MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Plans C, D, and E: Moving down the treatment algorithm for refractory anxiety

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Disclosures

If you have disclosures, state:

"My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

I am the author of the book "Almost Depressed" and have received payments from Harvard health Publications

“In theory there is no difference between theory and practice.

In practice there is.”

~Yogi Berra

Guide for Pharmacotherapy of Anxiety Disorders

Plans A & B include: SSRIs, venlafaxine, duloxetine

Plans B & C Include: buspirone, benzodiazepines and TCA's

Plans C & D include: mirtazepine, gaba-ergic anticonvulsants, beta-blockers, alpha agonists, selegiline

Plans D & E include: low dose atypical antipsychotics, quetiapine

ALL ARE OFF LABEL AS THER ARE NO FDA-APPROVED MEDICINES FOR ANXIETY IN CHILDREN

Plans A & B for Treating Anxiety Disorders includes…

Medication	Indications	Side effects	Dosing		
			Initial (mgs)	Range (mgs/day)	Schedule
SEROTONIN REUPTAKE INHIBITORS (SSRIs)	*First line treatment *Nonaddictive well tolerated.	Nausea Diarrhea Insomnia Somnolence	*denotes available in liquid form	Use lowest dose	
Escitalopram		Headaches, QTc	2.5-5	2.5-20	QD
Citalopram		Activation	5-20 QD*	10-40 or >	QD
Fluoxetine		Sexual dysfunction	5-20 QAM*	10-80	QD
Fluvoxamine			12.5-50 QHS	50-300	QD-BID
Paroxetine		Sweating	5-10mg	10-60	QD-BID
Sertraline		Tremor	12.5-25 mg	50-200	QD-BID
Duloxetine		Diastolic hypertension	20 mg	20-60 mg	QD
Venlafaxine			25 mg IR or 37.5 mg XR	25-300	QD-BID

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Three Questions

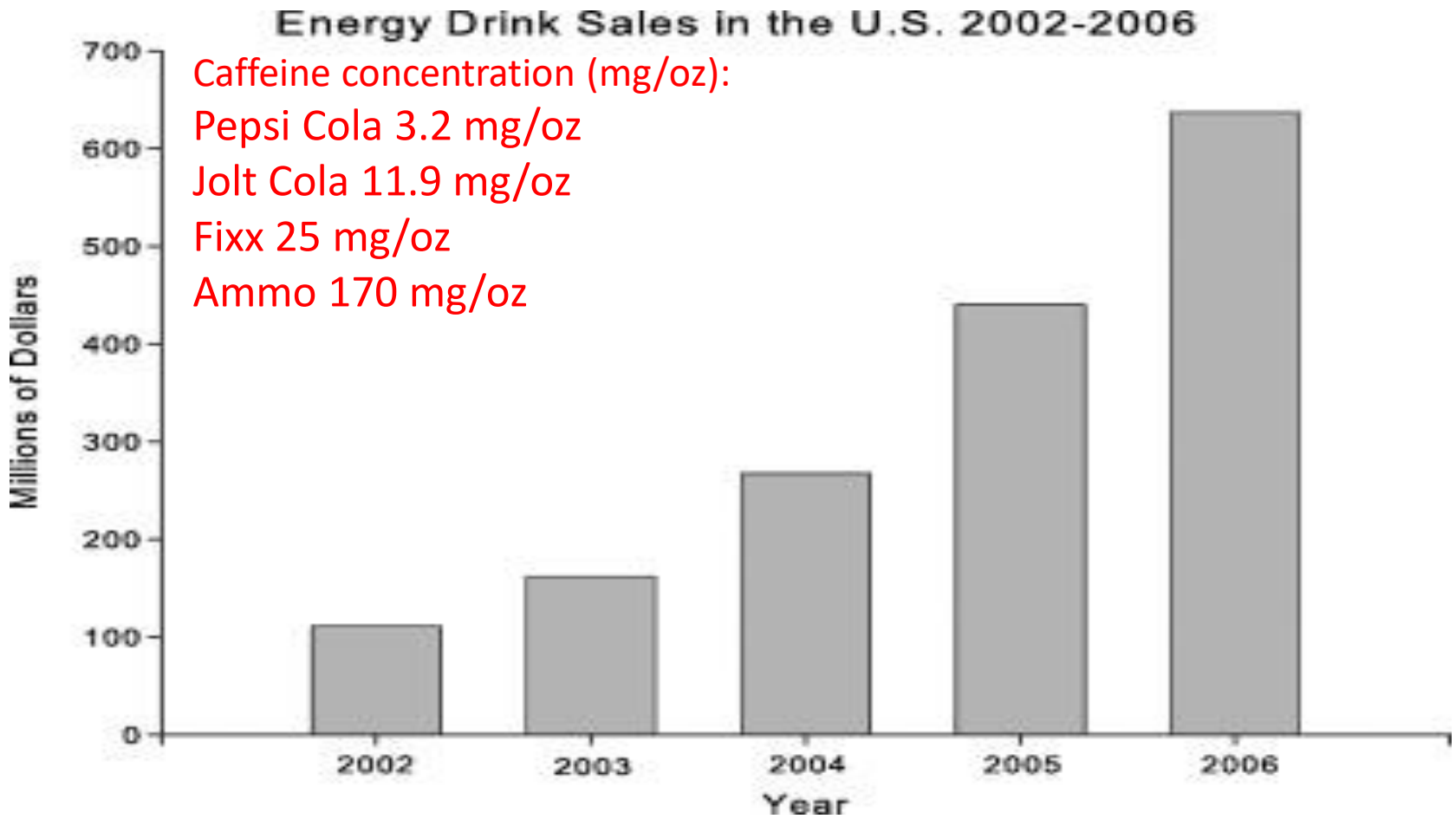
- What are my options?
- What are the benefits and harms?
- How likely are these?

Shepherd HL et al., Three questions that patients can ask to improve the quality of information physicians give about treatment options: a cross-over trial. Patient Educ Couns. 2011 Sep;84(3):379-85

Refractory Anxiety – Additional Considerations

- Adherence to current treatment (? Sexual side effects)
- Dietary caffeine: decrease in consumption to avoid over-stimulation
- Nicotine: similar caution
- Alcohol: toxic interactions not usually seen at mild/moderate doses, but normal response to alcohol may be altered
- Other Substances
- Decongestants (e.g. pseudoephedrine): should reduce dosage or stop stimulant for duration of use
- Diet: should be adjusted to avoid significant weight loss [i.e. <u>not</u> good diet medications!]
- Sleep is Necessary

Plan A, B & C includes getting rid of Caffeinated Energy Drinks



Reissig, Drug Alcohol Depend, 2009

America's Cannabis Experiment

"In weighing the costs and benefits of cannabis and other psychoactive drugs, we need to attend to the negative consequences of exposure, which are diverse and not necessarily measured sensitively or specifically with available tools. People using cannabis often and in potent forms are more likely to experience negative consequences. Yet, data on the effects of heavy exposures are lacking, even as access to potent cannabis is becoming easier. The burden of cannabis' effects may fall more heavily on people who, because of genetic makeup or early life exposures, are at greatest risk for brain structural changes, psychosis, or addiction. It is safer not to expose people to psychoactive drugs. However, in evaluating safety, it is important to dissociate correlation from causation, even in longitudinal studies. People predisposed to use cannabis differ from nonusers, regardless of whether they choose to use the drug."

Goldman D. "America's Cannabis Experiment" *JAMA Psychiatry.* 2015;72(10):969-970.

Opioid users now start with prescription opioids and transition to heroin

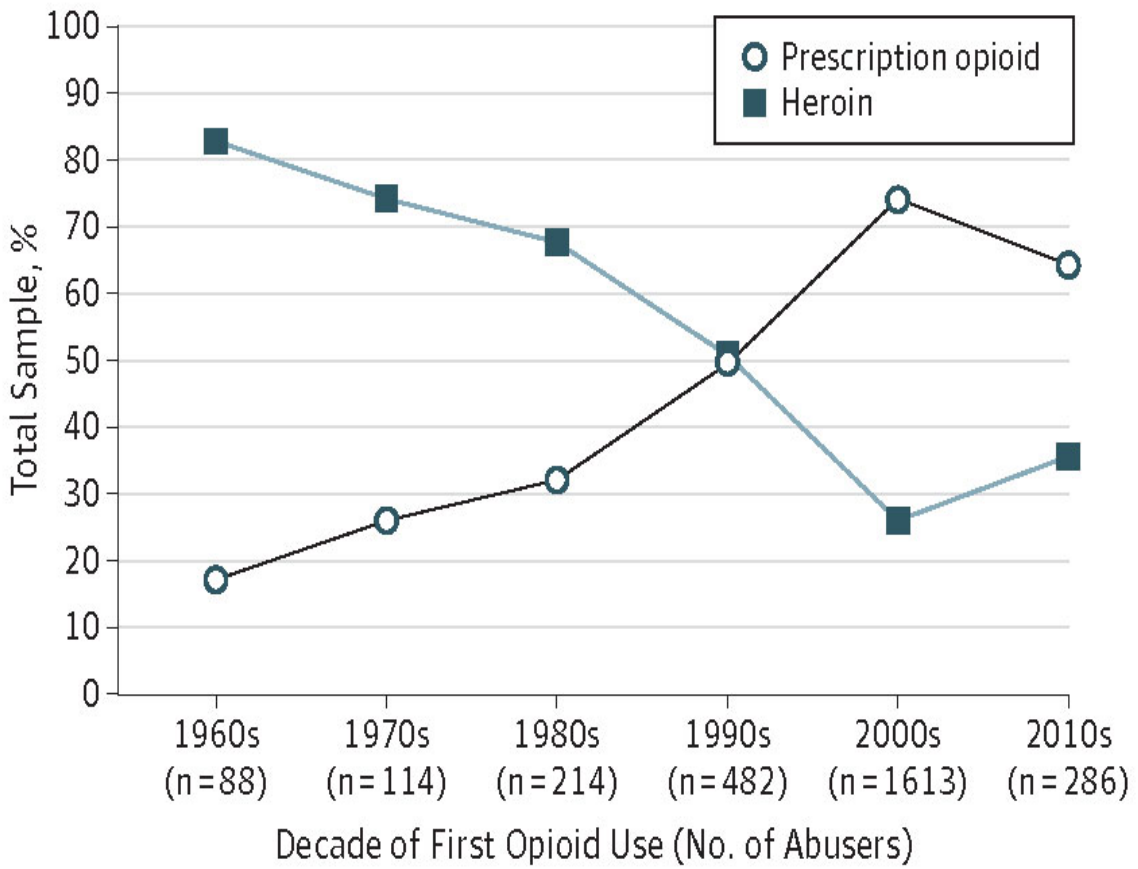


Figure: Percentage of current heroin dependent sample that used heroin or prescription opioids as 1st opioid of abuse

Other demographic trends:

- *Started in 1960's:* 82.8% men; mean age of 1st opioid use 16.5
- *Started in 2000's:* 49% men, 51% women; mean age of 1st opioid use 22.9; 75% live in small urban or non urban areas

Cicero TJ et al 2014 JAMA Psychiatry

Plans B & C for Treating Anxiety Disorders includes…

Medication	Indications	Side effects	Dosing		
			Initial (mgs)	Range (mgs/day)	Schedule
OTHER ANXIOLYTICS Buspirone	*Second line treatment for generalized anxiety *Nonaddictive well tolerated	Headache Nausea Dizziness Lightheaded Somnolence	5 BID	5-60	BID-TID

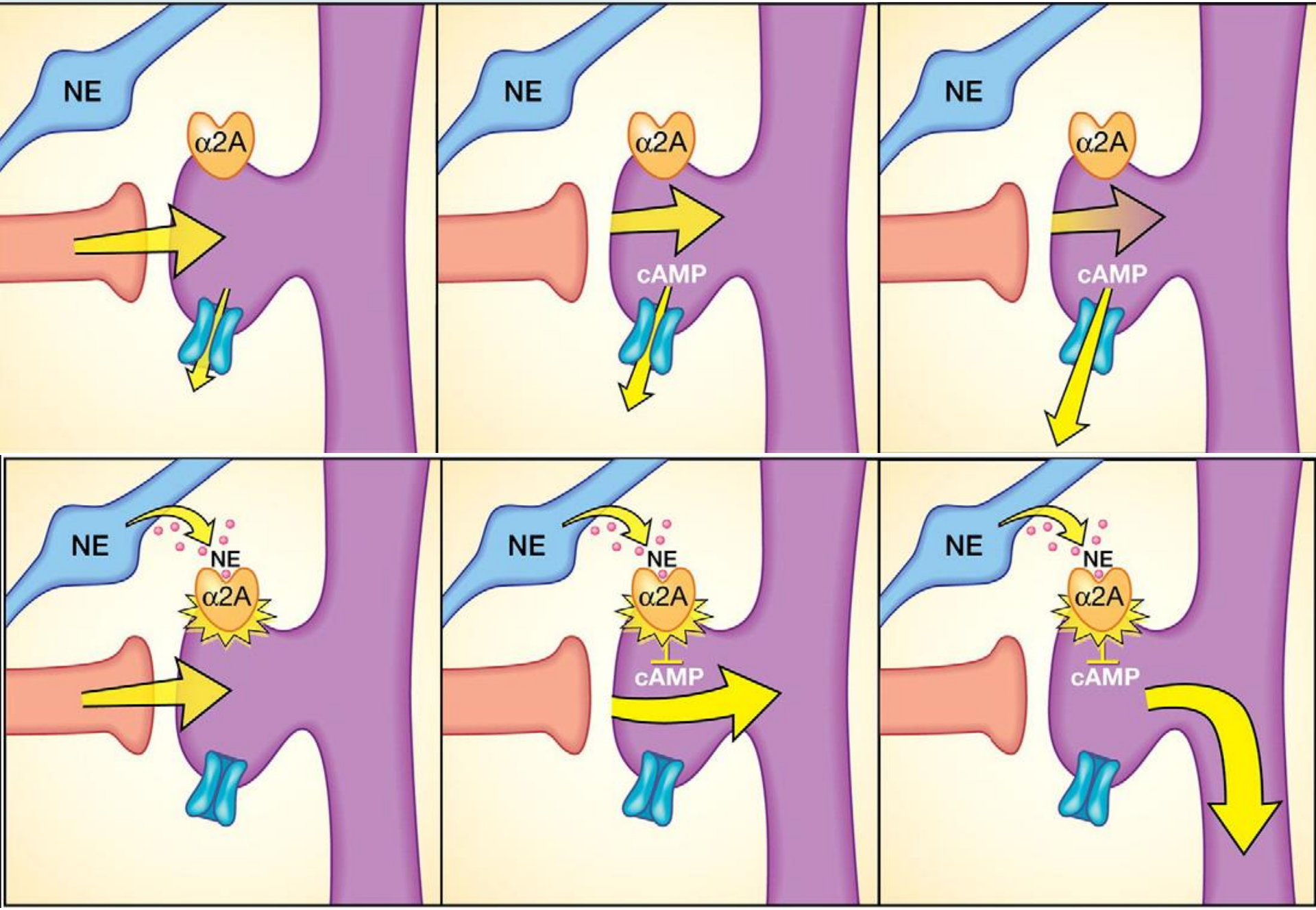
Plans A,B & C for Treating Anxiety Disorders include…

Medication	Indications	Side effects	Dosing		
			Initial (mgs)	Range mgs/day	Schedule
BENZODIAZEPINES Adjunctive Rx only!!	*Second line treatment *Addictive potential and cognitive blunting *time-limited circum-stances	Sedation Cognitive blunting Dizziness Ataxia Memory disturbance Constipation Diplopia Hypotension			
Diazepam			1-2 HS	0.25-4	HS-BID
Clonazepam			0.125-0.5	0.125-3.0	HS-BID
Lorazepam			0.125-0.5 BID	0.125-4.0	HS-TID

FDA Approved Non-stimulants Medications for ADHD that may be helpful for Plans B & C

Medication	Starting dose	Target dose*	Usual daily dosing	Duration of effect
Norepinephrine reuptake inhibitor				
Atomoxetine (Strattera)	0.5 mg/kg/d	1.2 mg/kg/d	Once	Up to 24 hours
Alpha-2a receptor agonist				
Guanfacine XR (Intuniv)	1 mg/d	1 to 4 mg/d	Once	About 12 hours
Clonidine Extended Release (Kapvay)	0.1 mg	0.1 to 0.2	BID	About 12 hours

Pliszka SR et al. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf. Accessed September 19, 2008
Sallee et al. *J Am Acad Child Adolesc Psychiatry*. 2009;19(3):215-226. Sallee et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2):155-165.



Arnsten & Pliska (2011) Pharmacology, Biochemistry and Behavior 99 (2011) 211–216

Plans C & D for Treating Anxiety Disorders Include…

Medication	Indication	Side effects	Dosing		
			Initial (mgs)	Range (mg/d) Target (mg/kg/d)	Schedule
TRICYCLIC ANTI-DEPRESSANTS (TCAs)	*Second line treatment *non-addictive low tolerance *require blood level and ECG monitoring	Sedation Headaches Dry Mouth Constipation Nausea Orthostasis Blurred vision Urinary retn Cardiac Conduction delays			
Clomipramine			12.5-25 HS	25-150, [2-5]	QHS-BID
Desipramine			10-25 QHS	10-250, [1-2]	QHS-BID
Imipramine			10-25 QHS	10-200, [2-5]	QHS-BID
Nortriptyline			10 QHS	10-150, [1-3]	QHS-BID
Amitruptyline			10-25 QHS	10-100 [0.5-2]	BID-QID

Plans C & D for Treating Anxiety Disorders Include…

Medication	Indication	Side effects	Dosing		
			Initial (mgs)	Range (mg/d) Target (mg/kg/d)	Schedule
Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs)	*MDD Panic, Phobias *require low tyramine diet	Drowsiness Insomnia Paresthesias Myoclonic Jerks Constipation Dry Mouth Dizziness Anorexia GI Sexual			
Isocarboxazid			10	30-50	QD
Phenelzine			10	45-90	QD
Tranylcypromine			10	20-60	QD
Irreversible MAO-B Inhibitor Selegiline Transdermal			6 mg/day	12 mg/day	daily

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Plans C & D for Treating Anxiety Disorders includes…

Medication	Indication	Side effects	Dosing		
			Initial (mgs)	Range mgs/day	Schedule
OTHER	*Third line treatment *Non addictive	Sedation Dry mouth Constipation			
Mirtazapine		Fatigue Drowsiness	7.5-15 HS	15-45	QHS
Propranolol		Orthostatic hypotension	10 QDBID	10-100	QD-BID
Betaxolol		Blurred vision	5	5-20	QD

Additional Antidepressants for Plans C & D include…

- **desvenlafaxine** (Pristiq®)
- **doxepin** (Sinequan®)
- **levomilnacipran** (Fetzima®)
- **trazodone** (Desyrel®)
- **vilazodone** (Viibryd®)
- **vortioxetine** (Trintellix®)

Plan D May Include…
Second-Generation Antipsychotic Medications

Medication (Brand Name)	Dose Range	FDA indications
Risperidone (Risperdal)	0.5- 3 mg/d oral; divided BID-TID (max 6 mg/d)	>13 y for schizophrenia & bipolar; >6 y irritability in ASD
Olanzapine (Zyprexa)	2.5-10 mg/d; oral; divided BID-TID	13-17 y as second-line treatment of schizophrenia
Quetiapine (Seroquel)	25-800 mg/d; oral; divided BID-TID	>13 y for schizophrenia and bipolar
Aripiprazole (Abilify)	2-30 mg/d by mouth divided BID-TID	13-17 y for schizophrenia and bipolar
Ziprasidone (Geodon)	20-160 mg/d; oral with food; divided BID	For Schizophrenia and Bipolar in Adults
Asenapine (Saphris)	5-20 mg/d; sub-lingual, BID	For Schizophrenia and Bipolar in Adults
Lurasidone (Latuda)	20-160 mg/d; oral with food, QD	For Schizophrenia in Adults
Iloperidone (Fanapt, Zomaril)	1-6 mg/d; oral; BID	For Schizophrenia in Adults

Recommended Monitoring of AAPs in Youth

Parameter	Reference	Schedule
Fasting total cholesterol	<5.2 mmol/L	Baseline; 3, 6, &12 mo then annually
Fasting LDL-C	<3.35 mmol/L	Baseline; 3, 6, &12 mo then annually
Fasting HDL-C	≥1.05 mmol/L	Baseline; 1, 2, 3, 6, 9 &12 mo then annually
Fasting triglycerides		Baseline; 1, 2, 3, 6, 9& 12 mo then annually
AST		Baseline, 6 & 12 mo then annually
ALT		Baseline, 6 & 12 mo then annually
TSH		Baseline, 6 & 12 mo then annually
Prolactin		Baseline, 3 & 12 mo then annually
ECG		Unknown
Pharmacogenetics		Unknown

1. Pringsheim T et al. CAMESA Guideline Group. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. J Can Acad Child Adolesc Psychiatry 2011;20:218–33.
2. Garcia G et al., Management of Psychotropic Medication Side Effects in Children and Adolescents. Child and Adolescent Psychiatric Clinics of North America Volume 21, Issue 4, October 2012, Pages 713–738
3. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry 2008;47:9–20.
4. IDF Consensus Group International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation (IDF), 2006

Recommended Monitoring of AAPs in Youth

Parameter	Reference	Schedule
Fasting plasma glucose	≤5.6–6.1 mmol/L	Baseline; 3, 6, and 12 mo then annually
Fasting insulin	≤100 pmol/L	Baseline; 3, 6, and 12 mo then annually
Waist circumference	Percentile	Baseline; 1, 2, 3, 6, 9 and 12 mo then annually
Height (cm)	Percentile	Baseline; 1, 2, 3, 6, 9 and 12 mo then annually
Weight (kg)	Percentile	Baseline; 1, 2, 3, 6, 9 and 12 mo then annually
BMI (kg/m^2)	Percentile	Baseline; 1, 2, 3, 6, 9 and 12 mo then annually
Blood pressure (mm Hg)	Percentile	Baseline; 1, 2, 3, 6, 9 and 12 mo then annually

OGTT *When fasting plasma glucose* = 5.6–6.1 *or fasting insulin levels >100 pmol/L*

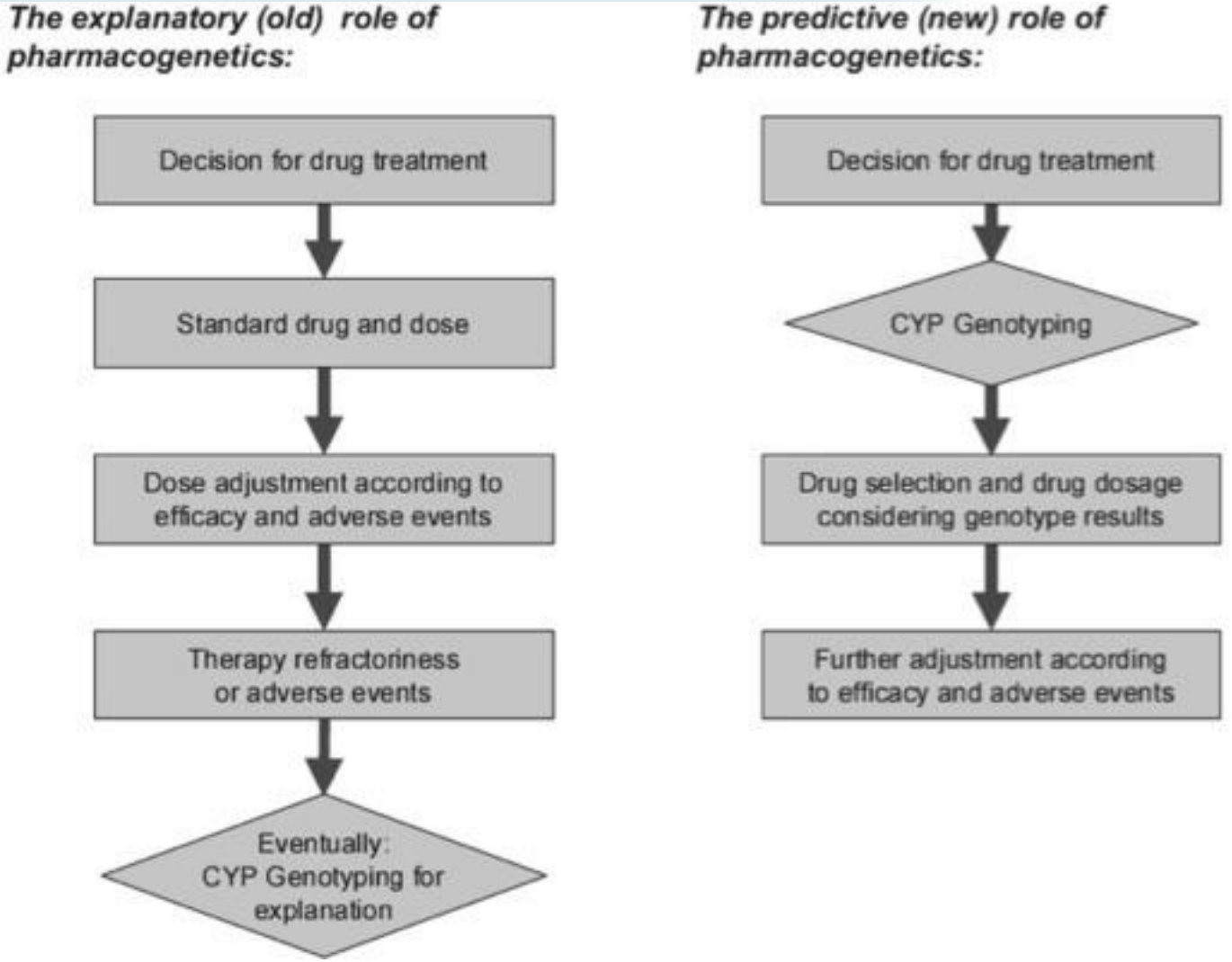
Plans D & E May Include…

- Non response to several (at least more than three) adequate medication trials and/or serious adverse events or ongoing need for higher level of care
- DRUG-GENE TESTING
  - AKA pharmacogenomics or pharmacogenetics.
  - A small blood or saliva sample can help determine:
  - How well certain medications may be tolerated and effective
  - Best dose range

Genetic Information Nondiscrimination Act (GINA)

- A federal law that generally makes it illegal for health insurance companies to discriminate against you based on your genetic information.
- This federal law does not protect you against genetic discrimination by life insurance, disability insurance or long-term care insurance companies.

Explain or Predict?

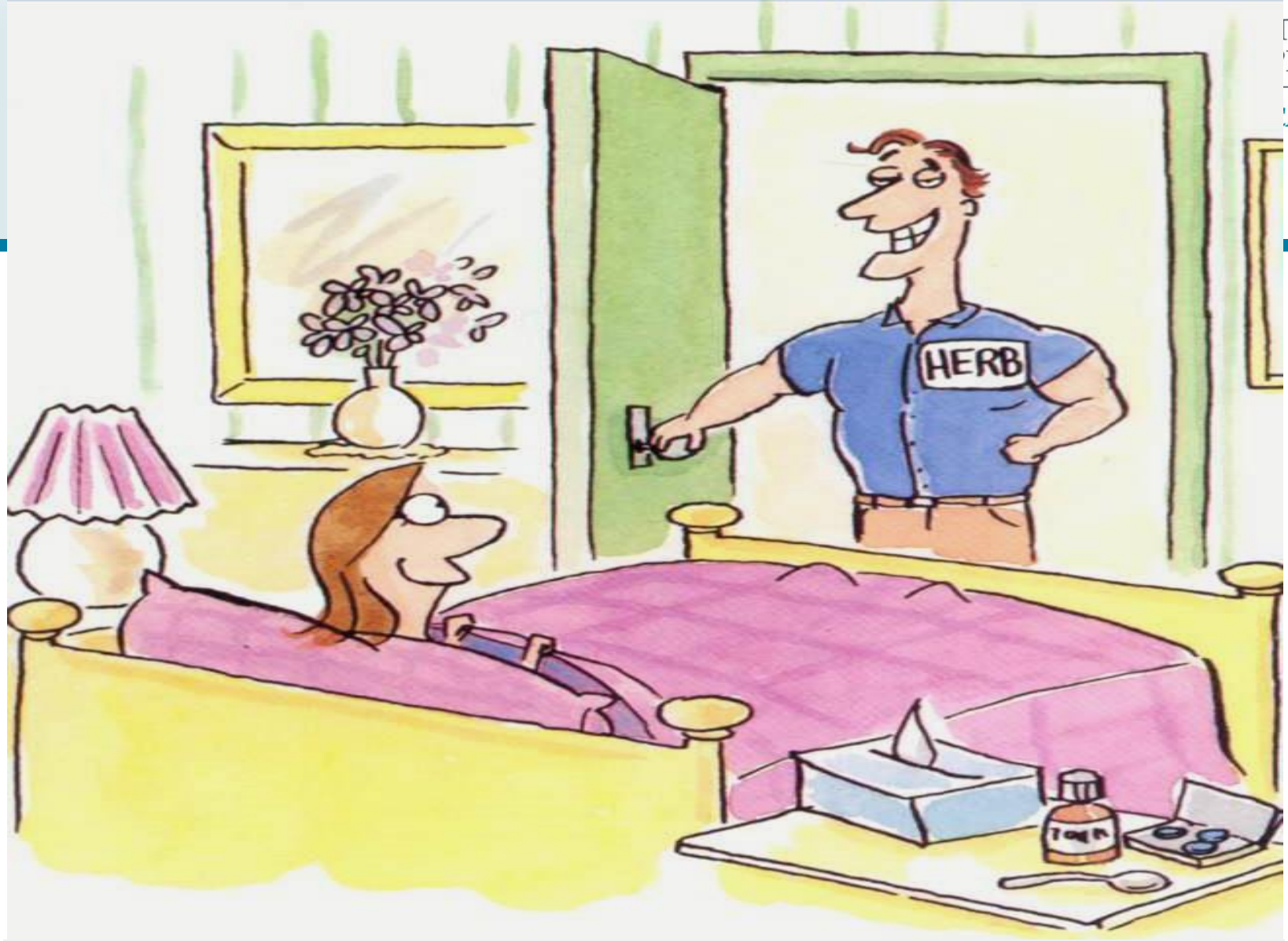


From Brockmöller J, Kirchheiner J, Meisel C, Roots I. Pharmacogenetic diagnostics of cytochrome P450 polymorphisms in clinical drug development and in drug treatment. Pharmacogenomics 2000;1(2):137;

www.mghcme.org

Current limitations of pharmacogenomics testing

- EXPENSIVE
- Cannot be used to determine how you will respond to all medications.
- No tests for aspirin and many over-the-counter pain relievers.
- In my hands better for guiding what not to take rather than what is/may be most effective



Dissatisfied with her cold medicine, Claire decides to try a Herb remedy.

Slide courtesy of Andrew Adesman, M.D.

Complementary and Alternative Treatments

- Omega-3-fatty acids
- Inositol
- St. John's wort
- SAMe
- Melatonin
- Lecithin
- Acupuncture
- Light Box for Depression
- Folate, Leucovorin, L-Methylfolate
- Micronutrients
- Vitamin D

For Review of some of these treatments see Potter M et al., Child Adolesc Psychiatr Clin N Am. 2009 Apr;18(2):483-514

Pharmacotherapeutic Alliance

"…state of mind in which expectation is coloured by hope and faith is an effective force with which we have to reckon, strictly speaking, in all our attempts at treatment and cure. We could not otherwise account for the peculiar results which we find produced by medicaments and therapeutic procedures.

Freud S. (1905). Psychical (or Mental) Treatment. Standard Edition, 7: 283-302. London: Hogarth Press. 1953.

BACKGROUND SLIDES

Anxiety Disorders

A great social and economic burden

- US National Comorbidity Survey
  - Anxiety disorders are the most prevalent class
- National Comorbidity Survey Replication Adolescent Supplement
  - Anxiety disorders are the most prevalent class
  - Persistence appears due to recurrence rather than chronicity
- Anxiety disorders cost the U.S. more than $42 billion/year, almost 1/3 of the total U.S. mental health bill

Kessler et al, Arch Gen Psychiatry. 2012 Apr;69(4):372-80.
Kessler et al, Arch Gen Psychiatry. 2005 Jun;62(6):617-27
Pagura et al, J Nerv Ment Dis. 2008 Nov;196(11):806-13.
http://www.adaa.org

DSM V Anxiety Disorders

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Panic Attack (Specifier)
- Agoraphobia
- Generalized Anxiety Disorder
- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition
- Other Specified Anxiety Disorder
- Unspecified Anxiety Disorder

Child/Adolescent Anxiety Multimodal Study (CAMS)

- Randomized, controlled trial of 488 children (7-17 yrs)
- SAD, GAD or social phobia
  - 14 sessions of CBT
  - Sertraline (to 200 mg/day)
  - Combined CBT and sertraline
  - Placebo for 12 weeks
- Categorical and dimensional ratings of anxiety severity and impairment

Walkup et al, *NEJM* 2008

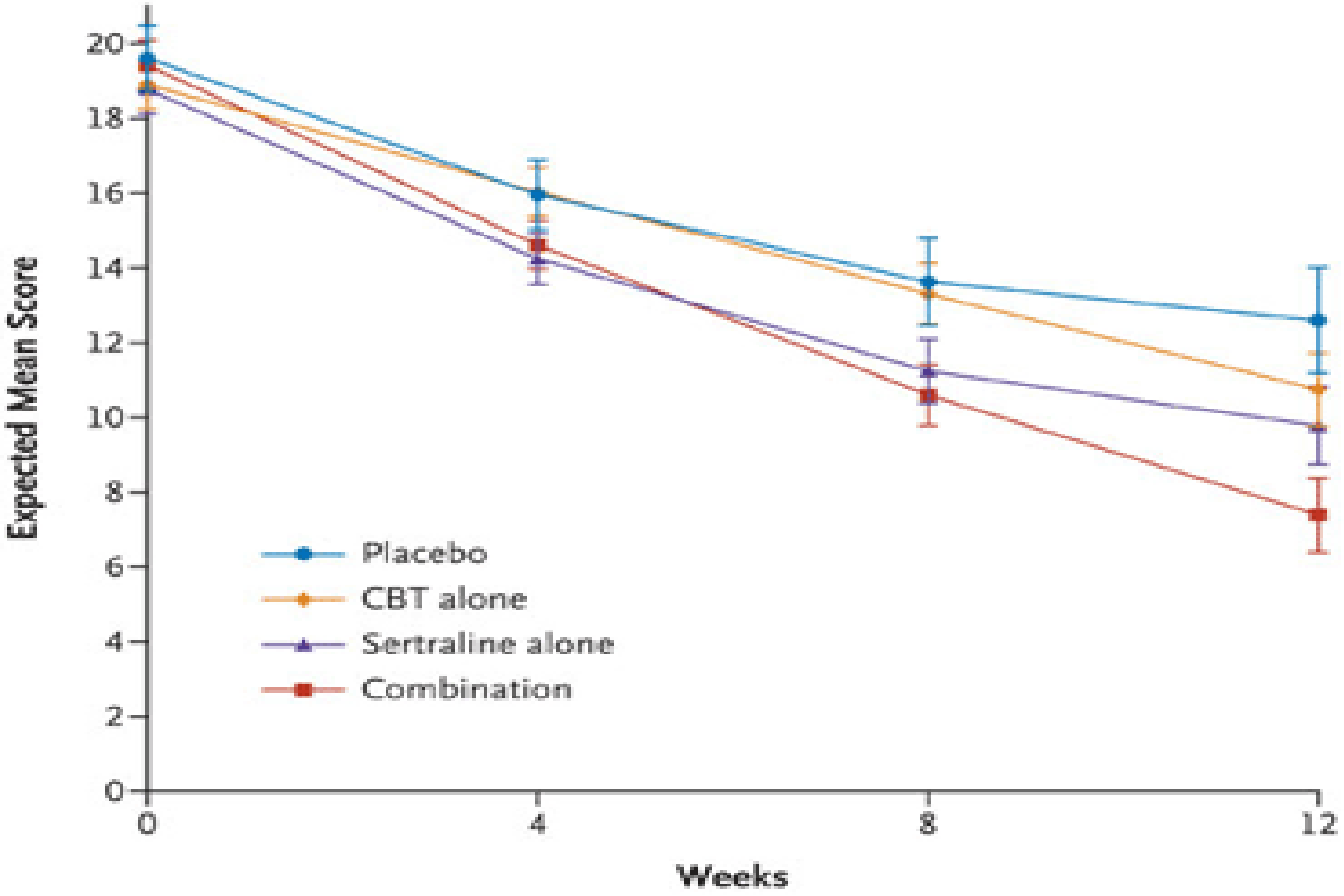
Child/Adolescent Anxiety Multimodal Study: % CGI-I response

- Sertraline (N=133) [a]
  - 4 wk = 19%; 8 wk = 47%; 12 wk = 55%
- CBT (N=139) [a]
  - 4 wk = 9%; 8 wk = 30%; 12 wk = 60%
- Combination (N=140) [a, b]
  - 4 wk = 21%; 8 wk = 54%; 12 wk = 81%
- Placebo (N=76)
  - 4 wk = 7%; 8 wk = 22%; 12 wk = 24%

a P<0.001 vs. placebo
b P<0.001 vs. sertraline + vs CBT

Walkup et al, *NEJM* 2008

Quantitative Scalar Outcome: CAMS Pediatric Anxiety Rating Scale



Walkup et al, *NEJM* 2008

Other CAMS Outcomes

- Younger kids with anxiety do best with all treatments..
- Medication is well tolerated, but younger kids also have more side effects – endpoint dose Sertraline 130 mg/day (highest safe dose)
- Technical expertise required for optimal dosing or risk under treatment and poor outcome
- Adolescents likely require psychosocial rehab

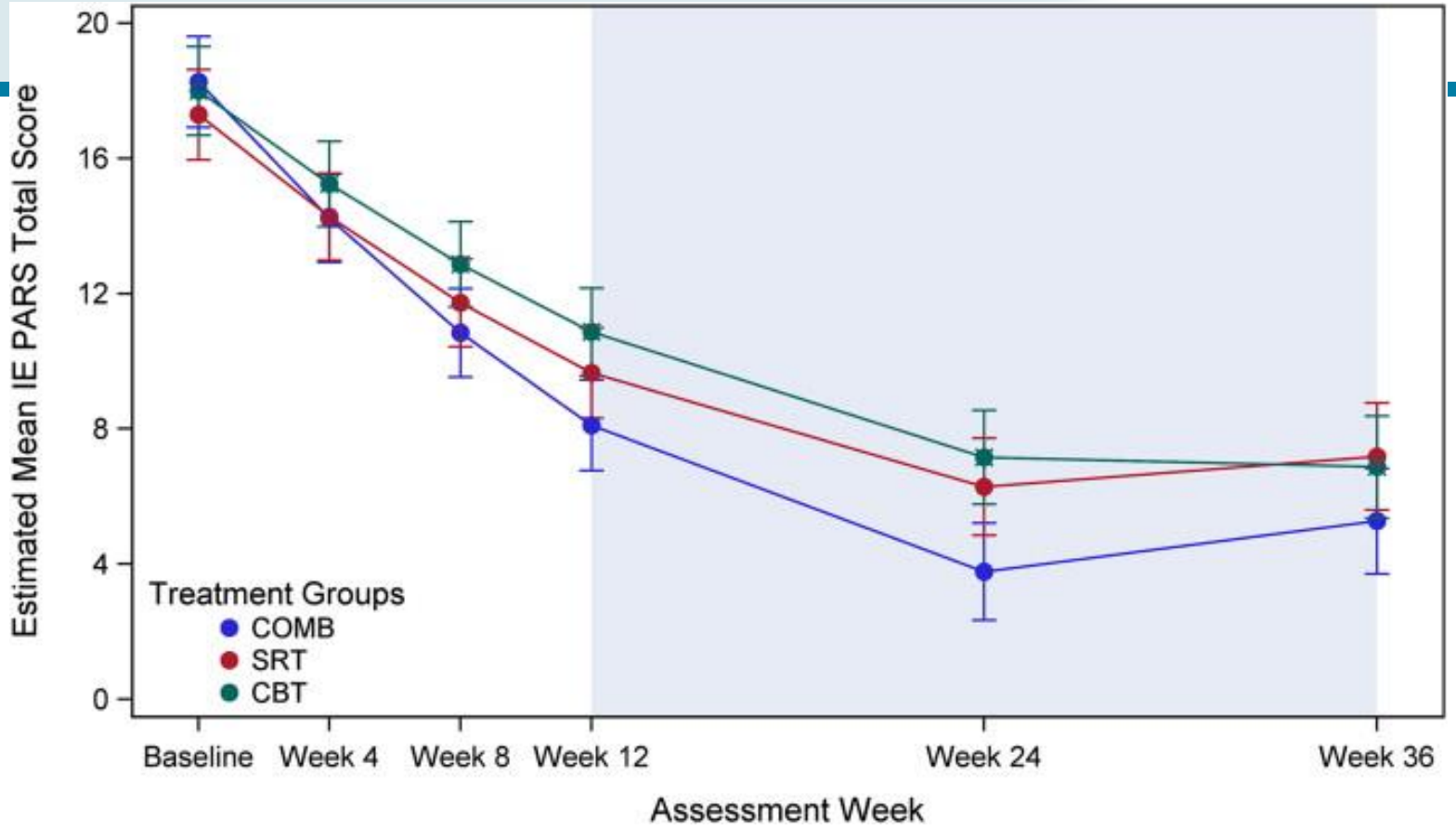
Child/Adolescent Anxiety Multimodal Study: AEs

- Rates of adverse events, including suicidal and homicidal ideation, were not significantly greater in the sertraline group than in the placebo group
- No child in the study attempted suicide

- Most common adverse effects in sertraline group was headache (16%), GI distress (11%)

Walkup et al, *NEJM* 2008

24- and 36-Week Outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS)



Estimated mean scores for the Pediatric Anxiety Rating Scale (PARS) by treatment group over 36 weeks. *Note: Shaded area indicates follow-up period.* CBT = cognitive-behavioral therapy; COMB = combined (CBT + sertraline) treatment; SRT = sertraline.

Piacentini J et al. Journal of the American Academy of Child & Adolescent Psychiatry, 2014 Volume 53, Issue 3, 2014, 297 - 310

Meta-analysis of Pharmacology of (Non-OCD) Anxiety Disorders

- Randomized placebo controlled trials of antidepressants in youth; 6 trials; N=1136
- Generalized anxiety disorder
  - Rynn et al., 2001 (Sertraline to 50 mg)
  - Rynn et al., 2007 (Venlafaxine to 225 mg)
- Social anxiety disorder/social phobia
  - Wagner et al., 2004 (Paroxetine to 50 mg)
  - March et al., (Venlafaxine to 225 mg)
- Social phobia/separation/generalized anxiety
  - RUPP 2001 (Fluvoxamine to 300 mg)
  - Birmaher et al., 2003 (Fluoxetine to 20 mg)

Bridge et al, 2007

Meta-analysis of Pharmacology of Anxiety Disorders (Non-OCD)

- Clinical Global Impression– Improvement (CGI-I) scale as primary measure in all trials
- 2-4 months treatment duration
- Pooled rates of response
  - 69% (95% CI, 65%-73%) in antidepressant-treated participants
  - 39% (95% CI, 35%-43%) in those receiving placebo
  - NNT of 3 (95% CI, 2 to 5)
  - (SI/SA – 1% med/0.2% placebo; NNH of 143)
- All studies favored antidepressant treatment, yet large variation in the degree of benefit across trials

Bridge et al, 2007

Meta-analysis of Pharmacology of Anxiety Disorders (Non-OCD)

"..the strength of evidence ..... supports the cautious and well-monitored use of antidepressant medications as one of the first-line treatment options, with the recognition that efficacy appears greatest for non-OCD anxiety disorders, intermediate for OCD, and more modest for MDD."

Bridge et al, 2007