

Mood Disorder

Depression and Substance abuse

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Outline To Presentation

- Epidemiology
 - Prevalence of depression
 - Prevalence of substance abuse (comorbid Substance abuse)
- Diagnosis of Depression
 - DSM IV diagnosis
 - Differential diagnosis of depression

Outline Of Presentation (cont)

- Management of depression
 - Psychotherapy vs.. Medical Management
 - When to refer a patient for medical management
- Medical management of depression
 - Classification of antidepressant
 - How to choose a Medical treatment
 - What is an adequate trial

Outline of presentation (cont)

- Side effect from medication
 - Class specific side effects
 - Drug specific side effects
 - Sexual side effects with SSRI's
- Does treatment of depression decrease the use of substance abuse
- Conclusions:
 - First line agent vs. second line agent.

Epidemiology of depression

| Mood Disorder | Life time prevalence |
|---|--|
| Depressive disorder | |
| 1. Major depressive d/o | 10 –25 % for women 5-12% for men |
| 2. Recurrent with full inter-episode recovery, superimposed on dysthymia disorder | App 3% of persons with MDD |
| 3. Recurrent without full inter-episode recovery, superimposed on dysthymia (double depression) | App 25% of persons with MDD |
| 4. Dysthymic disorder | App 6% |
| Bipolar disorder | |
| 1. Bipolar type I | 0.4 –1.6% |
| 2. Bipolar type II | App 0.5% |
| 3. Bipolar type II, with Rapid cycle | 5-15% of persons with bipolar disorder |
| 4. Cylothymic disorder | 0.4-1.0% |

Comorbidity

- Co-occurrence
 - Depression and Cocaine 33-53%
 - Depression and Opiates as high as 75%
 - Depression and ETOH 15-67%
- 98% of individuals presenting for the treatment of substance abuse have some features of depression (Jaffe and Ciranulo)

DSM IV Criteria For Major Depression

- Five or more of the following symptoms have been present during the same 2 week period and represent a change from the previous functioning; at least one of the symptoms either (1) depressed mood or (2) loss of interest or pleasure
 - **Note:** do not include symptoms that are clearly due to general medical condition, or mood-incongruent delusions or hallucinations.
 1. Depressed mood most of the day, nearly every day,
 2. Markedly diminished interest or pleasure in all or almost all, activities most of the day, nearly every day (as indicated by subjective account or observations by others)
 3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day.
 4. Insomnia or hypersomnia nearly every day
 5. Psychomotor retardation or agitation nearly everyday (observable by others not merely subjective feelings of restlessness or being slowed down).
 6. Fatigue or loss of energy nearly every day
 7. Feeling of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt being sick)
 - 7 Diminished ability to think or concentrate or indecisiveness, nearly every day (either by subjective feelings or as observed by others)
 - 8 Recurrent thoughts of death (not just fear of dying) recurrent suicidal ideation, without a specific plan or suicide attempt or a specific plan for committing suicide.

DSM IV Criteria For Major Depression (Cont)

- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The symptoms are not due to the direct physiological effects of a substance or a general medical condition.
- D. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by markedly functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

SIGECAPS

- Sleep disturbance
- Interest, loss of
- Guilt, excessive
- Energy, lack of
- Concentration, poor
- Appetite, increased or decreased
- Psychomotor, retardation or agitation
- Suicidal ideations, plan or intent

Substance Induced Mood Disorder

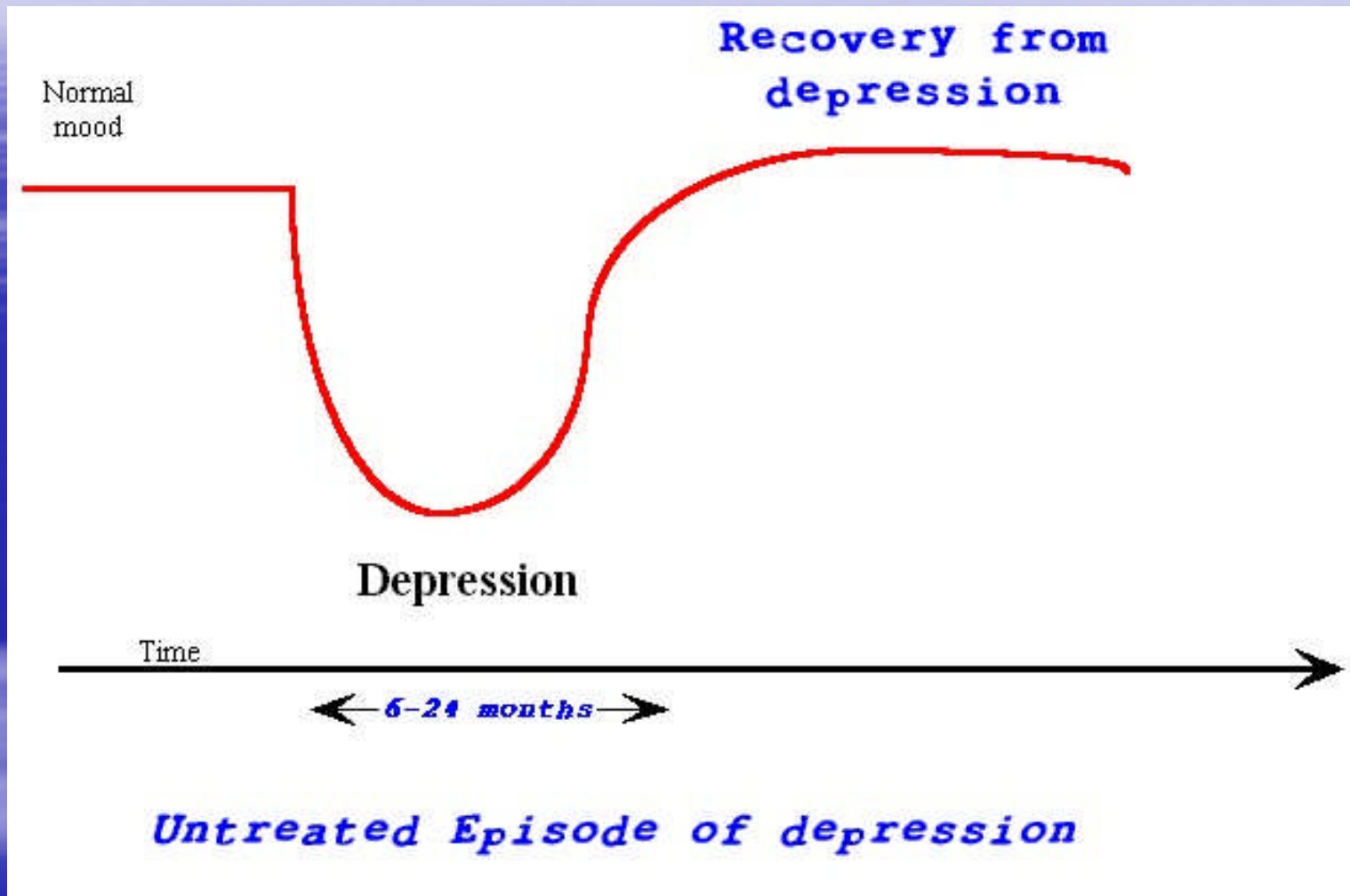
- A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
 1. Depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
 2. Elevated, expansive, or irritable mood
- B. There is evidence from the history, physical examination, or laboratory findings or either (1) or (2):
 1. The symptoms in criterion A developed during, or **within a month** of, substance intoxication or withdrawal.
 2. Medication use is etiologically related to the disturbance

Substance Induced Mood Disorder (cont)

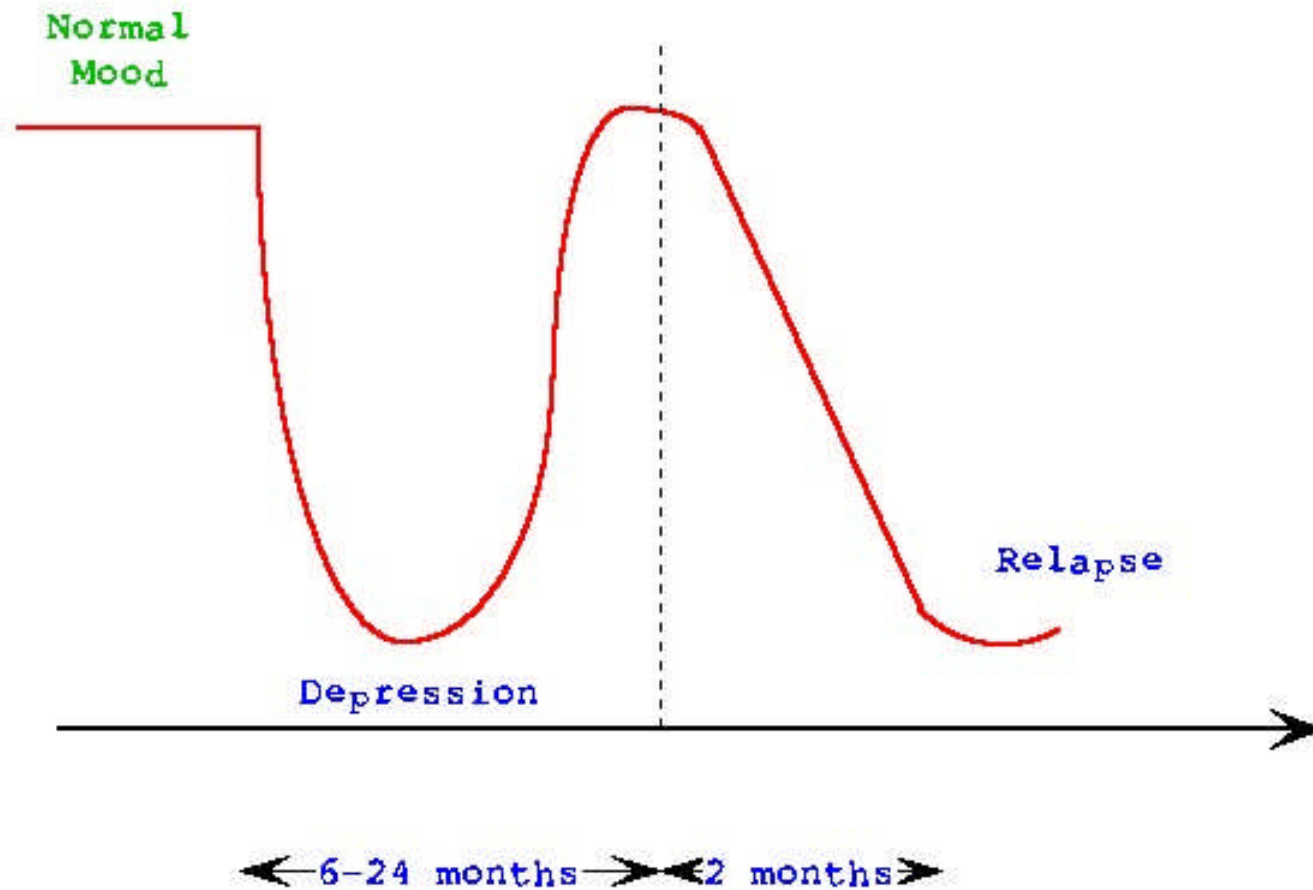
- C. The disturbance is not better accounted for by a mood disorder that is not substance induced. Evidence that the symptoms are accounted for by a disorder which is not substance induced is are:
- The symptoms precede the onset of the substance use
 - Symptoms persists for a substantial period of time (about a month)
 - Symptoms are substantially in excess of what would be expected given the type of the substance used or the duration of the use.
 - There is other evidence that suggests the existence of an independent non substance induce mood disorder (e.g h/o recurrent major depressive episodes)
- D. The disturbance does not occur exclusively during the course of a delirium.
- E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Differential Diagnosis of Depression

- **Medical and Organic Factors**
 - Medical illness and medical treatment
 - Hypothyroidism, cardiovascular disorder, anemia, diabetes mellitus,
 - Beta blockers, sedative hypnotics, barbiturates, antineoplastic agents,
 - Discontinuation of other prescribed medications
 - Corticosteroids and psychostimulants, antidepressants
 - Substance abuse
 - Cannabis, cocaine, narcotics oxycodone hydrochloride,
 - *Withdrawal from nicotine and caffeine* can mimic depression and anxiety
- **Other psychiatric disorders**
 - Bipolar disorder
 - Negative Symptoms of Schizophrenia
 - Diminished interest, pleasure, energy, or motivation along with psychomotor retardation and impaired ability to concentrate are relevant overlapping features
 - Schizoaffective Depression
 - Clinically difficult to distinguish from depression in schizophrenia
 - It includes A) depressive mood B) delusions or hallucinations in the absence of mood symptoms
- **Neuroleptic-Induced EPS**
 - Positive association between extrapyramidal symptoms and depressive symptoms
 - Neuroleptic-induced akinesia (impaired ability to initiate and sustain motor behavior)
 - Neuroleptic-induced akathisia

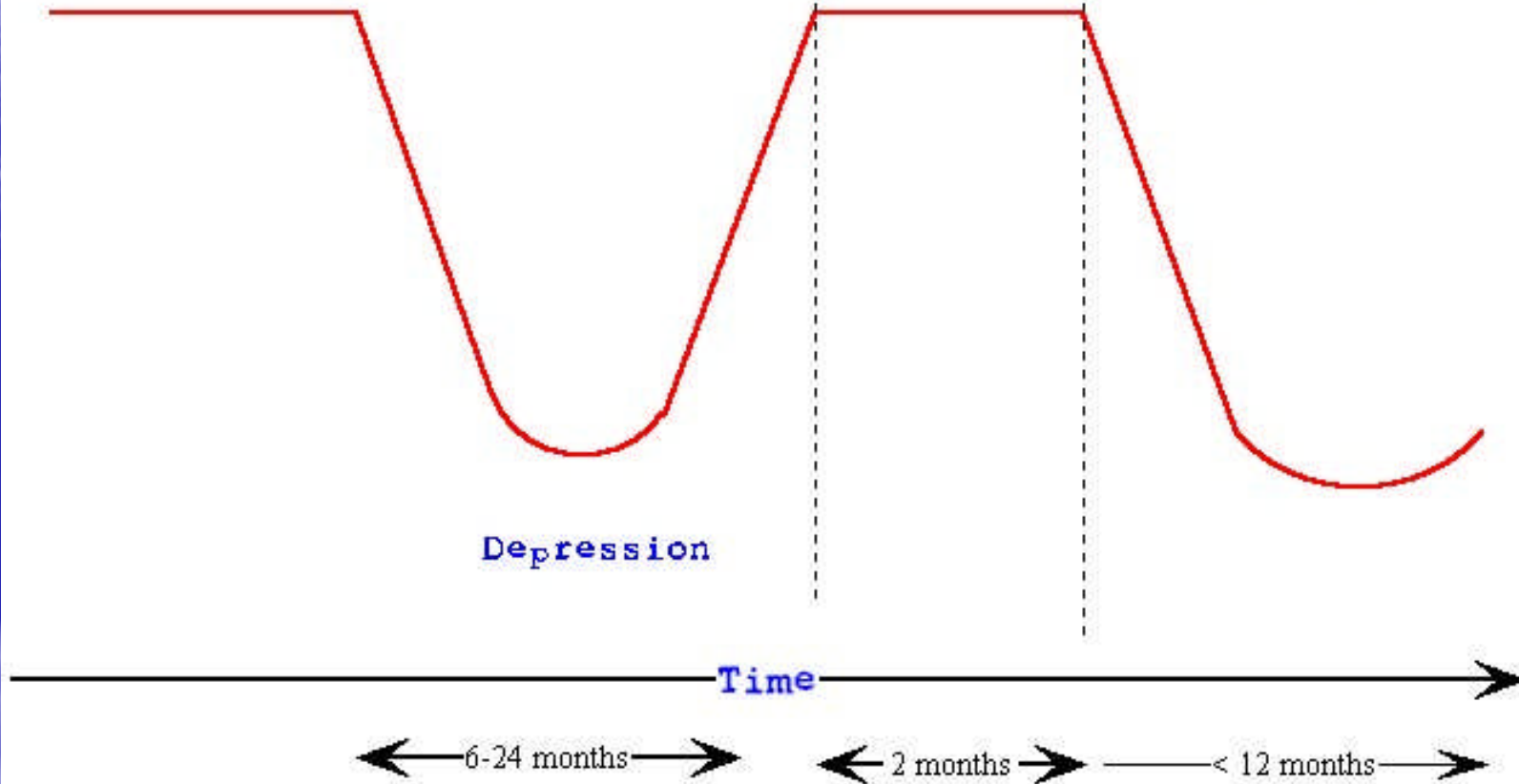


Depression within 2 months of recovery is called relapse



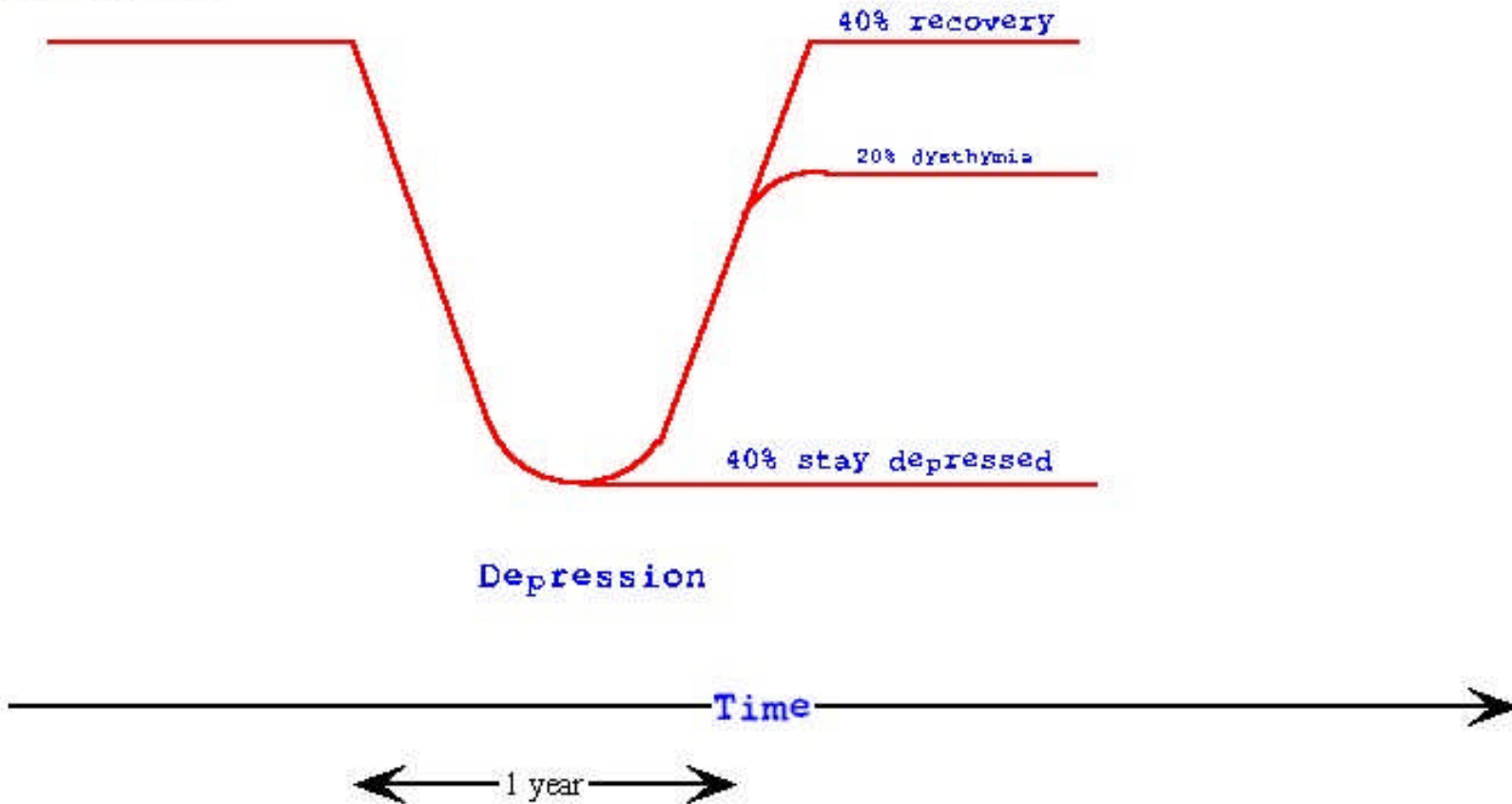
Normal mood

Recurrence



When depression returns after greater than 2 months following recovery, it is called as "Recurrence"

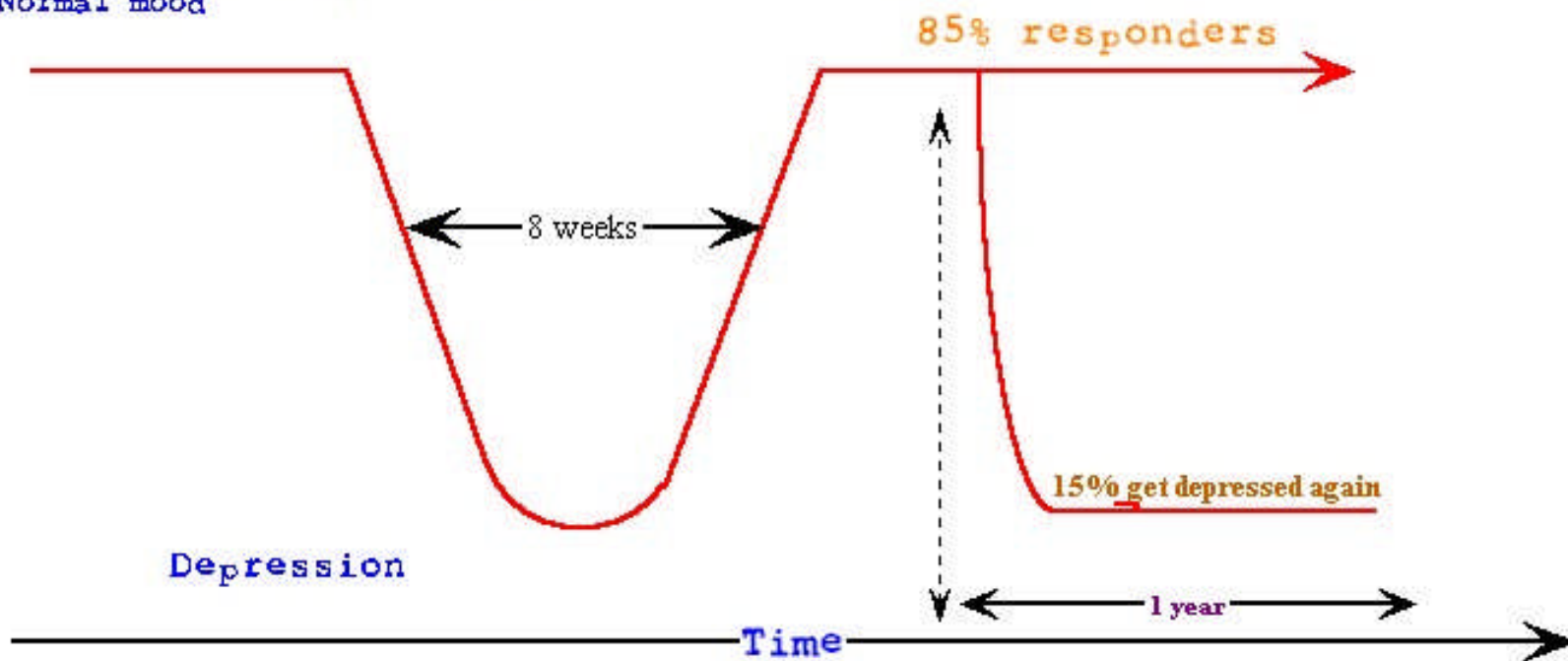
Normal mood



Follow up studies with untreated depressed patients shows the above pattern of recovery

Medication Continuation Responders

Normal mood



Placebo

Normal mood

33% responders

Placebo started

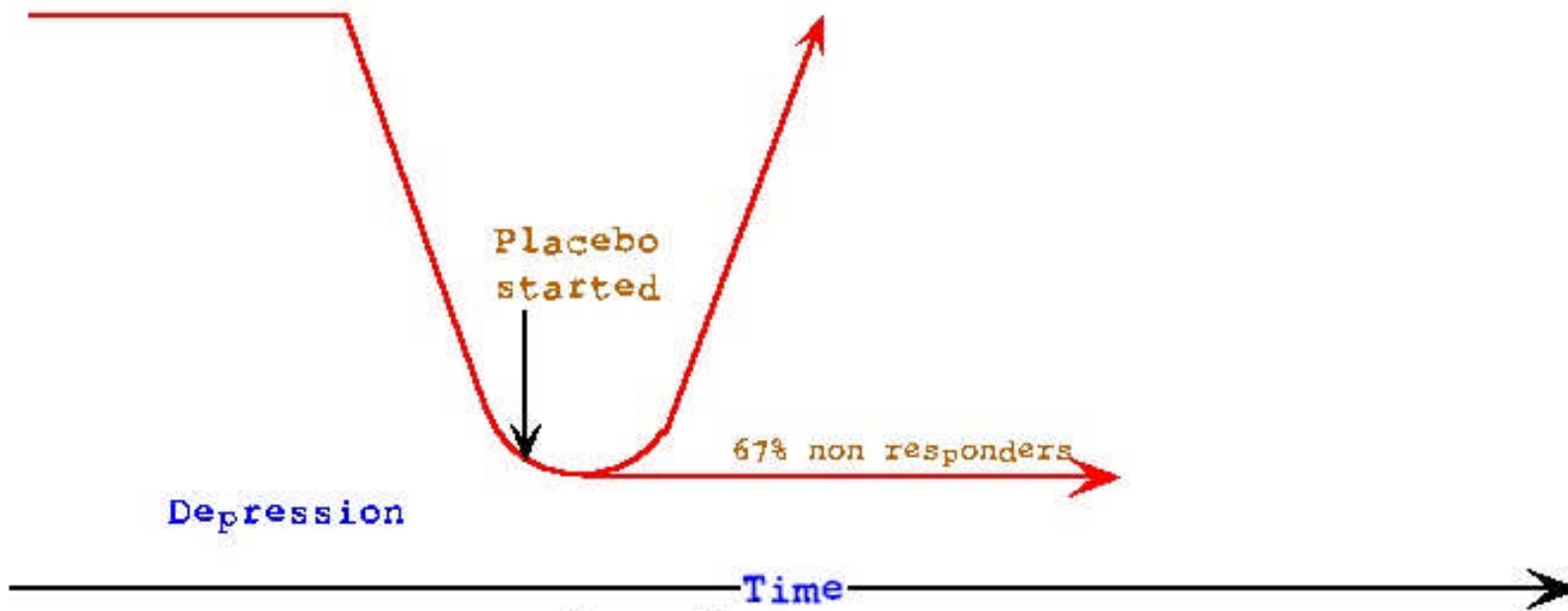
67% non responders

Depression

Time

← 8 weeks →

Placebo Response rate



Conditions That Could Warrants An Inpatient Stay

- Severe depression, esp. with serious suicidal plans or intentions, lasting for more than 1 to 3 days after the acute effects of the substance or of its withdrawal have passed.
- Psychotic feature persisting for 1 to 2 days, after the immediate effect of the substance
- Repeated outpatient failures
- Intractable and unremitting use of the substance.
- a history of severe alcohol or sedative withdrawal.
- Any severe psychiatric or medical problem that coexists with the substance abuse
- Lack of motivation for any form of treatment
- Lack of family support
- Extreme availability of more addicting substance (e.g., cocaine)

Medical Management

- No class of antidepressant is considered the gold standard
- Choose an agent based on the characteristics that are independent of the substance use disorder.
- If sleeping is considered a serious complaint than a more sedating agent may be indicated.
- Agents that have a low therapeutic index and that are more toxic and lethal in overdose are avoided
- Benzodiazepines should be prescribed with caution.

Biological Basis Of Depression

- Monoamine Theory
 - First major theory
 - Depression is due to deficiency of monoamine neurotransmitters, NE and 5HT

Normal State

Depression

Neurotransmitter Receptor hypothesis

- Posits that something is wrong with the receptors
- NT are depleted and this theory take one more step
- This depletion causes compensatory up-regulation of post synaptic receptors.

Receptor up-regulation

Classification of Antidepressant

- MAOI inhibitors
- Tricyclic antidepressant
- Serotonin selective reuptake inhibitors
- Norepinephrine and Dopamine reuptake blockers
- Serotonin-Norepinephrine reuptake inhibitors
- Serotonin-2 antagonist/reuptake inhibitors

MAOI Inhibitors

- Classical MAOIs- irreversible and nonselective
 - Phenzelzine*
 - Tranylcypramine*
 - Isocaboxazid
- RIMAs- Reversible inhibitors of MAO A
 - Moclobemide
- Selective inhibitors of MAO B
 - Deprenyl* (prescribed by neurologist for the treatment of Parkinson's disease)

MAOI (Cont)

- First clinically effective antidepressant discovered
- Accidentally discovered (Iproniazid antituberculosis medication with antidepressant effects)
- Effective for
 - Depression
 - Anxiety
 - Social phobia
- MAO has two subtypes
 - MAO A metabolizes; serotonin, norepinephrine dopamine
 - MAO B metabolizes; norepinephrine, dopamine

MAOIs (Cont)

- Effects on specific organs
 - Decrease sleep and insomnia, sometime daytime drowsiness
 - orthostatic hypotension
 - With penalize, or isocaboxazid is severe
 - Weight gain
 - Sexual dysfunction
 - tyramine induce hypertensive crisis
 - Food rich in tyramine
 - Meat: beef liver, chicken liver, fermented sausages.g. pepperoni, salami
 - Fish: caviar cured unrefrigerated fish
 - Beverages chianti wine, beers containing yeast (unfiltered)
 - Others: chocolate, coffee, beer, wine
 - MAO A inhibition in the GI results in increase absorption of tyramine which than acts as pressor in general

Tricyclic Antidepressants

- Block the reuptake
 - serotonin, norepinephrine, and also dopamine
- TCA binds to site near to the receptor and cause physical changes in the receptor to prevent reuptake of neurotransmitters.
- Block (side effects)
 - muscarinic cholinergic receptors
 - Dry mouth, blurred vision, urinary retention, and constipation
 - Blockade of H1 histamine receptors
 - Sedation and weight gain
 - Blockade of alpha 1 adrenergic receptors
 - Orthostatic hypotension, dizziness

Tricyclic Antidepressants

- Therapeutic indications
 - Depression
 - Panic disorder with agoraphobia
 - Generalized anxiety disorder
 - Obsessive-Compulsive disorder
 - Eating disorders
 - Pain disorder
 - Childhood enuresis (imipramine)

Precautions and side effects

- Possibility of inducing manic episode
- anticholinergic effects
 - Dry mouth, constipation, blurred vision, and urinary retention
 - Narrow angle glaucoma can be exacerbated
 - CNS anticholinergic syndrome with Confusion and delirium
 - Amitriptyline, imipramine, trimipramine, and doxepine are the most anticholinergic
 - Amoxapine, nortriptyline, maprotiline are less anticholinergic
- Sedation
- Orthostatic hypotension
- Cardiac effects
 - Cause tachycardia, flattened T waves, prolong QT interval
 - Contraindicated in patients with preexisting conduction disorders
 - At high doses they are arrhythmogenic

Precautions and side effects

- Neurological effects
 - Sedation, myoclonic twitches, delirium, confusion
 - Maprotiline can cause seizures
- Precautions
 - Avoided during pregnancy
 - Drug pass through breast milk
- Overdoses
 - Serious and can be fatal
 - Agitation, delirium, convulsions, hyperactive deep tendon reflexes, bowel and bladder paralysis, dysregulation of blood pressure and temperature. And mydriasis.
 - Coma and respiratory depression, cardiac arrhythmias

DRUG INTERACTIONS

- Antihypertensives
 - TCA block the reuptake of guanethidine, which is required for the antihypertensive activity.
 - It blocks the effects
 - Beta blockers (propranolol, clonidine)
- Antipsychotics
 - When co-administered plasma concentration increases
- CNS Depressants
 - Additive effects with Opiates, opioids, alcohol, anxiolytics, hypnotics, OTC cold med.
- Oral Contraceptives
 - OCP decreases TCA levels by hepatic enzyme inductions.

Serotonin Selective Reuptake Inhibitors

- Lack the side effects of TCAs
- Block 5HT transport.
- Lack antihistamine, anti-alpha-adrenergic receptors activities, low anticholinergic activity
- Have additional efficacy for OCD which most TCAs lacks.
- Easier to administered
- Increase patients compliance
- Therapeutic Indications
 - Depression
 - Anxiety disorders
 - OCD
 - Panic disorders
 - PTSD
 - Social phobia

Mechanism of Action

- Stage I
- Stage II
- Stage III
- Stage IV
- Stage V

SSRIs (Cont)

- Fluoxetine (Prozac), sertraline(Zoloft), paroxetine(Paxil), fluvoxamine (Luvox), citalopram (Celexa)
- All are clinically efficacious in treating depression

| | FL X | FLV | PAR | SER | CIT |
|-------------------|---------|-----|-----|-----|-----|
| Half life (hr) | 84 | 15 | 21 | 26 | 35 |

SSRIs

- Have minimal effect on
 - Blood pressure, cardiac function.
- Major system affected is GI
 - Nausea, anorexia, diarrhea
- Sexual dysfunction
- Weight loss with fluoxetine, weight gain with paroxetine occasionally with or fluvoxamine

Side Effects

| Side effects | Sertraline N=1,568 | Placebo N861 | Fluoxetine N=1,378 | Fluvoxamine N=222 | Paroxetine N=1,387 | Imipramine N=599 |
|----------------------|-----------------------|-----------------|-----------------------|----------------------|-----------------------|---------------------|
| Nausea, vomiting | 21% | | 37% | 29% | | |
| Headache | | 20% | | 22% | 29% | 19% |
| Dry mouth | | | | 26% | 20% | 76% |
| Sedation | | | | 26% | 24% | 30% |
| Nervousness, anxiety | | | 21% | | | |
| Dizziness | | | | | | 27% |
| Insomnia | | | 19% | | | |
| Sweating | | | | | | 21% |

SSRI Discontinuation Syndrome

- Abrupt discontinuation of SSRI, esp. one with shorter half life.
- Somatic symptoms
 - Dysequilibrium (dizziness, vertigo, & ataxia)
 - Nausea, vomiting, fatigue, lethargy, myalgia, paresthesias, tremor, insomnia, and migraine like aura
- Psychological symptoms
 - Anxiety, agitation, crying spells, irritability, overactivity, depersonalization, poor concentration, lowered mood, confusion, memory problems, and vivid dreams
- **Venlafaxine, paroxetine** are two most common drugs associated

SSRI Discontinuation Syndrome (Con)

- Occur in up to one third of patients who stop these medication abruptly
- Should taper the medication to avoid the discontinuation syndrome
- Less likely to happen with sertraline and fluoxetine
- Fluoxetine can be used to treat the discontinuation treatment.

Norepinephrine and Dopamine Reuptake blockers

- Bupropion (wellbutrin)
- It has an active metabolite (more powerful norepinephrine and dopamine reuptake blocker than bupropion itself but also concentrated in brain)
- Effective antidepressant, more activating or stimulating
- More incidence of grand mal seizures compared to other antidepressants
- Low incidence of sexual dysfunction
- Useful for patients
 - Who can not tolerate side effects of serotonin
 - Who fails treatment with SSRIs

Bupropriion Cont...

- Most common adverse effects
 - Headache, insomnia, upper respiratory complains, and nausea.
 - Psychotic symptoms
 - Hallucinations, delusions, catatonia and delirium
- Absence of
 - Orthostatic hypotension, weight gain, daytime drowsiness, and anticholinergic effects.
- Seizures
 - Dose < 450 mg day the incidence of seizures is 0.4%
 - Doses > 450 – 600 mg the incidence of seizures 5%
 - **Contraindicated in patients with**
 - H/O head trauma, brain tumors, and other organic brain diseases
 - **Recent withdrawal from ETOH, or sedative-hypnotics, EEG abnormality increase the risk for seizures.**
- Less likely to cause mania compared with TCAs
- **Give a false positive result on urinary amphetamine screens.**

Serotonin-Norepinephrine Reuptake Inhibitors

- Also called Dual Reuptake inhibitors or sometimes SNRIs
- Venlafaxine (effexor)
- It has different degrees of inhibition of
 - 5HT reuptake (most potent and present at low dose),
 - NE reuptake (mod. potency and present at higher dose)
 - DA reuptake (least potent and present at highest doses).
- Effective for severely depressed patients
- Rapid onset of antidepressant effects
- Adverse effects
 - Nausea, somnolence, dry mouth, dizziness, nervousness, constipation, asthenia, blurred vision
 - Increase in blood pressure. (use with caution in

Serotonin-2 Antagonist/Reuptake Inhibitors(SARIs)

- Dual actions as antagonists of serotonin-2 (5HT₂) receptors as well as serotonin reuptake inhibition
- With 5HT reuptake inhibition, serotonin is available to stimulate all serotonin receptors
 - 5HT_{1A} receptor in median raphe:- depression
 - 5HT₂ receptor in forebrain:- agitation, anxiety
 - 5HT₂ receptor in spinal cord:- sexual dysfunction
- Lack the activating properties
 - Agitation, anxiety, akathesia, and also lack sexual dysfunctions

SARIs Cont...

- Agents available
 - Trazodone
 - Nefazodone
- Trazodone also blocks alpha 1 receptors and histamine receptors - more sedating
 - Trazodone associated with priapism (prolong erections in men, usually painful) Rx by injecting alpha adrenergic agonist into the penis to reverse the priapism and prevent vascular damage to penis
- Nefazodone
 - Also inhibit NE uptake
 - Less sedating, no cases of priapism

Mirtazapine (Remeron)

- Antagonism of central presynaptic alpha₂-adrenergic receptors
- It blocks 5HT₂, 5HT₃ and cause activation of 5HT_{1A} receptor.
- Side Effects
 - Sedation
 - Weight gain (7.5% have 7% weight gain)
 - Increase in serum cholesterol >20% above normal limits in 15% of patients
 - Increase triglycerides to >500 mg/dl in 6% of patients
- Agranulocytosis and neutropenia
 - Up to .3% of patients may develop absolute neutrophil count of <500 per mm³
 - Immediate medical attention if patient develops
 - Fever, chills, sore throat, mucous membrane ulceration, or other signs of infection
 - 3 of 2,796 patient in premarketing experience this
 - No cases reported in 13,500 patients in Netherlands

Conclusions

- All antidepressants are equally efficacious
- First line agents
 - SSRIs
- MAOI, and TCA, high incidence of side effects and not safe in over dose.
- Chose an antidepressant with less side effects