

The bipolar controversy in children and adolescents

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Conflicts of interest

Currently a principle investigator on an NHS HTA funded trial of psychological treatment in adolescent depression

Outline

- Background: the bipolar controversy
- International differences
- US/UK cross national study
- Diagnostic issues
- The case for early intervention
- Treatment dilemmas



Diagnostic controversies in youths began in 1990s: ?increased BPD in ADHD

Children with ADHD reported to have
11% lifetime rates of BP; high rates in
clinical samples, ~50% (Biederman 1996)

Similar controversy in adults

- Up to 20% depressed adults may have BP (Smith BMJ 2011)
- ‘Bad medicine: Bipolar II disorder’
Spence, BMJ, May, 2011
‘...criteria too loose...definition of hypomania has no real world validity..’
- Letters: Ian Anderson – *issue of subthreshold disorder not confined to psychiatry, e.g. diabetes, hypertension, etc*

Media and bipolar:

'I want to be bipolar...'

Chan & Sireling, *the Psychiatrist*, 2010



Rise in US diagnoses

Rapid rise in C&A clinic visits for BP in US:

1994-5: 25/100 000

2002-2003: 1003/100 000

i.e. ~40 fold increase

(Moreno AGP 2007)

US Hospital discharges for BP

- Children:

1996 1.3/10 000

2004 7.3/10 000

- Adolescents: increased 4x

- Adults: increase of 56%

Blader & Carlson Biol Psych 2007

Uncommon in international epidemiological samples: similar prevalence

Adolescents:

- US: 1% BP, broad definition
only **0.1% BP-I** (Lewinsohn JAACAP 1995)
- Dutch study: 1.9% mania, 0.9% hypomania
(Verhulst 1997)
- Canadian Community Health Survey:
2.1% bipolar (Kozloff, JAD, 2010)

Community samples: children and younger adolescents

- No cases of BP-1 in US Great Smoky Mountains Study (Costello 1996)
- No cases in UK ONS study (Ford, 2003)

International differences: clinical

Soutullo et al, Bipolar Disorders, 2005

country	author	N (age)	prevalence	Diagnostic criteria	sample
Denmark	Thomsen 1992	3250 (<15) nationwide	1.2%	Clinician assigned	Psychiatric inpatients
Finland	Rasanen 1998	(10-19) nationwide	0.00006% (1.7/100 000)	DSM-III-R	Psychiatric inpatients
Finland	Sourander 2004	475 (2-18)	1.7%	ICD-10	Psychiatric inpatients
Spain	Soutullo 2003	714 (<18)	4%	DSM-IV	outpatients
India	Reddy 1997	840 C&A	2.5%	DSM-III-R	outpatients
India	Alexander 1997	119 (10-13)	4.2%	DSM-IV	inpatients
Brazil	Tramontina 2003	35 (<15)	(7.2%)	DSM-IV	outpatients
(Germany	Holtmann 2010	national, 2000-07	1.13-1.91/ 100 000		Inpatients)

UK clinics

author	N (age)	prevalence	diagnostic criteria	sample
Sigurdsson 1999	38 over 22 years (11-18)	~1.7 cases/year Retrospective case review	ICD-9 &10	Inpatients & outpatients
Harrington 2003	2500 (<11)	None reported	Clinician report	outpatient
Thapar 2011	200 (6-18)	1 case (DSM-IV BP NOS and ICD-10 hypomania)	DMS-IV &ICD-10 (CAPA)	ADHD cases outpatients

Cross national study of pre-pubertal mania

Dubicka, Carlson, Vail & Harrington,
ECAP, 2008

Examine diagnostic differences
between US and UK clinicians

Method

- US/UK clinician study using vignettes
n 58 US vs 45 UK clinicians
- Clinicians prompted to check mania symptoms and state differential diagnoses and treatment

Vignettes: diagnostic complexity

- Case 1: 11 yr old, Lynda, Hx **ADHD**, change in behaviour over 1 year, psychosocial problems
- Case 2: **young child**, 5 yr old, Daniel, developmental problems, hyperactive
- Case 3: 12 yr old, Luke, mood swings, **suicidal after parental loss**
- Case 4: 10 yr old, Kyle, rigid, **obsessional** behaviour, temper tantrums
- Case 5: 12 yr old, Nicola, '**classical case**'

Classic Bipolar I Disorder

- **Nicola, 12 yrs, shy, no behaviour problems or SA**
- **Aged 10, brief depressive episode after Grandma's death; -> psychotherapy; anxiety related to school transition.**
- **3 weeks before referral, personality change (parents):**
 - ◆ **sexy clothes, talking to strangers, meeting boys on internet chat rooms; up all night; vulgar language.**
 - ◆ **Mood changes throughout the day from laughing hysterically, to being irritable, swearing and smashing things to becoming tearful and crying uncontrollably.**
 - ◆ **Sleep patterns had changed; up late talking in chat rooms, sleep for a few hours but would wake early and rearrange room, waking the neighbours by using the vacuum cleaner at 6 am.**

Nicola continued

Mental state

- Loud, intrusive, talked fast and laughed loudly. Hard to follow train of thought- rapidly changing subject to unrelated topics.
- Convinced a TV actor whom she had been trying to contact, would call her and she'd have a relationship with him.
- Became suspicious and hostile when asked about drug use which she adamantly denied; would not allow the interviewer to see her parents alone.
- Expressed a fear that her food may have been poisoned and that her brain had been damaged.

Comorbid ADHD and bipolar (?)

- Lynda, aged 11, hyperactive and impulsive since a toddler
- Aged 10, behavior worse; worse peer relationships; increased irritability and aggression; rages when thwarted; parents concerned for younger sister
- Started expressing interest in pornographic magazines, undressed in front of boys
- Told parents not to worry about her grades; she knew she could get into medical school when she grew up.
- One parent severe cyclothymia, other chronically depressed; chronic family stress

Lynda continued Mental Status

- Tried to be seductive; provocative; argumentative.
- Admitted trouble paying attention, following directions, remembering things, and sitting still; Said she talks so fast that others have trouble keeping up with her though this was not evident during interview.
- Described temper problems/irritability; denied euphoria; felt sad, and even suicidal during periods of anger
- She thought that she could go to law school if she brings up her grades.
- Heard dead grandma's voice saying it was OK to smoke.

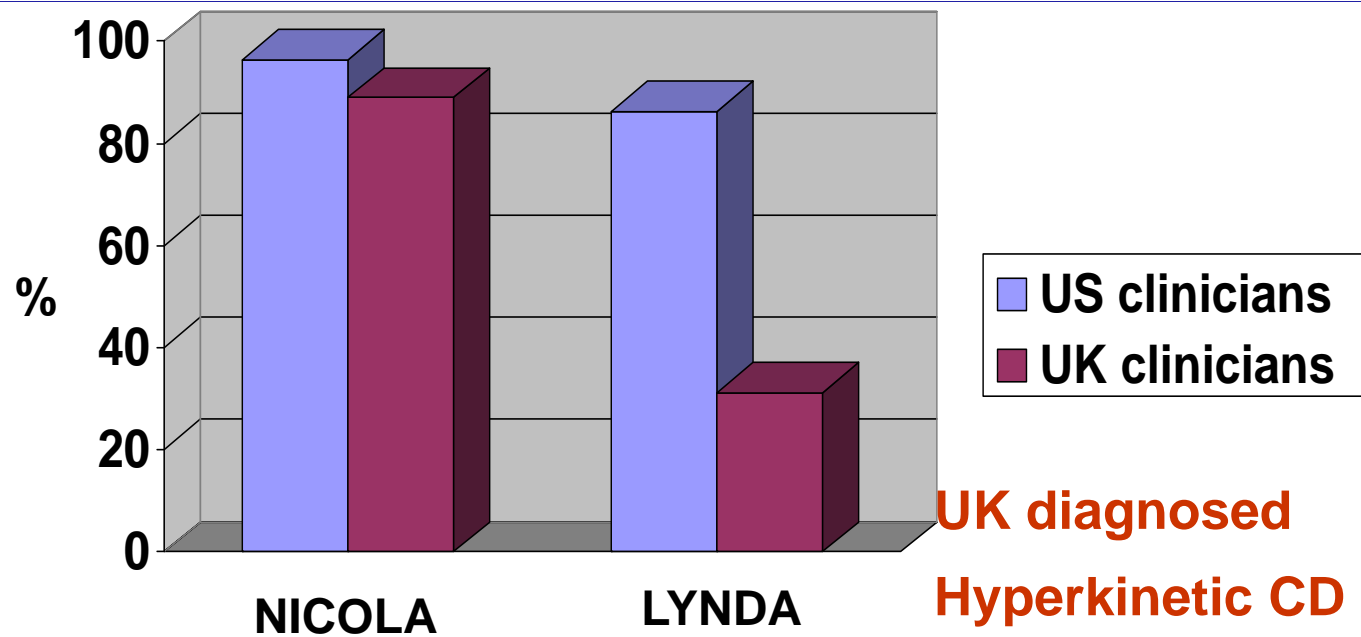
Results

- US clinicians more likely to recognise mania, except in 'classical' case where similar rates of diagnosis
- Therefore, clinicians appear to interpret symptoms differently

Agreement between clinicians in the US and UK on Nicola and Lynda

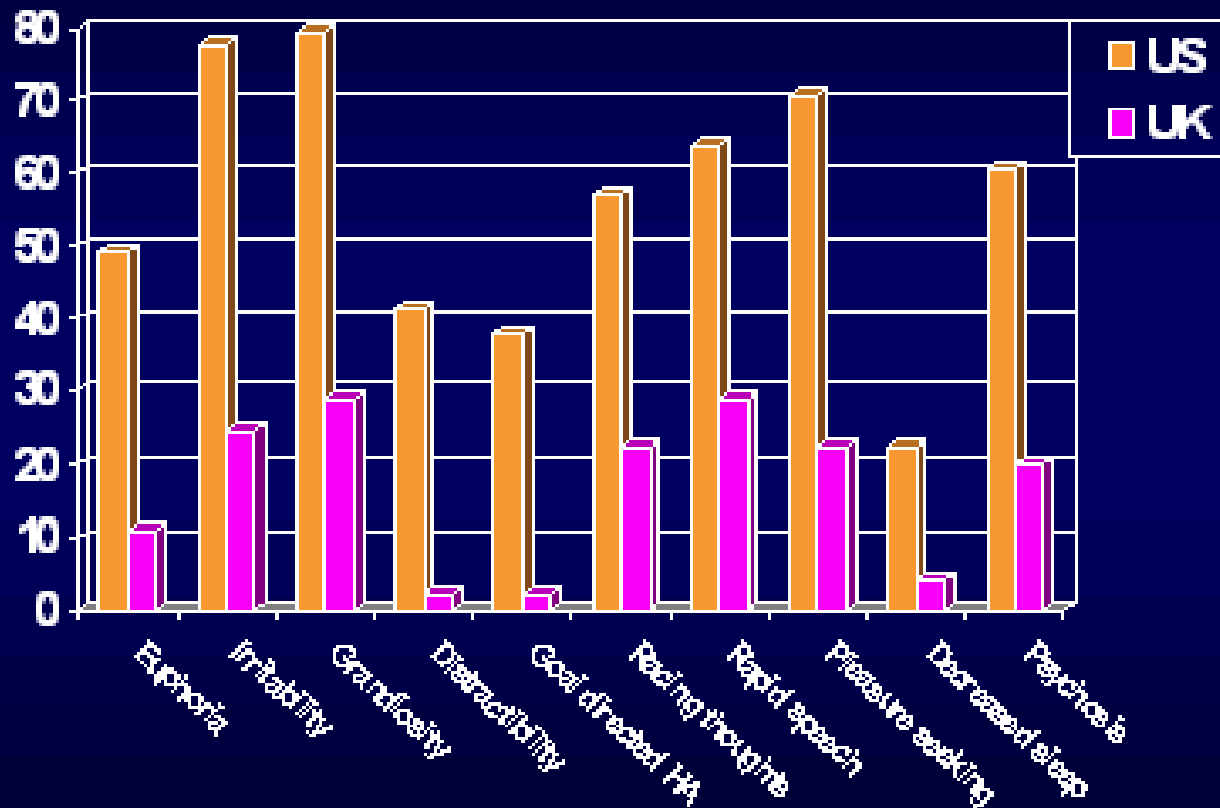
Dubicka, Carlson, Vail and Harrington, EJCAP, 2008

Prevalence of mania diagnoses made by US and UK clinicians



Dubicka, Carlson et al ECAP 2008

Symptom Endorsements for Lynda

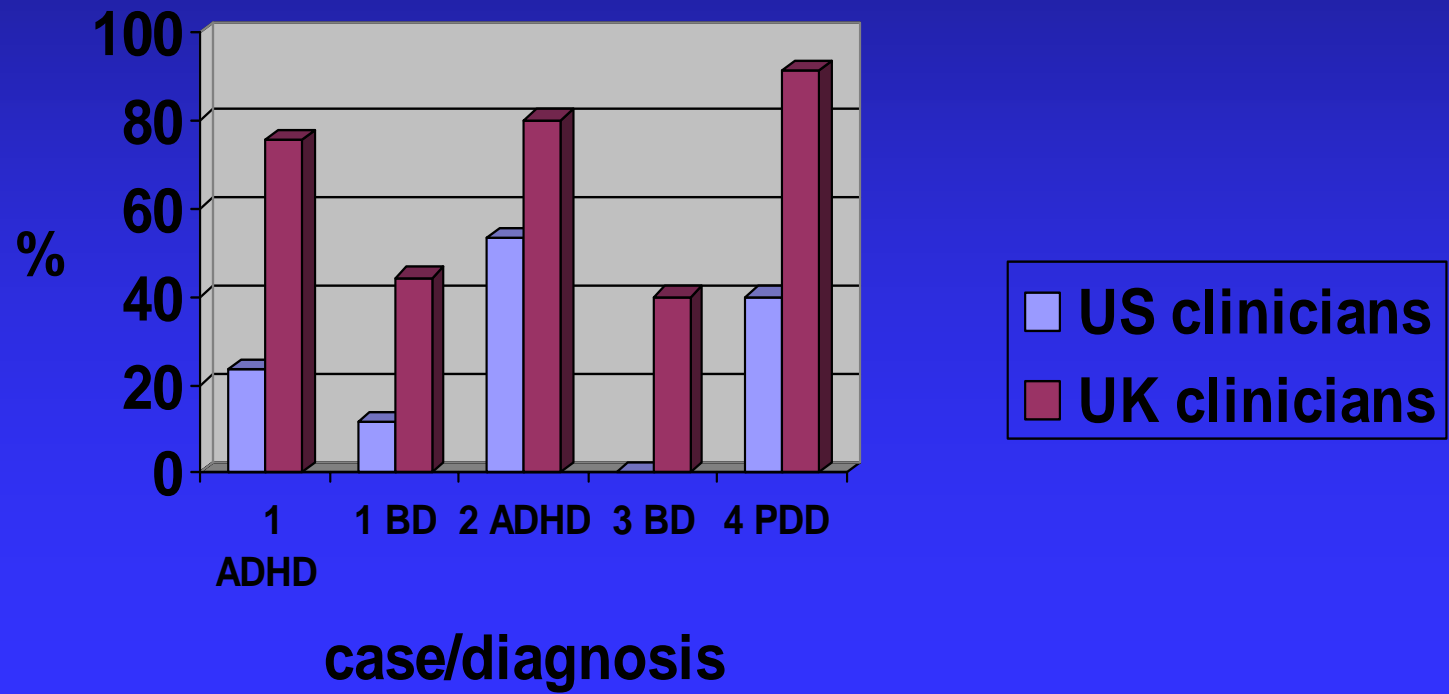


G Carlson, MD

UK clinicians more likely to diagnose ADHD, behaviour disorder, developmental disorder

Dubicka, Carlson et al, ECAP 2008

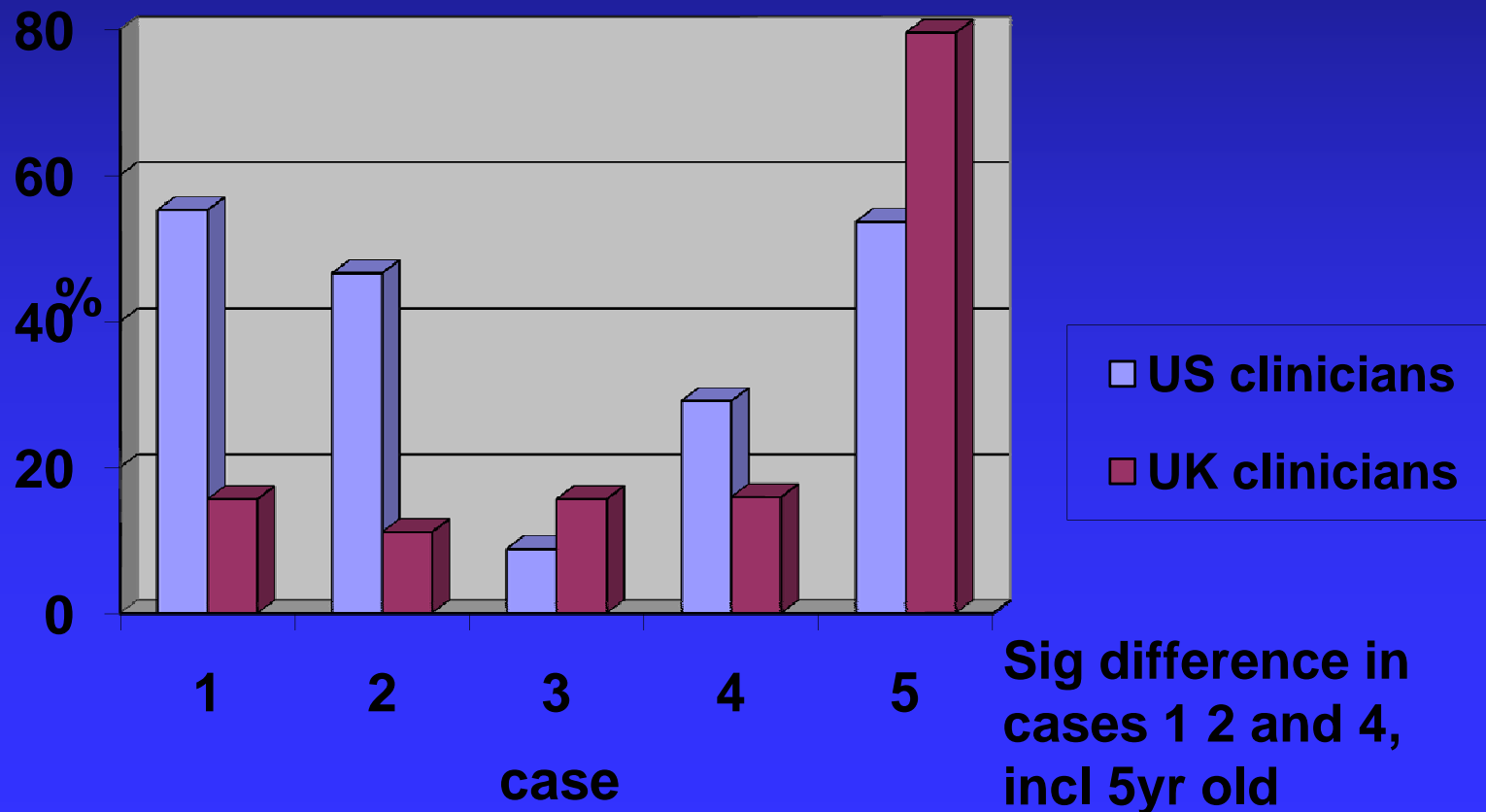
Other significant diagnostic differences
between US and UK clinicians



Antipsychotics use

US > UK except in classical case
Dubicka, Carlson et al, ECAP 2008

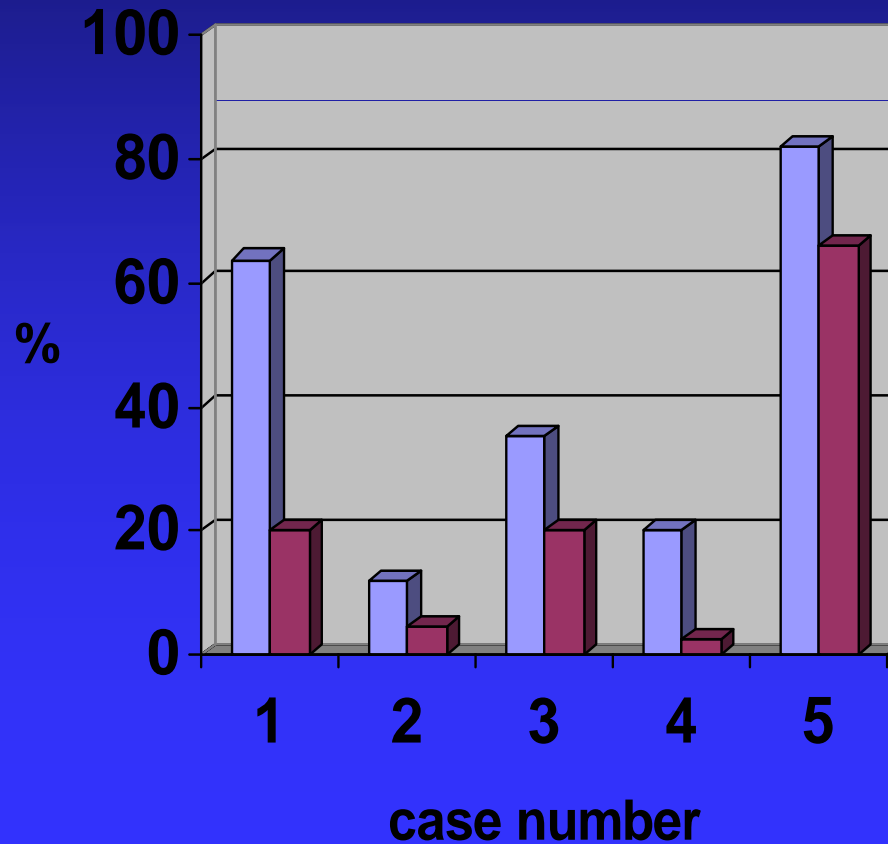
Antipsychotic use



Mood stabiliser use US>UK

Dubicka, Carlson et al, ECAP 2008

Mood stabiliser use

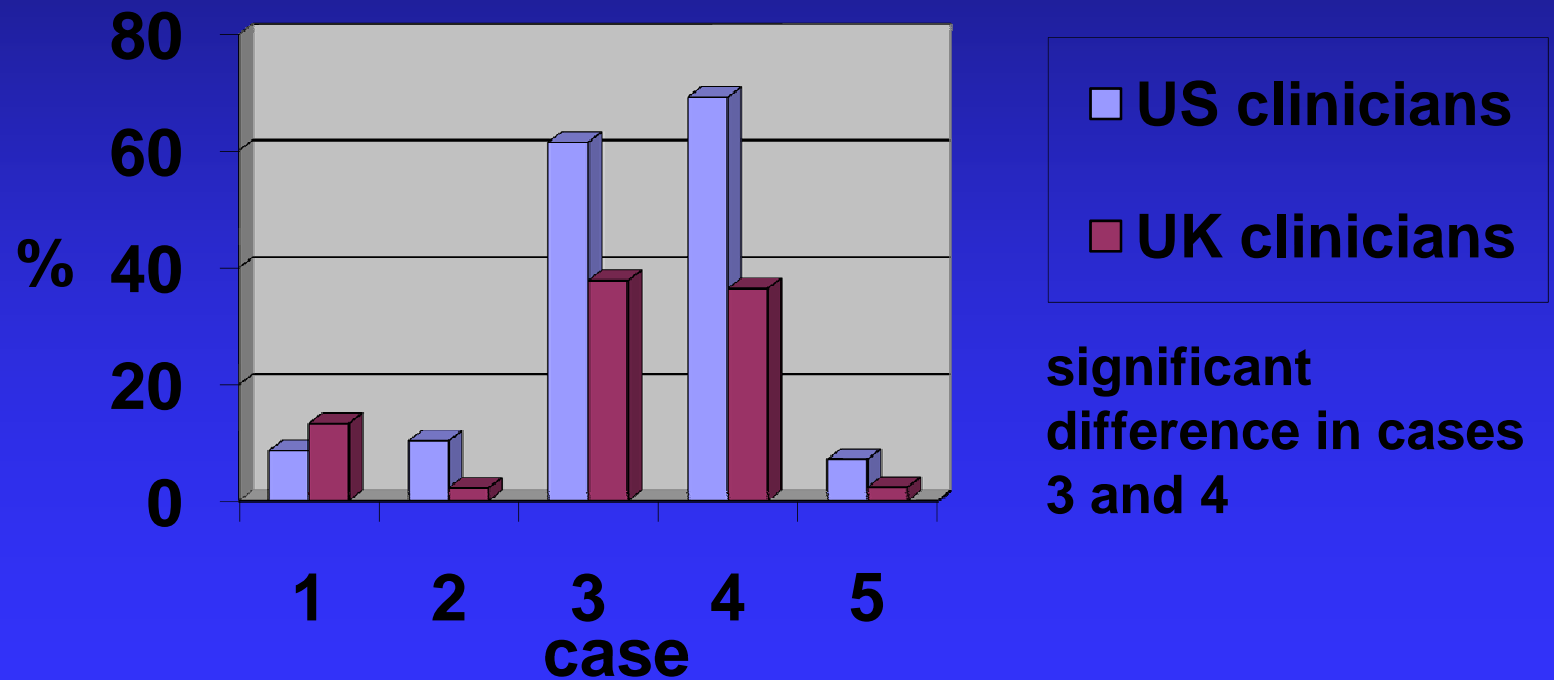


US clinicians
UK clinicians

significant difference
in
cases 1 and 4

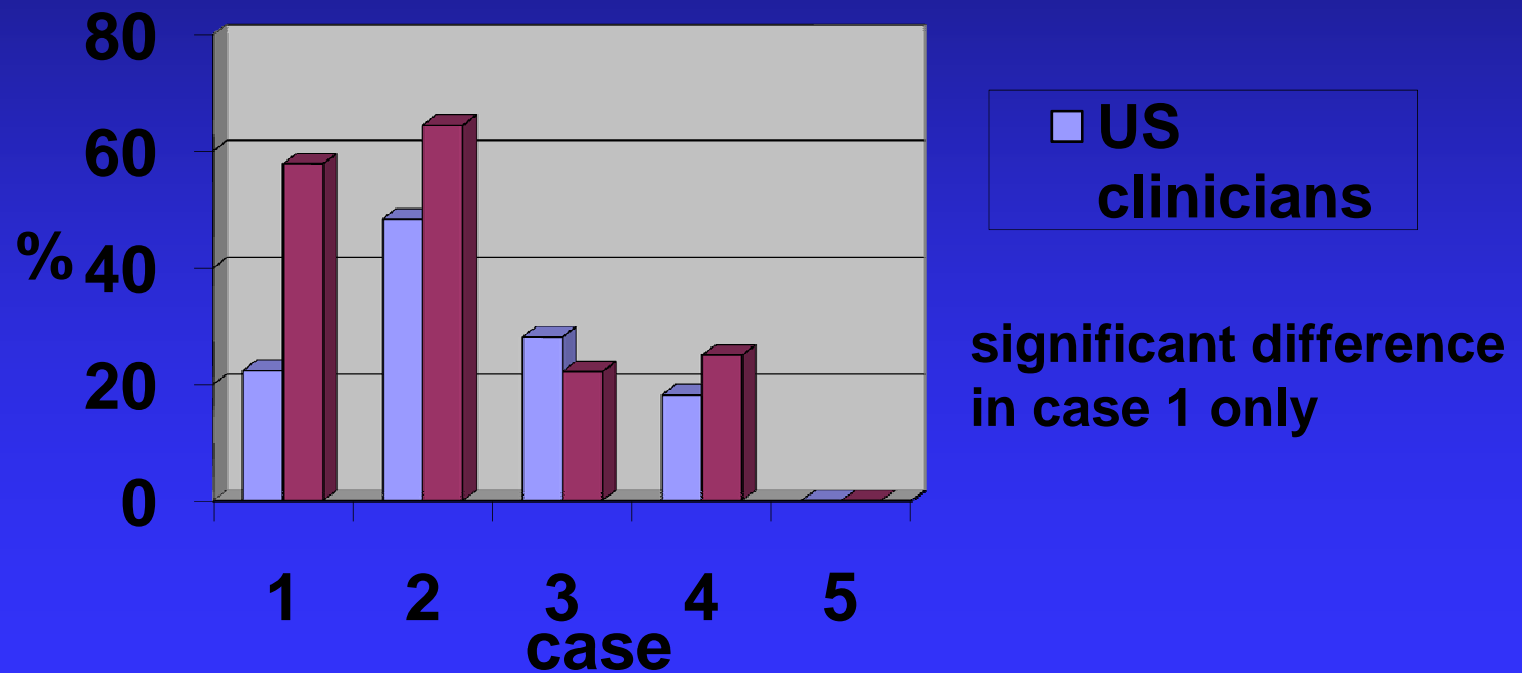
US clinicians more likely to use antidepressants

Antidepressant use



UK clinicians more likely to use stimulants

Stimulant use



Possible explanations

- Cultural bias between US and Europe resulting in selective observations
 - effect of media coverage and requirement for diagnosis to access health care packages in US (Liebenluft AJP 2011)
- Differences in diagnostic systems?
 - but Thapar study used ICD and DSM
- Broader cultural differences re use of diagnoses and medication

US clinicians may use looser definitions

- only 40% C&A psychiatrists in US survey reported sufficient DSM symptoms before making diagnosis

Galanter JCAPP 2009

Early onset BP US studies

AACAP, Toronto 2011

- Kowatch: 3-7yrs
improved (CGI)
valproate 75%, **risperidone 87%**,
placebo 9%
- TEAM study: mean age 10 (youngest 6)
improved **risperidone 69%**,
lithium 36%, vaproate 24%

NB virtually all cases had ADHD

?effect of national guidelines and
licensing indications

NICE: Diagnosis of bipolar disorder – conservative approach

- Irritability should not be regarded as core symptom in younger C&A; euphoria necessary
- Cases should meet diagnostic criteria before treating with meds
- Avoid BP II diagnosis in younger C&A

Guidelines and Licensing in mania and bipolar disorder in C&A in the UK and US

Dubicka et al, Advances Psychiatric Treatment, Nov 2010

NB for up-to-date licensing information, refer to SPCs (www.medicines.org.uk/EMC/default.aspx)

Licensing and guidelines: Antipsychotics

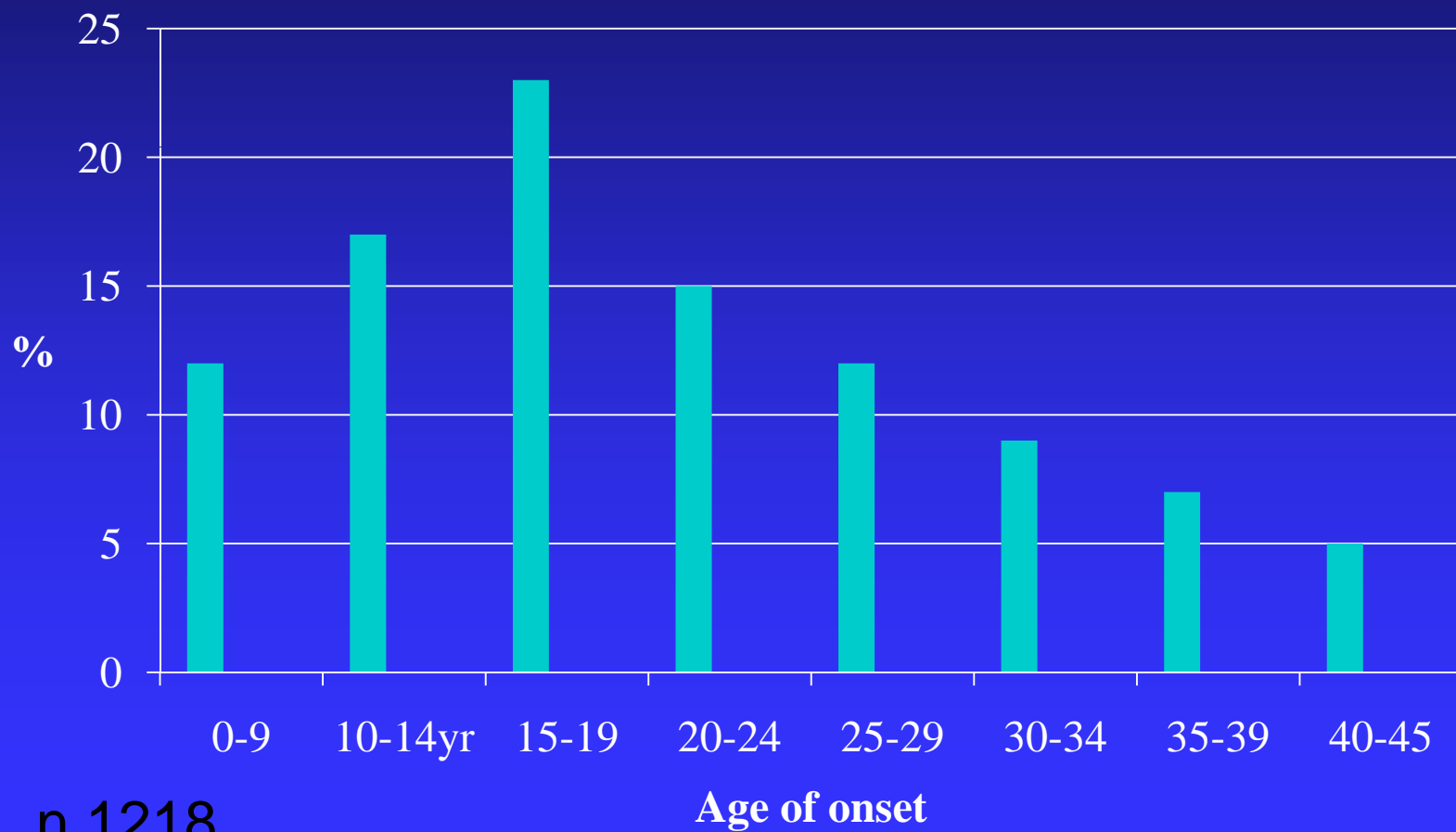
Drug	NICE	AACAP '07 (follow FDA approval)	UK licence	US licence
aripiprazole	-	First-line	18+ (mania, prophylaxis)	10+ (mania/mixed)
olanzapine	First-line, maintenance	First-line, maintenance	18+ (mania, prophylaxis)	13+ (mania /mixed, prophx)
quetiapine	1st-line, chronic /recurrent depression	First-line	18+ (acute mania/dep; prophylaxis)	10+ (mania, standard release)
risperidone	First-line	First-line	18+ (mania)	10+ (mania/mixed)
ziprasidone	-	First-line	Not licensed	18+ (adjunct maintenance)
asenapine	-	-	Under Europ review	18+ (mania/mixed)
Olanzapine/ fluoxetine	-	BP depression	Not licensed	18+ (BP depression)

Licensing and guidelines: mood stabilisers

Drug	NICE	AACAP (follow FDA approval)	UK licence	US licence
Lithium carbonate	Second-line, maintenance, (1 st line: if prev success)	First-line, maintenance	12+ (Liskonium only, mania, prophylaxis)	12+ (mania/mixed)
Carbamazepine	Third-line	Second (1 st in CPWBP)	18+	18+
Lamotrigine	Third-line (esp BP II, recurrent dep)	maintenance	18+ (depression recurrence)	18+ maintenance
Valproate semisodium	Second-line, prophx, not in girls <18yrs/fertile women (1 st : previous success)	First-line	18+ (mania)	18+ (mania – extended release also approved)

However, evidence that symptoms of
BP start in childhood-
?how to improve early recognition
?UK clinicians missing cases++

Age of onset of first episode bipolar, Stanley centre Chengappa, AJP, 2003



STEP-BD

Perlis, Bipolar Disorders, 2009

- 2/3s adults report onset BD in childhood or adolescents
- 29% onset <13 yrs

Diagnosis complicated

- ***Definition of episode:*** very rapid cycling/mixed episodes more common in C&A; do not meet diagnostic criteria, relationship with adult BP unclear (Stringaris 2010)
- ***Irritability:*** common in childhood disorders; ?should not be core BP symptom (Geller)
- ***Developmental issues:*** symptoms need to be seen in developmental context, e.g. grandiosity
- ***Comorbidity*** common

Comorbidity: ADHD

ADHD	MANIA
immature behaviour	elated mood
easily frustrated	irritable
hyperactive	goal directed activity
trouble sleeping	reduced need for sleep
Bragging, class clown	grandiosity
off topic	flight of ideas
impulsive	activities result in bad outcomes
present since <7yrs	Acute, episodic

ADHD follow up

- No evidence that increased rates of BPI at FU
- e.g. 20% ADHD clinic sample with manic symptoms – only one still had symptoms at 6 yr FU (Hazell, 2003)

Narrow vs broad phenotype

- Narrow: BPI, with discrete manic episodes *Nicola*
- Broad (not meeting criteria) *Lynda*:
manic symptoms, non-episodic
Washington modified mania criteria (Geller –
symptoms not concurrent; no irritability)
BO-NOS – shorter duration, fewer symptoms
severe mood dysregulation (Liebenluft)



Evidence base for broad criteria

Manic symptoms more common in community studies

- 5% 8-19yr olds in UK community: BPI 0.1% (Stringaris, JCPP, 2010)
- 43% US 6-12 yr olds had parent-endorsed symptoms of mania (Findling, 2010)

Follow up of manic symptoms

- Oregon adolescent community study: 5.7% 'at risk' of BP; remained impaired but none became manic over 4yrs (Lewinsohn, '95, 2000)

Severe mood dysregulation

Liebenluft 2003

- Abnormal mood most days
- Increased reactivity
- Hyperarousal
- Racing thoughts
- Intrusiveness
- Onset <12yrs
- 80% community sample had ADHD+ODD
- DSM-V: 'temper dysregulation dysphoric disorder'

Severe mood dysregulation follow up: no BP

- Community sample of SMD, 9-13 yrs, behaviour problems continued, developed depression, not BP (Brotman, '04, '09)
- Boys 8 yrs old with severe temper tantrums become impulsive, moody, irritable adults, not BP (Caspi 1990)

Longitudinal outcomes of cases

COBY study, Birmaher, AJP, 2009

4 yr FU, n413, 7-17yrs:

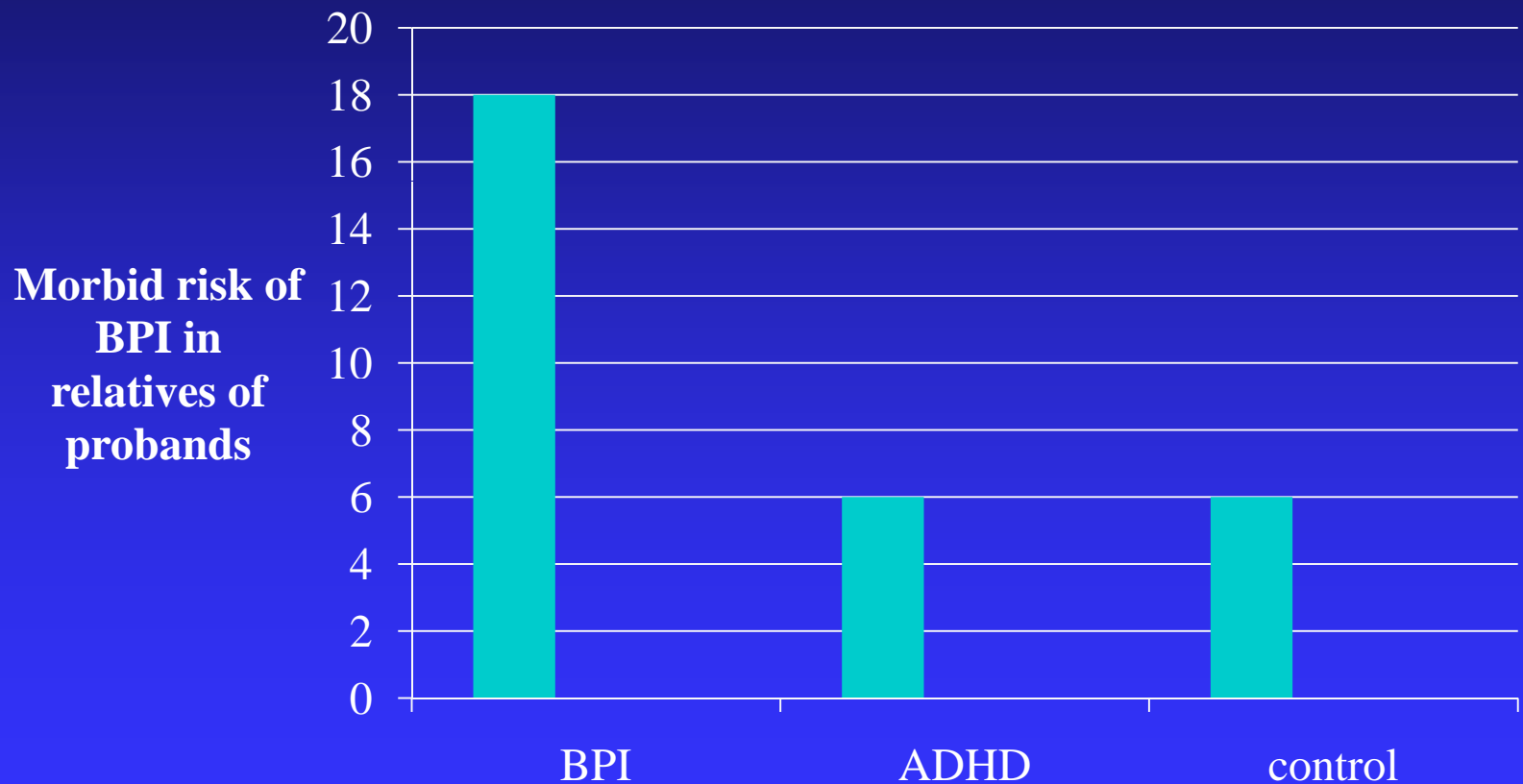
- BPI, BP II, NOS (reduced duration)
- Cases symptomatic 60% of FU period
- 60% recurred 1.5 yrs after recovery (most subsyndromal: mixed, depressed)
- NOS: **38%** converted to BPI/II
- NOS similar to BPI, but less severe
- BPI youths more symptomatic, more cycling than adults (29% vs 6% - Judd 2002)

High risk offspring studies: BP uncommon

- Amish children n110: 2% BPI, 2% BPII in late teens; other problems++ (Shaw/England)
- BIOS: n388 vs 251 controls
11% BP spectrum vs 1% controls (OR 13)
if 2 parents, OR 3.6 (Birmaher 2009)

Increased risk of BPI in children with first degree relatives with BPI

Wozniak, Psychol Med, 2010



Early intervention?

- NICE approach prevents overtreatment/diagnosis and potential serious adverse effects
- But ? benefits (and risks) of early intervention in high risk cases
- May miss cases with conservative approach, but need strong signal to justify earlier diagnosis and intervention (Parker, BJP, 2010)

Prediction of transition from adolescent affective symptoms to BP

Tijssen, BJP, 2010

- N3021 adolescents/young adults, FU 10yrs
- Depressive and hypomanic symptoms
- Increased number of affective symptoms predicted increased healthcare use and (hypo)mania
- Experiences common and transitory
- Only 1% had BP disorder at FU

?elusive BP prodrome

- Up to 60% adult BD cases have onset in adolescence, but up to 10 yr diagnostic lag (Skjelstad, JAD, 2009)
- Problem as symptoms non-specific (Luby, JCPP, 2010)
- Correll '07: retrospective reports of BPI and SZ; overlap ++ in prodromal symptoms
 - the most frequent symptoms present in at least 50% were reduced functioning, mood swings, irritability/anger, increased energy, low mood, inattention

Meta-analysis of prodrome of BP

Skjelstad, JAD 2010

- 8 studies
- Low specificity of symptoms: irritability, aggressiveness, sleep problems, depression, manic symptoms, anxiety, mood swings
- Not possible to predict development of BP based on early symptoms

However, outcomes of cases hospitalised
for mania, poor
Clinical dilemma: when to treat

One year outcomes after hospitalisation for mania/mixed episode Delbello, AJP, 2007

71 adolescents

- Only 20% achieved full recovery (symptoms and functioning)
- Still symptomatic 1/3 of the time
- 58% recurrence

Risks/benefits of early intervention?

Adverse Effects

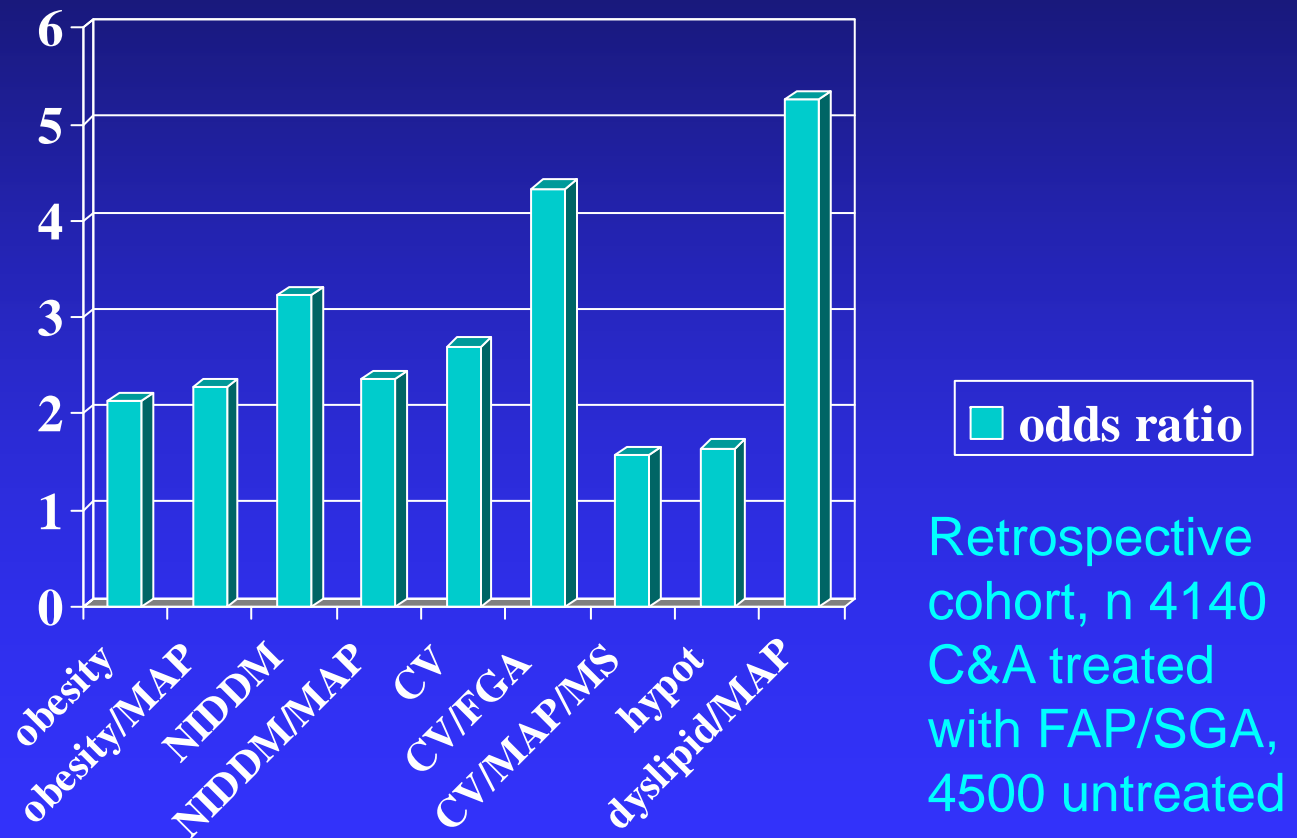
Atypical anti-psychotics

- Major problem
- Youths more sensitive to adverse effects
(Kumra, Schizophrenia Bulletin, 2008; *Correll & Carlson, JAACAP, 7, 2006; Correll et al, JAMA, 2009)
- Metabolic syndrome
- Weight gain++, more likely than in adults
(Correll, Bipolar Disorders, 2010)
- Raised prolactin

‘First do no harm...’ Panagiotopoulos et al, JCACAP, 2010

Metabolic and cardiovascular adverse events associated with antipsychotic treatment in C&A

McIntyre and Jerrell, APAM, 2008



MAP=multiple antipsychotics; FGA=first generation antipsychotics; CV=cardiovascular

Benefits of medication in C&A bipolar disorder

Limited evidence: few RCTs, few positive

Howard , JAACAP, 2011

Dubicka, APT, 2010

RCTs in mania: lithium and valproate

Lithium:

- one positive placebo controlled RCT (Geller, 1998)
one **negative** (Kafantaris, 2004)
large RCT underway (Findling, CoLT study, 2008)

Valproate:

- **Negative** trial of divalproex vs placebo
(Wagner et al, JAACAP, 2009)
- **Negative** trial of valproate in BP spectrum disorder
with BP parent (Findling et al, JCP, 2007)
- Maintenance trial: Li = valproex
(Findling, JAACAP, 2005)

RCTs in mania: other anticonvulsants negative trials

- Oxcarbazepine vs placebo: **negative**

Wagner, AJP, 2006

- Topiramate vs placebo: **negative**

Delbello, JACAAP, 2005

Antipsychotic RCTs in mania: positive

- Olanzapine > placebo (Tohen, AJP, 2007)
- Risperidone > placebo (Haas, BPD, 2009)
- Quetiapine > valproate (Delbello, 2006)
- Quetiapine > placebo (FDA, 2009)
- Aripiprazole > placebo (Tramontina, 2009; Findling, 2009)

Clinical conundrums

- Presentations complex in adolescents with mood dysregulation
- Disrupted attachments, psychosocial problems++, trauma, drug & alcohol use, family mental health problems
- Diagnoses rarely clear, prognoses often poor, psychosocial interventions often of limited value
- ?role of meds: risks/benefits unclear

Conclusions

- Problematic issues of identifying subthreshold/prodromal cases not unique to C&A mental health
- Need to integrate research (early intervention in psychosis, adult bipolar, diagnostic systems, treatment guidelines)
- Moody difficult children continue to have difficulties as adults, but not bipolar disorder

Psychosocial interventions

- Functional family therapy: promising treatment for high risk cases (Miklowitz 2009)

‘First do no harm’

- in light of current uncertainties,
conservative approach and non-
pharmacological first-line interventions
recommended in cases not meeting
criteria

