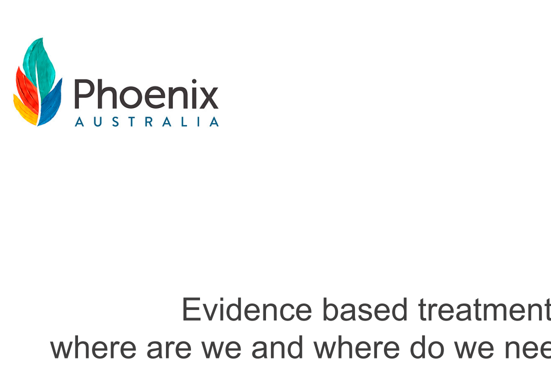

Evidence based treatment for PTSD:
where are we and where do we need to go in the future

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Overview

- **Current international PTSD treatment guidelines**
  - Psychological
  - Pharmacological
  - Alternate approaches
- **Where do we need to go**
  - Augmentation
  - Emerging and novel interventions
  - Dealing with comorbidity
  - Harnessing technology
  - Personalised medicine
  - Improving implementation…(not addressed here – major issue)

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For starters – what do the evidence based international PTSD guidelines say?

Remembering guidelines are:

- "Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Field & Lohr, 1990)
- Based on systematic review of the evidence
- Absence of evidence is not evidence of absence
- Support or recommend, not mandate

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Key treatment recommendations from the International Society for Traumatic Stress Studies PTSD Guidelines

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Psychological interventions ***for adults with PTSD***

Now an accumulated body of evidence
(over 230 high quality studies)
STRONG RECOMMENDATIONS FOR

- **Trauma-focused CBT (TF-CBT)**
- **Prolonged Exposure (PE)**
- **Cognitive Processing Therapy (CPT)**
- **Trauma-focused Cognitive Therapy (CT)**
- **Eye Movement and Desensitization Reprocessing (EMDR)**

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What does TFCBT treatment involve?

1. Assist the person to *confront their memories* in a gradual, safe and supportive manner

2. Assist the person to gradually *confront the places and activities* they are avoiding in order to reclaim their lives (address experiential avoidance)

3. Assist the person to *address the thoughts and interpretations* of what happened and what it means about themselves, others or the world that are blocking recovery (cognitive therapy/cognitive processing therapy, post-exposure processing)

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Interventions ***for adults with PTSD***

Next level - STANDARD RECOMMENDATIONS FOR

- **Guided internet-based TF-CBT**
- **Narrative exposure therapy (NET)**
- **Present-centred therapy (PCT)**

  Targets daily challenges associated with PTSD
- **TF-CBT (group)**
- **CBT**

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Pharmacological interventions for adults with PTSD?

Now approx. 50 high quality studies

Recommended interventions (though as stated with lower effect)

- **Serotonin reuptake inhibitors (SSRIs – Paroxetine, Fluoxetine, Sertraline)**
- **Serotonin noradrenaline reuptake inhibitor (SNRI – Venlafaxine)**

Interventions with Emerging Evidence:

- **Quetiapine**

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What are other considerations around pharmacological interventions in relation to psychological interventions (Aust NHMRC guidelines)

Conditional recommendation for use, when:

- The person is unwilling/unable to engage in or access recommended psychological therapy
- The person has a comorbid condition or associated symptoms (e.g., clinically significant depression and high levels of dissociation) where SSRIs are indicated
- The person's circumstances are not sufficiently stable to commence recommended psychological therapy (e.g., family violence)
- The person has not gained significant benefit from recommended psychological therapy
- There is a significant wait time before psychological treatment is available

Noteworthy unclear from psychological treatment trials, how many were on base levels of stabilizing medication –remains a question of interest

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Universal interventions ***for all exposed to trauma***

After a potentially traumatic event

- **Routine psychological debriefing is NOT RECOMMENDED**

- The best approach to helping people following a PTE is to offer information, emotional support, and practical assistance
- Watchful waiting
- Actions consistent with psychological first aid (PFA)

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Indicated interventions ***for those within the first three months***

Intervention with Emerging Evidence - ***Hydrocortisone*** within the first three months of a traumatic event has emerging evidence of efficacy for the prevention of PTSD symptoms in adults.

Insufficient Evidence to Recommend - There is insufficient evidence to recommend ***Docosahexaenoic Acid, Escitalopram, Gabapentin, Oxytocin*** or ***Propranolol*** within the first three months of a traumatic event for the prevention or treatment of PTSD symptoms in adults.

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Non-psychological and non-pharmacological treatments (over 30 RCTs)

- Increasing interest in a range of non-psychological and non-pharmacological interventions for people with PTSD
- Interventions with emerging evidence:
  - Acupuncture
  - Neurofeedback
  - Saikokeishikankyoto (SKK)
  - Somatic Experiencing
  - Transcranial Magnetic Stimulation
  - Yoga
- Will consider some of these in more detail

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BUT how effective are these even first line treatments?

Depends on benchmark definitions of improvement

No single authoritative study

However approximately….

- One third, dramatic improvement, no longer meeting the criteria for a diagnosis
- One third large reductions, although still with moderate symptoms
- One third, little if any meaningful change

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BUT how effective are these even first line treatments?

And in those who improve…

- Moderate improvements in associated problems like depression and anxiety
- Moderate improvements in relationships and quality of life

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Augmentation

- Potential benefit of an additional treatment (psychological, pharmacological or other) with the goal of improving the outcomes of a first-line treatment and/or preparing an individual for a first-line treatment
  - Pharmacotherapy on pharmacotherapy
    - agents with some evidence Prazosin, Risperidone (Bisson et al., 2020)
  - Psychotherapy and pharmacotherapy
    - VA/DoD guidelines – insufficient evidence for addition of medication for psychotherapy non responders
    - No current compelling evidence for addition of SSRIs to psychotherapy (Burton…Rothbaum., 2020)

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Augmentation

- Systematic review of 34 augmentation RCTs (Metcalf et al., 2020) that added an intervention to a first line intervention found:
  - **Ceiling effects-** 86% of the studies reported no significant additional effect of the augmentation intervention on PTSD symptoms at post treatment relative to the first-line treatment
  - However….

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Augmentation- What does work

- Promising augmentation methods added to psychological interventions (PE/CPT) were
  - rTBS
  - Acupuncture
  - Exercise
- Possible reasons?
  - Require little to no cognitive effort, which matters when you pair it with something as cognitively taxing as PE
  - Reduce hyperarousal, which matters when the first-line treatment can be distressing
  - Completely different mechanisms to PE (avoid ceiling effects)

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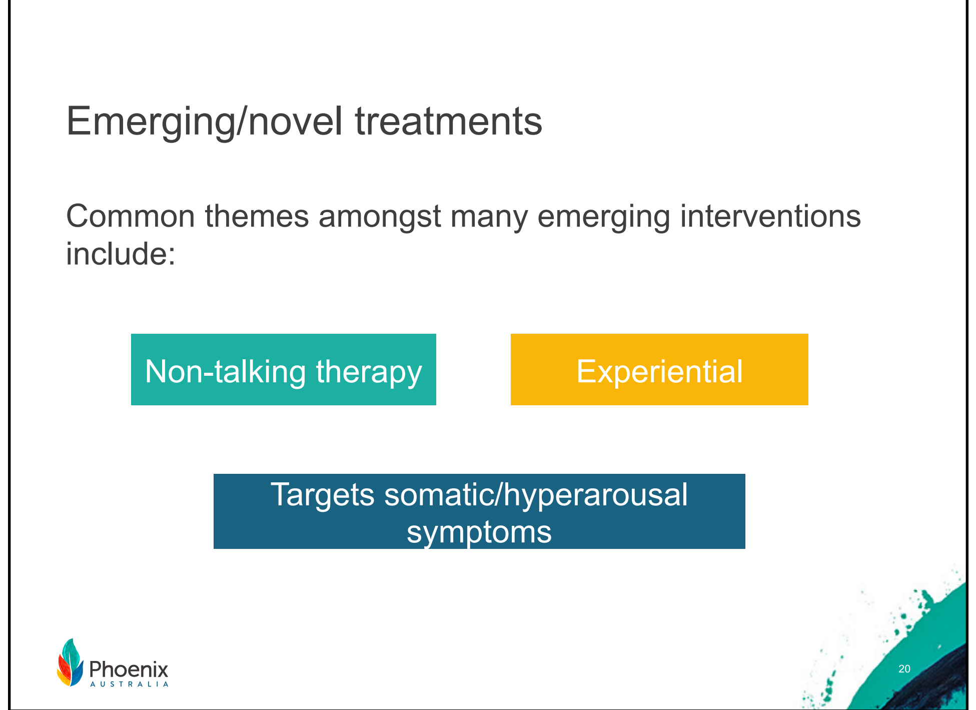

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Promising emerging complementary or alterative interventions

All these interventions had at least one high quality RCT indicating promising results	
1.	Acupuncture
2.	Mantra-based meditation and mindfulness
3.	Yoga

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Pharmacotherapy in PTSD

A Consensus Statement of the PTSD Psychopharmacology Working Group,
Biological Psychiatry, 2017

- Although evidence-based psychological treatments have come a long way, there remains a crisis in pharmacotherapy treatment for PTSD
- Only SSRIs/SNRIs are approved
- Reduce symptoms but do not remit PTSD
- No novel pharmacology approaches for past 20 years

Table 6. Top Therapeutic Targets for PTSD From Expert Group (*N* = 27)

Target	Score
NMDA Receptor Antagonists	78
Cannabinoid Receptor Modulators	70
Glucocorticoid Receptor Agonists	58
Non-SRI Antidepressants	50
Opioid Receptor Agonists	25
Alpha-1 Adrenergic Receptor Antagonists	21
$5HT_2$-D_2 Receptor Antagonist (Other Than Risperidone)	20
Riluzole	18
Alpha-2 Adrenergic Receptor Agonists	18
NPY Receptor Modulators	10
Glucocorticoid Low-Activity Partial Agonists And/Or Antagonist	10
Orexin Receptor Antagonists	9
NMDA Receptor Coagonists	9
Anticonvulsants	8
D_2 Receptor Agonists	8

D_2, dopamine type 2; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder; SRI, serotonin reuptake inhibitor; 5-HT_2, 5-hydroxytryptamine-2.

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Table 7. Recommendations

- The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority.
- There is a need to increase the number of early phase clinical trials through novel collaborations among government, industry, and academia.
- There is a need to develop new trial designs and/or methodologies specifically in the area of PTSD psychopharmacology trials.
- Foundational studies are required to inform the optimal prescription of commonly prescribed medications for the treatment of PTSD.
- The development of a psychopharmacology clinical trials workforce and infrastructure for PTSD would advance the goal of increasing clinical trials in this area.
- Studies exploring the pathophysiology of PTSD will be critical to inform the rational development of novel pharmacologic interventions.
- There is a need to continue to invest in initiatives in translational neuroscience to enhance the expansion of the pipeline of new PTSD pharmacotherapeutics.

PTSD, posttraumatic stress disorder.

A Consensus Statement of the PTSD Psychopharmacology Working Group, *Biological Psychiatry,* 2017

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Hallucinogens and novel agents

- Emerging evidence for 2 classes of “hallucinogen” interventions in mental health and to some degree PTSD
  - Psychedelics acting through the 5-HT system (e.g. LSD, psilocybin)
  - Dissociative anasthetics acting through the glutamatergic system (i.e., ketamine)
- Entactogens - eg MDMA
- Cannabinoids
- Considered both as adjunctive to psychological treatments or stand-alone treatments

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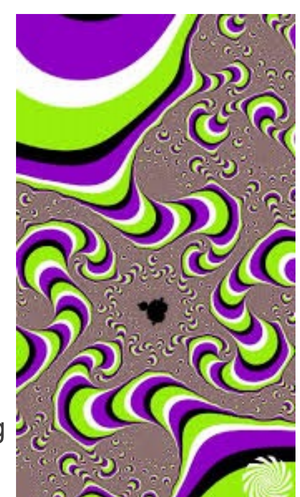
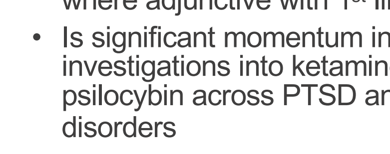
Emerging/novel treatments



- MDMA as an adjunctive treatment to psychotherapy has the strongest evidence (Varker et al., 2020)
  - Prosocial effects, which can promote a stronger therapeutic alliance and potentially decrease interpersonal alienation, which can contribute to trauma survivors' experiences of isolation
  - Adjunctive with non directive psychotherapy – question about testing where adjunctive with 1st line
  - Is significant momentum in investigations into ketamine and psilocybin across PTSD and other disorders



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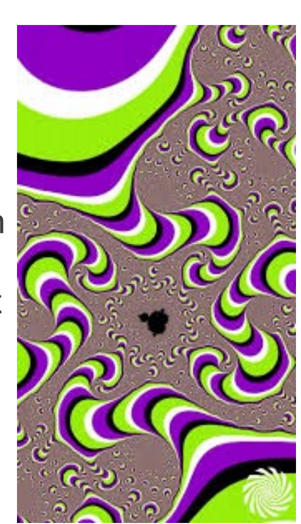
Emerging/novel treatments



- Emerging evidence for neuromodulation therapies
  - transcranial magnetic stimulation (TMS), theta burst stimulation (TBS); transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS)
- Adjunctive to psychological treatments
- Stand-alone treatments
- Still emerging

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Comorbidity - Transdiagnostic interventions & treatment sequencing

- Comorbidity is the rule rather than the exception:
  - The vast majority of individuals with PTSD reported at least one comorbid disorder, with the average being two additional diagnoses
  - Comorbidity also through associated features such as anger, guilt, shame, dissociation, suicidality
  - Current recommended treatments often insufficiently address co-morbidity or comorbidity interferes with treatment effectiveness
- Addressing comorbidity directly –what do we know about EBTs for association disorders and problems
- What do we know about co-delivery (COPE for SUD and PTSD) and then of the sequencing of treatment to optimise treatment effects
  - Sleep and PTSD; anger and PTSD,
- Transdiagnostic interventions

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Addressing co-morbidity

Targeted treatment of associated constructs (anger, sleep, pain, shame, guilt)

- Comorbid can limit treatment effectiveness in veterans
  - triad of dissociation, guilt and depression (Phelps et al., 2017)
  - anger and aggression (Forbes et al., 2011)
- Potential to intervene early in targeting risk related aggression to render TF treatment "safe"
- Actively addressing residual sleep problems, presenting otherwise as risk for subsequent relapse (Kartal et al., 2021)
- PTSD and physical health comorbidity including pain -needs attention

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Transdiagnostic interventions and addressing comorbidity

- Trans diagnostic psychological therapy approaches target PTSD and co-morbid disorder more efficiently and effectively than single protocols
  - Initial pilot study found Unified Protocol (Barlow) was effective in the treatment of PTSD (O'Donnell et al., 2020)
  - UP is a trans-diagnostic, emotion-focused CBT protocol
  - UP targets a number of transdiagnostic mechanisms which fall under the overarching umbrella of emotion regulation, including:
    - emotional awareness
    - emotion regulation flexibility,
    - addressing emotional avoidance
    - interoceptive and situational exposure

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Addressing co-morbidity

Increased understanding and awareness of moral injury (Litz et al., 2012) – not PTSD but can be associated with PTSD

- Psychological state that arises from events which involve "*perpetuating, failing to prevent, bearing witness to, or learning about acts that transgress deeply held moral beliefs and expectations*"
- Shame, guilt, loss of trust, self-depreciation, anger, alcohol abuse, impaired psychosocial functioning, relationship difficulties, suicidal ideation and desire for self-harm
- Often not addressed in traditional treatments (PE or CPT)
- Exploration of broader psycho-social-spiritual interventions (Williamson et al., Lancet Psychiatry 2021)

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Complex PTSD (ICD-11) & treatment

- PTSD symptoms of Re-experiencing; Avoidance; & Sense of current threat
- Plus Disturbances of Self Organisation (DSO): Affective dysregulation; Negative self concept & Difficulty in forming and maintaining interpersonal relationships
- Populations exposed to sustained interpersonal trauma (childhood abuse, domestic violence, combat veterans, torture and genocide survivors)
- Most evaluated intervention is Skills training in affect and interpersonal regulation (STAIR) includes sometimes with PE element (Cloitre et al., 2000)
  - Emotional awareness, emotional regulation, distress tolerance, positive activities, and interpersonal skills training
- Data very promising, from studies of populations exposure to trauma consistent with exposure of above
- Studies underway testing treatments using the ICD-11 criteria upfront on assessment - will be included in international guidelines as this data comes through

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Harnessing technology

- Can we increase treatment delivery options to make them more engaging, accessible, and acceptable?
  - Virtual reality has become a viable modality for exposure-based therapies (Rothbaum et al)
  - Telehealth modalities help overcome barriers including distance, travel time and cost, privacy concerns, lack of specialty or mental health providers, and perceived stigma
  - Wearables, sensors, smartphones and other passively or low-burden collected data provides opportunity for both a rich form of data as well as opportunity for intervention

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Personalised medicine

- More than 50 years ago, the field began asking "which treatment, for whom?"
  - Currently, clinicians personalise treatment based on clinical experience- is there a better, data informed way?
- Many *individual* predictors have been measured to predict treatment response to a given treatment
- Need machine learning approaches to refine and integrate a *composite predictor* of treatment response that encompasses multiplicity of the following:

Biological/physiological | Psychological | Cognitive/affective

- Ultimate goal is to conduct a pre-treatment workup that meaningfully predicts *which treatment, for whom* to reduce dropout and non response and maximize effectiveness

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Conclusions

- We have effective PTSD treatments but no silver bullet
- Need to enhance intervention effectiveness:
  - Particularly for the 30% who don't respond
  - Augment what currently works to improve effectiveness for those not gaining full benefit - addressing key mechanisms and barriers to recovery
  - Trial innovative approaches using advances in neuroscience and pharmacology and alternative approaches
  - Harnessing new technology
  - Improve personalisation and matching of treatment
  - Advance early intervention and engagement

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