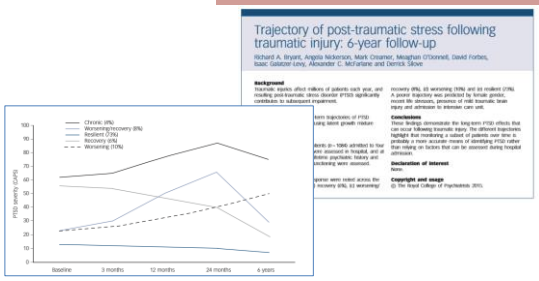
LEIDEN UNIVERSITY MEDICAL CENTER

Neurobiologie en farmacologie van PTSS – update and ontwikkelingen

Prof dr Col Eric Vermetten
Leiden University Medical Center
e.vermetten@lumc.nl

1

Trajectories of posttraumatic stress



Bryant et al., BJP, 2015

2

Trajectories of posttraumatic stress

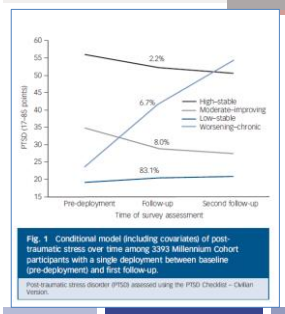


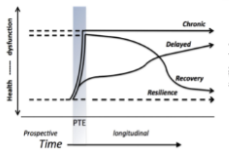
Fig. 1 Conditional model (including covariates) of post-traumatic stress over time among 3393 Millennium Cohort participants with a single deployment between baseline (pre-deployment) and first follow-up.

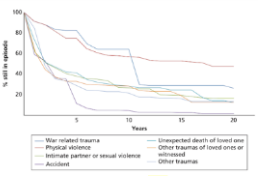
Post-traumatic stress disorder (PTSD) assessed using the PTSD Checklist – Civilian version.

Bonanno et al., BJP, 2012

3

Trajectories and speed of recovery of PTSD cases (by trauma category)

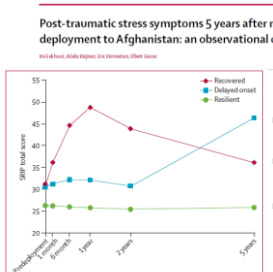




Galatzer Levy et al., Clin Psych Rev, 2018; Kessler et al., PTSD, in Nemeroff and Marmar, 2018

4

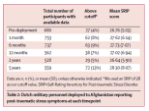
Trajectories of posttraumatic stress: 20 jaar longitudinale studie



Delayed onset 9.4 %

Recovered 5.3%

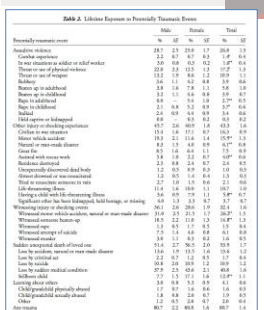
Resilient 85.2%

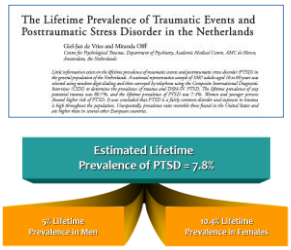


Eekhout et al., Lancet Psychiatry, 2016

5

Voorkomen van schokkende gebeurtenissen





6

Herhaling - wat is PTSS in 2019?

1. *Angststoornis → Trauma en stressor gerelateerde stoornis*
2. Etiologische stoornis
3. Met subjectieve klachten en symptoomscores op
   - Intrusies/herbeleving
   - Vermijding/verdoving
   - Cognities
   - Hyperarousal/prikkelbaarheid
4. Impact op functionele gebieden
   - Stress regulatie
   - Geheugen en cognitie
   - Emotionele regulatie
   - Dissociatie (derealisatie en depersonalizatie)

7

PTSD in DSM5 - CAPS

Criterion*	Description	Specific examples
Criterion A	Exposure to stressor	• Direct exposure • Witnessing trauma • Learning of a trauma • Repeat or extreme indirect exposure to aversive details
Criterion B	Intrusion symptoms	• Recurrent memories • Traumatic nightmares • Dissociative reactions (flashbacks) • Psychological distress at traumatic reminders • Marked physiological reactivity to reminders
Criterion C	Persistent avoidance	• Trauma-related thoughts or feelings • Trauma-related external reminders such as people, places or activities
Criterion D	Negative alterations in cognitions and mood	• Dissociative amnesia • Persistent negative beliefs and expectations • Persistent distorted blame of self or others for causing trauma • Negative trauma-related emotions: fear, horror, guilt, shame and anger • Decreased interest in activities • Detachment or estrangement from others • Inability to experience positive emotions
Criterion E	Alterations in arousal and reactivity	• Irritable and aggressive behaviour • Self-destructive and reckless behaviour • Hypervigilance • Exaggerated startle • Problems concentrating • Sleep disturbance
Criterion F	Duration	Must experience criteria B, C, D and E for >1 month
Criterion G	Functional significance	Impairment in social, occupational or other domains
Criterion H	Exclusion	Not attributable to medication, substance use or other illness
Subtypes	• Dissociative subtype: used when depersonalization and derealization occur in tandem with other symptoms described above. • Delayed subtype: used to describe the emergence of symptoms following a period post trauma in which symptoms were not present or were present at a subthreshold level.	

Development and Evaluation of the Dutch Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

8

Self Assessments

- ***Vragenlijst naar Belastende Ervaringen (VBE)*** *(Traumatic Experiences Questionnaire, TEC) is vooral gericht op het bepalen van type II verwaarlozing en mishandeling (Nijenhuis, e.a. 1998).*
- ***De Trauma Screening Questionnaire (TSQ)*** *(Oorspronkelijke versie: Brewin e.a. 2002*
- **De Impact of Event Scale (IES) of Schokverwerkingslijst (SVL)** *(Oorspronkelijke versie: Horowitz, Wilner en Alvarez (1979); Nederlands vertaling: Brom en Kleber (1985) De lijst is vrij beschikbaar via Kleber*
- **De Impact of Event Scale Revised (IES-R) of Schokverwerkingslijst 22 of R (SVL-22, SVL-R)** *(Oorspronkelijke versie: Weiss en Marmar, 1997*
- **Davidson Trauma Scale (DTS)** *(Oorspronkelijke versie: Meltzer-Brody, Churchill, & Davidson, 1999*
- **Self-Rating Scale for PTSD (SRS-PTSD)** *(Oorspronkelijke versie: Structured Interview for PTSD, SI-PTSD, Davidson e.a. 1989; Nederlands vertaling:* Carlier, Lamberts, Van Uchelen & Gersons, 1998
- **PSS-SR** *(Oorspronkelijke versie: Foa, Riggs, Dancu, & Rothbaum,1993*
- **Harvard Trauma Questionnaire (HTQ)** *(Oorspronkelijke versie: Mollica et al., 1992*
- **Zelfinventarisatielijst Posttraumatische Stressstoornis (ZIL, Self-rating Inventory for Posttraumatic Stress Disorder, SRIP)** *(Oorspronkelijke versie: Hovens, van der Ploeg, Bramsen, Klaarenbeek, Schreuder, & Rivero, 1994*

9

Assessments

Algemene interviews

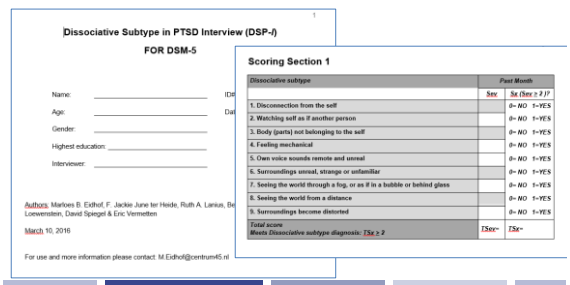
- Structured Clinician Interview for DSM-IVDiagnostic Interview Schedule (DIS; Robins e.a., 1981)
- Diagnostic Interview Schedule (DIS; Robins e.a., 1981)
- De MINI-International Neuropsychiatric Interview (MINI, Sheehan et al.,
- 1998).
- Composite International Diagnostic Interview (WHO, CIDI, 1990).

Specifieke op PTSS gerichte gestructureerde interviews

- Clinician Administered PTSD Symptom scale (CAPS; Blake e.a., 1995),
- The Structured Interview for PTSD (SI-PTSD; Davidson et al, 1989),
- PTSD Interview (PTSD-I; Watson e.a., 1991),
- PTSD Symptom Scale Interview (PSS-I; Foa e.a., 1993).
- Treatment-Outcome Posttraumatic Stress Disorder Scale (TOP-8; Davidson & Colket, 1997),
- Short Posttraumatic Stress Disorder Rating Interview (SPRINT; Connor & Davidson 2001).

10

DSP-I



Dissociative Subtype in PTSD Interview (DSP-I)

FOR DSM-5

Name: _____ ID#

Age: _____ Date

Gender: _____

Highest education: _____

Interviewer: _____

Authors: Marloes B. Eidhof, F. Jackie June ter Heide, Ruth A. Lanius, Be Lanius, Lanius, Loewenstein, David Spiegel & Eric Vermetten

March 10, 2016

For use and more information please contact: M.Eidhof@centrum45.nl

Scoring Section 1

Dissociative subtype	Past Month	
	Sev	Sx (Sev > 3)?
1. Disconnection from the self		0= NO 1=YES
2. Watching self as if another person		0= NO 1=YES
3. Body (parts) not belonging to the self		0= NO 1=YES
4. Feeling mechanical		0= NO 1=YES
5. Own voice sounds remote and unreal		0= NO 1=YES
6. Surroundings unreal, strange or unfamiliar		0= NO 1=YES
7. Seeing the world through a fog, or as if in a bubble or behind glass		0= NO 1=YES
8. Seeing the world from a distance		0= NO 1=YES
9. Surroundings become distorted		0= NO 1=YES
Total score Meets Dissociative subtype diagnosis: TSx ≥ 2	TSev=	TSx=

11

Risicofactoren voor PTSS

Timepoint	Risk factor	Protective factor
BEFORE	• Psychiatric history • Childhood abuse • Family psychiatric history • Earlier stressful life events • Prior (repeated) exposure to critical incidents at work	• Training and preparation to deal with threats or dangers • Pre-existing personality characteristics such as low neuroticism, hardiness
DURING	• Level of exposure • Experienced life threat • Physical injury • Disasters caused by a malicious intent/human failure • Peri-traumatic dissociation	
AFTER	• Continued media exposure • Legal procedures • Routine work environment stress • Blaming others, inducing guilt • Wrong jokes	• Perceived support from family, friends, colleagues • Perceived support

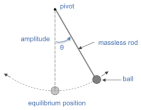
Alexander & Klein, 2009; Bonanno et al., 2010; Breslau, 1998; Brewin', Andrews, & Valentine, 2000; Heinrichs, Wagner, Schoch, Soravia, Hellhammer, & Ehlert, 2005; Iversen et al., 2008; Kleber & Van der Velden, 2003; Lowell et al., 2013; Marmar et al., 2006; McFarlane & Bryant, 2007; Ozer, Best, Lipsey, & Weiss, 2003; Pietrzak et al., 2014; Van der Ploeg, & Kleber, 2003; Wagner, Schoch, Soravia, Hellhammer, & Ehlert, 2005; Weisaeth & Tonnessen, 2003.

12

PTSS representeert een specifiek fenotype

'PTSD representeert een specifiek fenotype dat is geassocieerd met een onvermogen om te herstellen van de normale effecten van een schokkende gebeurtenis' (Yehuda and Ledoux, 2007)

zowel in cognities als in psychofysiologie



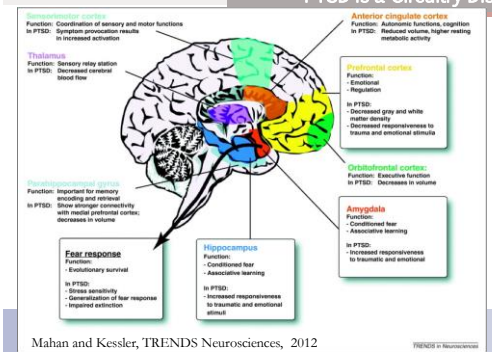
13

Vier decennia van PTSS sinds introductie in DSM-III

Decennium	Discipline/domein	Ontwikkeling
Eerste decennium 1980-1990	Epidemiologie	- 'Ruwe' prevalentie van de stoornis
	Biologie	-Validatie van de stoornis; relatie met modellen van experimentele stress inductie
	Psychotherapie	- Gericht op stress reductie, klassieke psychotherapie, nog weinig gecontroleerde studies
	Farmacotherapie	- Experimentele open label studies
Tweede decennium 1990-2000	Epidemiologie	- State-of the art epidemiologische studies, (lifetime prevalentie 8%)
	Biologie	- Toename interdisciplinaire interesse - Cross-sectionele studies, mn met structurele beeldvorming met MRI **'decennium van de hippocampus'**
	Psychotherapie	- Ontwikkeling en opkomst van CGT, met trauma focus, exposure gericht
	Farmacotherapie	- SSRI (paroxetine, sertraline)
Derde decennium 2000-2010	Epidemiologie	- Meer specifieke cohort studies, discrete focus groepen
	Biologie	- Toename in kennis neuronale circuits, genetica, toegenomen resolutie beeldvormend onderzoek, opkomst fMRI: **'decennium van de amygdala'**
	Psychotherapie	- Introductie en opkomst EMDR
	Farmacotherapie	- Nieuwe middelen naast SSRIs, waaronder antipsychotica, β blokkers (propranolol), prazosine
Vierde decennium 2010-		- Longitudinale cohortstudies - Rol van trauma in vroege levensfase - Toegenomen specificiteit in diagnostiek - Primaire preventie - Therapeutische toepassingen met internet **'decennium van de prefrontale cortex'?**

14

PTSD is a Circuitry Disoreder



Mahan and Kessler, TRENDS Neurosciences, 2012

15

EB Therapies

Cognitive Therapy (Ehlers)	Narratieve Exposure Therapy (Elbert)	Prolonged Exposure (Foa)	Brief Eclectic Therapy PTSD (Gersons)	Cognitive Processing Therapy (Resick)	EMDR Therapy (Shapiro)
(1) case formulation, (2) updating trauma memories, (3) discrimination triggers, (4) dropping unhelpful behaviors, (5) reclaiming life	Chronological construction of life story: (1) Empathic understanding. (2) Sensory memories, cognitions, emotions, and physiological responses. (3) Focus on reliving traumatic experiences	Emotional processing therapy (1) Imaginal exposure (2) 20 minutes processing (3) In vivo exposure	(1) psychoeducation; (2) imaginary exposure preceded by relaxation exercises, (3) writing tasks (4) meaning, (5) a farewell ritual	(1) education about different ways to think about problems, past or present. (2) difference between talking about *why* something happened and reexperiencing the memory of the trauma in *graphic* detail	(1) unprocessed memories of adverse life experiences, are stored inappropriately in episodic memory and underlie current dysfunctional responses (2) Dual task processing to restore memories by 30 s exposures, paired with sequential sets of bilateral eye movements

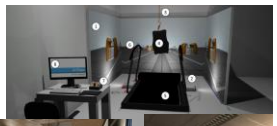
16

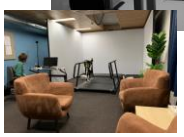
Trends

- Van 1x/wk naar HIT
- Combinaties van verbal - non verbaal, PMT, dagbehandeling
- Therapeutische mixes, blending
- Empowerment
- Gamification
- Body/Min orientation – Yoga, mindfullness, ACT
- Immersive realities, e.g. VR/HMD
- Remote therapies, web, internet - assisted therapies
- Nieuwe medicaties
- Medicatie ondersteunde therapie

17

3MDR – personalisation in structured exposure

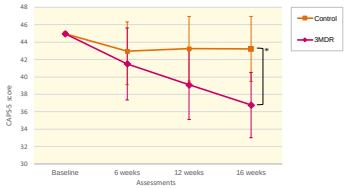




Lack of improvement
Drop out
Resistance
Motion
Reconsolidation
Empowerment
Cognitive avoidance
International collaboration (NETH, UK, US, CAN, ISR)

18

3MDR



Difference baseline-end: significant decreased in PTSD symptoms in 3MDR complared to control ($F=6.43$, $p=.016$).

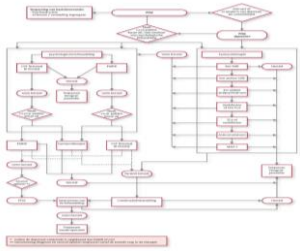
- Large effect (cohen's d = 0.83)
- 4 previous treatments did not result in effect

19

3MDR Global

20

Algoritme



21

Expert Consensus Guideline – 1999	First choise: SSRI's, venlafaxine, & nefazodone Second echelon: TCAs
Psychopharmacology Algorithm Project at Harvard South Shore Program – 1999	Early use of hypnotic agents for sleep; trazodone first choice, followed by SSRI for persistent PTSD symptoms
UK NICE – 2005	SSRI's bij PTSS revised → more modest effect demonstrated Psychotherapy as first line treratment
Canadian Clinical Practice Guideline – 2005	Eerste choise: one choise from fluoxetine, paroxetine, sertraline, & venlafaxine XR Second echelon: mirtazapine, fluvoxamine, phenelzine, moclobemide, plus adjuvant olanzapine of risperidone
International Psychopharmacology Algoritm Project – 2005	Once diagnosis of PTSD is made: SSRI first choise, followed venlafaxine & mirtazapine
ISTSS- 2008	SSRI's recommended as first choise intervention, followed up with addition with atypical antipsychotics Prazosine considered "promising"
APA guideline - 2009	Concludes new studies suggest SSRI's are less effective than previously thought Prazosine considered as promising option for sleep disturbance
VA/DoD Clinical Practice guideline for PTSD- 2010	Strongest recommendation SSRI's and SNRIs but give advantage to prazosine, mirtazapine, and adjuvant atypical antipsychotics Prazosine for nightmares as adjuvant treatment when trazodone and other hypnotics are not sufficiently effective

22

Nabilone, synthetisch cannabinoid (Jetly et al., 2014)

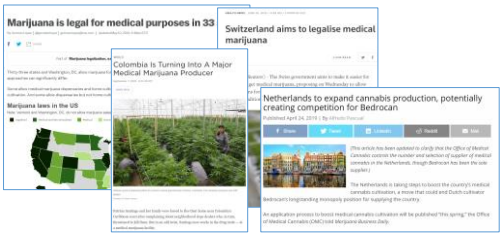
The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study

Rakesh Jetly[a,*], Alexandra Heber[a], George Fraser[b], Denis Boisvert[b]

- Klinische trial, nachtmerries
- Double blind cross over
- Synthetisch
- Vermindering nachtmerries
- Medicatie werd goed getolereerd

23

Decriminaliseren em medicaliseren



https://www.youtube.com/watch?list=PLY8Je3lLWYrfhFvH2WBJbYFns_L_ZBuuj&v=hR5KZMMqWII

24

MDMA

Mithoefer et al., Lancet Psychiatry, 2018

PROGRESS in Neurology and Psychiatry

Opinion MDMA for PTSD

Could MDMA be useful in the treatment of post-traumatic stress disorder?

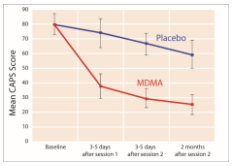
Ben Sessa *BSc, MRCPsych*

In recent studies, 3,4-methylenedioxymethylamphetamine (MDMA) has shown promise in the treatment of post-traumatic stress disorder (PTSD) as an adjunct to post-trauma psychological therapy. However, because of historical associations with its use as the recreational drug ecstasy, MDMA research remains a controversial subject. Dr Sessa discusses these controversies and describes a UK-based MDMA/PTSD currently in development.

- Relatief kortwerkend, geen afhankelijkheid; vermindert depressieve gevoelens, verhoogt verbondenheid, engagement – bereidheid voor psychotherapie, 'gedachtenvrij'; medicatie werd goed getolereerd

25

MDMA



Time*Group Interaction $p=0.015$

26

MDMA

Six Completed Phase 2 Studies
MDMA-Assisted Psychotherapy for PTSD

	Study		Sample (N)	Dose Comparison	
	Location	Code	Intent to Treat	Active	Comparator
Published J. Psychopharm	Charleston, SC	MP-1	N=23	125 mg	0 mg
	Switzerland	MP-2	N=14	125 mg	25 mg
Published Lancet Psychiatry	Vancouver, BC	MP-4	N=6	125 mg	0 mg
	Charleston, SC	MP-8	N=26	75 or 125 mg	30 mg
	Tel Aviv, Israel	MP-9	N=8	125 mg	25 mg
Published J. Psychopharm	Boulder, CO	MP-12	N=26	100 or 125 mg	40 mg
	All Studies		Intent to Treat N=105	Active (75-125 mg) vs. Comparator (0-40 mg)	

27

Tenslotte

PTSS is een dynamische stoornis
Duidelijke neurobiologie
Therapie in ontwikkeling – psychotherapie, en farmacotherapie
Inrichting GGZ?
Opleiding
Samenwerkingen interdisciplinair +++

28

Tenslotte

LUMC, arq, Ministry of Defence, UVH, TNO innovation for life, Erasmus Universiteit Rotterdam, University of Amsterdam, UM, TU Delft, University Medical Center Utrecht, NWO, amc, PsyQ, interapy, Radboud Universiteit, Radboudumc, umcg, Kempenhaeghe Expertisecentrum voor epilepsie, slaapgeneeskunde en neurocognitie, Maastricht University

29

Vragen:
e.vermetten@lumc.nl

30