Psychopharmacotherapy of PTSD

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Psychopharmacologic Management of PTSD

- SSRIs
- 2nd generation antidepressnats
- MAOI
- TCAs
- Antiadrenergic agents
- Anticonvulsants
- Lithium
- Benzodiazepine
- Antipsychotic agents

SSRIs

- Sertraline and Paroxetine(FDA approved)
- Fluoxetine : effective in multisite trial and smaller open trials
- Citalopram, Fluvoxamine : effective in open trial
  - reduce DSM-IV B, C, and D symptoms
  - Produce improvement on CGI
  - effective treatment for psychiatric disorders that are cormobid with PTSD
  - reduce associated symptoms(rage, aggression, impulsivity, suicidal thought)
  - relatively benign side-effect profile

Sertraline in PTSD
Preliminary Studies

Reference	N	Subjects	Dosing/ Duration	Response Rates
Kline et al, Am J Psychiatry 1994	**19**	**Depressed Vietnam Combat Veteran**	**50-150mg/d (98.5mg/d) 12 Weeks**	**63% (12/19)**
Brady et al, J Clin Psychiatry, 1995	**9**	**Comorbid PTSD and Alcohol Dependence**	**50-200mg/d 12 Weeks**	**Significance on IES, HAM-D, MPSS Decreased Alcohol Use**
Rothbaum et al, J Trauma Stress, 1996	**7**	**Rape Victims**	**50-200mg/d 12 Weeks**	**80% Response (4/5 Completers)**
Pieraccini, Palloto, Castrogiovani, Biol Psychiatry, 1997	**12**	**Outpatients**	**50-150 mg/d 52 Weeks**	**100% Clinical Response**

Sertraline in PTSD
Acute Randomized Controlled Studies

Reference	N	Study Design	Dosing/ Duration	Response Rates
		Civilian Population		
Davidson, Arch Gen. Psychiatry 2001	**202 S=98 Pl=104**	**1-wk SB placebo run-in**	**50-200mg/d Flexible 12 Weeks**	**60% vs 38% (p=.004)**
Brady, JAMA 2000	**183 S=93 Pl=90**	**2-wk SB placebo run-in**	**50-200mg/d Flexible 12 Weeks**	**53% vs 32% (p=.008)**
		Veteran Population – Predominantly Combat Induced		
Zohar, J Clin Psychopharmacol 2002	**42 S=23 Pl=19**	**1-wk SB placebo run-in 50mg/d starting dose**	**50-200mg/d Flexible 10 Weeks**	**41% vs. 23% (p=.238)** *Inadequate power*

Sertraline in PTSD
Long-term Studies

Reference	N (ITT)	Study Design	Dosing/ Duration	Response Rates
		Long-term Continuation Study		
Londborg, J Clin Psychiatry, 2001	**249 Acute Phase S=128**	**Open-label**	**50-200mg/d Flexible 24-weeks**	**92% in Acute Phase Responders 54% in Acute Phase Non-Responders**
		Long-term Relapse Prevention Study		**Relapse Rates**
Davidson, Am J Psychiatry, 2001	**84 S=38 Pl=46**	**DB Relapse Prevention**	**50-200mg/d Flexible 28-weeks**	**5% vs. 26% (p=.017)**

Paroxetine in PTSD

- 20mg and 40mg of paroxetine were equally efficacious and improved all of the 3 symptom cluster
- Social and occupational impairment also improved
- Rate of remission 29.4%
- Initiated at the lower dose range of 10mg, titrate up to 40mg over 4 weeks

Am J Psychiatry 2001;158:1982-1988
J Clin Psychiatry 2001;62:860-868

Citropram in PTSD

- Adolescent, 12-week open-label study, moderate to severe PTSD

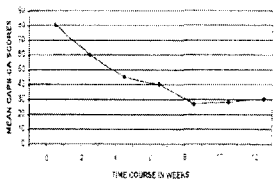


Table 3. CAPS-CA symptom clusters (sum of frequency and severity scores)

	Mean score		
	Baseline	12 weeks	*P* value
Re-experiencing	27.0 (5.5)	6.1 (7.8)	0.001
Avoidance	27.7 (7.8)	11.8 (8.1)	0.0001
Hyperarousal	26.3 (6.9)	11.8 (5.8)	0.001

t-test: paired two sample for means ($n = 7$)

2nd Generation Antidepressants

- Nefazodone ; 8 week open label trial(n=36)
- Venlafaxine and bupropione – little data
  ; comorbid major depression
- Mirtazapine
  ; 8-year old, 7.5mg at bedtime
  ; good response in the context of intensive inpatient treatment following a partial response to an SSRI
  ; open and double-blind trial in patients with PTSD

J Clin Psychopharmacology 2000;20:159-164
Curr Opin Psychiatry 2001;16:21-25

MAOIs and TCAs

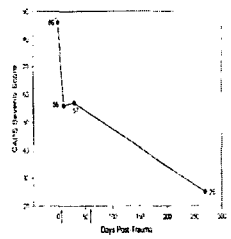
- MAOIs
  - Moderate to good global improvement and reduction of reexperiencing symptoms for PTSD
  - Little experimental attention due to clinician concerns about potentially serious side effect
- TCAs
  - two randomized clinical trials with veterans
  - imipramine and amitriptyline produced global improvement and reduced reexperiencing symtpoms

J Nerv Ment Dis. 1991;179:366-370

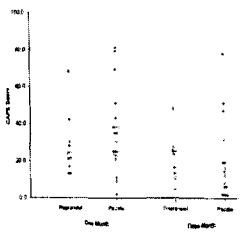
Arch Gen Psychiatry 1990;47:259-266

Antiadrenergic Agents

- Propranolol (postsynaptic beta-adrenergic antagonist)
  - sexually or physically abused children with chronic PTSD
    -> reduction in reexperiencing and arousal symtpoms
  - reduce sympathetic arousal and the encoding of highly charged emotional memories during the immediate aftermath of traumatic event -> *acute 10 day course of* propranolol exhibited less sympathetic NS hyperactivity at the 3 –month follow-up



Case report : a 44-year old woman, 6th accident, 48 hours after trauma, propranolo 120mg



Pilot study : within 6 hours of the event, a 10-day course of double-blind(propranolol=18) versus placebo(n=23), 40mg four times daily

J Traumatic Stress 2002;15 433-437

Biol Psychiatry 2002;51:189-142

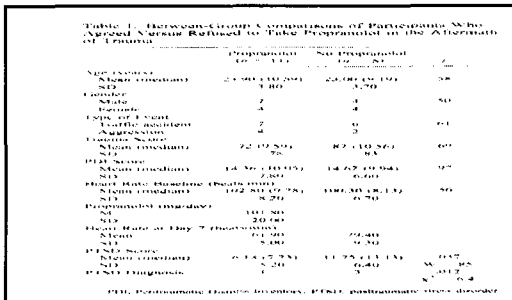


Table 1. Between-Group Comparisons of Participants Who Agreed Versus Refused to Take Propranolol in the Aftermath of Trauma

	Propranolol (n = 11)	No Propranolol (n = 8)	t
Age (years)			
Mean (median)	25.90 (30.00)	25.00 (25.00)	.08
SD	9.80	8.70	
Gender			
Male	7	4	.00
Female	4	4	
DSM-IV Event			
Traffic accident	7	6	.01
Aggression	4	2	
Trauma Score			
Mean (median)	72.10 (80)	82.13 (85)	.07
SD	25	8.5	
PTSD Score			
Mean (median)	14.36 (10.00)	14.62 (10.00)	.07
SD	2.80	6.60	
Heart Rate Baseline (beats/min)			
Mean (median)	102.81 (97.78)	100.36 (98.13)	.06
SD	8.20	6.70	
Propranolol (mg/day)			
M	101.80		
SD	20.66		
Heart Rate at Day 7 (beats/min)			
Mean	91.00	72.40	
SD	5.80	9.30	
PTSD Score			
Mean (median)	6.14 (2.78)	11.75 (11.13)	.037
SD	5.20	9.40	χ^2 = .85
PTSD Diagnosis	1	5	χ^2 = .017
			χ^2 = 5.4

PTSD, Posttraumatic Stress Inventory; PTSD, posttraumatic stress disorder.

- 40mg of propranolol 3 times daily for 7 days was delivered 2-20 hours after the trauma, followed by a taper period of 8012 days
- 2 month after trauma, psychiatrist blind to the Tx. assess

Biol Psychiatry2003;54:947-949

Antiadrenergic Agents

- Prazocin (postsynaptic alpha1 receptor antagonist)
  - marked reduction in traumatic nightmares, improve sleep, and global improvement among veterans with PTSD
- Clinidine and guanfacine (presynaptic alpha2-receptor agonists)
  - disinhibition of adrenergic neurons with the alpha2- adrenergic antagonist yohimbine(panic, dissociative symptoms, PTSD flashback among PTSD veterans)
  - benefit in dissociation and flashbacks figure prominently
  - prefer clonidine in Southeast Asian refugees with PTSD

Semin Clin Neuropsychiatry 1999;4:242-248

Anticonvulsants

- Carbamazepine

: reducing polysynaptic responses and blocking posttetanic potentiation
: induce hypnotic effect and decrease sleep latency without disrupting REM sleep
: interferes with kindling, and in humans it can reduce noradrenergic arousal
-> case reports and small open trials
-> increase up to a maximum of 800mg, symptom relief within 3-5 days
-> reducing reexperiencing and aggressive symptoms

- Valporate

: decrease limbic kindling, increasing GABA levels in the limbic system
-> open label study
-> reducing intrusion and hyperarousal symptoms

Clin Neuropharmacology 2002;25:225-229

Lithium and Benzodizepines

- Lithium
  : antikindling agent and effective agent for recurrent affective D.
  -> 2 small open-label case report 20 years ago
  ; reduced autonomic arousal, irritability, aggression, anxiety, insomnia, alcohol consumption
- Benzodiazepins
  : anxiolytics
  -> *no proven efficacy against core PTSD symptoms(alprazolam and* clonazepam)
  -> risk for exacerbate depressive symptoms(CNS depression), drug misuse, rebound anxiety

J clin Psychiatry 1990;51:236-238

Antipsychotic Agents

- Conventional antipsychotics in the 1970s with Vietnam veterans for intense hyperarousal, hypervigilance, dissociative symptoms, aggressivity, and reexperiencing symptoms
  -> Conventional antipsychotics nare not recommended
- Atypical antipsychotics(olanzapine, risperidone, quetiapine)
  -> preliminary data suggest that they may be effective
  -> augmentation treatment for partial responder to SSRIs or other first- or second-line agents
  -> patients with intense hypervigilance/paranoia, dissociation, or brief psychotic reaction

Am J Psychiatry 2002;159:1777-1779
Ann Pharmacother 2002;36:1875-1878
Int Clin Psychopharmacol 2001;16:331-337

Others

- **DHEA(dehydroepiandrosterone)**
  - adrenal neurosteroid, mediator of HPA axis adaptation to extreme stress and the psychiatric symptoms associated with PTSD
  - high at birth due to the transient presence of the *adrenal fetal zone*
  -> drop until adreache(6-8 years of age) -> rapidly increase from adrenache through adolescence, peak in the second to third decade
  : lack of neuroprotection by DHEA may contribute to more toxic effect of stress on the brain when DHEA levels are low
  : antiglucocorticoid properties of DHEA may contribute to an upregulation of HPA axis response as well as mitigate possible deleterious effects of high cortisol level on the brain in some PTSD subpopulation
  : higher DHEA levels may protect against comorbid depression in PTSD

Dysregulation of HPA axis in PTSD

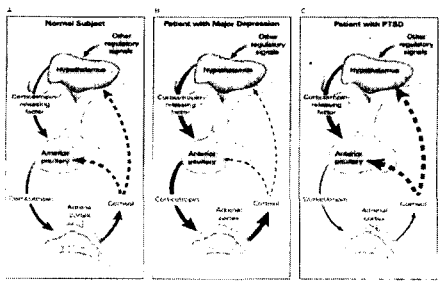


TABLE 1. 24-HOUR URINE CORTISOL STUDIES IN PTSD: FINDINGS AND EXPERIMENTAL DESIGN

	4 Weeks Off Medications	4 Weeks Off ETOH/Drugs	Activity Matched	Nicotine Matched
Reduced Cortisol Output in PTSD				
Authors (Year) - Study Population				
Mason et al (1990) - Male veterans	No	No	No	No
Yehuda et al (1993) - Male veterans	No (2 weeks)	No	No	No
Yehuda et al (1995) - Male veterans	No	No	No	No
Yehuda et al (1995) - Male/postmenopausal female Holocaust survivors	Yes	No[a] (ETOH)	Yes	No
Cortisol Output in PTSD Not Patterned				
Kosten et al (1992) - Male veterans	No	No	No	No
Baker et al (1999) - Male veterans	Yes	Yes	Yes	No
Mason et al (2002) - Male veterans[a]	Yes	Yes	No	No
Increased Cortisol Output in PTSD				
Putnam and Orr (1992)[a] - Male veterans	Yes	Yes	Yes	No[a]
Lemieux and Coe (1995) - Premenopausal females	No	Yes	Yes	No
De Bellis et al (1999) - Male/female children	Yes	Yes	Yes	Yes
Maes et al (1995) - Male/female burn victims	Yes	No[a] (ETOH)	Yes	No
Rasmusson et al (2001) - Premenopausal females (trend level)	Yes	Yes	Yes	Yes
Friedman et al (2001) - Perimenopausal women	No	No	Yes	No

[a] Male veterans with PTSD were compared with combat controls and had only somewhat lower rates and intensities of smoking;[a] therefore, nicotine use was probably fairly well matched.

Adapted with permission from: Rasmusson AM, Friedman MJ. The neurobiology of PTSD in women. In: Kimerling R, Ouimette, PC, Wolfe J, eds. *Gender and Post-Traumatic Stress Disorder: Clinical, Research, and Program Level Applications*. New York, NY: Guilford Publications, Inc.; 2002:43-75.

PTSD=posttraumatic stress disorder; ETOH=alcohol; †=unspecified if study controlled for alcohol or nicotine use.

Rasmusson AM, Vythilingam M, Morgan III CA. *CNS Spectr* Vol 8, No 9. 2003.

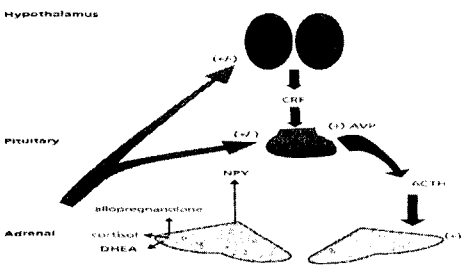


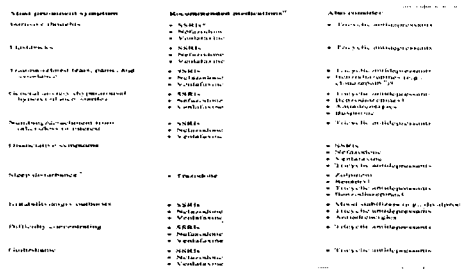
FIGURE. Hypothalamic-Pituitary-Adrenal Axis

+=positive feedback; -=negative feedback; CRF=corticotropin-releasing factor; AVP=arginine vasopressin; NPY=neuropeptide Y; ACTH=adrenocorticotropin; DHEA=dehydroepiandrosterone

Rasmusson AM, Vythilingam M, Morgan III CA. *CNS Spectr* Vol 8, No 9. 2003.

Expert Consensus Guideline for PTSD

- Preferred Classes of Medication Based on Different Target Symptoms



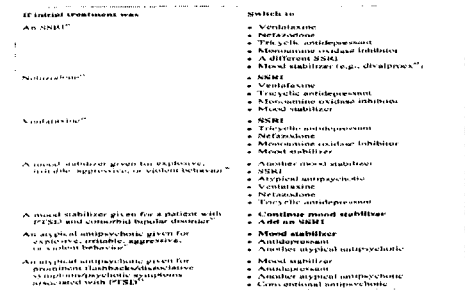
Preferred Classes of Medications Based on Different Types of Stressors

Military combat	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Mood stabilizers (e.g., divalproex)**
	Venlafaxine	
Sexual trauma as an adult	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Benzodiazepines (e.g.,clonazepam)**
	Venlafaxine	
Sexual or physical abuse in childhood	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Mood stabilizers**
	Venlafaxine	
Accidents	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Benzodiazepines**
	Venlafaxine	
Natural disasters	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Benzodiazepines**
	Venlafaxine	
Victim of violent crime or torture	**SSRIs**	**Tricyclic antidepressants**
	Nefazodone	**Mood stabilizers**
	Venlafaxine	

Defining an adequate initial medication trial

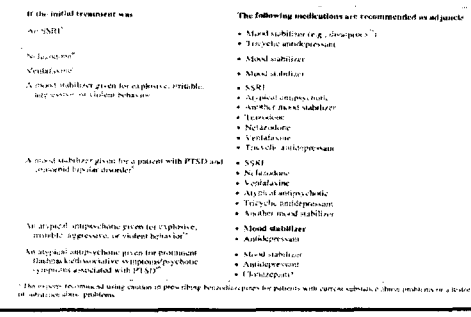
	no response	partial response
• Antidepressant	6 weeks	8 weeks
• Antipsychotic	3 weeks	4 weeks
• Benzodiazepine	2 weeks	3 weeks
• Buspirone	4 weeks	5 weeks
• Mood stabilizer	4 weeks	6 weeks
• Antiadrenergic	2 weeks	3 weeks

Choosing the Next Medication



If initial treatment was	Switch to
An SSRI*	• Venlafaxine • Nefazodone • Tricyclic antidepressant • Monoamine oxidase inhibitor • A different SSRI • Mood stabilizer (e.g., divalproex*)
Nefazodone*	• SSRI • Venlafaxine • Tricyclic antidepressant • Monoamine oxidase inhibitor • Mood stabilizer
Venlafaxine*	• SSRI • Tricyclic antidepressant • Nefazodone • Monoamine oxidase inhibitor • Mood stabilizer
A mood stabilizer given for explosive, irritable, aggressive, or violent behavior*	• Another mood stabilizer • SSRI • Atypical antipsychotic • Venlafaxine • Nefazodone • Tricyclic antidepressant
A mood stabilizer given for a patient with PTSD and comorbid bipolar disorder*	• **Continue mood stabilizer** • **Add an SSRI**
An atypical antipsychotic given for explosive, irritable, aggressive, or violent behavior*	• **Mood stabilizer** • Antidepressant • Another atypical antipsychotic
An atypical antipsychotic given for prominent flashback/dissociative symptoms/psychotic symptoms associated with PTSD*	• Mood stabilizer • Antidepressant • Another atypical antipsychotic • Conventional antipsychotic

Selecting Adjunctive Medications



If the initial treatment was	The following medications are recommended as adjuncts
An SSRI*	• Mood stabilizer (e.g., divalproex*) • Tricyclic antidepressant
Nefazodone*	• Mood stabilizer
Venlafaxine*	• Mood stabilizer
A mood stabilizer given for explosive, irritable, aggressive, or violent behavior*	• SSRI • Atypical antipsychotic • Another mood stabilizer • Nefazodone • Nefazodone • Venlafaxine • Tricyclic antidepressant
A mood stabilizer given for a patient with PTSD and comorbid bipolar disorder*	• SSRI • Nefazodone • Venlafaxine • Atypical antipsychotic • Tricyclic antidepressant • Another mood stabilizer
An atypical antipsychotic given for explosive, irritable, aggressive, or violent behavior*	• **Mood stabilizer** • **Antidepressant**
An atypical antipsychotic given for prominent flashback/dissociative symptoms/psychotic symptoms associated with PTSD*	• Mood stabilizer • Antidepressant • Clonazepam*

* Use extreme caution in prescribing benzodiazepines for patients with current substance abuse problems or a history of substance abuse problems.

What the patient has not responded to multiple previous treatments

Assessment strategies	*Assess for substance abuse problems*
	Reevaluate for psychiatric comorbidity
	Assess for the presence of a complicating neurological or other general medical condition
	Assess for secondary gain
	Reevaluate diagnosis of PTSD
Medication interventions	Combine medications:
	Preferred combination: antidepressant + mood stabilizer
	Also consider
	Antidepressant + antipsychotic *or*
	Antidepressant + antipsychotic + mood stabilizer *or*
	Two antidepressants *or*
	Adjunctive benzodiazepine* or trazodone
Psychosocial interventions	Combine psychotherapy techniques *and/or*
	Add special rehabilitation programs(social skill training or vocational rehabilitation) *and/or*
	Add family therapy
Indications for hospitalization	*Risk of suicide* or *Risk of harm to others*

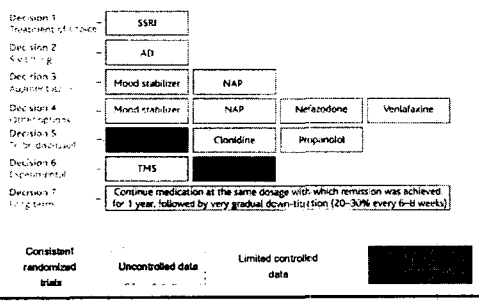
Medication Issues

- Duration of treatment before considering tapering Medication
  - Acute PTSD: 6-12 months
  - Chronic PTSD with excellent response: 12-24 months
  - Chronic PTSD with residual symptoms: usually at least 24 months and possibly longer, especially if the indications listed below are present
    - Indications for continuing medication treatment for a longer period
      - Current life stressors
      - Poor social supports
      - Persistence of some symptoms
      - High suicide risk in the past
      - History of violence
      - Presence of comorbid Axis I disorder(s)
      - Long duration of PTSD symptoms
      - Poor functioning when symptomatic
      - History of severe PTSD symptoms

Medication Issues

- Frequency of medication visits
  - Months 3-6: monthly
  - Months 6-12: every 1-2 months
  - After 12 months: every 3 months
- Recommended method of tapering medication
  - to avoid discontinuation/withdrawal syndrome: Taper medication over 2 weeks - 1 month, except for the benzodiazepines, which experts recommend tapering over 1 month or longer
  - to lessen the likelihood of relapse in a patient with risk factors for relapse: Taper medication over a longer period, 4-12 weeks, except for the benzodiazepines, for which experts recommend tapering for longer than 12 weeks

Treatment Decisions for PTSD



Conclusions

- **SSRIs** 특히 **paroxetine**과 **sertaline**을 선택할 수 있다
- 치료에 반응이 없는 경우 다른 항우울제를 선택하고, 호전을 보이지 않으면 기분조절제 또는 비전형 항정신병 약물을 병용투여한다
- 외상 사건 후 **PTSD**로 진행을 감소시키기 위해 **propranolol**을 사건 직후 투여를 고려한다