ALGER, 12-13 Mai 2005

Première Rencontre Franco-Algérienne sur les Troubles Bipolaires

2ème Congrès de la SFAP

Sub-types of Bipolar Disorders: Current Epidemiological & Clinical Pictures

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ALGER, 12-13 Mai 2005

First Franco-Algerian Meeting on Bipolar Disorder

Most patients report having been mis-diagnosed (USA)

National Depressive and Manic Depressive Association (NDMDA) surveyed members with bipolar disorder

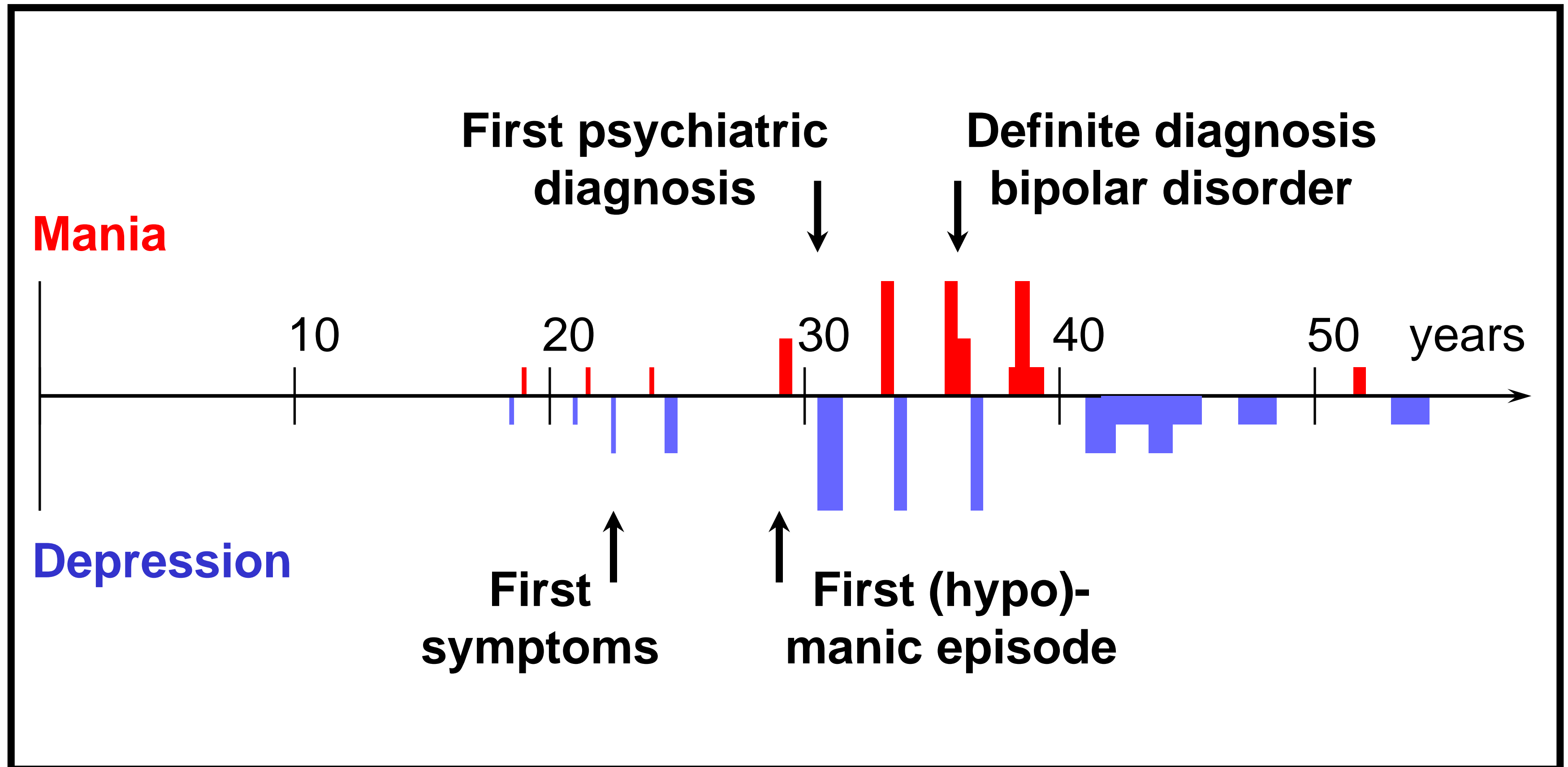
	1994	2000
Misdiagnosis (%)	73	69
Most frequent misdiagnosis	Unipolar depression	Unipolar depression
Without correct diagnosis* for ≥10 years (%)	24	35

- Mean age of onset early 20s
- Long delays before correct diagnosis
- Rates of misdiagnosis have remained high

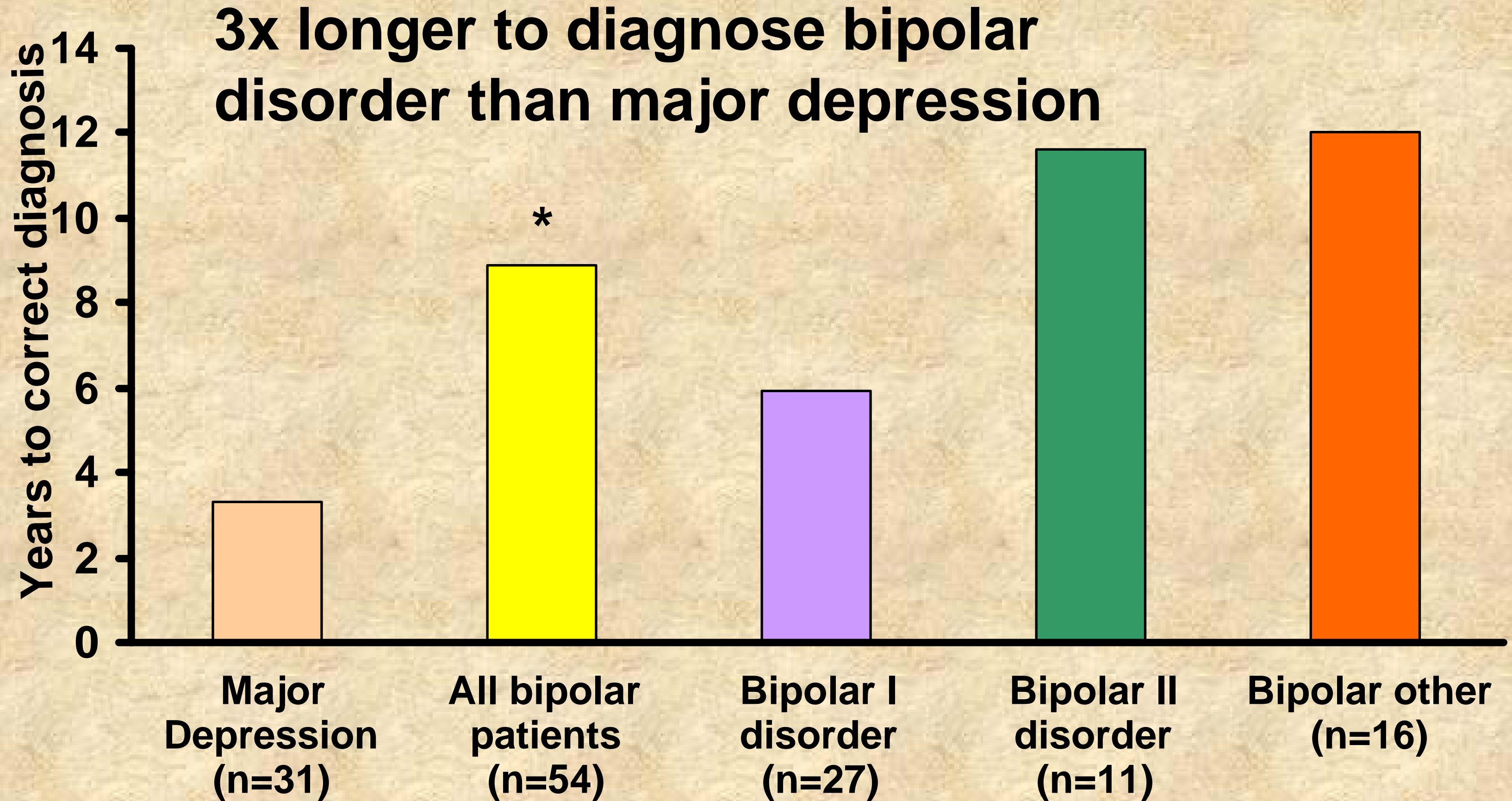
*Bipolar disorder

Lish JD, et al. J Affect Disord 1994;31:281–94
Hirschfeld RMA, et al. J Clin Psychiatry 2003;64:161–74

Diagnostic delay in bipolar disorder: Typical pattern



Time to diagnosis



*p=0.003 vs major depression

Ghaemi et al 2000

Bipolar Disorders

- Major problem : Under-/ Misdiagnosis +++
- High frequency rate: more than 50% of all Major Depressive Episodes
- Complex and instable clinical picture
- Associated risks: behavioral problems at school age, anxiety comorbidity, suicide, offending behavior, hospitalizations, recurrence, disability, chronic physical disease, worsening by antidepressants…
- Lack of evidence or experts consensus for appropriate treatment of acute BP-II Depression and long term management of the soft BP spectrum (BP-II, BP-II1/2, BP-III, and BP-IV)

DSM-IV Bipolar Disorder

- Schizoaffective disorder, bipolar type
- BD I
- BD II
- Cyclothymia
- BD NOS
  - Recurrent or sporadic brief hypomania (>several hours <4 days)
  - Medication-induced hypomania
  - Substance-induced hypomania
  - Recurrent depression (± a family history of mania/hypomania)

Akiskal HS et al. J Affect Disord. 2000;59:S5-S30.

Bipolar disorder is a highly prevalent illness

	Life time prevalence
• Bipolar I disorder	0.2-1.6%
• Bipolar spectrum disorder	3-7%

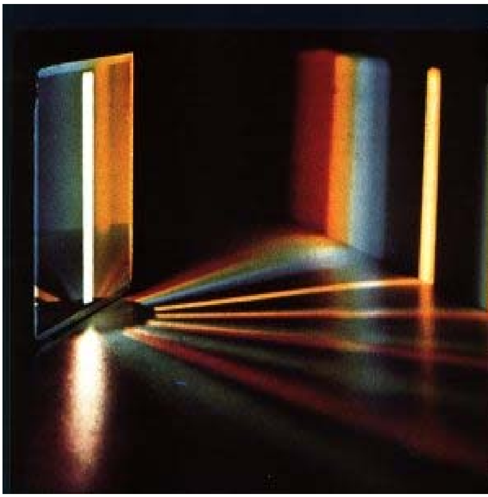
- Bipolar spectrum disorder
  - Bipolar I disorder
  - Bipolar II disorder
  - Cyclothymia
  - Bipolar disorder NOS
  - secondary mania (somatic illness, drugs)

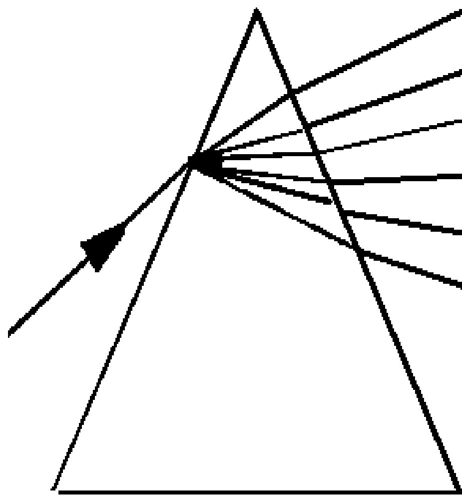
Goodwin FK, Jamison KR. Manic-depressive illness. Oxford University Press, 1990;
Angst J & Marneros A. J Affect Disord 2001;67:3-19

Methodological factors influencing rates of Bipolarity

- Breadth of criteria
- Instruments used
- Lay vs clinical interviewers
- Population studied
- Sample size
- Single vs repeated observations
- Interview of patient vs relatives
- Timing of interview relative to phase of illness

Akiskal et al, JAD 2000





…distinction apparemment qualitative dérivant d'un continuum quantitatif.

The Mood Spectrum

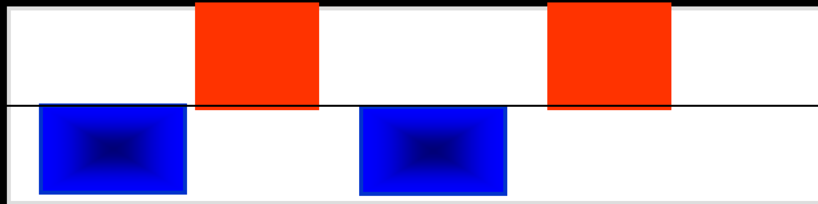
psychotic mood congruent or mood incongruent	D	Dm	DM	Md	M
non-psychotic	D	Dm	DM	Md	M
subthreshold	d		dm		m
”normal“	dsx		dmsx		msx

Bipolar Spectrum

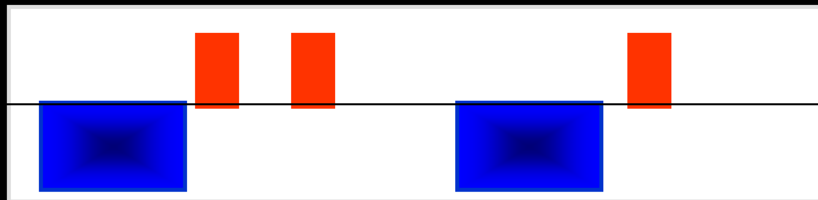
• Bipolar 1/2	Psychosis, depression and mania
• Bipolar I	Mania
• Bipolar I - 1/2	Protracted hypomania
• Bipolar II	Depression + hypomania (4 D or +)
• Bipolar II - 1/2	Cyclothymic depression
• Bipolar III	Pharmacologic hypomania
• Bipolar III - 1/2	Hypomania + alcohol/stimulants
• Bipolar IV	Hyperthymia + depression

(modified from Akiskal et Pinto, 1999)

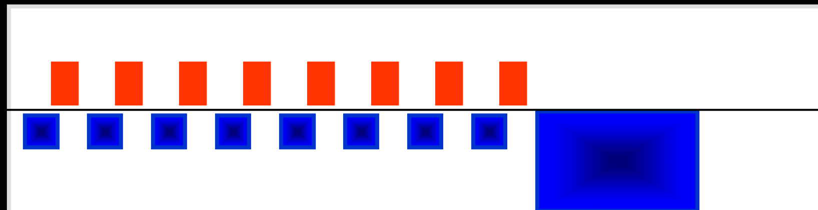
Spectre Clinique Bipolaire



Trouble Bipolaire type I :
Présence d ’au moins un épisode maniaque

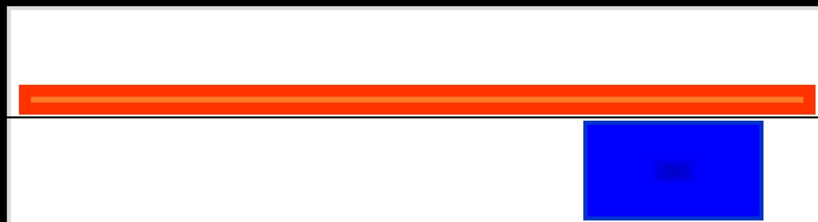


Trouble Bipolaire type II :
Dépression majeure avec des épisodes hypomaniaques spontanés



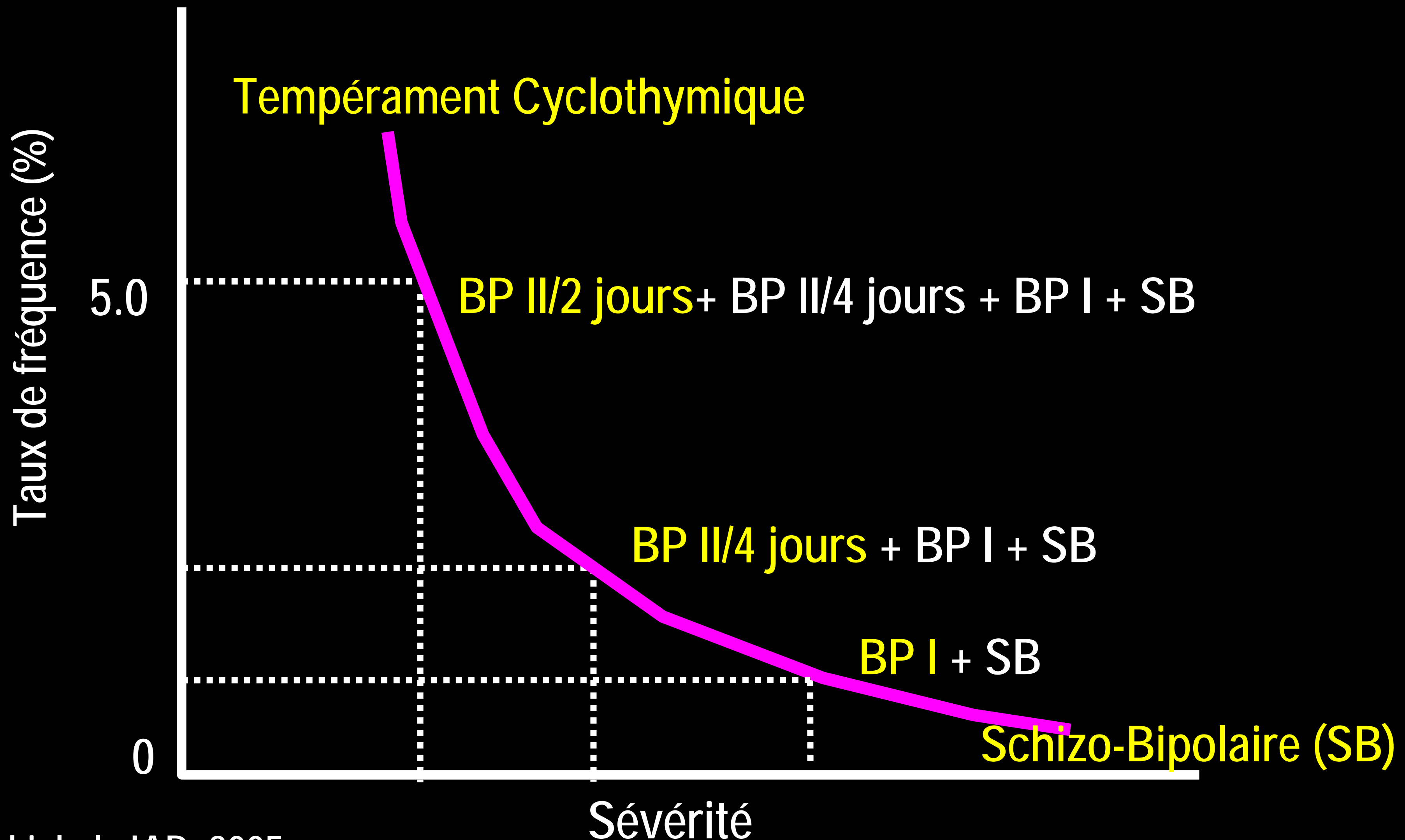
Trouble Bipolaire type II 1/2 :
Dépression majeure avec cyclothymie

Trouble Bipolaire type III :
Dépression majeure avec ou manie hypomanie induite par le traitement



Trouble Bipolaire type IV :
Dépression majeure avec tempérament hyperthymique

Prévalence des phénotypes bipolaires en fonction de la sévérité



Akiskal, JAD, 2005

The challenge: hypomania as specifier for bipolar-II and minor bipolar depression

DSM-IV criteria

- Mood symptoms
- 3 / 4 of 7 symptoms
- Duration: ≥4 days

Zurich strict criteria

- Overactivity
- 3 of 7 symptoms
- Duration: ≥ 1 day
- Consequences

Zurich broad criteria

- Overactivity
- 2 of 7 symptoms
- Duration: ≥1 day

Angst,IRBD LYON, April 2005

Dépression =

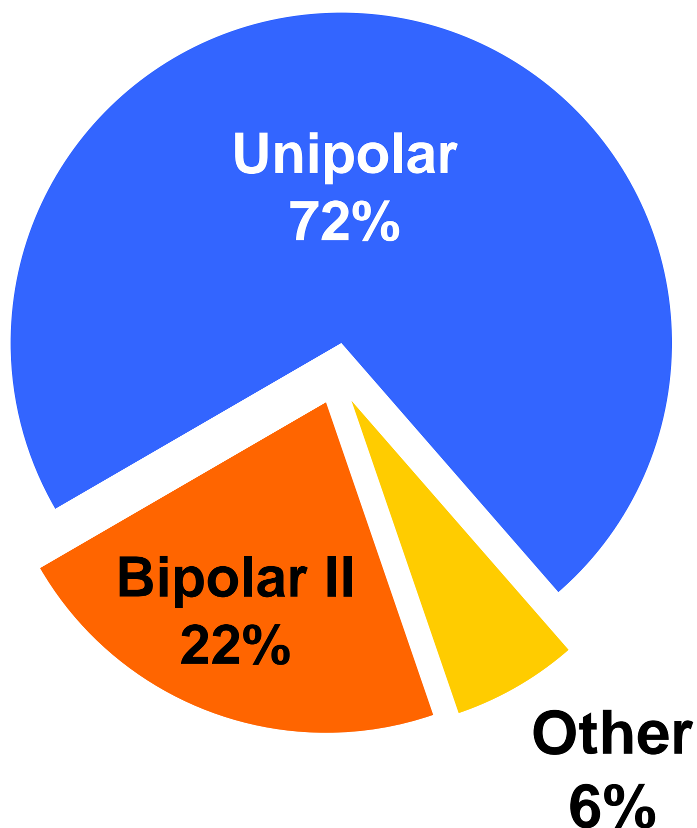
Masque le plus trompeur

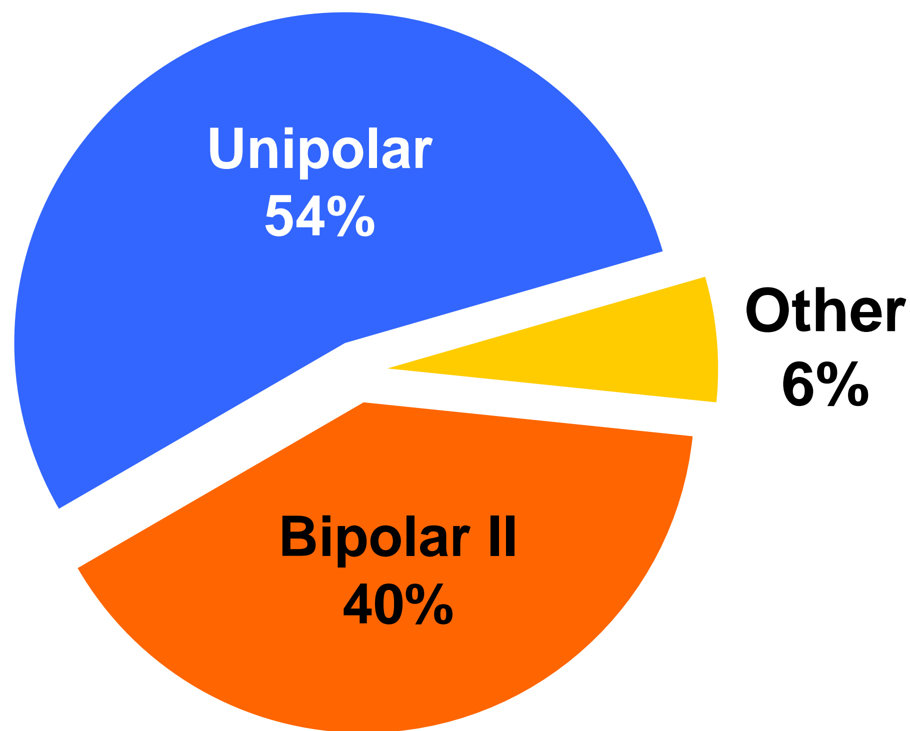
de la bipolarité

How many major depressives are bipolars? Patient studies

	Proportion of bipolar II (%)
Akiskal, et al. 1987	50
Cassano, et al. 1992	30
Dunner, et al. 1993	38
Manning, et al. 1999	39
Allilaire, et al. 2001 (EPIDEP)	40
Akiskal, et al. 2003	56
Benazzi, et al. 2003	60
Review of Akiskal 2002	27–65

Under-recognition of bipolar II in patients presenting with major depression (France)





Hantouche EG, et al. J Affect Disord 1998;50:163–73
Allilaire JF, et al. Encephale 2001;27:149–58

The challenge: hypomania as specifier for bipolar-II and minor bipolar depression

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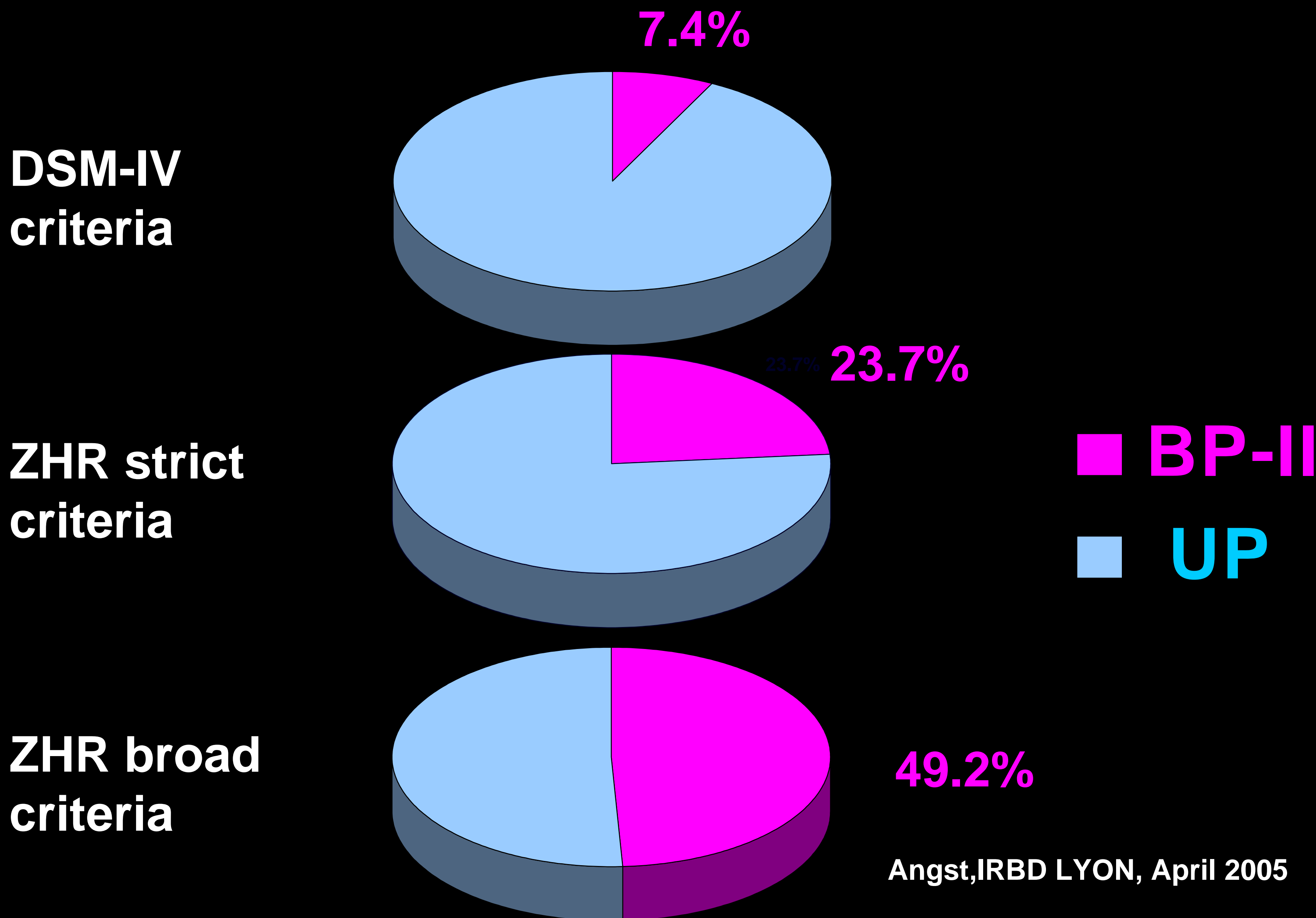
Angst,IRBD LYON, April 2005

BP-II as % of major depressive episodes

Age 40/41 years



Towards a re-definition of subthreshold bipolarity

- Hyperactivity as major criteria for the Dx of hypomania.Together with euphoric or irritable mood
- Hypomanic symptoms when in alternation with Major or “Minor” Depression = Bipolarity
- “New”definition of Bipolar II : prevalence 10.9%
- “Minor” Bipolar Disorder or Temperamental manifestations: prevalence of 12.8%
- Bipolar Spectrum: 23.7%
- Criteria for hypomania needs redefinition

Angst J et al. *J Affect Disord.* 2003. Jan.

Classification of Bipolar Disorder
By Ritti, 1880

- First degree: Melancholic states with simple exaltation

  (TYPE I)

- Second degree: melancholic states with frank acute mania (psychotic features)

  (TYPE II)

Before Ritti, similar classification in a medical thesis by Geoffroy, 1861

Hantouche, “Double Folie”
In press, Odile Jacob, Paris

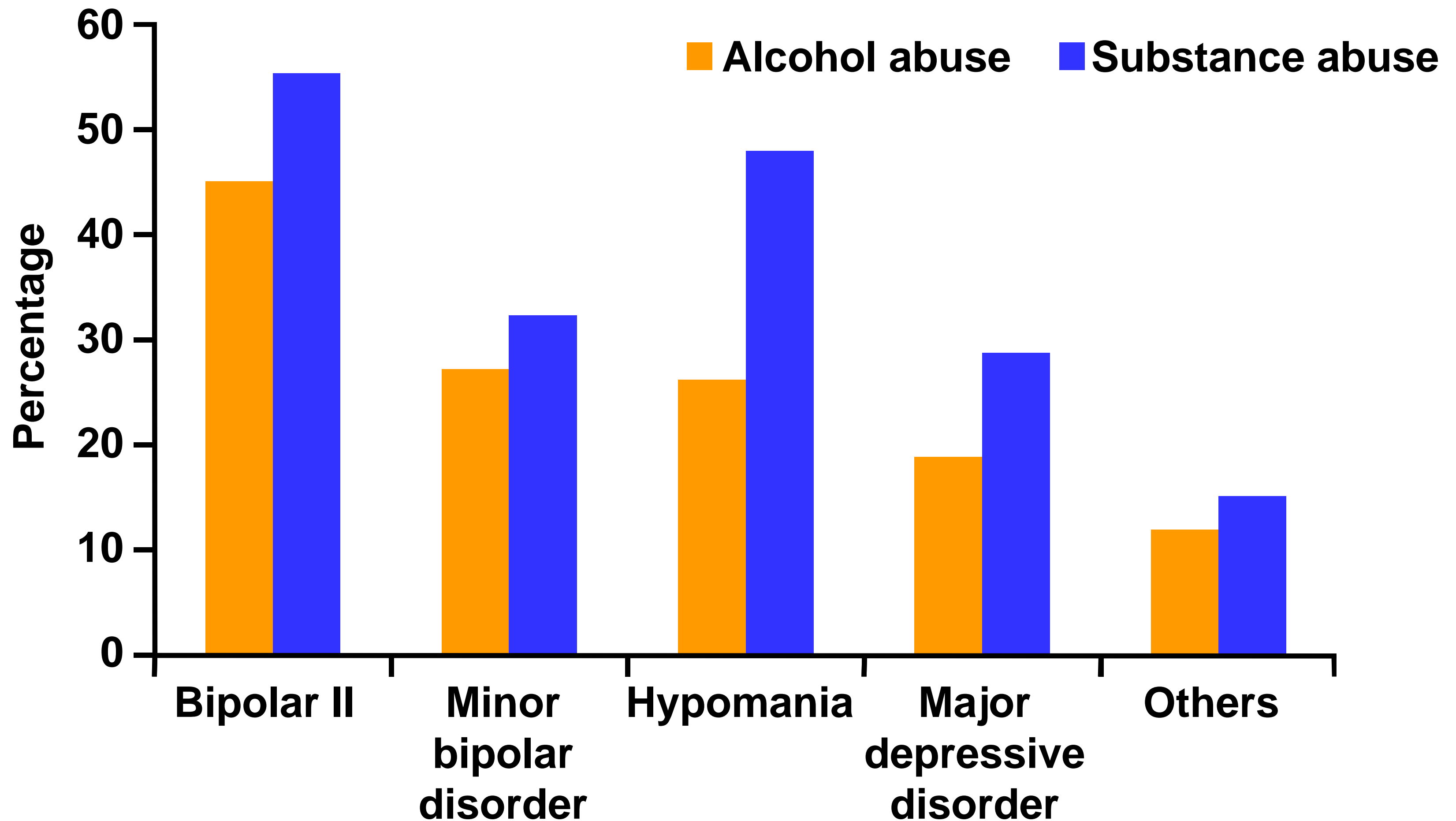
Dual diagnosis: high prevalence of comorbid psychiatric disorders

Disorder	Lifetime comorbidity with BPI disorder	
	Prevalence (%)	Odds ratio
Generalised anxiety disorder	42.4	14.0*
Social phobia	47.1	5.9*
Panic disorder	32.9	14.0*
PTSD	38.7	8.9*
Any anxiety disorder	93.0	34.8*
Alcohol dependence	61.2	9.8*
Drug dependence	40.6	8.6*
Any substance use disorder	71.1	6.9*
Dysthymia	49.7	14.9*
Conduct disorder	59.5	10.0*

*$p<0.05$

Kessler RC. In: Tohen M, editor. Comorbidity in Affective Disorders. New York: Marcel Dekker, Inc., 1999. p.1–26

Comorbidity of alcohol and substance abuse in psychiatric disorders



Angst J, et al. J Affect Disord 2003;73:133–46

Abus Multiples

Cocaïne
Stimulants

Alcool
Cannabis

Opiacés
Sédatifs
Antalgiques

HYPOMANIE

MANIE

ETAT MIXTE

DEPRESSION

Himmelhoch et al., 1976; Estroff et al., 1985; Mirin et al., 1988; Brady & Sonne, 1995; Winokur et al., 1995; Maremmani et al., 2000

Hypomanie

Hypophorie

CRAVING (DESIR DE LA SUBSTANCE)

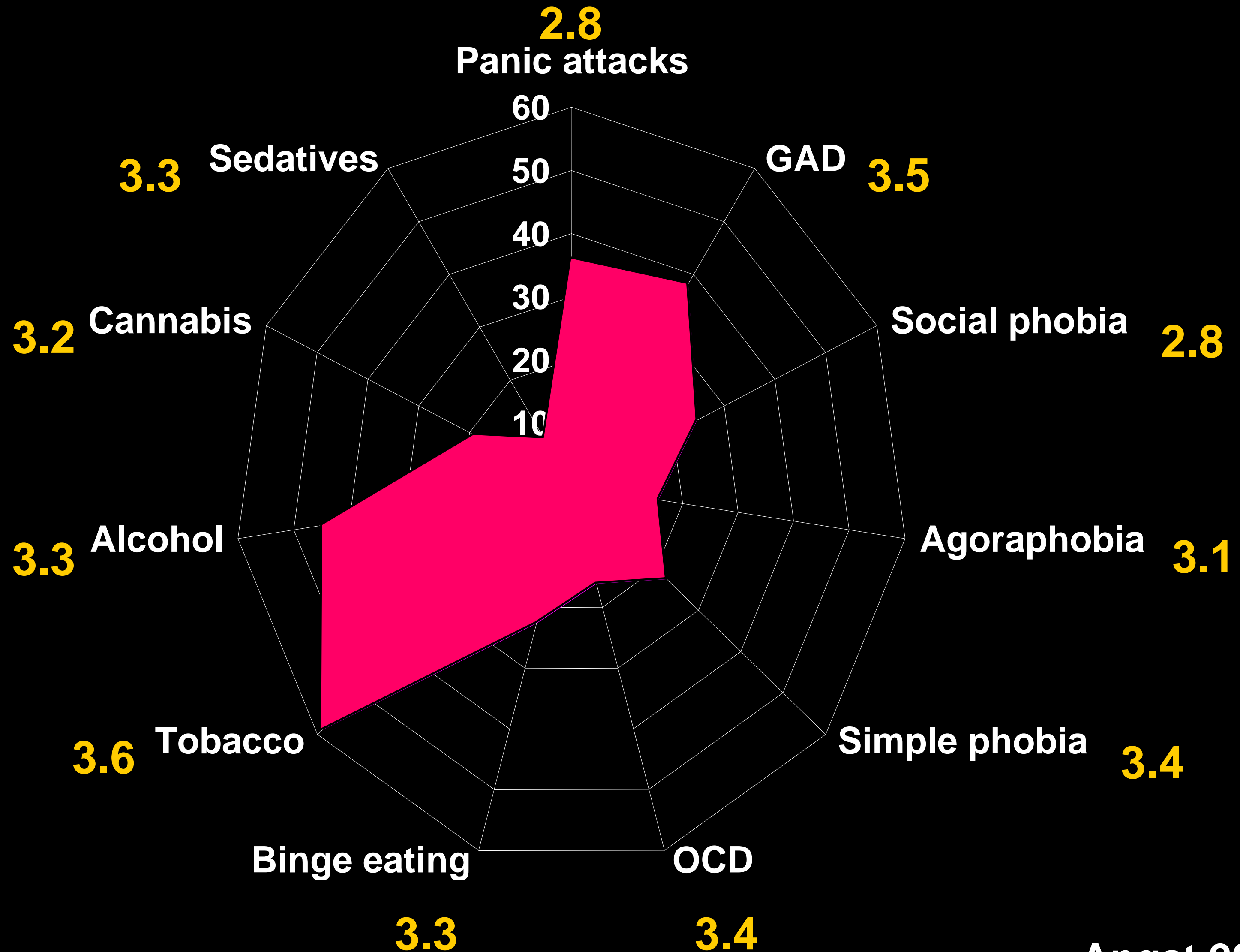
USAGE COMPULSIF

ADDICTION COMPULSIVE

COMPORTEMENT ADDICTIF

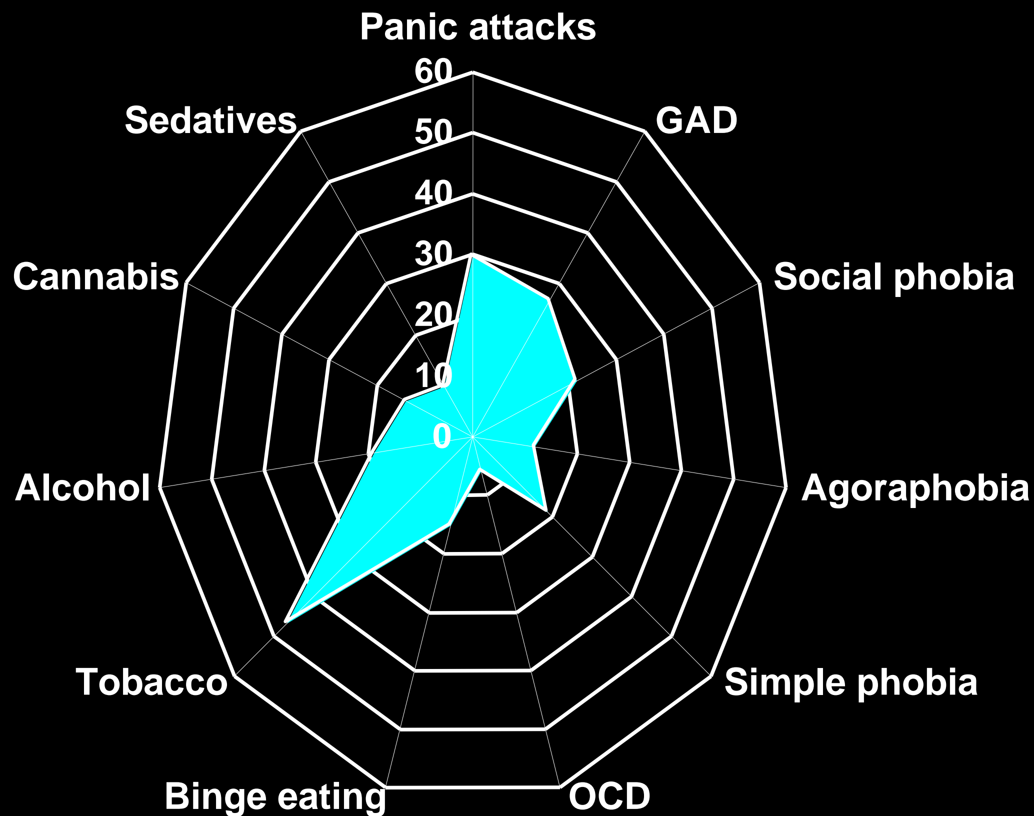
Comorbidity of BP-II (N=89)

Numbers are Odds Ratios, adjusted for stratified sampling



Angst 2004

Comorbidity of MDD (N=101)

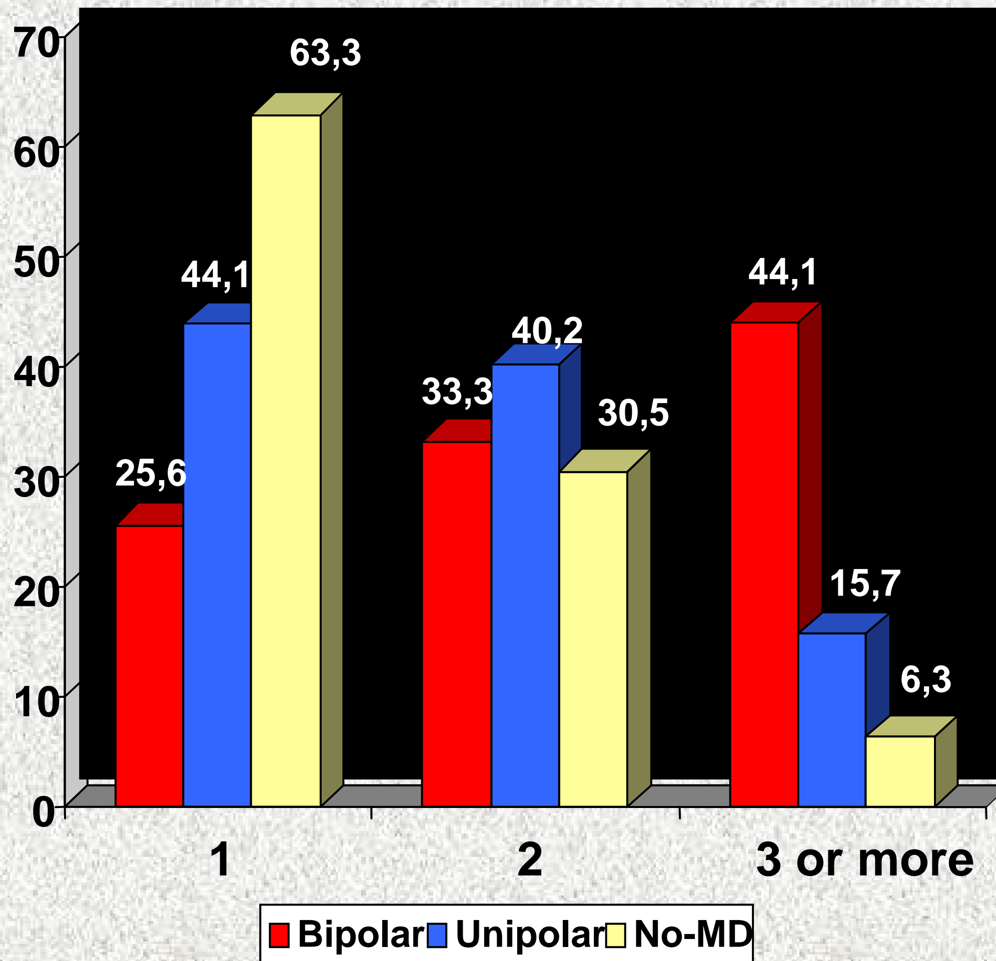


Angst 2004

Bipolar II: Reasons for treatment other than depression

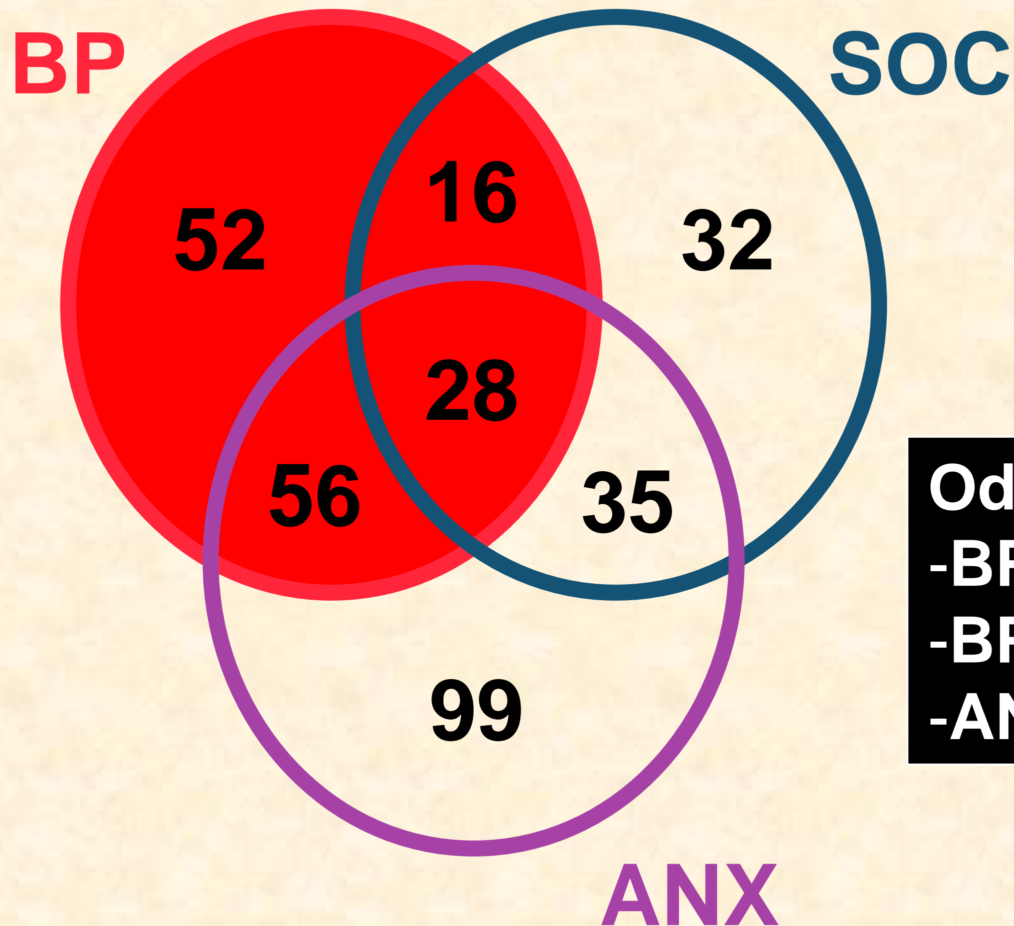
- Anxiety Disorders (PD, SP, OCD)
- Impulse Control Disorders
- Eating disorders (ABP, BN, BED)
- Aggression (CD, APD)
- Personality disorders (BPD, HyPD)
- Drug and alcohol abuse
- Drug Addiction

Comorbidité avec les troubles anxieux au sein des troubles Bipolaires (n=43) vs Unipolaires (n=107) Vs Sans Dépression (n=101)



Perugi et al., J Pych Res, 1998

Chevauchements des syndromes Bipolaires (BP), Anxieux (ANX) et Obsessionnels-Compulsifs (OC)



Odds Ratios:
- BP * ANX = 2,8 (1,9-4,1)
- BP* SOC = 2,3 (1,5-3,5)
- ANX* SOC = 2,8 (1,8-4,2)

Angst, Hantouche et al, 2005

AFTOC

“TOC & ROC” Survey

Reactivity to anti-OCD drugs

	R>0 (n=91)	ROC (n=159)	Do not Know (n=110)
Worsening	10%	21%	14%
Switching*	27%	42%	41%

* Switching includes aggressive behavior, severe insomnia, suicidal thoughts, bizarre behaviors, delusions, hallucinations, homicide thoughts…

Hantouche, SOPSI, Rome, Feb 2005

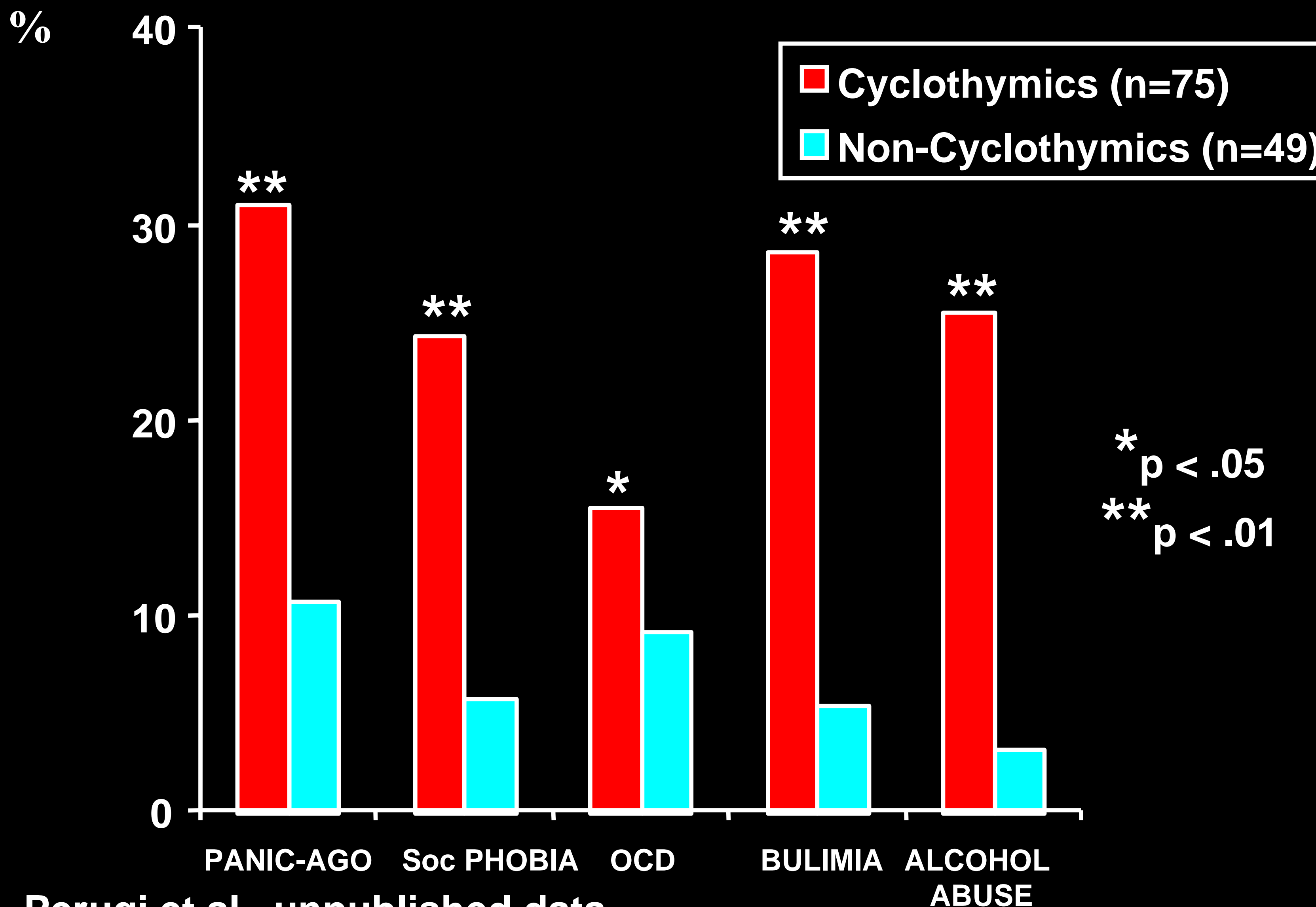
AFTOC

"TOC & ROC" Survey
Temperament Profile

	R>0 (n=91)	ROC (n=159)	p
Hyperthymic	28%	24%	NS
Depressive	53%	72%	0,004
Cyclothymic	43%	63%	0,003
Irritable	09%	21%	0,02

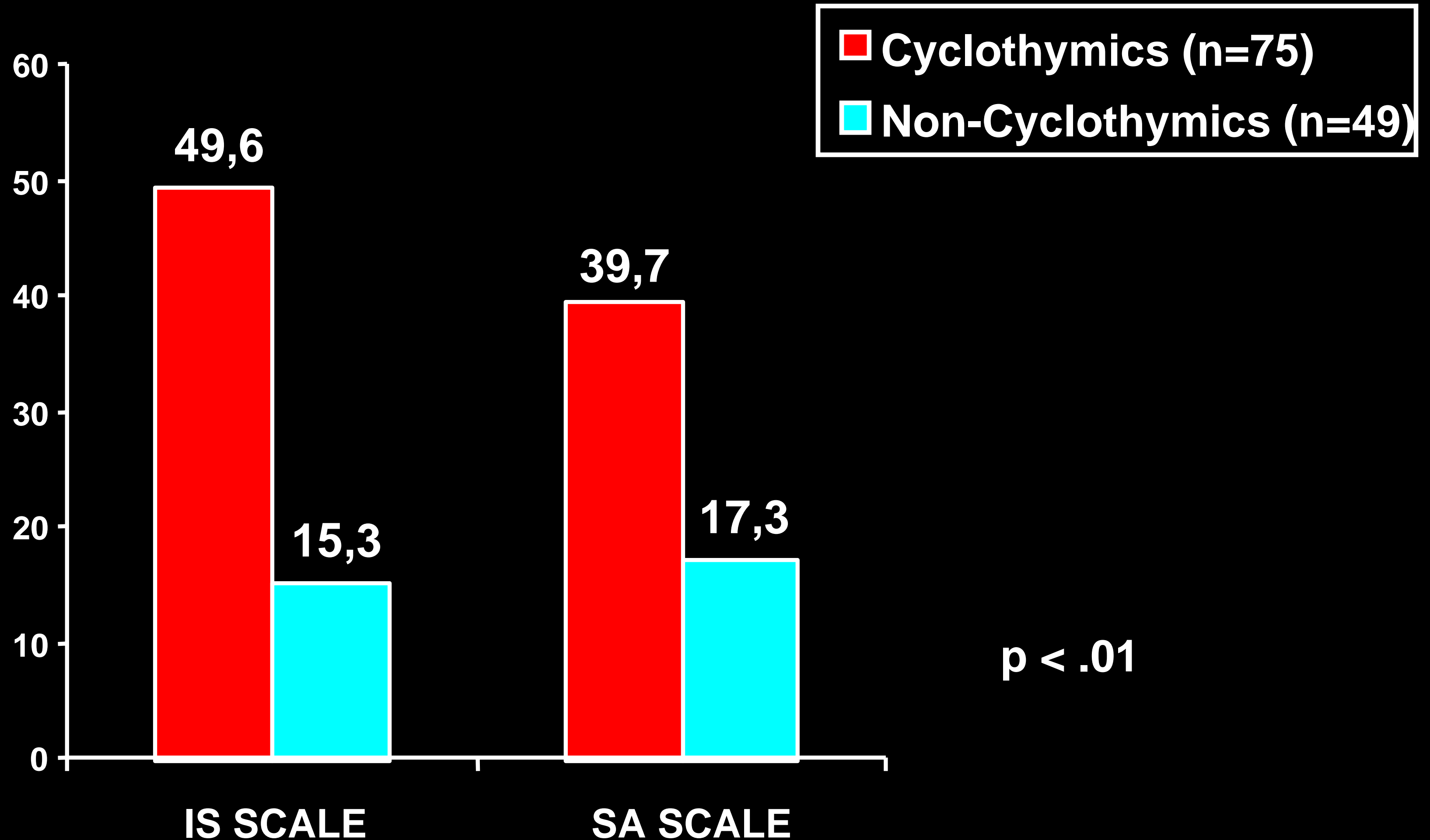
Hantouche, SOPSI, Rome, Feb 2005

Comorbidity on Axis I in BP-II Disorder: Cyclothymics versus Non-Cyclothymics



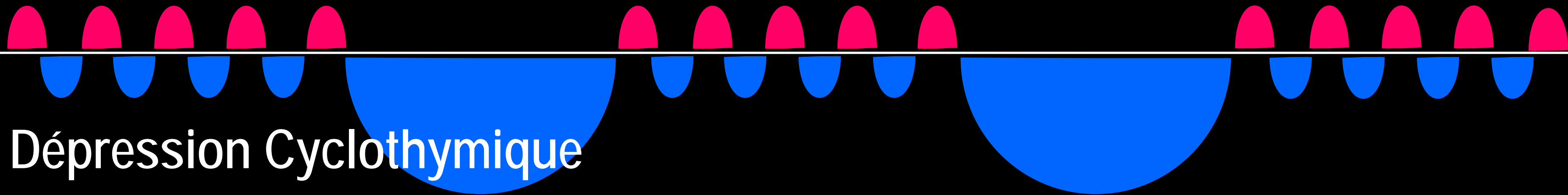
Perugi et al., unpublished data

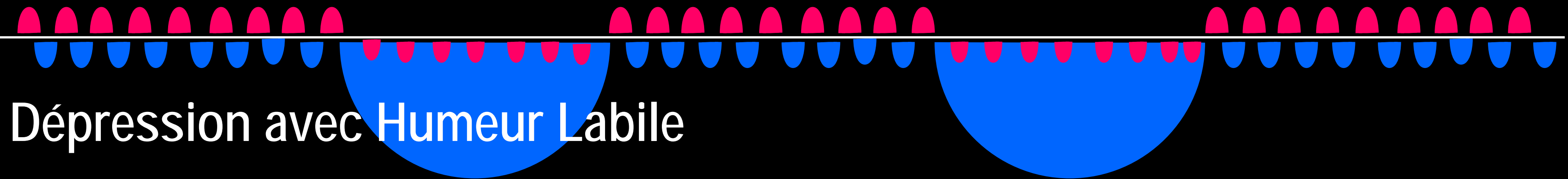
Interpersonal sensitivity & Separation Anxiety: Cyclothymic BP-II vs Non-Cyclothymic BP-II

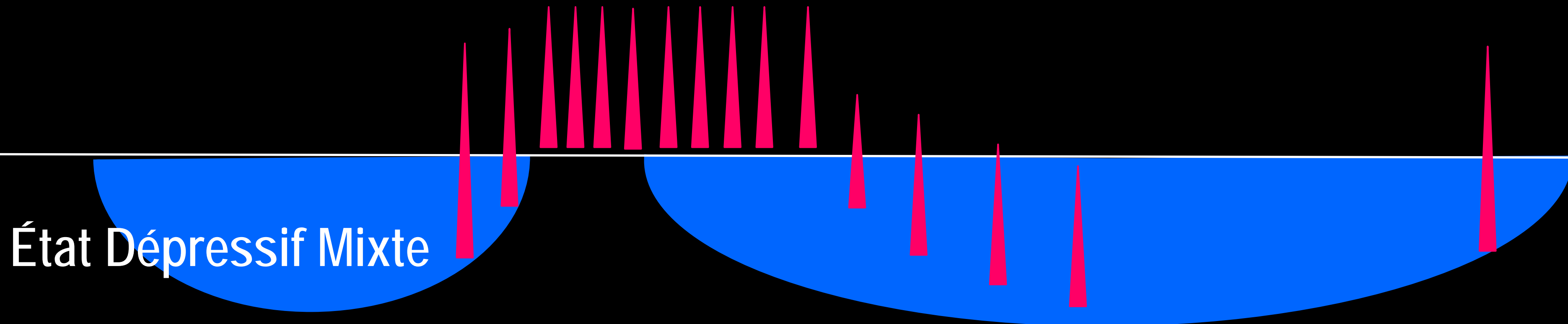


Perugi et al., unpublished data

Tableau clinique complexe du “Trouble BP-II”







Consequences of inaccurate diagnosis and inadequate treatment

- Suicide
  - attempts in 25–50% of patients[1]
  - completed suicide 6–15%[2]
  - correct treatment may help prevent suicide[3]
- Higher physical morbidity and mortality[4]

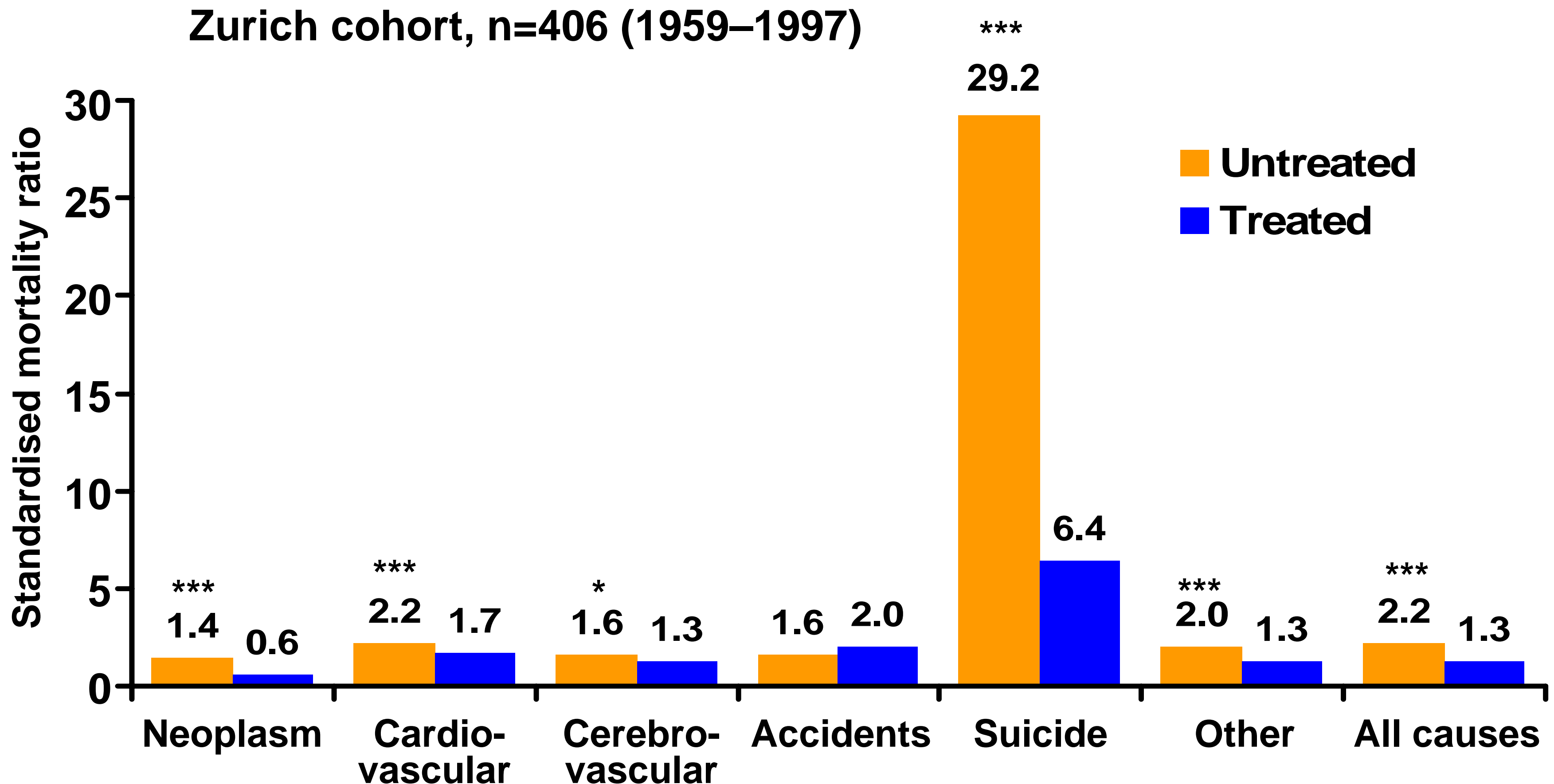
[1]Goodwin FK, Jamison KR. Manic-depressive illness. Oxford: Oxford University Press, 1990
[2]Young AH, et al. BMJ 2000;321:1302–3; [3]Nilsson A. J Clin Psychiatry 1999;60(Suppl. 2):85–8
[4]Angst J, et al. Int J Psychiatry Clin Pract 1998;2:115–19

Major impact on psychosocial functioning

- Important problems in daily life
  - 54% reported ever being fired/laid off work, compared with 29% non-bipolar
  - 26% reported being jailed, arrested or convicted of a crime, compared with 5% non-bipolar

Calabrese JR, et al. J Clin Psychiatry 2003;64:425–32

Bipolar disorder: medical benefits of appropriate treatment



*p<0.05; ***p<0.001 vs treated

Angst F, et al. J Affect Disord 2002;68:167–81

Screening for bipolar disorder: Mood Disorder Questionnaire

- A brief, simple self-report questionnaire for bipolar disorder
  - 13 yes/no items regarding bipolar disorder
- Well validated in psychiatric and general population samples
- Translated into several languages

Hirschfeld RMA, et al. Am J Psychiatry 2000;157:1873–5

Hypomania Checklist

HCL (20 items) is filled out by patients

- Score 9 or more indicates the diagnosis of BP-II

- New version with 32 items is currently in running validation in 12 languages (Angst et al, 2005 in press)

Angst, 1992;
Angst, Hantouche, Akiskal, et al,ECNP,2004

Is self-assessment of Hypomania suitable for screening BP-II Disorder?

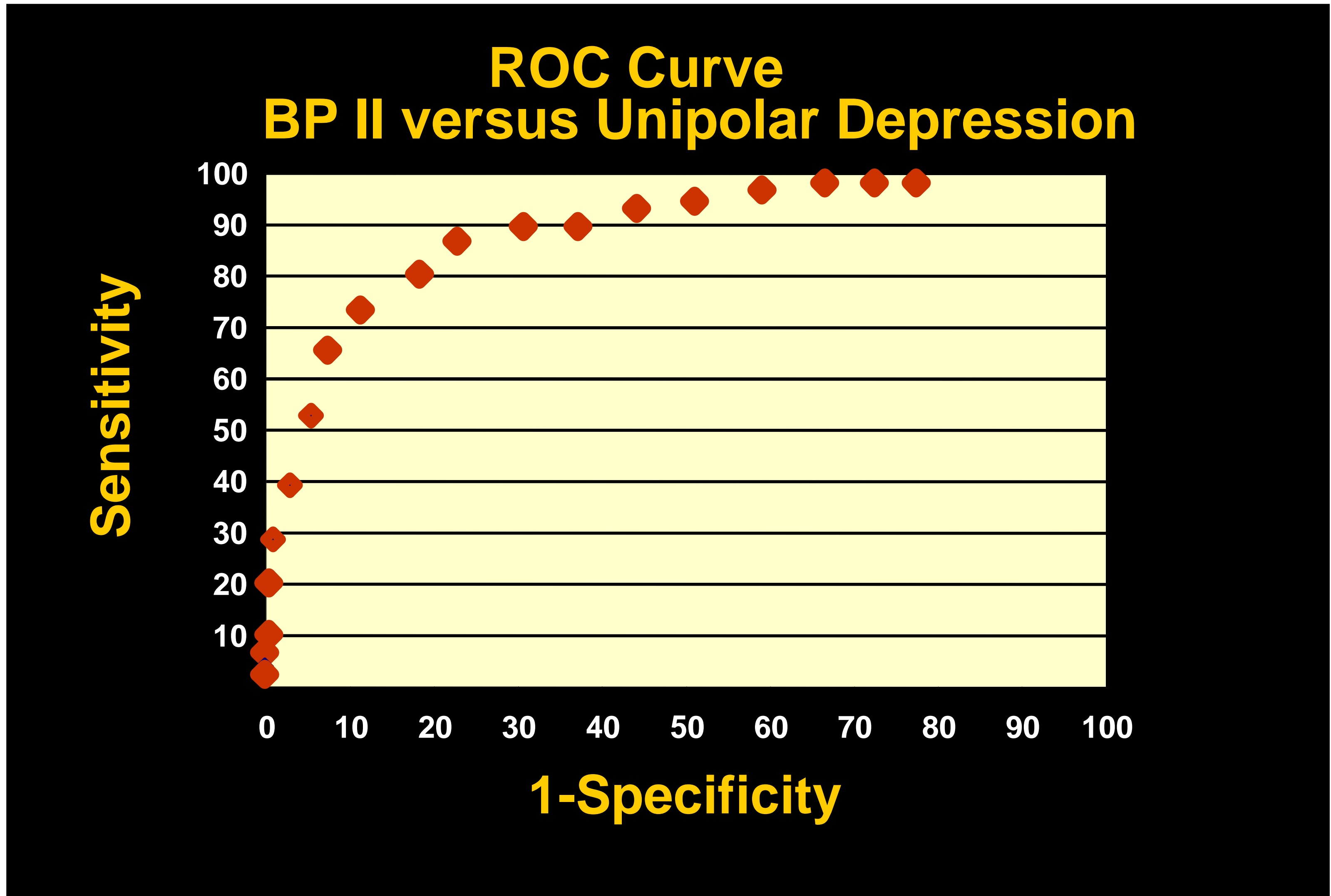
DIAGNOSIS	BEST SCORE*	CORRECT DIAGNOSIS§	SENSITIVITY	SPECIFICITY
- Spontaneous Hypomania	9	81%	86,5%	77,1%
- BP-II +BP-III	10	79%	80,2%	78,1%
- BP-I (Mania)	11	86%	74,4%	88,6%

* Checklist of Hypomania, 20 items (HC)

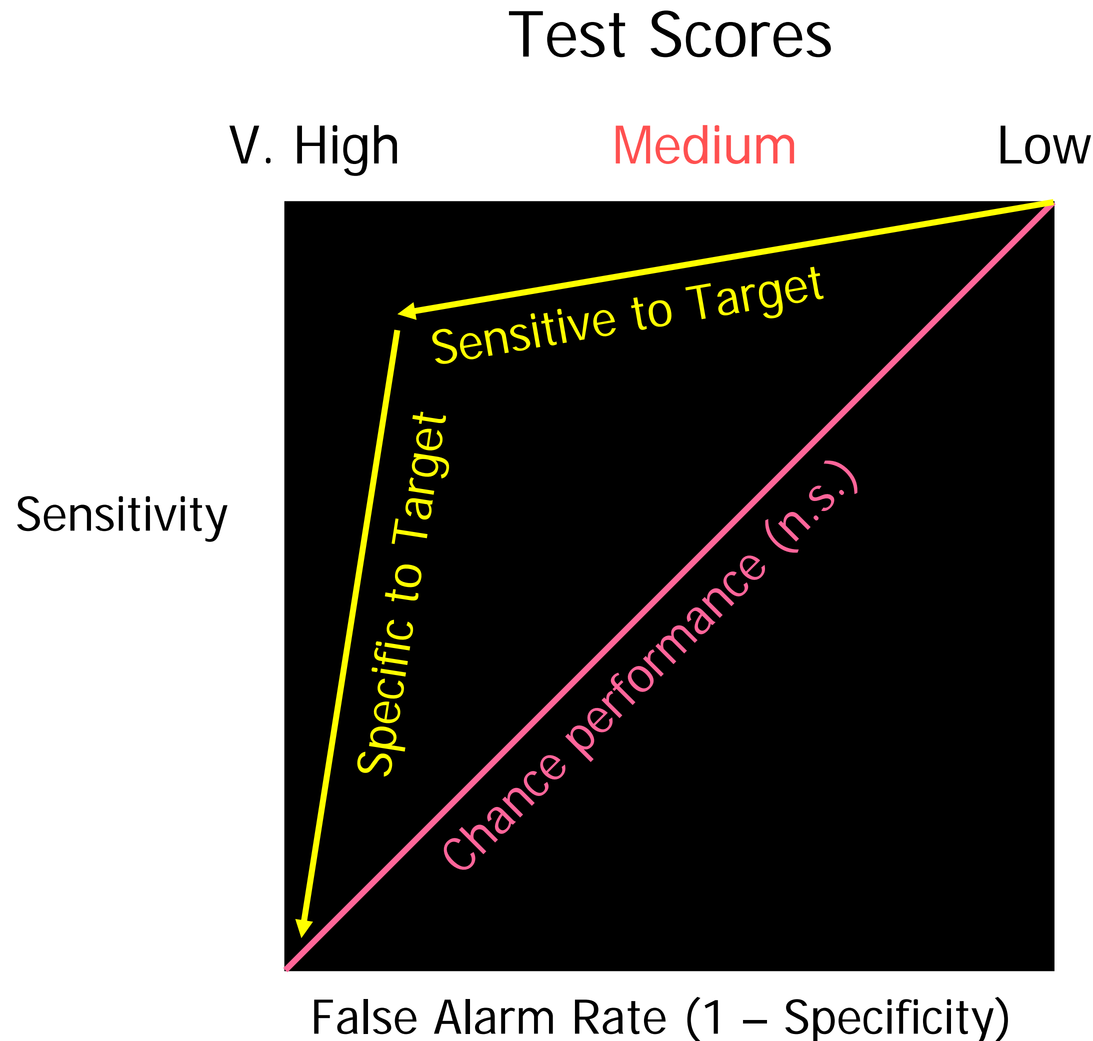
§ ROC Analysis comparing diagnostic value of HC with DSM-IV criteria

Angst, Hantouche, Akiskal, et al,ECNP,2004

Self-assessment of Hypomania by using Hypomania Checklist of Angst



Evaluating Diagnostic Efficiency:
Receiver Operating Characteristics (ROC)



Phenomenology of Hypomania

Relationship with Cyclothymia

Factor 1 : 'SUNNY' SIDE OF HYPOMANIA

(eigenvalue : 4,8)

- Less sleep
- More drive and energy
- More self-confidence
- Increased work motivation
- Increased social activity
- Increased physical activity (in work also)
- More plans and ideas
- Less shy, less inhibited
- More talkative than usual
- Extremely happy mood, over-euphoric
- More puns and jokes, laughing more
- Faster thinking

Hantouche, Angst, Akiskal, JAD 2003

Factor 2 : 'DARK' SIDE OF HYPOMANIA

(eigenvalue : 2,1)

- More traveling, imprudent driving

- Increased spending and/or buying

- Foolish business behavior or investment

- More irritable, impatient

- Attention too easily drawn

- Increased sex drive and interest in sex

- Increased consumption of coffee, cigarettes

- Increased consumption of alcohol

Hantouche, Angst, Akiskal, JAD 2003

Temperament Profile in BP-II Disorder

	Unipolar (n = 256)	Bipolar II (n = 196)	p
CL-Hypomania (Angst)	5.6 (4.5)	12.0 (4.1)	< .001

Temperament

- Cyclothymic	6.3 (4.9)	10.1 (5.2)	< .001
- Hyperthymic	4.6 (4.8)	7.8 (5.5)	< .001
- Irritable	3.6 (3.1)	5.2 (3.2)	< .001
- Depressive	11.3 (5.3)	9.9 (4.9)	.004

Allilaire, Hantouche et al, Encephale, 2001

Relationships between Hypomania & Cyclothymia

Cyclothymia (self-rated)

- Score F1 ‘Sunny’ r = .07 NS
- Score F2 ‘Dark’ r = .37 $p < .0001$

Hantouche, Angst, Akiskal, JAD 2003

Dimensions de l'Hypomanie dans les sous-types du spectre bipolaire

	Hypomanie	
	F1 «Soleil»	F2 «Sombre»
▪BP-II 1/2 (n = 161)	8.1 (3.5)	3.2 (1.8)
▪BP-II (n = 60)	8.6 (3.1)	2.7 (1.9)
▪BP-III (n = 28)	8.6 (3.7)	1.9 (1.8)
▪BP-IV (n = 17)	5.8 (4.2)	1.6 (1.5)
▪UP (n = 161)	4.1 (3.2)*	0.7 (1.1)**

* P <.001: II1/2, II, III > IV > UP

** P <.001: II1/2 > II > III = IV > UP

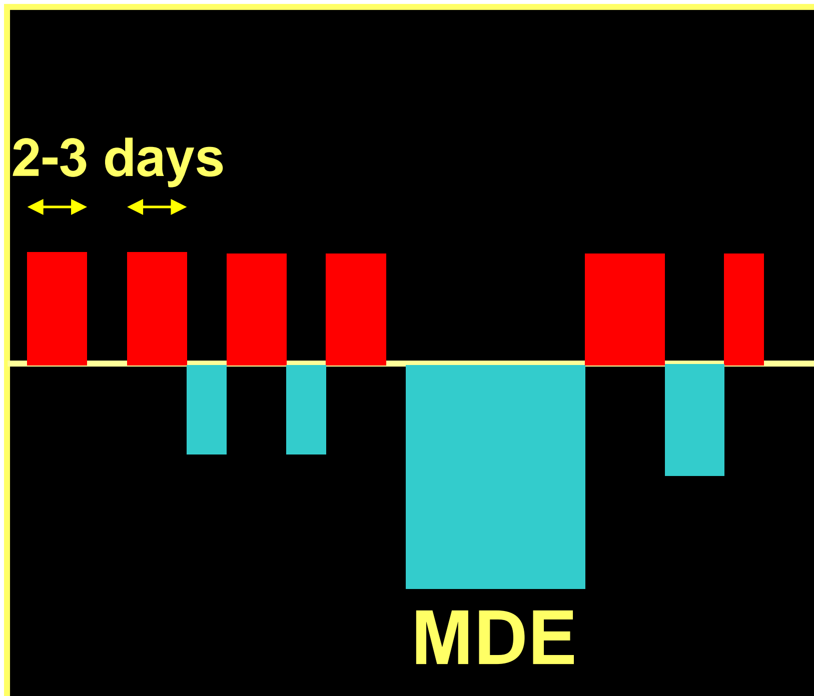
Hantouche, Angst, Akiskal, JAD 2003

Redefining the Bipolar Spectrum

• BP-I (MDE + M)	41	8%
• BP-II 1/2 (MDE + CT)	166	31%
• BP-II (MDE + m Sp, Wo CT)	61	11%
• BP-III (MDE + m AA)	30	6%
• BP-IV (MDE + HT)	22	4%
• Strict UP	217	40%

Hantouche et al, 2003, Akiskal et hantouche, 2005

MDE + CYCLOTHYMIA (BP-II1/2) (Recurrent Brief Hypomania - Angst)



- «Dark side» of Hypomania
- Duration 1-3 days
- Highly recurrent (+ BRD)
- Prevalence in GP : 1,5%
- Younger age of onset
- High depressive intensity
- Persistent Mood lability
- High comorbidity with :
  - Dysthymia
  - OCD / OCS
  - Panic attacks
  - Tobacco dependence

Angst, JAD, 1998
Hantouche et al, JAD, 2003
Akiskal et al, JAD, 2003

Correlations between Temperaments (TEMPS-A) and Personality (TCI)

	"Harm avoidance"	"Novelty seeking"
Dysthymic	.58	–.10
Cyclothymic	.49	.35

Akiskal, Maremmani, Signoretta et al, TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego. JAD, 2004

Bipolar Spectrum, “Self-stimulating” and “Sensation-seeking” behaviour

Work

Sex

Drugs

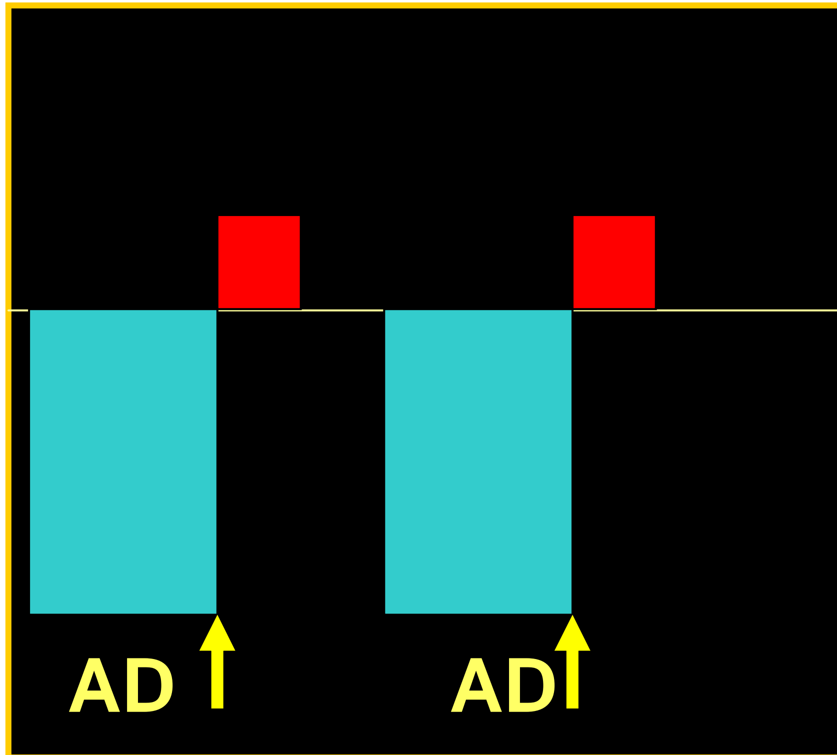
Food

Light

Traveling

Gambling

MDE + PHARMACOLOGIC HYPOMANIA (BP-III)
(Sporadic Hypomania - Angst)



- Typical symptoms of Hypomania
- Duration 2-4 days
- Prevalence in GP : 1,3%
- Severity of MDE
- Atypical MDE
- Depressive temperament or 'Dysthymia' (Double Depression)
- Agoraphobia comorbidity
- Family history of completed suicide

Akiskal, Hantouche, Allilaire, JAD; 2003

Validating « BP-III » sub-type

	BP-II Sp (n = 144)	BP-II AA (n = 52)	p
Hypomania score	12.2	11.4	NS
FH of BP Disorder	14.1 %	11.8 %	NS
Prior ECT	4.2 %	15.7 %	.02
FH of Completed Suicide	3.5 %	13.7 %	.024
Temperament			
- Cyclothymic	10.7	8.4	.006
- Depressive	9.5	11.1	.04

EPIDEP Data, Akiskal et al, JAD 2003

Clinical Spectrum of Hypomania

Angst (1998)	Hantouche & Akiskal (2000)	Akiskal & Pinto (1999)
‘m’ DSM IV	Spontaneous ‘m’	BP-II
‘m’ Brief Recurrent	‘m’ + Cyclothymia	BP-II1/2
‘m’ Sporadic	‘m’ Associated to AD	BP-III

Bipolaire II - DSM-IV (Bipolaire I)

- Changements thymiques spontanés
- Cyclicité de l'humeur
- Irritabilité
- Culpabilité
- Impulsivité phase dépendante
- Fuite des idées, pensées rapides
- Réponse au stimuli internes
- Variation diurnale classique
- Suicide

BP II avec Cyclothymie (Personnalité Borderline)

- Changements thymiques réactifs
- Instabilité émotionnelle
- Colère
- Hostilité
- Impulsivité trait
- *Crowded thoughts, day-dreaming*
- Sensibilité interpersonnelle
- Variation diurnale inversée
- Tentatives de suicide et auto-mutilations

Perugi, IRBD, LYON 2005

Bipolaire II - DSM-IV (Bipolaire I)

- Troubles psychomoteurs sévères
- Libido augmentée
- Troubles cognitifs
- Cycling sous antidépresseurs
- Lithium: bonne réponse
- Abus erratique de drogues
- Pas de trauma dans l'enfance
- HF bipolaire unilatérale
- Hypothyroïdie

BP II avec Cyclothymie (Personnalité Borderline)

- Pas de troubles PM sévères
- Problèmes d'identité sexuelle
- Peu de troubles cognitifs
- Hypomanie transitoire sous antidépresseurs
- Lithium: réponse mitigée
- Addiction médicamenteuse
- Abus sexuel dans l'enfance
- HF bilatérale thymique et addictive
- Pas d'hypothyroïdie

Perugi, IRBD, LYON 2005

SPECTRE EVOLUTIF DES TROUBLES BIPOLAIRES

TYPIQUEMENT EPISODIQUE :

-Inter-épisode stable
-Absence d'états mixtes
-Peu de récurrence
-Bonne rémission
-Faible incidence des complications

INSTABILITE EMOTIONELLE RADICALE:

-Inter-épisode instable
-Etats Mixtes
-Episodes fréquents
-Rémission incomplète
-Trop de complications
-Début précoce
-Forte charge génétique

Swann, IRBD, LYON 22 avril- 2005

Cours Evolutif du trouble

- Début précoce
- Susceptibilité à la Récurrence
- Tendance vers l'accélération des cycles
- Stresseurs, abus de substance
- Trauma dans l'enfance : début plus précoce, cycles rapides, tentatives de suicide

Garno et al, Br J Psychiatry 186: 121-125, 2005

And for the rest of his life, the young reptile suffered deep emotional scars.

Temperament as endophenotype?

Cyclothymic and anxious reactivity best distinguishes controls from healthy relatives

TEMPS-A Means

Mean Scores

20
18
16
14
12
10
8
6
4
2
0

Dysthymic
Cyclothymic
*Hyperthymic
Irritable
*Anxious

150 families

Evans, Akiskal, Kelsoe et al, *JAD*, 2004

Zurich Study;
Lessons for BP Disorders

- There is a broad bipolar spectrum with fluid borders to major depressive disorders.
- About 50% of depressives are probably bipolar
- Therefore the burden of bipolar disorder may be higher than that of depression
- A broad definition of bipolar II disorder seems to be valid:

  FH mania, conduct problems in childhood and/or adolescence, ups & downs, GBI scales for hypomanic and cyclothymic temperament, number of manic symptoms, course
- Criterion A of DSM-IV and ICD-10 for mania (elated or irritable mood) needs revision. It should include overactivity.

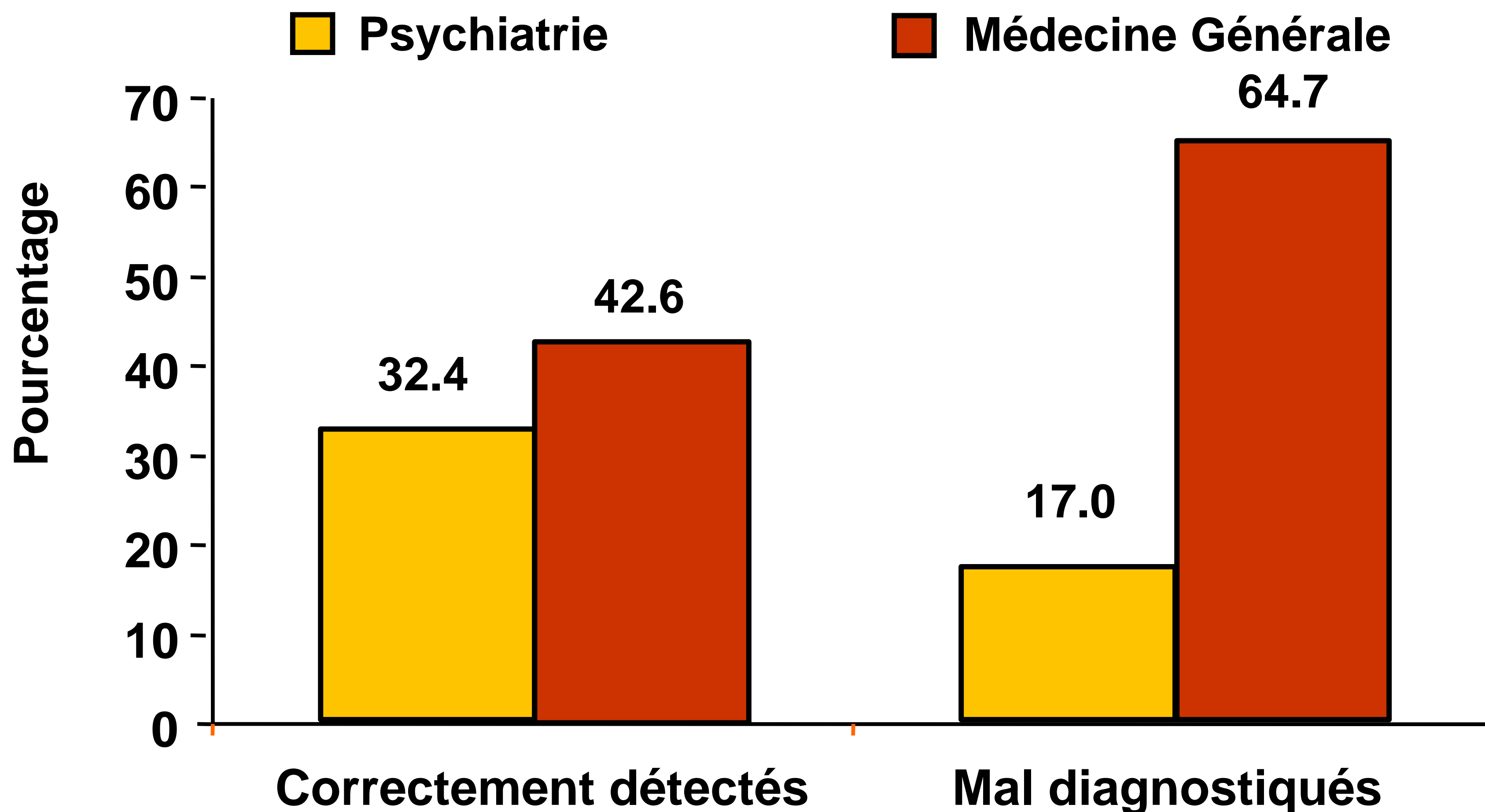
Angst,IRBD LYON, April 2005

Take Home Messages for Clinicians

- Accept the reality of "Bipolar Spectrum"
- Systematic search for Bipolar "indicators" or "specifiers"
- Use self-rating of Hypomania and Cyclothymia
- Involve family members in clinical assessment
- Consider radical instability as a distinct subtype (BP-II1/2)
- "Think bipolar", especially in depressed patients with "red signs" or "rule of 3 or more" (3 episodes, 3 doctors, 3 antidepressants, 3 disorders, 3 marriages, 3 languages, 3 talents, 3 jobs…)

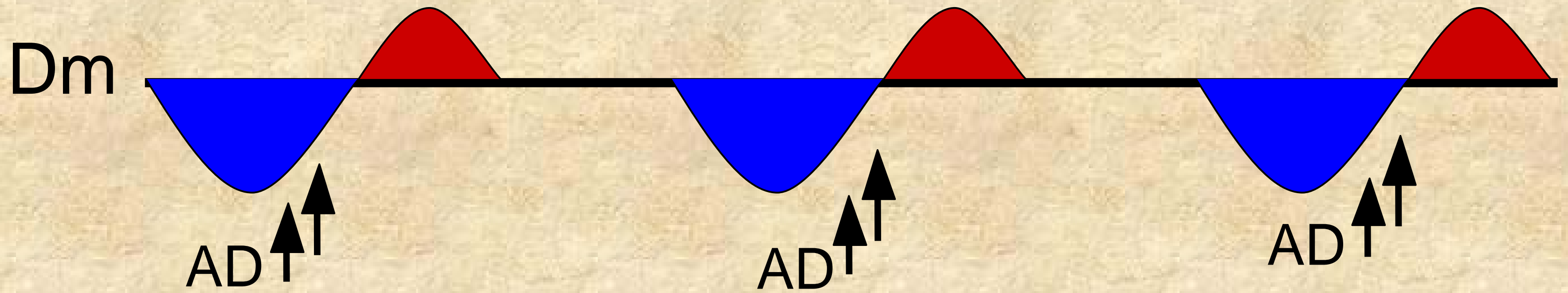
Angst, 2003; Hantouche et al, 2003; Akiskal 2005

Usage des Antidépresseurs sans Stabilisateurs ou Antipsychotiques



Calabrese JR, Hirschfeld RM J Clin Psychiatry 2003 Apr;64(4):425-432

UP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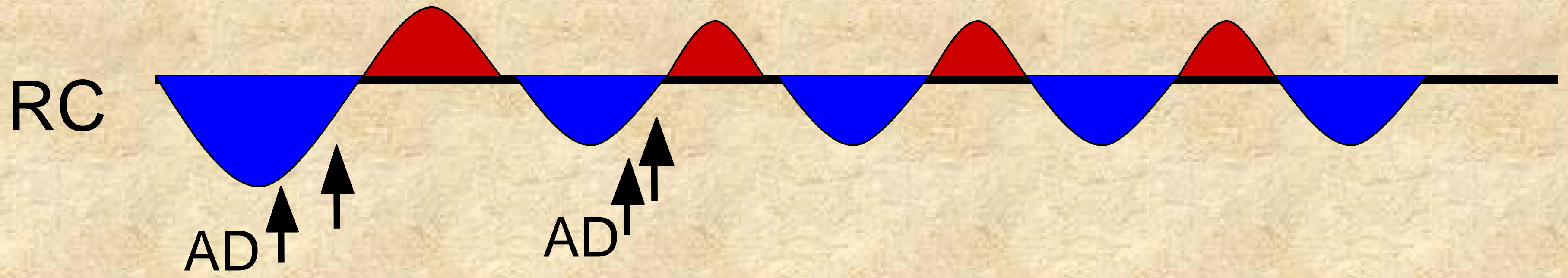
RC
AD
AD

Merci de votre écoute