CURE Activity

Program Starts at 12:15pm

Depression: A Multifaceted Disease

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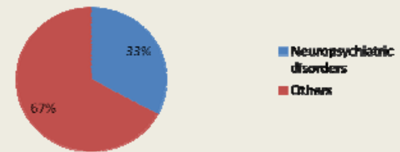
Objectives

Attendees will

- Describe the diagnostic evaluation process to distinguish between a major depressive episode and a bipolar disorder episode.
- Describe common medical and substance-related causes of depression.
- Identify pharmacologic treatment options for patients with multiple co-morbidities and medications.

WHO Data
Neuropsychiatric Disorders: Depression, Alcohol use, Bipolar, Schizophrenia



More than 150 million persons suffer from depression at any point in time
Nearly 1 million commit suicide every year

WHO Statistics 2004

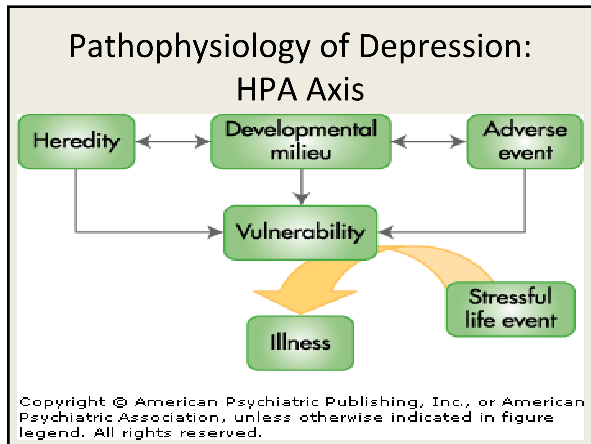
Disease or injury	DALYs (millions)	Per cent of total DALYs
1 Lower respiratory infections	94.5	6.2
2 Diarrhoeal diseases	72.8	4.8
3 Unipolar depressive disorders	**65.5**	**4.3**
4 Ischaemic heart disease	62.6	4.1
5 HIV/AIDS	58.5	3.8
6 Cerebrovascular disease	46.6	3.1
7 Prematurity and low birth weight	44.3	2.9
8 Birth asphyxia and birth trauma	41.7	2.7
9 Road traffic accidents	41.2	2.7
10 Neonatal infections and other	40.4	2.7

Disability adjusted life years (DALYs) = loss of equivalent of one year of full health

"Iceberg" Phenomenon

Watts, 1966
WPA/PTD Educational Program on Depressive Disorders

Pathophysiology of Depression: HPA Axis



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More on Pathophysiology

Brain imaging and postmortem findings:

- Widespread gray matter volume reductions in regions affecting cognition and emotion;
- Basal ganglia connectivity with limbic system and prefrontal cortex disrupted

Genetics accounts for 35–70% variance : BDNF, 5-HT, 5HTT , CRH, FKBP5

Link between depression and:

- Neurotransmitters: 5HT, NE, DA, GABA and glutamate
- Inflammation
- Hypothalamic Pituitary Growth Hormone axis
- Hypothalamic Pituitary Gonadal axis

http://www.brainwaves.com/images/brain-basic_and_limbic.gif
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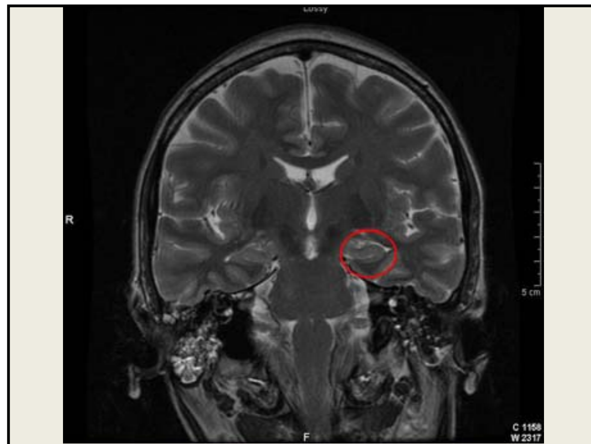


Major Depressive Episode (DSM IV)
Lifetime Prevalence 15%

A. ≥Five during the same 2-weeks;

Depressed mood (in children can be irritable mood) OR

Loss of interest or pleasure

Weight loss/ weight gain or decrease/increase in appetite nearly every day (significant, unintended)

Insomnia or Hyper-somnia nearly every day

Psychomotor agitation or retardation nearly every day (observable by others)

Fatigue or loss of energy

Major Depressive Episode (DSM IV)

Worthlessness or excessive/inappropriate guilt

Diminished ability to think or concentrate, or indecisiveness, nearly every day

Thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode
C. Significant impairment in function.
D. Not due to substance (drug of abuse, medication) or a general medical condition (hypothyroidism).
E. Not Bereavement: > than 2 months; marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Case 1

A 45 years old man was brought to the ER after a series of suicidal gestures, culminating in an ***attempt to strangle himself*** with a piece of wire. Four months before the event he started feeling ***depressed***; at home he spent long time sitting in a chair, he ***slept longer than usual***, he had ***given up reading the paper*** and puttering around the house. In the past month, he became ***unable to get out of bed and go to work***. Although he feels ***guilty***, he could not make up his mind to seek help until his family forced him. He had no response to 2 months outpatient treatment with antidepressants. He attempted to cut his wrists superficially before the serious attempt that brought him to the ER. At physical exam he revealed signs of increased intracranial pressure and a CT scan showed a large frontal lobe tumor.

Adapted from Kaplan and Sadock, Synopsis of Psychiatry, 10th Ed, Wolters Kluver Health, Lippincott, Williams and Wilkins, 2007.

Depression and Other Medical Illness

- ***Systemic Lupus Erythematosus:*** 75-90% have psychiatric manifestations: depression (50%), cognitive dysfunction (80%), psychosis, delirium
- ***HIV***: depression (HIV increases risk x2; does depression ↑ the risk for HIV infection?); dementia; delirium
- ***Diabetes Mellitus***: depression risk 2-3x higher than general population
- ***Stroke***
- ***Cardiovascular disease (CVD)***
  - Presence of depression predicts the risk of CVD as well as mortality and morbidity in people with CAD and CHF
  - Depression 1 year post MI: 25-31%; under-recognized

Depression and Other Medical Illness

- ***Excess glucocorticoid*** (Cushing Syndrome): 66% depression, also agitation, anxiety, confusion, memory impairment, insomnia, paranoia
- ***Hypothyroidism***: depression, also dementia, psychosis, anxiety
- ***Fibromyalgia***
- ***Chronic fatigue:*** 80% have depressive symptoms
- ***Irritable Bowel Syndrome***
- ***Neurodegenerative diseases:*** Parkinson's, dementia
- ***Acute intermittent porphyria:*** depression along with anxiety, delirium, psychosis

Medication with Effects on Mood

- ***Steroids***: depression in periods when steroids are NOT taken, euphoria, psychosis, anxiety during treatment
- ***Interferon alpha***: "May cause or aggravate severe psychiatric adverse events (eg, depression, psychosis, mania, suicidal behavior/ideation, homicidal ideation)"
- ***Isotretionin***: "may cause depression, psychosis, aggressive or violent behavior, and changes in mood. Rarely, suicidal thoughts and actions have been reported"
- ***Varenicline***: "depression, suicidal thoughts, and suicide"

Case 2

A 55 years old business executive had ***several brief (one mo long) episodes of depression***. Each followed a stressor and remitted after cognitive therapy without medication. The current episode of ***depressed mood*** started with a business reversal but unlike previously, it did not resolve as the business improved. Instead, her depression worsened and within 6 weeks she ***spent her day lying in bed*** facing a blank wall. She was ***unable to work***, reported that she can fall asleep easily but **wakes up before sunrise**, paces and becomes very **agitated** and sometimes ***feels like killing herself***. She ***lost 25 pounds*** and she ***cannot take pleasure in anything,*** does ***not even have energy*** to play with her grandchildren. She *feels* ***guilty*** and like a failure at work but has no bizarre delusions. She feels "***dead inside***" and described her emotional ache as "horrid beyond words".

Adapted from Kaplan and Sadock, Synopsis of Psychiatry, 10th Ed, Wolters Kluver Health, Lippincott, Williams and Wilkins, 2007.

Subtypes of Major Depression

Melancholic

- Loss of pleasure
- Lack of reactivity to positive stimuli
- Distinct mood quality
- Worse in AM
- Psychomotor agitation or retardation
- Anorexia/weight loss
- Excessive guilt

Atypical

- Mood reactivity
- Increased appetite/weight gain
- Hypersomnia
- Leaden paralysis (heavy feelings in limbs)
- Long standing pattern of interpersonal rejection sensitivity

Other Qualifiers for Major Depressive Episode

- **Psychotic**
- **Post partum onset**: within 4 weeks
- **Catatonic**:
- – Motor immobility
- – Excessive motor activity
- – Negativism
- – Posturing, mannerisms, grimacing
- – Echolalia/echopraxia

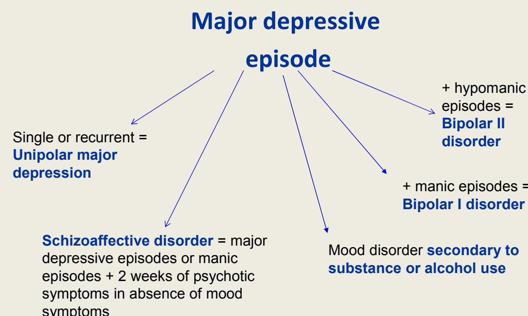
Case 3

A 48 years old married man comes to your office stating that he feels he is dying of a mysterious disease that no one has been able to diagnose. He tells you that ***"I'm dying"***, my skin is coming off in clumps", "my bowels are shut down", "I'm losing my hair". In the past 2 weeks he ***refused to go to work or to participate in the family life*** in any way. He ***spends most of this time in bed***. His ***mood has been gloomy*** and pessimistic and he has been ***irritable*** when the family suggested that he seeks help. He thinks ***he would be better off dead***.

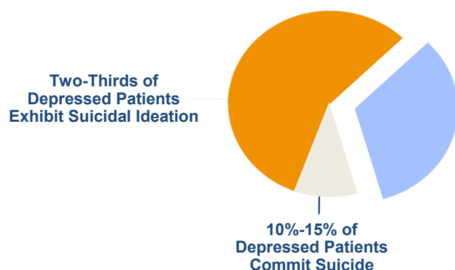
He has a history of 2 previous hospitalizations for suicide attempts. His wife reports that throughout his marriage he always fluctuated between episodes of depression when he cannot function and sudden bursts of energy when he plans elaborate vacations, is extremely productive at work and plunges into volunteer activities. During these times the family unsuccessfully tries to keep up with him. After returning from one of the vacations, he impulsively bought a piece of land because it resembled an Austrian farm he admired.

Adapted from Kaplan and Sadock, Synopsis of Psychiatry, 10th Ed, Wolters Kluver Health, Lippincott, Williams and Wilkins, 2007.

Diseases Which Involve Major Depressive Episodes (DSM IV)



Suicide Rates in Depressive Disorders



Kaplan & Sadock, 1991
WPA/PTD Educational Program on Depressive Disorders

Suicide Risk Assessment

- **Current presentation of suicidality**

Suicidal thoughts, plans, behaviors, and intent
Methods, lethality , access to firearms
Hopelessness, impulsiveness, anhedonia, panic attacks, or anxiety
Reasons for living and plans for the future
Alcohol or other substance use
Thoughts, plans, or intentions of violence toward others

- **Psychiatric illnesses**

Mood disorders , schizophrenia, substance use disorders, anxiety disorders, and personality disorders (primarily borderline and antisocial)

- **History**

Previous suicide attempts, other self-harm
Medical
Family history of completed or attempted suicide, mental illness, substance abuse

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Suicide Risk Assessment (Con't)

- **Psychosocial situation**

Crises and chronic stressors: losses, financial difficulties, family discord, domestic violence, abuse or neglect
Employment, living situation (are there infants or children in the home?), external support
Cultural or religious beliefs about death or suicide

- **Individual strengths and vulnerabilities**

Coping skills, ability to tolerate psychological pain and satisfy psychological needs
Personality traits
Responses to stress
+/- reality testing

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Antidepressants: SSRIs

Action: Inhibit 5HT Reuptake

Side Effects:

- ***Gastrointestinal*** 5HT3 receptors activation
- ***Sexual*** D2, Ach blockade, 5HT reuptake inhibition
- ***Endocrine*** SIADH; hyponatremia
- ***Discontinuation syndrome:*** flu-like symptoms, headache, vertigo
- ***Pregnancy*** paroxetine - class D
- ***Increased suicidal behavior in children & adolescents***
- ***Serotonin syndrome*** with other serotonergic agents: *neuromuscular*-myoclonus, *autonomic* instability, *mental status*, *GI* symptoms
- ***CYP450 interactions***: fluoxetine, paroxetine, fluvoxamine-*most*, citalopram and sertraline-*least*

Antidepressants

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs):
venlafaxine, duloxetine, desvenlafaxine
BP elevation at higher dose, CYP450 drug interactions

NE, DA reuptake inhibitor (*NDRI*):
Bupropion: dose dependent seizures; CI in eating d/o

Mirtazapine: Selective *α2 adrenergic antagonism* with increase in serotonergic and noradrenergic activity; 5HT2c and 5HT3 receptor blockade → 5HT1A activation; sedation, weight gain, neutropenia

5HT2 antagonists/reuptake inhibitors:
Nefazodone: sedation, visual trails, MANY drug interactions CYP450 3A4, hepatic failure-rare
Trazodone (metabolite mCPP a strong serotonin agonist- anxiogenic and induces anorexia), priapism

Antidepressants

TRICYCLICS: inhibit NE and 5HT uptake and less DA
- Sedation, anticholinergic toxicity (treat with bethanechol), CV-arrhythmias (order EKG >40 years old, avoid in heart disease)
- CYP450 interactions
- **Lethal in overdose:** wide-complex arrhythmia, seizure, hypotension
- Nortriptyline therapeutic window: 50-150 ng/ml

Monoamine-oxidase inhibitors (MAOIs): Inhibit MAO-A and B which metabolize NE, 5HT and DA; *nonselective*-phenelzine, tranylcypromine; *selective*-selegiline; *reversible*-moclobemide
- Serotonin syndrome with SSRIs, SNRIs, triptans
- Hypertensive crisis with adrenergic agents, meperidine and high monoamine content foods; treat with phentolamine, chlorpromazine, nifedipine; DO NOT GIVE β BLOCKERS
- Require low monoamine diet

Generic-Brand Antidepressant Names

Generic	Brand
Sertraline	Zoloft
Fluoxetine	Prozac (weekly available)
Fluvoxamine	Luvox (XR)
Paroxetine	Paxil (CR)
Citalopam	Celexa
Escitalopram	Lexapro
Venlafaxine	Effexor (XR)
Des-venlafaxine	Pristiq
Duloxetine	Cymbalta
Bupropion	Wellbutrin (SR, XL), Zyban
Mirtazapine	Remeron
Nefazodone	n/a
Trazodone	Desyrel
Phenelzine	Nardil
Tranylcypromine	Parnate
Selegiline	Emsam (patch), Deprenyl (oral)
Amitriptyline	Elavil
Nortriptyline	Pamelor

How Do We Measure Remission in Major Depression

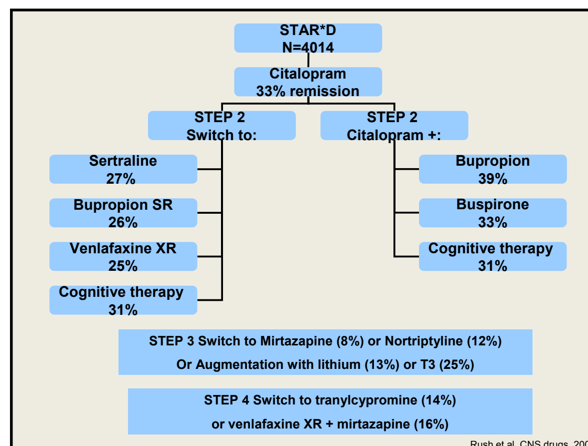
No or minimal depression
HAM-D score ≤7
AND/OR
Clinical Global Impression - Improvement score = 1
CGI-S score =1

No functional impairment
Sheehan Disability Scale score ≤1 (mildly disabled)

HAM-D Hamilton Rating Scale for Depression
CGI Clinical Global Impression
J Clin Psychiatry 2J Clinical 001;62 (suppl 12)

"ABCD" Evaluation Approach to Antidepressant Treatment Resistance

- **Adequacy of prior treatment**
  - Duration of treatment
  - Dosage of medication
- **Behavioral/Environmental factors**
  - Personality disorder
  - Psychosocial stressors
- **Compliance/Adherence**
  - Patient education
  - Treatment intolerance
- **Diagnosis**
  - Missed medical diagnosis
  - Missed psychiatric diagnosis
    - Substance use disorders
    - Bipolar
    - Co-morbid anxiety



Rush et al, CNS drugs, 2009

Antidepressant Augmentation for Refractory Depression

- Lithium
- T3
- Atypical antipsychotics
  - Aripiprazole – in combination with antidepressants
  - Quetiapine- acute depressive episodes associated with bipolar disorder; adjunctive treatment of major depressive disorder
- Transcranial Magnetic Stimulation
- Vagal Nerve Stimulation

ECT for severe, refractory depression. Need to re-start or continue antidepressant post-ECT

*Augmentations: Evidence-Base

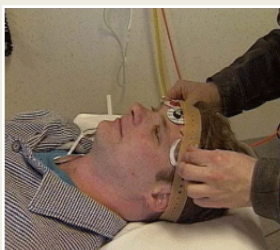
Augmentation	Evidence Rating*
lithium 900 mg (to TCA)	A
T3 25 ug (to TCA)	A
mirtazapine 15 mg	A/B
buspirone 40 mg	B
bupropion SR 300 mg	B
olanzapine 10 mg	B
modafinil 200 mg	B/C
nortriptyline 100 mg	C
pindolol 10 mg	C
lithium 900 mg (to SSRI)	C
T3 25 ug (to SSRI)	C
venlafaxine XR 150 mg	C
other atypicals	C

*Thase ME. CNS Spectrums 2004;9(11):808-821.(updated)

A= >1 RCTs
B= 1 RCT, plus c
C= Case series, anecdotal report, expert opinion
D= Anecdotal reports but experts have not endorsed

Electroconvulsive Therapy (ECT)

- 1st administered in 1938 (in Rome)
- FDA - approved since 1979 (grand-fathered)
- ECT remains a gold standard treatment for severe depression and has yet to be superseded by medication or by any other brain stimulation treatment



Transcranial Magnetic Stimulation (TMS)

Non-invasive Technology

Approved: Canada, Israel, Europe, US-2008

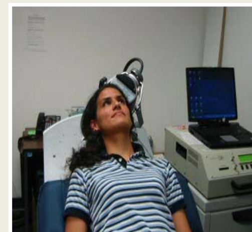
Strong, pulsed (e.g., 2/28 sec) magnetic fields pass through skull unimpeded

Coil placed on head in awake patient

Induces electrical current in cortex which depolarizes neurons

Greater control over site and intensity of stimulation (e.g, left DLPFC)

No anesthesia, no cognitive adverse effects



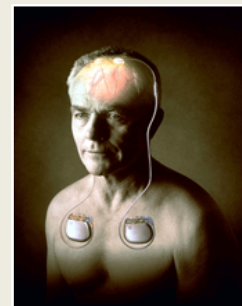
This information concerns a use that has not been approved by the U.S. Food and Drug Administration.

Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy; FDA approved for TRD July, 2005
- Pulse generator implanted in left chest wall area, connected to leads attached to left vagus nerve
- Mild electrical pulses applied to CN X for transmission to the brain

Deep Brain Stimulation (DBS)

- FDA Approved for Parkinson's and Tremor
- Investigational for OCD, TRD
- Stereotactic Target from MRI
- Two chest-wall Pulse Generators
- Burr holes in skull for electrode placement
- Stimulation parameters programmed by computer, through "wand"



This information concerns a use that has not been approved by the U.S. Food and Drug Administration.

Neuromodulation Overview

ECT non-invasive, hospital procedure, requires anesthesia, safe, very efficacious, but stigmatized

TMS is non-invasive, office based, most flexible, possible multiple applications, very acceptable to patients, but is it robust enough?

VNS bottom-up modulation, limited surgery, but efficacy less than hoped for, & access problems

DBS most invasive, only preliminary data to date, but looks robust

Psychotherapy

Cognitive therapy in STAR*D:

- Remission rate for cognitive therapy 31% and medication augmentation 33%
- Time to remission 55 days cognitive therapy and 40 days medication
- 31% remission with cognitive therapy switch vs. 27% medication switch

Cognitive Therapy Prevents Recurrence of Depressive Episodes at Long Term Follow Up

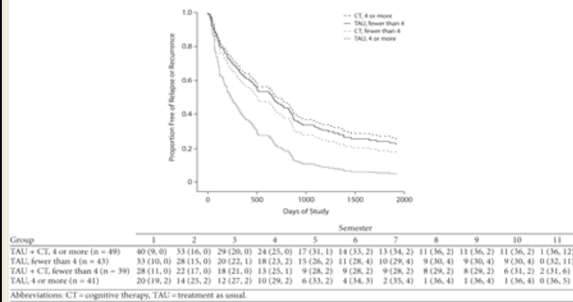


Figure 3. Proportion of Relapse/Recurrence in Patients With 4 Previous Episodes and Patients With 4 or More Previous Episodes in the TAU Group Versus the TAU + CT Group Over 5.5-Year Follow-Up

Group	Semester 1	2	3	4	5	6	7	8	9	10	11
TAU + CT, 4 or more (n = 49)	40 (9, 0)	33 (16, 0)	29 (20, 0)	24 (25, 0)	17 (31, 1)	14 (33, 2)	13 (34, 2)	11 (36, 2)	11 (36, 2)	11 (36, 2)	1 (36, 12)
TAU, fewer than 4 (n = 43)	33 (10, 0)	28 (15, 0)	20 (22, 1)	18 (23, 2)	15 (26, 2)	11 (28, 4)	10 (29, 4)	9 (30, 4)	9 (30, 4)	9 (30, 4)	0 (32, 11)
TAU + CT, fewer than 4 (n = 39)	28 (11, 0)	22 (17, 0)	18 (21, 0)	13 (25, 1)	9 (28, 2)	9 (28, 2)	9 (28, 2)	8 (29, 2)	8 (29, 2)	6 (31, 2)	2 (31, 6)
TAU, 4 or more (n = 41)	20 (19, 2)	14 (25, 2)	12 (27, 2)	10 (29, 2)	6 (33, 2)	4 (34, 3)	2 (35, 4)	1 (36, 4)	1 (36, 4)	1 (36, 4)	0 (36, 5)

Abbreviations: CT = cognitive therapy, TAU = treatment as usual.

Bockting et al for the DELTA study group, J Clin Psychiatry, Dec 2009

Coding

- 90801 Diagnostic interview
- 90805 Individual psychotherapy 20-30 minutes with evaluation and medication management
- 90862 Pharmacologic management
- 99213 Established patient visit – low-moderate severity

Abbreviations

- WHO = World Health Organization
- HPA = hypothalamus-pituitary-adrenal
- BDNF = brain derived neurotrophic factor
- 5-HT = serotonin
- 5HTT = serotonin transporter
- CRH = corticotrophin release hormone
- FKBP5 = glucocorticoid receptor chaperone protein gene
- NE = norepinephrine
- GABA = γ-Aminobutyric acid
- T3 = Triiodothyronine
- FDA = Food and Drug Administration
- DLPFC = Dorsolateral prefrontal cortex
- TRD = treatment resistant depression
- OCD = obsessive compulsive disorder
- STAR*D = Sequenced Treatment Alternatives to Relieve Depression

References

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QUESTIONS?

Evaluation

- Attended Live Activity on September 14, 2010
  http://www.surveymonkey.com/s/CURE8
- Attended Archived Activity September 15, 2010 or later
  http://www.surveymonkey.com/s/CURE8Archived