[연수강좌]

일차진료의가 처방하는 항우울제, 항불안제

홍 진 표

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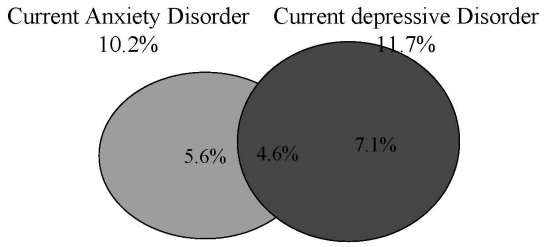
1차 진료에서 정신장애



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Anxiety and Anxiety Disorders

- Categories of Anxiety Disorder: DSM-IV
  - Panic Disorder 공황 장애
  - Phobic Disorder 공포 장애
  - Post-traumatic Stress Disorder (PTSD) 외상 후 스트레스 장애
  - Acute Stress Disorder 급성 스트레스 장애
  - Generalized Anxiety Disorder (GAD) 범불안장애
  - Anxiety Disorder due to general medical condition
  - AD NOS

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불안장애의 증상

- 정신증상
  - 극심한 공포
  - 죽음의 두려움
  - 불안, 초조
- 신체증상
  - 빈맥
  - 심계항진
  - 호흡곤란
  - 발한
  - 어지러움, 현기
  - 오심, 복통

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Antianxiety Drugs

- Classes
  - Benzodiazepines (BZDs)
    - 5 actions (SHAMA): Sedation, Hypnotics, Antianxiety, Muscle relaxant, Anticonvulsant
  - Non-BZD anxiolytics and hypnotics
    - Antihistamines (e.g., hydroxyzine)
    - Beta-blockers (e.g., propranolol)
    - Azaspirone anxiolytic (e.g., buspirone)
    - Barbiturates (e.g., amobarbital, phenobarbital)
    - Clonidine

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BZDs

		Anxiolyt.	Sed/Hypn.	Anti-convulsant	Potency
Short	Midazolam (M)	+	+++		-
	Triazolam (H)	+	+++		High
Intermediate	Alprazolam (X)	++	+	+	High
	Bromazepam (L)	++			High
	Lorazepam (A)	+++	++	++	High
	Clotiazepam (R)	+	+		Low?
Long	Chlordiazepoxide (L)	++			Low
	Clonazepam (R)	++	+	+++	High
	Diazepam (V)	+++	++	+	Medium
	Flurazepam (D)	+	+++	+	Medium

Approved Indications of Anxiolytics

- Mild to moderate anxiety, tension, agitation
- GAD
- Acute & chronic alcohol withdrawal
- Convulsions
- Insomnia
- Panic disorder (alprazolam)
- Muscle spasm, dystonia
- Other: endoscopy, bronchoscopy etc.

Pharmacokinetics of BZDs

- Marked inter-individual variation
- Well absorbed after oral administration
- Absorption and lipid solubility determines onset of action
  - BZDs have high Vd (tissue concentration much higher than blood concentration)
- Duration of action
  - Determined by 1) elimination half-life 2) tissue distribution
- Major pathway
  - Hepatic microsomal oxidation and demethylation

Adverse Effects of BZDs

- CNS Effects
  - Generalized sedative effect
  - Impaired psychomotor speed, memory, concentration
  - Anterograde amnesia (high potency)
  - Behavioral dyscontrol (irritability, paradoxical agitation)
  - Confusion and disorientation
  - Excessive dosage: respiratory depression
  - Dysarthria, muscle weakness, ataxia, headache

Adverse Effects of BZDs

- Non-CNS Effects
  - Anticholinergic effects: blurred vision, dry mouth
  - Sexual dysfunction
  - Dizziness
  - Increased salivation (clonazepam)
  - Few documented allergies

Withdrawal Symptoms and Management

- Variable risk of physiological dependence
  - Individual/ Drugs potency/ Elimination half-life
- Symptoms
  - 1~2 days to 5~6 days following discontinuation
  - Insomnia, agitation, anxiety, perceptual changes, dysphoria, headache, muscle aches, twitches, tremors, loss of appetite, GI troubles, depression
- Management
  - Change to long-acting (diazepam or clonazepam)
  - Reduce by 25% per week
  - Carbamazepine or propranolol may aid
  - Alternative dosage if needed
  - Physical dependence and psychological dependence

AA: Alprazolam

- General description
  - Xanax 0.25mg, 0.5mg
  - Usual dosage: 0.5mg
  - Peak plasma level (p.o.): 1~2 hour
  - Lipid solubility: moderate
  - Elimination half-life: 9~20 hour
  - Rapid and complete absorption, 80% protein bound
- Clinical
  - Anxiety, agitated depression, panic attack prophylaxis
  - T.i.d. dosing
  - Frequent WD symptoms
  - Sleep stage 4, REM↓
  - Low degree of sedation

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AA: Diazepam

- General description
  - Valium 2mg, 5mg
  - Usual dosage: 5mg
  - Peak plasma level (p.o.): 1~2 hour
  - Lipid solubility: high
  - Elimination half-life: 14~70 hour / metabolites 30~200 hour
  - Quick and complete absorption, with rapid onset
- Clinical
  - Anxiety, sedative, anticonvulsant, akathisia, muscle relaxant
  - Sleep stage 4, REM ↓
  - High degree of sedation

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AA: Bromazepam

- General description
  - Lectopam 3mg
  - Usual dosage: 3mg
  - Peak plasma level (p.o.): 0.5~4 hour
  - Lipid solubility: low
  - Elimination half-life: 8~30 hour
- Clinical
  - Anxiety
  - B.i.d or t.i.d. dosing

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AA: Clonazepam

- General description
  - Rivotril 0.5mg
  - Usual dosage: 0.25mg (1/2 T)
  - Peak plasma level (p.o.): 1~4 hour
  - Lipid solubility: low
  - Elimination half-life: 19~60 hour
  - Quick and complete absorption, but slow onset
- Clinical
  - Different dosing
    - Anxiety: 0.5~8 mg/day; Panic: 2~8 mg/day; Acute mania: 4~24 mg/day; Aggression: 1~3 mg/day
  - Anticonvulsant, anxiety, akathisia, aggressive behavior
  - B.i.d or t.i.d. dosing
  - Moderate degree of sedation

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AA: Lorazepam

- General description
  - Ativan 0.5mg
  - Usual dosage: 1mg
  - Peak plasma level: (p.o.) 1~6 hour, (i.m.) 45~75 min
  - Lipid solubility: low
  - Elimination half-life: 8~24 hour
  - Conjugation to lorazepam glucuronide
- Clinical
  - Anxiolytic, sedative, acute dystonia, akathisia, muscle relaxant
  - Slow onset of action
  - Used b.i.d. ~ q.i.d.
  - Anterograde amnesia possible
  - Withdrawal symptom possible
  - Half-life and Vd doubled in liver cirrhosis

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AA: Clotiazepam

- General description
  - Rize 5mg
  - Similar to diazepam with mild antianxiety effect
  - Less GI disturbance

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Non BZD AA: Buspirone

- General description
  - Buspar 5mg, 10mg
  - Azaspirone derivative
    - 5-HT1A agonist, no effect on GABA-BZD complex
- Clinical
  - Use: Anxiolytic
    - Antidepressant (40~90mg/day), augmentation for OCD Tx
    - No anticonvulsant or muscle relaxant effect
  - Advantage
    - Little or no sedative or psychomotor impairment
    - Low potential for abuse or addiction
    - No cross tolerance to BZDs
  - Disadvantage
    - Onset of action after 1~2 weeks; peak action in 3~4 weeks
  - Side effects
    - Dizziness, headache, nervousness

Hyp: Triazolam

- General description
  - Halcion 0.125mg, 0.25mg
  - Usual dosage: 0.25mg
  - Peak plasma level: (p.o.) 1~2 hour
  - Lipid solubility: moderate
  - Elimination half-life: 1.5~5 hour
  - High hepatic clearance: negligible accumulation
- Clinical
  - Hypnotic
  - Rebound insomnia and anxiety reported
  - Dose-related anterograde amnesia, rage, automatism reported

Hyp: Flurazepam

- General description
  - Dalmadom 15mg
  - Usual dosage: 15mg
  - Peak plasma level (p.o.): 0.5~1 hour
  - Lipid solubility: high
  - Elimination half-life: 0.3~3 hour / metabolites 40~250 hour
  - Quick and complete absorption, with rapid onset
- Clinical
  - Hypnotic
  - Increase stage 2 sleep; no effect on REM
  - Daytime sedation, hangover (+)

Hyp: Midazolam

- General description
  - Midazolam 7.5mg (iv 5, 15mg)
  - Usual dosage: 7.5mg,
  - Peak plasma level: (p.o.) 0.5~1 hour, (i.m.) 0.5~1 min
  - Lipid solubility: high
  - Elimination half-life: 1~4 hour, metabolites: 1~20 hour
- Clinical
  - Sedative, IV induction of anesthesia, post-ECT agitation, sleep GFS
  - Fast onset of action
  - Anterograde amnesia frequent

Non-BZD Hyp: Zolpidem

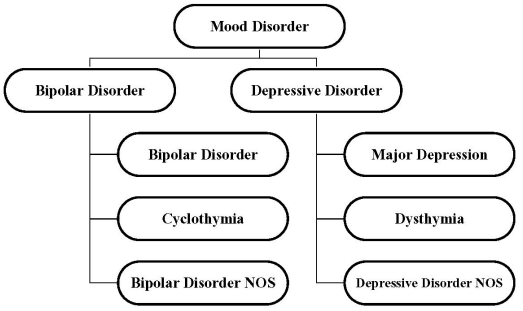
- General description
  - Stilnox, Ambien, 10mg
  - Usual dosage: 10mg (5~20)
  - Peak plasma level: 1.5h, Onset: 30 min
  - Half-life: 1.5~4.5 hour
  - Imidazopyridine derivative
- Clinical
  - No tolerance after 50 weeks of use
  - Sleep architecture similar to physiologic sleep
  - Recommended for old age

Benzodiazepine

약물 사용 원칙

- 내과적 검사를 소홀히 하지 말 것
- 심리적 환경적 요인 파악
- 약에 대한 의사 및 환자의 태도
- 주의 사항 및 부작용을 미리 알려 줄 것
- 약의 선택 : 발현 속도, 반감기, 활성 대사물, 지속시간, 남용 가능성, 과거 경험 참작
- 사용 기간 : 가능한 급성기 2주 이내, 만성 불안의 경우 장기간, 3개월 이상 사용 시 매달 지속적 투여 여부를 신중히 검토

Classification of Mood Disorder



Mood Disorders: Depression

- "Major Depressive Disorder :MDD"
- Life time prevalence: 15%
- Hallmark
  - Mood and volition
    - Depressive mood + Loss of interest
  - Physiological function
    - Appetite, sleep, libido, somatic symptoms, etc.
  - Thought and Cognition
    - Pessimistic ideas, negativism, delusions

우울장애의 증상

- 정신증상
  - 우울한 기분
  - 흥미나 즐거움감소
  - 식욕 및 체중변화
  - 불면/수면과다
  - 피로감, 활력감소
  - 집중력감소
  - 자살사고
- 신체증상
  - 두통
  - 요통, 근육통
  - 오심, 구토, 변비
  - 호흡곤란
  - 흉통

Issues in Depression (1/2)

- Endogenous vs. Reactive
- Masked depression
  - Depression without prominent mood symptoms
  - Frequently misdiagnosed as "Somatization"
- Agitated depression
  - Prominent anxiety, agitation, pacing, sleep disturbance, etc.
- Minor depressive disorder
- Mood disorder due to general medical condition

Issues in Depression (2/2)

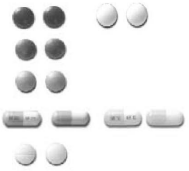
- Pseudodementia
  - Cognitive dysfunction predominant
    - Memory, concentration, disorientation, psychomotor retardation
- Sleep disturbance
  - Middle insomnia and terminal insomnia (early morning awakening)
  - Induction usually OK
  - REM sleep increase: dreaming↑
- Risk of suicide
  - 15% of depressive patients attempt suicide
    - Direct questioning is the key

Classes of Antidepressants

	EXAMPLES
• Cyclic Antidepressants	
– Selective Serotonin Reuptake Inhibitors (**SSRI**)	Fluoxetine, etc.
– Norepinephrine Dopamine Reuptake Inhibitor (**NDRI**)	Bupropion
– Selective Serotonin-Norepinephrine Reuptake Inhibitor (**SNRI**)	Venlafaxine
– Sertonin-2 Antagonist/ Reuptake Inhibitors (**SARI**)	Nefazodone
– Noradrenergic/ Specific Serotonergic Agent (**NaSSA**)	Mirtazapine
– Non-Selective Cyclic Agents (TCA: Mixed reuptake inhibitor/ receptor blocker)	
• NE-Reuptake Inhibitors	Desipramine
• Mixed NE/5-HT Reuptake Inhibitors	Amitriptyline
• Serotonin-Reuptake Inhibitors	Clomipramine
• MAOI	
– Reversible MAO-A Inhibitor	Moclobemide
– Irreversible MAO-A-B Inhibitors	Phenelzine

Traditional ADs

- TCA
  - Amitriptyline (A, E) 10,25mg
  - Imipramine (I) 25mg
  - Nortriptyline (N) 10mg
  - Clomipramine (G) * 10, 25mg
  - Trazodone (G) * 25mg
- MAOI
  - Moclobemide (A) 150mg



Characteristics of TCAs

- Advantages
  - Improves sleep quality, esp. trazodone (T)
  - Reduces agitation
- Disadvantages
  - Takes long (up to 6 weeks) for effect
  - Anticholinergic side effects
    - Dry mouth, blurred vision, constipation, urinary difficulty, etc.
  - GI trouble
    - Anorexia, dyspepsia
  - Weight gain
  - Sedation

New antidepressants

- SSRI: Selective serotonin reuptake inhibitor
  - Fluoxetine (P)
  - Paroxetine (S)
  - Sertraline (Z)
  - Fluvoxamine (D)
- SNRI: Serotonin and norepinephrine reuptake inhibitor
  - Venlafaxine (E)
- NaSSA: Noradrenergic and specific serotonergic antidepressant
  - Mirtazapine (R)
- SARI: Serotonin antagonism and reuptake inhibitor
  - Nefazodone (S)

Characteristics of New ADs

- Advantages
  - Ease of use (q.d. or b.i.d.) / Fast effect (1~2 weeks)
  - No anticholinergic S/E
  - Seldom sedated
- Disadvantages
  - Sleep disturbances (SSRI, SNRI)
    - Exception: Mirtazapine, Nefazodone
  - Anxiety or agitation
  - Sexual dysfunction
  - Anorexia (acute), weight gain (chronic)
  - GI trouble (nausea, dyspepsia)
  - Serotonin syndrome: anxiety, agitation
  - Serotonin withdrawal syndrome: apathy and lethargy

Differences of Side Effect in New ADs

	Drug Interaction	Sexual Dysfunction	Sleep Disturbance	Serotonin Syndrome	Weight Gain	Sedation
SSRI: Fluoxetine	++	++	++	+	+	-
SSRI: Paroxetine	++	++	++	+	+	-
SSRI: Sertraline	+	++	++	+	+/-	-
SNRI: Venlafaxine	-	++	++	+	-	-
SARI: Nefazodone	++	-	-	+/-	-	+
NaSSA: Mirtazapine	-	-	-	-	++	++

MAOI: Moclobemide

- General description
  - Aurorix 150mg
  - Reversible inhibitor of MAO-A
- Clinical
  - Target: atypical depressive symptoms
  - Advantage: refractory depression, for epileptic patients, for social phobia
  - Disadvantage: food restriction, drug interaction
  - Side effects: hypertensive crisis, serotonin syndrome, anticholinergic side effect

SSRIs

- Fluoxetine
  - Prozac (10, 20mg)
  - Usual dosage 10~60mg
- Paroxetine
  - Seroxat (10, 20mg), Paxil
  - Usual dosage 10~40mg
- Sertraline
  - Zoloft (50mg)
  - Usual dosage 50~200mg
- Fluvoxamine
  - Dumirox (50mg), Luvox
  - Usual dosage 50~250mg

SSRIs: Common Characteristics

- General description
  - Serotonin RI
  - Stimulating ADs
- Clinical
  - Target: Depressive episodes, irritability, OC, phobia, atypical depression (hypersomnia, hyperphagia)
  - Advantage: First line for depression, panic, obsession, eating disorders
  - Disadvantage: drug interaction
  - Side effects: Anxiety, akathisia, insomnia, weight loss, sexual dysfunction

SNRI: Venlafaxine

- General description
  - Efexor: 37.5mg, 75mg
  - NE RI + 5-HT RI
  - Usual dosage: 75~300mg
- Clinical
  - Stimulating antidepressant
  - Advantage: no severe drug interaction (low protein binding), dose-dependent responsiveness
  - Disadvantage: in HTN patients, 3 times with meals
  - Side effects: hypertension, psychosexual dysfunction

NaSSA: Mirtazapine

- General description
  - Remeron: 15mg, 30mg
  - Usual dosage: 10~40mg
  - Presynaptic alpha2 antagonism → NE, 5-HT release↑
  - Postsynaptic 5-HT2,3 blockade → NE, 5-HT1A↑
- Clinical
  - Sedating antidepressant
  - Target symptoms: Anxiety and insomnia, depression
  - Advantage: No severe drug interaction
  - Disadvantage: Leukopenia, agranulocytosis?
  - Side effects: sedation, dizziness, orthostatic HoTN, weight gain

St John's wart : Jarsin

- General description
  - Jarsin: 300mg
  - Usual dosage: 900mg
- Clinical
  - Non sedating antidepressant
  - Target symptoms: Mild to Moderate depression, Anxiety, somatoform (dizziness, headache)
  - Advantage: Minor side effects
  - Side effects: GI trouble, photosensitivity

Other: Bupropion

- General description
  - Wellbutrin
  - NE RI + DA RI
- Clinical
  - Stimulating antidepressant
  - Target symptoms: anergia, anhedonia, psychomotor retardation, poor concentration
  - Advantage: in attention deficit patients, sexual dysfunction, anti-smoking agent
  - Side effects: anxiety, insomnia, weight loss, seizure

FAQ

- 불안증, 공황장애 등에서 BZD 사용기간?
  - Dose titration: 4~8 weeks
  - Maintain: 6~12 month
  - Taper to D/C: 6~12 month
  - Behavior + Cognitive Therapy important
- Xanax tapering 실패 시 대처방안
  - Symptom delineation
  - Change to / combine with longer acting BZD
  - For panic disorder: use SSRI

FAQ

- Insomnia에서 BZD 처방은 언제 고려?
  - Sleep disturbance with anxiety (initial insomnia)
  - Combined use of TCA
  - PRN use not recommended
  - Special case: night terror in children
- 수면제 복용 습관화된 환자들의 처치 방법
  - Sleep hygiene: non-pharmacological management FIRST!
  - TCA or new ADs provide better sleep profile
  - Use of antipsychotics in selected cases

FAQ

- 항 우울효과가 나타날 때까지의 manage
  - Acute stage: consider ECT
  - Weekly follow up
  - Drugs with rapid onset of action: SSRIs, NaSSA
  - Addition of ample Aas
- 우울증 치료 시 항우울제의 평균 사용기간?
  - Single episode: titration 4~8 weeks → Maintenance: 6 month → Tapering 3~6 month
  - Multiple episodes (recurrent MDD): at least 2 years in remission
  - Special cases