Neurobiology of PTSD and Medications

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Synaptic Neural Transmission

Axon of Sending Neuron

Synapse

Dendrite of Receiving Neuron
The Amygdala in PTSD

- Receives information about external stimuli
- Determines significance of external stimuli
- Significance triggers emotional responses including “fight, flight or freezing”

The Amygdala in PTSD

- Responses triggered lead to alterations in stress hormones and catecholamines
- Influenced by hippocampus and medial prefrontal cortex in determining the final fear response
1. In PTSD there is an Xs activation of the amygdala by stimuli perceived to be threatening.

2. This leads to outputs to a number of brain areas that mediate:
   - memory consolidation of emotional events and spatial learning (hippocampus);
   - memory of emotional events and choices (OFC);
   - autonomic and fear reactions (LC, Thalamus; and hypothalamus);
   - instrumental approach or avoidance behaviour (dorsal & ventral striatum). (striatum - a striped mass of white and grey matter located in front of the thalamus in each cerebral hemisphere; consists of the caudate nucleus and the lenticular nucleus)

3. In PTSD the normal checks and balances on amygdala activation have been impaired, so that the restraining influence of the medial PFC (PFC especially the anterior cingulate gyrus and OFC) is severely disrupted.

4. Disinhibition of the amygdala produces a vicious spiral of recurrent fear conditioning where with ambiguous stimuli are more likely to be appraised as threatening. Mechanisms for extinguishing such responses are nullified and key limbic nuclei are sensitised, thereby lowering the threshold for fearful reactivity.

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**Neurobiology of PTSD**

- PTSD represents a failure of medial prefrontal/anterior cingulate networks to regulate amygdala activity resulting in hyperreactivity to threat
Patho Physiology of PTSD
Systems involved:

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Patho Physiology of PTSD

Systems involved:
• Glutamate – gamma amino butyric acid (GABA)
• Nor epinephrine (Nor Adrenaline) (NA)
• Neuro peptide Y (NPY)
• 5-Hydroxytryptamine (5HT) serotonin
• HPA-Axis

Others: dopamine, opiates, thyroid hormones

Methodology of research:
Mostly Pre clinical studies including:

• Fear Conditioning
• Stress sensitisation
• Stress related hippocampal dysfunction
• Altered corpus callosum development
• Amygdala hyper responsivity
• Stress related pre frontal cortical (PFC) impairment
• Over consolidation of memory for traumatic events
Consolidation and Reconsolidation of Memory

Animal and some human studies

- Short term memory unstable until consolidated
  - A few hour window of intervention opportunity following traumatic events
- Memory retrieval leads to unstable memory
  - A few hours window for reconsolidation blockade

Memory consolidation research

Preventing the return of fear in humans using reconsolidation update mechanisms
Daniela Schiller1,2, Marie-H. Monfils1,3, Candace M. Raio2, David C. Johnson2, Joseph E. LeDoux1 & Elizabeth A. Phelps1,2 (Nature 2010)

Recent research on changing fears has examined targeting reconsolidation. During reconsolidation, stored information is rendered labile after being retrieved. Pharmacological manipulations at this stage result in an inability to retrieve the memories at later times, suggesting that they are erased or persistently inhibited. Unfortunately, the use of these pharmacological manipulations in humans can be problematic. Here we introduce a non-invasive technique to target the reconsolidation of fear memories in humans. We provide evidence that old fear memories can be updated with non-fearful information provided during the reconsolidation window. As a consequence, fear responses are no longer expressed, an effect that lasted at least a year and was selective only to reactivated memories without affecting others. These findings demonstrate the adaptive role of reconsolidation as a window of opportunity to rewrite emotional memories, and suggest a non-invasive technique that can be used safely in humans to prevent the return of fear.

(Schiller et al., 2010) reported that extinction training, administrated during memory reconsolidation, can erase fear responses.

These studies have been replicated
Complexity

• Nervous system is complex in responses to fear and trauma

• Most studies investigate one brain region and one neurotransmitter at a time; whereas hormones, NTs and Neuro-peptides interact constantly.

(For example: Locus Coereleus (LC) regulated by many NTs and NPs with inhibitory effects of NA, A, endogenous opiates, GABA, 5HT and stimulating effects of CRF and glutamate)

Complexity

• Even more complex relationship between NTs and behaviour – eg arousal influenced by multiple NTs (NE, DA, ACh, 5HT) – simultaneously active in different parts of the brain.

• Chronic alterations in arousal systems highly complex and involve long term changes in neural function

• Studies labour intensive, expensive: eg investigation of PFC, Amygdala, hippocampal function in same subject will require separate scans.

• CNS difficult to access in humans – reliance on peripheral markers – 24 hr urine, peripheral blood, -platelets and lymphocytes, receptor binding and plasma NTs, hormones and metabolite levels.

• Specific human brain stds rely on – electro physiology, neuropsychology, neuro imagery

• Post mortem studies in humans difficult to arrange.

• Accuracy of diagnosis; what about co-morbidity; medications, tobacco, medications?

• Does an isolated Neuro-biological system really relate to a diagnosis of PTSD.

• Influence of genetics? Internal phenotypes, specific endotypes – eg account for symptoms such as intrusive memories; hyperarousal, numbing, and reduction of hippocampal volume.
Neuro-biological evidence so far

• Cardio physiology
• Glutamate and GABA
• Monoamines eg 5HT
• NA
• NPY
• HPA axis

Cardio physiology:
• Increased heat rate in PTSD sufferers – consistent findings in many controlled studies where presentations of trauma related sounds, videos, images. (eg studies combat veterans without PTSD vs those with PTSD vs those with other mental illness vs those not deployed).
• Other studies also demonstrate similar increased skin conductance and eye blink
Neuro-biological evidence so far

Glutamate and GABA

- **Glutamate** an **AA that is brain’s primary excitatory NT** – rapidly released in response to arousing and dangerous situations mediates nearly all fast, excitatory point to point synaptic transmission in brain.

- **GABA brain’s primary neuro inhibitor.** At rest non threat situations GABA counters excitation by glutamate. Exerts tonic inhibition on glutamate in many brain regions eg thalamus and amygdala – allows brain to filter out continuous flow of irrelevant sensory information.

- If excitation is increased in danger situations then glutamate can overwhelm GABA triggering off cascade of protective responses.

- Additional GABA and neuro steroids are released to protect brain cells from Xs high glutamate as brain cell death can occur if glutamate levels are too high.

- Thus GABA receptor activation provides CNS inhibition during non stressful states and enhanced CNS inhibition during stressful events.

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Neuro-biological evidence so far

Glutamate (excitatory) and GABA (inhibitor)

- **Pre clinical research** – GABA a key NT in stress induced behavioural deficits that mirror depression and PTSD - eg in learned helplessness studies decreasing GABA renders naive rats helpless. Conversely increasing GABA in selected parts of the brain ameliorates many aspects of stress.

- **Decreased GABA** in parts of brain (eg medial PFC and amygdala), associated with PTSD.

- Decreased GABAs results in insufficient protection against the activating effects of NA and Glutamate.

- Possible that intrusive recollections, hyperarousal and disinhibited social and emotional behaviour may be due to such deficient GABAergic function. It has been noted that pre treatment of animals in in escapable shock experiments with benzodiazepines blocks stress induced increases in NA in the amygdala, cortex. LC, hypothalamus and hippocampus.

- **Increased Glutamic activity involved in pathophysiology of PTSD.**
Neuro-biological evidence so far

Glutamate and GABA

- N-methyl – D- aspartate (NMDA) receptors are one of a few glutamate receptors that influence the membrane ion conductance.
- In Humans low GABA predisposes to development of PTSD and high levels are protective. Low GABA plasma levels in PTSD sufferers and reduced benzodiazepine receptors in amygdala, PFC, and other areas.
- Administration of NMDA antagonist Ketamine which increases glutamate release produces dose dependent increases in dissociative symptoms.
- Preloading with GABA agonist benzodiazepines reduces dissociative effects of Ketamine.
- Mood stabilizer Lamotrigine through inhibition of Na, Ca and K channels also reduces dissociation and cognitive deficits—reduces the effects of Ketamine.
- Very strong theoretical support that mood stabilizers have potential to ameliorate PTSD symptoms via actions on GABA/glutamate systems.
- 5-TH enhances GABergic suppression of the amygdala—a major mechanism through which serotonergic agents ameliorate both the acute stress response as well as PTSD.

Neuro-biological evidence so far:
Mono amines – 5-HT

- 5-HT is a monoamine synthesised from Tryptophan.
- Neurones located in raphae nuclei in brain stem which have connections to limbic system and all areas of cerebral cortex (eg PFC, amygdala, LC, hippocampus, nucleus accumbens & hypothalamus).
- 5-TH implicated in pathophysiology of PTSD in PFC, amygdala, LC, hippocampus. Complex effects.
- Orbito-frontal-cortex particularly sensitive to effects of 5-HT – OFC role is filtering, processing, evaluating social and emotional information.
- Impaired OFC associated with PTSD symptoms seen including impulsivity, aggression, misinterpretation of emotional stimuli, deficits in processing affective memory.
**Neuro-biological evidence so far**

**Mono amines – 5-HT**

- Fourteen 5-HT receptors have been identified: both excitatory and inhibitory.
- Multiple regulatory roles: sleep, aggression, CVS, respiratory, motor output, anxiety, mood, neuroendocrine and analgesia.

**Mono amines – 5-HT**

**Pre clinical research:**

- Psychosocial stress diminishes 5HT-1A receptor density in limbic system but
- Adrenalectomy prevents this – suggests that post synaptic 5HT-1A gene expression is under tonic inhibition by adrenal steroids.
- Therefore possible sequence in which stress induced increases in corticotrophin releasing hormone (CRH) and cortisol down-regulate 5HT1A receptors with an accompanying lowered threshold for anxiogenic stressful life events.
- Alternatively low 5HT1A receptor density may have a genetic origin or represent the combined result of inheritance or psychosocial stress.
Mono amines – 5-HT

Clinical –5-HT studies

• 5-HT dysregulation: evidence from traumatised clinical subjects at rest in response to neuro endocrine challenge clinical paradigms

In PTSD sufferers:

– Decreased platelet 5HT uptake – as measured by Paroxetine binding.
– Blunted prolactin response to serotonin releasing and uptake inhibitor d-fenfluramine
– Exaggerated reactivity to serotonergic probe meta-chloro phenyl piperazine (MCPP)
– Clinical response to SSRIs – strongest evidence of involvement of 5-HT

Other 5-HT evidence for symptoms of Aggression, suicidality, impulsivity, depression – symptoms found commonly in PTSD sufferers

• Aggression high in those with depleted tryptophan.
• Suicide victims who die through violent means have low 5-HT metabolite 5-hydroxyindoleacetic acid.(5-HIAA) in CSF; as do impulsive men and aggressive psychiatric patients.
• Prolactin response to partial serotonin agonist MCPP (m-Chlorophenyl piperazine) is inversely associated with measures of hostility, irritability, and depression in abstinent alcoholics – further demonstrates link between hostility and serotonin.
• MCPP can provoke panic reactions and dissociative flashbacks in PTSD sufferers but not in controls.
5-HT and Amygdala

• When 5-TH levels reduce – threshold of amygdala firing decreases (ie increased activation of amygdala) – through the effects of the inhibitory GABAergic interneurons that modulate excitatory glutamatergic input.

• This ability of 5-HT to modulate glutamatergic activity is dependent on corticosterone presence.

• Increased 5-HT has been found to stimulate GABAergic interneurons which inhibit glutamatergic activity and increase the threshold of amygdala firing. This results in decrease in vigilance and fear related behaviours. Efficacy of SSRIs in patients with PTSD may be related to an increased threshold of amygdala firing.

5-TH and Locus Coeruleus

• Lesion, electrophysiological and biochemical studies demonstrate inhibitory role of 5-HT on LC.

• Increases in tyrosine hydroxylase and firing rate of NE neurones in the LC have been reported following lesions to the raphe neurons or pre-treatment with 5-HT synthesis inhibitors (which effectively increase the inhibitory control of the LC by 5-HT).

• Rats with lesions to the 5HT raphe nuclei had 50% greater firing activity of NE neurons than intact, non lesioned animals.

• Administration of citalopram for 14 or 21 days led to progressive decrease in the firing activity of NE neurons.
5-TH and Hippocampus: Relationship between chronic stress, 5-TH and Hippocampal Volume:

- In animals inescapable stress associated with hippocampal damage and inhibition of neurogenesis.
- Fluoxetine administration on the other hand shown to block stress induced decrease in hippocampal cell proliferation.
- Pre-treatment with an SSRI has been shown to prevent development of fear induced behaviours in animals.
- In humans, replicated studies show reduced hippocampal volume and deficits in hippocampal–based declarative verbal memory among traumatised individuals with PTSD.
- In a study in female PTSD sufferers, long term use of SSRI paroxetine showed significant increase of hippocampal volume and verbal memory (Vermetten et al, 2003).

Genetic Evidence for 5-TH, aggression, and stress induced psychopathology - depression

- Gene that codes for tryptophan hydroxylase – individual variation accounted for by gene polymorphism.
- Increase in risk of depression in response to life stresses associated with having one or two copies of short allele of the 5-HT transporter polymorphism.
- Increased amygdala neuronal activity in response to fear inducing stimuli reported in healthy subjects with the 5-HT transporter polymorphism and is associated with reduced 5-HT expression and increased fear and anxiety.
**In PTSD sufferers: Norepinephrine (Nor-Adrenaline)**

Compelling evidence for exaggerated NA activity in traumatised humans with PTSD:

- Increased 24 hour urine NE excretion
- Increased 24 hour plasma NE levels
- Decreased platelet alpha-2 adrenergic receptor number (Reduction of these receptors seen as an adaptive down regulation in those with chronically increased NE levels)
- Exaggerated NE and epinephrine responses to traumatic reminders – challenge paradigm experiments eg sounds of combat in combat veterans.
- Exaggerated MHPG response to yohimbine (MHPG=NE metabolite 3-Methoxy-4-HydroxyPhenyl Glycol); (yohimbine=alpha-2 adrenergic receptor antagonist - blocks alpha-2 auto-receptor)
- Blunted prolactin response to clonidine – suggests a blunted post synaptic alpha-2 adrenergic receptor sub-sensitivity, potentially secondary to increased adrenergic activity.
- Genetic: alpha-2 adreno-receptor gene polymorphisms play a role in baseline catecholamine levels, intensity of stress activation and rate of catecholamine return to baseline after stress.

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**Norepinephrine (Nor-Adrenaline)**

- All three principal adrenergic receptor systems involved in fear conditioning circuitry:
  - Beta, alpha₁ adrenergic activity may be related to intrusive recollections, dissociative flashbacks, and psychological-physiological reactivity provoked by exposure to traumatic stimuli.
  
- This postsynaptic noradrenergic input promotes activation of the amygdala. In addition the amygdala’s projections into the LC generate additional adrenergic input – resulting in an upward spiral of adrenergic stimulation.
Therapeutic goals targeting the adrenergic system are:

- To inhibit Xs alpha-1 and beta receptor activation and to augment the inhibitory influence of alpha-2 adrenergic receptors.
- This would result in reduction of amygdala activation, enhance PFC function and inhibit stimulation of the LC and its secondary activation of other cortical and subcortical structures.

Neuropeptide Y (NPY)

- NPY – 36 AA NT
- Found peripheral Sympathetic Nervous System (SNS) and multiple stress responsive brain regions incl: LC, amygdala, hippocampus; PAG, PFC.
- In most NA neurones NPY is co-localised with NE. However NPY is only co-released with NE only during intense activation/stress and not during brief or mild stress.
- At high levels of stimulation NPY is released with and potentiates effects of NE at post-synaptic noradrenergic receptors. A metabolite of NPY then serves to inhibit further release of NE.
NPY

- **Preclinical Stds**: NPY inhibits firing rate of LC and release of CRF and NE; and to be anxiolytic.
- Association between NPY and superior performance
- Significant **negative relationship between NPY and dissociation** in elite soldiers in survival training. In these soldiers robust increases in NPY may advantageously modulate the effects of simultaneously observed robust increases in NE.
- Unlike effects of acute stress – chronic stress decreases NPY and increases the noradrenergic response to a novel stressor.
- Low levels of NPY with significantly high levels of NE seen in combat veterans with PTSD. Stress induced increases in plasma NPY were insufficient to hold high levels of NE in check. It is likely that rapid levels of NE contribute to increases in HR, BP, Resp Rate, anxiety, panic, vigilance and intrusive combat related memories.

1. In comparison with healthy controls those with PTSD have reduced baseline NPY levels and blunted response to NPY in response to yohimbine stimulation.
2. Based on these findings Friedman has suggested that medications that enhance NPY function might ameliorate acute stress reactions, PTSD and other stress related disorders.
3. No pharmacological products are available at present.
Hypothalamic-Pituitary-Adrenal Axis

- Under conditions of acute and chronic stress the Para Ventricular Nucleus (PVN) of the Hippocampus secretes Corticotrophin Releasing Factor (CRF).
- CRF stimulates anterior pituitary to release adrenocorticotrophic hormone (ACTH) which in turn stimulates synthesis and release of adrenocortical glucocorticoids.
- Whereas the sympathetic nervous system (SNS) prepares the organism to react to stressful stimuli, the HPA facilitates defensive responses as well as restore homeostasis. Cortisol in particular helps to metabolise and replenish energy stores, inhibits growth and reproductive systems, contains the immune response and contains sympathetic noradrenergic responses and affects behaviour through actions on multiple neurotransmitter systems and brain regions.

Hypothalamic-Pituitary-Adrenal Axis & PTSD

- Increased CSF CRF
- Abnormal 24-hour excretion of cortisol
- Abnormal 24-hour plasma levels of cortisol.
- Increased lymphocyte glucocorticoid number
- Exaggerated suppression of cortisol dexamethasone
- Increased cortisol response to CRH and ACTH
- Increased ACTH response to metyrapone

- BUT findings for HPA axis and PTSD are very inconsistent across studies - ? Effects of co morbidity, gender, time form trauma exposure, genetic factors etc – affect the HPA adaptation to chronic / traumatic stress.

**Hypothalamic-Pituitary-Adrenal Axis and PTSD**

- Enhanced negative feedback
- Low cortisol levels
  - Disinhibition of traumatic memory retrieval
  - Failure to contain sympathetic response
- CRF increases LC firing and noradrenaline release
- Adrenergic surge consolidates traumatic memories

*Note: There is conflicting evidence for low cortisol levels (Meewisse et al. 2007)*
Neuroendocrine Alterations in Posttraumatic Stress Disorder
Primary Psychiatry | February 1, 2002
Yehuda

- Implications of Low Cortisol in the Immediate Aftermath of a Trauma

If cortisol levels are low in the immediate aftermath of a traumatic event, this might result in a failure of cortisol to completely contain the sympathetic nervous system (SNS) response, resulting in an initial problem of a failure of normal memory consolidation. Indeed, there is evidence that catecholamines, particularly epinephrine, enhance memory consolidation in laboratory rats. This effect appears to be modulated at least in part by adrenal steroids, since removing the adrenal glands of animals makes them more sensitive to the effects of epinephrine on memory consolidation. Furthermore, when such animals are given replacement doses of glucocorticoids, they become less sensitive towards the memory-enhancing effects of epinephrine.

It has been hypothesized that PTSD results from an exaggerated response of neuropeptides and catecholamines at the time of the trauma, and that increased levels of these stress hormones initiate a process in which memories of the traumatic event might be “overconsolidated” or inappropriately remembered due to an exaggerated level of distress. The failure of cortisol to contain other neuropeptides would facilitate this effect. It would also explain why non-PTSD patients do not overconsolidate their traumatic memories and why reminders of the traumatic event are accompanied by distress in individuals with PTSD. However, this process might represent only one of many pathways to the development of PTSD.

HPA

- Abnormal HPA may have neurotoxic effects through activation of excitatory amino acids (AAs) and resulting in calcium influx into susceptible neurons.

- Acute or chronic cortisol elevation or glucocorticoid receptor supersensitivity is neurotoxic and has been used to explain reduced corpus callosum and intracranial volumes seen in sexually traumatised children and reduced hippocampal volumes and cognitive impairment in adults with PTSD.

Hippocampal Volume

- Association between hippocampal volume and cognitive impairment in PTSD patients demonstrated; with improvement after increased hippocampal volume after treatment with paroxetine (SSRI).

- Prevention of neurotoxicity may also be achievable with glutamate antagonists such as anticonvulsants which through blockade of excitatory AAs actions protect neurons by preventing toxic calcium influx.

- Reversal of neurotoxicity may be achieved with treatments that promote neurogenesis eg paroxetine Rx increased hippocampal volume in PTSD sufferers.
Dopaminergic System

- During incontrollable stress amygdala activation produces PFC dopamine release.
- Evidence that D1 receptor agonists can produce stress-induced PFC impairments on working memory and that both D1 and D2 receptor agonists can prevent such cognitive deficits.
- Xs dopamine release may have a role in PTSD hyperarousal, hypervigilance and possibly provoking brief paranoid/psychotic states sometimes seen in some PTSD patients.
- Research has surprisingly not focussed on dopamine as compared to other NTs.
- Elevated urinary DA levels seen in PTSD subjects.
Randomised Controlled Trials (RCTs)

- Control and comparison group
- Well defined population form which a representative sample is drawn
- Randomisation of groups to treatment and control
- Blind design to assess outcomes

- An RCT indicates that an experimental treatment is statistically better than a comparison treatment and is not considered a successful trial if the magnitude of this treatment is too small to influence clinical practice.

Randomised Controlled Trials (RCTs)

- Identified specific treatment outcomes must be quantified accurately – eg use of CAPS gold standard.
- Reliable diagnostic inclusion and exclusion criteria established at the outset.
- Reliable methods of assessing symptom severity in order to ensure that the experimental and comparison groups are appropriately balanced.
- Medication dosage chosen in order to optimise efficacy and minimise toxicity. – Both fixed and flexible dosage protocols may be used: pros and cons fixed dosages are less naturalistic and enforce constraints.
- Placebos used for comparison groups must fulfil ethical considerations. There may be positive effects of placebos to note.
- Subject compliance must be monitored in drug trials eg pill counts, plasma blood levels.
- Sample size should be estimated before the trial commences in order to determine statistical power. (At present the common measure is the effect size (Cohen, 1988) – this is the standardised mean difference between the experimental and comparison groups. Kraemer 2004 critical of this suggesting alternative analytic strategies such as the area under the curve (AUC) or number need to treat (NNT) as a better statistical method).
- Ethics Committee must be consulted – current controversy is comparison with placebo as opposed to a drug that has been shown to work – controversy in PTSD research as only 2 antidepressants approved by NICE and FDA.
State of Research

• Research has been carried out into antidepressants and anxiolytics to treat depression and anxiety! – relatively little has been conducted to treat PTSD directly.
• Hence medications will have had approval from NICE or FDA to treat other conditions and not PTSD.
• Main impetus for looking at PTSD and medications was finding that SSRIs had efficacy in treating other neurotic disorders eg OCD, Panic Disorder and social phobia.
• At this point in time research focussed on clinical trials with medications developed to treat depression. Seizure disorders, mood fluctuations, and schizophrenia.
• 5-TH mechanism have received most attention.
• Medications targeting CRF, Glutamate/GABA, NA etc have received little attention.

Medications and PTSD

• Guidelines: NICE; FDA; International Society for Traumatic Stress Studies (ISTSS) Treatment Guidelines; Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder 2007 (Australian Centre for Posttraumatic Mental Health – ACPMH); VA/DoD 2010; other – WHO;
• APA guidelines for Personality Disorders including Borderline Personality Disorders
• UK Trauma Group: Complex PTSD presentations review of treatment guidelines
• Algorithms based on clinical practice and research
• What are we treating? Co-Morbidity?
• Practical Strategies
NICE Guidelines for Pharmacotherapy

Acute reactions

Three small studies with Temazepam, Propranolol, and use of hydrocortisone in ICU patients — not enough evidence for prevention of PTSD if administered in acute phase.

NICE Recommends:

- Offer immediate practical, social and emotional support
- Don’t debrief individuals
- Consider acute phase symptomatic pharmacological management
NICE
Drug Treatments for Chronic PTSD

- Majority treated with medication
  - 77% with PTSD alone, 89% PTSD & depression
- SSRI antidepressants.
  (of which two – paroxetine and sertraline are licensed for PTSD in the UK).
- Other antidepressants.
- Atypical antipsychotics.
- Antiepileptics
- Other drugs are in use but no clinical trials, meeting the NICE criteria, are available.

NICE
Adult Guideline Summary I

- All PTSD sufferers should be offered a course of trauma-focused CBT or EMDR, normally on an individual OP basis, regardless of time since trauma.
- Usually 8-12 sessions, some at 90 minutes.
- May need to be longer than 12 sessions if multiple trauma, co-morbidity, traumatic bereavement...
- Training and competence essential.
NICE
Adult Guideline Summary II

• If there is little or no improvement after one of these psychological treatments, consider
  – An alternative trauma-focused treatment
  – Augmentation with pharmacological treatment.

NICE
Adult Guideline Summary III

• Drug treatments for PTSD should not be used a routine first-line treatment (1’ or 2’ care).
• Limited role for paroxetine and mirtazapine (non specialists) and amitriptyline, phenelzine (mental health specialists) - eg
  – Patient choice
  – Serious ongoing threat
  – Augmentation for psychological treatment
• Full discussion about potential side effects
US Food and Drug Administration - FDA

- Approval for two medications – both SSRIs - Sertraline and Paroxetine as indicated treatments for PTSD.

USA Clinical Guidelines & Evidence

- Algorithms
- Four independent clinical practice guidelines Incl:
  - APA 2004;
  - Davidson et al, 2005;
  - Friedman et al, 2000;
Pharmacological Management

Medications
SSRIs

- Two SSRIs – sertraline and paroxetine FDA approval for PTSD Rx: Multi site RCTs with these medications. It was seen that when medication was extended from 12 to 36 weeks that 55% of non responders converted to responders.
- Evidence that discontinuation of SSRIs associated with clinical relapse and return of PTSD symptoms.
- RCTs with fluvoxamine, fluoxetine and cipramil indicate these also effective.
- SSRIs broad spectrum of effects on PTSD symptoms incl: reexp, avoidance, numbing, hyperarousal, rapid improvement of quality of life which is sustained during treatment.
- Very exciting study into paroxetine an neurogenesis with improvement in cognitive deficits – Vermitten et al 2003 – assessed declarative memory and hippocampal volume among 20 PTSD patients – found significant improvement in logical, figural, and visual memory after Rx. Also 4.6% increase in hippocampal volume on MRI scan.

Other serotonergic Antidepressants

- Nefadozone and Trazodone
- These are serotonergic medications which act tjthrough pre-synaptic 5-TH 2 blockade.
- RCT showed Nefadozone as effective as sertraline (Saygan et al, 2002), also good evidence from open label trials (Davis et al, 1999) – Nefadozone withdrawn because of liver toxicity.
- Trazodone limited efficacy in mono-therapy but very useful due to serotonergic and sedative effects used in conjunction with SSRIs to counter medication induced insomnia (Friedman 2003).
**Tricyclic Antidepressants**

- TCAs block pre synaptic reuptake of both 5-HT and NA.
- Some act on 5-HT reuptake – amitrypamine
- Others on NA reuptake – desimipramine
- Others on both eg imipramine

- TCAs and PTSD ultimately actions result in a reduction of adrenergic activity in amygdala, PFC, LC.
- RCTs with imipramine and amitryptyline but not desimipramine demonstrated reduced PTSD symptoms.

- Loss of interest in TCAs studies because of lower and more benign side effect profile of SSRIs

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**Mono Amine Oxidase Inhibitors (MAOIs)**

| Phenelzine       | Blocks enzymatic (MAO) degradation of NA, 5-TH (and dopamine) | Enhances serotonergic action at 5-HT₁A receptors
|                  |                                                           | Down regulates post synaptic beta receptors and reduces LC activity. |
| Meclobemide      | Selective MAOI inhibitor                                  | Promotes neurogenesis                                               |
Newer Antidepressants

Mirtazepine two actions at:
1. Serotonergic – blockade of postsynaptic SHT$_2$ and SHT$_3$ receptors
2. Presynaptic alpha-2 adrenergic receptor action

- One RCT (Davidson et al 2003) vs placebo and one open label trial (Bahk et al, 2002) reduction of PTSD symptoms
- One study demonstrated reduction in nightmares and post waking memories for nightmares in 300 subjects who had had no benefit from any previous medications (Lewis 2002).

Newer Antidepressants

- **Venlafaxine**: blocks pre synaptic reuptake of NA and 5-HT; much less potent effect at blocking Dopamine reuptake.
- Two large multicenter trials of Venlafaxine XL showed superiority over placebo; one of 12 weeks duration; other of 6 months duration (Davidson et al 2006 a&b).
- Study showed that resilience improved and that over extended period substantial percentage of patients went into remission (after several months).
### Adrenergic Agents

- Few studies compared to SSRIs
- Antiadrenergic agent: **Prazocin** would be expected to increase PFC activation and reduce amygdala activation.
- **Prazocin** study – One RCT study: nightmares and other PTSD symptoms reduced (Raskind et al., 2003).

- Beta-adrenergic antagonist: **Propranolol**: reduced enhancement of emotional memories in volunteers (Cahill & McGaugh, 1996).
- Small clinical studies – benefit in reducing intrusive recollections, and reactivity to traumatic stimuli (Famularo et al., 1984).

- Alpha-2 agonists **Clonidine and guanfacine** would expect to improve PFC function as well as directly reducing amygdala activity.
- Animal studies – enhance PFC working memory (Franowicz et al, 2002)
- Clinical studies sparse but favourable (Kinze & Friedman, 2004; Kolb et al 1984).

### Direct Strategies to Reduce Noradrenergic Overactivity

- Alpha 1 adrenergic receptor blocking – e.g. prazosin
- Postsynaptic beta adrenergic blocking – e.g. propranolol
- Alpha 2 adrenergic receptor agonist – e.g. clonidine
Anticonvulsants/Anti-kindling Agents

- Sporadically tested, small single site studies. For past 20 years.
- Antikindling actions and recent interest in Glutamate/GABA systems and theories and increase in new anticonvulsant medications recently.
- All anticonvulsants block sensitization/kindling although their specific mechanism of action differs.

- **Carbamazepine**: three open label studies veterans and adolescents (Lipper et al 1986; Loof et al, 1995; Wolfe et al 1988) improved PTSD symptoms severity and impulse control, anger and violence
- Case reports for Carbamazepine and Oxycarbamazepine positive.

- **Valproate**: Four open label studies and two case reports: (eg Goldberg et al 2003).

- **Lamotrigine**: one study is the only RCT with an anticonvulsant. 10 week trial with 15 patients randomised Lamotrigine vs placebo 50% better from PTSD, VS 25% OF placebo – although data was challenged – insufficient statistical power (Hertzberg et al 1999; Berlant, 2003).

- **Gabapentin**: three case reports
- **Tiagabine**: three case reports re effectiveness in PTSD.
- **Vigabatrin**: five patient report improved anxiety, startle response anxiety and insomnia.

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**Pregabalin**

- **Abstract**
  - This study evaluated the efficacy of pregabalin augmentation of antidepressant treatment in patients with posttraumatic stress disorder (PTSD). Nine patients meeting DSM-IV criteria for PTSD who were on stable doses of antidepressants were treated open label with flexibly dosed pregabalin for 6 weeks.

  - All patients were assessed with the Short PTSD Rating Interview, Montgomery-Asberg Depression Rating Scale, Patient Global Impression-severity, Visual Analog Scale-pain, and Sheehan Disability Scale at baseline and weeks 2, 4, and 6.

  - Significant reductions were observed in all effectiveness measures from week 4 to the end of the study. In particular, the numerical improvement of the Visual Analog Scale-pain score was most robust (-53.4%, \( P=0.007 \)).

  - Pregabalin augmentation was effective and well tolerated during the study.

  - Our findings warrant adequately powered, placebo-controlled clinical trials to confirm the usefulness of pregabalin augmentation of antidepressants in patients with PTSD.

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Brief post-stressor treatment with pregabalin in an animal model for PTSD: Short-term anxiolytic effects without long-term anxiogenic effect

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Hagit Cohen 2008

Abstract

Background:
The short- and long-term behavioral effects of a brief course of pregabalin, an antiepileptic structural analogue of α-aminobutyric acid with analgesic and anxiolytic effects, were assessed in an animal model of post-traumatic stress disorder (PTSD).

Method:
Two-hundred thirty-three adult male Sprague–Dawley rats were employed. Behavioral responses to traumatic stress exposure (predator urine scent) were assessed immediately after (1 h) and 30 days after treatment with saline or pregabalin (at doses of 30, 100 and 300 mg/kg) in terms of behavior in the elevated plus maze (EPM) and the acoustic startle response (ASR) paradigms. At day 31 the freezing response to a trauma cue (clean cat litter) was assessed. The same treatment regimen initiated at day 7 was assessed at day 30 and in response to the trauma cue on day 31 in a separate experiment.

Results:
In the short term, doses of 100 mg/kg and 300 mg/kg of pregabalin effectively attenuated anxiety-like behaviors. In the longer-term, pregabalin did not attenuate the onset of PTSD-like behaviors or the prevalence rates of severe cue-responses, for either the immediate or the delayed treatment regimens.

Conclusion:
Pregabalin may present an alternative compound for acute anxiolytic treatment after exposure to trauma, but has no long-term protective/preventive effects.

D-Cycloserine (DCS)
Partial N-methyl-D-aspartate agonist

- Positive effects on memory of animals, elderly volunteers and Alzheimer’s patients – cognitive enhancer.
- Significant reduction in PTSD symptoms and anxiety in 12 week double blind cross over study vs other medications vs placebo. (Heresco-Levy et al 2002).
**D-Cycloserine (DCS)**
Partial N-methyl-D-aspartate agonist

- Administration of benzodiazepines or serotonin reuptake inhibitors in combination with behavior therapy for the treatment of many anxiety disorders has generally lead to only modest gains. In this article we suggest that pharmacotherapy aimed not at treating the symptoms of anxiety but instead aimed at improving the learning that takes place in exposure therapy might actually improve the effectiveness of exposure therapy. This idea was based on animal work showing that the partial N-methyl-D-aspartate (NMDA) agonist D-cycloserine (DCS) facilitated extinction of fear when given either before or shortly after exposure to fearful cues, reduced return of fear that is normally seen when extinction training is followed by stress, and led to generalized extinction, where DCS given in combination with exposure to one fearful cue led to extinction to another cue previously paired with the same aversive event. These finding suggested that DCS might facilitate exposure-based psychotherapy, which was verified in a small clinical study showing that DCS facilitated exposure therapy for fear of heights in a well-controlled virtual reality environment.

**GABA-ergic Agonists**

- Might expect benzodiazepines which act at GABA\(_A\) receptors might ameliorate PTSD symptoms – not so
- RCT study with alprazolam did not improve re-exp/avoidance/numbing although improved anxiety, and insomnia (Gelpin et al, 1996).
- Other open trials with Benzodiazepines unsuccessful
**Atypical Antipsychotics**

- General consensus that conventional antipsychotics – haloperidol, chlorpromazine have no place in the treatment of PTSD – questionable usefulness, problematic unjustifiable side effect profile.
- Small but growing literature of favourable results for Atypicals. Including small open label studies and randomised studies as adjuncts to treatment resistant patients with chronic PTSD. Risperidone, quetepine, olanzepine.
- Impressive as they have been generated in treatment resistant populations such as US military veterans in VA centers.
- Atypicals work on D2 receptor blockade and a unique 5-HT2 antagonism. As a result much more benign side effect profile.
- **In PTSD patients used as adjuncts with SSRIs for this who have failed to respond to antidepressants.**
- Little evidence to guide practice – but can be used to ameliorate dissociation, hypervigilance/paranoia, psychosis, hyperarousal, irritability and aggression.

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**HPA system**

- Pre clinical studies only
- Hydrocortisone treatment of septic shock has been shown to prevent PTSD development.
HPA & Corticotropin Releasing Factor (CRF)

• Given CRFs key role in mobilizing the human stress response as well as its increased expression among PTSD patients, there is good reason to predict that CRF antagonists might have beneficial clinical effects on PTSD-related symptoms. Although CRF antagonists are currently utilized in animal research and under development by pharmaceutical companies, none is available for clinical use.

• Future pharmacological treatment for acutely traumatized individuals will seek to reduce the magnitude of the stress response and to promote rapid recovery of normal function. This might be accomplished in the following ways:
  – By reducing CRF activity with CRF antagonists or enhancing NPY activity
  – By reducing HPA activation with glucocorticoids (such as cortisol or hydrocortisone) with an adrenal steroid such as dehydroepiandosterone (DHEA).
  – By reducing adrenergic activation with NPY agonists and/or a variety of antiadrenergic agents (such as clonidine/guanfacine, propranolol, or prazosin)

Concerns

• Lack of studies in older population and children
• Most studies in VVets and middle aged women adult survivors
• Concerns about generalizability.
PTSD and Medications
Practical Considerations

Phasic Treatment Strategy
Chronic Disease Management
2005 NICE Guidelines for treatment of Veterans with PTSD
Treatment with medications is just one tool in the armoury

1. Initial preparation
2. Stabilisation and safety
3. Disclosure and working through of the traumatic material and psychotherapy on an individual basis
4. Rehabilitation and reintegration within society; normalising activities of daily living and maintenance within the chronic disease model
5. Relapse Prevention / maintenance
Reasons for as to why medications are prescribed. Use of medications and use for the management of PTSD and comorbidity.

• to target and reduce symptoms of PTSD
• to treat comorbidity especially depression
• to do other things – eg detox, remove cravings etc
• to stabilise
• to stabilise enough and allow individual to do trauma focussed therapy and psychoeducation
• once therapy is delivered medications should be reviewed aiming at reducing or even stopping medication if appropriate – but some studies show that if medication is stopped even after using it for a long time patients might relapse – see VA/DoD guidelines.

Example of Co-morbidity: Combat Stress Population Clinical cases: Complex Bio-Psychosocial Presentations

Clinical Audit data (n=608), Psychometric Data Analyses (n=704) 2005-2009

Psychiatric Disorders
• High co-morbidity: 75% - primary diagnosis of PTSD of which 62% have co morbid PTSD, Depression, Alcohol misuse. (ie approximately 30% of those referred to Combat Stress – clinical and non-clinical cases have PTSD)

Behavioural Disorders
• Violence, aggression, schedule 1 offending

Physical Disorders
• Occupational
• Associated with Chronic PTSD: MIs, CVA.s Hypertension diabetes and Death 10 years prematurely!!

Social Exclusion
• Dysfunctional relationships, marriages.
• Isolation, living alone homelessness, unemployment.
When prescribing for complex cases:
Minefield of co-morbid medical problems. Multiple prescribing
Good liaison with GP and other speciality consultants essential

**Think:**
- Hypertension
- Cardiac disorders
- Stroke
- Diabetes
- Obesity
- Chronic Pain
  - Poly Pharmacy
  - Drug interactions
  - Drug Toxicity
  - Effects of medication/illicit drugs/over-the-counter medications/stimulants such as caffeine and nicotine on clinical presentation
  - Illicit drug misuse
  - Alcohol
  - Over the counter drug misuse

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**Treatment of PTSD: Medications**

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Medication:</th>
</tr>
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<tbody>
<tr>
<td>adrenergic</td>
<td>B-blockers, alpha-2-agonists</td>
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<tr>
<td>adrenergic &amp; serotonergic</td>
<td>TCAs &amp; MAOIs</td>
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<td>serotonergic</td>
<td>SSRIs, 5HT1a agonist; 5HT2antagonist</td>
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<td>antikindling drugs</td>
<td>SNRIs</td>
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<td>dopamine system</td>
<td>Carbamazepine, valproate</td>
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<td>GABA benzodiazepine system</td>
<td>Lithium, lamotrigine</td>
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<td>opioid system</td>
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<tr>
<td></td>
<td>alprazolam, benzodiazepines, clonazepam</td>
</tr>
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<td></td>
<td>naltrexone</td>
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</table>
**symptomatic/comorbidity use of Medication:**

**Medication**  
- Antidepressant  
  (SSRIs; Mirtazepine; trazodone)  
- Neuroleptics  
  (major tranquillizers)  
- Mood Stabilizers/ Antiepileptic  
  (Carbamazepine; valproate)  
- Anxiolytic  
  (Pregabalin)  
- Anti-impulse  
  (clonidine/ prazocin / propranolol)  

**Indication**  
- PTSD & Depressive symptoms  
  *(hyperarousal, re experiencing; sleep)*  
- Pseudo-psychotic presentations;  
  Dissociation; Tranquilization; co- 
  morbid psychotic depression  
- PTSD Symptoms, dissociation & Mood  
  stabilizing properties / anger  
  *(nightmares, flbks, hyperarousal)*  
- Severe anxiety/hyperarousal /anger  
  *(Mood stabilizer, hyperarousal, re – 
  experiencing)*  
- Impulse control - self- harm *(clonidine)*  
  *(also nmares: prazocin, sleep)*

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**Effects of over the counter drugs and illicit drugs on PTSD**

**Stimulators**  
Taken to reduce emotional numbing

- Increase hyperarousal  
- Increase re-experiencing  
- Increase behavioural problems relating to impulsivity, anger,

**Depressants**  
Taken to help avoidance

- Make comorbid depression worse  
- Enhance avoidance and exacerbate emotional numbing  
- Increase isolation
Less than desirable medications: sedatives; benzodiazepines

- Some medications are detrimental: benzodiazepines generally can be useful or detrimental – they are best avoided, especially clonazepam which is highly addictive.
  
- The same goes for sedatives such as Zopiclone.
  
- Benzodiazepines like alcohol and cannabis may increase the frequency and severity of nightmares and flashbacks: can deliver a film like quality with a soundtrack and in Technicolor!!!

Side effects of Medication

- Balance between benefits and side effects
- Medical review essential
- Blood tests may be required incl monitoring
- Drug interactions need to be understood
- Short term versus long term prescribing.
Compliance

- Are you taking your medication?
- Tell your doctor what you are doing

Pain and PTSD
Primary Care
General Practice Interventions

Advice – referral to local gym facilities etc

Medications
Simple pain killers – eg Paracetamol

• Effects of anti-inflammatories:
• Analgesics including opiate based analgesics – possibility of addiction, inhibition of cognitions including concentration and memory; impulse control issues and loss of temper – interaction with poor affect regulation and PTSD.

Physiotherapy
• Exercises delivered by and supervised by a physiotherapist.

PTSD and Pain

• Pain is one of the commonest physical problems reported by people with PTSD — irrespective of the type of traumatic event experienced (for example RTA, physical assault or combat).

• PTSD sufferers are also more likely to report disability due to pain. For example, one study of volunteer firefighters with PTSD found that approximately 50% were experiencing pain (mostly in the form of back pain) as compared with only about 20% of firefighters without PTSD. Two other studies found that 20 to 30% of patients with PTSD experience frequent and persistent pain symptoms.

• Conversely, many patients with chronic pain problems have PTSD: between 10 to 50% of people getting treatment for chronic pain have PTSD. These rates of PTSD are higher than what is found among people in general.
Why Do PTSD and Pain Commonly Co-Exist?

- Many traumatic events may lead to the experience of pain. For example, combat, natural disaster, physical or sexual assault, and RTAs. All can lead to serious injuries that could cause chronic pain.

- The more severe a traumatic event, the more likely it is that a person will experience some kind of physical injury as well as developing PTSD.

- Certain symptoms of PTSD may lead to the experience of pain:
  - Hyperarousal Symptoms of PTSD may cause increased muscle tension that can result in chronic pain.
  - Flashbacks to the moment of the trauma can result in pain sensations – which are pain flashbacks. It is important to distinguish between pain that is present and flashback pain as for the former analgesics should be prescribed where for the latter medications to reduce re experiencing symptoms of PTSD may be more beneficial. In addition the experience of pain may also trigger PTSD symptoms, such as memories or thoughts about the traumatic event.

- Co morbid disorders occurring with PTSD can contribute to the development of pain.
  - Eg: Depression, which frequently is experienced by people with PTSD, may cause a person to avoid or limit physical activities, resulting in disability and poorer health which eventually increases the likelihood of problems with pain.

The effect of PTSD on Chronic Pain and Depression

- PTSD and Depression are commonly experienced by individuals living with trauma related chronic pain. How PTSD relates to mood disorders and pain severity in chronic pain patients has remained a mystery.

- A study from the University of Michigan demonstrated that:
  - PTSD and depression are significantly correlated and that both disorders are associated with perceived disability attributed to chronic pain.
  - Therefore, in cases of disabling chronic pain with co morbid depression, symptoms of PTSD may be critical to understanding both disorders.
  - Increased attention to treating PTSD in the rehabilitation of patients with chronic pain and co morbid depression is important when prior treatment efforts for pain and depression have not been successful.
  - This means that treating PTSD effectively may also improve/alleviate chronic pain and depression.
Amputees and severe physical injuries.

- Studies conducted by the Israeli Military in the 1990s showed that being wounded protected against the development of psychiatric disorders including PTSD, as the injury could be seen by all and was a badge of courage to be admired by all.

- Later studies conducted in US soldiers injured in Iraq did not demonstrate this but showed that depression and PTSD can be exacerbated.

- No British studies exist. It is important that those who have been seriously injured including amputees are monitored psychologically and that thinking currently is that they are prone to the development of mental health disorders including PTSD.

- Physical injuries can act as a trigger and reminder for PTSD re-experiencing symptoms. Chronic pain and its pain such as phantom limb pain can also be problems.

- Many charities offering practical help, inclusion in sports and activities now exist. The issue of the NHS providing prostheses that are as good as those provided by the MOD is still a huge problem that has not been resolved.

Chronic Pain is common in PTSD sufferers

- Simplify analgesic medication regimes.

- Rationalize medications for those who suffer from PTSD combined with chronic Pain and depression.

- Use of antidepressants such as Duloxetine (SNRI); and analgesics which treat neuropathy such as Pregabalin (mood stabilizer and anxiolytic) - also helpful in treatment of anxiety and early open label studies for the treatment of PTSD symptoms such as re-experiencing symptoms and hyperarousal symptoms.

- Review of medications and joint prescribing with a pain specialist

- TENS Machine.

- Pain management programmes – MDT Consultant Anesthetist, clinical psychologist, OT, Physiotherapist.
Chronic Pain and PTSD

- Change antidepressant to Duloxetine; - efficacious in reducing pain

- Change pain relieving Gabapentin for Pregabalin. Licensed for pain and anxiety.

- Pharmacotherapy can be used to stabilise the patient to allow psychotherapy to take place and medications then can be stopped.

- Caution in relation to dosage and duration of use is essential in the elderly because of side effects.

Pregabalin Mechanism of Action

- Binds to alpha 2-delta subunit of voltage-gated calcium channels
  - Reduces $\text{Ca}^{2+}$ influx during depolarization
  - Binding required for analgesic, anxiolytic, and anticonvulsant activity

- Reduces release of neurotransmitters (eg, glutamate, norepinephrine, substance P)

- Effective in trials of epilepsy, neuropathic pain, and generalized anxiety
Case Study and Discussion

Evidence Informed Suggestions

• Full biopsychosocial assessment
  – NB complex presentations and co-morbidity
• Paroxetine, fluoxetine or venlafaxine with increased dose if no/limited response after 4 weeks
• If still no response change antidepressant and repeat
• If still no response consider augmentation
  – Antipsychotic, antiadrenergics, anti-epileptic
Suggested Further Work

- Improve neurobiological understanding of PTSD
- Head to head psychological treatment versus pharmacological treatment
- Further work on agents with theoretical potential
  - ? antiadrenergics, cortisol, ?MDMA, newer agents
- Cognitive enhancers
  - D-cycloserine
- Effectiveness studies

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