Current Advances in Pharmacotherapy Approaches for Posttraumatic Stress Disorder

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PTSD Criteria in DSM5

- Persistent re-experiencing and intrusive symptoms
  - eg: flashbacks, intrusive thoughts...
- Avoidance
  - eg: thoughts/feelings & places/people...
- Alterations in cognitions and mood
  - eg: distorted cognitions about cause consequences of trauma
- Anxiety or hyperarousal symptoms
  - eg: sleep disturbances, startle...
- ≥1 month

Trauma Event (prior DSM-IV A2 fear/helplessness response no longer required)

APA, 2013
PTSD Criteria in DSM5 (2)

### Criterion A: Stressor

<table>
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<tr>
<th>≥ 1 Criterion A</th>
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<tr>
<td>• Direct exposure.</td>
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<td>• Witnessing, in person.</td>
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<td>• Indirectly, by learning that a close relative or close friend was exposed to trauma. <em>If the event involved actual or threatened death, it must have been violent or accidental.</em></td>
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<td>• Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (<em>e.g.</em>, first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). *This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.</td>
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### Criterion B: Intrusion

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<th>≥ 1 Criterion B</th>
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<td>• Recurrent, involuntary, and intrusive memories.</td>
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<td>• Traumatic nightmares.</td>
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<td>• Dissociative reactions (<em>e.g.</em>, flashbacks) <em>which may occur on a continuum from brief episodes to complete loss of consciousness</em>.</td>
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<td>• Intense or prolonged distress after exposure to traumatic reminders.</td>
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<td>• Marked physiologic reactivity after exposure to trauma-related stimuli.</td>
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Criterion E: Alterations in Arousal and Reactivity

2 Criterion E Required

- Irritable or aggressive behavior
- Self-destructive or reckless behavior
- Hypervigilance
- Exaggerated startle response
- Problems in concentration
- Sleep disturbance

Criterion E & G: Duration and Function

- Greater than one month
- Significant symptom-related distress or functional impairment (*e.g.*, social, occupational).

*Specify if:* With dissociative symptoms (depersonalization, derealization)

*Specify if:* With delayed expression

- *Full diagnosis is not met until at least six months after the trauma(s), although onset of symptoms may occur immediately.*
Diagnoses May Vary for DSM-IV and DSM5 PTSD

- Study of 1822 US Soldiers (946 deployed to Iraq or Afghanistan) based on PTSD checklist self report (PCL-S and PCL5)
- 13% screened in PTSD DSM-IV vs 12% DSM5 criteria
  - if combat exposed, 19 vs 18%
- Of n=221 with DSM-IV PTSD, 30% did NOT meet DSM5
- N=59 met DSM5 but NOT DSMIV
- Fully 45% (n=126 of 280) with a PTSD diagnosis had discordant results
- Potential impact detection for treatment as well as disability status need to be considered

Hoge et al, 2014
Psychiatric Comorbidity in PTSD

- Major Depressive Episode
- GAD
- Panic Disorder
- Social Anxiety Disorder
- Agoraphobia
- Alcohol Abuse/Dependence
- Drug Abuse/Dependence

Kessler, et al. 1995
Pharmacologic Treatment of PTSD

- Early interventions to prevent (Secondary Prevention)
- PTSD treatment (once full diagnosis PTSD present)
Early Intervention to Prevent PTSD

- RCT in patients with acute stress disorder symptoms (mean 9.6 days after event)
- 12-weeks:
  - Prolonged Exposure (n=63) vs.
  - Cognitive therapy (n=40) vs.
  - Escitalopram (10-20 mg; n=23) vs.
  - Placebo (n=23) vs.
  - Waiting-list group (n=93)
- Starting M=29 days after trauma

Shalev et al., Arch Gen Psychiatry, 2012.
Early Intervention to Prevent PTSD: Results

- Effect of CBT
- Effect of PE
- No effect of escitalopram

Shalev et al., Arch Gen Psychiatry, 2012.

**Figure 3.** Progression of symptoms of posttraumatic stress disorder (PTSD) during early treatment. Because the waiting list (WL) group of participants did not have therapy sessions (they eventually received delayed prolonged exposure [PE]), only the first and second clinical assessment (CA-1 and CA-2, respectively) PTSD Symptom Scale–Self-Report (PSS-SR) scores are recorded for that group. CT indicates cognitive therapy; and SSRI, selective serotonin reuptake inhibitor.
Propranolol for prevention?
...Initial promise but failed support

- 10-day propranolol (40mg) (n=18) vs. placebo (n=23) within 6 hours of traumatic event (Pitman et al. 2002)
  → At 1 month: no differences in completers
  → At 3 months: 0% propranolol vs. 43% PCB patients physiologic responders during script-driven imagery, p = .04

- 14-day propranolol (n=17) vs. gabapentin (n=14) vs. PCB (n=17) within 48 hours of injury in surgical trauma center (Stein et al., 2007)
  → No differences at 1, 4, and 8 months post-injury

- 19-day propranolol (240mg) (n=21) vs. PCB (n=20) (Hoge et al., 2011)
  → At 1 month and 3 months: no difference in Sx or physiological reactivity
  → Only in high drug adherence group: difference in physiological reactivity
Hydrocortisone (n=25): Role for controlling acute stress responses?

- RCT of patients with acute stress Sx
- Within 6 h of a traumatic event
- Single IV hydrocortisone (100–140mg) (n=15) vs. PCB (n=10)

Zohar J et al, 2011
Hydrocortisone: replication

- 10-day RCT 40-mg hydrocortisone vs. placebo
- Within 12h trauma
- N=64
- Hydrocortisone associated with lower depressive and PTSD Symptoms

**Figure 2.** Adjusted mean CAPS total PTSD symptom scores (± std. error) for the placebo and hydrocortisone groups at 1 and 3 months posttrauma.

This information concerns a use that has not been approved by the US FDA.
Opiates

- Retrospective study
- N=696 military personnel
- The use of morphine during early resuscitation and trauma care was significantly associated with a lower risk of PTSD after injury.

Table 3. Unadjusted and Adjusted Odds Ratios for the Association between Morphine Use and the Risk of PTSD.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>PTSD (N=243)</th>
<th>No PTSD (N=453)</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Odds Ratio Adjusted for ISS (95% CI)</th>
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<tr>
<td>Morphine use</td>
<td>147 (60)</td>
<td>346 (76)</td>
<td>0.47 (0.34–0.66)†</td>
<td>0.48 (0.34–0.68)†</td>
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* CI denotes confidence interval, and ISS Injury Severity Score.
† P<0.001.

Holbrook et al. 2010
Impact of Early Benzodiazepine on PTSD

Alprazolam (N=3) or clonazepam (N=10) vs. no treatment (N=10); Gelpin et al. 1996

This information concerns a use that has not been approved by the US FDA.
PTSD Extinction as Learning

- Benzodiazepines (and ethanol) interfere with extinction learning
- New evidence that *early CBT with as few as 3 sessions can decrease PTSD development* (Rothbaum et al ER study, J Clin Psychiatry 2014)
- Non-benzodiazepine medications that reduce arousal, pain, inflammation and/or enhance sleep may support extinction learning
  → Consistent with Cochrane review only hydrocortisone moderate efficacy meds for PTSD prevention (Amos et al, 2014)
Pharmacological Treatments for PTSD

- 1) Antidepressants  SSRIs/SNRIs
- 2) What about benzodiazepines?
- 3) Other medications
  - Mood Stabilizers
  - Antipsychotics
  - Adrenergic Blockers (prazosin)
• **Level A**: Significant
  - Antidepressants SSRIs and SNRIs

• **Level B**: Some Benefit
  - Mirtazapine, TCAs
  - Prazosin for nightmares
  - Adjunct atypical antipsychotics
  - MAOIs (caution re food and drug interaction)
VA DOD 2010 Guidelines for Pharmacotherapy of PTSD: Evidence Levels (2)

• **Level C:** Unknown benefit
  - Prazosin monotherapy
  - Atypical antipsychotic monotherapy
  - Conventional antipsychotics
  - Buspirone, Bupropion
  - Propranolol, trazodone (adjunctive)
  - Gabapentin, Lamotrigine, Clonidine
  - Non Benzo hypnotics

• **Level D:** No Benefit
  - Benzodiazepines (“Harm”)
  - Valproate, Topiramate
  - Tiagabine, Guanfacine
Low Remission Rates in PTSD: Antidepressants are effective options but low remission.
Positive but relatively small effect sizes in SSRI Meta-analysis: Possible greater signal for paroxetine, fluoxetine and venlafaxine

Hoskins et al. 2015
Continuation Phase Outcome with Sertraline Treatment of PTSD Based on Acute Phase Response Category

Responder = \geq 30\% \text{ decrease CAPS and CGI-S} = 1 \text{ or } 2

What about Benzodiazepines and PTSD?

- APA 2004 Guidelines; Benzodiazepines cannot be recommended as monotherapy for PTSD
- IOM report 2009: evidence is inadequate to determine the efficacy of benzodiazepines in the treatment of PTSD
- VA DOD Guidelines: there is theoretical, animal, and human evidence to suggest that benzodiazepines may actually interfere with the extinction of fear conditioning or potentiate the acquisition of fear responses and worsen recovery from trauma.
- Risk substance abuse and interference with extinction learning. Not first line for sleep either.
- Clearly NOT recommended monotherapy
- Possible cautious adjunctive or brief use associated symptoms (e.g. panic, insomnia) but not first line and not early
Systematic reviews and growing data vets support prazosin for insomnia and nightmares in PTSD

- 4 RCT’s (n=113)
  - Doses range from 1-16mg/day
  
- 3 RCTs found significantly decreased nightmares
  - Raskind et al. 2003 (n=10)
  - Taylor et al. 2008 (n=13)
  - Raskind et al. 2007 (n=40)

- 1 RCT negative result:
  - Germain et al. 2012 (n=50)

- Additional recent positive RCT for nightmares and PTSD sxs in soldiers (n=67) with PTSD (Raskind et al. 2013)

- Possible role in comorbid AUDs?
  
- Small 6 week pilot RCT (n=30) prazosin to 16mg (split TID) for PTSD plus alcohol Dependence (Simpson et al 2015)
  
- Reduction in heavy drinking days but not PTSD symptoms, and high drop prazosin arm

Prazosin Preferable to Quetiapine in Military PTSD: Naturalistic Study

- 237 Veterans with PTSD
- n=62 received prazosin, and 175 received quetiapine.
- Short-term effectiveness similar for prazosin (61.3%) and quetiapine (61.7%; P = 0.54).
- Prazosin group significantly more likely to continue their therapy to study end date compared with quetiapine (48.4% vs 24%; P < 0.001; odds ratio, 3.0; 95% confidence interval, 1.62-5.45)

**Conclusion:**

*Similar efficacy but greater tolerability and acceptability prazosin*

Prazosin vs Hydroxyzine for Sleep and PTSD?

- Patients with PTSD randomized to 8 weeks of prazosin (n=33), hydroxyzine (n=34), or PCB (n=33)

- Prazosin started 1mg and **titrated 15mg** by day 10
  - Hydroxyzine started at 10mg and **titrated up to 100mg** by day 10

- Both prazosin and hydroxyzine superior to PCB for:
  - Sleep duration, sleep onset latency, sleep quality, nightmares, PSQI total score, PTSD M.I.N.I. score

- Prazosin significantly superior to hydroxyzine in improving:
  - Sleep duration, nightmares, and PTSD M.I.N.I. score

Ahmadpanah et al. 2014

PSQI=Pittsburgh Sleep Quality Index

This information concerns a use that has not been approved by the US FDA.
Support for Eszopiclone for PTSD and Insomnia

- Eszopiclone 3 mg/bedtime (n=12) superior to placebo (n=12) in reducing PTSD symptoms and insomnia

\*p<.05 vs. PBO

This information concerns a use that has not been approved by the US FDA.

A Review of Atypical Antipsychotic Medications for PTSD

• N=18 trials (10 RCTs)
• risperidone & quetiapine: positive effects
  – Mainly on hypervigilance and intrusions
  – ES small
  – No data on long-term SE (metabolic)
• Other antipsychotics: not enough data

Ahern et al. 2011
Support for Olanzapine monotherapy in PTSD (n=28)

- 8 week flexible-dose RCT (mean dose 9mg/d)
- Olanzapine group v. placebo showed greater reduction of CAPS score at week 8, LOCF
- Substantial weight gain in 6/14 Olanzapine subjects


*\( p<0.05 \) vs. placebo
Olanzapine Augmentation of SSRIs: Combat-Related PTSD (n=19)

Mean Olanzapine dose = 15mg/day
*P < 0.05.  **P = 0.01.
PSQI = Pittsburgh Sleep Quality Index.

This information concerns a use that has not been approved by the US FDA.
Adjunctive Risperidone for Military–related Antidepressant-Resistant PTSD

- N=247 diagnosed with military-related PTSD and ongoing symptoms despite at least 2 adequate SRI treatments
- Results:
  - Change in CAPS scores from baseline to 24 weeks was not significantly different between the groups
  - Risperidone did not reduce symptoms of depression or anxiety

This information concerns a use that has not been approved by the US FDA.
Anticonvulsants for PTSD

- **Mostly Case Reports and Open Series**

- Valproate (Depakote)
- Gabapentin (Neurontin)
- Pregabalin (Lyrica) *Positive RCT
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lamotrigine (Lamictal) *Mixed RCTs
- Topiramate (Topamax) *Negative RCTs
- Tiagabine (Gabitril) *Negative RCTs

This information concerns a use that has not been approved by the US FDA.
Low Sample Sizes and Mixed Results
Topiramate for PTSD: Role comorbid AUD?

• Open-label monotherapy study (n=35, 10 bipolar)\(^1\)
  - Reduced nightmares and flashbacks at 25-500 mg/d, but mean <100 mg/d

• Small RCT (Topiramate n=19, PCB n=19, civilian trauma) topiramate monotherapy vs placebo\(^2\)
  - Dosed 50-400mg/d
  - Failed primary outcome CAPS, some effect re-experiencing

• RCT in PTSD (Topiramate n=17, PCB n=14)\(^3\)
  - No differences at 12 weeks in ITT analyses (except avoidance/numbing)
  - Mean topiramate dose: 102.94 mg/d

• RCT veterans PTSD plus alcohol use disorder (Topiramate n= 14, PCB n=16)\(^4\)
  - Significant reduction 12 weeks drinking days (51% fewer); trends self rated PTSD (PCL)
  - Transient reduction learning and memory week 6

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\(^1\)Berlant J, van Kammen 2002; \(^2\)Tucker et al. 2007; \(^3\)Yeh et al. 2011; \(^4\)Batki et al. 2014

This information concerns a use that has not been approved by the US FDA.
Anticonvulsants for PTSD: Mixed Results

• Divalproex: Open reports but 2 negative RCTs

• Tiagabine:
  – Initial promise open label, but lack of effect double blind discontinuation $^1,^2$
  – Large (n=232) RCT tiagabine 4-16mg/day vs placebo$^3$: No difference from placebo on CAPS or other measures


This information concerns a use that has not been approved by the US FDA.
Anticonvulsants for PTSD: Early Support for gabapentin and pregabalin

• Gabapentin\(^1\) (n = 30, refractory, retrospective)
  – Improved sleep/nightmares at 300-3600 mg/d

• Pregabalin

• RCT pregabalin\(^2\) 300mg/d vs Placebo (n=37 combat vets): reduced PTSD on PCL but not anxiety, depression or QOL

→ Open label SSRI augmentation with pregabalin\(^3\) 150-300mg/d (n=9) also positive

\(^1\) Hamner MB et al. 2001; \(^2\)Baniasadi 2014; \(^3\)Pae 2008
Lack of evidence for Naltrexone for comorbid combat PTSD and alcohol dependence (n=88)

- 12 week RCT: four arms
  1. Paroxetine + naltrexone (n=22)
  2. Paroxetine + placebo (n=20)
  3. Desipramine + naltrexone (n=22)
  4. Desipramine + placebo (n=24)

  Naltrexone reduced craving but did not significantly reduce any alcohol use outcome relative to placebo

- However, Desipramine relative to Paroxetine reduced heavy drinking days (F=7.22; p<0.01) and number of drinks per drinking day (F=5.04, p<0.05)

- Desipramine was superior to paroxetine with respect to study retention

Combined treatments?

- Cochrane review (Hetrick et al. 2010):
  - n=4 papers
  - Not enough evidence available to support / refute effectiveness of combined psychotherapy + pharmacotherapy
PE+paroxetine vs. PE+Placebo

- Adult survivors of 9/11 with PTSD
- 10-week PE+paroxetine (n=19) vs. PE+PCB (N=18)
- PE plus paroxetine resulted in greater improvement in PTSD symptoms and remission at 10 weeks
- But: The subset of patients who continued randomized treatment for 12 additional weeks showed no group differences.

Schneier et al. 2012

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**Figure 2.** Clinician-Administered PTSD Scale Scores During Acute Treatment With Prolonged Exposure Therapy Plus Paroxetine or Prolonged Exposure Therapy Plus Placebo Among Patients With PTSD Related to the World Trade Center Attack

- Bars indicate standard deviation.
PE vs. Paroxetine vs. Combination

- 228 participants with PTSD from motor vehicle accident
- Randomized to 12 weeks of PE (N=144), paroxetine (N=57), or a combination (N=57)
- PE significantly greater SCID assessed remission rate compared to paroxetine
- No other significant differences in PTSD remission (SCID and PDS)

**chi-square = 4.83, df = 1, p = .027

Popiel et al. 2015
Combined Approaches May Address PTSD and Alcohol Use Disorder: Seeking Safety and Sertraline

- 69 participants with PTSD (full or sub-threshold) and drug dependence
  - Randomized to Seeking Safety (SS) treatment (12 sessions) with sertraline or placebo
  - SS is a present focused CBT for ETOH + PTSD
- Greater reduction in PTSD symptoms in combined SS + sertraline group from pre to post (M difference = -16.15, p = .04, d = 0.83)
- Sustained at 6- and 12-month follow up
- No differences in alcohol use disorder symptoms

Hien, J Consult Clin Psychol. 2015
D-Cycloserine Augmentation of Exposure Therapy: Promise but Failed Efficacy Trials

• Early preclinical data demonstrated promise for DCS and fear extinction

• 4 Trials to date with a total of 274 adults with PTSD
  – 1 found significant improvement with DCS but only at 6 month follow up (Difede et al. 2014)
  – 1 found DCS led to worse outcome than placebo (Litz et al. 2012)
  – 2 found no differences between groups (de Kleine et al. 2012, Rothbaum et al. 2014)

• Consistent with Ori et al. 2015 meta-analysis:
  – No effect of DCS augmentation of cognitive and behavioral therapies across anxiety and PTSD
24 Veterans with PTSD
Randomized to 30 mg oral hydrocortisone or PCB before PE sessions
Hydrocortisone group experienced greater reduction in PTSD symptoms (CAPS Total score)
  – Can be explained by significantly higher patient retention in hydrocortisone compared to PCB group
  – 7 out of 8 dropouts were from the PCB group
Yehuda et al, 2014
Ketamine for PTSD

**Experimental treatment only**

- Ketamine = antagonist of glutamate N-methyl-D-aspartate (NMDA) receptor
- Small study (n=41)
  - 18-55 year-olds with primary Dx PTSD (DSM-IV) and CAPS ≥ 50
- Ketamine hydrochloride (0.5mg/kg) vs. midazolam (0.045 mg/kg), one IV infusion
- **Rapid reduction in core PTSD symptoms in patients with chronic PTSD, and benefit up to 1 week**

- Ketamine SE’s:
  - short-lived dissociative symptoms (< 120 min)
  - 3 patients required acute treatment with β-blockers b/c of blood pressure elevation (systolic bp>180 mm HG and/or diastolic bp > 100mm HG
  - Blurred vision, dry mouth, restlessness, fatigue, nausea/vomiting

This information concerns a use that has not been approved by the US FDA.

Feder et al, 2014
Marijuana and PTSD

- Cannabinoid system interesting potential target for drug development PTSD:
  - Preclinical data supporting roles in fear consolidation and extinction (Ganon-Elazar, 2013) and amygdala (Hill et al., 2013)
  - Human PET imaging data suggest abnormal CB-1 receptor signalizing (upregulation with low occupancy) in PTSD (Neumeister et al., 2013)
  - Lower circulating endocannabinoids in PTSD (Hill et al., 2013)
• Media and anecdotal reports marijuana helpful for PTSD symptoms, and now legalized in some states
• Open support and small RCT (n=10) synthetic cannabinoid (nabilone) may reduce PTSD related nightmares (Frasier 2009; Jetly et al 2015)
• Lack study smoking MJ (THC) and PTSD outcomes
  **Risks:** depression, drug dependence
• Marijuana use may in long term exacerbate underlying pathophysiology PTSD through CB-1 receptor adaptations: More research targeted agents needed
Transcranial Magnetic Stimulation (TMS): Promise for PTSD in small RCTs with 10 TMS sessions targeting dorsolateral prefrontal cortex

- Meta Analysis (Karsen et al., 2014) large effect size for TMS in Prefrontal Cortex
  - Cohen et al., 2004: (right) hi vs lo vs sham N=24, CAPS decreased, hi>lo
  - Boggio et al., 2010: right vs left vs sham N=30, PCL decreased
  - Watts et al., 2012: (right) lo vs sham N=20
- Nam et al. 2013: (right) lo vs sham, N=18, CAPS decrease
- Second meta-analysis n=64 PTSD similar findings (& Berlim et al 2014)
- **Mechanism**: Potentiates fear extinction, disrupts traumatic memories
Exercise: can it treat PTSD?

- Cross sectional and treatment studies suggest efficacy mostly aerobic exercise for depression, anxiety and panic
  - Most studies 8-14 weeks, 3-4X week, 20-30 minutes
  - **Limitations**: adherence in practice
- Much less data in PTSD
- 3 small open trials non-military adolescents and adults with decreased PTS symptoms
- RCT support for exercise augmentation inpatient usual care with 12 week exercise program (n= 81)

How Might Exercise Help

- Reduced fear of anxiety and physical sensations (Anxiety Sensitivity)
  - eg: interoceptive exposure equivalent
- Reduced physiological arousal with stress
  - eg: adaptation stress hormone responses, HPA Axis, endorphins, BDNF
- Improved sleep
- Sense of mastery and self-efficacy and/or social component if group
- Increased positive affect (mood effects)

Asmundson et al 2013
Conclusions

• A variety of effective pharmacologic therapies exist for PTSD, in addition to psychological treatments
• There is still a significant unmet need for more efficacious prevention and treatment interventions
• More work needed on early intervention and prevention PTSD
• More research needed on who responds to what treatment, how to personalize the interventions
Massachusetts General Hospital
Department of Psychiatry

Presents

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