screen all individuals for possible pre-trauma PTSD-related risk factors. As such, in an attempt to curb the risk that trauma-exposed patients will progress to psychiatric illness, a number of studies have attempted to investigate the efficacy of various putative first-line therapies that can be administered immediately following trauma in all exposed individuals. These approaches have been conceived based on theory-driven approaches and will be summarised here.

Inhibiting exaggerated adrenergic responses

Based on the notion that an inflated hyperadrenergic state during and immediately following trauma results in the overconsolidation of fear memory,[14-16] research has attempted to establish whether PTSD can be prevented should the effects of trauma induced noradrenalin release be controlled. Regrettably, the results of these investigations, most of which were employing early post-trauma administration of the non-selective $ß_{1/2}$ adrenergic receptor blocker, propranolol, have been inconsistent, with some authors reporting lower incidences of PTSD symptoms 2–3 months following trauma,[17-18] while others, although not reporting detrimental effects of drug administration, failed to demonstrate the same.[19-21] However, possible reasons for these inconsistencies may include varying sample sizes, the nature and severity of the trauma inflicted and the significant age differences across the various samples.[11] Another approach to prevent the influence of noradrenalin in the consolidation of fear memory is to decrease the release of the neurotransmitter during the fear response, e.g. by administering the α_2 adrenergic receptor agonist, clonidine. Few investigations have attempted this approach[22-23] and, as such, studies still aim to elucidate the exact role of early antiadrenergic pharmacotherapy in trauma exposed individuals.

Manipulating the stress-related corticosteroid response

It has frequently been proposed that acute administration of corticosteroids immediately following trauma may improve the prognosis of patients.[24-26] This is based on observations that a dysfunctional hypothalamic-pituitary-adrenal axis, resulting in low levels of circulating cortisol before exposure to trauma, may prolong the adrenergic response and inflate fear memory consolidation.[27] Indeed, it has been demonstrated that risk of progressing from trauma-induced fear to clinical PTSD can be decreased by the administration of hydrocortisone immediately following exposure.[28-31]

Opioids: More than just analgesics

Opioids are widely prescribed for the nociceptive symptoms of trauma in emergency care and have been under continuous investigation for their effects on the consolidation of fear memory. In fact, clinical[32-34] and pre-clinical[35-36] evidence demonstrate that the early administration of opioids following trauma may inhibit noradrenergic activity and moderate inflated fear learning. Studies in both adults[34] and children[32] revealed lower degrees of PTSD symptoms within 3 and 6 months post-trauma, respectively. Importantly, these effects were only observed if opioid administration occurred within 48 hours, and not 1 week, post-trauma.

The question of immediate anxiolytic treatment and trauma counselling

It cannot be debated that benzodiazepines, agonists at the $GABA_A$ receptor, are commonly prescribed to patients following trauma. Due to their ameliorating effects on anxiety and considering their sedative, hypnotic and muscle relaxant properties,[37] the benzodiazepines do indeed have a beneficial role to play in the acute treatment of patients following severe trauma. However, in patients who are at risk of developing PTSD, adminstration of benzodiazepines may have significant detrimental consequences. Benzodiazepines enhance emotional processing and can further escalate the already inflated consolidation of fear memory.[38] Furthermore, the administration of benzodiazepines immediately following injury has been shown to worsen emotional responses to future contextual reminders of trauma, and as such have been proposed to undermine the normal emotional recovery processes in trauma victims.[39] Although this response to benzodiazepine treatment was not demonstrated in children following burn injuries, it is improbable that one would know whether a patient will present with any of the pre-trauma riks factors for PTSD, and it is therefore advisable that clinicians exercise caution when treating patients with acute symptoms of trauma.

Trauma counselling is considered in many scenarios as a logical first tier intervention and, although it has shown clinical benefit in the long-term treatment of established PTSD,[40] controversy remains about whether interventions such as trauma counselling immediately post exposure are appropriate. In fact, previous attempts to prevent progression to psychiatric illness with single session trauma counselling have proved unfruitful (for a full review, see Rose et al. 2003)[41] while it may even be possible that immediate emotional debriefing after the occurence of a traumatic incident can accelerate the onset and exacerbate the severity of PTSD symptomology by interfering with the normal recovery process following trauma.[42]

Chronic pharmacological treatment for patients with established PTSD

Although different trauma aetiologies may significantly influence the response of PTSD symptoms to pharmacotherapy,[11] and

considering that a multitude of compounds have been employed in the treatment of PTSD (see Koek et al. 2016 for a comprehensive review),[11] the present paper will only highlight the mainstay of treatment for recurring PTSD symptoms, i.e. antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics (APs).

SSRIs, e.g. escitalopram, paroxetine, sertraline, and fluvoxamine, have been demonstrated to improve at least three of the DSM-5 specified symptom clusters, viz. re-experiencing, avoidance and hyperarousal.[6] Furthermore, it is advised that antidepressant treatment should continue for at least 12 weeks before a change in treatment strategy is considered. Residual symptoms of PTSD and comorbid psychiatric manifestations, e.g. psychotic episodes, may demonstrate sensitivity to atypical antipsychotics such as risperidone, quetiapine and olanzapine. Moreover, in patients who are refractive to SSRI monotherapy, augmentation strategies that combine both SSRIs and APs, have been found to be effective in at least some investigations.[11]

Summary and key points

The present paper summarised important and valuable aspects of PTSD that need consideration in the approach to and treatment of patients who have been exposed to severe trauma. Importantly, we emphasise that:

- individuals differ with respect to their salutogenic abilities and responses to fear and severe trauma;
- although most individuals will experience trauma to some extent during their lives, certain pre-exposure risk factors exist that may prime some individuals to progress to psychiatric illness, while others remain resilient;
- it is highly unlikely that clinicians will be aware of whether such predisposing risk factors will be present in a patient during the first consultation post-trauma; and
- although certain inferences, such as benzodiazepine treatment and trauma counselling, may be beneficial for the treatment of the acute sequelae of severe trauma, they may have negative cognitive effects in patients who are prone to develop PTSD, and caution needs to be exercised when such inferences are considered.

References

1. Williams SL, Williams DR, Stein DJ, Seedat S, Jackson PB, Moomal H. Multiple Traumatic Events and Psychological Distress:The South Africa Stress and Health Study. J Trauma Stress. 2007;20(5),845-55.
2. Antonovsky A. Health, stress, and coping. San Francisco: Jossey-Bass Publishers; 1979.
3. Wilker S, Elbert T, Kolassa I-T. The downside of strong emotional memories: How human memory-related genes influence the risk for posttraumatic stress disorder – A selective review. Neurobiol Learn Mem. 2014;11:75-86.
4. DiGangi JA, Gomez D, Mendoza L, Jason LA, Keys CB, Koenen KC. Pretrauma risk factors for posttraumatic stress disorder: A systematic review of the literature. Clin Psychol Rev. 2013;33(6):728-44.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American Psychiatric Association: Washington, DC, 2013; Vol 5.
6. Vieweg WV, Julius DA, Fernandez A, Beatty-Brooks M, Hettema J M, Pandurangi AK. Posttraumatic stress disorder: clinical features, pathophysiology, and treatment. Am J Med. 2006;119(5):383-90.
7. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048-60.
8. Bryant RA, Friedman MJ, Spiegel D, Ursano R, Strain J. A review of acute stress disorder in DSM-5. Depress Anxiety. 2011;28(9):802-17.
9. Gordon RP, Brandish EK, Baldwin DS. Anxiety disorders post-traumatic stress disorder and obsessive–compulsive disorder. Medicine. 2016; 44(11):664-71.
10. Helmuth L. Fear and trembling in the Amygdala. Science. 2003;300(5619):568-69.
11. Koek RJ, Schwartz HN, Scully S, Langevin J-P, Spangler S, Korotinsky A, Jou K, Leuchter A. Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future. Prog Neuropsychopharmacol Biol Psychiatry. 2016;70:170-218.
12. Marek R, Strobel C, Bredy TW, Sah P. The amygdala and medial prefrontal cortex: Partners in the fear circuit. J Physiol. 2013; 591(10):2381-91.
13. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. Biol Psychiatry. 2009;66(12):1075-82.
14. McFarlane AC, Barton CA, Yehuda R, Wittert G. Cortisol response to acute trauma and risk of posttraumatic stress disorder. Psychoneuroendocrinology. 2011;36(5):720-7.
15. Delahanty DL, Nugent NR, Christopher NC, Walsh M. Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. Psychoneuroendocrinology. 2005;30(2):121-8.
16. Bryant RA, Marosszeky JE, Crooks J, Gurka JA. Elevated resting heart rate as a predictor of posttraumatic stress disorder after severe traumatic brain injury. Psychosom Med. 2004;66(5):760-1.
17. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry. 2002;51(2):189-92.
18. Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, et al. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry. 2003;54(9):947-9.
19. Nugent NR, Christopher NC, Crow JP, Browne L, Ostrowski S, Delahanty DL. The efficacy of early propranolol administration at reducing PTSD symptoms in pediatric injury patients: A pilot study. J Traum Stress. 2010;23(2):282-7.
20. Stein MB, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: Results from a randomized controlled proof-of-concept trial in physically injured patients. J Trauma Stress. 2007;20(6):923-32.
21. Cohen H, Kaplan Z, Koresh O, Matar MA, Geva AB, Zohar J. Early post-stressor intervention with propranolol is ineffective in preventing posttraumatic stress responses in an animal model for PTSD. Eur Neuropsychopharmacol. 2011;21(3):230-40.
22. McIntyre FL, Gasquoine P. Effect of clonidine on post-traumatic memory deficits. Brain Inj. 1990;4(2):209-11.
23. Morris P, Hopwood M, Maguire K, Norman T, Schweitzer I. Blunted growth hormone response to clonidine in post-traumatic stress disorder. Psychoneuroendocrinology. 2004;29(2):269-78.
24. McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. Ann N Y Acad Sci. 1997;821:437-41.
25. Resnick HS, Yehuda R, Acierno R. Acute post-rape plasma cortisol alcohol use and PTSD symptom profile among recent rape victims. Ann N Y Acad Sci. 1997;821:4336.
26. Yehuda R, Resnick HS, Schmeidler J, Yang RK, Pitman RK. Predictors of cortisol and 3-methoxy-4-hydroxyphenylglycol responses in the acute aftermath of rape. Biol Psychiatry. 1998;43(11):855-9.
27. Yehuda R. Clinical relevance of biologic findings in PTSD. Psychiatr Q. 2002;73(2):123-33.
28. Mouthaan J, Sijbrandij M, Reitsma JB, Luitse JS, Goslings JC, Gersons BP, Olff M. The role of early pharmacotherapy in the development of posttraumatic stress disorder symptoms after traumatic injury: An observational cohort study in consecutive patients. Gen Hosp Psychiatry. 2015;37(3):230-5.
29. Schelling G. Effects of stress hormones on traumatic memory formation and the development of posttraumatic stress disorder in critically ill patients. Neurobiol Learn Mem. 2002;78(3):596-609.
30. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhäusler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry. 2001;50(12):978-85.
31. Schelling G, Stoll C, Kapfhammer HP, Rothenhäusler HB, Krauseneck T, Durst K, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. J Crit Care Med. 1999;27(12):2678-83.
32. Saxe G, Stoddard F, Courtney D, Cunningham K, Chawla N, Sheridan R, et al. Relationship between acute morphine and the course of PTSD in children with burns. J Am Acad Child Adolesc Psychiatry. 2001;40(8):915-921.
33. Stoddard FJ, Sorrentino EA, Ceranoglu TA, Saxe G, Murphy JM, Drake JE, et al. Preliminary evidence for the effects of morphine on posttraumatic stress disorder symptoms in one- to four-year-olds with burns. J Burn Care Res. 2009;30(5):836-43.

34. Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. A Study of the Protective Function of Acute Morphine Administration on Subsequent Posttraumatic Stress Disorder. Biol Psychiatry. 2009;65(5):438-40.
35. Good AJ, Westbrook RF. Effects of a microinjection of morphine into the amygdala on the acquisition and expression of conditioned fear and hypoalgesia in rats. Behav Neurosci. 1995;109(4):631-41.
36. McNally GP, Westbrook RF. Temporally Graded Context-Specific Retrograde Amnesia and its Alleviation by Context Preexposure: Effects of Postconditioning Exposures to Morphine in the Rat. J Exp Psychol Anim Behavr Process. 2003;29(2):130-42.
37. Baldwin DS, Aitchison K, Bateson A, Curran HV, Davies S, Leonard B, et al. Benzodiazepines: Risks and benefits. A reconsideration. J Psychopharmacol. 2013;27(11):967-71.
38. Zohar J, Juven-Wetzler A, Sonnino R, Cwikel-Hamzany S, Balaban E, Cohen H. New insights into secondary prevention in post-traumatic stress disorder. Dialogues Clin Neurosci. 2011;13(3)301-9.
39. Matar MA, Zohar J, Kaplan Z, Cohen H. Alprazolam treatment immediately after stress exposure interferes with the normal HPA-stress response and increases vulnerability to subsequent stress in an animal model of PTSD. Eur Neuropsychopharmacol. 2009;19(4):283-95.
40. Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, Middleton JC, et al. Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. Clin Psychol Rev. 2016;43:128-41.
41. Rose S, Bisson J, Wessely S. A systematic review of single-session psychological interventions ('debriefing') following trauma. Psychother Psychosom. 2003;72(4):17684.
42. Sijbrandij M, Olff M, Reitsma JB, Carlier IV, Gersons BP. Emotional or educational debriefing after psychological trauma: Randomised controlled trial. Br J Psychiatry. August 2006;189:150-5.