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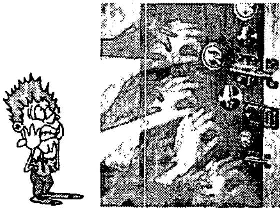
분당서울대학교병원 신경정신과
하 태 현

Brief Review of Biological Therapies for Anxiety Disorders



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Treatment Decision for Panic Disorder

Decision 1 treatment of choice	SSRI1				
Decision 2 Switching	SSRI2	AD	HPBZ		
Decision 3 Augmentation	HPBZ				
Decision 4 Other options	TCA	MAOI	RIMA		
Decision 5	Mirtazap.	Nefazod.	Venlafax.	Reboxet.	MS
Decision 6 Experimental	Pindolol	BAP			
Decision 7 Long term	Continue, at same dose that achieved remission, for 1 years, followed by very gradual down-titration				

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Treatment Decision for SAD

Decision 1 treatment of choice	SSRI1				
Decision 2 Switching	SSRI2	MAOI	RIMA	Venlafax	
Decision 3 Augmentation	Buspirone				
Decision 4 Other options	HPBZ	Gabapen.			
Decision 5	Nefazod.	SNRI			
Decision 6 Experimental	Ondansetr.	Pindolol	NAP		
Decision 7 Long term	Continue, at same dose that achieved remission, for 1 years, followed by very gradual down-titration.				

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Treatment Decision for PTSD

Decision 1 treatment of choice	SSRI				
Decision 2 Switching	AD				
Decision 3 Augmentation	MS	NAP			
Decision 4 Other options	MS	NAP	Nefazod.	Venlafax.	
Decision 5	BZ	Clonidine	Propranol.		
Decision 6 Experimental	TMS	Inositol			
Decision 7 Long term	Continue, at same dose that achieved remission, for 1 years, followed by very gradual down-titration.				

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Treatment Decision for OCD

Decision 1 treatment of choice	SSRI1				
Decision 2 Switching	SSRI2	Clomipram.			
Decision 3 Augmentation	NAP	Buspir. /Li	SSRI + Clomipram.	Clonazep.	
Decision 4 Other options	i.v. Clomipram.	Venlafax.	MAOI	Clonazep.	Inositol
Decision 5	ECT	Anti-androgen	Surgery		
Decision 6 Experimental	5-HT agonist	TMS	VNS		
Decision 7 Long term	Continue, at same dose that achieved remission, for 1 years, followed by very gradual down-titration				

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Pharmacotherapy for Anxiety Disorder: Summary

- treatment of choice: SSRI
- 1st switching strategy: SSRI
- Differences

	Panic	SAD	PTSD	OCD
non 5-HT	effective	effective	effective	*negative*
MS	may	-	may	*negative*
BZ	effective	effective	*negative*	augment

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Comorbidity in Anxiety Disorders

Any anxiety disorder	74.1%
Panic disorder	92.2%
Agoraphobia	87.3%
Social phobia	81.0%
Simple phobia	83.4%
Generalized anxiety disorder	91.3%
Post-traumatic stress disorder	81.0%

Rates of comorbidity among people with lifetime NCS/DSM-III-R anxiety disorder (Kessler et al., 1997)

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Meaning of Comorbidity

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Comorbidity

- Feinstein, 1970
  - ✓ any distinct additional clinical entity, that has existed or that may occur during the clinical course of a patient who has the index disease under study
- into psychiatry
  - ✓ the presence of an antecedent or concurrent psychiatric syndrome.., with a *hierarchy* between the *principal diagnosis* and the others (Strakowsky, 1995)
  - ✓ distinction of "co-occurrence" (Andrews, 1996)

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Definition of Comorbidity

- Two or more disease, with distinct etiopathogenesis (or, if the etiology is unkwon, with distinct pathophysiology of organ or system), that are present in the same individual in a defined period of time (Vella et al., 2000)

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Diagnostic System

- reliability and validity
  - ✓ before DSM-III, e.g. 'anxiety neurosis'
    - low reliability
    - low validity
  - ✓ DSM-III, DSM-IV, e.g. 'GAD'
    - high reliability
    - low validity
  - ✓ DSM-?, e.g. 'anxiety associated with psychobiological markers x, y, z'
    - high reliability
    - high validity

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Diagnostic System and Comorbidity

- concept highlighting both the strength and weakness of current diagnostic system (Feinstein, 1970)
- an artifact of diagnostic system? (Maj, 2005)
- complex and confusing pictures in psychiatry
  - ✓ high prevalence (anxiety disorders, personality disorders)
  - ✓ within-category heterogeneity
  - ✓ between-category overlapping constructs
  - ✓ hierarchical ?
  - ✓ frequent changes in criteria

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Forms of Comorbidity

- co-occurrence

Different phenomenology of basic abnormality
Key cerebral disturbances consequential perturbation

- lifetime comorbidity

Prodrome
Complete picture
Vulerability
Florid illness

Complete picture
Sequalae
Florid illness
Copying or Decompensation

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Comorbidity among Anxiety Disorders

	Panic disorder	Agoraphobia	Social phobia	Simple phobia	GAD
Panic disorder	-	-	-	-	12.3
Agoraphobia	11.9	-	7.1	8.7	5.8
Social phobia	4.8	-	-	-	3.8
Simple phobia	7.9	-	7.8	-	4.9
GAD	-	-	-	-	-
PTSD	3.9	4.2	2.8	3.8	3.9

Odds ratio significant at the 0.05 level (Kessler et al., 1997)

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COMORBIDITY with DEPRESSION

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Epidemiology

- **frequent than expected**
- **of patients with lifetime depression**
  - ✓ **47% in ECA study** (Reiger et al., 1998)
  - ✓ **58% in the NCS** (Kessler et al., 1996)
  - ✓ **57% in a meta-analysis** (Clark, 1989)
- **Odds ratio** (Kessler et al., 1996)
  - ✓ **2.9 for SAD**
  - ✓ **4.0 for panic disorder and PTSD**
  - ✓ **6.0 for GAD**

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Impact of Comorbid Anixety Disorders

- **More severe symptoms**
- **More chronic illness**
- **Decreased psychosocial function**
- **Increased work absenteeism**
- **Greater suicidal potential**
- **Greater refractoriness to treatment**

(Angst, 1993; Bronisch and Wittchen, 1994; Brown et al., 1996; Clayton et al., 1991; Coryell et al., 1992; Emmanuel et al., 1998; Gaynes et al., 1999; Kendall et al., 1992; Kessler et al., 1994; Levitt et al., 1993; Lewinsohn et al., 1995; Pawlak et al., 1999; Sartorius et al., 1996; Shafii et al., 1998; Tollefson et al., 1993)

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Differentiation

Anxiety	Overlap	Depression
Hypervigilance, Startle response	Irritability, Apprehension/panic	Depressed mood, anhedonia
Worries about future	Negative rumination/worry	Rumination about past
Agoraphobia	Social withdrawal, distress, dysfunction	Loss of interest
	Agitation	Retardation
	Insomnia, decreased concentration, chronic pain, GI complaints, fatigue	Weight gain/loss

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Key Differentiation

- **Distinction of Affect**
- **Two or Three factor model**
  - ✓ High negative affect in both conditions
  - ✓ Absence of positive affect in depression
  - ✓ Hyper-arousal in anxiety disorder

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Temporal relationship

- **anxiety-to-depression**
  - ✓ SAD and simple phobias
  - ✓ cf) other anxiety disorders: at the same time as or after depression

  (Kessler et al., 1996; Schatzberg et al., 1998)
- **mechanism proposed**
  - ✓ dysfunction in GABA system may ultimately lead to changes in monoamine systems and depression (Roy-Byrne and Katon, 1997)
  - ✓ maternal separation, protest (a prototype of anxiety), then later despair (a prototype of depression) (Bowlby, 1980)
  - ✓ early uncertain helplessness in the face of stressors become apparent (Beck, 1967)

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Treatment Decisions for Depression

Decision					
Decision 1 treatment of choice	AD1	AD1 + BZ			
Decision 2 Switching	AD2				
Decision 3 Augmentation	Lithium	T	NAP	Buspirone	Tryptophan
	Pindolol	D agonists	Hormonal agents	AD1 + AD2	
Decision 4 Other options	ECT	LT	[illegible]	St. John's wort	SD
Decision 5	Surgery				
Decision 6 Experimental	TMS	VNS			
Decision 7 Long term	Continue, in same dosage that achieved remission				

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Treatment issues

- **broad spectrum agents**
  - ✓ SSRIs
  - ✓ new ADs
- **may need higher dose than usual**
- **trial duration**
  - ✓ depression, panic, GAD, PTSD: 6-8 weeks
  - ✓ OCD or SAD: upto 12 weeks

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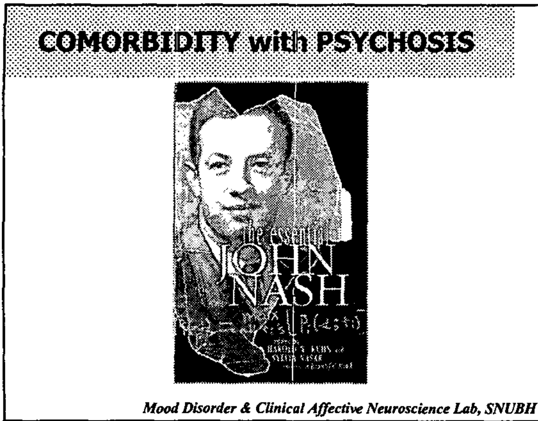
Science and Charity, 1897, Picasso.
Oil on canvas, Museo Picasso, Barcelona, Spain.

COMORBIDITY with PSYCHOSIS



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Panic in Psychosis

- **Epidemiology**
  - ✓ **in schizophrenia 28-63%** (Boyd, 1986; Hofman, 1999; Argyle, 1990)
- **Implication of comorbidity**
  - ✓ **higher rates of MDD, phobia, AN, substance abuse (not GAD and OCD)** (Goodwin et al., 2001)
  - ✓ **poor rehabilitative outcomes, QOL** (Goodwin et al., 2001)
  - ✓ **more psychotic symptoms, suicidality** (Goodwin et al., 2002)
  - ✓ **more positive symptoms** (Craig et al., 2002), **paranoid subtype** (Bayle et al., 2001), **hostility** (Chen et al., 2001)

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OCD in psychosis

- **prevalence in schizophrenia: 1.1% to 59.6%** (Hwang, 2005)

"Schizo-obsessive"
- ***Three types suggested*** (Hwang, 2005)
  - ✓ **"psychotic or malignant" OCD**
    - **often refractory to anti-OC medication**
  - ✓ ***new onset concurrent with schizophrenic onset***
    - **worse course and prognosis**
  - ✓ **transient and varied OC symptoms during course**
    - **little *difference in course and prognosis***
- **AAPs and OC developments reported**

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Differentiation

Craig et al., 2002

more than 90% patients with anxiety symptoms were not recognized!

anxiety disorders found in 43-45% inpatients with schizophrenia, schizoaffective disorder, and bipolar disorder

Cosoff et al., 1998

almost none of those were recognized and treated

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Treatment of Panic Symptoms in Schizophrenia

- **Paucity of data**
  - ✓ **Quetiapine** (Takahashi et al., 2004)
  - ✓ **dose reduction of neuroleptics** (Higuchi et al., 1999)
  - ✓ **CBT** (Arlow et al., 1997)
  - ✓ **imipramine** (Siris et al., 1989)
  - ✓ **alprazolam reduced positive and negative symptoms** (Kahn et al., 1988; Sandberg et al., 1987)

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Treatment of OC symptoms in Schizophrenia

- **SRIs efficacious in many open label studies**
- **controlled studies**
  - ✓ **Clomipramine**
    - **in a double-blind placebo controlled study** (Berman et al., 1995)
  - ✓ **Fluvoxamine**
    - **in a controlled trial** (Reznik et al., 2000)
- **Clozapine monotherapy may be effective**
  - ✓ **in second group**
  - ✓ **in first group, combination needed** (Reznik, 2004)

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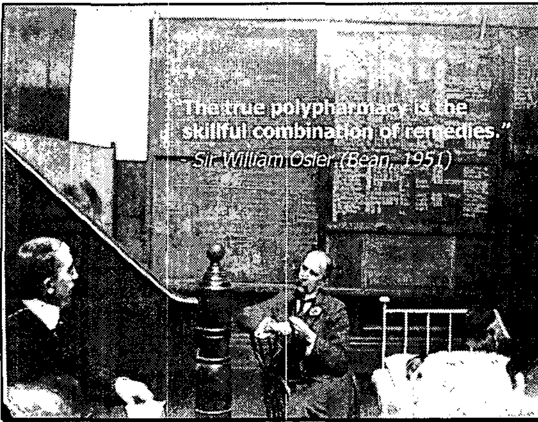

COMORBIDITY with BIPOLAR DISORDER

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Epidemiology

- **any anxiety disorder lifetime 18-51%** (Strakowski and Sax, 1998; Simon et al., 2004; Bauer et al., 2005)
- **lifetime prevalence**
  - ✓ **GAD 5-32%**
  - ✓ **OCD 9-35%**
  - ✓ **Panic disorder 16-37%**
  - ✓ **PTSD 7-50%**
  - ✓ **SAD 10-31%**

  (Simon et al., 2004; Goodwin et al., 2002; McElroy et al., 2001; Strakowski and Sax, 1998; Kruger et al., 1995)

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Current and Lifetime Prevalence

TABLE 2 Current and Lifetime Anxiety Disorder Comorbidity in Bipolar Disorder Patients Enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) by Bipolar Subtype and Relative to the General Population

Anxiety Disorder Diagnosis	Current: Bipolar I Disorder (N=360)		Current: Bipolar II Disorder (N=115)		Current: Full Sample (N=475)		Lifetime: Bipolar I Disorder (N=360)		Lifetime: Bipolar II Disorder (N=115)		Lifetime: Full Sample (N=475)		Lifetime Prevalence, General Population (%)[a]
	N	%	N	%	N	%	N	%	N	%	N	%	
Any anxiety disorder	123	34.2	22	19.1[b]	145	30.5	190	52.8	53	46.1	243	51.2	—[c]
Panic disorder (with or without agoraphobia)	33	9.2	5	4.4	38	8.0	66	18.3	16	13.9	82	17.3[d]	3.5
Agoraphobia no panic disorder	20	5.6	1	0.9[e]	21	4.4	37	10.3	3	2.6[b]	40	8.5[f]	5.3
Social anxiety disorder	50	14.0	10	8.7	60	12.7	81	23.2	21	18.3	104	22.0[d]	13.3
Obsessive-compulsive disorder	24	6.7	3	2.6	27	5.7	39	10.9	8	7.0	47	9.9[f]	2.5
Posttraumatic stress disorder	23	6.4	1	0.9[b]	24	5.1	67	18.8	14	12.2	81	17.2[d]	7.8
Generalized anxiety disorder	46	12.9	12	10.4	58	12.3	68	19.1	19	16.5	87	18.4[d]	5.1

[a] From the National Comorbidity Survey (3, 17). Data on OCD from the Epidemiologic Catchment Area study (16).
[b] Significantly different than rate for bipolar I subtype (p<0.01, Fisher's exact test).
[c] Not available for any anxiety disorder as defined.
[d] Significantly different than rate for general population (p<0.001, Fisher's exact test).
[e] Difference from rate for bipolar I subtype approached significance (p<0.05, Fisher's exact test).
[f] Significantly different than rate for general population (p<0.05, Fisher's exact test).

Simon et al., STEP-BD data, 2004

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Impact

- younger age at onset
- greater suicidality
- severe illness
- poorer functioning
- lower responsiveness to lithium
- worse outcome
  - ✓ type (GAD, SAD) more important than number (Boylan et al., 2004)

(Young et al., 1998; Cassano et al., 1999; Feske et al., 2000; Frank et al., 2000; Simon et al., 2004; Boylan et al., 2004)

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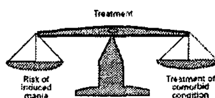
Therapeutic Delimma

- agents that are most effective for anxiety are potentially harmful for bipolar disorders
  - ✓ triggering manic episode
  - ✓ cycle accerelation
  - ✓ precipitating suicidality



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Treatment Decision for Panic Disorder

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Decision 6 Experimental	Pindolol	NAP			
Decision 7 Long term	Continue, at same dose that achieved remission, for 1 years, followed by very gradual down-titration				

Valproic acid (double blind placebo controlled, Guay, 1995)
Carbamazepine (uncontrolled study, Uhde et al., 1988)
Gabapentin (suggested, Perugi et al., 1999)

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OCD and Bipolar Disorder

- **mostly bipolar II patients**
- ***more episodic course of OCD***
- **frequent MDE**
- **higher rates of sexual and religious obsessions**
- **higher rates of panic disorder, substance abuse and hospitalization**
- ***less favorable response to anti-OCD treatment***
  (Kruger et al., 2000; Perugi et al., 2002; Hantouche et al., 2002; Raja and Azzoni, 2004)

- **Is episodic OCD bipolar?** (Swartz and Shen, 1999)

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Case Series of OCD with Bipolar Disorder

Case	Temporal relation between mood and OCD symptoms	First degree relatives with mood disorder	Psychotic symptoms	Current or past evidence of manic episodes or induction of (hypo)mania by antidepressants	Worsening of OCD symptoms with antidepressants	Improving of OCD symptoms with mood stabilizers or atypical antipsychotics
1	Yes	Yes	No	Yes	No	?
2	Yes	Yes	No	Yes	No	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	No	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	No	Yes
6	Yes	No	Yes	Yes	No	Yes
7	Yes	Yes	Yes	Yes	Yes	Yes

Case	Hostility	Need of hospitalization	Abrupt onset of OCD symptoms	Symptom subtype	Suicidal intent	Course
1	No	No	Yes	Error obsessions, checking	No	Episodic
2	Yes	Yes	Yes	Doubts, need for precision, checking	Yes	Continuous
3	Yes	No	Yes	Somatic concern, avoidance	Yes	Continuous
4	No	Yes	Yes	Contamination, cleaning	Yes	Deteriorative
5	Yes	Yes	Yes	Contamination, checking	Yes	Continuous
6	No	Yes	Yes	Contamination, cleaning	Yes	Deteriorative
7	Yes	Yes	Yes	Somatic concern, checking	Yes	Continuous

Raja and Azzoni, 2004
hierarchical priority of a bipolar diagnosis

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Differentiation

- atypical features of bipolar spectrum disorders
  - ✓ more unrecognized bipolar than anxiety
  - ✓ therefore, reconsider diagnosis in resistant cases with anxiety
- the course of the target anxiety symptom ?
  - ✓ associated with mood episodes
  - ✓ cycling with full remission

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Treatment

- first goal should be mood stabilization
- combination
  - ✓ of mood stabilizers
  - ✓ of AAPs
- HPBZ
- ECT
- *SSRIs or RIMA with extreme cautions*

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Conclusion

- comorbidity predicts worse course and needs special therapeutic options
- precise diagnosis: *Do not miss!*
  - ✓ current system: not hierarchical
  - ✓ therefore, structured interview (at least, screening questions) should be used
- hypothetical hierarchy can be made by thorough evaluation of longitudinal course
- broad spectrum agents are preferred, with cautions of drug-drug interactions and impacts of the medication on the course
- psychosocial approach should be considered

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