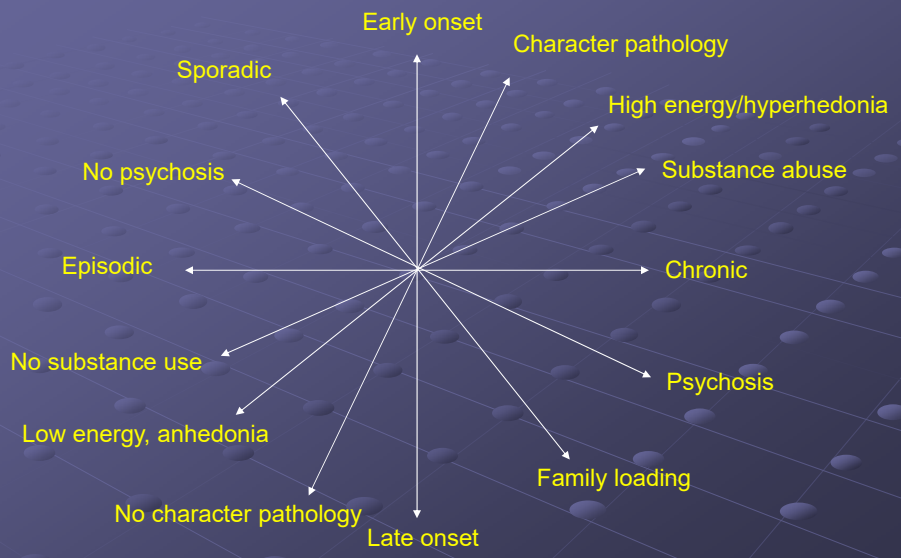
Treatment of Depression in Complex Patients

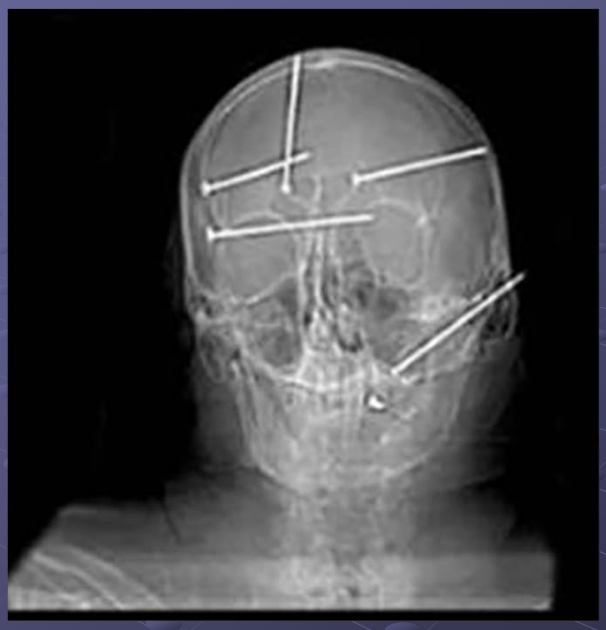
Steven L. Dubovsky, MD..

Do You Have Mutual Climax?
No- State Fam

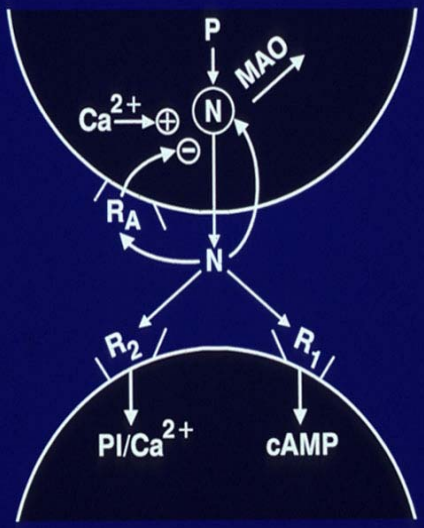
Mood Disorder Dimensions

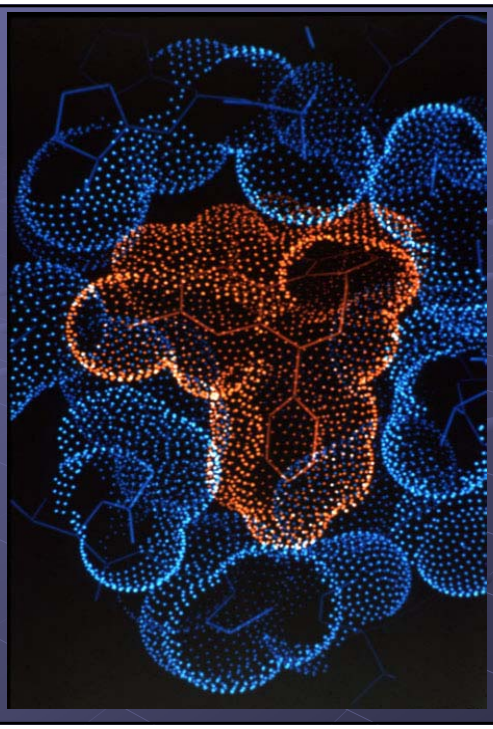


Pathophysiology



Monoamine Neurotransmission





Neurotransmitter and Receptor Changes in Depression

Transmitter System	Change	Implications
Norepinephrine	Increased	Increased arousal
Serotonin	Decreased	Altered appetites and circadian rhythms, impaired regulation of arousal and aggression
Dopamine	Decreased	Reduced reward, motivation, energy
Glutamate/NMDA	Increased	Solidified maladaptive neuronal connections, excitotoxicity

Pathophysiology of Depression

- Hyperactivity in
  - Amygdala
  - Subgenual cingulate cortex (Cg25)
  - Nucleus accumbens (striatum; reward and hedonic tone)
- Second messenger changes
  - Calcium binding protein (p11) downregulated in depression; transgenic p11 overexpression has antidepressant effect
  - Abnormal regulation of cyclic AMP response element binding protein (CREB)
    - Stress activates CREB in Nac and causes depression
    - Antidepressants up-regulate CREB

Pathophysiology of Depression

- Increased activity in default mode network (DMN)
  - Ventromedial prefrontal cortex, posterior cingulate cortex and inferior parietal lobe
  - Focused on internal events
    - Self-referential thought
    - Thinking about one's past
    - Inability to detach from depressive thinking and perception
  - Overrides externally focused networks (task-focused networks)
    - Respond to context-appropriate events
    - Salience network (SN)
      - Dorsal anterior cingulate cortex and insula
    - Central executive network (CEN)
      - Lateral frontal and parietal regions
  - MDD associated with hyerconnectivity within DMN and between subgenual ACC and mPFC (i.e., increased influence of DMN)
- Antidepressants decrease DMN hyperactivity and restore goal-directed activity
  - Posterior DMN may respond better to antidepressants than anterior subnetwork
    - Marker of residual depression susceptibility?

J Posner et al: JAMA Psychiatry 2013;70:373-382; B Li et al: Biol Psychiatry 2013;74:48-54

Network Model

- Predominance of DMN over executive network
- Antidepressants but not placebo reduce excess connectivity of DMN
- Comparison of IV ketamine to placebo in MDD and controls
  - Rapid antidepressant response correlated with rapid improvement of connectivity between DMN and CEN

Dubovsky SL: Psychother Psychosom 2018;87:129–13

Delay Discounting

- Ignoring a future large reward in favor of an immediate small reward
- Neurobiology: failure of executive control over limbic system
- Psychology: Impulsivity and intolerance of uncertainty overwhelm future thinking
- Treatment
  - Explain to patient
  - Practice future thinking

M Amlung et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.2012

Pathophysiology of Depression

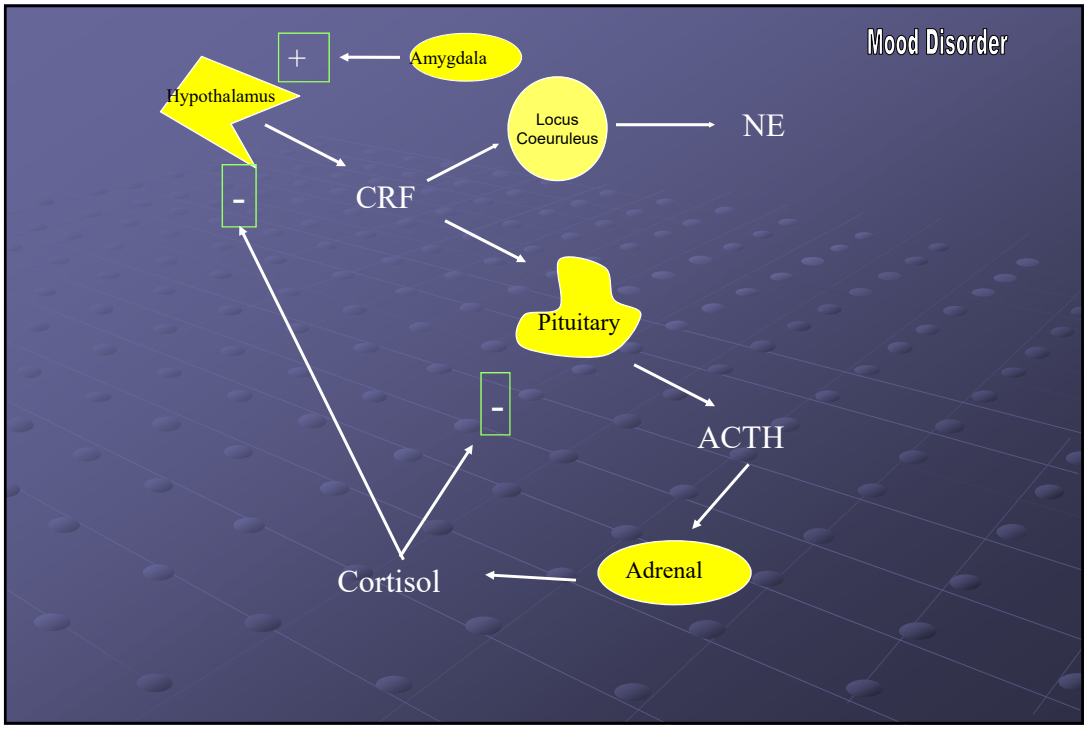
- Excess HPA activity (discussed later)
  - Atypical depression associated with hypo-cortisolemia
- Cytokines (see next slide)
  - Inflammatory cytokines increased in depression
    - IL-1, IL-6, TNF-α, acute phase proteins, chemokines, adhesion molecules, TNF soluble receptors I and II
    - Inflammatory proteins may act on GR to exacerbate resistance to feedback inhibition
  - Elevated inflammatory markers associated with antidepressant resistance
  - Loss of regulatory functions of immune system with lack of exposure to "old friend" microorganisms eliminated in industrialized society may increase inflammatory cytokines
    - Could contribute to increasing incidence of depression
- Altered BDNF activity
  - Stress reduces BDNF signaling in hippocampus
    - Silencing of BDNF promoter via histone methylation
  - Antidepressants increase BDNF signaling
  - BDNF infusion has antidepressant effect in animal studies
  - BDNF can also have a pro-depressant effect
  - Effects seem to be region specific
- DNA hypermethylation in nucleus accumbens reduces response to reward
  - Animal studies show antidepressant effect of DNA methyltransferase inhibitor 5-azaD
  - Histone deacetylase inhibitors also have antidepressant effect in animals
  - Long-term treatment with either can induce tumor growth

V Krishnan and Nestler EJ: Nature 2008;455:894; Raison CL et al: Arch Gen Psychiatry 2010;67:1211-1224; M. Schroeder et al: Clin Pharmacol Ther 2012;91:310

Some Actions of Inflammatory Cytokines

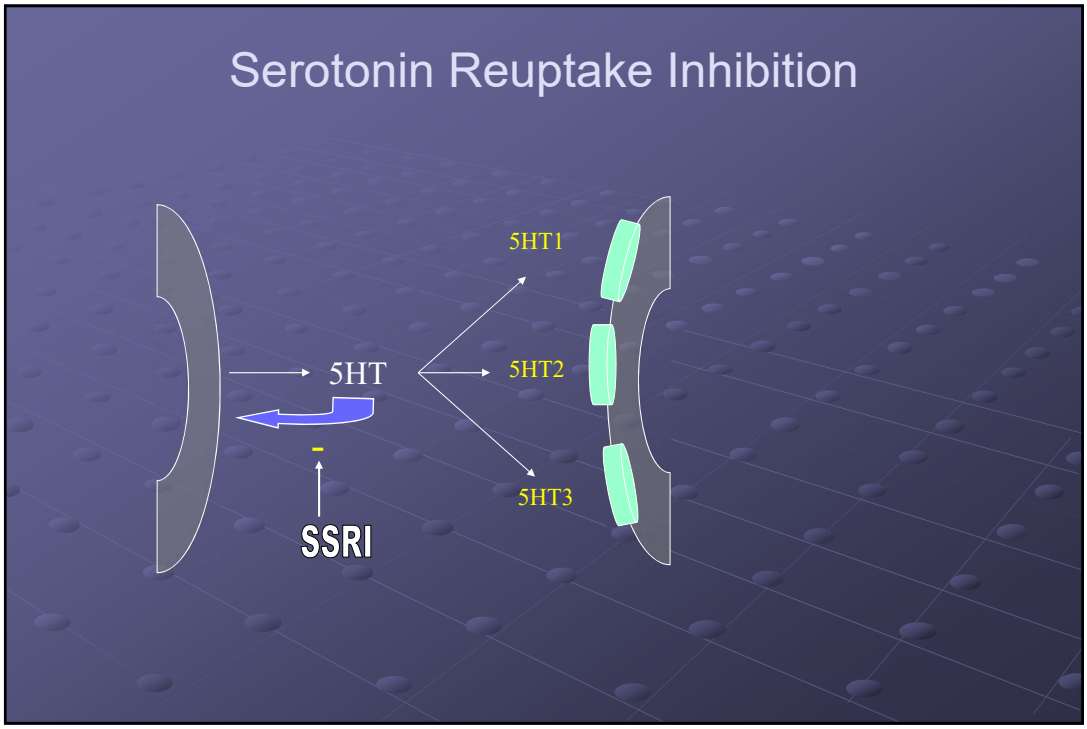
- Increased expression of monoamine transporters
- Decreased activation of rate limiting enzymes in neurotransmitter synthesis
- Inhibition of neurogenesis via activation of nuclear factor κβ
- Decreased glutamate uptake in astrocytes
  - Increased glutamate excitotoxicity

CL Raison et al: Arch Gen Psychiatry 2013;70:31-41

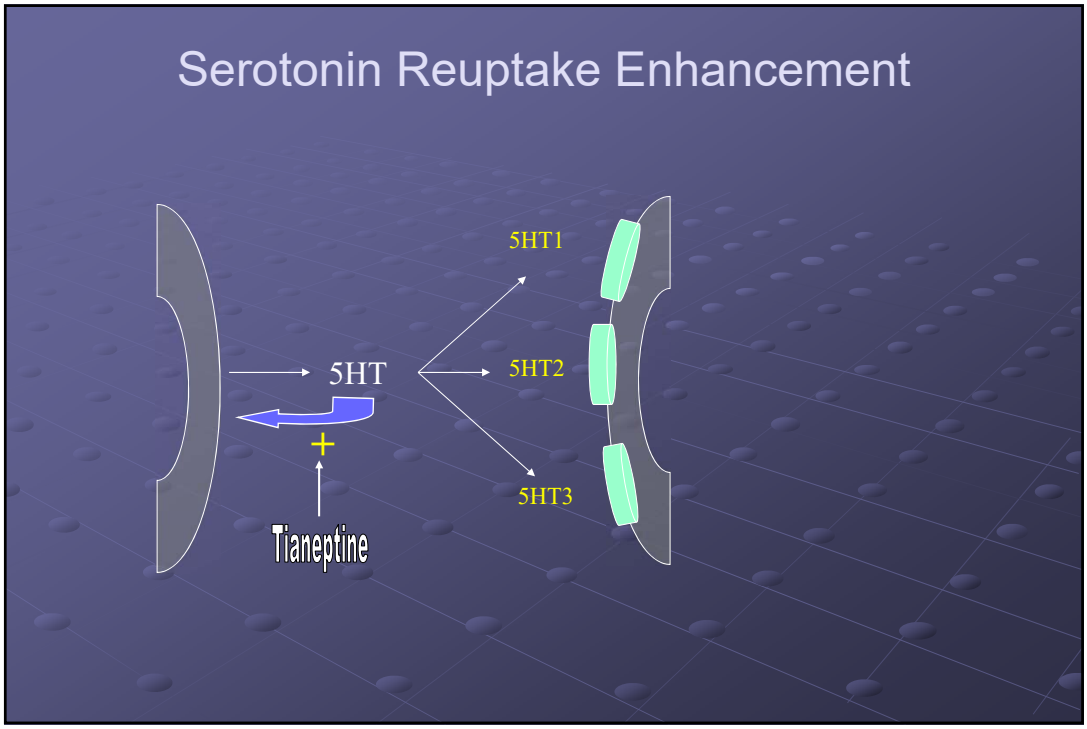


Antidepressant Actions

Serotonin Reuptake Inhibition



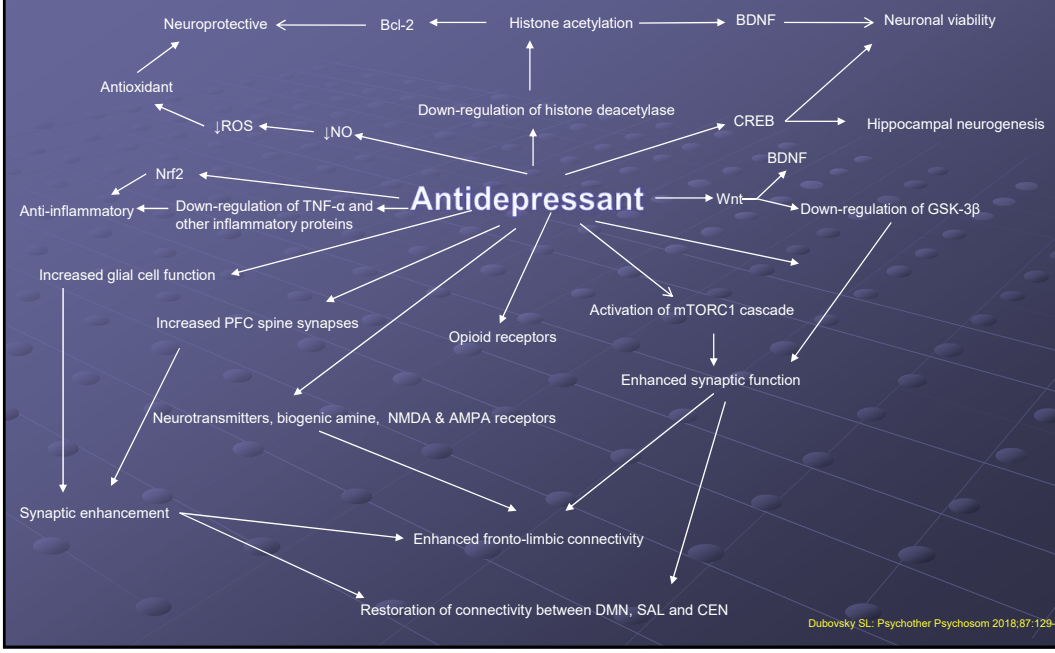
Serotonin Reuptake Enhancement



Gene Expression and Antidepressant Response

- Ketamine responders have alter gene expression in hippocampus and amygdala
- Imipramine responders had most altered gene expression in nucleus accumbens and amygdala
- Patterns of altered gene expression similar in PFC
- Changes in gene expression with antidepressants:
  - Induction of genes expressed in resilient animals
  - Down-regulation of genes expressed in susceptible animals
  - Alteration of other genes
- Treatment-resistance associated with different patterns of gene expression than treatment response
- Treatment resistance not just absence of response
  - Involves additional abnormal expression of genes in reward system that do not respond to ketamine or imipramine
- Treatments might be developed depending on patterns of altered gene expression (not genotype)

RC Bagot et al: Biol Psychiatry 2016 doi:http://diagnosis.doi.org/10.1016/j.biopsych.2016.06.012



Dubovsky SL: Psychother Psychosom 2018;87:129–13

Do Antidepressants Work?

- Antidepressants have been said to be more effective for more severe depression
- Reanalysis of all 6-week RCTs in major depression of fluoxetine and venlafaxine
  - 33 adult studies
    - N=5096
  - 4 geriatric
    - N=960
  - 4 youth
    - N=2421

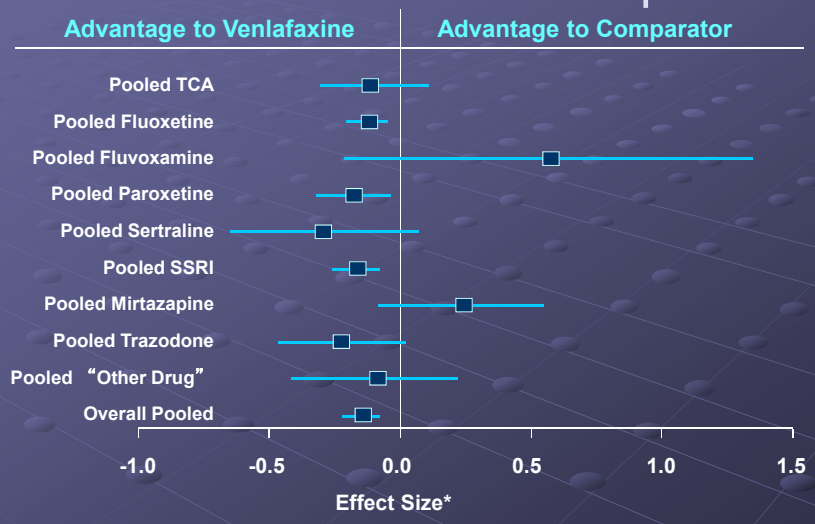
RD Gibbons et al: Arch Gen Psychiatry 2012; doi:10.1001/archgenpsychiatry2011.2044

Do Antidepressants Work?

- Adult and geriatric studies
  - Response
    - 58% (antidepressant) vs 40% (placebo)
      - O.R. 2.11
      - NNT 5.41
  - Remission
    - 43% (antidepressant) vs 29% (placebo)
      - O.R. 2.00
      - NNT 7.30
  - Lowest effect with geriatric studies of fluoxetine
    - Response O.R. 1.42 (NS)
      - NNT 16.95
    - Remission O.R. 1.26 (NS)
      - NNt 38.71
- Child studies
  - Response
    - 30% (antidepressant) vs 5.7% (placebo)
      - O.R. 6.66
      - NNT 4.16
  - Remission
    - 47% (antidepressant) vs 17% (placebo)
      - O.R. 4.23
      - NNT 3.33
- Baseline severity did not affect antidepressant response rate
- No difference between fluoxetine and venlafaxine
  - IR > XR for venlafaxine

RD Gibbons et al: Arch Gen Psychiatry 2012; doi:10.1001/archgenpsychiatry2011.2044

Meta-Analysis: Pooled Efficacy of Venlafaxine vs Other Antidepressants



*Bars indicate 95% CI.
Adapted from Smith D, et al. *Br J Psychiatry*. 2002;180:396-404.

Meta Analysis of Newer Antidepressants

- 234 studies from 1980-2011
- No clinically relevant differences in effectiveness or efficacy for
  - Acute treatment
  - Continuation
  - Maintenance
- No patients seemed more responsive to specific antidepressants

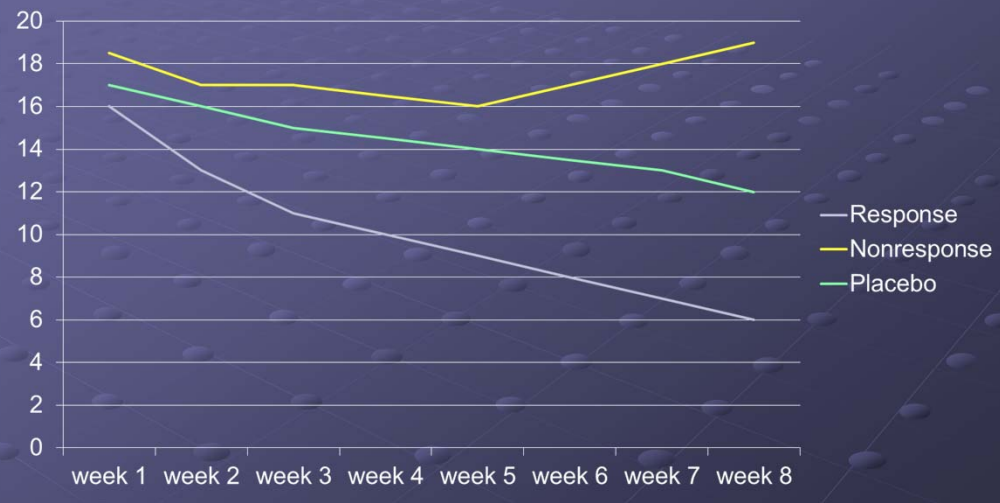
G. Gartlehner et al: Ann Intern Med 2011;155:722

Trajectories of Depression Response

- Re-analysis of seven 8-week randomized comparisons of duloxetine, placebo and an SSRI
  - Fluoxetine
  - Paroxetine
  - Citalopram
  - 2515 patients
- Response trajectories
  - Response trajectory with active treatment (75%): gradual progressive improvement starting by week 2
  - Nonresponse trajectory with active treatment (25%): fluctuation but no better or worse at end of treatment
  - Placebo trajectory: slow gradual modest improvement < response trajectory but > nonresponse trajectory

R. Gueorguieva et al: Arch Gen Psychiatry 2011;68:1227-1237

Response Trajectories



Trajectories of Depression Response

- Conclusions
  - Average final depression scores do not accurately characterize response to antidepressants compared with placebo
    - Patients who get worse will decrease overall average improvement, but response trajectory is clearly differentiated from placebo trajectory
  - Placebo response does not occur immediately
  - Rapid early response to antidepressant predicts further continued response, not placebo response
  - No difference between SSRIs and duloxetine in treatment response
  - Patients with nonresponse trajectory may be worse off than if they took placebo

R. Gueorguieva et al: Arch Gen Psychiatry 2011;68:1227-1237

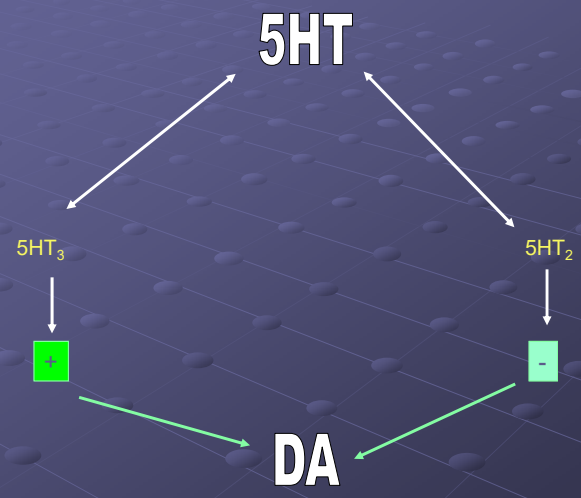
Cost Effectiveness

- 56,805 depressed patients in Florida Medicaid system from 1996-2006
- Over the study period
  - Antidepressant use increased from 81%-87%
    - Adequate doses increased from 59%-68%
  - Antipsychotic drug use increased from 26%-42%
    - Mostly quetiapine and risperidone
  - Hospitalizations decreased from 9%-5%
  - Overall cost of care increased by 29%
    - Primarily due to 949% increase in antipsychotic costs
  - Psychotherapy visits decreased from 57%-38%
  - Adequate follow-up for outpatients and inpatients decreased
  - 10-14% had at least 4 psychotherapy sessions (no change)

C.A. Fullerton et al: Arch Gen Psychiatry 2011;68:1218-1226

Adverse Effects

Serotonin-Dopamine Interactions



Consequences of Antidopaminergic Effect of SSRIs

- Emotional blunting
- Decreased motivation and activity
- Memory loss
- Akathisia
- Increased prolactin release
- EPS
- Tardive dyskinesia?

Treatment of Antidopaminergic Side Effects

- Stimulant
- Bupropion
- Other dopaminergic medication
  - Pramipexole

Antidepressants and Falls

- Elderly patients taking antidepressants have twofold increase in risk of falls
  - Especially if demented
  - Risk higher in women
- Risk with antidepressants similar to BZDs
  - Falls per dose
    - Nortriptyline: 0.0021
    - Sertraline: 0.0012
    - Diazepam: 0.00052
  - Increased postural sway with SSRIs

Mendelson WB: Sleep 1998;19:698-701

SSRIs and Bleeding

- Platelets cannot synthesize 5HT
  - Dependent on uptake from plasma
  - SRIs could increase blood loss caused by disease or other medications (e.g., NSAIDs)
  - Would not cause bleeding themselves
  - SRIs inhibit platelet 5HT uptake; $5HT2_A$ antagonist antipsychotics inhibit platelet response to 5HT
- Case control study of 28,289 patients with hospitalization for GI, intracranial or female genital tract bleeding versus 50,786 controls
  - Serotonergic medications associated with increased risk of hospitalization for bleeding in
    - GI tract: O.R. 1.49
    - Intracranial: O.R. 1.42
    - Female genital tract: O.R. 2.08
    - 2 or more serotonergic drugs increased risk of GI and genital tract bleeding 2.5 times
  - Antidepressants increased risk of all 3 bleeding types
  - Antipsychotic drugs increased risk of GI (O.R. 1.79) and intracranial (O.R. 1.44) bleeding
  - Risks greatest in new versus established users

BM Verdel et al: Clin Pharmacol Ther 2011;89:89-96

SRIs and Hyponatremia

- Retrospective study of 199 elderly psychiatric inpatients
  - 74 taking SSRI or venlafaxine
  - Controlled for other factors that cause hyponatremia
    - E.g., medical illness, diuretics, age, sex
  - Patients taking SSRIs or venlafaxine were 5.6 times as likely to have hyponatremia
    - 39% of SSRI/venlafaxine patients versus 10% of controls
- 1391 patients taking antidepressants with serum sodium <130
  - 79% taking an SSRI compared with 49% of 38,000 patients taking other antidepressants
- Caused by SIADH

Kirby et al 2002; Movig et al 2001

SSRIs and Bone Loss

- Chronic but not acute fluoxetine causes decreased bone density
  - Not seen with citalopram, escitalopram
- Animal study demonstrates biphasic effect on bone
  - Early inhibition of osteoclast differentiation via a serotonin-independent action on calcium-calmodulin signaling that alters CREB
  - Later desensitization of 5HT2 receptors in hypothalamus eventually decreases 5HT inhibition of NE release
  - Increased NE/epinephrine promotes bone resorption
    - Predominates over osteoclast inhibition
- Propranolol reverses catecholamine effects on bone and prevents bone loss in mice

MJ Ortuno et al: Nature Medicine doi:10.1038/nm.4166

Depression and CHD

- Depression increases risk of later
  - CHD: RR 1.7-2.1
  - MI: RR 2.1
  - CHD mortality: RR 2.7-3.9
- Risk greatest in men and older patients
- 20% of CHD patients meet criteria for major depression
- 45% of post-MI patients have significant depressive symptoms

W. Jiang et al: Am Heart J 2005;150:871

Depression and CHD

- Depression increases six-month cardiac mortality five times
- Major depression increases 18-month mortality after MI seven-fold
- Depressive symptoms without diagnosis of depression increase 18-month post MI mortality six-fold
- Two-year mortality following CABG six times greater in depressed versus non-depressed patients
- Treatment of depression may decrease mortality

W. Jiang et al: Am Heart J 2005;150:871

Effects of Depression Treatment on Cardiac Outcome

- ENRICHD
  - Patients with acute MI randomized to
    - Usual care
    - CBT for six months with or without antidepressant
      - Clinical decision
      - Usually sertraline, sometimes another SSRI or NOR
  - At study onset
    - 39% depressed
    - 26% low perceived social support
    - 34% both
    - 4.8% of depressed patients were taking antidepressants
  - At follow-up
    - 21-28% of depressed patients received antidepressants
    - Adjusted HR with antidepressants for recurrent MI or death from any cause .57-.63

SSRIs and Heart Failure/CHD

- SADHEART study found no benefit of sertraline
- More recent German study randomized 372 patients with significant heart failure to placebo or 10-20 mg escitalopram
  - Planned for 24 months
  - Stopped at 18 months due to lack of efficacy
  - No difference between placebo and SSRI in all cause mortality, medical hospitalization, or depression
    - Patients were only mildly depressed to start with
    - An antidepressant that actually improved depression might improve compliance and adverse autonomic effects of depression
    - Authors recommend CBT + exercise/diet + adherence

CE Angermann et al: JAMA 2016;315:2683

Antidepressant Cardiovascular Effects

- Alpha 1 blockade can cause hypotension
  - TCAs
- NE, DA uptake inhibition and alpha 2 blockade can elevate blood pressure
  - TCAs
  - Venlafaxine, bupropion, ?duloxetine
  - Mirtazepine
- MAOIs are antihypertensives
- Variable effects of SRIs on platelet aggregation
- Antiplatelet effect of $5HT_2$ antagonists
- Anticholinergic and adrenergic effects increase heart rate
  - TCAs, paroxetine, bupropion, mirtazepine, some MAOIs
- Slowing of intraventricular conduction with TCAs
  - Next slide

TCAs and Cardiac Rhythm

- Type Ia antiarrhythmic effect can aggravate heart block
- CAST trials showed increased mortality with type Ia antiarrhythmics in attempt to prevent sudden death following MI
  - TCAs are type Ia antiarrhythmics
  - TCA overdose has cardiovascular effects
  - QT widening predicts toxicity > serum level
- EKGs recommended in children, elderly and patients with cardiac disease

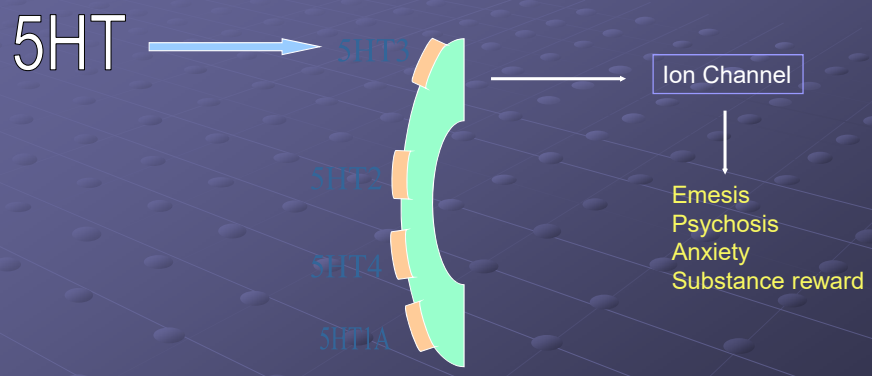
Initial Antidepressant Choices in Cardiac Disease

- SSRI
- $5HT_2$ antagonist
  - Nefazodone
  - Mirtazepine
  - Trazodone
- Bupropion
- Venlafaxine, duloxetine
  - Except in hypertension
- MAOI
- Artificial bright light
- Psychotherapy

Antidepressants and Chronic Pain

- SSRIs not reliably effective for chronic pain
  - 2D6 inhibition reduces conversion of codeine to morphine
- TCAs most effective for chronic pain
  - Additive effect with analgesics
- Nefazodone effective for fibromyalgia
  - Correction of sleep disorder
  - Mirtazepine, s-milnacepran could also be useful
- Duloxetine approved for neuropathic pain
- Venlafaxine reduces pain in animal and human laboratory experiments
- MAOIs useful for some patients
- Some opiates have antidepressant effects
  - Buprenorphine used as antidepressant in Europe
  - Illegal to use narcotics for depression in U.S.

$5HT_3$ Receptors



Antidepressants and Cancer

- Mirtazapine
  - Treats insomnia, weight loss nausea
    - Especially nausea, insomnia and depression with carcinoid
    - Chemotherapy-induced nausea
- Nefazodone
  - Useful for associated pain and insomnia
- Stimulant
  - Can increase energy
- SSRIs
  - May increase nausea
  - Theoretical risk in breast cancer responsive to prolactin
  - Do not use in carcinoid

TCAs, Paroxetine, and Breast Cancer

- Saskatchewan prescription data base
- 5887 cases, 23,517 controls
- Women with >10 years TCA/paroxetine exposure had OR 1.15-2.14 for breast cancer
  - Risk increased with higher total TCA dose
- Weaknesses
  - No controls for cancer risk factors (e.g., smoking, oral contraceptives) in TCA study
    - Controlled in paroxetine study
  - 30 separate statistical tests
    - 79% chance of false positive

Antidepressant Enhancement of Chemotherapy Response

- P-glycoprotein (MDR [ABCB1] genes) extrude chemotherapy drugs from cancer cells
- In resistant mouse tumor cells, fluoxetine
  - Increased accumulation of doxorubicin within tumors
  - Decreased drug efflux from cancer cells
  - Enhanced cytotoxicity of doxorubicin, mitomycin, vinblastine and paclitaxel
  - Improved tumor response 2-3 fold
  - Prolonged survival
  - Below threshold for toxicity
- Amitriptyline synergistic with TNF-alpha in reducing chemotherapy drug efflux from human colon cancer and mouse lymphoma cells

Peer D et al: Cancer Research 2004;64:7562; Varga A et al: Anticancer Research 1996;16:209

Risks of Antidepressants in the Elderly

- Cohort study of 60,746 patients ≥65 with new episode of depression in 570 practices
- 89% got at least one antidepressant prescription
  - SSRIs: 55%
  - TCAs: 32%
  - MAOIs: 0.2% (not analyzed further due to small N)
  - Other: 14%
    - Mirtazepine, venlafaxine
- Median duration of treatment 1 year

C Coupland et al: BMJ 2011;343:d4551 doi: 10.1136/bmj.d4551

Risks of Antidepressants in the Elderly

- All antidepressant classes had increased risk of
  - All cause mortality
  - Attempted suicide
  - Falls
  - Fractures
  - Upper GI bleeding
- One-year risk for all-cause mortality
  - No antidepressant: 7.04%
  - TCA: 8.12%
  - SSRIs: 10.61%
  - Other: 11.43%

C Coupland et al: BMJ 2011;343:d4551 doi: 10.1136/bmj.d4551

ECT

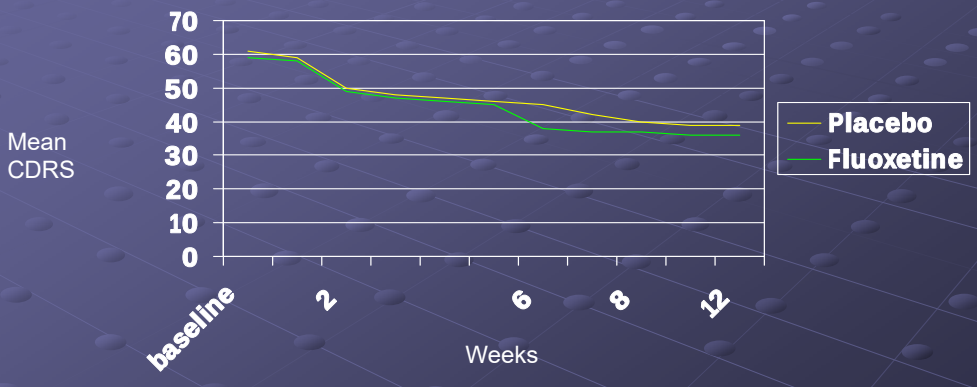
- Safe in most medical disorders
- Effective for delirium in 1-4 treatments
- Does not aggravate course of dementia
  - Greater acute confusion
- Effective in Parkinson's disease
  - Especially on-off phenomenon
- Safe following stroke
- Risk not absolute in brain tumor
- Not indicated in 6 months post-M.I.

Childhood Depression

How is Childhood Depression Different from Adult Depression?

- Irritability, anxiety, social dysfunction and behavioral problems more obvious than depressed mood
- Vegetative symptoms not as clear
  - More hypersomnia and lethargy
- More familial loading
- Greater impact of social factors
- Lower chance of antidepressant response
- Bipolar outcome more likely

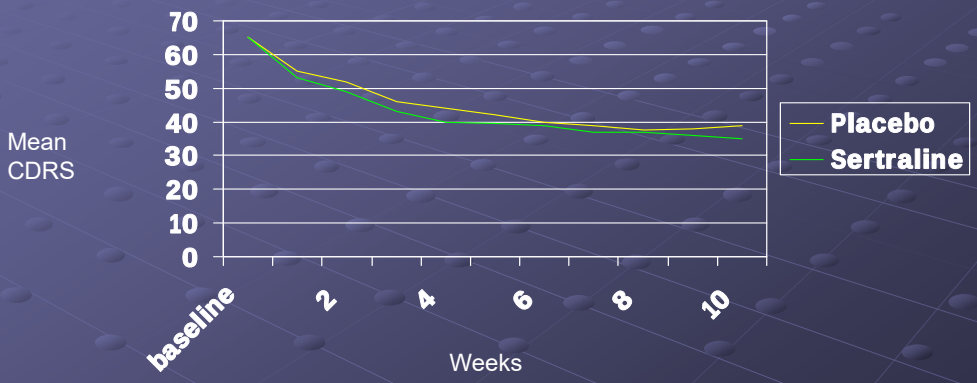
RCT of Fluoxetine in Childhood Depression



No difference in remission or self- or parent-rated depression ratings

NEJM 2004;351:1595-1598; CMAJ 2004;170:489-491

RCT of Sertraline in Childhood Depression



JAMA 2003;290:1033-1041

Industry Sponsored Studies of Antidepressants in Childhood Depression

- Seven industry sponsored RCTs of antidepressants in children
  - 464 patients took placebo and 477 fluoxetine, sertraline, paroxetine or venlafaxine
  - Of 42 outcome measures, 14 showed statistical advantage for antidepressant
    - None of 10 patient/parent reported measured improved significantly; only examiner ratings
  - Meta analysis of 5 SSRI studies showed effect size 0.26
- Average reduction in adolescent CDRS score 59 to 35 with fluoxetine versus 61 to 42 with placebo
  - Interpretation limited by very wide confidence intervals
- Positive studies for fluoxetine and sertraline
  - Improvement but not remission
  - Improvement with placebo 70% (fluoxetine) to 87% (sertraline) of improvement with active drug
  - Addition of unpublished data led to negative risk/benefit ratio for sertraline
- One small positive and one large negative study of citalopram
  - High dropout rate confounded results
- Three negative venlafaxine trials
  - Positive for adolescents when results stratified by age
- Paroxetine ineffective and increased suicidality and aggression
  - 7.5% hospitalized versus none on placebo (p=0.01)

Jureidini JN et al: BMJ 2004;328:879-883; Whttington CJ et al: Lancet 2004;363:1341-1345

Network Meta-Analysis of Antidepressants in Children and Adolescents

- 31 publications reporting 34 parallel RCTs
  - 5260 patients
  - Compared 14 antidepressants to placebo and/or another antidepressant
  - 7 trials unpublished
  - 2 trials not in English
  - Mean sample size 159
  - Mean age 13.6
  - Median trial duration 8 weeks
  - Antidepressants: fluoxetine, paroxetine, escitalopram, mirtazapine, duloxetine, nortriptyline, clomipramine, imipramine, desipramine, amitriptyline, nefazodone, venlafaxine
  - 22/34 studies industry sponsored
  - High risk of bias in 10 studies
    - Low risk in 4 studies

A Cipriani et al: Lancet 2016 doi:http://diagnosis.doi.org/10.1016/5-140-6736(16)30385-3

Network Antidepressant Meta-Analysis in Children and Adolescents

- Only fluoxetine was significantly > placebo
  - Mean difference in CDRS/HDRS score -0.51 (moderate effect size)
    - Large CI raises question whether this is meaningful
- Nortriptyline significantly < placebo and 7 other antidepressants
- Imipramine, venlafaxine, duloxetine significantly less well tolerated than placebo
- Venlafaxine had significantly more suicidal behavior or ideation than placebo, SSRIs, duloxetine and imipramine
- Most effective treatment: fluoxetine
- Least effective: nortriptyline
- Best tolerated: fluoxetine
- Least tolerated: imipramine
- Conclusions:
  - Use non-pharmacologic treatments first
  - If no response or not available, try fluoxetine first

A Cipriani et al: Lancet 2016 doi:http://diagnosis.doi.org/10.1016/5-140-6736(16)30385-3

Possible Reasons for Low Antidepressant Response Rate

- N's too small
- Children and adolescents grouped together
- Dosing not frequent enough
- Dose/level not high enough
- Symptoms more difficult to measure
- Very high placebo response rate (40-60%)
- Recent trials have recruited subjects who have symptoms but are not ill
  - Even higher placebo response rate
- Substantial influence of family stresses
- High rate of bipolarity
  - Number of patients who get worse = number who improve

Suicidal Ideation and Suicide in Children

- Ideation: 12% lifetime prevalence
  - Persists into adulthood
  - Predicts lifetime suicide attempts
    - 33% of ideators make an attempt within a year
  - Predicts adult mood/anxiety disorder
  - 60% of depressed adolescents
- Suicide rate age 5-14: 0.5-0.9/100,000
- Suicide rate age 15-24: 9.9-14.2/100,000
- 3% of adolescents make medically serious attempts
- Survey of adolescents grades 7-12:
  - 17% planned an attempt
  - 9% made an attempt
  - 3% made attempt requiring medical intervention
- Most common diagnoses associated with suicidality
  - Depression
  - Bipolar disorder
  - PTSD
  - Eating disorders
- <1/2 receive psychiatric treatment
  - Recent increase to 80%

Shain BN: Pediatrics 2007;120:669-676; Pelkonen M, Marttunen M: Paediatric Drugs 2003;5:243-265 ; MK Nock et al: JAMA Psychiatry doi: 10.100.1001/2013.jamapsychiatry55

Suicidality in Treatment of Adolescents with Depression (TADS) Study

- 12-week (short-term) and 9-month (long-term) phases
- Random assignment to placebo (short-term only), fluoxetine, CBT, or combined fluoxetine/CBT
- One-third had suicidality at baseline
  - Over 9 months, 10% made a suicide attempt
    - Usually in first few weeks
- All treatments reduced suicidality
- Fluoxetine most rapidly effective for depression
- Suicidality twice as likely with fluoxetine versus combination CBT/fluoxetine
- Secondary analysis showed more suicidality with fluoxetine versus placebo
  - NNH 50
- Study not designed to examine suicidality

Team: Arch Gen Psychiatry 2007;64:1132-1144

Warnings About Antidepressants in Children

- June 2003: GSK letter to all UK physicians advising against use of paroxetine in patients under age 18 because of increased hostility and suicidality
- June 2003: FDA recommended not using paroxetine in patients <age 18
- July 2003: UK Committee on Safety of Medicines warning against use of paroxetine in children
- August 2003: Wyeth warning about risks of venlafaxine in children
- December 2003: UK Committee on Safety of Medicines bans all SSRIs except fluoxetine in children
- October 2003: FDA public health advisory on use of antidepressants in children
- February 2005: FDA issues black box warning for antidepressants in children

FDA Meta Analysis

- FDA meta analysis of suicidality in childhood antidepressant trials (presented September 13-14, 2004)
  - Suicidality defined as spontaneous reporting or endorsement of one item on depression rating scale of
    - New suicide attempts
    - New suicidal ideation
    - Worsening of existing suicidal ideation
  - 4-16 week studies (N=24)
  - All but one study industry sponsored
  - Suicidality rate 1.8-2.19 times higher with antidepressants than placebo
    - 3.8% versus 2.1%
  - No increase in actual suicide
  - Risk mostly increased during first month of treatment, especially first 9 days

Newman TB: NEJM 2004;351:1595-1598; Benedetto V: NEJM 2004;350:1489-1491; Leon AC: J Clin Psychiatry 2004;65:915-918

Problems with FDA Meta Analysis

- Studies not designed to assess suicidality
- Duration of studies too short to assess risk realistically
- No correction for multiple statistical tests
- Placebo patients may have dropped out sooner
  - Before suicidality could be reported
- Only one study (TADS) had statistically increased risk of suicidality
- Reanalysis of data with additional studies indicated 0.7% greater risk with antidepressants
- Severely ill and suicidal patients excluded from studies

Do Antidepressants Really Contribute to Childhood Suicide?

- Suicide rate in adolescents age 15-19 decreased from 11.5/100,000 in 1989 to 8/1000,000 in 2001
  - Decrease is greater in areas where more antidepressant prescriptions written for adolescents
- In 58 suicides in people <18 years old, only 4 had detectable antidepressant levels
  - 15 adolescent suicides reported in UK from 1993-1999
    - None were taking antidepressants
  - Suggests juvenile suicide associated with *not* taking antidepressants

Newman TB: NEJM 2004;351:1595-1598; Benedetto V: NEJM 2004;350:1489-1491; Leon AC: J Clin Psychiatry 2004;65:915-918

Do Antidepressants Really Contribute to Childhood Suicide?

- Analysis of prescription data for patients aged 10-19 in 588 zip codes from 1990-2000
- Significant *negative* correlation between regional rates of antidepressant prescription and suicide rates
  - Adolescent suicide rate ↓ by 0.23/100,000 for every 1% increase in antidepressant prescriptions
  - Regions with more increases in antidepressant prescriptions had more decreases in suicide rates
  - More obvious in older adolescents and males
  - Not observed with TCAs
  - Suggests that antidepressants are prescribed more frequently in regions with more suicidal adolescents and that increasing antidepressant use reduces suicide rate in older adolescents

Olfson M et al: Arch Gen Psychiatry 2003;60:978-982

Autopsy Studies

- 49 completed youth suicides
  - 24% had been prescribed an antidepressant
  - None had antidepressant in body at autopsy
- 66 suicides < age 18
  - 3 had an antidepressant
  - None had paroxetine
- 36 adolescent suicides
  - 1 had antidepressants (sertraline + bupropion)

Gray et al 2003; Leon et al 2006

What if Suicidality With Antidepressants is a Real Phenomenon?

- Antidepressants prescribed as patient's mood is deteriorating
- Activation by antidepressant produces dysphoria
- Increased energy allows patient to report or act on thoughts that were present previously
  - Suicide risk traditionally reported to increase as patient improves
- Initial exacerbation of depression as antidepressant acts on noradrenergic systems eventually replaced by improvement with down-regulation of same system
  - Anxiety (arousal) seems to increase suicidality in depression
  - Studies of time course of suicidal thoughts suggests that suicidal ideation decreases after 30-90 days
- Unrecognized bipolar depression made worse by antidepressant

Impact of Black Box Warning

- Pediatric antidepressant prescriptions decreased by 10%/year
- Antidepressant prescriptions for adults also decreased
- Rate of diagnosis of childhood depression by pediatricians and FPs decreased to pre-1999 levels
- No increase in nonpharmacologic therapies for depression
- Psychiatrists changed to atypical antipsychotics
- Suicide risk in 10-24 year olds increased from 6.78-7.32/100,000

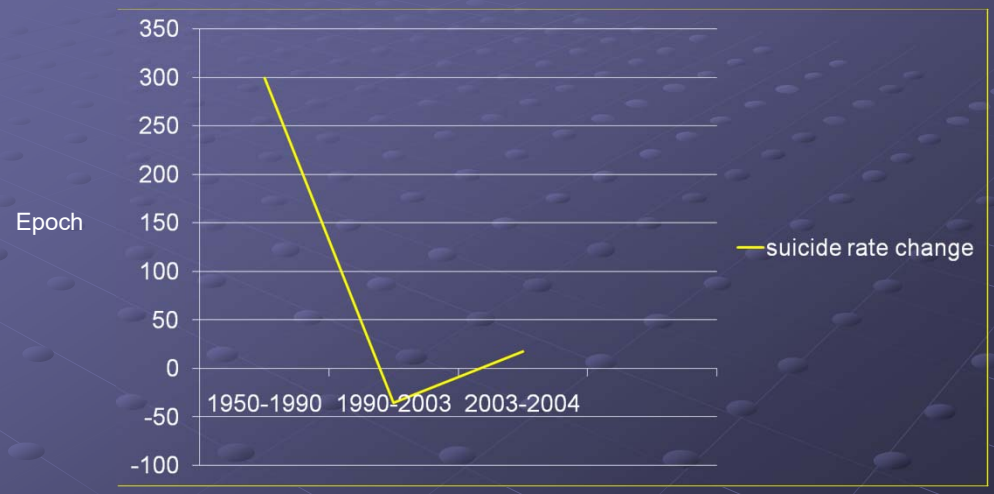
A Libby: Am J Psychiatry 2007;164:884-891

Persisting Effects of FDA Warning

- Medical claims data base from 1999-2007 for new episodes of depression in
  - Children (age 5-18): N=91,748 episodes
  - Young adults (age 19-24): N=70,311 episodes
  - Adults (25-89): N=630,748 episodes
- Rates of diagnosis of depression and prescription of antidepressants increased from 1999-2003 and then decreased from 2004-2007
  - 44% of predicted for children
  - 37% of predicted for young adults
  - 29% of predicted for adults
- Suicide rate increased
  - Adults: 13.94/100,000 in 2002; 16.88 in 2005

Libby AM: Arch Gen Psychiatry 2009:66:633-639

Changes in Suicide Rate By Epoch



Monitoring Recommendations

- FDA: see patients 7 times in first 3 months of treatment
  - Adhered to <5% of time
    - No increase after black box warning
- Consensus recommendation: see patients 3 times in first 3 months
  - Adhered to in 60% of children and 40% of adults
  - No change after warning

Implications of Pediatric Antidepressant/Suicidality Findings

- If suicidality increases, it will do so in first month and usually in first 9 days
- Examine carefully for bipolarity
- Monitor patient closely for positive and negative effects
- Not always necessary to stop antidepressant

Refractory Depression

Factors Associated with Treatment Resistance in Mood Disorders

- Long-standing symptoms
- Substance abuse
- Secondary mood disorders
- Double depression
- Psychotic depression
- Rapid cycling
- Character disorder

Risk of Chronicity- Unipolar Depression

- At episode onset: 10%-15%
- After 6 months of depression: 30%-40%
- After 1 year: 50%
- After 2 years: 95%

Risk of Relapse of Unipolar Depression

- With treatment: 10%-15%
- Without treatment: 40%-60%

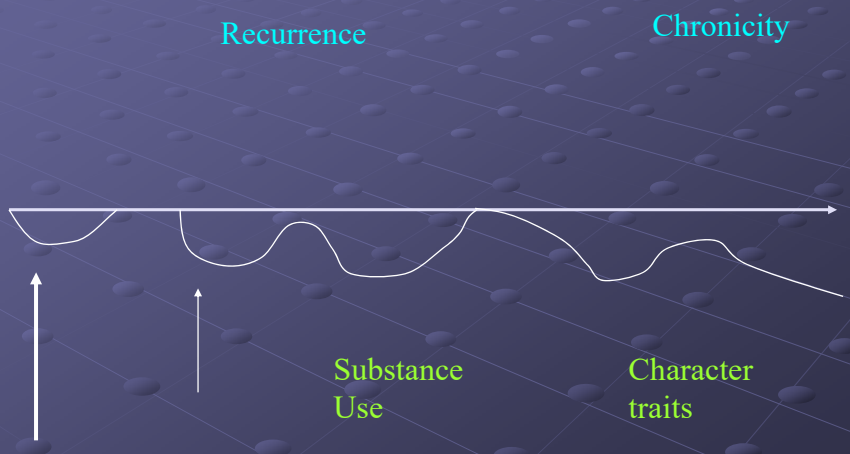
Risk of Recurrence of Unipolar Depression

- After first episode: ~50%
- After second episode: >70%
- After third episode: >80%
- After fourth episode: >90%

Average Number of Lifetime Affective Episodes

- Unipolar depression: 4
- Bipolar disorder: 8

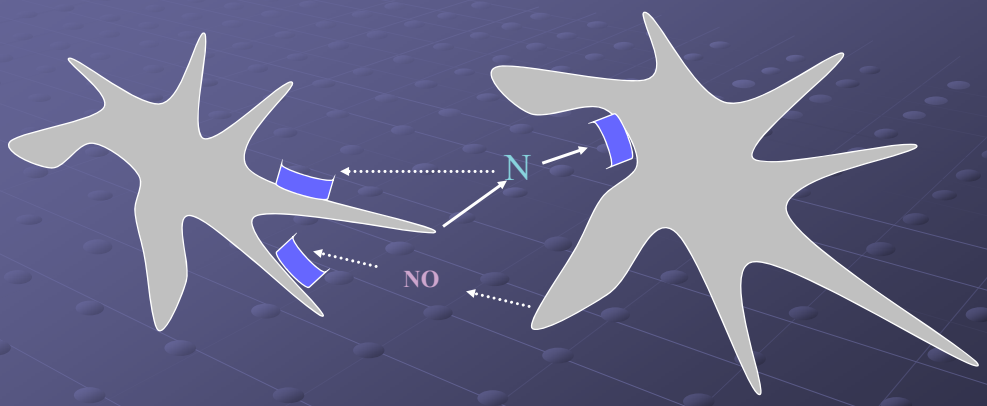
Evolution of Unipolar Mood Disorders



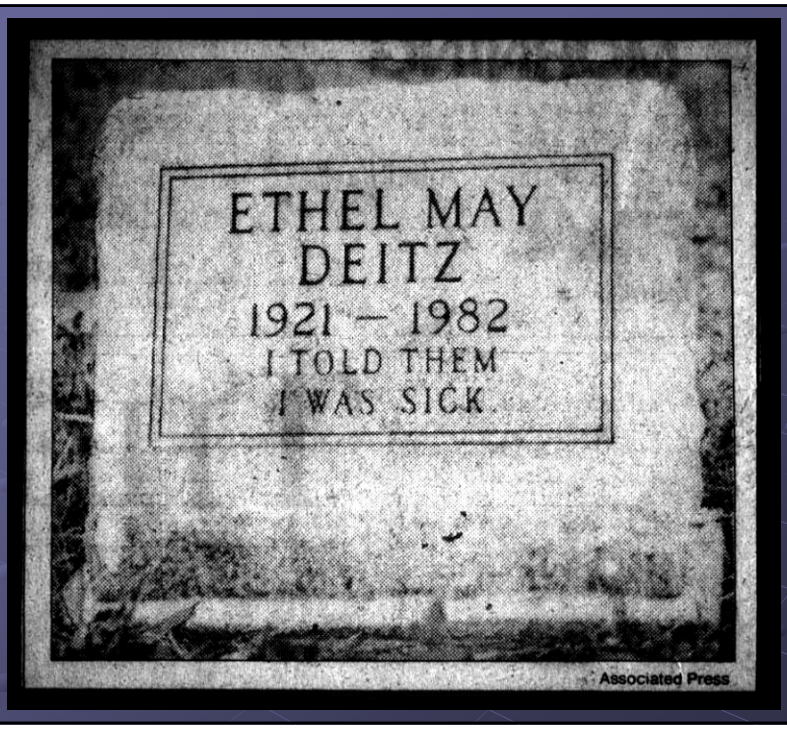
Physiology of Chronicity and Recurrence

- Synaptic homeostasis
  - Stability of well or ill state

Synaptic Homeostasis



Assessment of Failure to Respond to an Antidepressant



Questions to Ask About Poor Response to an Antidepressant

Are Symptoms Aggravated by a Medical Illness?

Illnesses that Commonly Aggravate Depression

- Hypothyroidism
  - Depression and thyroiditis
  - TRH stimulation test
- Anemia
- Hypercalcemia
- Viral disease
- TBI
- Cardiac disease

Questions to Ask About Poor Response to an Antidepressant

Are Medications Contributing to Depression?

Some Medications that Commonly Cause or Aggravate Depression

- Reserpine, methyldopa, propranolol, some CCBs
- Sedative hypnotics
- Benzodiazepines
- Interferon
- Antineoplastics
- Corticosteroids
- Progesterone
- Tamoxifen
- Disulfiram
- Isotretinoin

Oral Contraceptives and Depression

- Danish population study of 1,061,997 women mean age 24
  - Mean follow-up 6.4 years
  - 133,178 first antidepressant prescriptions over follow-up
  - 23,077 first diagnoses of depression
- Compared with women who did not use OCs, users had RR of
  - 1.2 for first use of antidepressant
    - 2.7 with medroxyprogesterone depot
    - 1.8 for combined OCs
    - 2.3 for progestin-only Ocs
  - Similar for first diagnoses of depression
  - RR of new antidepressant or depression diagnosis decreased with increasing age
    - Highest at age 15-19

CW Skovlund et al: JAMA Psychiatry 2016;73:1154-1162

Questions to Ask About Poor Response to an Antidepressant

What Substances is the Patient Using?

Substance Use

- High rate of comorbidity with mood disorders
  - Self-treatment
  - Sense of mastery
  - Common susceptibility factors
- Most substances aggravate mood disorders
- Depression inhibits response to substance abuse treatment
- Alcohol and smoking lower medication levels
- Cocaine is a potent kindling agent
- Continued substance use indicates attachment to self-destructive motivation
- Substance may enhance delay discounting

Questions to Ask About Poor Response to an Antidepressant

Is the Regimen Sufficient?

Antidepressant Regimens

- Many physicians still under prescribe
- Blood levels only for IMI, DMI, NOR,?AMI
- Dosing of new antidepressants not necessarily straightforward
  - Late therapeutic window for fluoxetine
- Sustained release preparations may require divided dose
  - Interdose withdrawal with venlafaxine XR
- Some patients require >6-8 weeks to respond

Questions to Ask in Refractory Mood Disorders

Is the Patient Taking the Medication?

Nonadherence

50% of Patients

- Side effects
- Complicated regimens
- Cost and trouble of obtaining medications
- Need to continue medication in the absence of active symptoms

Nonadherence

- Fear of addiction
  - Return of symptoms with discontinuation mistaken for dependence
  - True fear is of dependence on physician and treatment
  - Needing help is a sign of weakness
- Medication is something the doctor does to the patient
- Fear of being controlled
- Desire not to let prescriber feel gratified

Questions to Ask About Poor Response to an Antidepressant

Is the Depression Psychotic?

Psychotic Depression

- Prevalence 15-45%
- Patient may neglect to mention or conceal symptoms
- 25% response rate to antidepressants alone
- 40% response rate to antipsychotic alone
- Excellent response to combination therapy or ECT
  - Unknown if mild or transient psychosis requires same treatment

Clues to Psychosis in Depressed Patients

- Severity
- Confusion
- Gross pseudodementia
- Idiosyncratic thought
- Dissociation without abuse
- Post-dexamethasone cortisol > 10
- REM latency < 20 minutes

Relationship Between Psychotic and Bipolar Depression

- Both have similar laboratory findings
  - DST nonsuppression in 70%
  - Post-dexamethasone cortisol >10
  - Sleep onset REMs
- Bipolar depression more frequently psychotic
  - Mood incongruent psychosis more common in bipolar disorder
- Psychotic depression in children and adolescents is frequently bipolar
  - Especially with hallucinations but not delusions

Questions to Ask About Poor Response to an Antidepressant

Is the Depression Bipolar?

Clues to Bipolarity in a Depressed Patient

- Early onset
- High rate of recurrence
  - Increased recurrences on antidepressants
- Abrupt onset
- Intense irritability
- Extreme interpersonal sensitivity
- Overstimulation in interactions

Clues to Bipolarity in a Depressed Patient

- Psychosis before age 50
  - Mood incongruent symptoms
  - Hallucinations without delusions
- Appearance and behavior not as bad as depression
- Severe depression without anhedonia
- Family history of mood disorder in 3 consecutive generations

Questions to Ask About Poor Response to an Antidepressant

Is the Patient Really Depressed?

Psychiatric Disorders that Mimic Depression

- Anxiety
- PTSD
- Schizophrenia
- Dementia
- Personality disorder
- Addiction

Questions to Ask About Poor Response to an Antidepressant

Am I Ignoring Psychotherapy?

Mindfulness-Based Cognitive Therapy

- Group treatment
- For patients who have recovered from a recurrent episode of major depression
- Emphasizes disengagement from dysphoria-activated depressogenic thinking
- Daily homework
- Includes daily yoga or meditation
- Guided body awareness exercises
- Strategies for responding to early signs of relapse
- 50% reduction in risk of relapse

ZV Segal et al: Arch Gen Psychiatry 2010;67:1256-1264

Slide 1

Mindfulness-Based Cognitive Therapy

- 160 adults with a recurrent episode of nonpsychotic unipolar depression
  - Treated with citalopram or sertraline
    - Nonresponders switched to venlafaxine or mirtazepine
  - 84 (53%) achieved remission
    - Half had stable remission: HRSD ≤ 7 for five months
    - Half had unstable remission: breakthrough episodes of HRSD 8-14
  - After 7 months of remission, patients randomized to 18 months of
    - Maintenance antidepressant
    - Discontinue antidepressant + 8 weekly sessions of MBCT
    - Discontinue antidepressant + placebo and clinical management

ZV Segal et al: Arch Gen Psychiatry 2010;67:1256-1264

Slide 2

Mindfulness-Based Cognitive Therapy

- For patients with unstable remission
  - Maintenance antidepressant and MBCT reduced relapse rate by 73%
  - Medication = MBCT
- For patients with stable remission
  - 50% relapse rate with placebo
  - No difference between placebo, antidepressant and MBCT

ZV Segal et al: Arch Gen Psychiatry 2010;67:1256-1264

Mindfulness-Based Cognitive Therapy

- Individual patient data meta-analysis of 9 studies of 1258 patients with full or partial remission of depression
  - Random assignment to TAU (including psychotherapy), or antidepressant versus manualized MBCT
  - 60-week follow-up
- Relapse rate 21% lower with MBCT vs all other treatments
  - 23% lower vs antidepressant
- More obvious results in patients with residual depressive symptoms at baseline
  - Greater risk of relapse with residual patients
- Mindfulness alters circuits for
  - Attention
  - Emotion
  - Self-relevant processing (DMN)
- Not clear exactly which features predict better result with MBCT
  - Possibly patients with more attention to negative cognitions and emotions

W Kuyken et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.0076

Complicated Grief

- 7% of bereaved people
- Additional symptoms
  - Difficulty functioning
  - Overvalued guilt
  - Conviction that happiness is impossible
  - Avoidance of reminders of loss
  - Suicidal thoughts
  - About 50% have comorbid depression
- Associated with
  - Chronicity
  - Increased suicide risk
  - Impairment
  - Cancer and cardiovascular disease

Slide 1

MK Shear et al: Jama Psychiatry doi:10.1001/jamapsychiatry.2016.0892

Complicated Grief

- Complicated grief treatment (CGT)
  - 16 week manualized therapy involving
    - Not avoiding grief
    - Goal setting
    - Involving a significant other
    - Review of lost relationship through
      - Pictures
      - Memories
      - Imagined conversations
- 20-week RCT of CGT
  - CGT/placebo
  - CGT/citalopram 40 mg
  - Citalopram/placebo
  - Placebo

Slide 2

MK Shear et al: Jama Psychiatry doi:10.1001/jamapsychiatry.2016.0892

Complicated Grief

- Results:
  - CGT significantly > citalopram for improvement of CG
    - NNT 3.6
  - Citalopram no > placebo for CG
  - Combining citalopram and CGT did not produce better results for CG
    - Depressive symptoms improved more with CGT/citalopram
- Consider at least principles of CGT for complicated grief
  - Add antidepressant only for comorbid MDE

MK Shear et al: Jama Psychiatry doi:10.1001/jamapsychiatry.2016.0892

Questions to Ask About Poor Response to an Antidepressant

Have I Involved the Patient's Family?

Family Factors

- Assortive mating
- Genetic and psychosocial risk to children
- Family may have information patient does not report
- Family may be allies or hindrances

Treatment Approaches

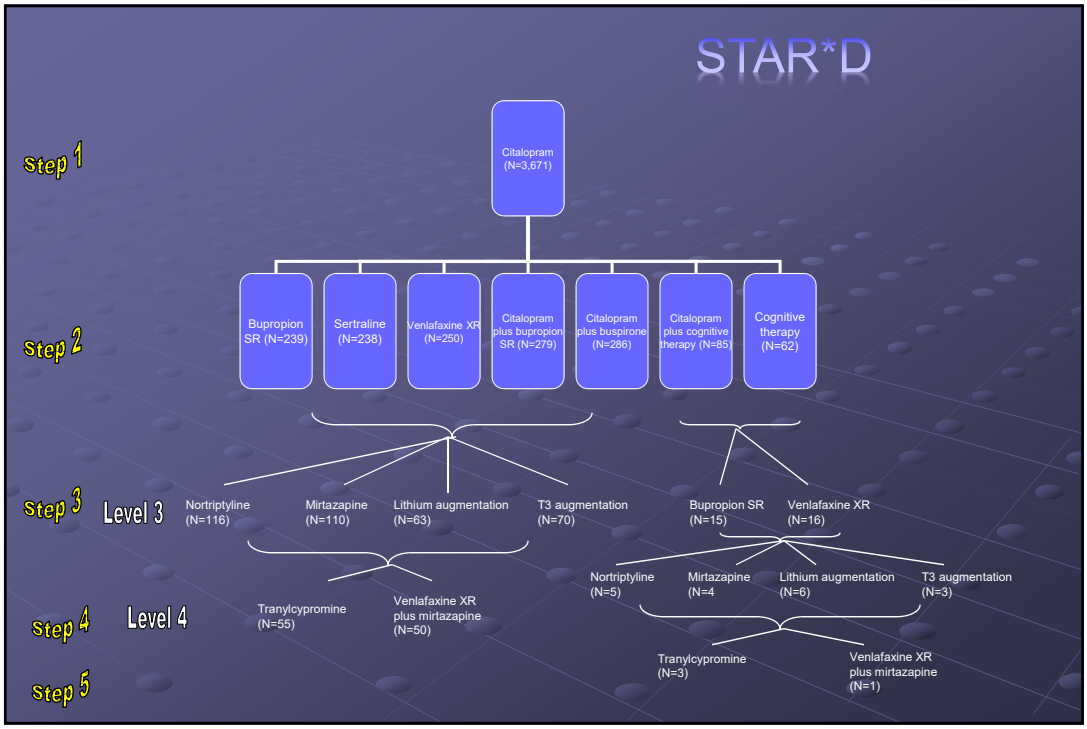
Treat Substance Use

- Antidepressants at best partially effective during active substance use
- Alcohol at bedtime disrupts sleep
  - Can worsen depression
- Wait 1-2 months after starting substance treatment or start both treatments concurrently
- Treatment of depression improves response to substance abuse therapy
  - It may be necessary to begin depression treatment while patient still uses substances
- Treating both improves long-term outcomes

TM Kelly et al: J Dual Diagnosis 2014;10:108; A Harnish et al: J Dual Diagnosis 2016;12:238-243; RE Drake et al: Schizophrenia Bull 2016;42:202

Augmentation Vs Medication Change

- No proven rationale for one over the other
- Augmentation may work better when there has been a partial response
- Changing antidepressants may be indicated when no response at all has occurred



STAR*D Findings

- Definitions
  - Response: 50% improvement in QIDS-SR16
  - Remission: QIDS-SR16 ≤ 5
    - Equivalent to HRSD17 ≤ 7
- Response rate in step 1: 47%
- Remission rates
  - Step 1: 37%
  - Step 2: 31%
  - Step 3: 14%
  - Step 4: 13%
- Dropouts after each intervention:
  - Step 1: 21%
  - Step 2: 30%
  - Step 3: 42%
- Remission and remaining well for 1 year
  - Step 1: 26%
  - Step 2: 14%
  - Step 3: 5%
  - Step 4: 3%

Rush AJ et al: Am J Psychiatry 2006;163:1905-1917; CR Conway, MS George: JAMA Psychiatry published online 10/26/16

STAR*D Findings

- Augmentation of citalopram equally effective with
  - Bupropion
  - Buspirone
  - CBT
  - Adding CBT slower to remission but better tolerated
- Switch from citalopram equally effective to
  - CBT
  - Sertraline
  - Bupropion
  - Venlafaxine
  - Equal speed of remission
- Relapse rates higher for patients with more treatment steps
- Relapse less likely if remission achieved at any step

Slide 2

Thase ME et al: Am J Psychiatry 2007;164:739-752

Augmentation Strategies in Unipolar Depression

- Lithium
- Buspirone
- Stimulant
- T3

Slide 1

Augmentation Strategies in Unipolar Depression

- Pindolol
- Dopamine agonist
  - Pramipexole
  - Bromocriptine
  - Pergolide
- Anticonvulsant
  - Carbamazepine
  - Gabapentin
  - Pregabalin
  - Lamotrigine
- Atypical antipsychotic drug
  - Useful for intractable nonpsychotic as well as psychotic depression

Folate and Methylfolate

- 33 patients with refractory depression compared with 16 controls
  - Not individually matched
  - Refractory=failure to respond to 3 antidepressant trials
    - Mean of 5 episodes
    - Longest episode duration > 1 year
- Cerebral folate deficiency (CFD) diagnosed in 12 patients
  - Normal serum folate
  - CSF 5-MTHF “low”
  - Caused by mutation of folate receptor gene or secondary to other metabolic changes
  - Methylfolate will not help because of decreased responsiveness of receptor

LA Pan et al: Am J Psychiatry doi:10.1176/appi.ajp.2016.15111500

Folate and Methylfolate

- All 12 CFD patients treated with folinic acid 1-2 mg/kg/day for 6 weeks
  - Added to ongoing antidepressant and other treatment
    - Changes to antidepressants also made
  - In 10/12 patients, average BDI decreased from 30.6-11 (p=0.022)
  - Suicidal rating decreased, but NS
- Even if deficiency of methylenetetrahydrofolate present, folinic acid is more stable and cheaper than L-methylfolate
- Problems with this study:
  - Open method
  - Nonrandom sample
  - No matching of controls
  - Other treatment changes beside folinic acid made during study

LA Pan et al: Am J Psychiatry doi:10.1176/appi.ajp.2016.15111500

Aripirprazole Augmentation

- Industry sponsored RCT
- Patients who had failed to respond to 1-3 antidepressant trials
  - 70% had failed one antidepressant trial
  - Substance abuse, severe treatment resistance, comorbidity excluded
- Phase 1: 7-28 days
  - 830 patients started, 651 completed, 266 responded
  - Antidepressants, anxiolytics discontinued
  - Patients who met criteria for MDE entered phase 2
- Phase 2: 8 weeks (N=381)
  - Patients given escitalopram (10 or 20 mg), fluoxetine (20 or 40 mg), paroxetine (37.5 or 50 mg), sertraline (100 or 150 mg), or venlafaxine (150 or 225 mg)
  - Single blind addition of placebo or aripiprazole
  - Patients who responded (N=) excluded
    - 50% ↓ in HAM-D OR
    - HAMD < 14 OR
    - CGI < 3
  - Patients who did not respond entered phase 3

RN Marcus et al: J Clin Psychopharmacol 2008;28:156–165

Aripirprazole Augmentation

- Phase 3 : 6 week, double-blind
  - Continue same antidepressant without dose adjustment + placebo or aripiprazole (mean dose 11 mg)
- Final MADRS reduction
  - Aripiprazole: 8.5
  - Placebo: 5.7
- Effect size .35 (clinically small)
- Response (HAM-D ↓ 50%)
  - Aripiprazole: 32.4%
  - Placebo: 17.4%
  - NNT 7
- Remission (not defined)
  - Aripiprazole: 25.4 %
  - Placebo: 15.2%
  - NNT=10
- NNT =5 (clinically important)

RN Marcus et al: J Clin Psychopharmacol 2008;28:156–165

Reduction in Total MADRS Scores

Aripiprazole Conclusions

- Some patients who are not severely treatment resistant may benefit from augmentation
- If 1/3 of patients had 50% decrease (13.3), the other 2/3 had decrease of 4.1 (15%)
- Higher antidepressant doses could have been equally effective
- Overall benefit modest
- No comparison with other augmenting agents
- Comparisons with STAR*D not justified because of different study populations and methods
- Results cannot be extrapolated to patients with
  - Severe, psychotic, bipolar, highly refractory depression
  - Failure to respond to multiple antidepressant trials
  - Comorbidity
  - Substance abuse
  - Significant suicidality

Details of Some Brexpiprazole Depression Augmentation Studies

6-week Open Label Previous Inadequate Response

Condition	From AD + Aripiprazole	From AD + Quetiapine	From AD	From Stimulant
N	12	10	31	6
MADRS ↓	12.8	18.4	19	17

8-Week DBPC Augmentation

Condition	AD + Brex	AD + P
N	188	191
MADRS ↓	8.27	5.15

8-Week DBPC Augmentation

Condition	AD + 1 mg Brex	AD + 3 mg Brex	AD + P
N	225	226	218
MADRS ↓	7.65	7.98	6.45 (NS)

Antidepressant Combinations

- TCA + SSRI
- Venlafaxine + Mirtazepine
- TCA/MAOI combinations discussed later

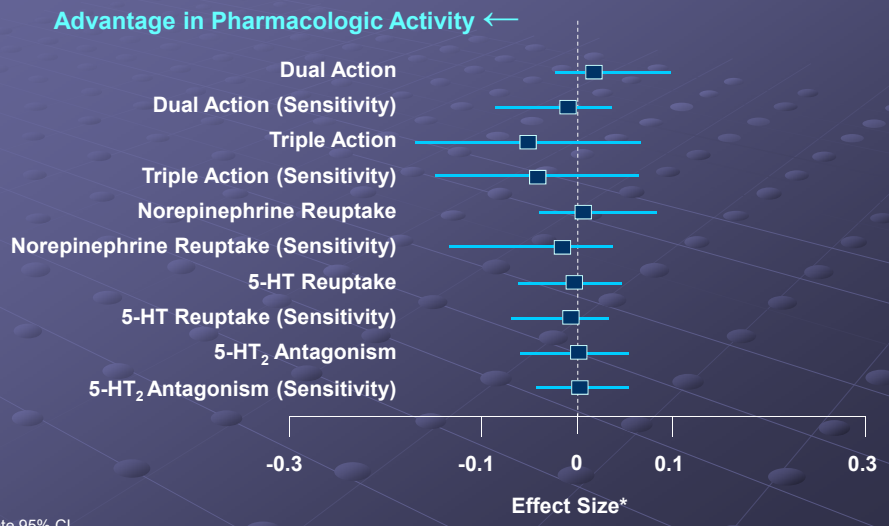
Combination Therapy in Unipolar Psychotic Depression

- Antipsychotic + antidepressant usually necessary
- 5HT2 antagonist antidepressant may reduce antipsychotic side effects
- High dose antipsychotic may be needed
  - 50-80 mg/day perphenazine
- Atypical antipsychotics may be advantageous
  - Antidepressant action
  - Lower risk of bradykinesia and TD
  - May be useful as monotherapy
    - Only loxapine shown to be effective by itself
- Best response to ECT

Changing Antidepressants

- No rationale for NE-5HT or SNRI switch
- Switching between SSRIs may work
- Try something with a different structure
- New antidepressants, MAOIs for specific indications

Predictive Value of Pharmacologic Activity for Relative Efficacy of Antidepressants



*Bars indicate 95% CI.
Adapted from Freemantle N, et al. *Br J Psychiatry*. 2000;177:292-302.

Newer and Alternative Antidepressants

Duloxetine

- Serotonin and norepinephrine reuptake inhibition both occur at low doses
  - Significance of neurotransmitter reuptake inhibition unclear
- Probably lower hypertension risk at high doses than venlafaxine
- No direct comparisons or controlled studies in refractory depression

Desvenlafaxine

- Active metabolite of venlafaxine
  - Venlafaxine is prodrug
- Blocks reuptake of NE, 5HT, DA
- Elimination half-life 9-10 hours
- 8-week multicenter trial in Europe and South Africa
- Random assignment to DV 200 mg, DV 400 mg or placebo
- Excluded patients with suicidality, bipolarity, other Axis I or medical/neurological illnesses
- 25% dropout rate

Septien-Velez L et al: Int Clin Psychopharmacol 2007;22:338-347

Desvenlafaxine

- Baseline HRSD 25
- HRSD decreased to
  - 12: DV 200 mg
  - 13: DV 400 mg
  - 16: Placebo
- Response rates;
  - 60%: DV 200 mg
  - 56%: DV 400 mg
  - 38%: Placebo
- More nausea, increased b.p., increased LFTs, and increased cholesterol with DV
- Sexual dysfunction 5-15% suggests inadequate reporting

Septien-Velez L et al: Int Clin Psychopharmacol 2007;22:338-347

Vilazodone (Viibryd)

- Indolealkyl/phenylpiperazine structure
- $5HT_{1A}$ partial agonist + SSRI
- Both anxiolytic and anxiogenic effects reported in rodent studies
- Similar to fluoxetine in rodent forced swim test, but only at moderate doses
  - Therapeutic window suggested
- No better than placebo in Phase II studies of 1163 depressed patients
- Significantly better than placebo in 410 patients with MDD in Phase III study
- Potent REM suppressor
- Common side effects: diarrhea, nausea, somnolence, dizziness

LA Dawson, JM Watson: CNS Neuroscience & Neurotherapeutics 2009;15:107-117

S-Milnacipran (Savella)

- SNRI
- Approved for fibromyalgia
- Also useful for diabetic neuropathy and depression
- Dose 2.5-100 mg BID
- Minimal sedation or weight gain

Vortioxetine (Trintellix)

- Multiple neurotransmitter/receptor actions
  - SRI
  - Antagonist: 5HT3A, 5HT7, 5HT1D, Beta-1
  - Agonist: 5HT1A
  - Partial agonist: 5HT1B
- Metabolized by CYP 2B6, 2D6, 2C8, 9, 19, 3A4/5
- Long half-life
  - Once daily dosing
- 5, 10 and 20 mg tablets
  - 20 mg probably > 10 mg
- No cardiac effects, weight gain or apparent psychomotor impairment
- Claim of cognitive improvement questionable
  - Improved processing speed

Vortioxetine (Trintellix)

- 8-week trial of 1, 5 and 10 mg in MDD
  - HDRS decrease greater with 10 mg than placebo
  - No correction for multiple comparisons
  - No difference in disability
- 5 mg in MDD
  - No difference from placebo
- 6-week study of MDD
  - Venlafaxine and vortioxetine 5 and 10 mg > placebo
- 8-week study of MDD
  - No difference from placebo with duloxetine or vortioxetine 5 and 10 mg
- 8-week study of MDD
  - Duloxetine > placebo
  - Vortioxetine 5 and 10 mg not > placebo
- Of 3 unpublished studies in MDD, 1 demonstrated benefit of 20 mg but not 10 mg; the other two indicated no benefit
- Two maintenance studies suggest benefit

Dubovsky SL: Expert Opin Drug Metab Toxicol. 2014 May;10(5):759-66

Indications for MAOIs in Depressed Patients

- Anxiety
- Mood reactivity
- Sensitivity to rejection
- Leaden paralysis
- Reverse vegetative symptoms
- ?Chronicity
- ?Character pathology

Using MAOIs

- Some traditional dietary restrictions unnecessary
- High doses may be necessary due to rapid metabolism
- Moclobemide has no dietary restrictions at moderate doses but does not work as well
- Selegiline patch may not require dietary restrictions at lower doses
  - Drug interactions may still occur
  - Small dosage adjustments easier with tablet
  - Oral selegiline often necessary at doses of 20-50 mg/day

MAOI-SRI Interactions

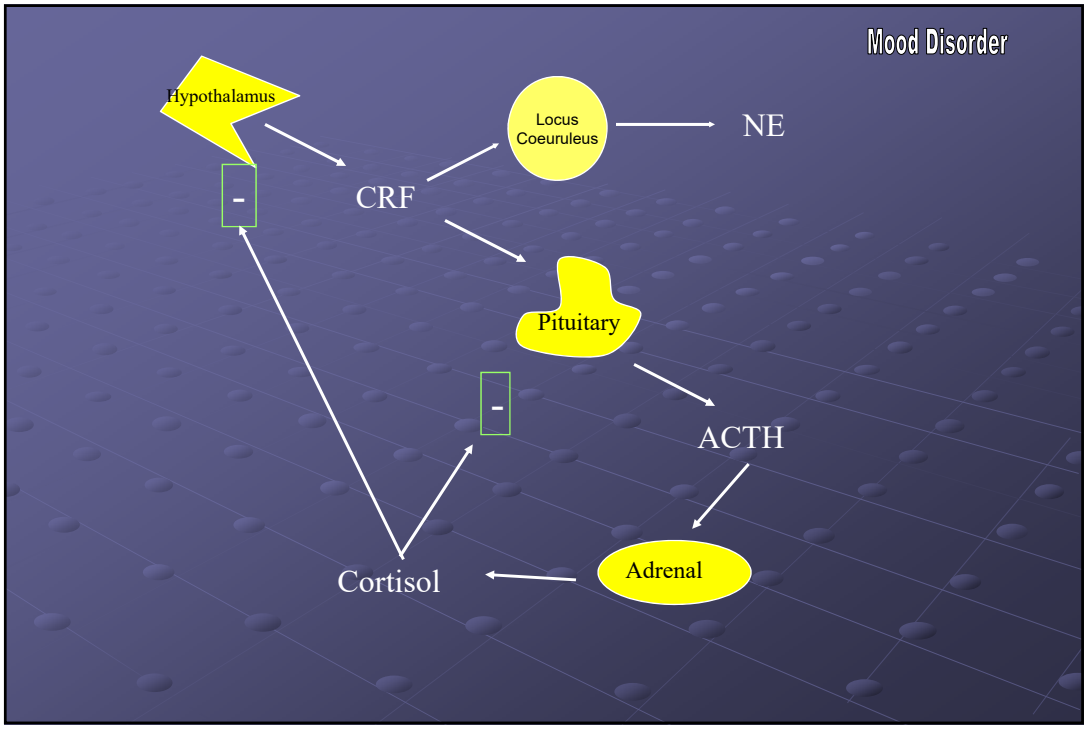
- Agitation
- Fever
- Tremor
- Myoclonus
- Confusion
- Seizures
- Cardiac arrhythmias
- Coma

MAOI-TCA Combinations

- DON'T use serotonergic antidepressants or bupropion
  - Avoid IMI, CLO, SSRI, VEN, NEFAZ, DUL, MIRT
  - TRAZ, AMI, other TCAs OK
- Add the MAOI to the TCA or start both together
- Start with low doses
- Increase doses gradually

MAOI-TCA-Stimulant Combinations

- One published report
- Can be effective in ECT resistance
- Stimulant can reduce postural hypotension and sedation



Antidepressants and the HPA Axis

- Therapeutic action of antidepressants correlated with decreased CSF CRF
- Depression may be mediated by CRF-1 receptors in limbic structures
- CRF-1 antagonists inhibit deleterious effect of stress on neurogenesis

G Racagni, Popoli M: Int Clin Psychopharmacology 2010;28:117

Cortisol Synthesis Inhibitors

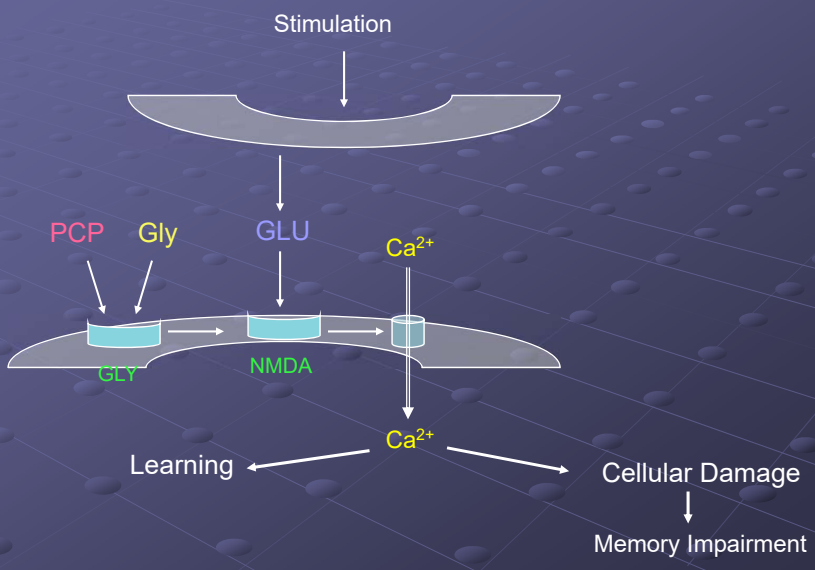
- Ketoconazole improved depression in patients with elevated cortisol
- Metyrapone vs placebo in augmenting SSRI
  - 56 moderately depressed patients
  - 3 weeks double-blind combination of placebo or 1 gm/day metyrapone to fluvoxamine or nefazodone
  - Antidepressant continued for 2 more weeks
  - More metyrapone augmentation patients responded at 5 weeks
- Dangerous side effects at doses that suppress cortisol synthesis
- Could be useful for toxicity of hypercortisolemia

Cortisol Antagonists

- Mifepristone (RU486)
  - Progesterone receptor and glucocorticoid receptor II (GR-II) antagonist
  - Multicenter industry-sponsored study of psychotic depression (N=221)
  - No treatment for 7 days, followed by:
    - Random assignment to placebo or 600 mg/day mifepristone for 7 days, followed by
      - 3 weeks of antidepressant and/or antipsychotic drug
  - More mifepristone patients had 50% decrease in psychosis
  - No difference in depression score changes
  - Benefit maintained at 3 and 7 weeks but patients treated with antidepressants at those times
  - Patients not severely depressed
  - No long-term data
- Improves spatial working memory in bipolar depression

DeBattista C et al: Biol Psychiatry 2006:60:1343-1349; S Watson et al: Biol Psychiatry 2012;72:943-949

Excitatory Amino Acid Transmission



Ketamine

- Known actions
  - NMDAR antagonism
  - Nicotinic and muscarinic cholinergic receptor antagonism
  - Inhibition of GSK3β
  - Increased DA and NE release in bed nucleus of stria terminalis
  - μ-opioid binding
    - Antidepressant effect blocked by oral naltrexone
  - Increased BDNF synthesis
  - Activation of mTOR
- Single IV dose for MDD produces rapid antidepressant response
  - Peaks in 24 hours
  - O.R. in controlled studies 7.55
  - Gone in 3 days
- Normalization of connectivity between insula/occipital cortex and DMN correlated with rapid antidepressant effect

Dubovsky SL: Psychother Psychosom 2018;87:129–13

Ketamine

- Review of 12 studies in unipolar depression and 7 in bipolar depression
  - 61% response rate in 24 hours
- Single IV dose of ketamine significantly > IV midazolam for suicidality (ES 0.75)
  - No > midazolam for depression ratings
- In systematic review and meta analysis
  - O.R. for continued response 1 week after single IV dose
    - 4.72 for unipolar depression
      - Only in 1/3 of studies
    - NS for bipolar depression
- Treatment resistance defined as failure to respond to 1-2 antidepressants in most studies
- Optimal dose not known
- No guidelines for ongoing treatment

Dubovsky SL: Psychother Psychosom 2018;87:129–13

Ketamine

- Ketamine alone IV produced antidepressant effect
  - Peaks within 1 day
  - O.R. for remission/response 7.55-14.47
  - Rapid reduction of suicidal ideation
  - Response lasted up to 2 weeks
    - Decreases rapidly within 1 week; <1 week in bipolar depression with augmentation of mood stabilizer
  - No significant effect of intranasal ketamine monotherapy
- Psychotic and dissociative side effects
- Ketamine maintenance
  - 3 days/week at lower dose ketamine for 2 weeks
  - Sustained response for 3 weeks after end of treatment
  - One patient had sustained remission for 3 months
- Ketamine augmentation of ECT (5 studies)
  - Ketamine used instead of or in addition to standard anesthetic
  - Longer seizure
  - Greater improvement after first ECT but not at end of course of ECT
  - Response the same for ECT with and without ketamine
  - Post-ECT disorientation and restlessness twice as common with ketamine
  - More hypertension with ketamine
    - Eliminated with addition of propofol

JW Murrough: Clin Pharmacol Ther 2012;91:303; DJ Newport et al: Am J Psychiatry 2015;172:950-966; MS Lener et al: Biol Psychiatry doi:http://diagnosis.doi.org/10/1016/j.biopsych.2016.05.005

Ketamine and Opioid Receptors

- Pre-treatment with naltrexone blocks antidepressant but not dissociative effects of IV ketamine
  - 12 patient crossover DBPC study
- Antidepressant effect may require NMDA and opioid receptor activation
  - Kappa receptors more relevant for mood
- Could repetitive treatment with ketamine increase risk of opioid abuse?

NR Williams et al: Am J Psychiatry 2018;175:1205; MS George: Am J Psychiatry 2018;175:1157

Assessment of Ketamine Data

- Hailed as “the most important breakthrough in antidepressant treatment in decades”
- “Truly alarming is the rapid proliferation of off-label ketamine administration in the absence of evidence of lasting therapeutic benefit or safety with long-term administration”
- Statements of efficacy and safety “illustrate the ostensibly cavalier nature of current clinical practice with ketamine in some quarters”

DJ Newport et al: Depression and Anxiety 2016;33:685-8

Ketamine Conclusions

- Summary of research
  - Apparent preferential benefit of ketamine may reflect actions other than NMDA receptor effects
    - Also affects phosphorylation of eukaryotic elongation factor 2 (eEf2), BDNF synthesis, activation of mTOR?
    - Potentiates AMPA receptors
    - Improves GABA signaling
  - No placebo response in studies of ketamine for TRD
    - Response rate to midazolam control 28% vs 64% for ketamine
  - Longest reported duration of treatment 6 weeks
    - Relapse rate within one month of serial ketamine infusions up to 89%
  - No additional benefit as anesthesia for ECT
  - Not a substitute for ECT
    - 90% relapse 4 weeks after repeated infusions
  - No data on chronic treatment
  - May be neurotoxic
    - Especially after chronic treatment
    - Not known if less of a problem with subanesthetic doses
  - Can be addicting
    - In Hong Kong, ketamine has replaced heroin as the primary drug of abuse
  - Antidepressant dose produced schizophrenia-like symptoms and attenuated ventral striatal reward response
  - Only use justified by current data is acute reduction of suicidality while waiting for ECT
    - Primary reason for ketamine clinics: financial
- Memantine
  - No benefit in three 8-week RCTs of monotherapy or augmentation

JW Murrough: Biol Psychiatry 2016;80:416C Zarate et al: Arch Gen Psychiatry 2006;63:856; DJ Newport et al: Am J Psychiatry 2015;172:950-966; DJ Newport et al: Depression and Anxiety 2016;33:688

Esketamine

- S-enantiomer of ketamine
- 3-4 times greater affinity than ketamine for NMDA receptor
- Industry sponsored studies highly restrictive
  - Treatment resistance: Failure to respond to 2 antidepressants
  - Chronic, severe, psychotic, bipolar, comorbid depression excluded
  - Suicide trials exclude patients without MDD

EJ Daly et al: JAMA Psychiatry doi: 10.1001/jamapsychiatry.2017.3739

Esketamine

- 67 patients with moderate-severe MDD refractory to at least 1 antidepressant (64%)
  - Two week random assignment to biweekly placebo or esketamine 28, 56, or 84 mg
    - Patients remained on antidepressant
  - Placebo patients who were still moderately-severely depressed re-randomized to placebo or esketamine for one week
  - Open label treatment for two months
    - Twice weekly, then once weekly
  - Follow-up for two months with no treatment
  - Higher ketamine doses consistently > placebo
  - Improvement maintained over 8 week observation without esketamine
  - Remission rate 45% at end of observation
- FDA submission for treatment-resistant depression

EJ Daly et al: JAMA Psychiatry doi: 10.1001/jamapsychiatry.2017.3739

Esketamine Acute Depression Study

- Treatment resistant depression= failure to respond to at least 2 antidepressants
- All studies compare addition of esketamine or placebo to ongoing antidepressant
  - No monotherapy studies
- Mean duration of current episode 111-118 weeks
  - 72-78% had received 1 or 2 antidepressants
- Baseline MADRS 37
- Inclusion: non-response to 1-5 antidepressants in current episode
- Exclusion: suicidality, psychosis, bipolar, personality disorder, OCD, SUD, nonresponse to ECT

Slide 1

V Popova et al: Am J Psychiatry 2019;176:428

Esketamine Acute Depression Study

- 3 phases:
  - 4-week open observation of response to current antidepressant
  - 4-week double-blind treatment with new antidepressant plus esketamine or placebo nasal spray
    - Escitalopram, sertraline, duloxetine, or venlafaxine XR
      - Sub-maximal doses of SNRIs
  - 6-month post-treatment follow-up
- Change from baseline-4 weeks double-blind treatment
  - Antidepressant + esketamine: -21.4; 69% responders
  - Antidepressant + placebo: -17; 52% responders
  - Difference: 4
  - NNT for response 6
  - Effect within 2 days
  - Effect size 0.30 (mild)
- The other 2 pivotal trials failed

Slide 2

V Popova et al: Am J Psychiatry 2019;176:428; J Kim et al: NEJM 2019;381:1-4

Questions About Acute Esketamine Trial

- Why not use as adjunct once or twice for 1-2 weeks rather than twice weekly for 4 weeks?
- Who should continue it?
- Why not just raise the antidepressant dose?
- Does esketamine work by itself?
- What should we do when it stops working?
  - Raise the dose?
  - Discontinue?

AF Schatzberg: Am J Psychiatry 2019;176:422-424

Esketamine Acute Suicidality Trial

- 66 patients (mean age 36) with MDD
  - Baseline MADS 38.6
  - All patients endorsed suicidality
    - 2/3 endorsed “severe” thoughts about suicide
- 4-week double blind treatment with antidepressant + esketamine 84 mg or placebo
  - 8-week follow-up
- Significantly greater MADRS decrease with esketamine on days 1-11 (effect size 0.65) but NOT at 4 week endpoint or 8-week f/U
  - Significantly greater decrease in suicidality after first dose (ES 0.67) but NOT 24 hours later or at 4 weeks
- Mild increased blood pressure and dissociation with esketamine

CM Canuso et al: Am J Psychiatry 2018;175:620-630

Esketamine Maintenance Study

- 455 patients with “TRD”
  - Failure to respond to ≥2 antidepressants for 4 weeks
    - ¾ did not respond to 1 or 2 antidepressants
- Patients randomized for 12 weeks to an antidepressant + esketamine or placebo twice weekly
  - Duloxetine, escitalopram, sertraline or venlafaxine XR
    - Low doses of venlafaxine and duloxetine
- Responders (↓MADRS≥50%) and remitters (MADRS≤12) re-randomized for 12 weeks to the same antidepressant + esketamine or placebo
- Relapse rates about twice as great with placebo vs esketamine
  - NNT 4-6
  - Patients still symptomatic
- Would raising the antidepressant dose or a different augmentation work as well or better?

EJ Daly et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.1189

Parameters of Esketamine Use

- Potential for abuse and diversion
- Patients must be observed for 2 hours after each dose
  - FDA only approved with risk evaluation and mitigation strategy (REMS)
    - Can only be distributed to REMS certified clinics
- Initial dose 56-84 mg twice weekly
  - Maintenance twice weekly to once every other week
- Major adverse effects
  - Transient increased blood pressure
    - Can be as high as 40 mm Hg
  - Dissociation
  - Sedation

J Kim et al: NEJM 2019;381:1-4

NMDA Agonists

- Sarcosine inhibits glycine transporter-1
  - Enhances NMDAR signaling
- Animal studies of sarcosine
  - Antidepressant-like effects in forced swim test, tail suspension test, novelty-suppressed feeding test, chronic unpredictable stress test in open maze
    - Similar to desipramine and citalopram
- Human study of 40 patients with MDE
  - Compared with 20-60 mg citalopram in 6-week double-blind study, significantly better
    - Reduction in HDRS scores (effect size 0.95)
    - Improvement of GAF (effect size 1.19)
    - Remission rate (effect size 0.63)

CC Huang et al: Biol Psychiatry 2013;74:734-741

Brexanolone

- Brexanolone is proprietary analogue of allopregnanolone
  - Neuroactive steroid positive allosteric modulator of GABA-A receptor
- Alloprenganolone levels increase during pregnancy and decrease postpartum
  - Can influence anxiety and depression in animals
  - Disruption of GABA-A signaling in animals can cause postpartum depression
    - GABA-A signaling may influence HPA axis
- Open label single dose study in 13 men and women with MDD
  - Baseline HDRS 27
    - Decreased by 20 the next day

H Gunduz-Bruce et al: Eur Neuropsychopharmaol 2017;27:S856-857; S Meltzer-Brody et al: Lancet 2018;392:1058-1070

Brexanolone

- Two concurrent phase 3 double-blind RCTs
- Manufacturer sponsored study, analyzed data, wrote article
- 60-hour infusion of placebo or brexanolone 90 µg/kg/h (study 2) or 60 µg/kg/h (study 1 and study 2)
- Patients followed for 30 days
- 375 women with postpartum depression screened
  - 138 enrolled
  - Mean age 27-28
  - Baseline HRSD 28-29 (study 1), 23 (study 2)
  - Exclusions: bipolar, psychosis, suicide attempt, substance use past 12 months, ECT planned
  - Despite depression being described as “moderate to severe,” “few would qualify or require inpatient care”

H Gunduz-Bruce et al: Eur Neuropsychopharmaol 2017;27:S856-857; S Meltzer-Bfody et al: Lancet 2018;392:1058-1070

Brexanolone

- Mean decrease in HDRS at end of infusion
  - Study 1: 17.7-19.5 brex versus 14 with placebo
  - Study 2: 14.6 brex versus 12.1 with placebo
- Mean decrease in HDRS at 30 days
  - Study 1: 19.5 brex versus 13.8 placebo
  - Study 2: 14.7 brex versus 15.2 placebo; brex > placebo only until day 7
- HDRS change in both studies similar in patients taking or not taking antidepressants
- Most common adverse effects: headache, dizziness, somnolence
- Weaknesses
  - Severe/complicated depression excluded
  - Benzodiazepine would be more meaningful control
  - What happens after 7-30 days?

H Gunduz-Bruce et al: Eur Neuropsychopharmaol 2017;27:S856-857; S Meltzer-Bfody et al: Lancet 2018;392:1058-1070

Botulinum Toxin A

- Injection to glabella
- Proposed mechanisms
  - Stop frowning and you'll feel better
  - Feedback through trigeminal nerve
- 30 depressed patients randomized to single injection
  - Botox then placebo 3 months later
    - HDRS-21 decreased 12.7 vs 0.4 at 6 weeks
  - Placebo then botox 3 months later
    - HDRS decreased 0.4 vs 8.4 at 6 weeks

M Magid et al: J Clin Psychiatry 2014;75:837

Botulinum Toxin A

- 250 depressed women assigned to 1 injection of
  - Botox 50 U
  - Placebo 50 U
  - Botox 30 U
  - Placebo 30 U
- Baseline MADRS 31-32
- No difference for 50 U
- 30 U: -12 vs -8

NCT02116361

Satisfied Customer

Psilocybin

- Rationale
  - Depression associated with excess activity of pro-inflammatory cytokines
  - Psilocybin is prodrug for psilocin (4-hydroxyl-dimethyltryptamine
    - 5HT2A agonist
    - Blocks TNF-α and normalizes fibrinolytic activity
      - Increased cleavage of pro-BDNF to BDNF
    - Normalizes medial PFC hyperactivity

RD Idell et al: Med Hypotheses 2017;100:46

Psilocybin

- Open-label feasibility study in 12 MDD patients
  - No placebo
  - 6 patients had HRSD 22-28
    - 17-19 in 6
  - No response to 2 antidepressant trials
    - Mean duration of depression 18 years
  - One low dose of psilocybin and one high dose 1 week later
    - Extensive psychological support during and after treatment
  - Psychedelic effects in all patients in 30 min-3 hours
  - 67% response rate at 1 week
    - Maximum decrease in QIDS scores in 2 weeks
    - 5/12 patients (42%) were improved after 3 months
      - Equals placebo response rate in major depression
  - Results could reflect increased suggestibility

RL Carhart-Harris Lancet Psychiatry 2016;3:619

Psilocybin

- Psilocybin and other psychedelics studied as adjuncts to psychotherapy, not monotherapy
- LSD and di-propyltryptamine (chemically similar to psilocybin) used for enhanced quality of life in terminal illness
  - Significant decrease in anxiety in small placebo controlled study
  - Reduction of alcohol and nicotine craving in small studies
- MDMA as adjunct to psychotherapy for treatment-resistant PTSD
  - 26 veterans, firemen or police officers
  - Phase 2 randomized trial
  - Random assignment to 3 doses of MDMA plus psychotherapy
    - Two 8-hour sessiions
    - The lowest dose was considered a control
    - Followed by open label crossover
    - Assessment 12 months after treatment
  - Combined with manualized psychotherapy
  - Greatest symptom reduction with intermediate dose
    - ES 2.1 for medium dose, 1.1 for high dose, compared with lowest dose
    - Crossover from lowest dose to higher doses produced additional improvement but not vice versa
  - AEs common

MC Mithoefer et al: Lancet Psychiatry 2016;3:481; MC Mithoefer et al: Lancet Psychiatry 2016;3:486

Instrumental Therapies

Artificial Bright Light

- Depression may involve desynchronization of circadian rhythms
  - Late dawn in winter affects master clock in suprachiasmatic nucleus to phase delay sleep relative to other rhythms
  - Early morning bright light phase advances sleep to resynchronize with other rhythms
    - Greater phase advance correlates with greater antidepressant effect
- Artificial bright light effective for
  - SAD
  - Depression in pregnancy
  - Nonseasonal depression
  - Benefit in first week
- Morning light for hypersomnia/sleep phase delay
- Later light may work for phase advanced sleep

S Dallaspezia. F Bemedetto: Expert Rev Neurother 2011;11:961-970

Artificial Bright Light

- Well established for SAD
- Nonseasonal, nonpsychotic, unipolar depression
  - 133 patients assigned to
    - 20 mg fluoxetine + 30 minutes bright light
    - 20 mg fluoxetine + inactive ion generator
    - Pill placebo + light
    - Placebo + ion generator
  - 8-week study
  - Fluoxetine + active light: ES 1.11
  - Active light: ES 0.80
  - Fluoxetine alone: NS
  - Combination but not either monotherapy significant for response (NNT 2.4) and remission (NNT 3.5)

RW Lam et al: JAMA Psychiatry 2015 doi:10.1001/jamapsychiatry.2015.2235

Sleep Deprivation

- 50-80% response to one night total sleep deprivation
  - Stay up all night and all day
- Relapse/rebound with recovery sleep or microsleep
  - Bright light and phase advancing sleep may reduce relapse
  - Combine with antidepressant
  - May make psychotic depression worse
  - Tricky in bipolar depression
    - Works better but can induce mania
- Sleep phase advance for 1-3 weeks may also treat depression

S Dallaspezia. F Benedetto: Ex[ert Rev Neurother 2011;11:961-970

Whole Body Hyperthermia (WBH)

- 6-week study of 29 MDD patients
  - Mean HDRS 20-22
  - Episode duration 100-126 months
  - Had 1 antidepressant
  - <1 previous episode
- WBH using lights and infrared coils
  - Increase core temperature to 38.5°C
  - 1 ½ hour treatment + 1 hour cool-down
  - Sham condition with only mild heating
- Significant reduction in HDRS with active not sham treatment
  - Present at 1 week
  - Lasted 6 weeks
- Heat activates regions that appreciate pleasurable warmth and are turned down in depression
  - Including pregenual anterior cingulate cortex (see DBS)

CW Janssen et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.1031

ECT in Refractory Depression

- Response rate if inadequate antidepressant trials: 90%
- Response rate in refractory depression: 50%
  - Treatment resistance a trait of patient
- Stimulus intensity 3-6 times seizure threshold for unipolar depression
  - Mainly necessary for unilateral placement
  - ?Lower stimulus intensity for bipolar
- Bilateral ECT, especially for bipolar depression

ECT in Refractory Depression

- Longer trial, with less frequent treatments
  - Confusion can aggravate or mimic depression
  - Twice weekly treatment works as well with less cognitive impairment
- Stop antidepressants
- Try again 6 months later

Mechanism of Action of ECT

- 10% increase in volume of hippocampus and amygdala
  - Normalization of shape and topography facilitates connections with DLPFC and other limbic structures
  - Increased volumes correlate with improvement of depression
- Smaller hippocampus predicts better response
- >80% increase in neurogenesis
  - Localized to relevant regions
    - No increase in total brain volume
      - Hippocampus volume is decreased in depression; increases with treatment
- Increased synapses

KRR Krishnan Biol Psychiatry 2016;79:264; SH Joshi et al: Biol Psychiatry 2016;79:282

FEAST

- Focal electrically administered seizure therapy
- Differences from ultrabrief pulse RUL
  - FEAST: unidirectional current
    - Other forms: bidirectional
  - FEAST: large posterior electrode anterior to right motor cortex; small anterior electrode over orbitofrontal cortex
    - Other forms: equal size electrodes; standard placements
- Purpose: Location of stimulus and current direction determine therapeutic and adverse effects
  - Inhibition greater at site of seizure initiation, not seizure propagation
  - Therapeutic effect of ECT related to prefrontal suppression of hyperactivity
  - Amnestic effect related to medial temporal lobe actions

GL Sahlem et al: J ECT 2016;32:197

FEAST

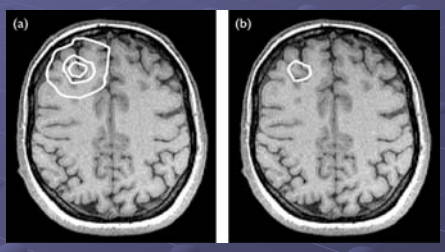
- Open-label study in 20 patients with MDE
  - 3 bipolar
  - Mean age 49
  - Average duration of current episode: 77 months
  - Average initial HRSD24: 37
- FEAST administered at 6-9 times seizure threshold
  - Mean # of treatments 9
- Mean improvement 58%
- 65% response; 55% remission
- 5 nonresponders to FEAST
  - 1 responded to RUL
  - No remissions
- No change in global cognitive status
  - No retrograde or anterograde amnesia
  - No autobiographical amnesia

GL Sahlem et al: J ECT 2016;32:197

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Induction of localized electrical current with focally applied magnetic field
- Can improve Parkinsonism
- Continued treatment necessary to prevent relapse
- Occasionally causes myoclonus and generalized seizures
- Mixed results of clinical trials
  - Slow rTMS unpredictable
  - Fast rTMS more likely to be effective

MEG after rTMS



Dipole density analysis of spontaneous slow wave focal magnetic brain activity before (a) and after (b) rTMS over the left prefrontal cortex. Iso-contour lines, representing magnetic activity, are projected onto respective cranial magnetic resonance tomography slices of the patient. Note the marked reduction of slow wave MEG activity over the DLPFC following rTMS treatment.
From: Maihofner: Neuroreport, Volume 16(16).November 7, 2005.1839-1842

Neurobiology of rTMS

- Tyrosine receptor kinase B (TrkB)
  - Receptor for BDNF
  - Expressed in brain, immune system
  - Promotes early gene expression, connections to NMDAR, LTP
- rTMS increases BDNF-TrkB signaling in cortex and lymphocytes
  - Increased TrkB affinity for BDNF
  - Increased plasma but not CNS BDNF levels
  - Increased cortical excitability
  - Enhanced synaptic plasticity
- Hypoactivity of left and hyperactivity of right DLPFC postulated
  - Slow (≤ 1 Hz) increases brain activity
  - Fast (≥ 10 Hz) decreases brain activity

H-Y Wang et al: J Neuroscience 2011;31:11044-11054

Sham Vs Real rTMS

- 190 patients randomized to 3 weeks of active or sham rTMS
- 14% remission with active versus 5% with sham
- 30% remitted with another 3 weeks of open label active treatment
- Average HDRS change not significant
- Average MADRS change statistically significant but not impressive
- Best response was in patients without much resistance to antidepressants
- No data on maintenance treatment

MS George et al: Arch Gen Psychiatry 2010;67:507-516

Additional Studies

- RCT of 301 patients
  - 20 sessions
  - No significant difference between active and sham
  - Effect size 0.26
- 3 week RCT in 64 patients
  - 15 treatments
    - 52 completed
  - Baseline MADRS=30
  - 1.79 failed antidepressant trials
  - Antidepressants continued
  - Effect size 0.49
  - 28% decrease in MADRS with active rTMS
  - Superiority to sham only evident for MADRS scores, not other depression measures
- Predictors of poor response to rTMS
  - Longer duration of depression
  - Failure to respond to >1 antidepressant
  - Comorbid anxiety disorder

C. Allan et al: Br J Psychiatry 2012;200:10; CK Loo et al: Br J Psychiatry 2012;200:52

Novel rTMS Methods

- Deep (H-coil) over left DLPFC
  - Stimulates deeper cortical/subcortical structures
- Theta-burst stimulation (TBS)
  - Inhibits (continuous) or stimulates (intermittent) left DLPFC
  - Short session duration (5 minutes)
- Low-field synchronized rTMS
  - Stimulation synchronized to patient's frequency
- Accelerated HF-rTMS: 4 or more fast sessions/day
- Priming LF-rTMS: Delivers fast rTMS to prime for slow left frontal rTMS

Brunoni AR et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3644

rTMS in Refractory Depression

- 68 patients with failure to respond to or inability to tolerate 2 antidepressant trials currently or in past
  - Average # antidepressants 1.46
    - Indicates intolerance main problem
- Patients not severely depressed
- 15 treatments with 10 Hz rTMS or sham rTMS
- Response rates
  - rTMS: 31%
  - Sham: 6%
- Remission rates
  - rTMS: 20%
  - Sham: 3%
- Effect size 0.58

Avery DH et al: Biol Psychiatry 2006;59:187-194

Meta Analysis of rTMS RCTs

- 81 studies
  - 4233 patients
    - Mean age 46
  - Most frequent comparison: fast rTMS versus sham
  - Most common method: treatment resistant depression with 10-15 rTMS sessions
- Only priming, bilateral, TBS and left frontal were > sham
  - Priming rTMS and bilateral rTMS > other methods

Brunoni AR et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3644

Meta Analysis of rTMS RCTs

- Deep, synchronized and accelerated rTMS no > sham
- All rTMS methods well tolerated
- Blinding was flawed in most studies
  - Unclear risk of bias
- Primary conclusion: bilateral rTMS should probably be first line intervention

Brunoni AR et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3644

Magnetic Seizure Therapy

- Transcranial magnetic stimulation used at intensity that induces seizure
- Magnetic stimulator that develops stimulus at 2-3 times seizure threshold
- Animal study showed
  - No neuropathological lesions
  - Astrocyte activation less than with ECT
- Fewer cognitive side effects and faster recovery than ECT
- Not enough clinical data

Kosel M et al: Neuropsychopharmacology 2003;28:2045-2048

Transcranial Direct Current Stimulation (tDCS)

- Low intensity DC current from anode over left DLPFC to cathode over right DLPFC
  - Anode stimulates cortical activity
  - Cathode decreases activity
  - ?Restore inter-hemispheric balance
- 120 MDD patients in RCT
  - 103 completed
  - Six week trial
    - tDCS: 12 sessions; 30 minutes each
    - 4 conditions:
      - Active tDCS + placebo (tDCS only)
      - Active tDCS + 50 mg sertraline (combination)
      - Sham tDCS + sertraline (sertraline only)
      - Sham tDCS + placebo (placebo only)

AR Brunoni et al: JAMA Psychiatry doi: 10.1001/2013.mamapsychiatry.32

Transcranial Direct Current Stimulation (tDCS)

- Baseline MADRS 31
  - Decreases after 6 weeks: combination>tDCS>sertraline=placebo
  - Melancholic and more severe depression responded better to tDCS
    - Benzodiazepines decreased response to tDCS
- Sertaline dose too low to draw conclusions
- No treatment resistance or chronicity
  - Median episode duration 3 months
  - Mean number of previous episodes 3
  - No bipolarity, psychosis or comorbidity other than anxiety

AR Brunoni et al: JAMA Psychiatry doi: 10.1001/2013.mamapsychiatry.32

Vagus Nerve Stimulation

- Physiologic effects
  - Stimulation affects afferent and efferent fibers
  - VNS enhances activity of
    - Thalamus
    - Ventromedial prefrontal and orbitofrontal cortex
  - Reduces recall of negative words but not positive or neutral words in depression
    - Could counteract negative recall bias in depression

VNS Acute Study

- 10-week randomized industry sponsored study
- VNS vs sham
- 222 patients with nonpsychotic depression
  - 25 bipolar
  - Mean duration current episode 49 weeks
  - Average 16 treatments before entering study
    - 54% had had ECT
  - Mean HRSD (24 item) 29
  - All patients taking concomitant medications
- HRSD response rates
  - VNS: 15%
  - Sham: 10%
  - P=NS
- No corrections for multiple comparisons in any analysis

Rush AJ et al: Biol Psychiatry 2005;58:347-354

VNS 12-Month Study

- 205 patients from acute trial got open VNS
  - 177 completers
  - VNS group got another 9 months of active treatment
  - Sham group got 12 months of active VNS
  - 95% also took multiple medications adjusted as needed
  - Mean baseline 24-item HRSD=28
- Average HRSD decrease=8.3
- Response rate 27%
- Remission rate (HRSD < 9)=16%
- 7 patients made suicide attempts

Rush AJ et al: Biol Psychiatry 2005;58:355-363

VNS 12-Month Comparison

- Patients in 12-month open VNS study compared with 124 patients in another study receiving various treatments
  - TAU group not randomized
    - More TAU patients had >10 prior episodes
- Mean decrease in HRSD
  - VNS: 8.3
  - TAU: 5.1
- Mean remission rate
  - VNS: 17%
  - TAU: 7%
- No correction for multiple comparisons

George MS et al: Biol Psychiatry 2005;58:364-373

Long-Term VNS Outcome in Pivotal Trial

- Responders (50% improvement)
  - Early responders: 15% (N=30)
  - Late responders: 20% (N=40)
  - Nonresponders: 65% of sample
- Maintenance of response at 12 months
  - Early responders: 63%
- Maintenance of response at 24 months
  - Early responders: 77%
  - Late responders: 65%
- Could be explained by medication changes
- Conclusion: VNS may keep helping the few patients it helps initially

Sackheim HA et al: Journal of Neuropsychopharmacology 2007; 10817-26

Transcutaneous VNS

- Vagus nerve is near skin at tragus of ear
- Two single-blind comparisons of active (tVNS) and sham (stVNS) treatment
  - Patients mildly-moderately depressed
  - stVNS: electrode on outer ear
  - Self-administered treatment
  - Twice a day, 5 times/week for 1 month
  - Single-blind protocol

J Fang et al: Biol Psychiatry 2016;79:266; J. Fang et al: Biol Psychiatry doi: http://dx.doi.org/10.1016/j.biopsych.2015.03.025

Transcutaneous VNS

- 34 patients with random assignment
  - tVNS produced significantly greater reduction of HRSD
    - Mean decrease 13.5
    - Correlated with reduced connectivity between DMN and limbic system
- 34 patients in similar protocol
  - Mean HRSD decrease 15 versus 6
  - Normalization of hyperactive connections between DMN and affect generating systems
- Normalization of DMN connections allows executive network to assess environmental and internal data without excess affective charge
- No studies of severe or refractory depression

Neuroanatomy of Depressed Mood

- Depressed/negative affect associated with hyperactivity of
  - Subgenual anterior cingulate cortex
  - Medial and dorsolateral PFC
  - Amygdala
- Mindful acceptance: acceptance of negative memories as events that no longer are part of present identity
  - Activates left PFC
    - Same occurs to lesser degree with analyzing reasons for negative emotions

E Koss et al: Biol Psychiatry 2009;65:361-366

Neuroanatomy of Depressed Mood

- Reappraisal of negative stimuli: alter meaning of situation to reduce its negative impact
  - Activates dorsomedial and dorsolateral PFC and orbitofrontal cortex
    - Reduces activation of amygdala
- Prefrontal regions can reduce hyperactivity of limbic system associated with negative/depressed mood
- Neurosurgical approaches aimed at hyperactive limbic system/prefrontal circuits

EM Drabant et al: Biol Psychiatry 2009;65:367-373; CS Carter Biol Psychiatry 2009;65:359-360

Cingulotomy for Depression

- Increased rCBF in rostral (anterior) cingulate cortex reported in depression
- Study of 13 patients with refractory depression receiving bilateral anterior cingulotomy
  - 11 unipolar
  - Mean preoperative BDI 44
  - All patients had trials of every antidepressant class with augmentation and ECT
  - Mean postoperative BDI 31
    - 4 patients had postoperative BDI = 0-6
  - Response more likely in patients with increased rCBF in left subgenual prefrontal cortex and left posterior thalamus

Dougherty DD et al: J Neurosurgery 2003;99:1010-1017

Lesion Location in Cingulotomy

- Retrospective review one-year postop of 8 patients
- Severe depression for average of 9 years
- Failed 11 antidepressant trials and ECT
- At review
  - Mean HRSD decreased by 50%
  - 3 patients remitted; 2 responded
- Higher likelihood of response with
  - Anterior lesion
  - Smaller lesion
- Lesions in hyperactive region of cingulate cortex (usually anterior) more likely to be effective
  - Extending lesion in case of nonresponse not helpful
  - Anterior placement or placement in area of demonstrated hyperactivity most efficient

Steele JD: Biol Psychiatry 2008;63:670-677

Stereotactic Subcaudate Tractotomy

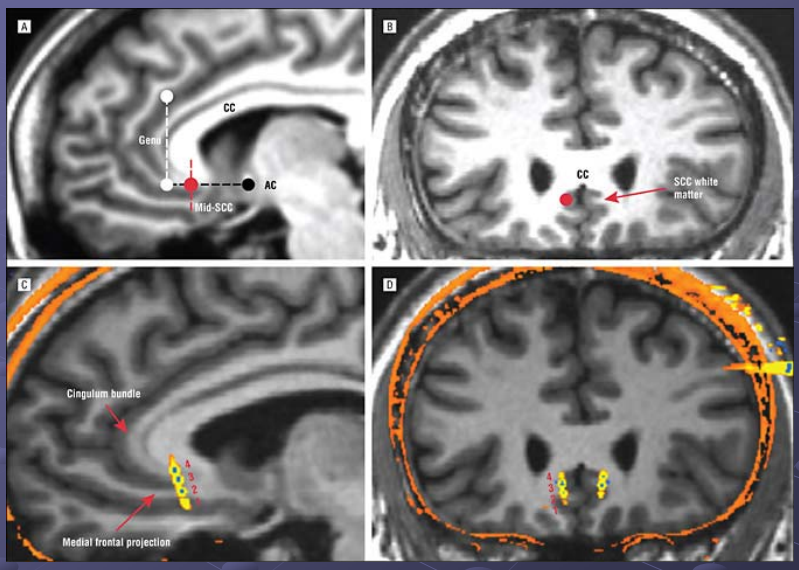
- Long term follow-up on 18 patients
- A few patients require no further treatment
- Affective episodes continue in the rest but less severe
- Mania better controlled than depression
- Complications:
  - Cognitive dysfunction
  - Psychosis

Deep Brain Stimulation for Depression

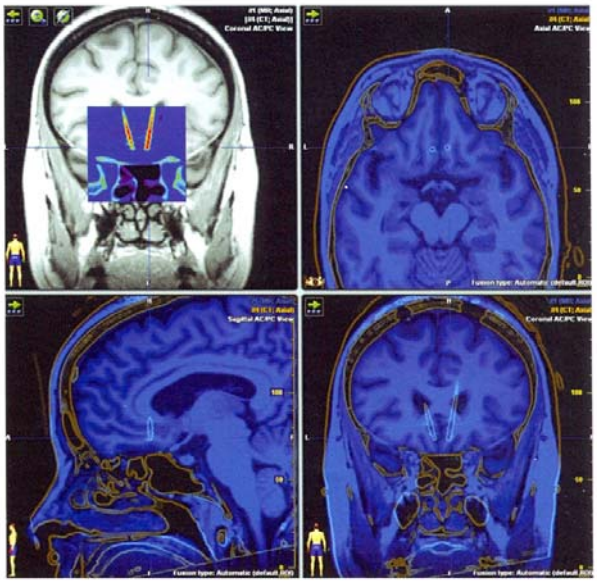
- Regional blood flow in subgenual cingulate gyrus found in some patients with treatment-resistant depression but not other forms of depression
- DBS increases BDNF signaling
- MRI guided electrode placement in this area in 6 patients with highly refractory depression allowed deep brain stimulation
- 4 patients responded; 2 had remissions
- Optimal electrode location not routinely studied with neuroimaging

Mayberg HS et al: Neuron 2005;45:1-10; C Hoyer et al: Neuropsychobiology 2012;63:147-152

DBS of Subcallosal Cingulate Cortex



PE Holtzheimer et al: Arch Gen Psychiatry 2012; doi:10.1001/archgenpsychiatry2011.1456



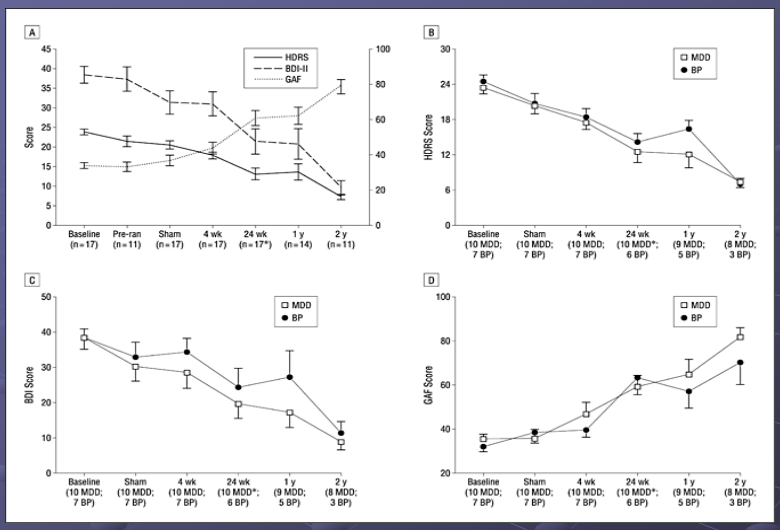
Preoperative T1-weighted MRI fused with the postoperative CT scan showing the position of the quadrapolar electrodes in the subcingulate gyrus.

Treatment-Resistant Unipolar and Bipolar Depression

- 10 patients with treatment resistant MDD, 7 with treatment resistant bipolar depression
  - All but 2 taking medications
    - Mean # of medications: 3
- Subcallosal cingulate DBS
- 4 week single blind sham stimulation
- 24 weeks open stimulation
- Attempt at single blind sham substitution
  - 3/3 patients relapsed, this phase discontinued
- 2 years open treatment
- Equal response in unipolar and bipolar
- Neurological A/Es rare
- 2 suicide attempts

PE Holtzheimer et al: Arch Gen Psychiatry doi:10.1001/archgenpsychiatry.2011.1456

Change in depression severity (left axis) and function (right axis) over time for the entire sample (A) and by diagnosis (B-D) With Subcallosal Cingulate DBS



Holtzheimer, P. E. et al. Arch Gen Psychiatry 2012;0:archgenpsychiatry.2011.1456v1-9.

Long-Term Follow-Up of DBS

- 20 patients followed for a mean of 42 months
  - Mean age: 47
  - Duration of current episode: 6.9 years
  - Lifetime number of episodes: 4
  - Failed multiple medications, ECT, psychotherapy
- Bilateral DBS of sucallosal cingulate gyrus
- Response rate (observed cases/intent to treat)
  - 1 year: 62%/55%
  - 2 years: 46%/45%
  - 3 years: 75%/60%
  - Last visit: 64%/55%

SH Kennedy et al: Am J Psychiatry 2011;168:502-510

Long-Term Follow-Up of DBS

- Remission rate (observed cases/intent to treat)
  - 1 year: 19%/20%
  - 2 years: 15%/20%
  - 3 years: 50%/40%
  - Last visit: 43%/35%
- Improved social, mental and physical functioning between baseline and last visit
- No difference between functioning at different follow-up points
- Decreased use of antidepressants
- Two suicides

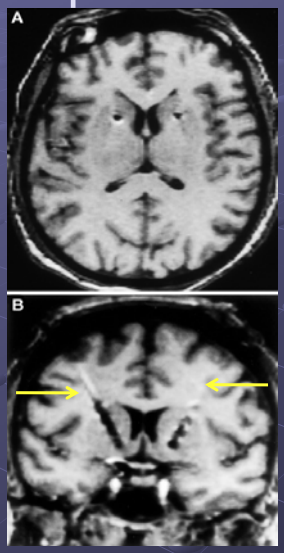
SH Kennedy et al: Am J Psychiatry 2011;168:502-510

Subcallosal Cingulate White Matter DBS Long-Term Outcome

- 28 patients
  - MDD or bipolar II
  - Mean age 45
  - At least 3 current antidepressant failures
  - First 8 years of data
- By year 1 HRSD scores decreased by 50%
- Over 8 years
  - Response rate 50%
  - Remission rate 30%
- CGI improved from 6.1 (severely ill) to <3 (mildly ill or better)
- 5 of 8 bipolar patients had good response
- Most patients needed antidepressants to maintain response

AL Crowell et al: Am J Psychiatry 2019;176:949

Electrode in Anterior Limb of Internal Capsule



DBS in Internal Capsule for Depression

- 15 patients with refractory depression
  - Illness duration 21 years
    - Current episode >2 years
  - Failed on
    - 6 trials of antidepressant monotherapy
    - 6 trials of augmentation
    - ECT
    - VNS (2 patients)
- DBS in ventral internal capsule/ventral striatum
- Mean symptom reduction at one year 42-46% (depending on rating scale used)
  - Response rate: 53%
  - Remission rate: 33-40%

D Malone et al: Biol Psychiatry 2009;65:267-275

Negative Controlled Studies

- Three RCTs in MDD demonstrated DBS no > sham
  - No intraoperative adjustment of electrode location or current flow
  - No target assignment based on PET
  - Lesion itself may have produced positive results in both groups
- DBS may be most effective targeted at domains of dysfunction, not total diagnosis
  - Different targets affect different domains
    - Classify responders according to
      - Neuroimaging findings
      - Biomarkers
      - Endophenotypes
    - Sucallosal cingulate for negative mood
    - MFB for anhedonia

AK Widge et al: Biol Psychiatry http://dx.doi.org/10.1016/j.biopsych.2015.06.005; PE Holtzheimer et al: Lancet Psychiatry 2017;4:839

Positive Controlled Study

- 25 patients with MDD
  - 15 years' duration
  - Failed 11 antidepressant trials + 2 ECT trials
- Electrodes bilaterally in ventral anterior limb of interior capsule
- Voltage and contacts adjusted for up to 52+ weeks during open label phase
  - Depression rating scale scores decreased significantly
  - 40% responded (half with remission)
  - 24% partial response (25-50% improvement)

IO Bergfeld et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.0152

Positive Controlled Study

- Followed by blinded assignment to real or sham DBS or reverse order in 9 responders and 7 nonresponders of initial 25 patients
- Depression scores significantly lower during “on” phase
  - Rapid relapse during “off” phase
  - Response restored by turning stimulation back on
- Flexible initial dosing and targeting stimulation differently for different patients is a more promising approach

IO Bergfeld et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.0152

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AL Crowell et al: Am J Psychiatry 2019;176:949

Psychological Issues

Conclusions

- Goal of treatment of any acute episode is elimination of all symptoms
  - Including social dysfunction
- Residual symptoms increase risk of relapse/recurrence
- No antidepressant appears uniformly superior
- Psychotherapy equivalent to antidepressants in some settings
  - Different target symptoms in other settings
- Complex forms of depression require complex treatment
- Refractory mood disorders are easier to prevent than treat
  - Neurobiology, genetics and psychology become more complex with recurrence
  - Treat depression vigorously and completely
  - Maintenance treatment same as acute treatment
  - Address reluctance to accept help
  - Address desire to reduce treatment when feeling better

Conclusions

- Refractory unipolar depression
  - Augment if some benefit
    - Antipsychotic drug for psychotic depression
  - Change medication if no benefit
  - Allow enough time for medication to work
  - Do not continue an ineffective treatment indefinitely
  - Do not withdraw an effective treatment
- Patients who continue to describe one symptom after another may be communicating in the only language they feel interests the prescriber

Conclusions

- Ketamine safety and long-term efficacy not established
- Esketamine promising but no data as monotherapy or in complex or truly refractory cases
- Benefit of brexanolone over benzodiazepine or duration >1 month not studied
- Esketamine and brexanolone
  - Require REMS
  - Are expensive
- DBS still looks promising but target needs more study

Conclusions

- If you insist on only hearing about symptoms, that is all the patient will tell you
- The psychology of mood disorders is as important in the clinician as the patient
- Maintain merciless introspection
  - Recognize negative feelings about patient
- Don't be unrealistic
- Keep trying!