DISTURBI DELL'UMORE IN ETA' EVOLUTIVA: AGGIORNAMENTI E LINEE DI INTERVENTO

Dott.ssa Giulia Serra

Clinical and Research Fellow,
Child Neuropsychiatry Unit, Dept. of Neuroscience, I.R.C.C.S. Children Hospital Bambino Gesù, Rome (Italy)
Post-Doctoral Research Fellow
McLean Hospital, Department of Psychiatry, Harvard Medical School, Boston (MA)
Research Fellow,
NESMOS Dep., Sant'Andrea Hospital, Sapienza University, Rome (Italy)
Psychiatrist
Centro Lucio Bni, Roma

Aggiornamenti in Neuropsichiatria
Ospedale Pediatrico Bambino Gesù
Roma, 12 Ottobre 2015

giulia.serra@opbg.net

COLLABORAZIONI

Centro Lucio Bini

Dott. Athanasios Koukopoulos (1931-2013)

Dott.ssa Daniela Reginaldi

Dott.ssa Lavinia De Chiara

Dott.ssa Alexia Koukopoulos

Dott. Giovanni Manfredi

Dott. Gabriele Sani

Prof. Gino Serra (Dip Scienze Biomediche, Univ. SS)

Prof. Leonardo Tondo

2009–ora

Ospedale Sant'Andrea,

Dipartimento NESMOS,

Università Sapienza

Dott.ssa Lavinia De Chiara

Dott.ssa Alexia Koukopoulos

Dott. Giovanni Manfredi

Dott. Gabriele Sani

Prof. Paolo Girardi

2010–ora

McLean Hospital,

International Consortium of Bipolar Disorders,

Harvard Medical School

Prof. Ross J Baldessarini

Dr. Paola Sanvatore

Dr. Gianni L. Faedda (NYC)

Dr. Leonardo Tondo

2012–ora

Massachusetts General Hospital,

Pediatric Bipolar Disorder clinical and research program,

Harvard Medical School

Dr. Janet Wozniak

Dr. Joseph Biederman

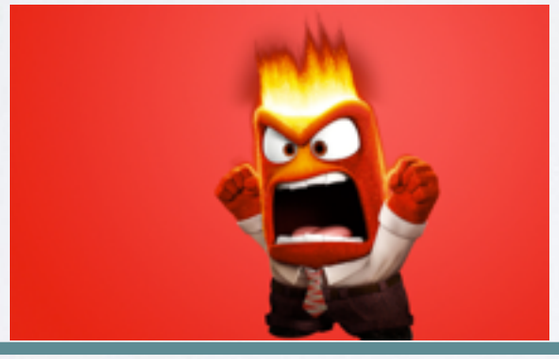
Dr. Mai Uchida

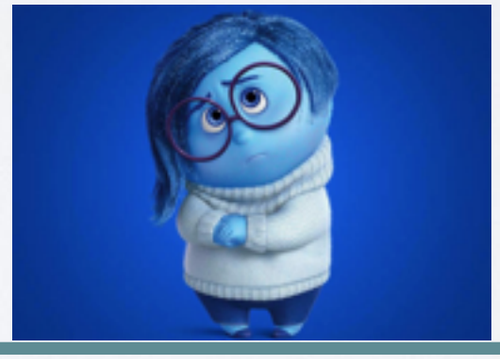
2013–ora

OUTLINE

1. Osservazioni longitudinali e retrospettive

2. Sintomatologia clinica: sintomi cardinali della mania pediatrica e depressione bipolare





3. Nuove prospettive terapeutiche

FATTORI PREDITTIVI DI DIAGNOSI, MORBOSITÀ E SUICIDIO

- Studi retrospettivi e longitudinali identificano una **fase prodromica del disturbo bipolare ad esordio in età infantile e adolescenziale** [Faedda, Serra, Marangoni et al. 2015 JAD & Faedda, Marangoni, Serra et al. 2015 JCP for review of longitudinal studies]

- Resta aperto il problema di valutare la **sensibilità, specificità** e **valore predittivo differenziale** di questi sintomi per diversi outcome diagnostici

- Fattori predittivi di morbosità a lungo termine sono perlopiù inerenti il disturbo stesso

- **Esordio di BD e MDD in età infantile è un fattore predittivo di peggiore prognosi: maggiore morbosità ed aumento del rischio suicidario**

- Polarità [ipo]maniacale al I Ep. Affettivo è altamente predittiva di una predominante polarità maniacale del disturbo a lungo termine

- Polarità depressiva al I Ep. Affettivo è altamente predittiva di una predominante polarità depressiva del disturbo a lungo termine e in generale predittiva di una peggiore prognosi

- Ampia letteratura su fattori di rischio di suicidio in eta' pediatrica ed adulta **ma assenza assessment sul potenziale valore predittivo di fattori di rischio pediatrici per comportamento suicidario in età adulta**

Serra, Koukopoulos, De Chiara et al et al., JAD 2015; Zizook 2004; Perlis et al. 2004; Leverich 2007; Baldessarini 2012, 2014; Geller 2001; Van Noorden 2011; Weissman 1999; Williams et al. 2012

AIMS OF THE STUDY

1. Identificare antecedenti infantili e adolescenziali, la loro specificità, sensibilità ed il loro potenziale valore predittivo in grado di distinguere una futura diagnosi di Disturbo Bipolare *vs.* Disturbo Depressivo Maggiore

2. Identificare caratteristiche demografiche, familiari e antecedenti infantili e adolescenziali associati con la morbosità totale, depressiva, (ipo)maniacale e con la polarità predominante (rapporto D/M) in pazienti adulti affetti da Disturbo Bipolare e Depressivo Maggiore

3. Identificare e quantificare antecedenti infantili e adolescenziali predittivi di comportamenti suicidari in pazienti adulti affetti da Disturbi dell'Umore

HYPOTHESES

1. ***Aspetti psicopatologici dello sviluppo*** *di soggetti adulti affetti da disturbi dell'umore dovrebbe* ***far luce sulla storia naturale*** *di questi disturbi supportando una diagnosi precoce ed aiutando a predirne il decorso*

2. *Sara' possibile* ***predire caratteristiche di base dei disturbi dell'umore adulti a partire da antecedenti*** *psicopatologici infantili e adolescenziali, inclusa la loro diagnosi e la polarità prevalente*

3. *Esistono* ***associazioni predittive tra fattori di rischio infantili e adolescenziali e comportamenti suicidari*** *in soggetti adulti affetti da Disturbi dell'umore*

4. **Queste considerazioni suggeriscono che una stretta collaborazione tra la psichiatria pediatrica e quella adulta dovrebbe aiutare a chiarire decorso e prognosi di disturbi infantili e predire diagnosi, decorso e prognosi dei disturbi dell'umore adulti**

METODO E ANALISI STATISTICA

- Revisione di *clinical records* di **334 pazienti adulti affetti da disturbi dell'umore** secondo i criteri del DSM-IV (**BD-I 109, BD-II 106, MDD 119 casi**) seguiti e trattati a lungo termine dal Dott. Athanasios Koukopoulos presso il Centro Lucio Bini di Roma

- ***Sintomi antecedenti:*** sintomi psicopatologici ed alterazioni comportamentali identificate in eta' infantile e adolescenziale e precedenti il primo episodio affettivo ed il primo tentativo di suicidio

- ***Sindromi antecedenti (o esordi atipici):*** sindromi non-affettive secondo DSM-IV-TR precedenti il primo episodio affettivo

- Sintomi e sindromi antecedenti sono stati comparati usando bivariate standard, modelli di regressione logistica multivariata e metodo Bayesiano per differenziare: **[a] pazienti con diagnosi di BD vs. MDD in eta' adulta** e **[b] pazienti che in eta' adulta avevano effettuato TS vs. non-TS**

- Il **follow-up** dei pazienti e' stato analizzato mediante uso del metodo ***life chart (numero, durata, polarità e tipo degli episodi di malattia)*** per la valutazione della **morbosità totale, depressiva e (ipo)maniacale e del loro rapporto D/M calcolata come %-tempo di malattia** durante il periodo *tra il primo episodio affettivo* e *l'ultima visita al Centro Bini*.

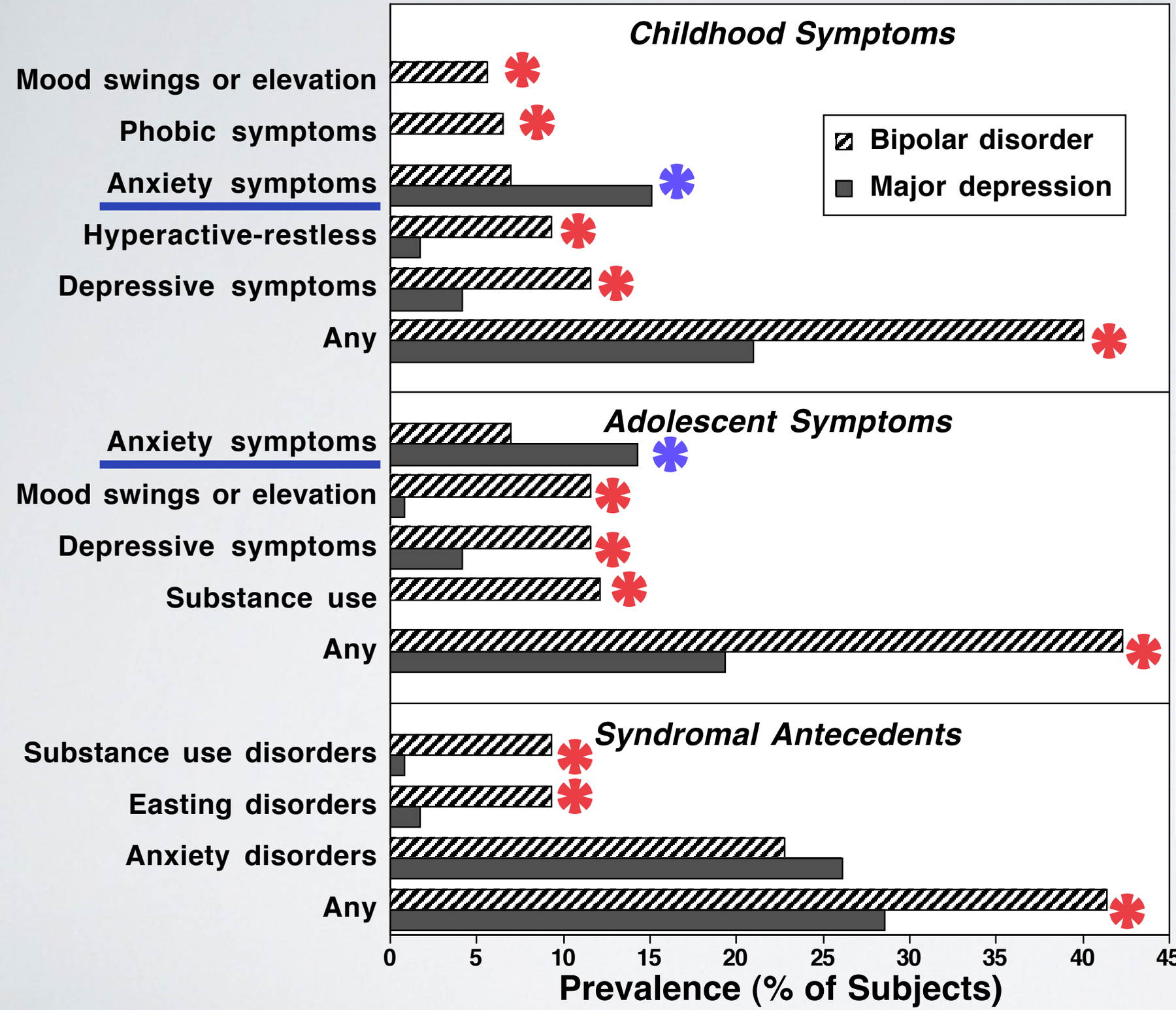
- Analisi bivariate preliminari di **fattori associati con la morbosità totale, depressiva, (ipo)maniacale e con i loro rapporto D/M.** Fattori identificati come associati nelle bivariate sono stati inseriti gradualmente in modelli di regressione lineare multivariata per l'identificazione di fattori predittivi delle diverse misure di morbosità a lungo termine in pazienti con diagnosi di BD e MDD.

RISULTATI

Measure	All (n=334)	Diagnostic Groups (% or mean)		Statistic and *p*-value	
		BD (n=215)	MDD (n=119)	BD vs. MDD	
F hx of BD	27.8	**34.9**	15.1	14.9	<0.001
Ciclo-hyperthymic Temperament	73.2	**80.7**	60.5	14.9	<0.001
Anxious Temperament	12.4	8.33	**19.3**	7.91	<0.01
Age at first affective episode	30.8±13.3	**27.5±10.3**	**36.9±15.6**	6.71	<0.001
Age at diagnosis	36.4±14.1	36.2±13.3	36.9±15.5	0.42	0.68
Years: first event to diagnosis	18.1±14.7	22.4±13.8	10.7±13.2	7.47	<0.001
Suicide attempt, ever (%)	23.1	27.0	16.0	5.23	0.02
Antecedent Sx < 12 years	**44.9**	**52.6**	**31.1**	**14.3**	**0.0001**
Antecedent Sx 13-18 years	**50.3**	**60.0**	**32.8**	**22.7**	**<0.0001**
Antecedent Non-Affective Syndromes	36.9	41.4	28.6	5.41	0.02
Antecedents/100 person-years	**8.31±8.74**	**10.3±9.08**	**4.64±6.50**	**6.04**	**<0.001**
Age at first event	18.3±15.5	13.8±9.89	26.2±19.7	7.52	<0.001

Serra, Koukopoulos, De Chiara et al., 2015 JAD

SINTOMI ANTECEDENTI *VS.* DIAGNOSI



- **Antecedent features** in childhood were identified as first occurring at approximately **age 7.41±2.72** years, and **in preschool years in 14% of children.**

- *Numerous other symptoms and behavioral changes were noted, but did not differ significantly between subjects later diagnosed with BD vs. MDD*

Serra, Koukopoulos, De Chiara et al., 2015 JAD

ETÀ AL PRIMO EVENTO PSICOPATOLOGICO E LATENZA TRA PRIMO EVENTO E DIAGNOSI FINALE

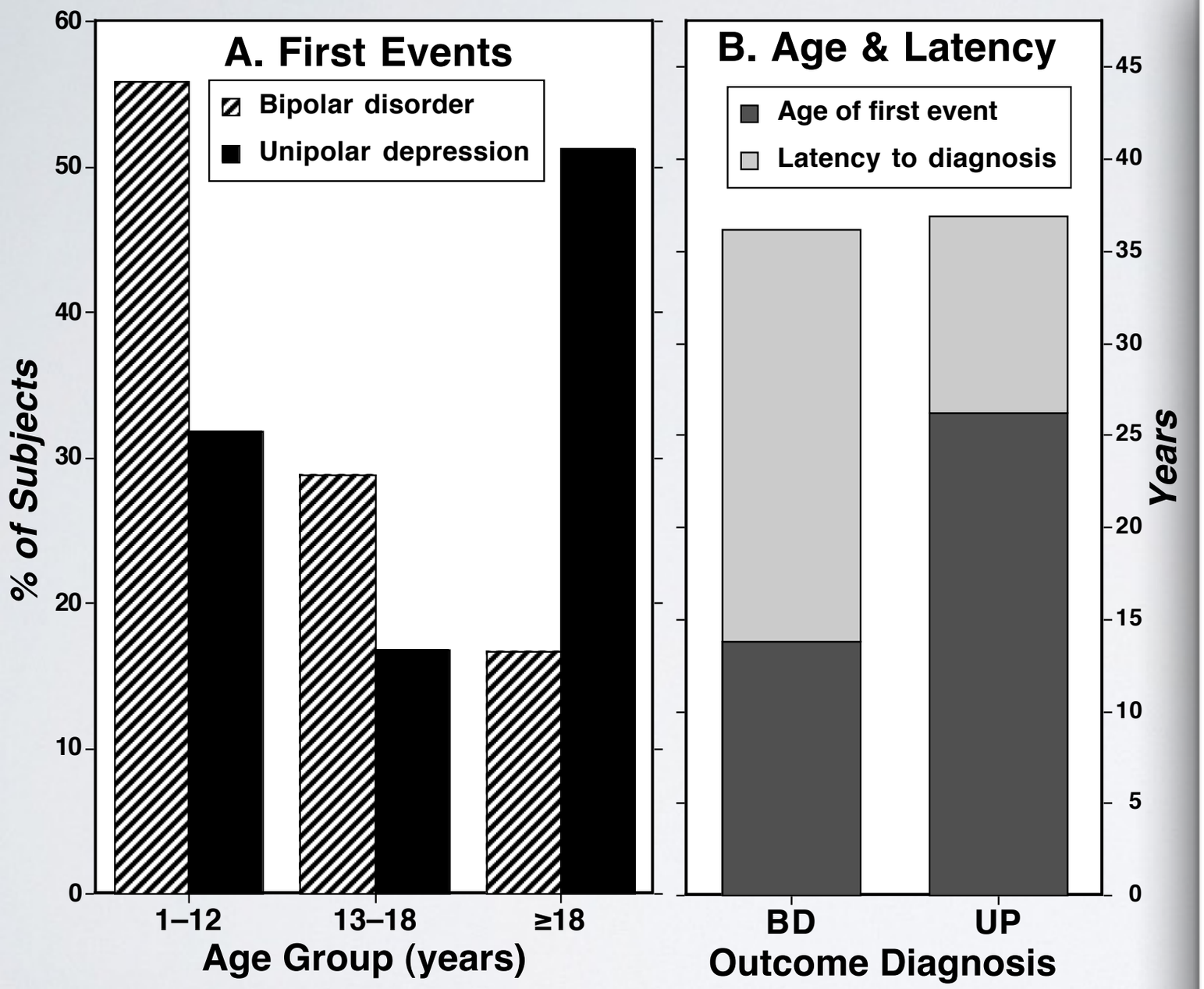


FIGURE 1A: Proportion of subjects later diagnosed with BD or UD with first events (including antecedent symptoms, non-affective syndromes, or major depressive episodes) versus age-group:

Age1–12 y: BD 55.9% vs. MDD 31.9%;p<0.0001

Age13–18 y: BD 27.5% vs. UD 16.8%; p=0.03

Age ≥18 y: BD 16.7% vs. UD 51.3%; p<0.0001

FIGURE 1B: Age at first antecedent event and latency from that event to final diagnosis.

Age at first event: BD 13.8±9.89 vs. UD 26.2±19.7 years (p<0.0001);

Latency from that event to final diagnosis: BD 22.4±13.8 vs. UD 10.7±13.2 years (p<0.0001).

Serra, Koukopoulos, De Chiara et al., 2015 JAD

FATTORI ANTECEDENTI SELETTIVAMENTE ASSOCIATI CON BD VS. MDD

MODELLO DI REGRESSIONE LOGISTICA

Antecedent Factors	Ratio BD/ MDD	Bayesian Measures (%)			OR [95% CI]	χ^2	p-value
		Sensitivity	Specificity	PPV			
All ages before onset							
Younger at first event	1.68	60.8	63.9	74.3	1.05 [1.03–1.07]	20.8	<0.0001
Male sex	1.64	44.2	73.1	74.8	2.62 [1.47–4.65]	10.8	0.001
Family history of bipolar disorder	2.31	34.9	84.9	80.6	2.89 [1.52–5.47]	10.6	0.001
Cyclothymic or hyperthymic temperament	1.24	72.1	42.0	69.2	2.60 [1.46–4.63]	10.6	0.001
More antecedents/person-year	2.77	44.2	84.1	84.1	2.58 [1.32–5.04]	7.72	0.006
Ages 1–12 years							
Hyperactive or restless	5.54	**9.30**	**98.3**	90.9	5.14 [1.17–22.6]	4.70	0.03
Depressive symptoms	2.76	**11.6**	**95.8**	83.3	3.01 [1.10–8.27]	4.58	0.03
Ages 13–18							
Mood swings or elevations	13.8	**11.6**	**99.2**	96.2	15.0 [2.00–112]	6.95	0.008
Depressive symptoms	2.77	**11.6**	**95.8**	83.3	2.85 [1.05–0.76]	4.22	0.04
Nonaffective syndromes before diagnosis							
Eating disorder	5.54	**9.30**	**98.3**	90.9	6.63 [1.52–28.9]	6.34	0.01
Substance abuse disorder	11.1	**9.30**	**99.2**	95.2	13.3 [1.75–100]	6.28	0.01

ANALISI BAYESIAN A E CURVA ROC (RECEIVER-OPERATOR CURVE)

Factors per person	% of Subjects			Sensitivity (%)	Specificity (%)	Correctly Classified (%)
	BD	MDD	BD/MDD Ratio			
≥1	100	100	1.00	100	0.00	64.4
≥2	95.8	85.7	1.12	95.8	14.3	66.8
≥3	83.3	41.2	2.02	**83.3**	**58.8**	**74.6**
≥4	63.3	15.1	4.19	**63.3**	**84.9**	**71.0**
≥5	38.6	5.88	6.56	38.6	94.1	58.4
≥6	17.7	1.68	10.5	17.7	98.3	16.4
≥7	7.91	0.00	>7.91	7.91	100	40.7
≥8	2.33	0.00	>2.33	2.33	100	37.1

- L'area sotto la curva (AUC) per la curva ROC generata dalla relazione tra BD outcome e il numero di fattori/persona dei 11 fattori e **0.791 [CI: 0.743–0.838]** e indica una **forte relazione tra i fattori con diverso valore predittivo per BD vs. MDD**

- La presenza di almeno 3 o 4 fattori predittivi per paziente:

1. Migliore combinazione di una **buona-moderata sensibilità e specificità**
2. Identifica il **73.3% dei soggetti BD**, in confronto al solo 28.2% di soggetti MDD (una percentuale **2.6 volte maggiore**)

MORBOSITÀ IN 323 PAZIENTI AFFETTI DA DISTURBI DELL'UMORE

Measures	Diagnostic Groups (% or mean [SD])				p-value (t-score)	
	BD-I (n=111)	BD-II (n=96)	All BD (n=207)	MDD (n=116)	BDI vs BDII	BD vs MDD
At risk (months)	221±131	234±156	227±143	204±175	0.20 (1.29)	0.50 (0.68)
Total % time ill	**28.4±22.9**	**40.2±27.1**	33.9±25.5	**25.3±24.1**	0.003 (2.95)	0.001 (3.42)
(h)M % time ill	13.9±13.9	14.2±17.0	14.0±15.3	00.0±00.0	—	0.87 (0.17)
D % time ill	14.3±16.8	**26.1±19.7**	19.8±19.1	25.3±24.1	0.02 (2.38)	<0.0001 (4.63)
D/M ratio	**1.96±4.39**	**5.74±8.74**	3.67±6.93	—	<0.0001 (4.01)	—

Serra, Koukopoulos, De Chiara et al., 2015, manuscript in preparation

MODELLI DI REGRESSIONE LINEARE MULTIVARIATA PER FATTORI ASSOCIATI CON MORBOSITÀ IN BD E MDD

FATTORI ASSOCIATI A MORBOSITÀ DEPRESSIVA IN 207 BD

Factors	β [95% CI]	t-score	p-value
Years at risk	–0.478 [–0.678 to –0.278]	4.72	<0.0001
1st Aff Ep.: agitated, mixed, or psychotic depression	4.02 [–6.45 to –1.59]	3.26	0.001
Type II bipolar disorder	8.00 [2.95–13.1]	3.12	0.002
Any antecedent syndrome	6.09 [1.41–10.8]	2.57	0.01
Comorbid eating disorder	12.2 [2.69–1.6]	2.53	0.01

FATTORI ASSOCIATI A MORBOSITÀ (IPO)MANIACALE IN 207 BD

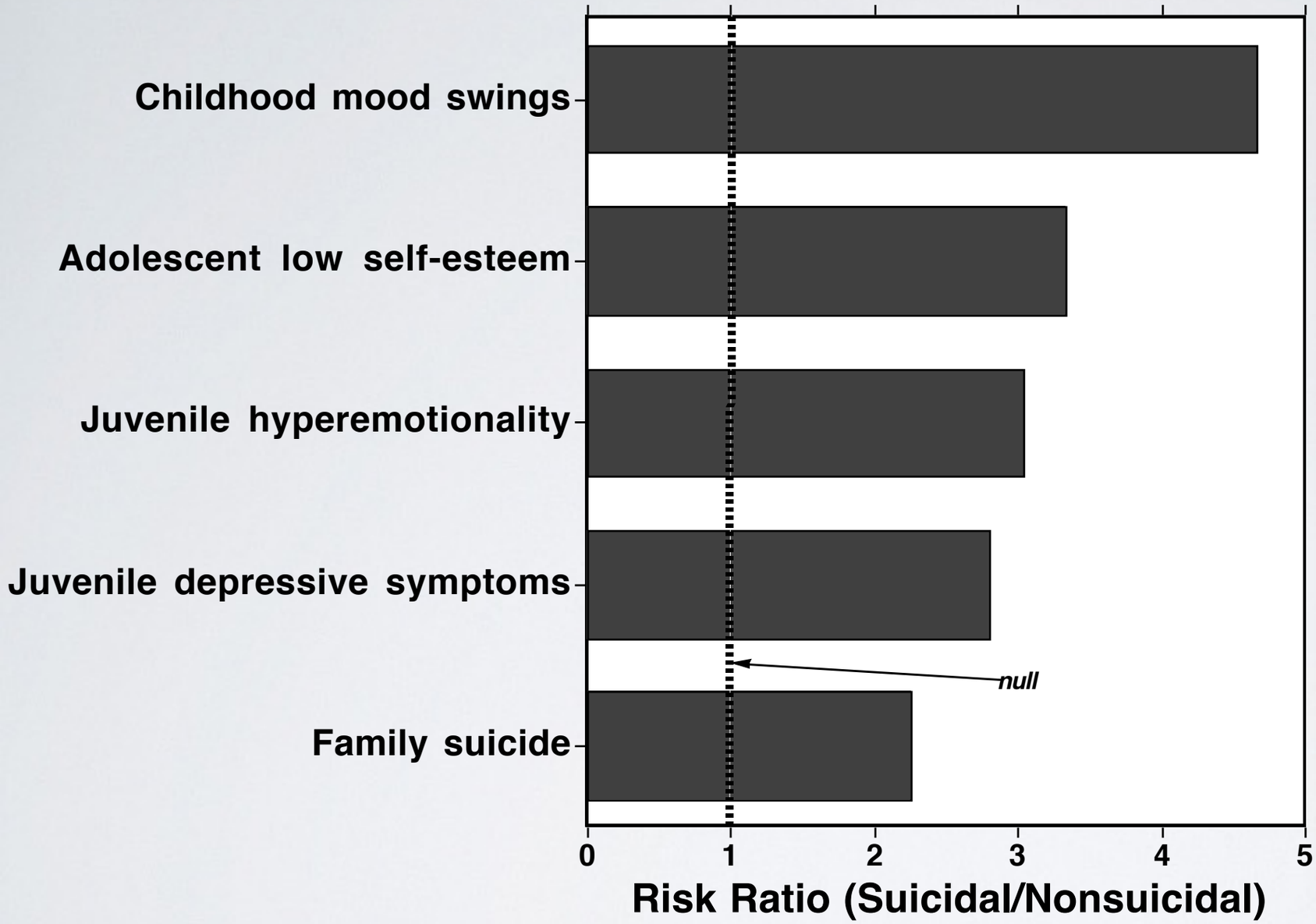
Factors	β [95% CI]	t-score	p-value
Years at risk	–0.394 [–0.567 to –0.221]	4.50	<0.0001
1st Aff Ep.: [hypo]manic	5.54 [1.49–9.60]	2.69	0.008

FATTORI ASSOCIATI A MORBOSITÀ IN 116 MDD

Factors	β [95% CI]	t-score	p-value
Years at risk	–0.765 [–1.04 to –0.49]	5.56	<0.0001
Childhood anxiety symptoms	17.0 [7.02–27.0]	3.37	0.001
Initial depression: agitated, mixed or psychotic	10.1 [2.48–17.2]	3.12	0.002
Older at first depression	0.265 [0.003–0.526]	2.01	0.05

FATTORI CLINICI IN ETÀ PEDIATRICA ASSOCIATI A RISCHIO DI SUICIDIO IN ETA' ADULTA

MODELLO DI REGRESSIONE LOGISTICA MULTIVARIATA



- IL 23% (77/334) dei pazienti ha effettuato almeno 1 TS
- 27% in BD vs 16% in MDD (p=0.02)
- Antecedenti <12y:
  SA 60% vs. Not-SA 41%,
  p=0.003
- Antecedenti 13-18y:
  SA 18% vs Not-SA 6.23%,
  p=0.001

Fattori associati indipendentemente e significativamente con un rischio >2 volte di TS in età adulta

Serra, Koukopoulos, De Chiara et al., submitted to JAD

COMMENTI

- Sostanziali e significative differenze tra fenomeni psicopatologici in età pediatrica antecedenti le due diverse categorie diagnostiche BD vs. MDD, con massima differenziazione quando si sommano 3 o 4 fattori.

"Unfortunately, there is in the domain of psychic disorders no single morbid symptom which is thoroughly characteristics of a definite malady" Emil Kraepelin [1921]

- Sintomi pediatrici e altre caratteristiche precedenti l'esordio del disturbo sono stati predittivi di outcome diagnostico BD vs.MDD

- Alcuni sintomi pediatrici si sono rivelati essere fattori di rischio per suicidio in età adulta

- L'eta' d'esordio dei sintomi di BD e' stata identificata a intorno ai 14 aa con una latenza media tra il 1sintomo e la Dg di BD di circa 22 anni. Questo e' un chiaro indizio dell'urgenza di identificare strumenti precoci che permettano di fare diagnosi di BD in eta' infantile adolescenziale.

OUTLINE

1. Osservazioni longitudinali e retrospettive

2. Sintomatologia clinica: sintomi cardinali della mania pediatrica e depressione bipolare

3. Nuove prospettive terapeutiche

DISTURBO BIPOLARE PEDIATRICO

". . . in those periods of life with which much heat and blood are associated, persons are most given to mania, namely, those about puberty, young men, and such as possess general vigour. "

Aretaeus di Cappadocia, ca. 150 A.D.

- Il Disturbo Bipolare (BD) in eta' infantile (<12 aa) ed adolescenziale (13-18 aa) venne ben descritto in antichità da Aretaeus (150 d.C.) e nei primi dell'800 da Esquirol e successivamente da Kraepelin e i suoi contemporanei [Faedda, 1995]

- La prevalenza del BD in eta' infantile e adolescenziale e' **1.8% [CI 1.1-3.0]**, con prevalenze simili in paesi europei e USA [Van Meter, 2011]

- **Alto tasso di familiarità per disturbo bipolare (familiarità multigenerazionale, numerosi familiari affetti)** [Akiskal, 1995; Strober 1982, Geller, 1994]

- Diagnosi complicata perché sintomatologia dibattuta e aspecifica, alto tasso di comorbidita' con altri disturbi ad esordio in eta' infantile (ADHD, ODD, CD), presentazione clinica molto diversa da quella della maggior parte dei pazienti adulti con **decorso RC/ultra-RC,/ultra-ultra-RC** e **varie sfaccettature di stati misti maniaco-depressivi**.

- Esordio dei sintomi spesso in **eta' prescolare (<5 aa)** con sintomatologia eta'-dipendente e conseguente necessita' di strumenti di assessment che siano sensibili per le diverse tappe psicopatologiche di sviluppo del disturbo [Faedda, 1995; Fergus, 2003; Serra, 2015].

- **Grave compromissione del funzionamento**, alto rischio di sviluppo di **disturbi di abuso di sostanze** e sovrapposizione di disturbi d'ansia, **comportamentali** e di personalità con **alti tassi di suicidio** ed aumento di mortalita' dovuto ad altre malattie mediche [Goodwin & Jaminson, 2007]

DISTURBO BIPOLARE PEDIATRICO

"A SPINNING STAR"

- SEVERITY: duration/ intensity
- FREQUENCY: daily/weekly
- AGE-APPROPRIATENESS

Distractibility

Increased activity or agitation (high energy)

Grandiosity and eleation

Flight of ideas or racing thoughts

Activities with bad outcome (hypersexuality, reckless behaviors, self-harm, suicidality)

Sleep

Talkativeness

"Positive parenting for bipolar kids", McDonnel &Wozniak, 2008

DISTURBO BIPOLARE PEDIATRICO: SINTOMATOLOGIA ED ETA' D'ESORDIO

Table 1. Characteristics of pediatric bipolar disorder subjects

Measure	Male (n = 54)	Female (n = 28)	All (n = 82)
Age at first symptoms	3.2 (3.5)	2.2 (3.8)	2.8 (3.9)
Age at first treatment	6.6 (3.4)	7.3 (3.9)	6.8 (3.6)
Age first BPD diagnosis	9.2 (3.4)	10.4 (3.7)	9.6 (3.6)
Age at clinic entry	10.1 (3.5)	11.5 (3.7)	10.6 (3.6)
Pubertal at entry	20.4	35.7	26.8
Family history present	90.7	89.3	90.2
Adopted	16.7	21.4	18.3
Special education	20.4	14.3	18.3
Age at first symptoms			
≤3	70.4	82.1	74.4
4–6	13.0	3.6	9.8
7–12	13.0	7.1	11.0
13–18	3.7	7.1	4.9
Initial symptoms			
Irritable, moody	44.4	75.0	54.9
Sleep disturbance	42.6	50.0	45.1
Hyperactivity	38.9	35.7	37.8
Aggressive	33.3	17.9	28.0
Anxiety (all forms)	24.1	10.7	19.5
Separation anxiety	9.3	3.6	7.3
Inattention, racing thoughts	7.4	0.0	4.9
Impulsive	1.9	3.6	2.4
Hypersexual	0.0	3.6	1.2
Pressured speech	1.9	0.0	1.2
Self-harm	1.9	0.0	1.2

- Familiarità per disturbi dell'umore, suicidio o abuso di sostanze nel 90% dei casi
- Esordio prima dei 3aa nel 74% dei casi e prima dei 13 aa nel 95%
- Oscillazioni dell'umore, irritabilità e temper tantrums piu' frequenti tra le bambine
- Aggressività e sintomi d'ansia più frequenti tra i bambini

Faedda, Baldessarini, Glovinsky et al., Bipolar Disorders, 2004

DISTURBO BIPOLARE PEDIATRICO
SINTOMATOLOGIA CLINICA

Table 3. Symptom frequency (%) at evaluation

Symptom	Boys (n = 54)	Girls (n = 28)	All cases (n = 82)
Irritability	96.3	100.0	97.6
Mood lability	96.3	100.0	97.6
Sleep disturbance	94.4	96.4	95.1
Angry	94.4	89.3	92.7
Impulsive	94.4	89.3	92.7
Agitated	88.9	96.4	91.4
Aggressive	90.7	89.3	90.2
Anxiety	81.5	78.6	80.5
Racing thoughts	77.8	78.6	78.0
Pressured speech	63.0	78.6	68.3
Euphoric, grandiose	59.2	60.7	59.8
Hypersexual	31.5	39.3	34.1
Psychosis	31.5	32.1	31.7
Suicidal ideation	29.6	32.1	30.5
Self-harmful acts	18.9	29.6	22.0
Homicidal thoughts	12.9	3.6	9.7
Suicidal acts	1.9	7.1	3.7
Homicidal acts	0.0	0.0	0.0

- Irritabilità, labilità emotiva, rabbia, aggressività, agitazione, impulsività e disturbi del sonno erano presenti in >90% dei casi
- Euforia e grandiosità appaiono comuni ma non sintomi cardine
- Circa 1/3 dei pazienti presenta ideazione suicidaria e circa 1/4 comportamenti autolesivi
- Non differenze significative nelle sintomatologia tra maschi e femmine

- Wozniak, 2015 Psy Res: **55% irritable only; 5.6% euphoria only; 40% irritable+euphoric**

Faedda, Baldessarini, Glovinsky et al., Bipolar Disorders, 2004

LE DUE FACCE DELLA MANIA PEDIATRICA

- **EUFORICA**: espansione del tono dell'umore, alti livelli di energia, associata a sintomi di grandiosità spesso con notevole aumento delle attività finalizzate. Decorso più ciclico con episodi distinti. Più simile alla classica mania adulta, più facile da diagnosticare.

- **IRRITABILE:** irritabilità estrema con comportamenti ostili, etero- e auto-aggressività e comportamenti distruttivi, minacce brutali e pensieri cupi e comportamenti a rischio/ impulsivi (simile agli stati misti adulti, spesso chiamata "dark mania"). Decorso spesso cronico/Ultra-RC. Diagnosi complicata e dibattuta.

DISTURBO BIPOLARE PEDIATRICO: DECORSO CLINICO

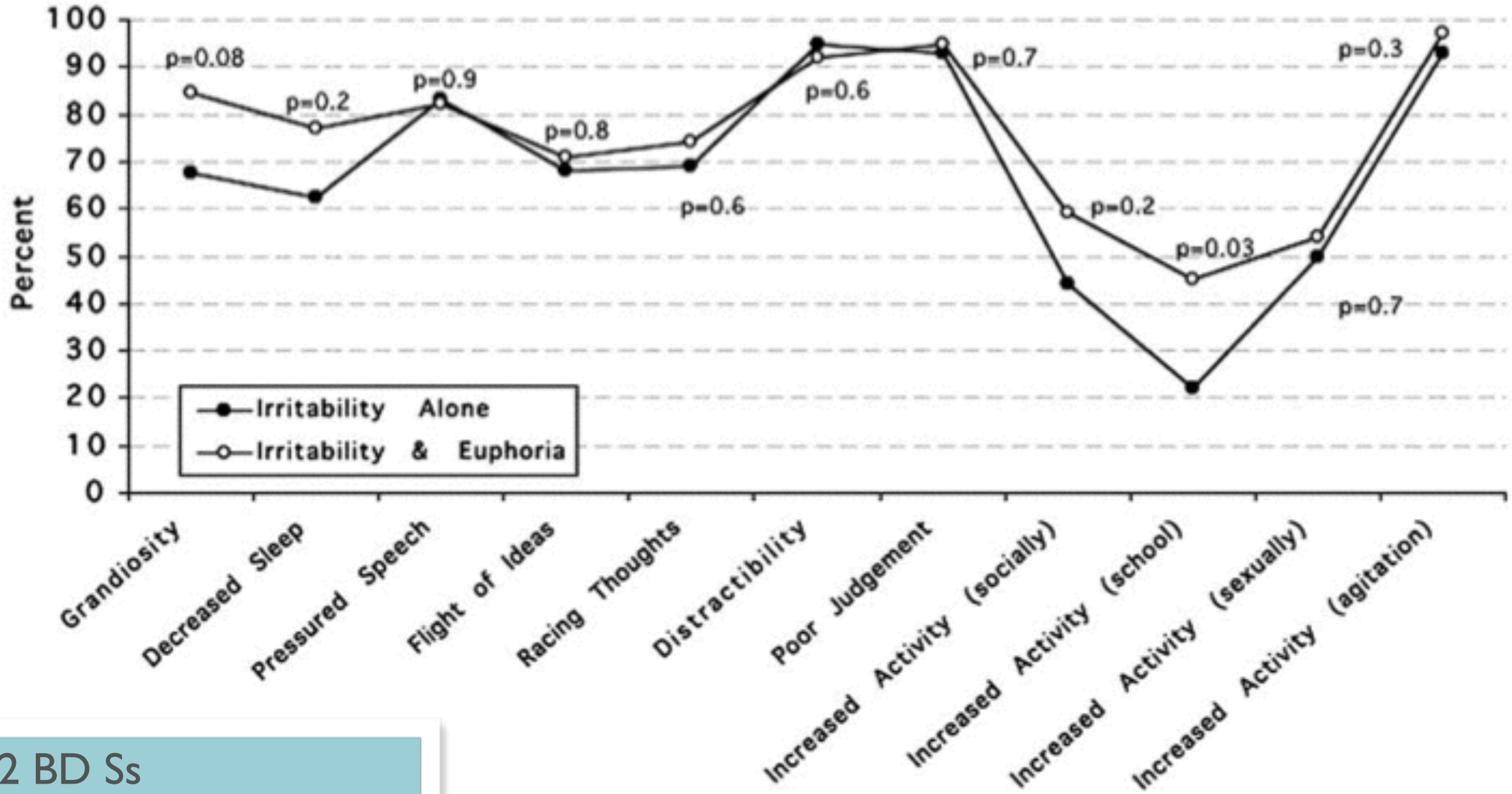
Table 4. Course characteristics

Variable	Boys (n = 54)	Girls (n = 28)	All cases (n = 82)
First episode type[a]			
Manic	55.6	46.4	52.4
Euphoric	35.2	35.7	35.4
Dysphoric	20.4	10.7	17.0
Mixed	25.9	39.3	30.5
Depressive	18.5	14.3	17.1
Bipolar subtype[a]			
Mania, BP-I	57.4	39.2	52.4
Hypomania, BP-II	37.0	46.4	40.2
Cyclothymia	3.7	14.3	7.3
Met DSM duration criteria	51.8	53.5	52.4
Cycling pattern[a]			
Ultra-ultra rapid	68.5	60.7	65.9
Seasonal	14.8	14.3	14.6
Ultra-rapid	9.3	17.9	12.2
Rapid	7.4	7.1	7.3

- Esordio nel 65% dei casi stati disforici o depressivi vs. 35% mania euforica
- Nel 23% dei casi l'esordio maniacale o disforico era stato indotto da trattamento con antidepressivi o stimolanti
- Decorso stagionale nel 15% dei pazienti mentre l'85% dei pazienti mostrava decorso UURC (>365 cicli/anno), URC (5-365 cicli/anno) o RC (>4 cicli/anno).

Faedda, Baldessarini, Glovinsky et al., Bipolar Disorders, 2004

CARDINAL SYMPTOMS:
IRRITABILITY *vs* EUPHORIA/GRANDIOSITY



82 BD Ss
5 Euphoria only
39 Euphoria+Irritability
42 Irritability only

Clinical relevance of severe irritability as most common presentation of mania in the young

Wozniak, Biederman, Known et al., Biol Psychiatry, 2005

BD-NOS: CARATTERISTICHE CLINICHE E OUTCOME

- Criteri dell'American Academy of Child and Adolescent Psychiatry Practice per la diagnosi del BD-NOS:

  1. **Non soddisfare i criteri** di durata o numero di sintomi del criterio B per l'episodio maniacale, misto o ipomaniacale

  2. **Non presentano episodi dell'umore distinti** (ipo)maniacali e depressivi

- I criteri variano considerevolmente tra i diversi studi [Axelson, 2011 for review of BD-NOS criteria]

- Prevalenza varia da **1.2% a 13.3%** in studi epidemiologici in eta' adolescenziale [Youngstrom, 2008; Kessler, 2009]

- Caratteristiche cliniche in continuum con quelle di pz con BD-I: simile eta' d'esordio, simile morbosità, comorbidita con altre diagnosi (ansia e abuso di sostanze), ideazione suicidaria e livello di compromissione del funzionamento sociale e scolastico [Axelson, 2006; ref]

- Decorso longitudinale: **rate di progressione da BD-NOS a BD-I-II i**n eta' infantile e adolescenziale (6-17 aa) che vanno dal **33% al 45% in follow-up dagli 1.5 ai 5 anni** [Alloy, 2011; Axelson, 2011; Birmaher, 2009; Martizez, 2012]

- BD-NOS **può seguire diverse traiettorie psicopatologiche** e portare ad altre categorie diagnostiche (traiettorie eterotipiche) [Shankman, 2009] o **seguire un decorso benigno** e scomparire con l'eta' adulta [Tijssen, 2010]

DISTURBO BIPOLARE PEDIATRICO: OUTCOME

Child Bipolar I Disorder

Prospective Continuity With Adult Bipolar I Disorder; Characteristics of Second and Third Episodes; Predictors of 8-Year Outcome

Barbara Geller, MD; Rebecca Tillman, MS; Kristine Bolhofner, BS; Betsy Zimerman, MA

Context: Child bipolar I disorder (BP-I) is a contentious diagnosis.

Objective: To investigate continuity of child and adult BP-I and characteristics of later episodes.

Design: Inception cohort longitudinal study. Prospective, blinded, controlled, consecutive new case ascertainment.

Setting: University medical school research unit.

Subjects: There were 115 children, enrolled from 1995 through 1998, aged 11.1 (SD, 2.6) years with first episode *DSM-IV* BP-I, mixed or manic phase, with 1 or both cardinal symptoms (elation or grandiosity) and score of 60 or less on the Children's Global Assessment Scale (CGAS). All *DSM-IV* severity and duration criteria were fulfilled. Separate interviews were conducted of parents about their children and of children about themselves.

Main Outcome Measures: Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS); Psychosocial Schedule for School Age Children–Revised; CGAS.

Results: Retention was 93.9% (n=108) for completing assessments at every one of the 9 follow-up visits. Subjects spent 60.2% of weeks with any mood episodes and 39.6% of weeks with mania episodes, during 8-year follow-up. During follow-up, 87.8% recovered from mania, but 73.3% relapsed to mania. Even accounting for family psychopathology, low maternal warmth predicted relapse to mania, and more weeks ill with manic episodes was predicted by low maternal warmth and younger baseline age. Largely similar to first episodes, second and third episodes of mania were characterized by psychosis, daily (ultradian) cycling, and long duration (55.2 and 40.0 weeks, respectively), but significantly shorter than first episodes. At 8-year follow-up, 54 subjects were 18.0 years or older. Among subjects 18.0 years or older, 44.4% had manic episodes and 35.2% had substance use disorders.

Conclusions: In grown-up subjects with child BP-I, the 44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences, strongly supporting continuity. The rate of substance use disorders in grown-up child BP-I was similar to that in adult BP-I.

Arch Gen Psychiatry. 2008;65(10):1125-1133

Strongly supported continuity between child BD-I and adult BD-I

DISTURBO BIPOLARE PEDIATRICO: OUTCOME

HIGH LEVEL OF PERSISTENCE OF PEDIATRIC BIPOLAR-I DISORDER FROM CHILDHOOD ONTO ADOLESCENT YEARS: A FOUR YEAR PROSPECTIVE LONGITUDINAL FOLLOW-UP STUDY

Janet Wozniak, MD[1,2], **Carter R. Petty, MA**[1], **Meghan Schreck, BA**[1], **Alana Moses, BA**[1], **Stephen V. Faraone, PhD**[3], and **Joseph Biederman, MD**[1,2]

[1] Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital; SUNY Upstate Medical University

[2] Department of Psychiatry at Harvard Medical School; SUNY Upstate Medical University

[3] Departments of Psychiatry and Neuroscience & Physiology, SUNY Upstate Medical University

Abstract

Objective—To examine the longitudinal course of pediatric bipolar (BP)-I disorder in youth transitioning from childhood into adolescence.

Methods—We conducted a four-year prospective follow-up study of 78 youth with BP-I disorder 6-17 years old at ascertainment followed up into adolescent years (13.4±3.9 years). All subjects were comprehensively assessed with structured diagnostic interviews, neuropsychological testing, psychosocial, educational and treatment history assessments. BP disorder was considered persistent if subjects met full criteria for DSM-IV BP-I disorder at follow-up.

Results—Of 78 BP-I participating youth subjects, 57 (73.1%), continued to meet full diagnostic criteria for BP-I Disorder. Of those with a non-persistent course, only 6.4% (n=5) were euthymic (i.e., syndromatic and symptomatic remission) at the 4-year follow-up and were not receiving pharmacotherapy for the disorder. The other non-persistent cases either continued to have subthreshold BP-I disorder (n=5, 6.4%), met full (n=3, 3.8%) or subthreshold (n=1, 1.3%) criteria for major depression, or were euthymic but were treated for the disorder (n=7, 9.0%). Full persistence was associated with higher rates of major depression and disruptive behavior disorders at the follow-up assessment and higher use of stimulant medicines at the baseline assessment. Non-Peristent BP-I was also characterized by high levels of dysfunction and morbidity.

Conclusions—This four-year follow-up shows that the majority of BP-I disorder youth continue to experience persistent disorder into their mid and late adolescent years and its persistence is associated with high levels of morbidity and disability. Persistence of subsyndromal forms of bipolar disorder was also associated with dysfunction and morbidity.

- 78 BD-I , age 13.4
- follow-up: 4 years
- after follow-up:
  - 73.1% BD-I
  - 9.0% EU with meds
  - 6.4% met sub-MDD
  - 6.4% EU with NO meds

DISTURBO BIPOLARE PEDIATRICO: OUTCOME

FOCUS ON CHILDHOOD AND ADOLESCENT MENTAL HEALTH

Notice of correction 4/12/2013:
The funding/support statement has been corrected to delete the reference to NIMH grant 1R01MH092450.

Irritability and Elation in a Large Bipolar Youth Sample: Relative Symptom Severity and Clinical Outcomes Over 4 Years

Jeffrey I. Hunt, MD; Brady G. Case, MD; Boris Birmaher, MD; Robert L. Stout, PhD; Daniel P. Dickstein, MD; Shirley Yen, PhD; Tina R. Goldstein, PhD; Benjamin I. Goldstein, MD, PhD; David A. Axelson, MD; Heather Hower, MSW; Michael Strober, PhD; Neal Ryan, MD; Lance Swenson, PhD; David R. Topor, PhD; Mary Kay Gill, MSN; Lauren M. Weinstock, PhD; and Martin B. Keller, MD

- Most bipolar youth eventually experienced both irritability and elation irrespective of history.

- **Irritable-only** youth were **at similar risk for mania** but **at greater risk for depression** compared with elated-only youth and youth who had both irritability and elation symptoms.

Hunt et al., 2013, J Clinical Psychiatry

Disruptive Mood Dysregulation Disorder (DMDD)

A. Severe recurrent temper outburst manifested verbally (e.g. verbal rages) and/or behaviorally (e.g. physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation

B. The temper outburst are inconsistent with the developmental level

C. The temper outburst occur, on average, three or more times per week

D. The mood between the temper outburst is persistently irritable or angry most of the day,

nearly every day, and is observable by others (e.g. parents, teachers, peers)

E. Criteria A-D have been present for 12 months or more months.

Throughout that time, the individual has not had a period lasting more than 3 or more consecutive months

without all the symptoms in Criteria A-D

F. Criteria A-D are present in at leas 2 or 3 settings (home or school) and are severe in at leas one of these

G. The diagnosis should not be made before age 6 years or after age 18 years

H. By history or observation, the age at onset of criteria A-E is before 10 years

I. There has been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic/hypomanic episode have been met

J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by other mental disorders (e.g. autism, PTSD, SAD, dysthymia)

K. The symptoms are not attributable to the physiological effects of a substance abuse or to another medical or neurological condition

DMDD: OUTCOME

Article

Adult Diagnostic and Functional Outcomes of DSM-5 Disruptive Mood Dysregulation Disorder

William E. Copeland, Ph.D.

Lilly Shanahan, Ph.D.

Helen Egger, M.D.

Adrian Angold, M.R.C.Psych.

E. Jane Costello, Ph.D.

Objective: Disruptive mood dysregulation disorder (DMDD) is a new disorder for DSM-5 that is uncommon and frequently co-occurs with other psychiatric disorders. Here, the authors test whether meeting diagnostic criteria for this disorder in childhood predicts adult diagnostic and functional outcomes.

Method: In a prospective, population-based study, individuals were assessed with structured interviews up to six times in childhood and adolescence (ages 10 to 16 years; 5,336 observations of 1,420 youths) for symptoms of DMDD and three times in young adulthood (ages 19, 21, and 24–26 years; 3,215 observations of 1,273 young adults) for psychiatric and functional outcomes (health, risky/illegal behavior, financial/educational functioning, and social functioning).

Results: Young adults with a history of childhood DMDD had elevated rates of anxiety and depression and were more likely to meet criteria for more than one adult disorder relative to comparison subjects with no history of childhood psychiatric disorders (noncases) or individuals meeting criteria for psychiatric disorders other than DMDD in childhood or adolescence (psychiatric comparison subjects). Participants with a history of DMDD were more likely to have adverse health outcomes, be impoverished, have reported police contact, and have low educational attainment as adults compared with either psychiatric or noncase comparison subjects.

Conclusions: The long-term prognosis of children with DMDD is one of pervasive impaired functioning that in many cases is worse than that of other childhood psychiatric disorders.

Am J Psychiatry Copeland et al.; AiA:1–7

Altri 2 lavori su outcome di SMD: Brotman (2006) e Stringaris (2010)

DMDD: OUTCOME

Prevalence, Clinical Correlates, and Longitudinal Course of Severe Mood Dysregulation in Children

Melissa A. Brotman, Mariana Schmajuk, Brendan A. Rich, Daniel P. Dickstein, Amanda E. Guyer, E. Jane Costello, Helen L. Egger, Adrian Angold, Daniel S. Pine, and Ellen Leibenluft

Background: *Controversy concerning the diagnosis of pediatric bipolar disorder (BD) has focused attention on children with chronic irritability and hyperarousal. This syndrome has been called the "broad BD phenotype" or severe mood dysregulation (SMD). This study examines prevalence, concurrent Axis I diagnoses, and longitudinal outcome of SMD in an epidemiologic sample.*

Methods: *Data were drawn from the Great Smoky Mountains Study, a longitudinal epidemiological study. Items from the Child and Adolescent Psychiatric Assessment were used to generate SMD criteria.*

Results: *Among 1420 children, the lifetime prevalence of SMD in children ages 9–19 was 3.3%. Most (67.7%) SMD youth had an Axis I diagnosis, most commonly attention-deficit/hyperactivity disorder (26.9%), conduct disorder (25.9%), and/or oppositional defiant disorder (24.5%). In young adulthood (mean age 18.3 ± 2.1 years), youth who met criteria for SMD in the first wave (mean age 10.6 ± 1.4 years) were significantly more likely to be diagnosed with a depressive disorder (odds ratio 7.2, confidence interval 1.3–38.8, p = .02) than youth who never met criteria for SMD.*

Conclusions: *Severe mood dysregulation is relatively common in childhood and predicts risk for early adulthood depressive disorders. Research should continue to explore the course of illness in children with SMD.*

Mean age at outcome 18.3: early adulthood depressive disorder is a predictor of future BD!

DMDD: OUTCOME

Pediatric Bipolar Disorder Versus Severe Mood Dysregulation: Risk for Manic Episodes on Follow-Up

Argyris Stringaris, M.D., M.R.C.Psych., Argelinda Baroni, M.D., Caroline Haimm, B.A., Melissa Brotman, Ph.D., Catherine H. Lowe, M.S.W., Frances Myers, R.N., M.S.N., Eileen Rustgi, Ph.D., Wanda Wheeler, M.S.W., Reilly Kayser, B.A., Kenneth Towbin, M.D., Ellen Leibenluft, M.D.

Objective: An important question in pediatric bipolar research is whether marked nonepisodic irritability is a manifestation of bipolar disorder in youth. This study tests the hypothesis that youth with severe mood dysregulation (SMD), a category created for the purpose of studying children presenting with severe nonepisodic irritability, will be significantly less likely to develop (hypo-)manic or mixed episodes over time than will youth with bipolar disorder (BD). **Method:** Patients with SMD (N = 84) and narrowly defined BD (N = 93) at baseline were followed up in 6-monthly intervals using the relevant K-SADS modules to ascertain (hypo-)manic or mixed episodes. **Results:** Only one of 84 SMD subjects (1/84 [1.2%]; 95% confidence interval CI = 0.0003 to 0.064) experienced a (hypo-)manic or mixed episode during the study (median follow-up = 28.7 months). The frequency of such episodes was more than 50 times higher in those with narrowly defined BD (58/93 [62.4%]; 95% CI 0.52 to 0.72). **Conclusions:** These data suggest that, over an approximately 2-year follow-up period, youth with SMD are unlikely to develop (hypo-)manic or mixed episodes. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(4):397–405. **Key Words:** bipolar disorder, pediatric, severe mood dysregulation, irritability, ADHD

NB: Narrow BD continuano a ciclare, gli altri hanno decorso diverso!

DEPRESSIONE BIPOLARE: FATTORI PREDITTIVI DI SWITCH DA UP-D A BP-D

Author, year	N, type of sample (years)	F-up (years)	Manic switches	Predictors of switching
Strober&Carlosn,1982	56 inpatient 13-16 y/o	4 y	21%	Rapid symptom onset Severe depressed mood Self-reproach Bodily concerns Diminished concentration Psychomotor retardation Mood-congruent psychotic features **Loaded family history of mood disorders; Family history of bipolar disorder** **Three generations of family history of mood disorder** **Pharmacologically induced hypomania**
Strober et al., 1993	58 inpatients 12-18 y/o	2 y	9%	Psychotic symptoms during MDD
Geller et al., 1994	79 outpatients, 6-12 y/o	5 y	32%	**Loaded family history of mood disorder** **Multigenerational family history of mood disorder** **Bullying behavior**
Geller et al.,2001	100 outpatients, 6-12 y/o	10 y	49%	**Family history of mania**
Kochman et al., 2005	80 inpatients, 7-17 y/o	1 y	43%	**Cyclothymic temperament**
Biederman et al., 2009	168 outpatients, 6-12 y/o	7 y	21%	**Comorbid ADHD** **Comorbid conduct disorder School behavior problems** **Family history of mood disorder** Subthreshold manic symptoms
Biederman et al., 2013	103 outpatients, 6-18 y/o	11 y	23%	Subthreshold manic symptoms; Emotional Dysregulation

Uchida M, Serra G, Zayas L et al., 2015a Journal of Affective Disorders

DEPRESSIONE UNIPOLARE vs DEPRESSIONE BIPOLARE: CARATTERISTICHE DEMOGRAFICHE E CLINICHE

Author, year	N, type of sample (years)	Predictors of bipolarity
Wozniak et al., 2004	109 UPD, 43 BPD 6-17 y/o	**Depression severity** **Hopelessness** **Suicidality** **Sad + mad mood** School behavior **Hospitalization and medication** Interpersonal difficulty Comorbid conduct, ODD or Alcohol abuse Family history of bipolar disorder, anxiety disorder and conduct disorder
Luby&Belden, 2008	54 UPD, 21 BPD 3-6 y/o	**Depression severity** **Irritability** Comorbid ADHD, conduct, ODD, anxiety
Merikangas et al., 2012	805 UPD, 246 BPD 13-18 y/o	**Depression severity** **Younger age of onset** **Recurrent episodes** Disability Comorbid anxiety, substance use, conduct Family history of mood disorder
Shon et al.,2014	143 UPD, 55 BPD 6-18 y/o	**Atypical features** **Pharmacologically induced hypomania** **Aggressive behaviors** Family history of psychiatric illness

Uchida M, Serra G, Zayas L et al., 2015b Journal of Affective Disorders

RISCHIO SUICIDARIO NEI DISTURBI DELL'UMORE PEDIATRICI

- Tasso di Tentati Suicidi nel **Disturbo Bipolare Pediatrico: 27.3% [CI: 20.4–34.2]**
- Tasso di Tentati di Suicidi nel **Disturbo Depressivo Maggiore Pediatrico: 14.0% [CI 9.36–18.7]**
- Fattori predittivi di suicidio nel Disturbo Depressivo Maggiore:
  - ★CARATTERISTICHE DEMOGRAFICHE: **Esordio pre-puberale**, eta' maggiore nei pz con comporamenti suicidari (rispetto a pz con depressione senza comp. suicidari).
  - ★CARATTERISTICHE CLINICHE: Sintomi psicotici, **sintomi misti (irritabilità, agitazione psicomotoria, racing thoughts)**, insonnia, **temperamento ciclotimico-ipertimico,** novelty-seeking behaviors, disregolazione dell'umore e labilità emotiva, grave episodio depressivo, bassa autostima, perdita di speranza, pensieri violenti / rabbiosi
- **Fattori predittivi di suicidio nel Disturbo Bipolare:**
  - ★CARATTERISTICHE DEMOGRAFICHE: **giovane eta' d'esordio**, eta' maggiore nei pz con comporamenti suicidari (rispetto a pz con depressione senza comp. suicidari), sesso femminile
  - ★CARATTERISTICHE CLINICHE: episodio depressivo severo, **comportamenti aggressivi etero e auto-diretti, storia di tentati suicidi o ideazione suicidaria precedente, familiarita' per suicidio**, bassa qualita' di vita, eventi stressanti, abuso fisico o sessuale e ritiro sociale [Halfon et al. 2013]

Serra G et al., manuscript in preparation

OUTLINE

1. Osservazioni longitudinali e retrospettive

2. Sintomatologia clinica: sintomi cardinali della mania pediatrica e depressione bipolare

3. Nuove prospettive terapeutiche

LONG-TERM PHARMACOLOGICAL TREATMENT OF PEDIATRIC BIPOLAR DISORDER

Pharmacological and non-drug treatment of child bipolar I disorder during prospective eight-year follow-up

Barbara Geller, **Rebecca Tillman**, **Kristine Bolhofner**, and **Betsy Zimerman**
Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, USA

Abstract

Objectives—The 'Phenomenology and Course of Pediatric Bipolar Disorders' study, a National Institute of Mental Health-funded study of child bipolar I disorder (BP-I) begun in 1995, is a prospective follow-up study that included collecting pharmacological and non-drug treatment data.

Methods—There were 115 first-episode subjects who fit full DSM-IV criteria for BP-I, mixed or manic phase, with severity scores in the clinically impaired range, ascertained by consecutive new case ascertainment. Subjects were assessed with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS), given separately to parents about their children and to children about themselves. All treatment was provided by the subjects' own community practitioners, exactly as if they had not been in the research study. Thus, families were only seen for research assessments, and research staff was not at all involved in their treatment. Data on type, dose, and duration of pharmacological and non-drug treatment were collected. During follow-up, 93.9% (n = 108) were assessed at each of the nine assessment times.

Results—During the eight years, only 62.6% received any antimanic medication (antipsychotic, anticonvulsant, lithium) at any time. Percents who received non-antimanic medication included 77.4% medication for attention-deficit hyperactivity disorder and 64.3% antidepressants. A total of 67.8% of subjects were taking two or more concurrent medication classes. Subjects ascertained from psychiatric versus pediatric sites received antimanics significantly more frequently (p = 0.006). Earlier recovery during eight-year follow-up was predicted by greater percent of weeks on lithium (p = 0.017).

Conclusions—Given these findings, and the poor prognosis from prospective follow-up of this sample reported elsewhere, there is a need for further research that informs the development of effective treatment strategies.

- 68% were taking 2 or more medication classes
- 62% antimanics at any time
- 75% antidepressants
- **77% stimulants (!!!!)**

Need for further research for effective treatment strategies!

Geller et al., 2010 Bipolar Disorders

LONG-TERM PHARMACOLOGICAL TREATMENT OF PEDIATRIC BIPOLAR DISORDER

- 17 studi (N=1467, eta' 12.6±2.3 aa; durata dei trial 14–78 settimane)
- 3 RCT (2 on Aripiprazole; 1 Lithium vs. Divalproex)
- 13 non-controlled studies (6 open-label on anticonvulsants and lithium; 5 on 2nd generation antipsychotics; 4 combination strategies)
- Misure di efficacia: prevenzione di ricadute e tempo di ricaduta.
- **Aripiprazolo puo' essere utile nella prevenzione delle ricadute nel BD pediatrico**
- Risultati positivi sono stati riportati per **Quetiapina e Litio** (nella prevenzione di ricadute) e per litio, quetiapina, ziprasidone e la combinazione di risperidone e Ac. Valproico o Litio per riduzione dei sintomi a lungo termine.
- **Urgent need for new well-designed studies in young peoples with BD which has led the US FDA and the National Institute of Child Health and Human Development to include Lithium among the 20 medication whose study in pediatric population is considered a priority**

Covadonga, Moreno, Llorente et al., 2014, JCPP

MEMANTINE: A NEW ANTI MANIC AND MOOD STABILIZING MEDICATION

- *Memantine is a selective non-competitive antagonist of NMDA glutamate receptors*, but unlike the more potent NMDA receptor blockers (such as Ketamine, Phencyclidine, MK-801) memantine has *low affinity for the receptor* and *its action is voltage-dependent*.

- It has been recently demonstrated that memantine has *neuroprotective properties*: it selectively *blocks the extrasynaptic (excitotoxic) receptors, but preserves the normal synaptic function*.

- The drug was marketed in *Germany in 1982 as Akatinol Memantine*. In 2004 it was approved by the US FDA for the treatment of moderate to severe *Alzheimer's Disease* and several pre-marketing and post-marketing studies **have demonstrated the *excellent safety and tolerability profile*** of the drug.

- It has been *used off-label in a number of psychiatric conditions, including depression, with contrasting results*.

Gillin et al, 2009; Johnson & Kotermanski, 2006, La Spada, 2009

MEMANTINE: PHARMACOLOGICAL BASIS

- On the basis of the effect of memantine on the forced swimming test (an animal model of depression), many authors suggest that the NMDA receptor blockers might have an antidepressant activity *(Rogoz et al, 2002; Trullas et al, 1990)*

- At variance with this hypothesis, ***it was recently shown that MK-801 and memantine have an antimanic and mood-stabilizing-like effect*** in the animal model of bipolar disorder resistant to standard treatment *(D'Aquila et al, 1992; Demontis et al, 2012)*.

- In keeping with this pre-clinical evidence, ***we observed a clinical relevant antimanic and long lasting mood stabilizing effect of memantine, as an augmenting agent, in the treatment resistant bipolar disorder.***

MEMANTINE: Clinical Observations

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Bipolar Disorders 2010: 12: 348–349

© 2010 The Authors
Journal compilation © 2010 Blackwell Munksgaard

BIPOLAR DISORDERS

Letter to the Editor

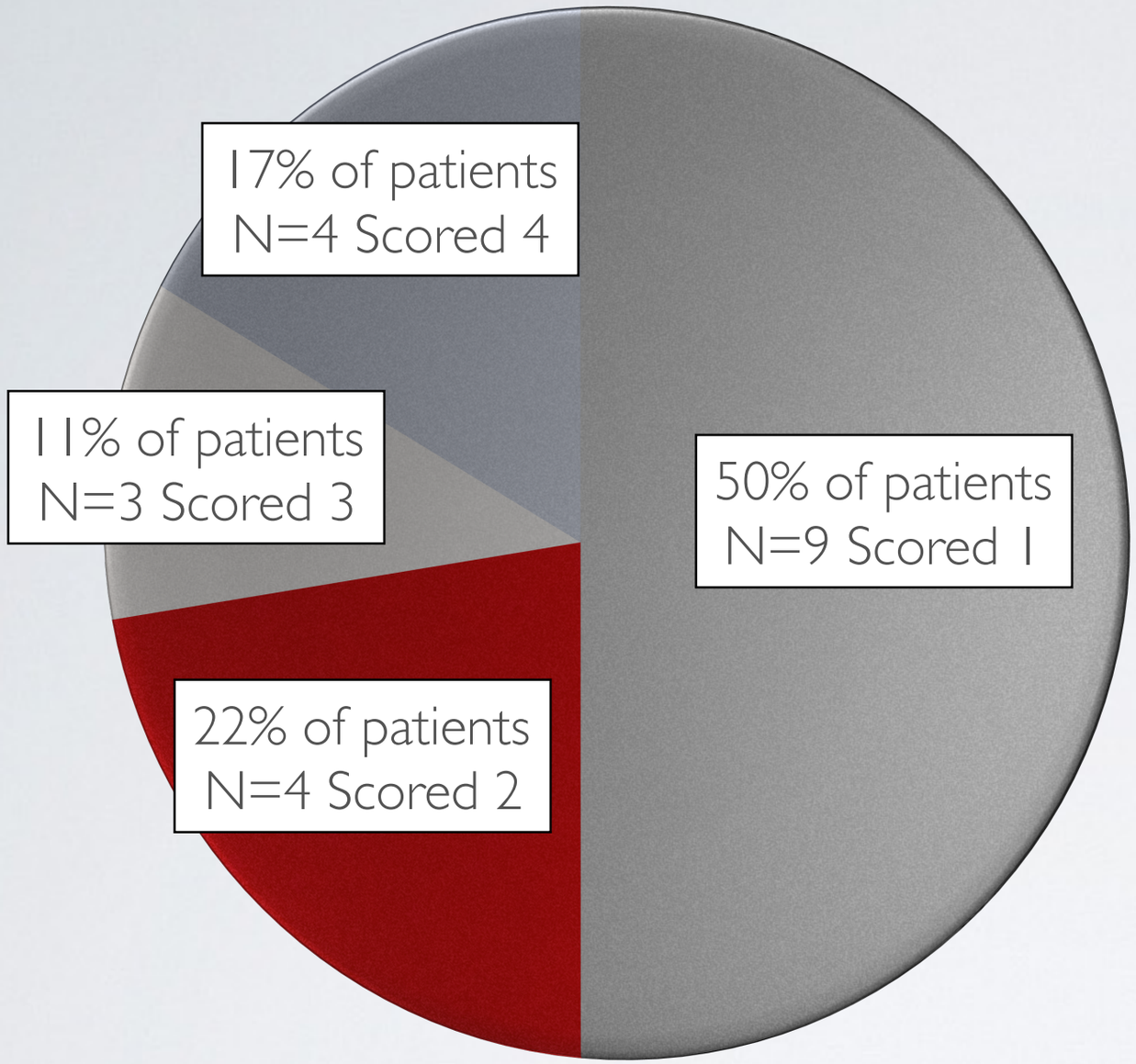
Antimanic and mood-stabilizing effect of memantine as an augmenting agent in treatment-resistant bipolar disorder

Memantine was added to the ongoing mood-stabilizing treatment at the daily dose of 10-30 mg/day

Koukopoulos A, et al, ***Bipolar Disord. 2010 May****; 12(3):348-9.*

Clinical Observations

N=18



- ***72%*** of pts were ***Very Much*** or ***Much improved***
- Mean time of improvement was ***55 days***

Among the 10 RC,
6 reached stability

These results suggest a meaningful ***antimanic*** and ***mood stabilizing effect*** of memantine.

Side effects: One pt complained of ***dizziness*** and One of ***constipation***

Clinical Observations

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

The sustained mood-stabilizing effect of memantine in the management of treatment resistant bipolar disorders: Findings from a 12-month naturalistic trial

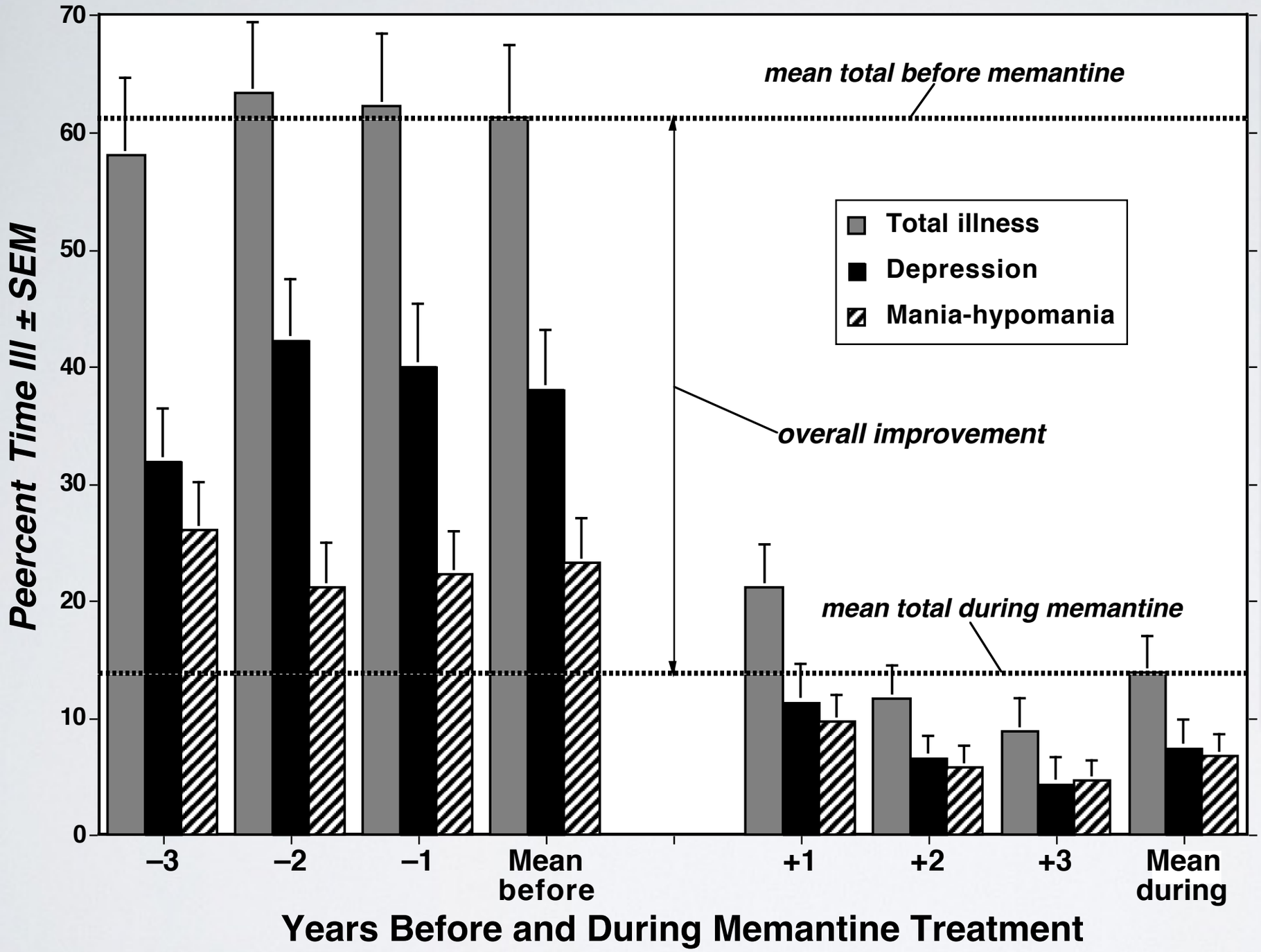
Athanasios Koukopoulos [a], Giulia Serra [b], Alexia E. Koukopoulos [a], Daniela Reginaldi [a], Gino Serra [c,*]

[a] Centro Lucio Bini, Roma, Italy
[b] Azienda Ospedaliera Sant'Andrea, Dipartimento NESMOS, II Facoltà di Medicina e Chirurgia, Università "La Sapienza", Roma, Italy
[c] Dipartimento di Scienze del Farmaco, Università di Sassari, Italy

This second study confirmed our previous observation and suggested a sustained mood stabilizing effect

*Koukopoulos A et al, **J Affect Disord. 2012 Jan**;136(1-2):163-6.*

THREE-YEAR NATURALISTIC, MIRROR IMAGE ASSESSMENT OF ADDING MEMANTINE OF 30 TREATMENT-RESISTANT PATIENTS WITH BIPOLAR DISORDER



- Clinical improvements **BD-I and II**
- Reduction of **number, duration, and severity** of episodes in both mania-like and depressive **morbidity**
- **RC and CC** subjects were particularly improved
- **Adverse effects mild and rare**

RCT Memantina vs. Lamotrigina attualmente in corso al S. Andrea

Serra G, Koukopoulos A, De Chiara L, et al. 2015, J Clinical Psychiatry

Memantine as augmenting treatment in autistic youth with irritability and hyperactivity

International Journal of Neuropsychopharmacology (2013), **16**, 783–789. © CINP 2012
doi:10.1017/S1461145712000880

Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial

Ali Ghaleiha[1], Mahtab Asadabadi[2], Mohammad-Reza Mohammadi[2], Maryam Shahei[2], Mina Tabrizi[3], Reza Hajiaghaee[4], Elmira Hassanzadeh[2] and Shahin Akhondzadeh[2]

[1] *Research Center for Behavioral Disorders and Substance Abuse, Hamadan University of Medical Sciences, Hamadan, Iran*
[2] *Psychiatric Research Centre, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[4] *Institute of Medicinal Plants (ACECR), Tehran, Iran*

"*the group that received memantine had greater reduction in ABC-C subscale scores for* ***irritability, stereotypic behaviour and hyperactivity***"
"The present study suggests that memantine may be a potential adjunctive treatment strategy for autism and it was generally well tolerated."

Int J Neuropsychopharmacol. 2013 May

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype

Demitri F. Papolos [a,b,*], Martin H. Teicher [c], Gianni L. Faedda [d,e], Patricia Murphy [f], Steven Mattis [g,h]

Results: Ketamine administration was associated with ***a substantial reduction in measures of mania, fear of harm and aggression.*** Significant improvement was observed in mood, anxiety and behavioral symptoms, attention/executive functions, insomnia, parasomnias and sleep inertia. Treatment was generally well-tolerated.

J Affect Disord. 2013 May

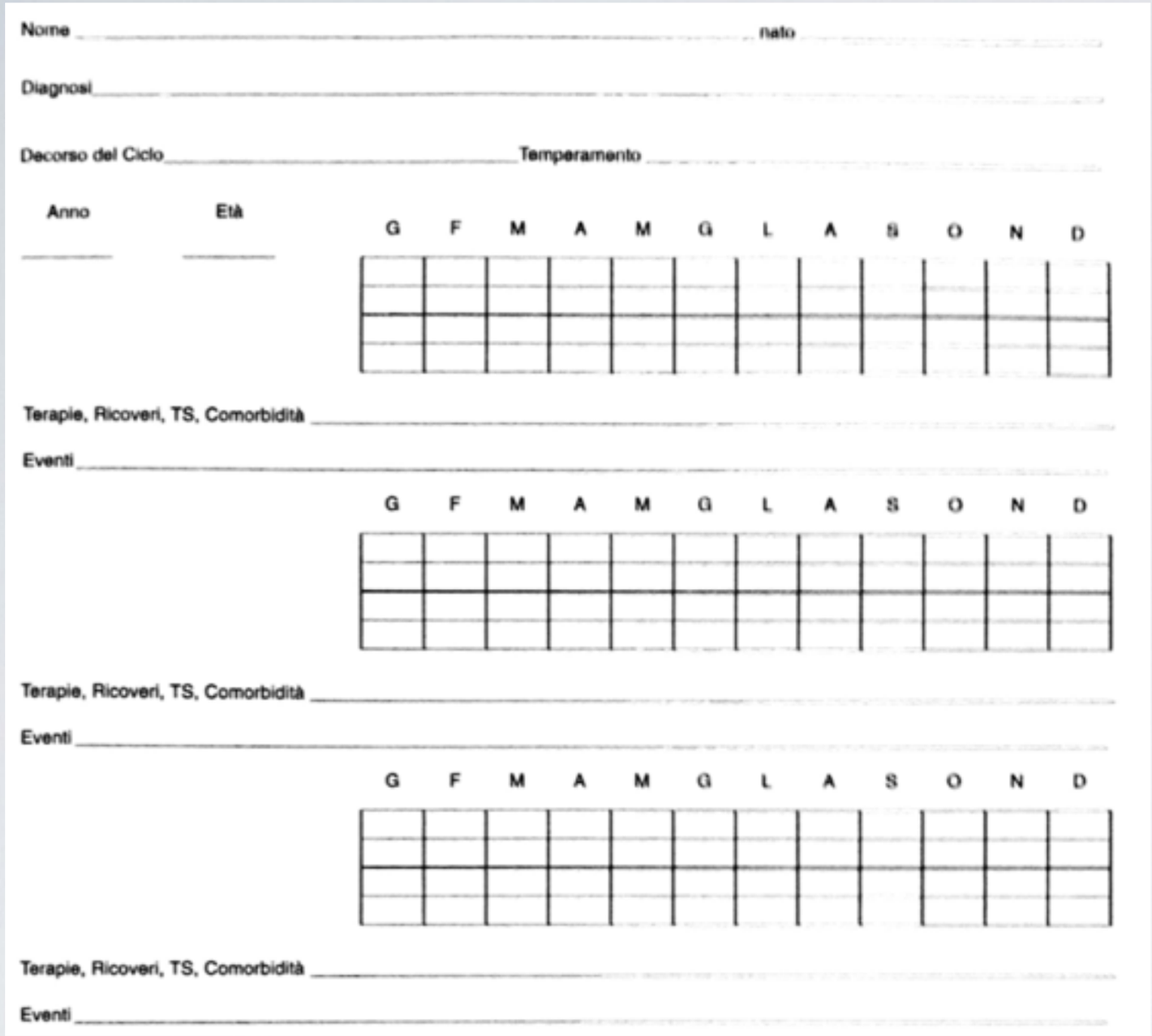
CONCLUSIONI E PROSPETTIVE FUTURE

- Necessita' di studi longitudinali di follow-up nei pazienti con disturbi dell'umore (uso di ***life charts*** con registrazione di numero, tipo, durata, severità episodi, eventi e terapie concomitanti)
- Dettagliato assessment della sintomatologia maniacale e depressiva per permettere descrizioni fenomenologie dettagliate (quantificazione dei sintomi maniacali con un rate di severità/frequenza)
- Valutazione specifica dei diversi tipi di irritabilità (eterogeneità dell'irritabilità) e del suo decorso
- Valutazione dei comportamenti suicidari e comportamenti a rischio
- Trial clinici per valutare l'efficacia di terapie stabilizzanti (litio e memantina)
- Gruppi di psicoeducazione per pazienti ad alto rischio (BD-NOS)
- Creazione di un link con i centri di trattamento dei disturbi dell'umore adulti per creare una osservazione a lungo termine condividendo gli strumenti di valutazione

PROGETTI IN CORSO

PROGETTI DI RICERCA	COLLABORAZIONI
Heterogeneity of irritability in children and adolescents (review)	MGH-Harvard Medical School (Dr. M. Uchida, Dr. J. Biederman)
Suicide attempts in juvenile Unipolar vs. Bipolar depressive disorder (metanalisi)	MGH e McLean H. - Harvard Medical School (Dr. J. Wozniak, Dr. Ross J. Baldessarini), NESMOS Dep (Prof. P. Girardi)
Developmental psychopathology of mood disorders: differences between bipolar and unipolar depressive disorder in children.	Casini, Battaglia, MGH-Harvard Medical School (Dr. M. Uchida, Dr. J. Biederman)
Cardinal symptoms in pediatric bipolar disorder: irritability vs. eleation and grandiosity	Casini, Battaglia, MGH-Harvard Medical School (Dr. J. Wozniak; Dr. J. Biederman)
CBCL as screening tool to differentiate bipolar vs severa mood dysregulation vs major depressive disorders in pediatric populations.	Casini, Battaglia, MGH-Harvard Medical School (Dr. J. Wozniak; Dr. J. Biederman)
Irritability in pediatric mania (invited review on a Special Issue on Current Neuropharmacology)	MGH-Harvard Medical School (Dr. J. Wozniak), NESMOS Dep. Sapienza U. (Dr. G. Sani, Prof. P. Girardi)

Life chart



Nome _____ nato _____

Diagnosi _____

Decorso del Ciclo _____ Temperamento _____

Anno	Età	G	F	M	A	M	G	L	A	S	O	N	D
_____	_____												

Terapie, Ricoveri, TS, Comorbidità _____

Eventi _____

	G	F	M	A	M	G	L	A	S	O	N	D

Terapie, Ricoveri, TS, Comorbidità _____

Eventi _____

	G	F	M	A	M	G	L	A	S	O	N	D

Terapie, Ricoveri, TS, Comorbidità _____

Eventi _____

	JAN	FEBR	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
2009												
2010												
2011												
2012												
2013												

MGH PEDIATRIC MANIA SYMPTOM CHECKLIST©

GUIDELINES FOR RATING

- Rate each of the following items for the past week
- Rate items relative to subject's baseline or what's expected for age / developmental level
- Assess behavior based on report from caretaker, subject, and rater observation
- Assess composite severity based on frequency and intensity of the behavior

SYMPTOMS		FREQUENCY			INTENSITY			COMPOSITE SEVERITY			
Start each item by saying - "In the last week did s/he have difficulties with..."		< ½ a week (< 4 days)	> ½ a week (≥ 4 days)	All week (Daily)	Mild	Moderate	Severe				
		1	2	3	1	2	3				
1. MOOD BEING *EUPHORIC*	Score	1	2	3	1	2	3	0	1	2	3
as suggested by sustained periods of: ○ **happy** or **excited** mood ○ **silly, giddy, goofy** mood ○ **laughing fits** or **baby talk**											
2. MOOD BEING *IRRITABLE*	Score	1	2	3	1	2	3	0	1	2	3
as suggested by sustained periods of: ○ extremely **irritable, angry, cranky, grouchy** moods ○ extremely **threatening, destructive,** or **assaultive** behaviors ○ extreme **anger outbursts** / meltdowns / rage											
3. INCREASED ENERGY OR ACTIVITY	Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ engaging in activities in an **urgent, pressured, rushed** way, or at a **faster pace** than expected *(does not slow down)* ○ working on **big projects** that are beyond the capacity of what is typical for age ○ **extreme involvement** in an activity of interest (*engages at earliest opportunity; difficult to disengage*)											
4. LACK OF SLEEP	Score	1	2	3	1	2	3	0	1	2	3
as suggested by sleeping fewer hours than expected											
5. DISTRACTIBILITY	Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ inability to stay on task ○ being highly **inattentive** ○ inability to **concentrate**											
6. TALKATIVENESS	Score	1	2	3	1	2	3	0	1	2	3
as evidenced by: ○ talking **loud, fast** or **too much** ○ **pressured speech** that is difficult to **interrupt**											
7. STAYING ON TOPIC / RACING THOUGHTS	Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ **jumping from topic to topic** or talking about many different topics at the same time ○ reporting **racing thoughts** or **mind being too active**											

Frequency:

- <1/2 week (<4 days)
- >1/2 week (>4days)
- All week (daily)

Intensity:

- Mild
- Moderate
- Severa

THE MODIFIED OVER AGGRESSION SCALE (MOAS)

Towards a new rating scale for irritability

Verbal aggression

_____ **0** No verbal Aggression
_____ **1** Shouts angrily, curses mildly, or makes personal insults
_____ **2** Curses viciously, is severely insulting, has temper outbursts
_____ **3** Impulsively threatens violence toward others or self
_____ **4** Threatens violence toward others or self repeatedly or deliberately
_____ **SUM VERBAL AGGRESSION SCORE**

Aggression against Property

_____ **0** No aggression against property
_____ **1** Slams door, rips clothing, urinates on floor
_____ **2** Throws objects down, kicks furniture, defaces walls
_____ **3** Breaks objects, smashes windows
_____ **4** Sets fires, throws objects dangerously
_____ **SUM PROPERTY AGGRESSION SCORE**

Autoaggression

_____ **0** No autoaggression
_____ **1** Picks or scratches skin, pulls hair out, hits self (without injury)
_____ **2** Bangs head, hits fists into walls, throws self onto floor
_____ **3** Inflicts minor cuts, bruises, burns, or welts on self
_____ **4** Inflicts major injury on self or makes a suicide attempt
_____ **SUM AUTOAGGRESSION SCORE**

Physical Aggression

_____ **0** No physical aggression
_____ **1** Makes menacing gestures, swings at people, grabs at clothing
_____ **2** Strikes, pushes, scratches, pulls hair of others (without injury)
_____ **3** Attacks others, causing mild injury (bruises, sprain, welts, etc.)
_____ **4** Attacks others, causing serious injury
_____ **SUM PHYSICAL AGGRESSION SCORE**

CATEGORY	SUM SCORE	WEIGHTS	WEIGHTED SUM
Verbal Aggression		x 1	
Aggression against Property		x 2	
Autoaggression		x 3	
Physical Aggression		x 4	
Total Weighted Score			

Aggiungere la parte sull'irritabilità lieve (più tipicamente depressiva) e validare!

Grazie per l'attenzione!