Psychiatric Comorbidities in Patients with ADHD: Treatment of Mood Disorders, Anxiety/OCD, and Complex Cases of ADHD

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LEARNING OBJECTIVES

1. Define attention and comorbidity.
2. Review attention's neurobiology (top/down, front/back) and potential link to mood, anxiety and OCD.
3. Understand the clinical importance of mood, anxiety and OCD comorbidities with ADHD to better identify treatment options.
4. Describe the diagnostic process to approach treatment.
5. Recognize the importance of various treatment options.

DISCLOSURES

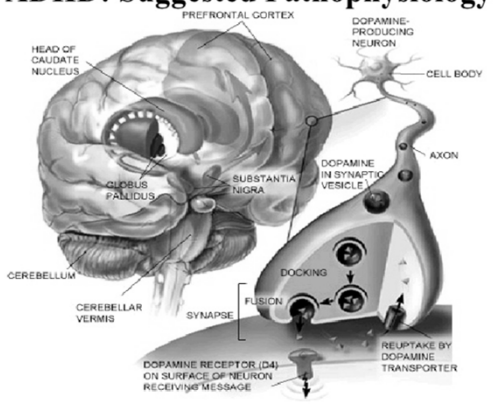
- Current Research Grants:
  - Forest
  - Lundbeck
  - Pfizer
  - Rhodes
  - Shire
  - Sunovion
  - Supernus
  - SyneuRX
- Owner
  - Harmonex Neuroscience Research/CliniCom
  - Dothan Behavioral Medicine Clinic

Type and Extent of Common Mental Disorders in Children and Adolescents

- Estimated 21% of US children, aged 9 to 17 years, have a mental or addictive disorder severe enough to cause impairment.
- Fewer than 20% receive treatment.
- WHO projects: By 2020, childhood neuropsychiatric disorders will increase by >50%, placing them among the 5 most common causes of childhood morbidity, mortality, and disability.

Source: National Institute of Mental Health. Brief notes on the mental health of children and adolescents. Available at: http://www.nimh.nih.gov/publicat/childnotes.cfm. Accessed July 10, 2003.

ADHD: Suggested Pathophysiology



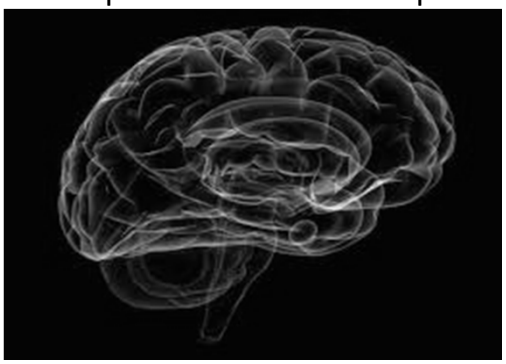
What is Attention?

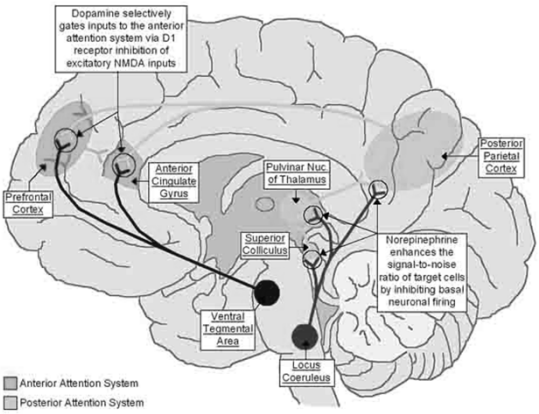
- Attention allows us to *engage with the environment by selecting information relevant for behavior*.
- Attention focuses the functionality of *working memory* with the functionality of other cortical areas.
- Attention is strongly influenced by functions in the *limbic system (fear-pleasure)*.
- *Motivation* is driven by a conflagration of *executive decisions* produced by working memory along with fear-pleasure from the limbic system

What is Attention?

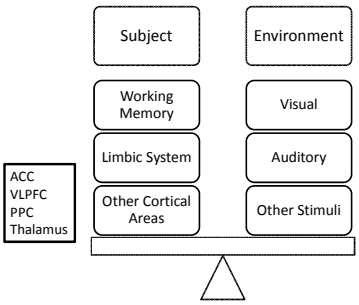
- The coordinated activity within the thalamus, anterior cingulate cortex (ACC), the ventral lateral prefrontal cortex (VLPFC), posterior parietal cortex (PPC), and the brain stem probably *regulate the content of consciousness through mechanisms of executive attention*. (Vogt, Cingulate Neurobiology, 384)
- Attention is broadly of two types -- *(1) bottom-up, caused by the sensory input, and (2) top-down, produced by the planning parts of the brain*. (Crick & Koch; Consciousness and Neuroscience, 39)

Top Down vs. Bottom Up

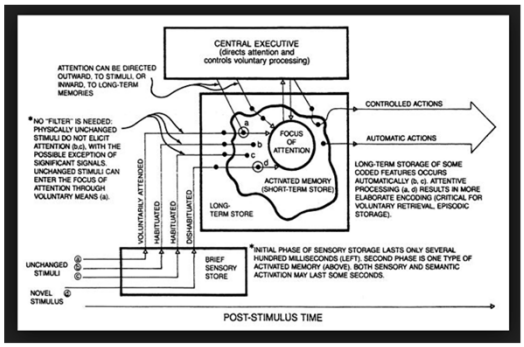




Selecting info -> Behavior



A basic model of information processing



(From N. Cowan, "Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information processing system," Psychological Bulletin, 104, p. 180, Fig. 1.)

What is Comorbidity?

- The term comorbidity first appeared mid 1980's.
- In 1986 there were only two such articles; by 1993 the number had increased to 243, Google today 3,240,000.
- *Comorbidity* has emerged as perhaps the *single most important concept in psychiatry*.

Comorbidity Definition

co·mor·bid (kō-môr′bĭd)

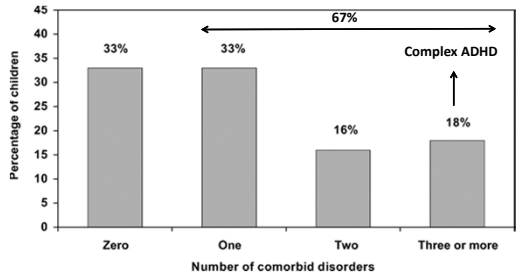
adj.

Coexisting or concomitant with an ***unrelated*** pathological or disease process: *patients with comorbid diabetes and depression.*

Relevance of Comorbidity

- **Multiple** comorbid disorders.
- Biederman, et al as suggesting that *"...attention deficit hyperactivity disorder is most likely a **group of conditions** with potentially different and modifying risk factors and different outcomes rather than a single homogeneous clinical entity."*

Percentage of children with ADHD who have comorbid disorders (N = 5 028)



Kandyce Larson et al. Pediatrics 2011;127:462-470

Percentage of Children with ADHD who have comorbid disorders (N = 5 028)

- Children with ADHD and 3 or more comorbidities, corresponding to more than 700 000 children nationally, had particularly severe functional deficits.
- They have very high prevalence of school problems (81%) and grade repetition (46%).

Kandyce Larson et al. Pediatrics 2011;127:462-470

Adult ADHD

- The most important comorbid disorders (since they influence the treatment) are:
- Drug and alcohol abuse (50%)
- Anxiety (40%)
- Depression (35%)
- Bipolar disorder (15%)

Pre-Schoolers

- Wilens identified 165 children with ADHD aged 4 to 6 years (preschool children) and 381 youths aged 7 to 9 years (school-age) with ADHD.
- Despite being younger, preschool children had similar rates of comorbid psychopathology compared with school-age youths with ADHD.

Psychiatric Comorbidity and Functioning in Clinically Referred Preschool Children and School-Age Youths With ADHD
TIMOTHY E. WILENS, M.D, et al Journal of the American Academy of Child & Adolescent Psychiatry
Volume 41, Issue 3, March 2002, Pages 262–268

ADHD Co-Morbid Conditions

This Presentation

- Major Depressive Disorder (MDD)
- Bipolar Disorder (BPD)
- Obsessive Compulsive Disorder (OCD)
- Anxiety Disorders (ANX)

OTHER CONDITIONS

- Oppositional Defiant Disorder
- Conduct Disorder
- Tourette's Syndrome
- Learning Disorders
- Communication Disorders
- Epilepsy
- Enuresis
- Substance Use Disorder
- Sleep Problems
- Autism Spectrum Disorder

COMORBIDITY

ADHD AND MOOD DISORDERS

Females MDD-ADHD

- Females with ADHD had a 2.5 times higher risk for MDD at adolescent follow-up compared with control females, adjusting for psychiatric comorbidity.
- MDD in females with ADHD was associated with an earlier age at onset, greater than twice the duration, more severe depression-associated impairment, a higher rate of suicidality, and a greater likelihood of requiring psychiatric hospitalization than MD in control girls.

JOSEPH BIEDERMAN, M.D
New Insights Into the Comorbidity Between ADHD and Major Depression in Adolescent and Young Adult Females
Journal of the American Academy of Child & Adolescent Psychiatry
Volume 47, Issue 4, April 2008, Pages 426–434

MDD-ANX-ADHD

- The risk for comorbidity is high.
- A comorbid diagnosis of ADHD and depression occurs in approximately 20% to 30% of patients.
- ADHD and anxiety in more than 25% of patients.
- Assessed older adults over a 6-year period for symptoms of ADHD, depression, and anxiety: *ADHD was associated with a higher risk for both depression and anxiety.*

Michielsen M, Comijs HC, Semeijn EJ, et al
The comorbidity of anxiety and depressive symptoms in older adults with attention-deficit/hyperactivity disorder: A longitudinal study. J Affect Disord. 2013;148:220-227.
–
See more at: http://www.psychiatrictimes.com/adhd/what-are-common-comorbidities-in-adhd#sthash.ex89j64f.dpuf

Depression in ADHD children:
"True" depression or demoralization?

- "ADHD and MDD had independent and distinct courses, indicating that ADHD-associated MDD reflects a depressive disorder and not merely demoralization. Limitations: This study may have reduced power due to stratification of our group of ADHD boys with persistent and remitting MDD".

J. Biederman MD et al, Journal of Affective Disorders
Volume 47, Issues 1–3, 1 January 1998, Pages 113–122

Mood Disorders

- Studies of clinically referred children with ADHD, suggest that
  - between 10 and 30% are likely to show evidence of some sort of mood disorder,
  - usually major depressive or dysthymic disorder (Johnson, et al, 2009).

ADHD and Mood Disorders

- The evidence for the co-occurrence of mood disorders, such as major depression or dysthymia (a milder form of depression), with ADHD is now fairly substantial (Daviss, 2008; Faraone & Biederman, 1997; Jensen, Martin, & Cantwell, 1997; Spencer, Wilens, Biederman, Wozniak & Crawford, 2000 for reviews).
- Between 15% and 75% of those with ADHD may have a mood disorder, though most studies place the association between 20% and 30% (Barkley, 2006; Barkley et al., 2008; Biederman et al., 1992; Cuffe et al, 2001; Fischer et al., 2002).
- The odds of having depression given the presence of ADHD in general population samples is 5.5 (95% CI 3.5-8.4) (Angold et al., 1999).

ADHD and Mood Disorders

- Some evidence also suggests that these disorders may be related to each other in that familial risk for one disorder substantially increases the risk for the other (Biederman et al., 1991, 1992; Faraone & Biederman, 1997), particularly where ADHD is comorbid with CD.
- Similarly, a recent follow-up study (Fischer et al., 2002) found a 26% risk of major depression among ADHD children by young adulthood, but this risk was largely mediated by the co-occurrence of CD. Current depression fell to 14% of the ADHD cases by adulthood (Barkley et al., 2008).
- Likewise, a meta-analysis of general population studies indicated that the link between ADHD and depression was entirely mediated by the linkage of both disorders to CD (Angold et al., 1999). In the absence of CD, ADHD was not more likely to be associated with depression.

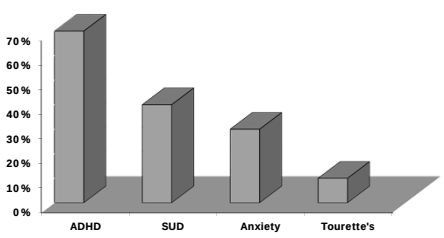
ADHD and Bipolar Disorder

- The comorbidity of ADHD with bipolar (manic-depressive) disorder is controversial (Carlson, 1990; Geller & Luby, 1997).
- Some studies of ADHD children indicate that 10% to 20% may have bipolar disorder (Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995; Spencer et al., 2000; Wozniak et al., 1995) – a figure substantially higher than the 2% risk for the general population (Lewinsohn, Klein, & Seeley, 1995; Skirrow et al., 2012; Youngstrom, 2010).
- Follow-up studies of hyperactive children, however, have not documented any significant increase in risk of bipolar disorder in children with ADHD followed into adulthood with rates typically close to those for the general population (Fischer et al., 2002; Klein et al., 2012; Mannuzza et al., 1993, 1998; Weiss & Hechtman, 1993).

ADHD and Bipolar Disorder

- ADHD children without bipolar disorder do not have an increased prevalence of bipolar disorder among their biological relatives (Biederman et al., 1992; Faraone, Biederman, & Monuteaux, 2001; Lahey et al., 1988), while ADHD children with bipolar disorder do (Faraone, Biederman, Wozniak, Mundy, Mennin, & O'Donnell, 1997; Faraone et al., 2001), suggesting that where the overlap occurs it may represent a familially distinct subset of ADHD.
- Children and adolescents diagnosed with childhood bipolar disorder often have a significantly higher lifetime prevalence of ADHD, particularly in their earlier childhood years (Carlson, 1990; Geller & Luby, 1997; Strober et al., 1988).

Comorbidity in Adolescent Inpatients with Bipolar Disorder



West et al, *Biol Psych* 1996

ADHD and Bipolar Disorder

- Where the two disorders co-exist, the onset of bipolar disorder may be earlier than in bipolar disorder alone (Faraone et al., 1997; Faraone et al., 2001; Sachs, Baldassano, Truman, & Guille, 2000).
- In bipolar cases that start in adulthood, comorbidity with ADHD may be only 20% to 25% while it may average 62% and in some studies be as high as 80% to 97% in cases where bipolar disorder begins in childhood (Skirrow et al., 2012; Youngstrom, 2010).
- In any case, the overlap of ADHD with bipolar disorder appears to be unidirectional – a diagnosis of ADHD seems not to increase the risk for bipolar disorder, whereas a diagnosis of childhood bipolar disorder seems to dramatically elevate the risk of a prior or concurrent diagnosis of ADHD (Geller & Luby, 1997; Spencer et al., 2000; Skirrow et al., 2012).

COMORBIDITY

ADHD AND OCD

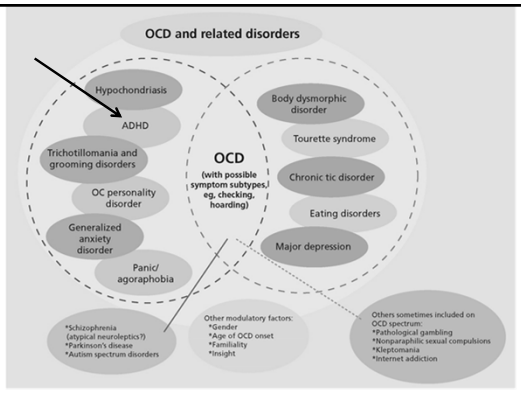
ADHD and OCD and ODD

- Limited literature and research
- OCD may mimic ODD
- The most common diagnosis: ADHD
- The most common misdiagnosis: OCD
- Stimulants can exacerbate OCD sx
- SSRIs can exacerbate ADHD sx
- Brain imaging suggesting similarities: *"qualitatively increased activity in the anterior medial aspects of the frontal lobes compared to the rest of the brain and when compared to the control group". "These findings indicate there may be an underlying biologic similarity between Oppositional Defiant Disorder and Obsessive-Compulsive Disorder".* (Daniel Amen, MD; Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, Volume 2, Issue 2, 1997 Oppositional Children Similar To OCD on SPECT.)

ADHD OCD ODD

- Disruptive disorders in ADHD + OCD
  - Children 51%
  - Adolescents 36%
- Oppositional Defiant Disorder in ADHD + OCD
  - Children 51%
  - Adolescents 47%

Bernard Boileau, MD, **A review of obsessive-compulsive disorder in children and adolescents**
Dialogues Clin Neurosci. 2011 Dec; 13(4): 401–411.



Obsessive-Compulsive Disorder, and Attention-Deficit/Hyperactivity Disorder: Heritability Analysis in a Large Sib-Pair Sample

- OCD and ADHD were highly heritable in these TS families.
- There were significant genetic correlations between TS and OCD and between OCD and ADHD, but not between TS and ADHD.
- In addition, significant environmental correlations were found between TS and ADHD and between OCD and ADHD.
- Parental OCD ADHD was associated with offspring OCD ADHD.
- **Conclusions:** This study provides further evidence for a genetic relation between TS and OCD and suggests that the observed relation between TS and ADHD may due in part be to a *genetic association between OCD and ADHD* and in part due to shared environmental factors.

Carol A. Mathews, M.D., AND Marco A. Grados, M.D., M.P.H.
J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(1):46–54.

Inattention?

"A kid may be sitting in class having an obsession about needing to fix something, to avoid something terrible happening. Then the teacher calls on him," says Dr. Jerry Bubrick, the senior director of the Anxiety and Mood Disorder Center at the Child Mind Institute. "When he doesn't know the answer to the question, it looks like he wasn't paying attention, but it's really because he was obsessing."

COMORBIDITY

ADHD AND ANXIETY DISORDERS

ANXIETY DISORDERS

- Between 25 and 30 % of clinically referred children with ADHD show evidence of some type of anxiety disorder (Johnson, et al, 2009).

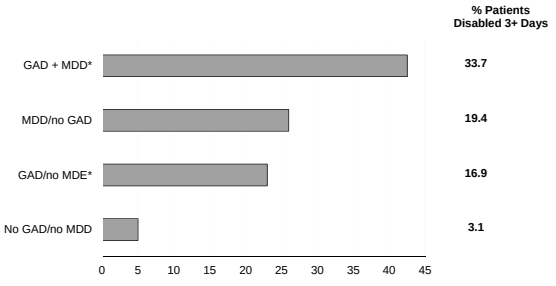
ADHD and Anxiety

- The overlap of anxiety disorders with ADHD has been found to be 10% to 40% in clinic-referred children, averaging to about 25% (see Barkley, 2006; Biederman, Newcorn, & Sprich, 1991; Schatz & Rostain, 2006; Tannock, 2011, for reviews).
- In longitudinal studies of ADHD children, however, the risk of anxiety disorders is no greater than in control groups at either adolescence or young adulthood (Mannuzza et al., 1993, 1998; Russo & Biedel, 1994; Weiss & Hechtman, 1993) but does rise to 33% of those children whose ADHD persists to age 27 (Barkley et al., 2008).
- The disparity in findings for children is puzzling. Perhaps some of the overlap of ADHD with anxiety disorders in children is due to referral bias (Biederman, Faraone, & Lapey, 1992; Tannock, 2011).

ADHD and Anxiety

- General population studies of children, however, do suggest an elevated odds ratio of having an anxiety disorder in the presence of ADHD of 3.0 (95%CI = 2.1-4.3), with this relationship being significant even after controlling for comorbid ODD/CD (Angold et al., 1999).
- This implies that the two disorders may have some association apart from referral bias, at least in childhood. The co-occurrence of anxiety disorders with ADHD has been shown to reduce the degree of impulsiveness relative to those ADHD children without anxiety disorders (Pliszka, 1992; Schatz & Rostain, 2006).
- Some research suggests that the disorders are transmitted independently in families and so are not linked to each other in any genetic way (Biederman et al., 1991; Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991).

GAD and Psychiatric Comorbid Disorders



*MDD = major depressive disorder, MDE = major depressive episode

Wittchen HU. *Depress Anxiety*. 2002;16:165-166.

COMORBIDITY

ADHD DIAGNOSTIC PROCESS HISTORY, INTERVIEW, SCALES, DSM V, CPT AND TBR

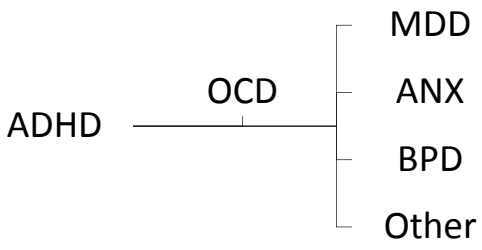
Important Assessment Questions: Preparing for Treatment

- **What is the**
  - Age?
  - Chief Complaint?
  - Secondary Complaint?
  - Primary Diagnosis?
  - Secondary Diagnosis?
  - Severity?
  - Family History?
  - Course of the Illness?
  - Past/Current Treatment(s)?
  - Functioning?
  - Pharmaco-genetics?
- **What are the Co-Morbid Conditions?**
  - Psychiatric
  - Non-Psychiatric/Physical

Clinical Global Impressions -Severity

- 1=normal, not at all ill
- 2=borderline mentally ill
- 3=mildly ill
- 4=moderately ill
- 5=markedly ill
- 6=severely ill
- 7=among the most extremely ill patients

Diagnosis Scheme



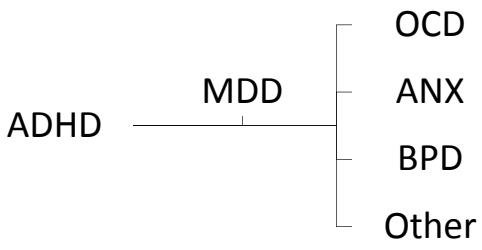
Assessment Questions/Treatment Approach

ADHD
OCD
MDD
ANX
BPD
ODD

- **What is the**
  - Age? 8 y/o male
  - Chief Complaint? Irritability
  - Secondary Complaint? Academic Problems
  - Primary Diagnosis? ADHD
  - Secondary Diagnosis? OCD –YBOCS Severe
  - Severity 7,6
  - Family History? ADHD, OCD and MDD
  - Course of the Illness? Chronic
  - Past/Current Treatment(s)? Treatment naïve
  - Functioning? Problem: Home and school
  - Pharmaco-genetics? 3A4 Ultra rapid, 2D6 Normal
- **What are the Co-Morbid Conditions?**
  - Psychiatric See above + Dyslexia+Communication
  - Non-Psychiatric/Physical BMI 14

Atomoxetine
Exposure Tx
CBT
Consider SSRI
IEP
Coaching

Diagnosis Scheme



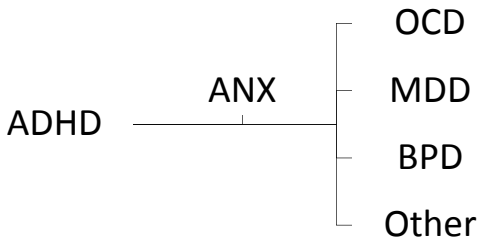
Assessment Questions/Treatment Approach

ADHD
MDD
OCD
ANX
BPD
CD

- **What is the**
  - Age? 13 y/o female
  - Chief Complaint? Withdrawn
  - Secondary Complaint? Academic Problems
  - Primary Diagnosis? ADHD
  - Secondary Diagnosis? MDD
  - Severity 7/6
  - Family History? ADHD and MDD
  - Course of the Illness? Chronic
  - Past/Current Treatment(s)? Therapy ineffective?, Prozac ineff +S/E
  - Functioning? Prob: Home, School and Socially
  - Pharmaco-genetics? 2D6 Ultra rapid, 3A4 Normal, 2C19 Normal
- **What are the Co-Morbid Conditions?**
  - Psychiatric OCD CYBOCS severe, R/O Eating D/O
  - Non-Psychiatric/Physical Lost 10 lbs. last month

Sertraline
MPH
Exposure Tx
CBT
Coaching

Diagnosis Scheme



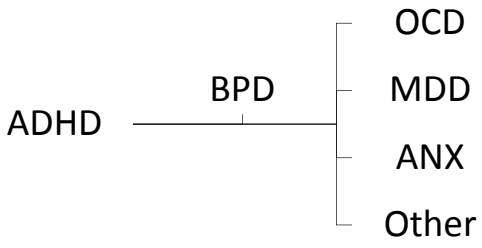
Assessment Questions/Treatment Approach

ADHD
ANX
OCD
MDD
BPD
ODD

Fluoxetine
MPH
Exposure Tx
CBT
Coaching

- **What is the**
  - Age? 17 y/o female
  - Chief Complaint? Anxiety
  - Secondary Complaint? Defiant
  - Primary Diagnosis? ADHD
  - Secondary Diagnosis? Social Anxiety
  - Severity 6,6
  - Family History? "None"
  - Course of the Illness? Chronic
  - Past/Current Treatment(s)? Therapy ineffective, Lexapro ineff.
  - Functioning? PROB: Home, school and socially
  - Pharmaco-genetics? 2C19 ULTRA RAPID, 2D6 & 3A4 nl
- **What are the Co-Morbid Conditions?**
  - Psychiatric See above, plus CYBOCS mild
  - Non-Psychiatric/Physical Vomiting before going to school

Diagnosis Scheme



Assessment Questions/Treatment Approach

ADHD
BPD
OCD
MDD
ANX
SUD

Mood Stabil.
Stimulant
Consider A2A
Therapy ind/fam
Sleep med
Rehab/12 step
Voc Rehab

- **What is the**
  - Age? 18 y/o male
  - Chief Complaint? Anger
  - Secondary Complaint? Alcohol Abuse
  - Primary Diagnosis? ADHD
  - Secondary Diagnosis? BPD II
  - Severity 6/5
  - Family History? Father "anger problems, and SUD"
  - Course of the Illness? Chronic
  - Past/Current Treatment(s)? Vyvanse "worse", no therapy.
  - Functioning? PROB: Home, School and Socially
  - Pharmaco-genetics? 3A4 Normal, 2D6 very slow
- **What are the Co-Morbid Conditions?**
  - Psychiatric See above plus insomnia
  - Non-Psychiatric/Physical MVA, BMI 30

ADHD Comorbidity and Treatment Outcomes in the MTA

- How do children with ADHD, conduct disorder, and anxiety differ from those with ADHD and conduct disorder alone?
- Newcorn and colleagues (2001) examine the validity of children's ADHD symptoms using an independent vantage point, namely continuous performance task (CPT) measures.
- The paper by Jensen and colleagues (2001) indicates that the three comorbidity profiles—
  - ADHD + Anx, respond equally well to bx tx and med tx
  - ADHD + ODD/ CD, respond best to med tx (w/w-out bx tx)
  - ADHD + Anx + ODD/CD respond best to combined tx
- Differed on many variables from "pure" ADHD (with no comorbidity). In addition, these subgroups showed different responses to treatment.

JAACAP 2001 ADHD Comorbidity and Treatment Outcomes in the MTA
PETER S. JENSEN, M.D.

ADHD Comorbidity and Treatment Outcomes in the MTA

- Examining outcomes from yet another perspective, Swanson and colleagues (2001) demonstrate that if one wishes to achieve an "excellent response" on the MTA ADHD rating scales, with symptoms rated as "little or none," one obtains best results with combined treatment interventions, followed by medication management, then behavioral treatment, and finally, community care.

JAACAP 2001 ADHD Comorbidity and Treatment Outcomes in the MTA
PETER S. JENSEN, M.D.

Summary

- Most ADHD patient have co-morbid psychiatric conditions.
- Comprehensive assessment and diagnosis for comorbid conditions in patients with ADHD is of primary importance.
- Treating ADHD with comorbid conditions requires a complete past history and combined treatment approaches.