

Parkinson's Disease and Mental Illness

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Outline

- Definition of Parkinson Disease
- Diagnosis
 - History
 - Physical Examination
 - Testing
- Differential Diagnosis
- Co-morbid Mental Illnesses
- Treatment

Parkinson's Disease

- The gradual onset of symptoms usually begins during the sixth decade of life.
- The diagnosis of Parkinson's disease is based primarily on the presence of four distinct features:
 - Bradykinesia (slowness of movements) or akinesia (difficulty initiating movements)
 - Truncal and limb muscle rigidity
 - Resting tremor or postural tremor
 - Postural instability and gait disorders later in the course of the illness.
- Bradykinesia, the hallmark of the disease, and at least one other of these primary features must be present in order to meet formal criteria of *possible Parkinson's disease*. When all four features are present, the physician can make a diagnosis of *definitive Parkinson's disease*

Clinical Features of Parkinson's Disease

Primary diagnostic features	Bradykinesia or, in its extreme form, akinesia (rarely present at the very beginning)
	Resting or postural tremor
	Rigidity
	Postural instability or stooped posture (usually later in disease course)
	Gait difficulty (usually later in disease course)
Other features	Dysarthria (difficulty with speech and enunciation)
	Masked face
	Micrographia (small handwriting)
	Voice disturbances, particularly loss of volume
	Altered affect, personality, and cognition (usually later in disease)
	Dysphagia (difficulty swallowing, also later in disease)
	Depression (patients may appear depressed or be depressed)
Features of advanced disease	Autonomic changes, including constipation, bladder control problems, sexual dysfunction, or orthostatic hypotension
	Dementia
	Falls

Depression and Dementia

- Depression and dementia accompany Parkinson's disease in approximately one-third of the patients
- The proportion of patients with dementia increases with age.
- Experts have identified dementia as the single most important risk factor for the higher mortality rate of patients with Parkinson's disease when compared with age-matched controls

Baker MG : Depression, psychosis and dementia in Parkinson's disease: diagnosis and treatment. *Neurology*. 1999;52 (Suppl 3):S1-29

Poewe WH, Wenning GK : The natural history of Parkinson's disease. *Ann Neurol*. 1998;44 (Suppl 1):S1-9

Neuroleptic Induced Parkinsonism

- dopamine D2-receptor-blocking agents or other drugs that can produce secondary parkinsonism
- Eliciting a careful drug history is important, because several agents can produce side effects that resemble Parkinson's disease.
- Neuroleptic-induced parkinsonism is common in nursing homes as well as among chronic psychiatric patients.
- Drugs that interfere with the availability of dopamine at its receptor sites, such as dopamine receptor-blocking neuroleptics, may cause Parkinson-like symptoms, usually after months of administration.
- Such agents may cause movement disorders in as many as 40% of treated patients

Drugs Causing Secondary Parkinsonism

- Alpha-methyldopa
- Butyrophenones
- Lithium (very rare)
- Metoclopramide
- Neuroleptics: e.g.,
 - haloperidol, olanzapine, or risperidone
- Phenothiazines
- Reserpine and similar dopamine-depleting agents

Differential Diagnosis

Neurodegenerative conditions, with and without cognitive changes	
Alzheimer's disease (AD) with parkinsonism	Conspicuous dementia as the primary clinical feature; disease involves changes in the nigrostriatal pathway
Diffuse Lewy-body dementia (DLBD)	Early hallucinations with fluctuating cognition as part of a progressively dementing illness in addition to typical PD-related changes, such as midbrain and cortical Lewy-body formation
Frontotemporal dementia with parkinsonism (FTDP)	Conspicuous dementia as the primary clinical feature with signs of basal ganglia involvement
Creutzfeldt-Jakob disease (CJD)	Rapidly progressive dementia, myoclonus, ataxia and/or pyramidal signs, visual disturbances. The commonest prion disorder in humans.

Diagnostic Criteria

- Diagnose Parkinson's disease based on the presence of bradykinesia and at least one of the other three primary features:
 1. truncal and limb muscle rigidity
 2. resting or postural tremor, and
 3. postural instability or gait disorder.When all four of these features are present, the physician makes a diagnosis of definitive Parkinson's disease
- Recognize the two subtypes of Parkinson's disease:
 - one characterized by a predominance of tremor (usually asymmetric) and
 - other by a predominance of postural instability, gait disorders, and more disabling bradykinesia.

DSM IV Criteria For Major Depression

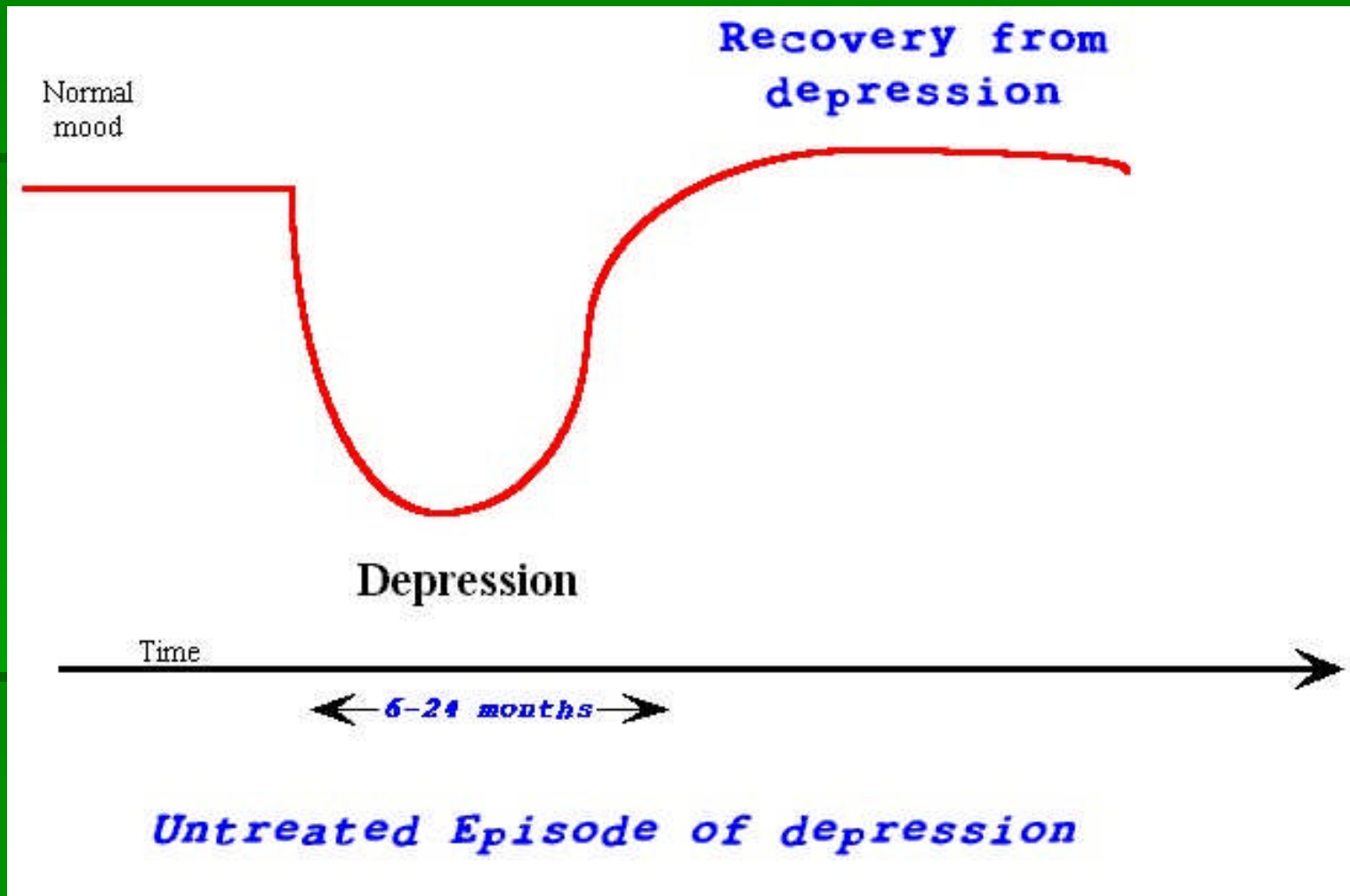
- Five or more of the following symptoms have been present during the same 2 week period and represent a change from the previous functioning; at least one of the symptoms either (1) depressed mood or (2) loss of interest or pleasure
 - **Note:** do not include symptoms that are clearly due to general 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)

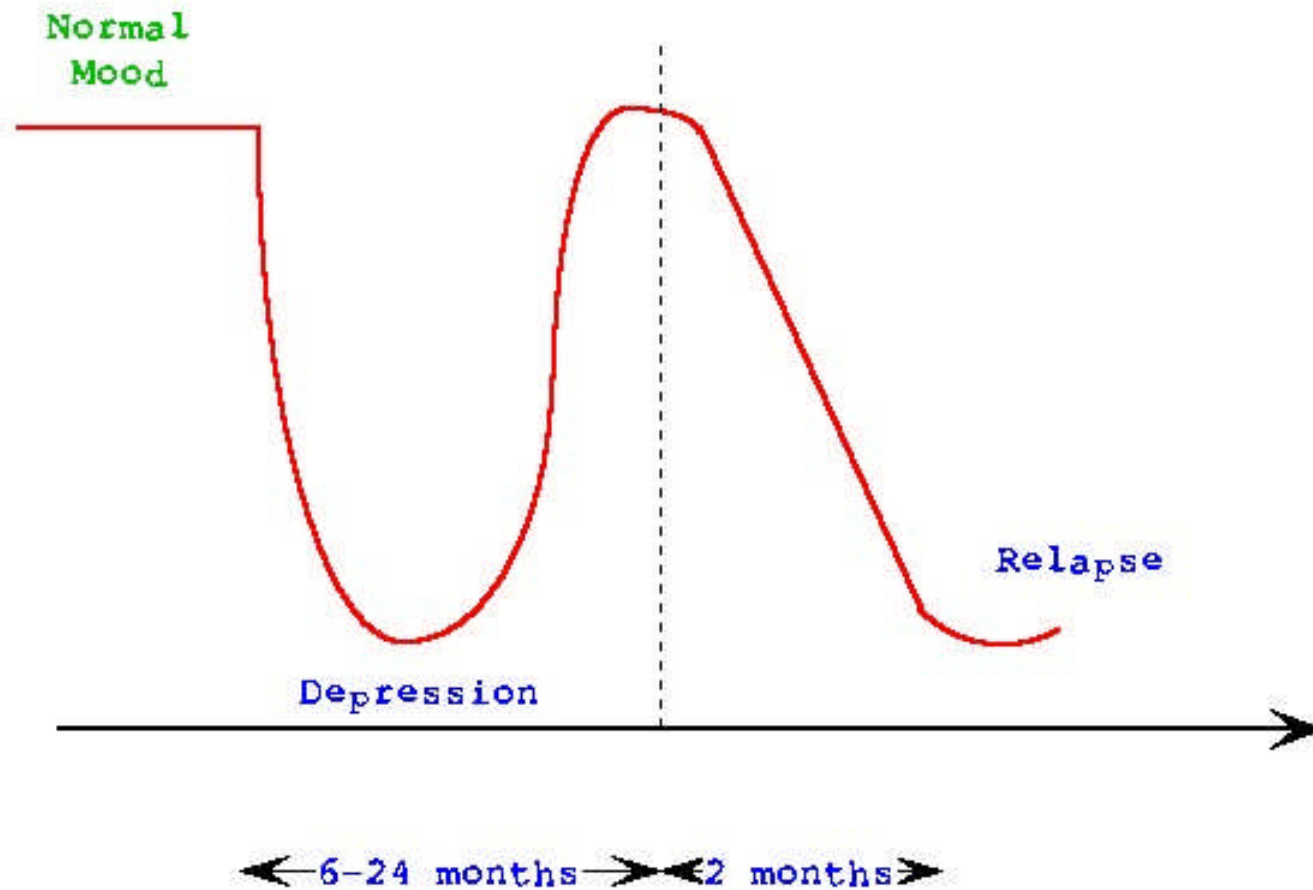
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The symptoms are not due to the direct physiological effects of a substance or a general medical condition.
- D. The symptoms are not better accounted for by bereavement, 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

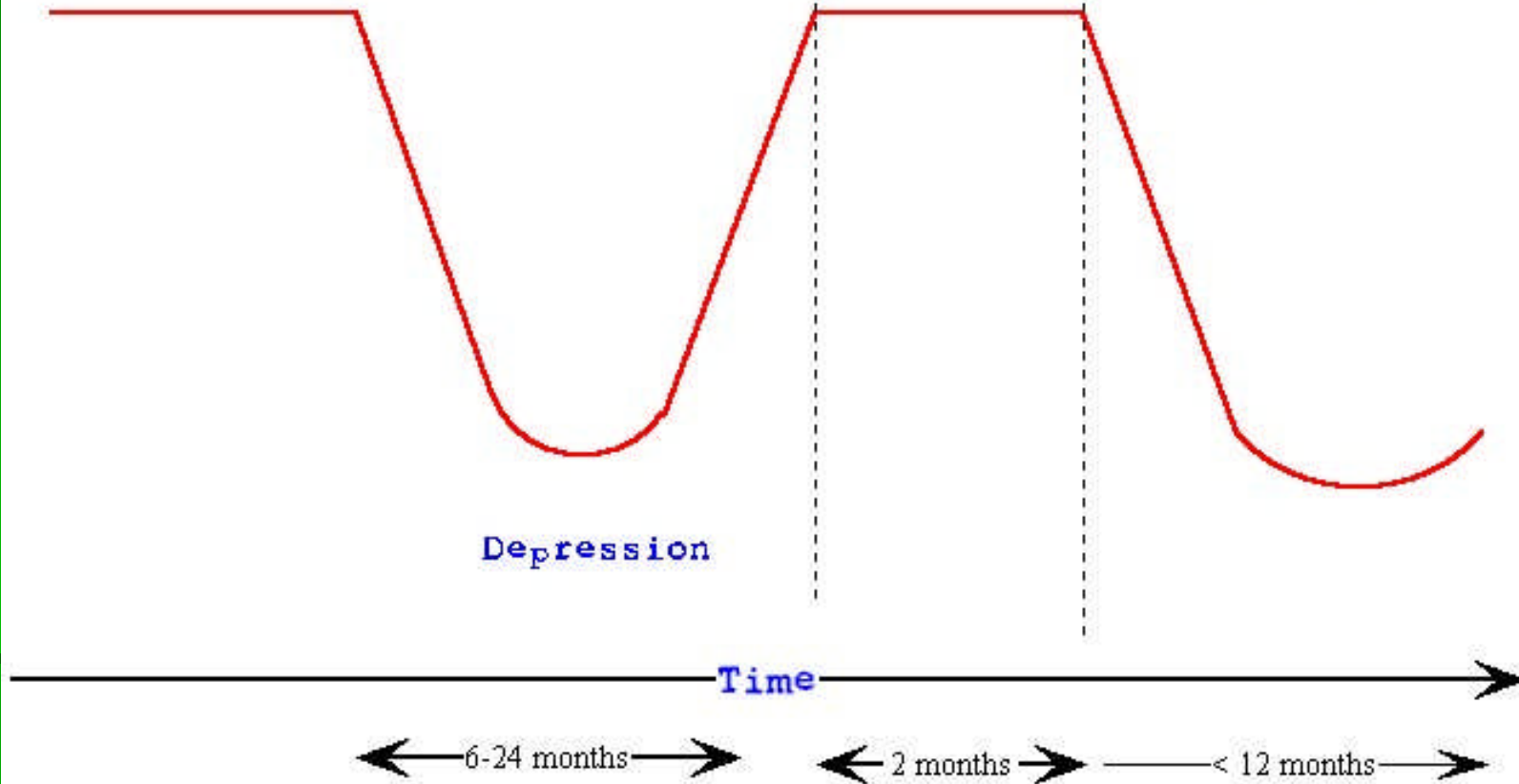


Depression within 2 months of recovery is called relapse



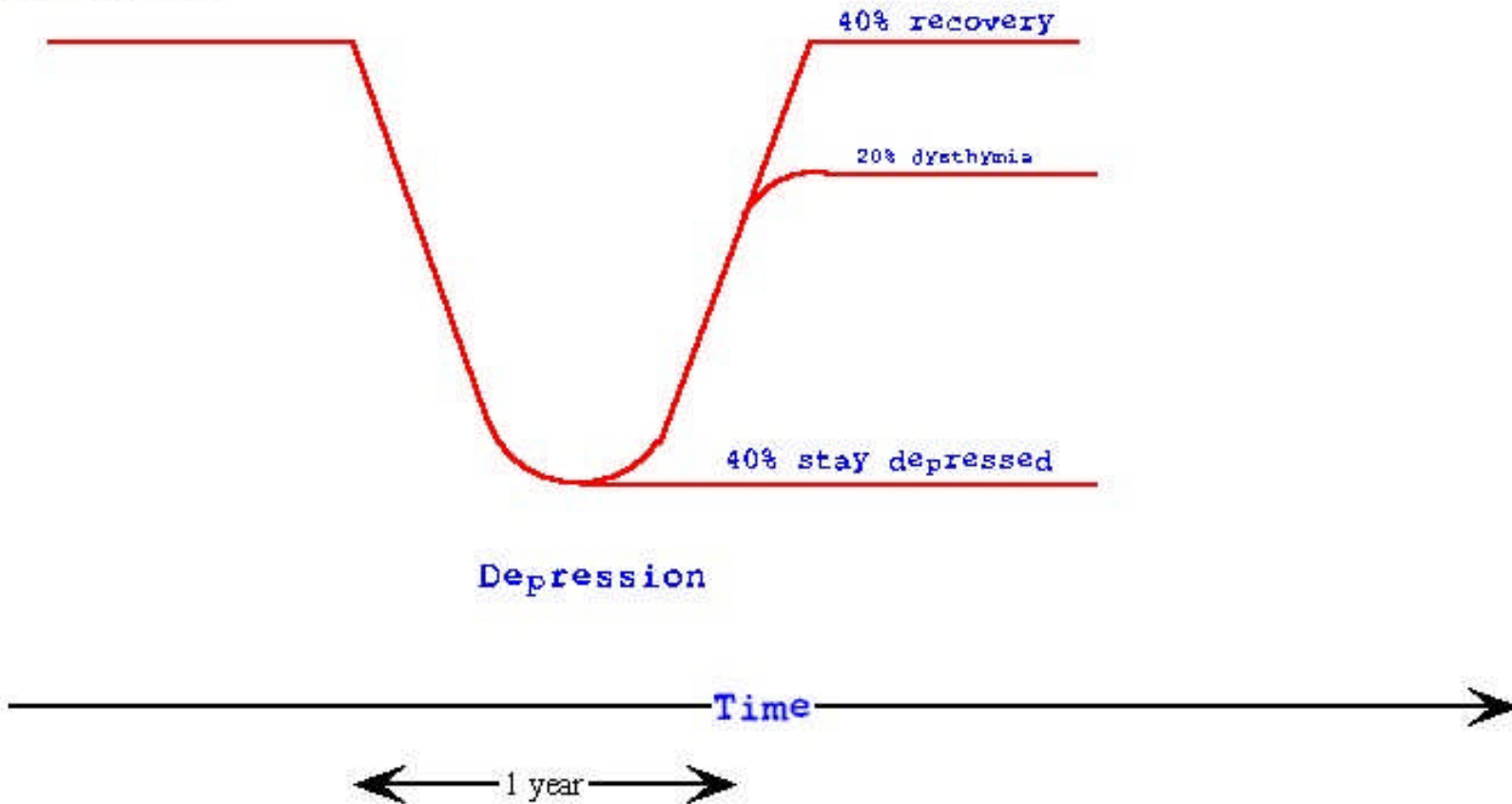
Normal mood

Recurrence



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

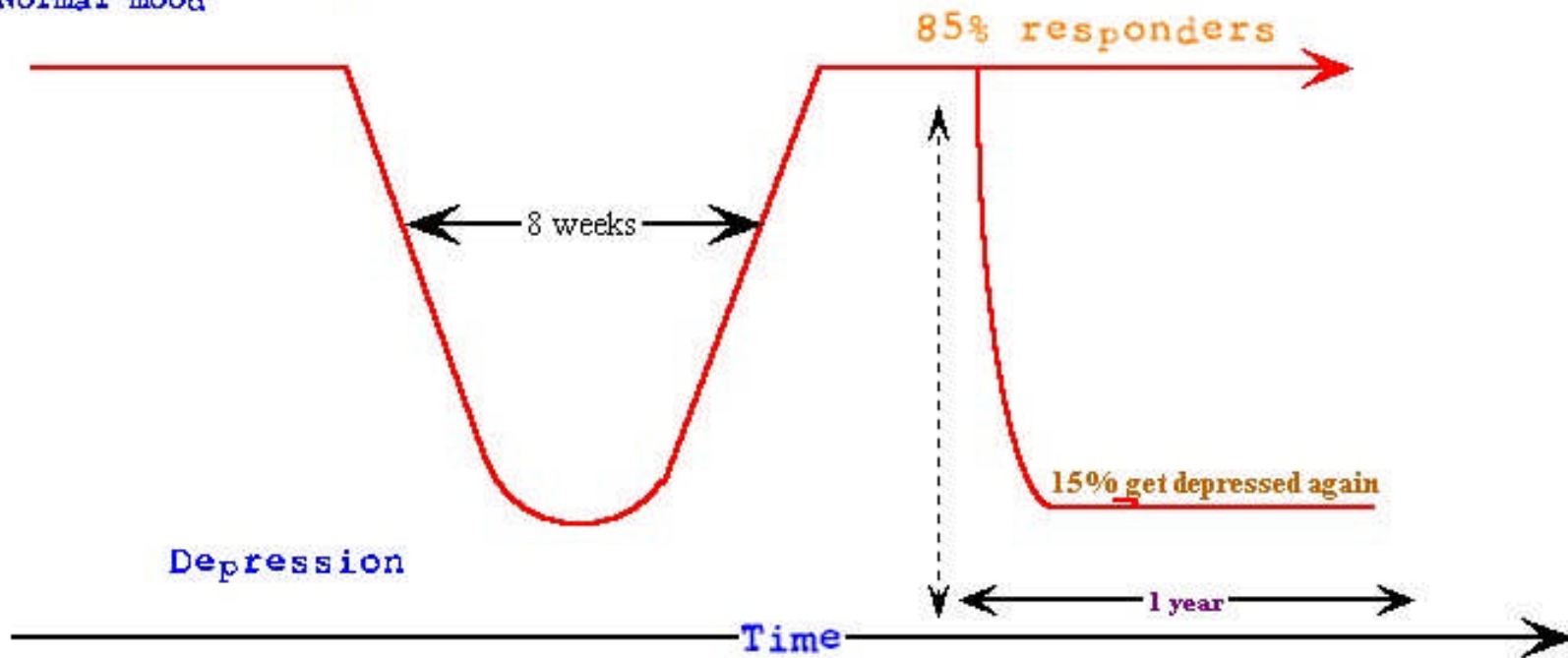
Normal mood



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

Medication Continuation Responders

Normal mood



Depression

Time

85% responders

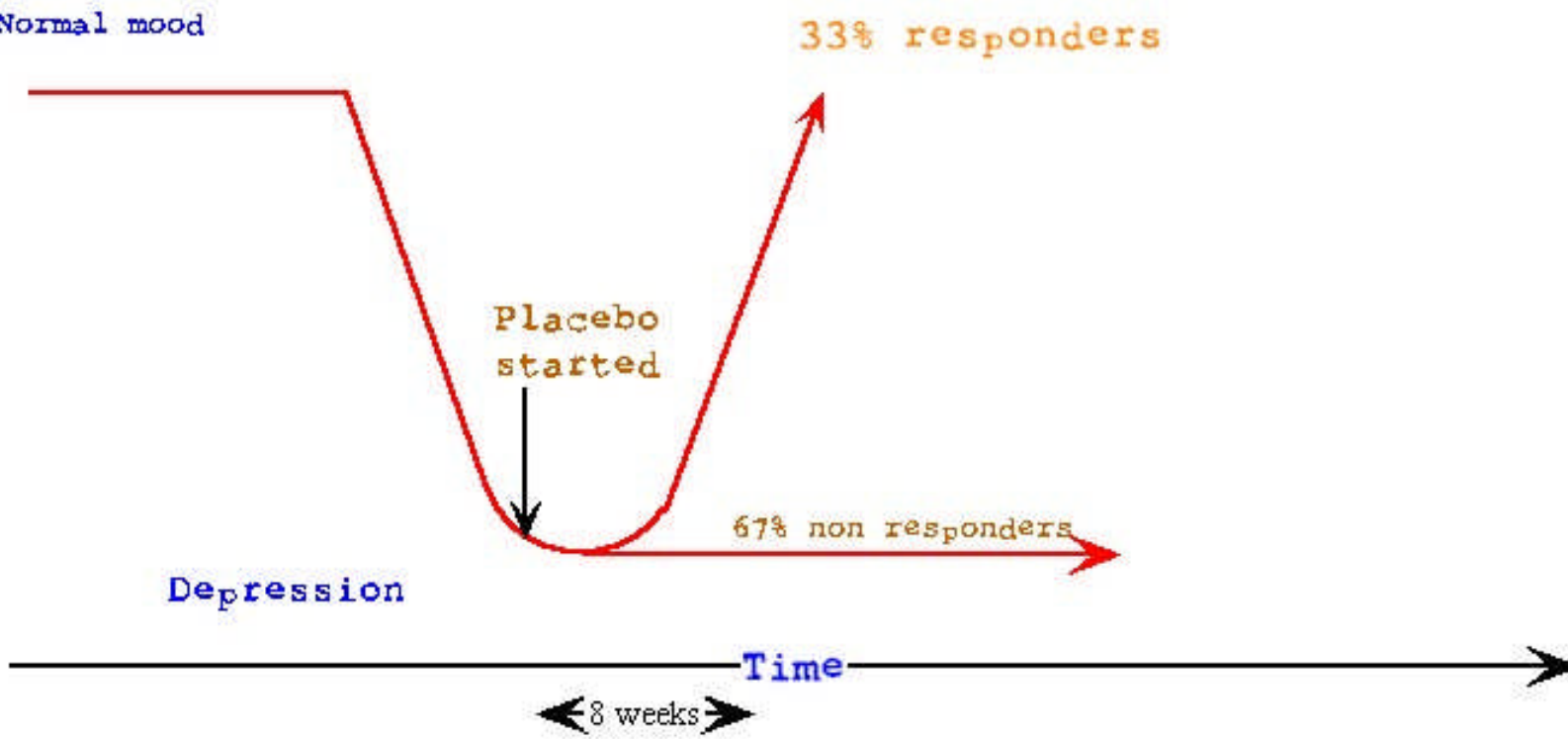
15% get depressed again

1 year

8 weeks

Placebo

Normal mood



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

To view the animation click on the boxes above

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

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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
 - Phenezine*
 - Tranylcypromine*
 - 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 circulation.

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](#)

To view the animation click on individual links above

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.

Dementia

History

- Careful and accurate history
- Distinguishing exceptional symptoms from complaints due to age-related cognitive decline
- Assess the patient for depression, and inquire about behavioral and psychotic disturbances
- Consider conditions whose symptoms and signs mimic those of neurodegenerative dementia
- Obtain and review the patient's medication history for drugs

History

- careful and accurate history
 - onset and course of memory and thinking problems
 - informed collateral source (generally a spouse or adult child)
 - patient's cognitive performance or behavior that negatively affect his/her daily life
 - temporal course of symptoms
 - chronic, stepwise, or progressive
 - patient's recent and long-term memory
 - everyday activities
 - driving, functioning at work, and/or interactions with family and peers
- functional loss is not due to physical decline (vision or hearing loss)

History (cont...)

- Distinguish exceptional symptoms
 - from complaints due to age-related cognitive decline
- Cognitive changes due to usual aging
 - limited attentional resources ("I forgot what I came in here to get")
 - or to diminished speed of information processing ("I couldn't remember his name until later").
 - Such changes usually do not progress nor do they seriously interfere with everyday activities.
- Assess the patient for depression, and inquire about behavioral and psychotic disturbances
 - patients with depressive "pseudodementia"
 - acute onset
 - past episodes of depression, anhedonia
 - memory deficits that are equal for recent and remote events (vs. greater for recent events in AD),
 - circumscribed (vs. global) cognitive defects
- Patients with mild to moderate AD have memory and other cognitive disturbances, but do not have the prominent delusions and gross perceptual distortions that are characteristic of psychotic disorders
- conditions whose symptoms and signs mimic those of neurodegenerative dementia
 - Ask about other medical problems that might complicate the patient's evaluation or management
- patient's medication history for drugs
 - drugs that may cause or exacerbate loss of mental capacity, especially
 - opiates, sedative-hypnotics, analgesics,
 - anticholinergics, anticonvulsants, corticosteroids,
 - centrally acting hypertensives, psychotropics, alcohol.

Diagnostic Criteria

- DSM-IV criteria
 - *Development of multiple cognitive deficits:*
 1. Memory impairment, and
 2. At least one of the following:
 - Aphasia
 - Apraxia
 - Agnosia
 - Disturbed executive functioning (planning, organizing, sequencing, abstracting).
 - Course is characterized by continued gradual cognitive and functional decline.
 - Deficits are sufficient to interfere significantly with social and occupational functioning and represent a decline from past functioning.
 - Other causes (medical, neurologic, psychiatric) of dementia are excluded.

Diagnostic Criteria

- NINCDS-ADRDA Probable Alzheimer's Disease
 - *Dementia established by examination and documented by objective testing for:*
 - Deficits in two or more cognitive areas
 - Progressive worsening of memory and other cognitive functions
 - No disturbance in consciousness
 - Onset between 40 and 90 years of age
 - Absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition
 - *Diagnosis supported by:*
 - Progressive deficits in language (aphasia), motor skills (apraxia), and perception (agnosia)
 - Impaired activities of daily living and altered patterns of behavior
 - Family history of similar disorders
 - Consistent laboratory or radiologic results (e.g., cerebral atrophy on computed tomography)

Diagnostic Indicators for the More Common Non-Alzheimer Dementias

- Dementia with Lewy bodies
 - Presence of dementia and at least one of the following three features early in the disease course:
 - visual hallucinations,
 - parkinsonism, and
 - fluctuating cognitive status
- Vascular dementia (VaD)
 - Presence of dementia with abrupt onset
 - within 3 months of stroke *or*
 - abrupt deterioration *or*
 - stepwise progression of dementia, and fluctuating course
- Frontotemporal dementias
 - Presence of dementia with
 - disinhibition, impulsivity, impaired judgment, and/or
 - amotivational states resulting in disturbed personality, behavior, and language
- Depression
 - Presence of dementia with noncognitive changes (lack of interest, loss of energy, and difficulty in concentrating)

Treatment

- Medical Therapy
 - focus pharmacotherapy
 - palliation of cognitive symptoms and
 - slowing of disease progression
 - cholinesterase inhibitors donepezil or rivastigmine
- Contraindications for this therapy
 - cardiac and gastroenteric complications
- antioxidant therapy as a treatment strategy for AD
 - Evidence for increased oxidative stress and free radical injury in AD motivated a large-scale trial of selegiline (a monamine oxidase inhibitor) and alpha-tocopherol (vitamin E at 1000 IU b.i.d.) for moderately demented AD patients
 - Both compounds used independently (not in combination) delayed progression to clinical milestones (e.g. institutionalization) by approximately 8 months.
 - Favorable safety and cost profiles of vitamin E make it acceptable to many patients in the absence of additional studies confirming efficacy.
- Neither estrogen therapy nor prednisone is recommended for the treatment of AD, based on available evidence
- Prevent new insult
 - Treat the underlying causes of vascular dementia (VaD) (e.g., hypertension, atherosclerosis, or diabetes)
- Treat reversible dementias
 - hypothyroidism, vitamin B12 deficiency, overmedication, depression, and opportunistic infections accompanying HIV infection
- no approved therapies for dementia with Lewy bodies or frontotemporal dementias.
- Treat behavioral symptoms
 - If moderate to severe mood, behavioral, or other neurologic disturbances are present, use psychotropic (e.g., antipsychotics and antidepressants) and antiepileptic agents for short periods of time, as appropriate

Lifestyle Measures

- safe, supportive, and orderly environment
 - most contentious issues for families to deal with
 - driving, cooking, independent living, control of financial affairs, self-medication, and participation in community affairs
- *Physician and caregiver working together*
 - *Recommend establishment of durable power of attorney*
 - for financial and health care decision-making
 - *Recommend establishment of daily routines*
- Constant supervision to monitor the safety of the residential setting
- *Recommend driving evaluation when necessary*
 - Driving evaluations may be obtained from independent driving evaluation centers, some occupational therapists, or from the state agency regulating driving privileges.
- *Nutrition and hydration*
 - increased risk for nutritional imbalance, dehydration, and weight loss
- Encourage maintenance of an active and healthy lifestyle.
 - *Exercise*
 - *Sleep-rest.*
 - consistent daily routine
 - reducing environmental stimuli in the evening,
 - avoiding caffeine and other stimulants,
 - establishing toileting routines, and
 - possibly the short-term use of a mild hypnotic to establish a normal sleep-cycle.
 - *Oral hygiene*