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)
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

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

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)
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

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
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

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)
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
  - Saikoikeishikankyo (SKK)
  - Somatic Experiencing
  - Transcranial Magnetic Stimulation
  - Yoga
- Will consider some of these in more detail
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

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
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)
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....

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)
Where we need to go: The roadmap

- Augmentation
- Personalised medicine
- Emerging/novel interventions
- Addressing co-morbidity
- Harnessing technology

Common themes amongst many emerging interventions include:

- Non-talking therapy
- Experiential
- Targets somatic/hyperarousal symptoms
Promising emerging complementary or alternative interventions

All these interventions had at least one high quality RCT indicating promising results

1. Acupuncture
2. Mantra-based meditation and mindfulness
3. Yoga

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)

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<th>Target</th>
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<tr>
<td>NMDA Receptor Antagonists</td>
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<td>Cannabinoid Receptor Modulators</td>
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<td>Glucocorticoid Receptor Agonists</td>
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<td>Non-SRI Antidepressants</td>
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<tr>
<td>D2 Receptor Agonists</td>
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</table>

D2, dopamine type 2; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder; SRI, serotonin reuptake inhibitor; 5-HET, 5-hydroxytryptamine-2.
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 anesthetics acting through the glutamatergic system (i.e., ketamine)

- Entactogens - eg MDMA

- Cannabinoids

- Considered both as adjunctive to psychological treatments or stand-alone treatments

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.

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

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
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 comorbidity 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
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

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
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)

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
Where we need to go: The roadmap

- Augmentation
- Personalised medicine
- Emerging/novel interventions
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- Harnessing technology

**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
Where we need to go: The roadmap

Augmentation

Personalised medicine

Harnessing technology

Addressing co-morbidity

Emerging/novel interventions

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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
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