Pharmacology of the central noradrenergic and serotonergic systems
Pharmacotherapy of mood disorders

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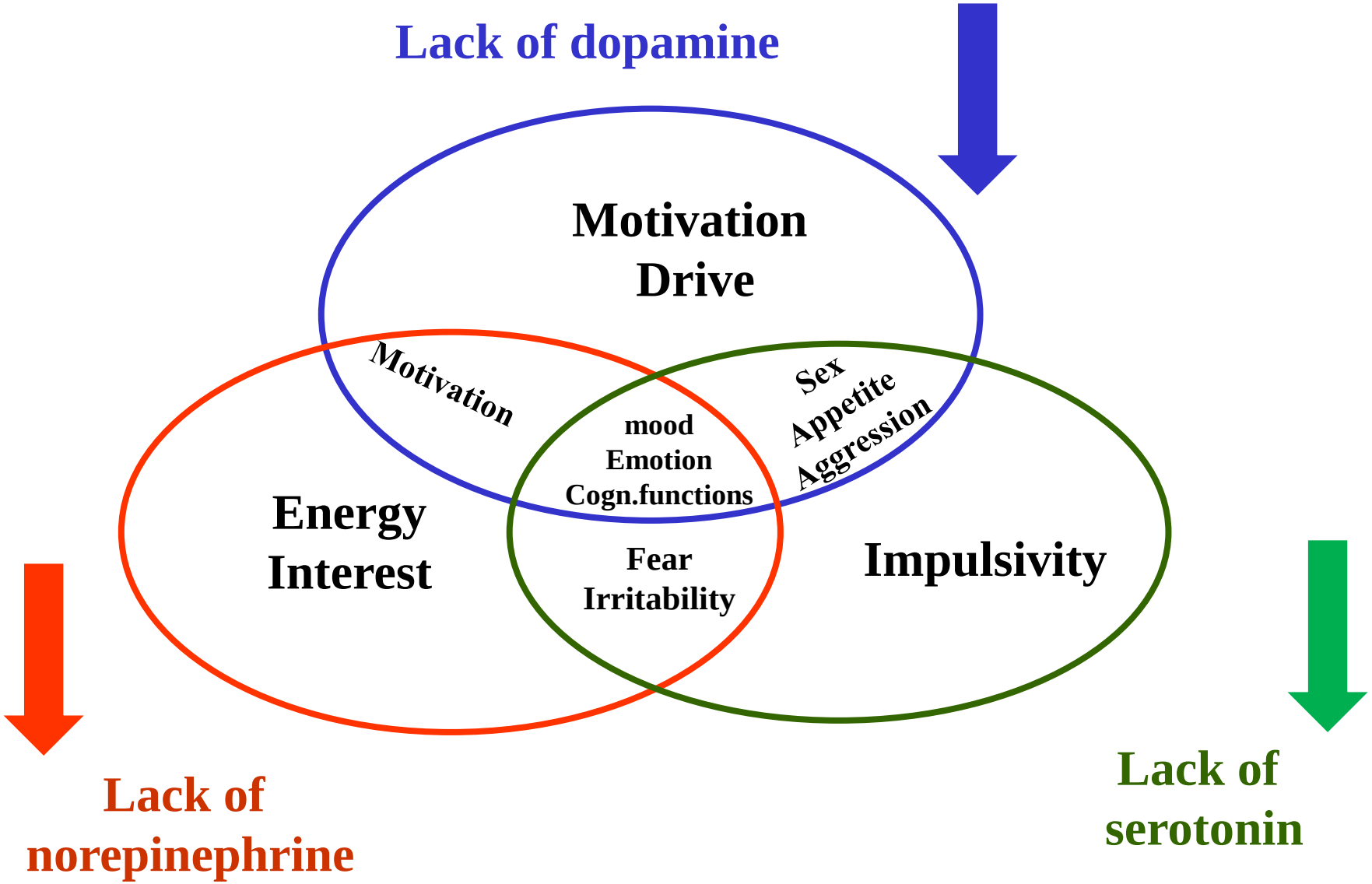
Monoamine levels and brain functions

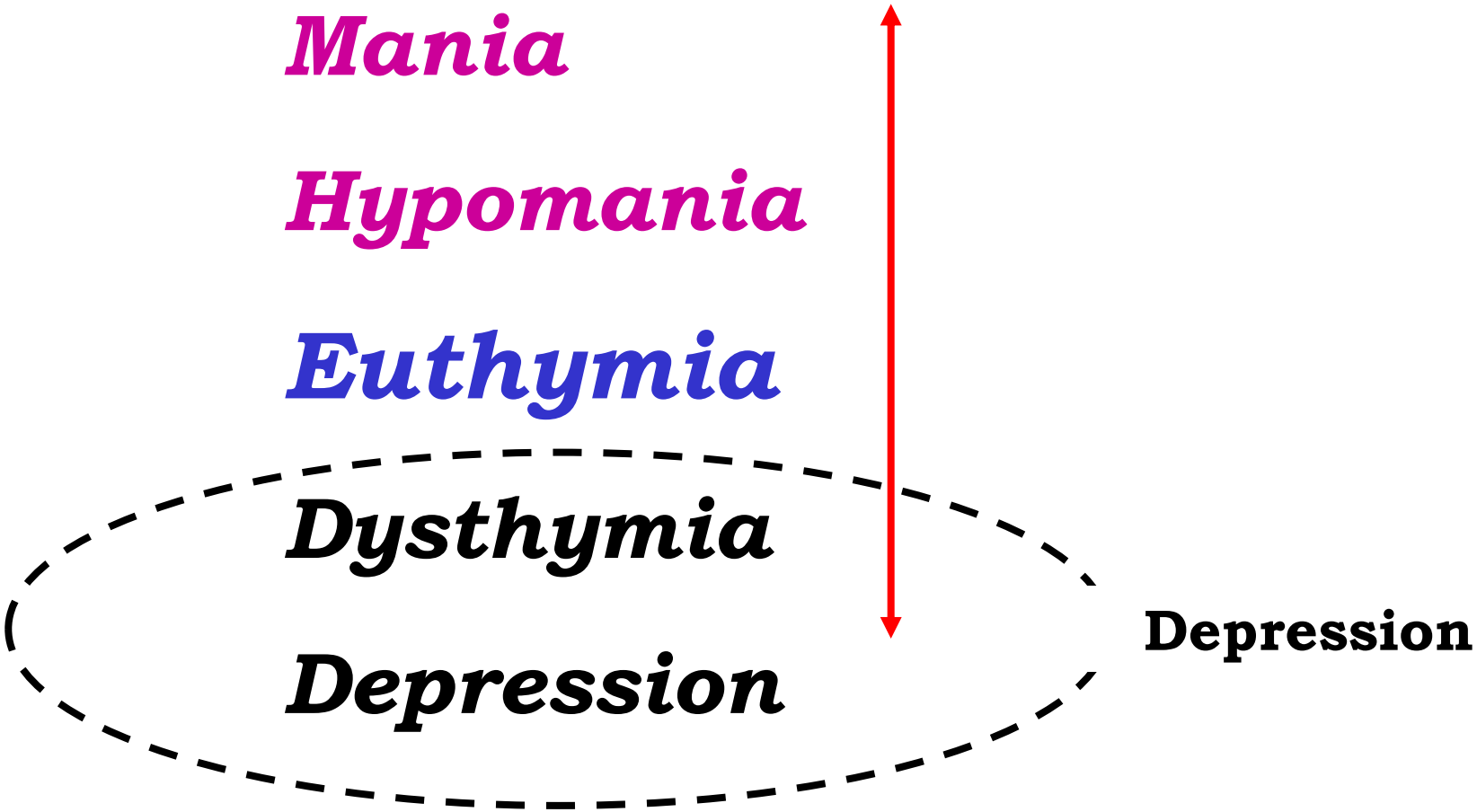
Healy and Moragle: Brain 128:1314-1322, 2005

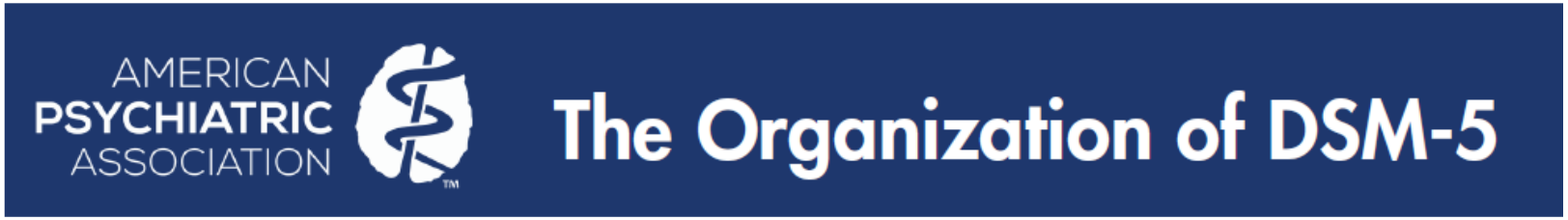


AFFECTIVE DISORDERS
(mood disorders)

- **depression (unipolar depression, major depression)**
- **bipolar disorder**
- **anxiety disorder**

MOOD VARIATIONS





Neurodevelopmental Disorders
Schizophrenia Spectrum and Other Psychotic Disorders
Bipolar and Related Disorders
Depressive Disorders
Anxiety Disorders
Obsessive-Compulsive and Related Disorders
Trauma- and Stressor-Related Disorders
Dissociative Disorders
Somatic Symptom Disorders
Feeding and Eating Disorders
Elimination Disorders
Sleep-Wake Disorders
Sexual Dysfunctions
Gender Dysphoria
Disruptive, Impulse Control and Conduct Disorders
Substance Use and Addictive Disorders
Neurocognitive Disorders
Personality Disorders
Paraphilic Disorders
Other Disorders

Depression

- **major depression – MDD**

genetic back ground ?

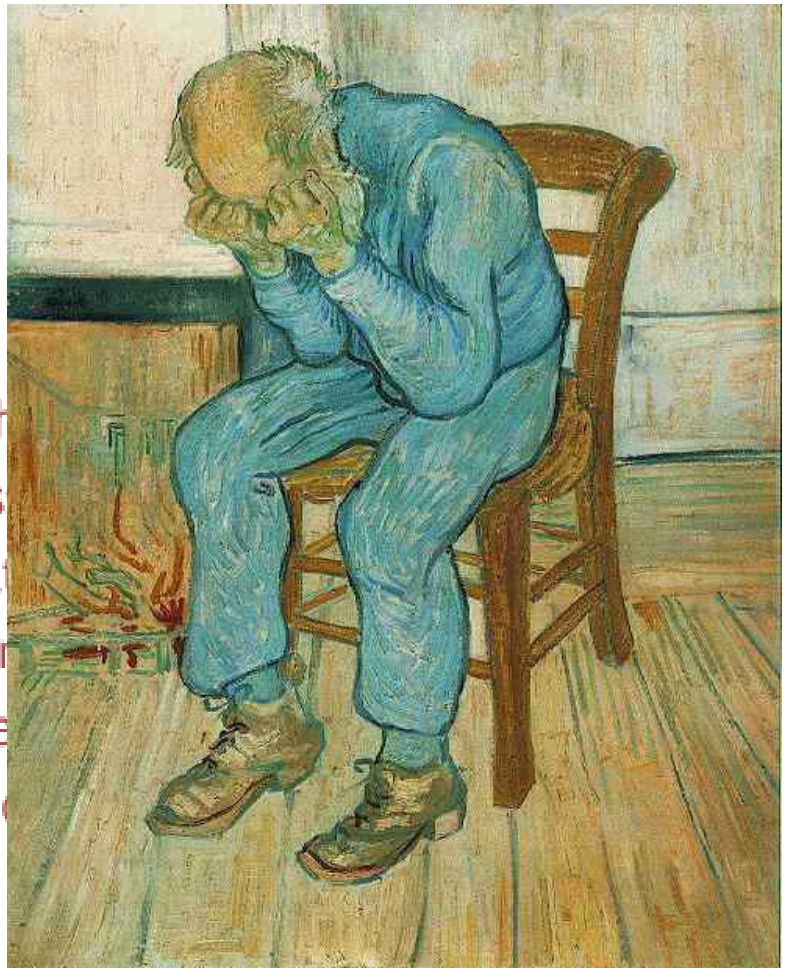
MDD prevents a person from functioning normally, it interferes with a person's ability to work, sleep, study, eat, enjoy once-pleasurable activities

- **dysthymia - characterized by long-term (2 years or longer) symptoms that may not be severe enough to disable a person but can prevent normal functioning or feeling well.**

- **minor depression - symptoms for 2 weeks or longer that do not meet full criteria for MDD. Without treatment, people are at high risk for developing MDD**

Psychotic depression, postpartum depression, seasonal affective disorder (SAD)

Depression



— Dr. Kevin Stark

van Gogh 1890

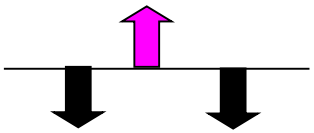
SYMPTOMS OF DEPRESSION

- Low mood
- Marked decrease in interest
- Marked lack of feeling joy
- Significant changes in the body weight (loosing or gaining weight)
- Insomnia or sleepiness
- Psychomotor agitation or retardation
- Fatigue
- Feeling of worthlessness or exaggerated consciousness of guilt
- Decrease of ability to concentrate
- Returning thoughts in relation to death and suicide

Bipolar disorder

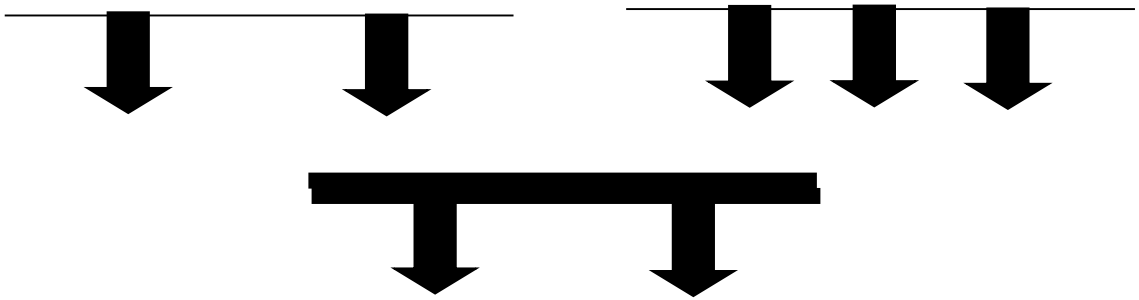
Mania
Hypomania
Euthymia
Dysthymia
Depression

depressive and manic phases may alternate

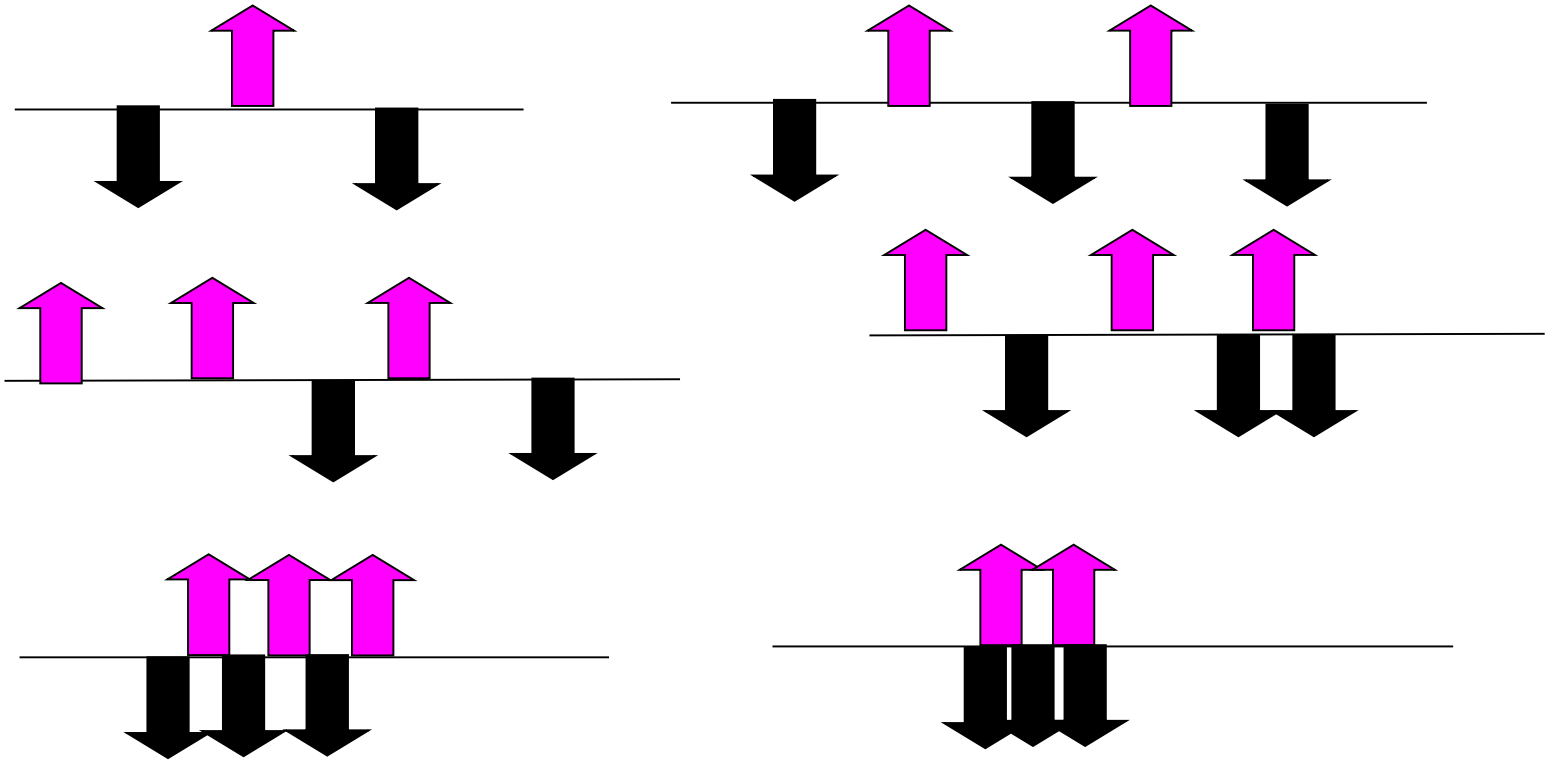


Both include subtypes and variations in severity

Depression



Bipolar disorder



Symptoms of hypomania

- Elevated mood
- Increased energy, motivation
- Optimism
- Decreased sleep
- Hypersexuality
- Increased creativity (not always, a significant difference compared with mania)

Mixed episodes

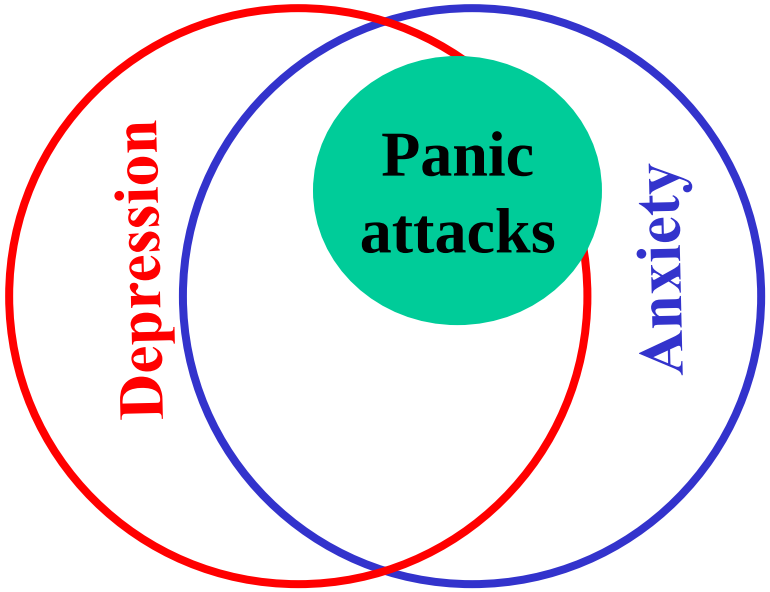
- Symptoms of depression and mania/hypomania appear at the same time
- **Very dangerous!!! – increased suicidal motivation**
- E.g: thinking of big things and feeling hopeless, running thoughts during depression, crying in manic episode

Anxiety disorders

- **Panic disorder** (dyspnoe, palpitation, tremor, sweating, nausea - gastrointestinal discomfort, depersonalizations, feeling of hot/cold, substernal pain, fear of death, general fear)
- **Obsessive-compulsive disorder** (OCD)
- **Posttraumatic stress disorder** (PTSD)
- **Generalized anxiety disorder** (GAD)
- **Premenstrual dysphoric disorder** (PMDD)

Depression and anxiety together

Schatzberg AF, J Clin Psych Monograph, 13:2, 1995

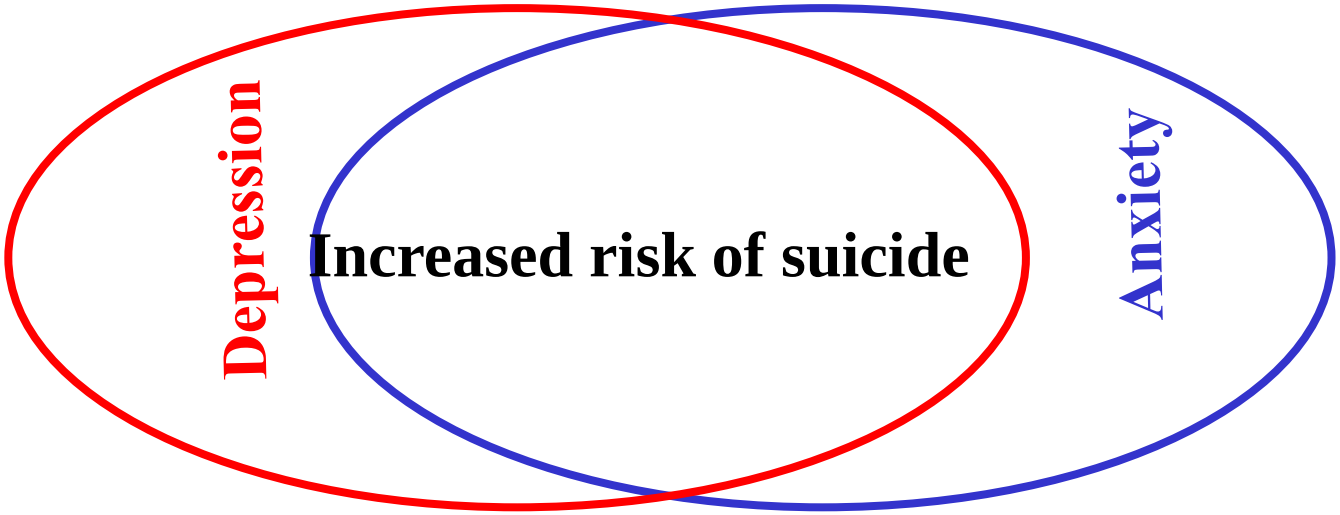


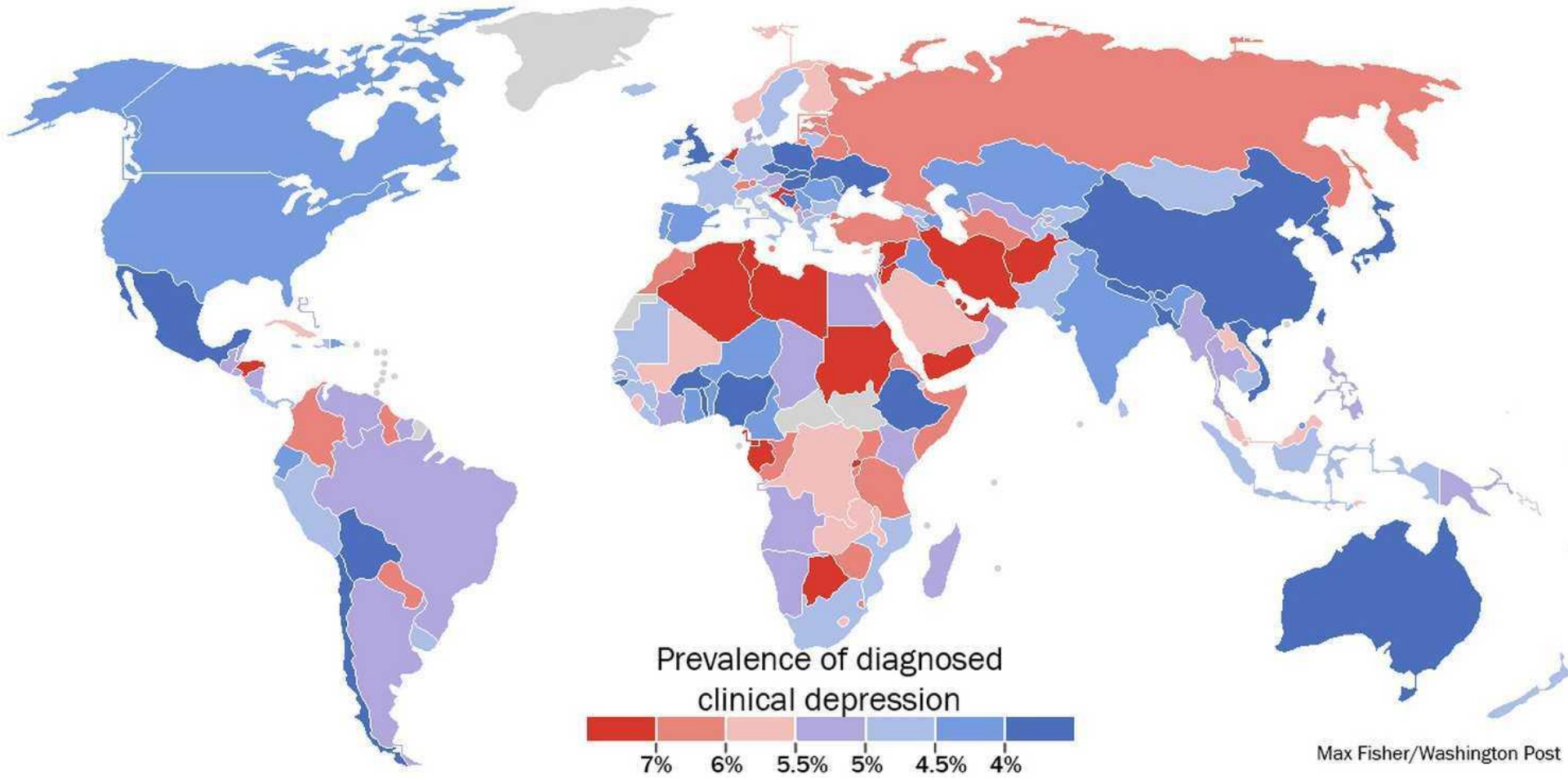
- 30-60% of patients suffering from general anxiety show depressive symptoms
- 60% of patients with depression may experience anxiety symptoms
  - In major depression the frequency of panic attacks is about 15-30%

Depression, anxiety, suicide

Culpepper L:. http://www.medscape.com/viewarticle/730857_print

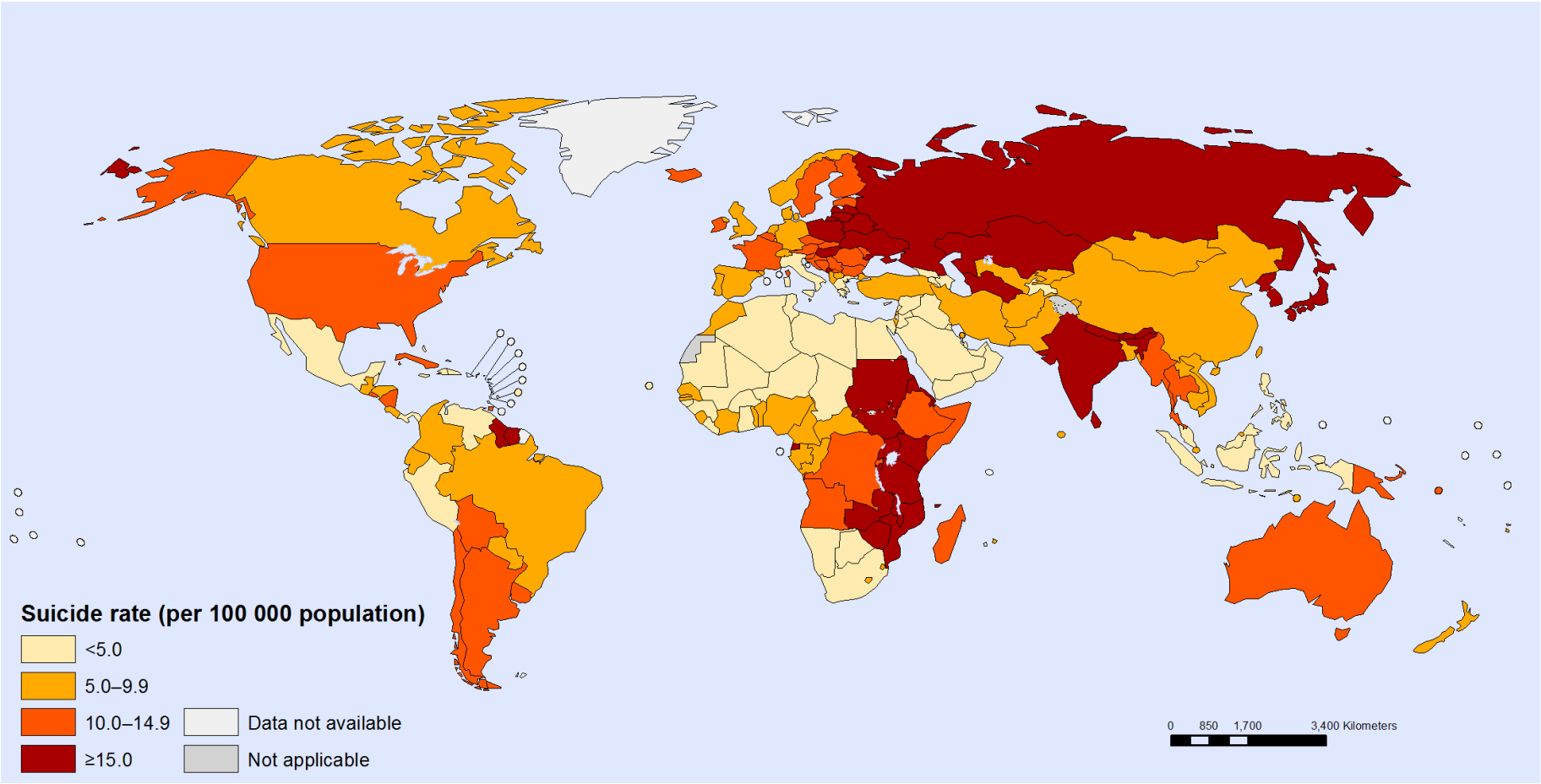
- 1 million people commit „successful” suicide a year
- The risk of suicide is 20-fold higher in depression than in the average population
- 8% of patients suffering from major depression try suicide during their lives
- Major depression can be diagnosed in 60 % of people who tried suicide
- Accompanied anxiety increases the suicide risk (panic disorde: 25% ; post-traumatic stress syndrome: 38%)




Prevalence of diagnosed
clinical depression
7%
6%
5.5%
5%
4.5%
4%
Max Fisher/Washington Post

2013

Age-standardized suicide rates (per 100 000 population), both sexes, 2012

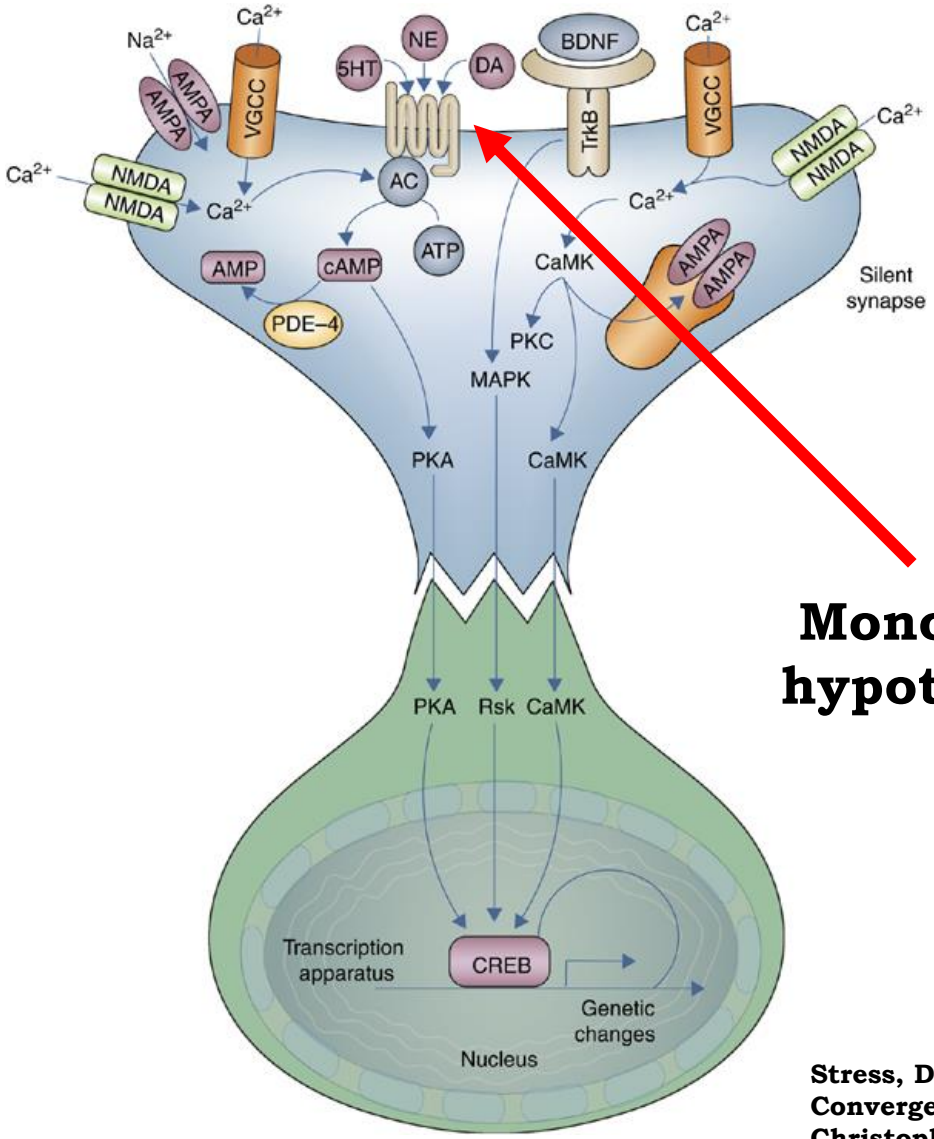


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

PATHOGENEZIS of MDD I



Monoamine (NE,5-HT, DA) hypothesis (Schildkraut)

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms
Christopher Pittenger and Ronald S Duman, Neuropsychopharmacology 2007, 33:88

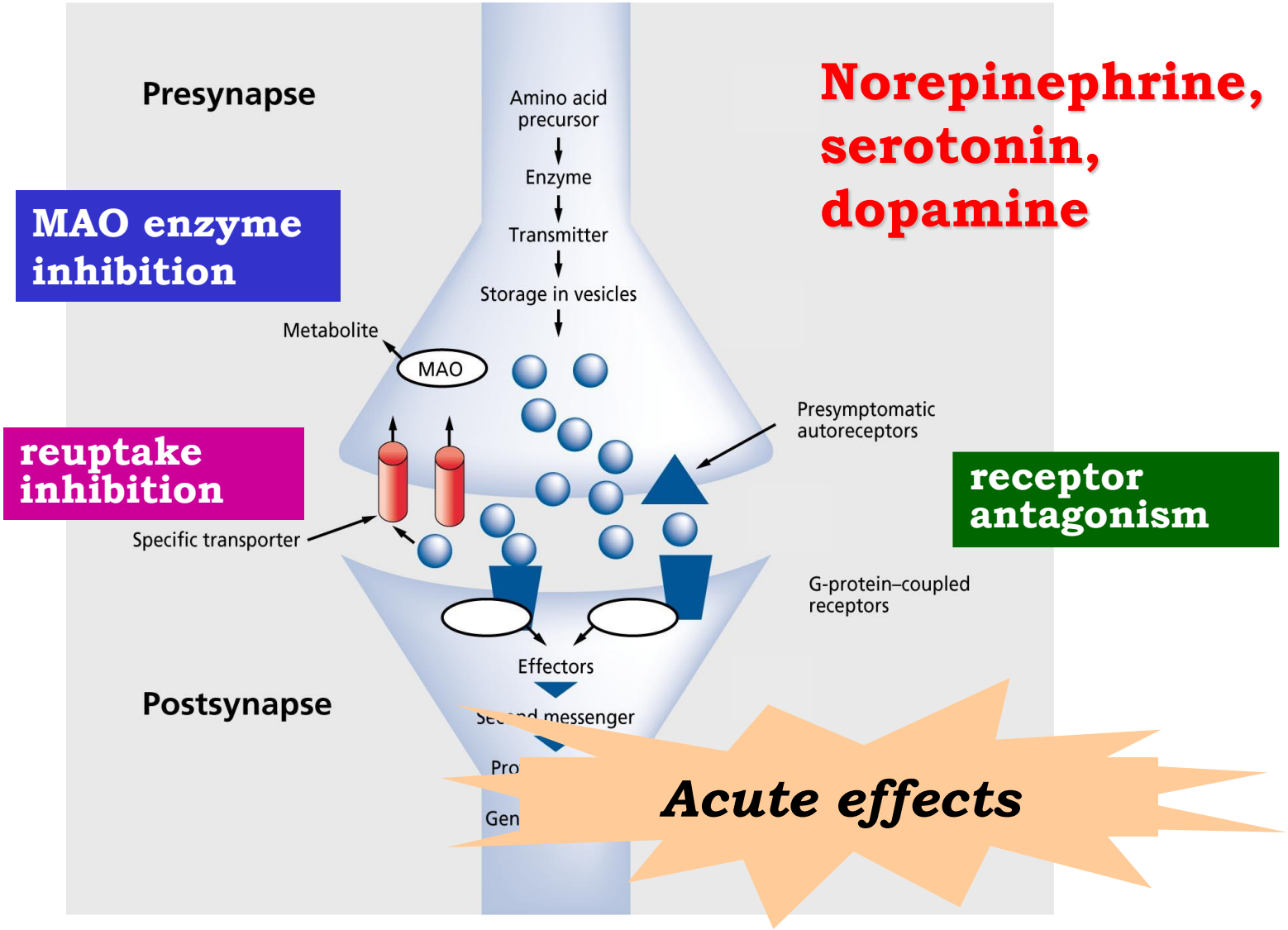
Monoamine (NE,5-HT) hypothesis (Schildkraut)

Some argues for it:

- **Monoamine depletors (reserpine) induce depression**
- **Genetic studies – functional polymorphism exists for SERT (5-HT transporter) gen**
- **Reduction of 5-HIIA (5-HT metabolite) in CSF is associated with violent and impulsive behavior (not specific for depression)**

- **Nearly all the antidepressants enhance the availability of NE and/or 5-HT and/or DA in the synaptic cleft**

Majority of the pharmacons used nowadays are based on the monoamine hypotheses



Weeks (4-6) are needed for development of antidepressant effect

????

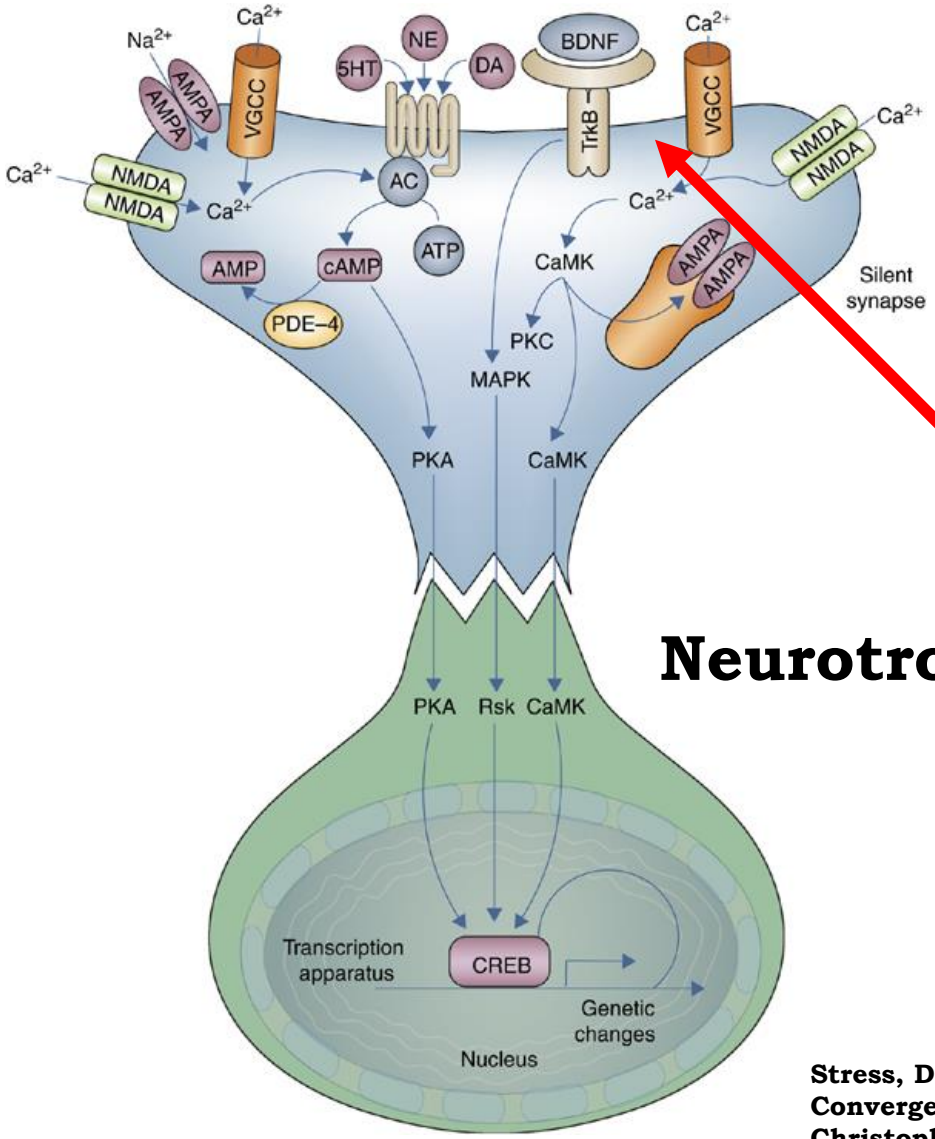
α_2 receptor desensitization (presynaptic)

5-HT_2 receptor desensitization

enhanced sensitivity of 5-HT_{1A} receptors

β receptor desensitization and down regulation

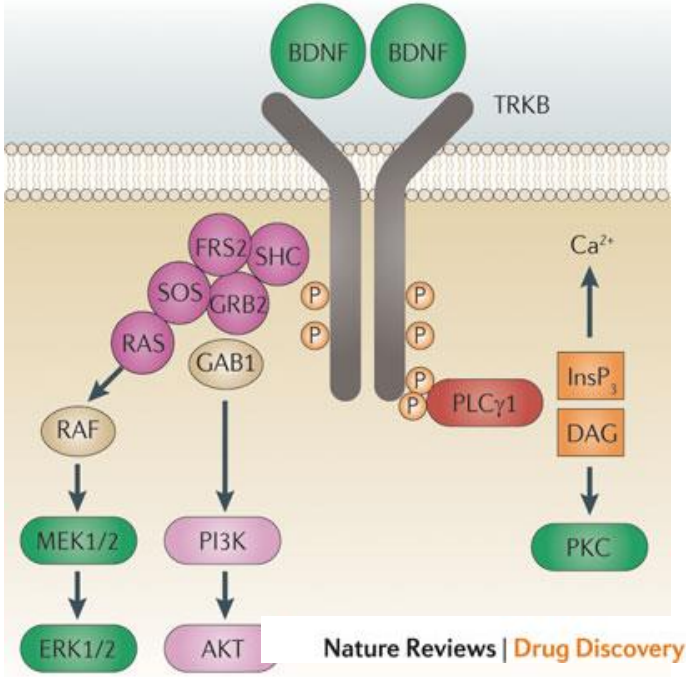
PATHOGENEZIS of MDD II

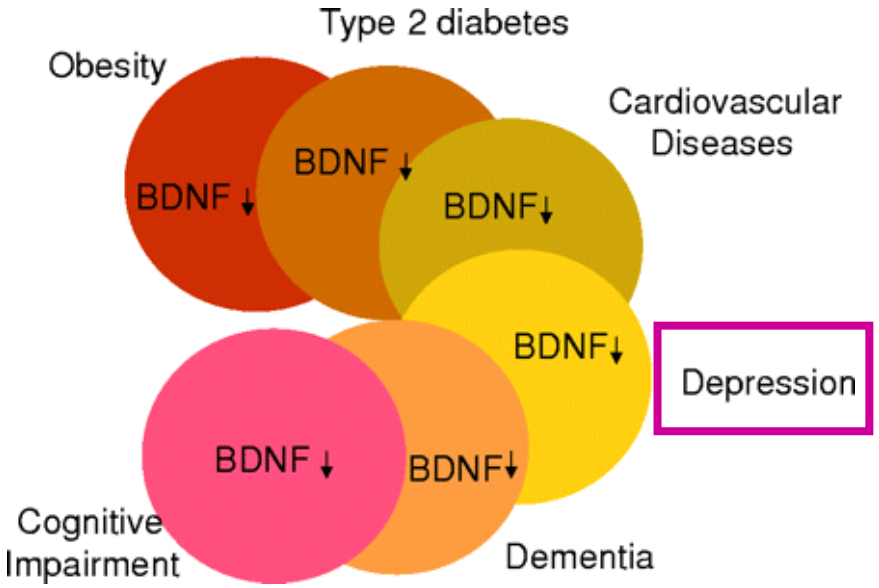


Neurotrophic hypothesis

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms
Christopher Pittenger and Ronald S Duman, Neuropsychopharmacology 2007, 33:88

BDNF receptor

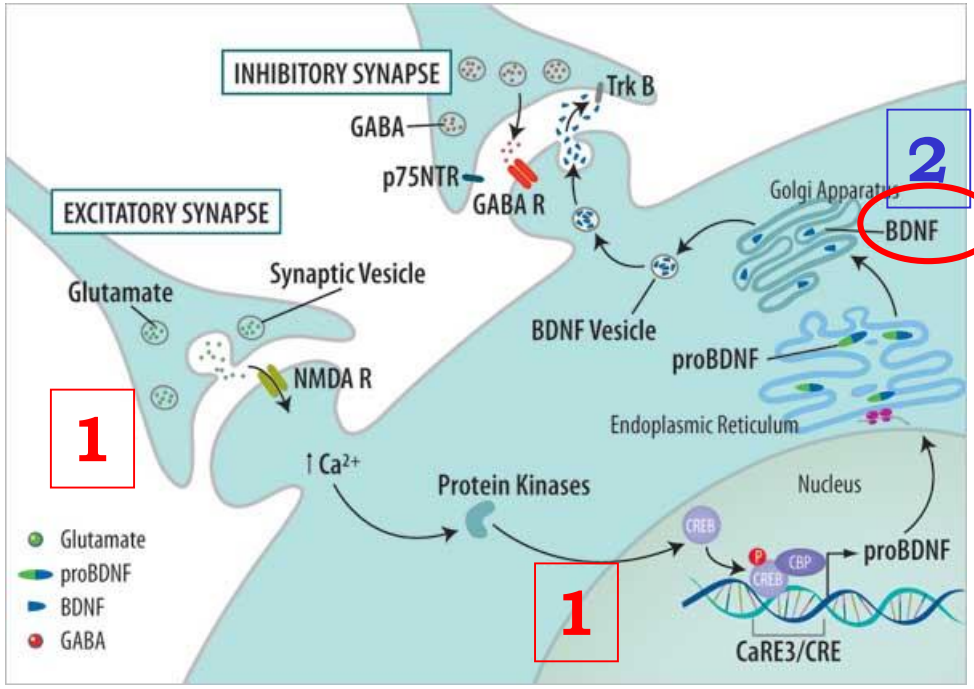




Experimental Physiology 94:1153, 2009

BDNF (brain-derived neurotrophic factor) plays critical role in regulation of neural plasticity, neurogenesis, neuronal survival, etc.

Neurotrophic hypothesis



Activity-dependent BDNF expression influences homeostatic plasticity

In animal experiments all the until used antidepressants (and also electroshock) enhances the BDNF level **(in chronic administration !!)**

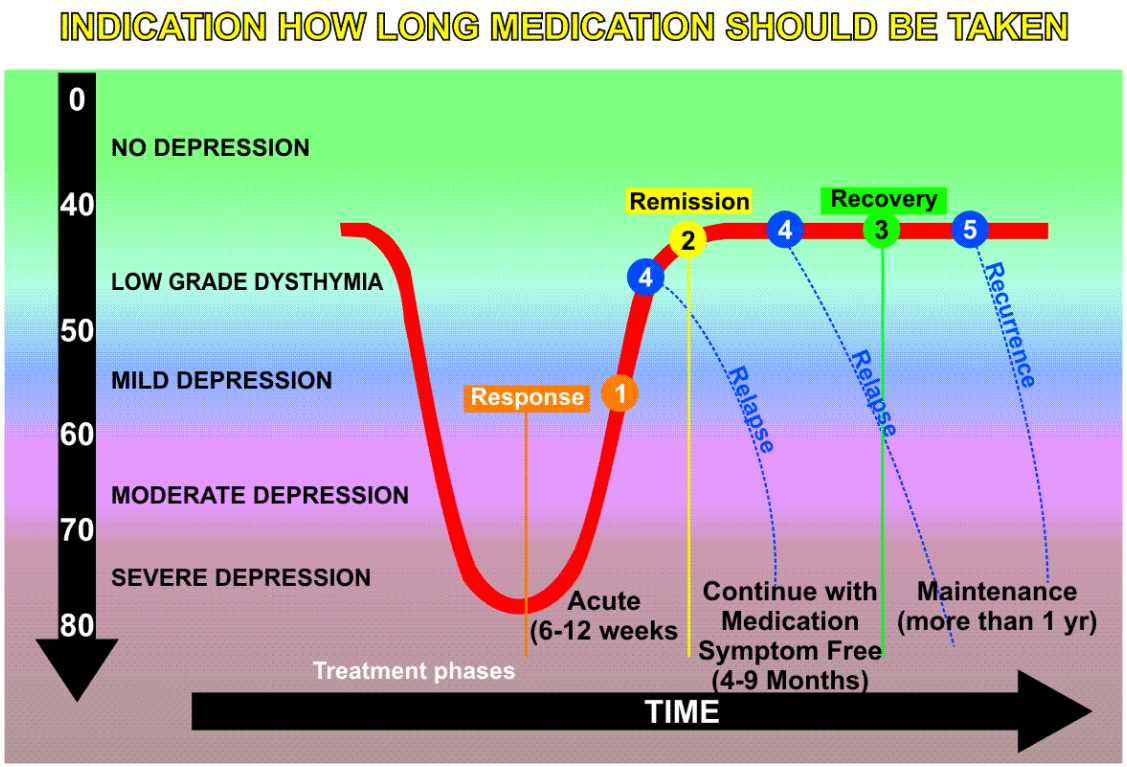
1. Glutamate neuronal activity increases postsynaptic BDNF levels via Ca^{2+} -dependent transcription factors

2. Postsynaptic release of BDNF subsequently promotes the formation of inhibitory GABAergic synapses.

https://www.rndsystems.com/resources/articles/synaptic-bdnf-connecting-physiology-therapy

AIM OF ANTIDEPRESSANT/ANTIMANIC TREATMENT

- **Relief of acute symptoms weeks**
- **Prevention of relapse (maintenance therapy) months**
- **Prevention of repeated episodes (prophylactic treatment) years**



Drugs in the treatment of depression

Monoamine re-uptake inhibitors

- SSRI (fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram) – usually first choice
- SNRI (reboxetine)
- SSNRI (venlafaxine, duloxetine) – venlafaxine is very popular, selectivity to serotonin transporter is lost over 200mg – drug switch is simply a dose escalation
- TCA (imipramine, desipramine, clomipramine, amitryptiline)
- NE/DA re-uptake inhibitor (bupropion) – in case of stuporous depression

Drugs in the treatment of depression

5-HT re-uptake inhibitor + receptor inhibitor

- 5-HT reuptake inhibitor and 5-HT2A antagonist (trazodon, nefazodon, (hepatotoxic)
- 5-HT reuptake inhibitor and 5-HT1A partial agonist (vilazodon)
- 5-HT reuptake inhibitor and 5-HT3A, 5-HT7 antagonist, 5-HT1B parcial agonist and 5-HT1A agonist (Vortioxetin)

5-HT re-uptake inhibitor + receptor inhibitor

- NA reuptake inhibitor, α2 és 5-HT2,(3) antagonist (mirtazapin, mianserin)

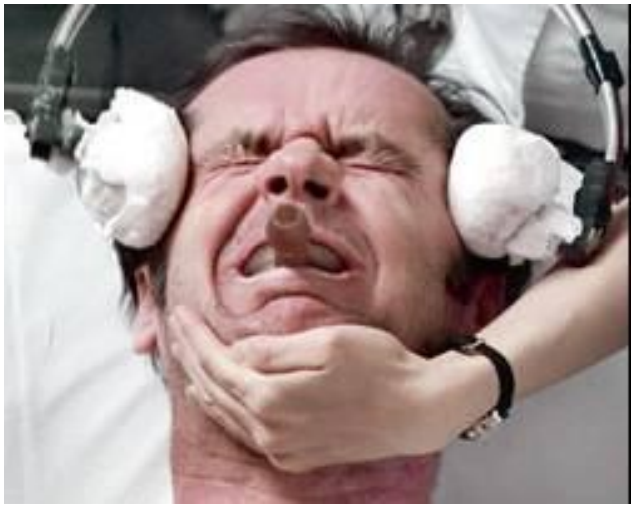
Melatonin MT1-2 agonist (agomelatin)

MAO inhibitors

- MAO-A selective (moclobemid)
- MAO-B selective (selegiline)

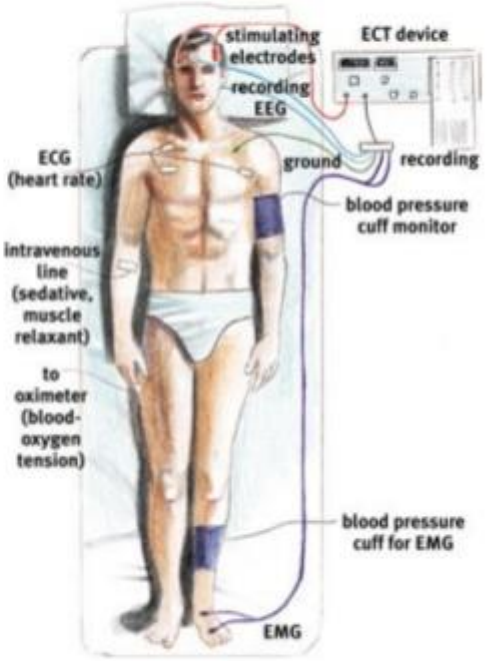
Antidepressant	Usual dose range (mg/day)	Common side effects
Selective serotonin reuptake inhibitors (SSRI)		
Fluoxetine	20-80	Sexual dysfunction, GI distress, weight loss/gain, anxiety, insomnia
Paroxetine	20-60	
Fluvoxamine	50-300	
Sertraline	50-200	
Citalopram	20-40	
Escitalopram	10-20	
Tricyclic tertiary amines (TCAs)		
Amitriptyline	50-200	Sexual dysfunction, anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, mild GI distress, weight gain
Doxepin	75-300	
Imipramine	75-300	
Clomipramine	75-300	
Tricyclic Secondary Amines		
Desipramine	100-300	
Nortriptyline	25-150	
Protriptyline	15-20	
Tetracyclic		
Maprotiline	50-75	
Unicyclic		
Bupropion	150-450	Mild GI distress, high risk of seizure after 450 mg/day
Norepinephrine Serotonin reuptake Inhibitors (NSRI)		
Venlafaxine	75-300	Mild anticholinergics effects, drowsiness, conduction abnormalities, GI distress
Duloxetine	20-60	
Milnacipran	50-200	
Desvenlafaxine		
Norepinephrine Serotonin Reuptake Enhance (NSRE)		
Tianeptine	25-50	Nausea, constipation, abdominal pain, headache, dizziness and changes in dreaming
Noradrenaline and Specific Serotonin Antidepressants (NaSSA)		
Mirtazapine	15-45	Mild anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, GI distress, weight gain
Atypical antidepressants/Serotonin Modulators		
Trazadone	150-300	Mild anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, GI distress, weight gain,
Nefazodone	100-300	

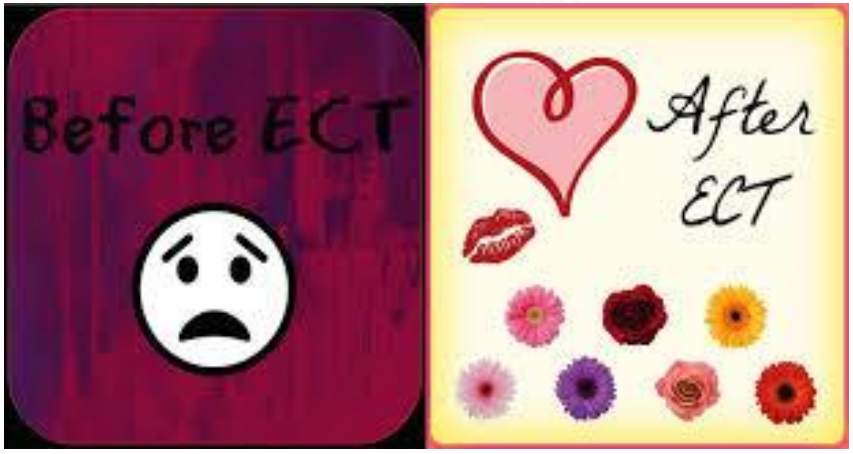
Brain Stimulation

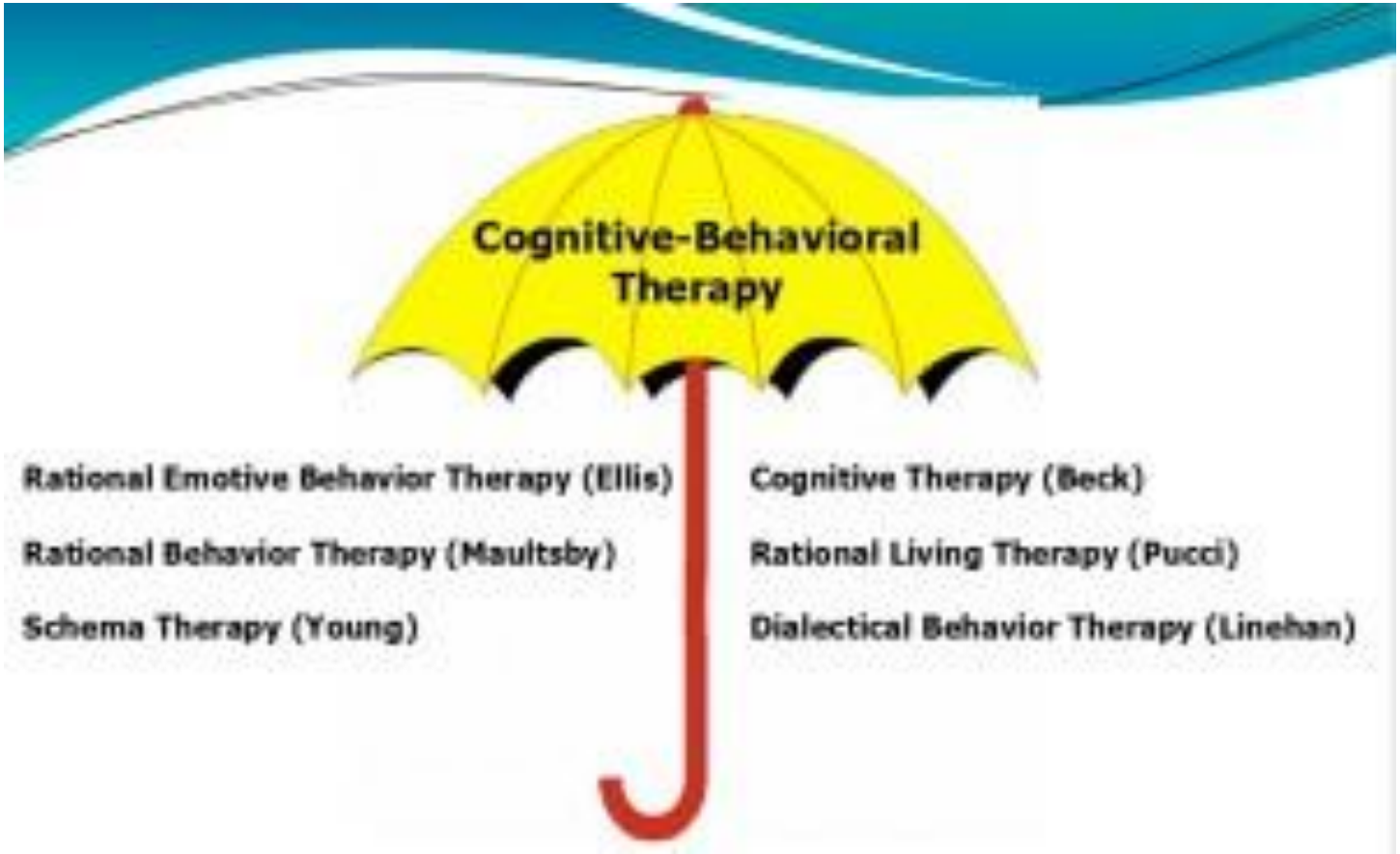


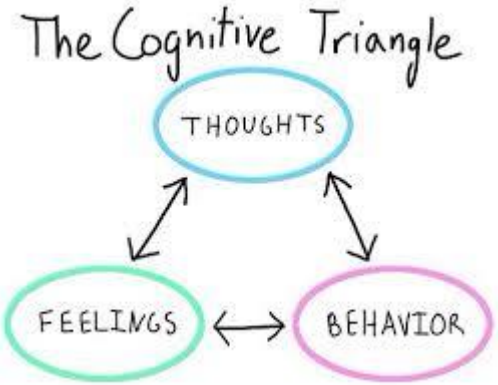
Electroconvulsive Therapy (ECT)

ECT is used for severely depressed patients who do not respond to drugs. The patient is anesthetized and given a muscle relaxant. Patients usually get a 100 volt shock that relieves them of depression.

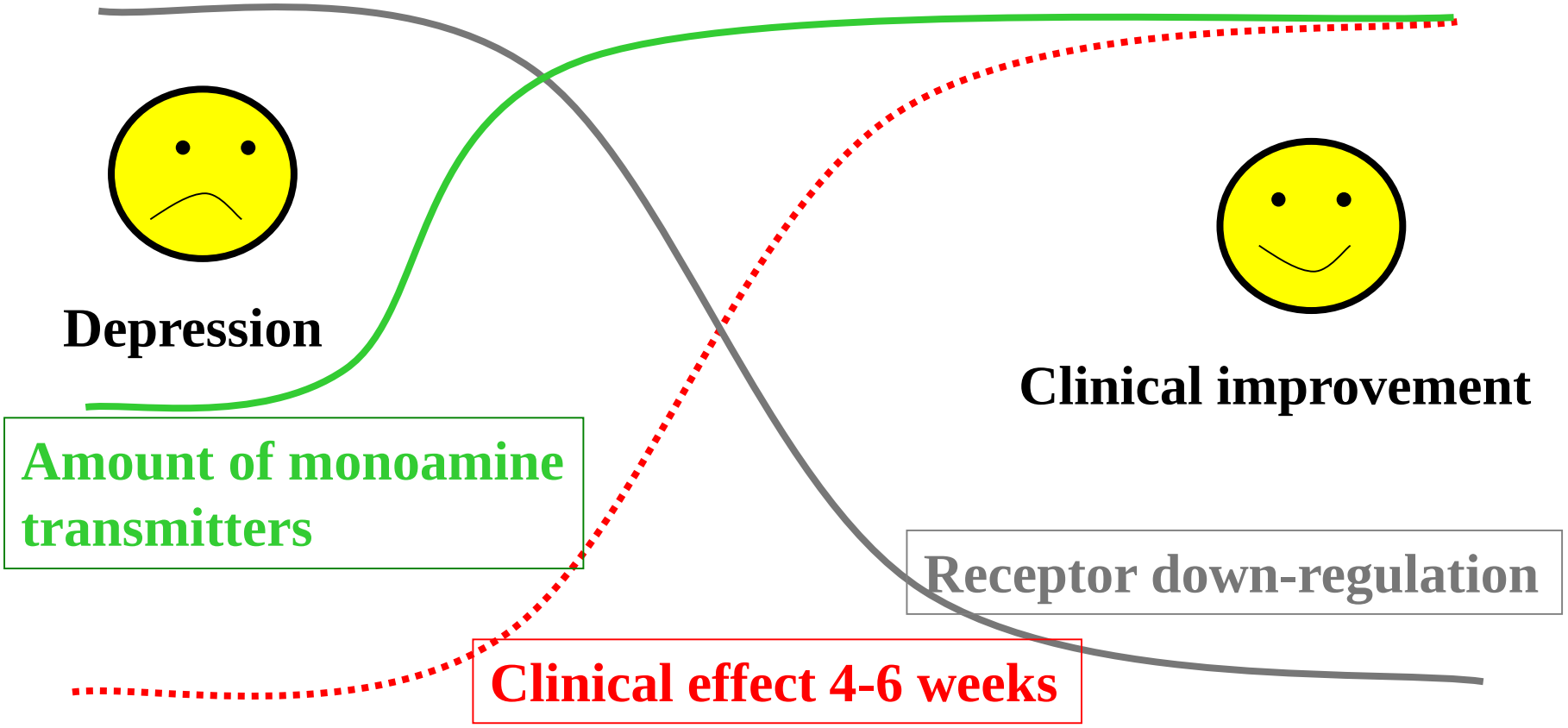





Cognitive-Behavioral Therapy
Rational Emotive Behavior Therapy (Ellis)
Rational Behavior Therapy (Maultsby)
Schema Therapy (Young)
Cognitive Therapy (Beck)
Rational Living Therapy (Pucci)
Dialectical Behavior Therapy (Linehan)

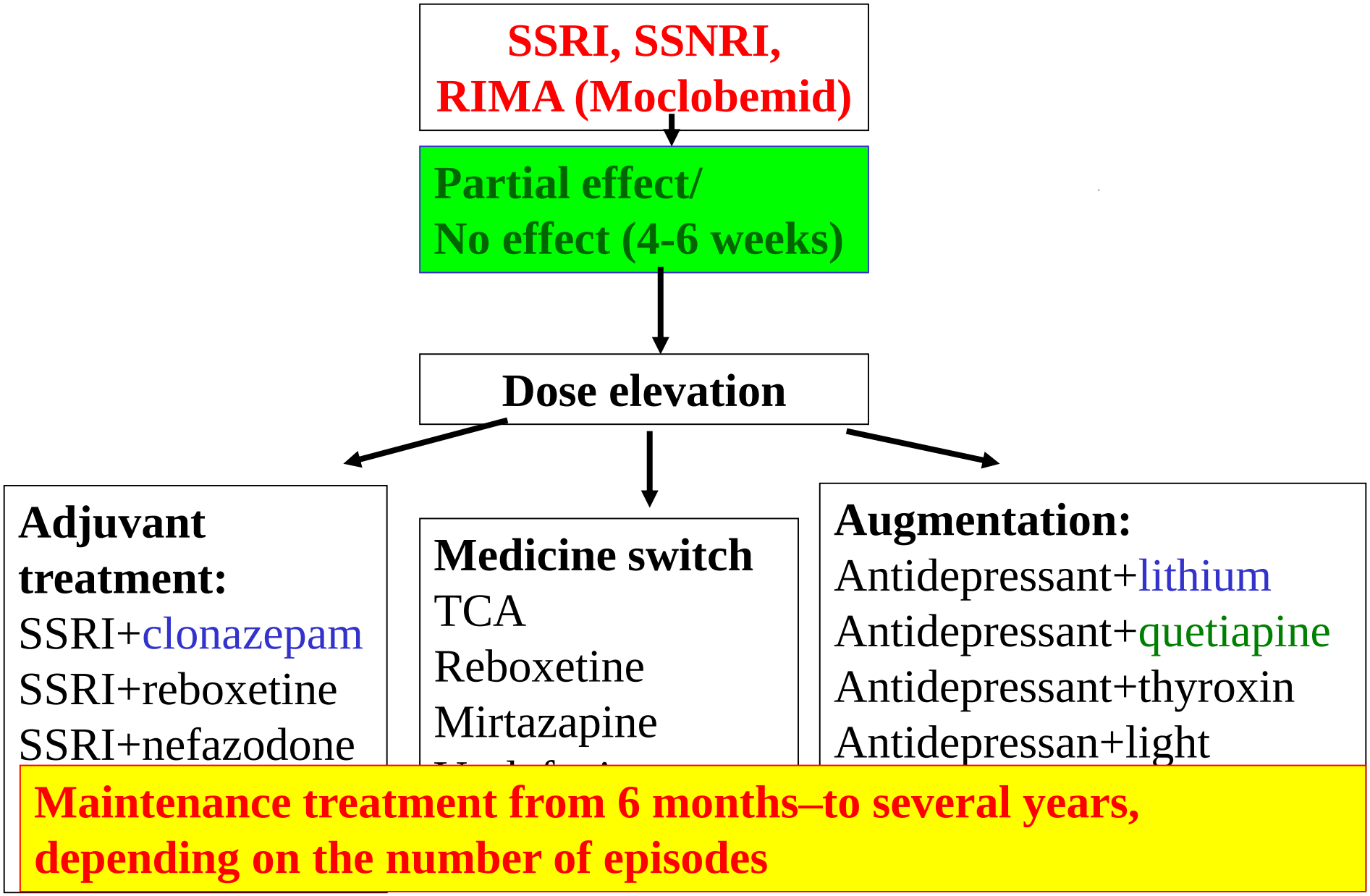

The Cognitive Triangle
THOUGHTS
FEELINGS
BEHAVIOR

Changes during the treatment of depression



- The clinical improvement correlates well with the receptor down-regulation (minimum 2-3 weeks)

Tretament scheme of major depression



Factors that determine the selection of Antidepressant Drug

Patient specific

- Patients preference
- Previous history of response/tolerability to medication in the patient or family member
- Past side effects with medication
- Other medication being taken – drug interactions
- Patient's age – with increasing age the pharmacokinetic and pharmacodynamic changes become more important
- Comorbid medical illness (e.g., glaucoma, cardiac conditions)
- Comorbid psychiatric disorder/symptoms
- Gender issues – sexual dysfunction
- Intellectual and psychological capacities

Drug specific

- Side effects
- Cost
- Dosing strategy
- Type of formulation - Tablet, Cap, Syrup
- Safety in overdose (Relative Toxicity) - fatal overdose is significantly
- Lower with SSRIs than with tricyclic antidepressants

Some of the physical illnesses commonly associated with depression

- Epilepsy
- Post stroke
- Parkinson's Disease
- Multiple Sclerosis
- Degenerative Brain Disease
- Alzheimer's Disease
- Coronary Artery
- Disease
- Depression in Malignancy
- Hypothyroidism
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's Syndrome
- Addison's disease
- Diabetes mellitus

Clinical Practice Guidelines for the management of Depression

Shiv Gautam, Akhilesh Jain, [...], and Sandeep Grover 2017 Jan Indian Journal of Psychiatry

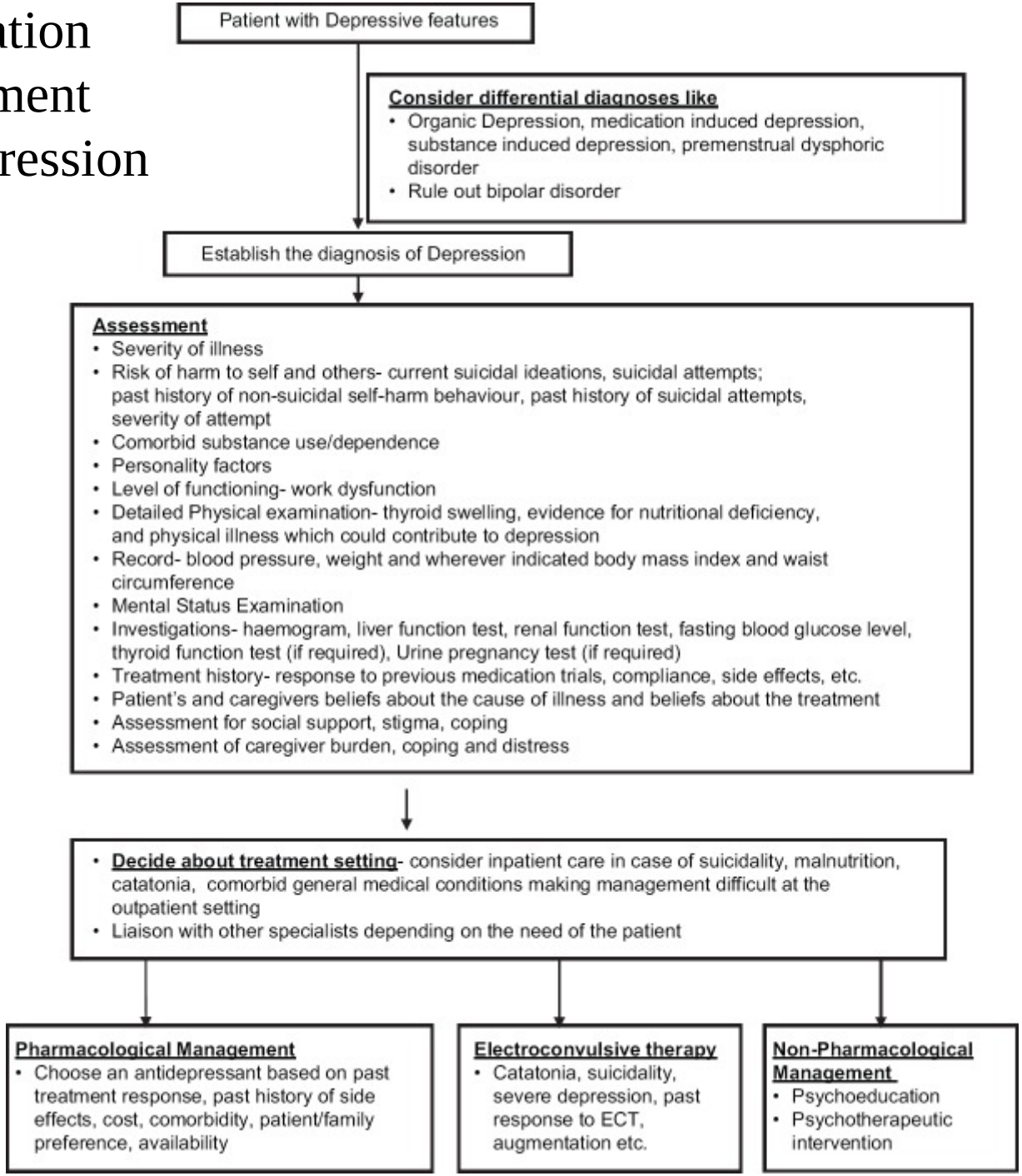
Medications known to cause depression

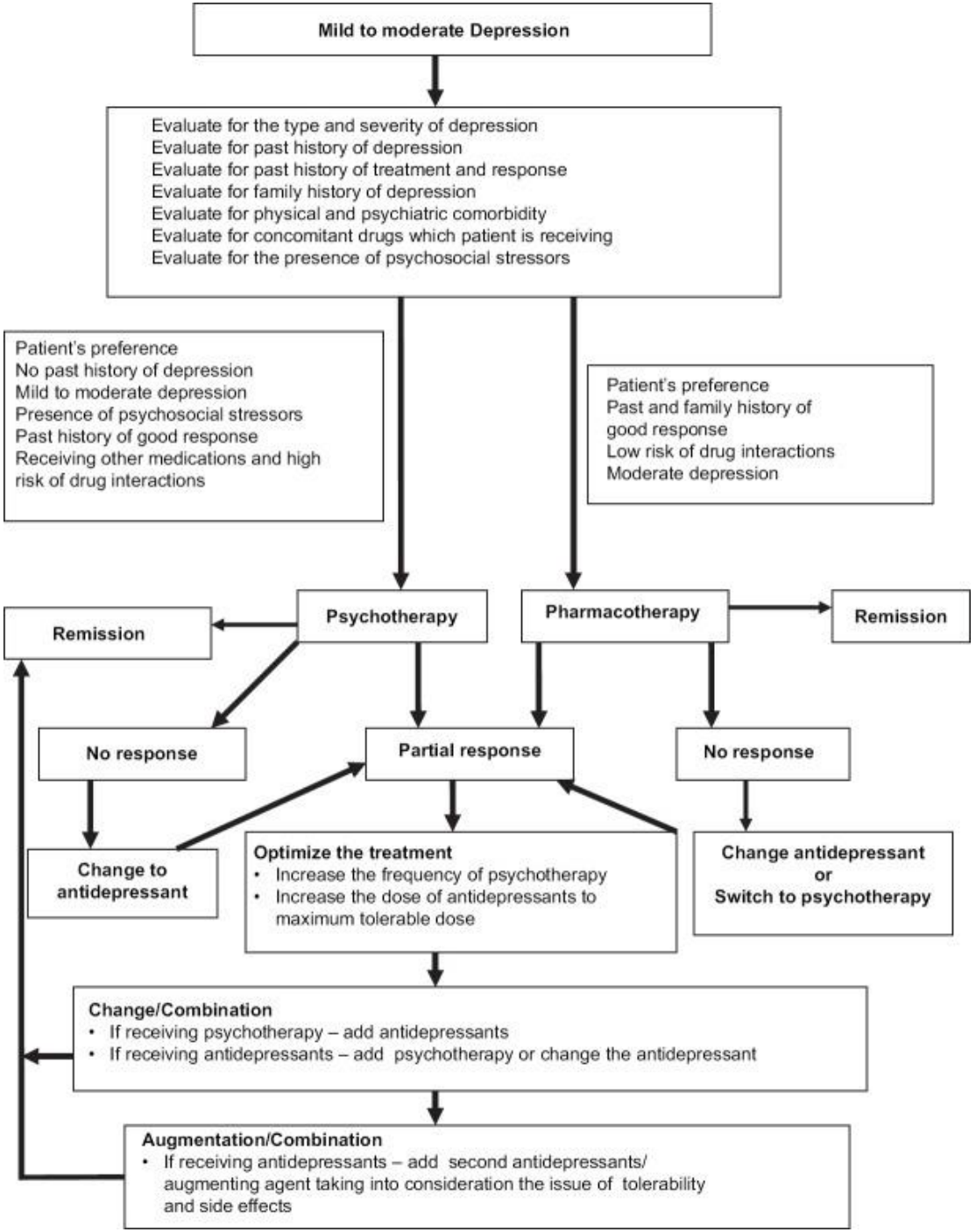
Cardiovascular drugs	Azathioprine	Ampicillin	Penicillin G	Benzodiazepines	Efavirenz
ACE inhibitors	Bleomycin	Chloramphenicol	procaine	Chloral hydrate	Enfuvirtide
Calcium channel	Cisplatin	Methylphenidate (Ritalin)	Streptomycin	Ethanol	Saquinavir
blockers	Cyclophosphamide	Chloroquine	Sulfonamides	**Other drugs**	Zidovudine
Clonidine	Doxorubicin	Clofazimine	Tetracycline	Choline	**Anticonvulsants**
Digitalis	Vinblastine	Cycloserine	Trimethoprim	Cimetidine	Ethosuximide
Guanethidine	Vincristine	Cyclosporine	**Hormones**	Disulfiram	Phenobarbital
Hydralazine	**Antiparkinsonian**	Dapsone	Adrenocorticotropin	Lecithin	Phenytoin
Methyldopa	**drugs**	Ethambutol	Anabolic steroids	Methysergide	Primidone
Procainamide	Amantadine	Ethionamide	Glucocorticoids	Phenylephrine	Tiagabine
Propranolol	Bromocriptine	Foscarnet	Oral contraceptives	Physostigmine	Vigabatrin
Reserpine	Levodopa	Ganciclovir	**Antipsychotic drugs**	Ranitidine	**Anti-inflammatory**
Thiazide diuretics	**Stimulants**	Griseofulvin	Fluphenazine	Statins	**agents**
Guanabenz	Amphetamines	Isoniazid	Haloperidol	Tamoxifen	NSAIDS
Zolamide diuretics	withdrawal)	Metoclopramide	**Sedatives and**	**Antiretroviral drugs**	
Chemotherapeutics	Caffeine	Metronidazole	**antianxiety**	Atazanavir	
6-Azauridine	Cocaine (withdrawal)	Nalidixic acid	**drugs**		
Asparaginase	**Anti-infective agents**	Nitrofurantoin	Barbiturates		

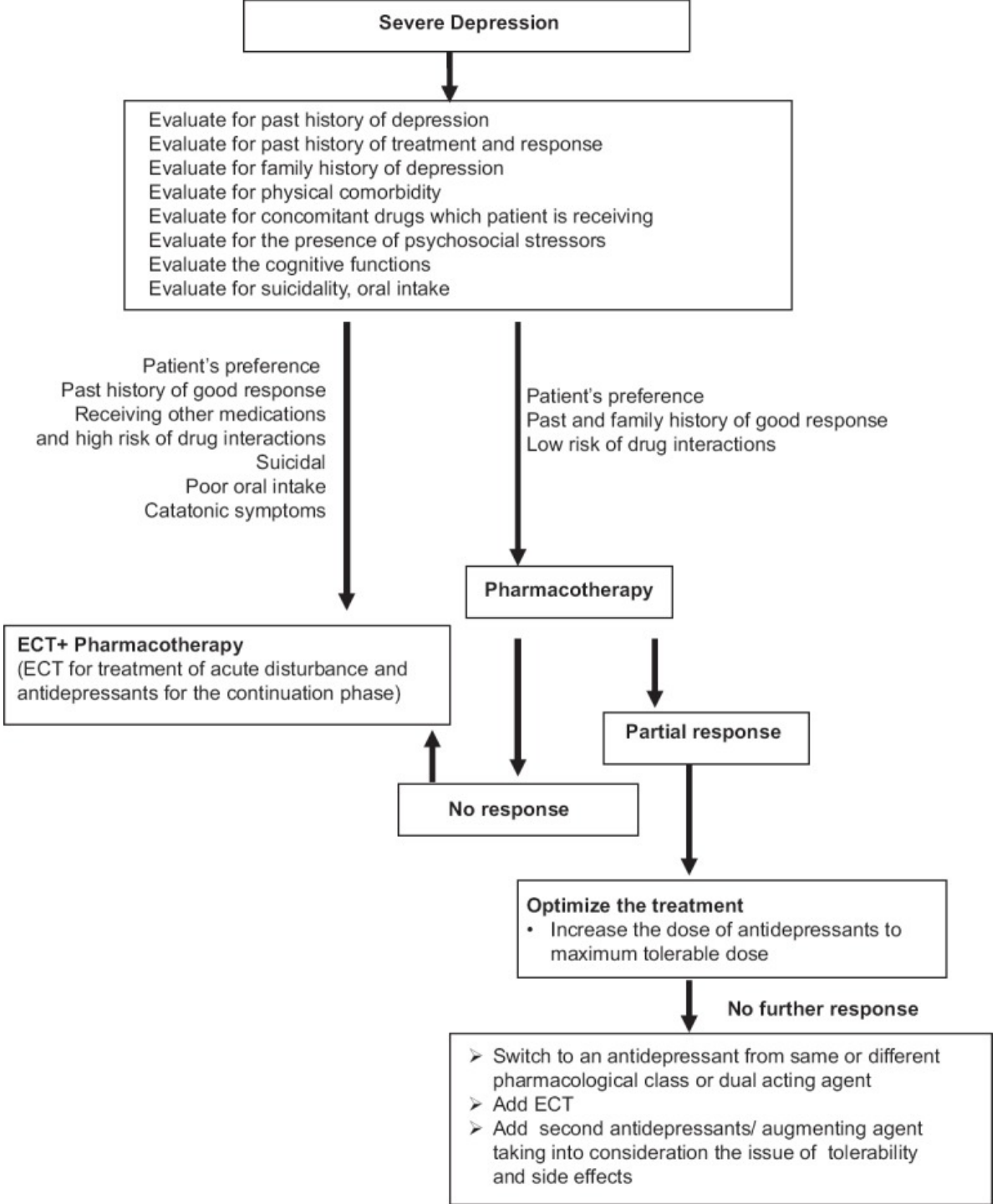
Clinical Practice Guidelines for the management of Depression

Shiv Gautam, Akhilesh Jain, [...], and Sandeep Grover 2017 Jan Indian Journal of Psychiatry

Initial evaluation and management plan for Depression




Mild to moderate Depression
Evaluate for the type and severity of depression
Evaluate for past history of depression
Evaluate for past history of treatment and response
Evaluate for family history of depression
Evaluate for physical and psychiatric comorbidity
Evaluate for concomitant drugs which patient is receiving
Evaluate for the presence of psychosocial stressors
Patient's preference
No past history of depression
Mild to moderate depression
Presence of psychosocial stressors
Past history of good response
Receiving other medications and high risk of drug interactions
Patient's preference
Past and family history of good response
Low risk of drug interactions
Moderate depression
Psychotherapy
Pharmacotherapy
Remission
Remission
No response
Partial response
No response
Change to antidepressant
Optimize the treatment
• Increase the frequency of psychotherapy
• Increase the dose of antidepressants to maximum tolerable dose
Change antidepressant or Switch to psychotherapy
Change/Combination
• If receiving psychotherapy – add antidepressants
• If receiving antidepressants – add psychotherapy or change the antidepressant
Augmentation/Combination
• If receiving antidepressants – add second antidepressants/ augmenting agent taking into consideration the issue of tolerability and side effects


Severe Depression
Evaluate for past history of depression
Evaluate for past history of treatment and response
Evaluate for family history of depression
Evaluate for physical comorbidity
Evaluate for concomitant drugs which patient is receiving
Evaluate for the presence of psychosocial stressors
Evaluate the cognitive functions
Evaluate for suicidality, oral intake
Patient's preference
Past history of good response
Receiving other medications and high risk of drug interactions
Suicidal
Poor oral intake
Catatonic symptoms
Patient's preference
Past and family history of good response
Low risk of drug interactions
Pharmacotherapy
ECT+ Pharmacotherapy
(ECT for treatment of acute disturbance and antidepressants for the continuation phase)
Partial response
No response
Optimize the treatment
• Increase the dose of antidepressants to maximum tolerable dose
No further response
➢ Switch to an antidepressant from same or different pharmacological class or dual acting agent
➢ Add ECT
➢ Add second antidepressants/ augmenting agent taking into consideration the issue of tolerability and side effects

Treatment considerations of major depression

New guideline issued by the American College of Physicians (ACP).
Ann Intern Med. 2008;149:725-733, 734-750

- Drug choice depends on the adverse effects, patients' preference and economical considerations
- In 38% of the patients there is no response in the first 6-12 weeks of the treatment
- In more than 50% of the patients remission cannot be achieved
- The risk of suicide is the highest in the first two months (it is a black box warning!!!)
- Length of the treatment
  - Usually for 4-9 months
  - In patients with more than 2 episodes the treatment should be carried out for several years

Risk of suicide

- The risk of suicide is the highest in the first two months (it is a black box warning!!!)
- Reason: the motivations and activity improve faster than the depressive symptoms disappear – higher motivation with suicidal thoughts – the patient may have the energy to commit it
- In young adults (18-25 years) the risk is the highest
- Very close observation!!!

Treatment strategy of bipolar disorder

- VERY IMPORTANT!!! – MOOD STABILIZERS
  - Lithium („gold standard”)
  - Carbamazepine
  - Valproate
  - Lamotrigine
- Antipsychotics with antimanic and mood stabilizing effets
  - olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole
- In depressive episode: SSRI or TCA – risk of onset of mania (4%, 10-60%, respectively) – always combined with mood stabilizers
- Children and adolescents: aripiprazole, ziprasidone

Anxiety disorders

- Localized in space and time:
  - Panic disorder
  - Panic disorder with agoraphobia
  - Agoraphobia
  - Special phobias
  - Social phobia
- Longer than 6 months – conditions connected with events or activities in most of the days
  - General anxiety disorder (GAD)
  - Acute stress syndrome
  - Obsessive-compulsive disorder
  - Posttraumatic stress disorder

Symptoms of panic disorder

Monthly occuring panic attacks with sudden feel of fear and at least 4 autonomic/cognitive symptoms associated

- Palpitation
- Sweating
- Shivering
- Dyspnea
- Choking sensation
- Chest pain
- Nausea, abdominal problems
- Dizziness, uncertainty
- Derealization, depersonalization
- Loss of control, fear of madness
- Death fear
- Paraesthesias
- Burning sensation or heat waive (flushing)

Drugs of choice in anxiety disorders

- Benzodiazepines (BZD)
  - Immediate action, high efficiency (high potential BZDs are chosen: clonazepam, alprazolam, lorazepam)
  - No sexual disturbance (selective anxiolytic doses are not sedative)
  - Risk of dependence, withdrawal symptoms – slow cessation, maximum length of use is few months
  - Impaired cognitive functions

Drugs of choice in anxiety disorders

- Antidepressants – especially in more severe cases
  - Primary choice: SSRIs
  - SSRIs may transiently increase anxiety – lower dose in the beginning, gradual increase
  - Can be combined with BZDs in the beginning of the treatment
  - Alternatives: TCAs, RIMA

Drugs of choice in anxiety disorders

- Buspirone ($5HT_{1A}$ partial agonist)
  - General anxiety disorder
    - In BZD naive patients
    - If cognitive impairment by the BZDs are severe
    - In agressive and irritated patients
    - The onset is slow, 2-4 weeks – can be combined with BZDs
    - If BZDs are inefficient buspirone will not act either
- Buspirone is ineffective in panic disorder!!!