# 2005 년도 대한불안장애학회 추계학술대회 및 대한정신약물학회 추계연수교육 - 불안장애의 이해와 집중적 치료 전략 ~

# 항불안제로서의 Benzodiazepine계 약물의 위치

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

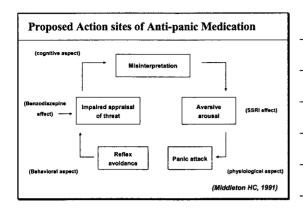
#### Pharmacological Properties of Benzodiazepines

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

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Major Benzodiazepines	
<ul> <li>Aprazolam(Xanax)</li> <li>Diazepam(Valium)</li> <li>Lorazepam(Ativan)</li> <li>Prazepam(Centrex)</li> <li>Triazolam(Halcion)</li> <li>Flurazepam(Dalmane)</li> <li>Quazepam(Doral)</li> <li>Mirtazepam</li> <li>Loprazolam</li> <li>Flunitrazepam</li> <li>Brotizolam</li> <li>Brotizolam</li> </ul>	
Benzodiazepines as Anxiolytics (I)	
<ul> <li>Indications</li> <li>short - term anxiety related conditions</li> <li>(e.g. adjustment disorder)</li> <li>short-term stabilization of anxiety symptoms in specific Anxiety Disorders</li> <li>long-term Tx. of Panic disorder, Social Phobia, G.A.D., O.C.D, P.T.S.D.</li> <li>as needed use for sudden surges of anxiety symptoms</li> </ul>	
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	

# 제 3 부 불안장애의 생물학적 치료 |

Benzodiazepines in the Treatment of Panic Disorder(I)	
<ul> <li>Alprazolam, Clonazepam : approved by FDA</li> <li>Lorazepam, Diazepam : small information</li> <li>Effective for         <ul> <li>frequency of panic attack ↓</li> <li>severity of anticipatory anxiety ↓</li> </ul> </li> </ul>	
- avoidance behavior ↓	
• Dose Initial Maintain alprazolam 0.25-0.5mg x 3,4/day 2-6mg x 3,4/day	
clonazepam 0.25-0.5mg x 2,3/day 1-3mg x 2,3/day	
Benzodiazepines in the Treatment of Panic Disorder(II)	
· Advantages	
1) Rapid antipanic response(less than 1 week) 2) Dose dependent( greater response rate in higher dose) 3) Comparable effects with TCA(imipramine) 4) Benefits on quality of life and work productivity	
Disadvantages & Side effects     Frequent administrations(due to inter dose fluctuation in benzodiazepine plasma level)	
Sedation, fatigue, cognitive & memory impairment     Possibility of dependency, abuse liability     Withdrawal symptoms : seizure, anxiety, headache, insomnia	
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Treatment Mechanism in Panic disorder	
Psychosicial Treatments	
- CBT, Psychotherapy, Family therapy	
- influencing "pre-fronted cortical neuronal functioning"	
Pharmacological Treatments	
- SSRIs, TCAs, BZD, MAOIs, New Antidepressants	
- stabilizing "Autonomic instability related to	
aberrant discharge of monoamine brainstem nuclei"	



Drug	Duration of Therapeutic Action
	-
Alprazolam	4 – 6 hrs
Clonazepam	6 – 8 hrs
Adinazolam XR	12 hrs 1
Alprazolam XR	9 – 16 hrs

Classes	SSRIs	TCAs	MAOIs	BZDs
Onset of action	slow	slow	slow	fast
Initial				
exacerbation	+/-	+1-	-	-
of anxiety				
Therapeutic				
tolerance				(little)
Withdrawal		•		**
symptoms				
Abuse potential	•	•		**
Sedation	•	**	•	***
Interaction			**	***
with ethanol				
Dietary		-	***	
restrictions				
Overdose		**	**	
risk				

### 제 3 부 불안장애의 생물화적 치료 1

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

	Frequency/Severity per Drug Class			
Conditions	High-potency BZD	TCAs	SSRIs	
Sedation/ psychomotor retardation	Moderate	Moderate	Not present/mild	
Anticholinergic effects	Not present	Marked	Not present/very mile	
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	

# Combining BZs with other agents in Panic disorder

- · Woods et al, 1990
  - alprazolm + 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, \displayarrow 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

# Response rate(%) 100 40 Alprazolam Gelemer et al. (1991) (1993)

# 제 3 부 불안장애의 생물학적 치료!

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Classes  Pheneizine		nin S/E nce, hypotension	Observations Risk of hypertrensionslow						
RIMAs		rtime sedation,	Not marketed in U.S.						
	Dry mouth, figi	ht-headedness	Hot that Release III o.o.						
SSRIs	+++ Sexual dysfun restles	sness	•						
Benzodiazepines	+++ Sedation, impair Memory in	red coordination, npairments	Slow taper maintains gains more than fast taper						
Atenolol	- Bradwardia h	motension/rafithh	ably useful in performance anxiety						
	Nausea, dizzir		Can be used with SSRIs	I					
Buspirone	- Nausea, QIZZII	ness,msonna	Can be used with 33Kis						
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Benzodiaze	epines in the T	reatment	of GAD(I)						
. Widoly no	and hust Not used	aa lat lima							
•	sed but Not used								
-	ve to AD during in		nent						
	m Tx. : controver								
	tained remission	-							
without o	dose escalation ov	ver 6 month	or longer				100000		
	tapering regimen long half life, or		to long-term use		ļ				
(switch to	iong num me, or	use other 1	,						
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Benzodiaze	epines in the T	reatment	of GAD(II)						
Diagonary	Alamanalam I	Class				11.711	11.20		
	Alprazolam, Loraz z × 3 or 5mg × 2(c	•	-						
• Advanta	ages								
- Rapio	d onset(max, effect : tolerable	within 2wks)	ı						
- Prom	iote sleep ele relaxation effects				<b>}</b> —	<u> </u>			
<ul> <li>Disadva</li> </ul>	ntages		arablam						
- Risk	of Dependence, Disc of abuse	continuation p	orobiem						
	itive impairments homotor impairmen	ts			1				
	vioral disinhibition								

Alprazolam, Clonazepam: 1 double and several open trials  Effective for -intrusive recollections -intrusive recollections -intrusive recollections -intrusive recollections -intrusive recollections -intrusive recollections -panic like anxiety attack  Combined with other drugs  Dose alprazolam: 3-5mg/day, clonazepam: 1-6mg/day  Disadvantages : withdrawal symptom(rage reaction), effects on mood : cautiousty use pt. with 1) poor impulse control, 2) prone to severe depression  Double blind and open label studies in PTSD  Braun et al, 1990 -alprazolm/placebo Sweeks crossover trial with 2 week interim phase in 10 Israeli PTSD pt minimal efficacy with maximal dose(4.25mg/d of alprazolam) - No effects on core symptoms of PTSD  Lowenstein et al, 1988(open-label) - clonazepam: 1-6mg for 6-21months - imporvements in nightmare, insomnia, intrusive recollection flashback, panic  Role of Benzodiazepines in the Treatment of PTSD  - not be the most useful treatment - as an adjunctive treatment with SSRIs - not advised for Monotherapy for PTSD/ prevention of PTSD  → should be used with caution	Benzodiazepines in the Treatment of PTSD	
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as an adjunctive treatment with SSRIs      not advised for Monotherapy for PTSD/ prevention of PTSD	Role of Benzodiazepines in the Treatment of P15D	
• not advised for Monotherapy for PTSD/ prevention of PTSD	• not be the most useful treatment	
	as an adjunctive treatment with SSRIs	
should be used with caution	<ul> <li>not advised for Monotherapy for PTSD/ prevention of PTSD</li> </ul>	
	should be used with caution	

# 제 3 부 불안장애의 생물학적 치료 I

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Benzodiazepines in the Treatment of Obsessive Compulsive Disorder	
Used as augmentation	
- Osed as augmentation	
• SRI + clonazepam	
· Clonazepam : serotonergic property ?	
Medications of Elderly Anxiety Disorders	
• Benzodiazepines	
Buspirone	
<ul> <li>Antidepressants : TCAs, SSRIs, SNRIs, MAOIs</li> </ul>	
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	
<ul> <li>Short-acting benzodiazepines</li> <li>: metabolized by conjugation</li> </ul>	
(e.g. lorazepam, oxazepam) : less toxic accumulation : less side effect — <del>Pre</del> ferable	
Long-acting     : useful in daytime anxiety and night-time insomnia	
<ul> <li>Alprazolam</li> <li>not preferred due to rebound anxiety, habituation</li> <li>Ultrashort-acting benzodiazepines</li> </ul>	
: contraindicated due to cognitive disruption (confusion, amnesia, hallucination)	
Characteristics of Benzodiazepines	
Drugs Daily Dose(mg) Half-life Rapidity of Metabolite Inactivation (hr) Absorption Mode	
alprazolam 0.5-20 12 +++ minor oxidation	
(Xanoax)	
clonazepam 1-5 34 ++ Yes oxidation (Klonopin)	
Clorazapate	
(Vallum)	
lorazepam 1-4 15 +++ No conjugation (Ativan)	
oxazepam 15-60 6 ++ No conjugation (Serax)	
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 3 부 불안장애의 생물학적 치료 |

Classes	Drugs	Therapeutic application	s Comments
SRIs	citalopram,fluoxetine fluvoxamine, paroxetine sertraline	Useful in all anxiety disorder Except specific phobia	First line drug Unique effect in OCD Well tolerated
TCAs	imipramine, Nortriptyline, desipramine	Useful in all anxiety disorders, Except OCD, specific phobia	2 <sup>nd</sup> line drug after SRIs Require ECG and LAB monitoring
	clomipramine	Only TCA for OCD	Use after 2-3 failed SRI trials
Benzodiaz	repines Alprazolam S Clonazepam, Iorazepam	ituation and anticipatory anxiety Across all anxiety disorders	Best for short-term use while waiting for SRI kick in Disinhibition and physiologica dependence
Others	Propranolol	Specific social phobia	Useful in performance anxiet
	Buspirone	GAD	Broad effect but, no effects on panic, OCI

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 hronic Generalized Anxiety	Single or intermittent course (2-4 wks followed hy 1-2 wks In tapering) Use with other Tx.	Antidepressants Beta-blocker Psychological Tx.
Panie dis. Phobie 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	
<ul> <li>Advised to use proper dose, duration for</li> </ul>	
indicated Anxiety Disorders	