

## 항불안제로서의 Benzodiazepine계 약물의 위치

성균관대학교의과대학  
 강북삼성병원 정신과  
 오 강 섭

---

---

---

---

---

---

---

---

---

---

### Indications of Benzodiazepine

- Anxiety Disorders : GAD, Panic Disorder, S.P, O.C.D, PTSD
- Sleep Disorders : Insomnia, PLMS
- Alcohol withdrawal syndrome
- Extrapyrmidal Syndrome
- Seizure Disorders
- Schizophrenia-associated stress/anxiety
- Other Stress-related Disorders
- Bipolar disorder-acute manic phase

---

---

---

---

---

---

---

---

---

---

### Pharmacological Properties of Benzodiazepines

- Anxiety-reducing
- Sedative-hypnotic
- Anticonvulsant
- Muscle relaxation
- Others : ataxic, amnesic, respiratory depression

---

---

---

---

---

---

---

---

---

---

Major Benzodiazepines	
• Aprazolam(Xanax)	• Clonazepam(Klonopin)
• Diazepam(Valium)	• Chlordiazepoxide(Librium)
• Lorazepam(Ativan)	• Oxazepam(Serax)
• Prazepam(Centrex)	• Clorazepate(Tranxene)
• Triazolam(Halcion)	• Temazepam(Restoril)
• Flurazepam(Dalmane)	• Midazolam(Versed)
• Quazepam(Doral)	• Flumazenil(Romazicon)
• Mirtazepam	• Lormetazolam)
• Loprazolam	• Clobazam
• Flunitrazepam	• Brotizolam

---

---

---

---

---

---

---

---

---

---

Benzodiazepines as Anxiolytics (I)
• Indications
- short - term anxiety related conditions (e.g. adjustment disorder)
- short-term stabilization of anxiety symptoms in specific Anxiety Disorders
- long-term Tx. of Panic disorder, Social Phobia, G.A.D., O.C.D, P.T.S.D.
- as needed use for sudden surges of anxiety symptoms

---

---

---

---

---

---

---

---

---

---

Benzodiazepines as Anxiolytics (II)
• Advantages
- Rapid onset of action
- Other helpful auxiliary effects (muscle relaxation, sedative-hypnotic effect, ...)
- Favorable side-effect profiles
• Disadvantages
- Tolerance
- Dependence & Withdrawal problems
- Cognitive dysfunctions

---

---

---

---

---

---

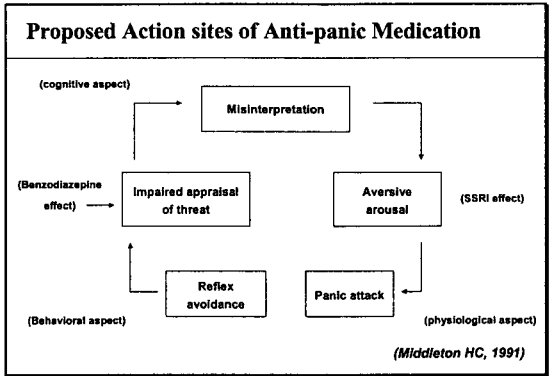
---

---

---

---






---

---

---

---

---

---

---

---

---

---

### Duration of Therapeutic Action of Benzodiazepines

Drug	Duration of Therapeutic Action
Alprazolam	4 – 6 hrs
Clonazepam	6 – 8 hrs
Adinazolam XR	12 hrs ↑
Alprazolam XR	9 – 16 hrs

---

---

---

---

---

---

---

---

---

---

### Comparisons of Anti-panic Medications

Classes	SSRIs	TCA's	MAOIs	BZDs
Onset of action	slow	slow	slow	fast
Initial exacerbation of anxiety	+/-	+/-	-	-
Therapeutic tolerance	-	-	-	+ (little)
Withdrawal symptoms	+	+	+	++
Abuse potential	-	-	-	++
Sedation	-	++	-	++/+++
Interaction with ethanol	+	+	++	+++
Dietary restrictions	-	-	+++	-
Overdose risk	-	++	++	+

---

---

---

---

---

---

---

---

---

---

### 제 3 부 불안장애의 생물학적 치료 I

#### Benefits of Pharmacotherapy for Panic Disorder

Conditions	Efficacy per Drug Class		
	High-potency BZD	TCA	SSRIs
Decrease in panic attacks	Marked	Marked	Marked
Rapidity of response	Marked	Mild	Mild
Decrease in anticipatory anxiety	Marked	Mild	Mild
Decrease in phobic avoidance	Moderate	Mild	Moderate
Antipanic efficacy	Marked	Marked	Marked
Antidepressant efficacy	None	Marked	Marked

(Rickel K, Schweizer E, 1998)

#### Risks of Pharmacotherapy for Panic Disorder

Conditions	Frequency/Severity per Drug Class		
	High-potency BZD	TCA	SSRIs
Sedation/ psychomotor retardation	Moderate	Moderate	Not present/mild
Anticholinergic effects	Not present	Marked	Not present/very mild
Orthostatic hypotension	Not present	Moderate	Not present
Hyperstimulation	Not present	Moderate	Mild/moderate
Physical dependence	Moderate	Not present	Not present
Discontinuation symptoms	Marked	Mild	Mild
Risk of abuse/dependence	Mild	Not present	Not present
Weight gain	Not present	Moderate	Not present/mild
Sexual dysfunction	Mild	Mild/moderate	Moderate/marked

(Rickel K, Schweizer E, 1998)

#### Combining BZs with other agents in Panic disorder

- Woods et al, 1990
  - alprazolam + imipramine for several weeks
  - followed by a taper of alprazolam
  - No particular advantages
- Goddard et al, 2001
  - clonazepam + sertraline
  - faster onset of symptom reduction

**Benzodiazepines in the Treatment of Social Phobia(I)**

- Clonazepam, Alprazolam : most widely studied
- Others : Bromazepam : small informed
- 10 or more open and placebo controlled studies
- Generalized type : long-term Tx.
- Non-generalized type : as-needed Tx.
- Effective for
  - performance anxiety
  - generalized social anxiety
  - fear and phobic avoidance
  - fear of negative evaluation

---

---

---

---

---

---

---

---

---

---

**Benzodiazepines in the Treatment of Social Phobia(II)**

- Rapid onset of action
- As- needed basis for performance anxiety
- Favorable side effect profile  
(but, ↓ anxiety /sedation interfering performance)
- High rate of relapse after discontinuation
- Multiple doses for short-acting agents
- Dose
  - clonazepam : 1-3 mg/day , alprazolam : 2-5 mg/day

---

---

---

---

---

---

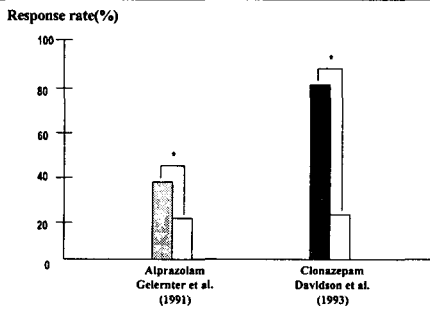
---

---

---

---

**Benzodiazepines**



---

---

---

---

---

---

---

---

---

---

제 3 부 불안장애의 생물학적 치료 I

Comparisons of Placebo controlled studies in Social Phobia

Classes	Efficacy	Main S/E	Observations
Phenelzine	+++	Sleep disturbance, hypotension	Risk of hypertension/low
RIMAs	**	Insomnia, daytime sedation, Dry mouth, light-headedness	Not marketed in U.S.
SSRIs	+++	Sexual dysfunction, nausea restlessness	
Benzodiazepines	+++	Sedation, impaired coordination, Memory impairments	Slow taper maintains gains more than fast taper
Atenolol	-	Bradycardia, hypotension/rarely useful in performance anxiety	
Busprone	-	Nausea, dizziness, insomnia	Can be used with SSRIs

Benzodiazepines in the Treatment of GAD(I)

- Widely used but Not used as 1st line
- Adjunctive to AD during initial treatment
- Long-term Tx. : controversial on BZs
- Effect sustained remission of anxiety symptoms without dose escalation over 6 month or longer
- Gradual tapering regimen needed due to long-term use (switch to long half life, or use other Tx.)

Benzodiazepines in the Treatment of GAD(II)

Diazepam, Alprazolam, Lorazepam, Clorazepate

Dose : 2mg x 3 or 5mg x 2(diazepam equivalent dose)

- Advantages
  - Rapid onset(max, effect : within 2wks)
  - Well tolerable
  - Promote sleep
  - Muscle relaxation effects
- Disadvantages
  - Risk of Dependence, Discontinuation problem
  - Risk of abuse
  - Cognitive impairments
  - Psychomotor impairments
  - Behavioral disinhibition





### 제 3부 불안장애의 생물학적 치료 I

#### Benzodiazepines in the Treatment of Obsessive Compulsive Disorder

- Used as augmentation
- SRI + clonazepam
- Clonazepam : serotonergic property ?

---

---

---

---

---

---

---

---

#### Medications of Elderly Anxiety Disorders

- Benzodiazepines
- Buspirone
- Antidepressants : TCAs, SSRIs, SNRIs, MAOIs
- Beta-receptor blockers
- Antihistamines
- Antipsychotics
- Others

---

---

---

---

---

---

---

---

#### Thresholds for Prescription of Anxiolytic Medications in Elderly

- 1) Severe or persistent anxiety symptoms
- 2) Previous positive treatment response
- 3) Failure or unavailability of psychosocial therapies
- 4) Patient preference
- 5) Quality of life considerations
- 6) Economics of health care

---

---

---

---

---

---

---

---

### Choices of Benzodiazepines in Elderly Anxiety

- Short-acting benzodiazepines
  - : metabolized by conjugation (e.g. lorazepam, oxazepam)
  - : less toxic accumulation
  - : less side effect — Preferable
- Long-acting
  - : useful in daytime anxiety and night-time insomnia
- Alprazolam
  - : not preferred due to rebound anxiety, habituation
- Ultrashort-acting benzodiazepines
  - : contraindicated due to cognitive disruption (confusion, amnesia, hallucination)

### Characteristics of Benzodiazepines

Drugs	Daily Dose(mg)	Half-life (hr)	Rapidity of Absorption	Metabolite	Inactivation Mode
alprazolam (Xanax)	0.5-20	12	+++	minor	oxidation
chlordiazepoxide (Librium)	15-60	18	+++	Yes	oxidation
clonazepam (Klonopin)	1-5	34	++	Yes	oxidation
clorazepate (Tranxene)	15-30	100	++++	Yes	oxidation
diazepam (Valium)	2-20	60	++++	Yes	oxidation
lorazepam (Ativan)	1-4	15	+++	No	conjugation
oxazepam (Serax)	15-60	8	++	No	conjugation

### Problems Associated with Benzodiazepine Use in the Elderly

- Daytime Sedation
- Cognitive Impairment : confusion
- Psychomotor Impairment : risk of fall
- Psychiatric Complications
  - : depression, explosive expression of feeling
- Intoxication
  - : overdose or even on therapeutic dose
- Respiratory Depression and other Breathing problems
  - : obstructive sleep apnea
- Abuse, Dependence, and Withdrawal

### 제 3부 불안장애의 생물학적 치료 I

#### Comparisons of Commonly used Medications in Child/Adolescents

Classes	Drugs	Therapeutic applications	Comments
SRIs	citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Useful in all anxiety disorder Except specific phobia	First line drug Unique effect in OCD Well tolerated
TCA's	Imipramine, Nortriptyline, desipramine	Useful in all anxiety disorders, Except OCD, specific phobia	2 <sup>nd</sup> line drug after SRIs Requires ECG and LAB monitoring
	clomipramine	Only TCA for OCD	Use after 2-3 failed SRI trials
Benzodiazepines	Alprazolam, Clonazepam, lorazepam	Situation and anticipatory anxiety Across all anxiety disorders	Best for short-term use while waiting for SRI kick in Disinhibition and physiological dependence
Others	Propranolol	Specific social phobia	Useful in performance anxiety
	Buspirone	GAD	Broad effect but, no effects on panic, OCD

#### Summary of Rational Benzodiazepines Use in Anxiety

Anxiety State	Duration of Tx.	Other Tx.
Mild anxiety	Not recommended	Psychological Tx.
Acute Stress Reaction	1-7 days	Psychological Tx.
Adjustment disorder	Single dose or a few days And initially	Antidepressants Psychological Tx.
Episodic Anxiety Chronic Generalized Anxiety	Single or intermittent course (2-4 wks followed by 1-2 wks in tapering) Use with other Tx.	Antidepressants Beta-blocker Psychological Tx.
Panic dis. Phobic dis.	Initial course 2-4 weeks Followed by 1-2 wks in tapering Use with other Tx.	Antidepressant Blockers Psychological Tx.
Generalized Anxiety dis.	4-6 Mo. Or longer	Antidepressant Psychological Tx.

#### Risk factors of Benzodiazepine Withdrawal Symptom

- Panic disorder > GAD
- Severe case reports in PTSD in long-term use(Risse et al 1990)  
: 2~9mg for 1~5years  
: anxiety, sleep disturbances, hyper-arousal  
: 75% reported homicidal ideation
- Social phobia  
: possible when long-term use for generalized type

**Summary**

- Benzodiazepines can be effective in treating Anxiety Disorders
- Efficacy of Benzodiazepines varies across Anxiety Disorders
- Proper diagnosis is important before prescribing
- Consider Side effects and withdrawal symptoms
- Periodic Evaluation of Risk / Benefit of BZ
- Advised to use proper dose, duration for indicated Anxiety Disorders

---

---

---

---

---

---

---