6th ASEAN CONFERENCE ON PRIMARY HEALTH CARE
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Update on Management of Anxiety Disorders

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Overview

- Challenges of Mental Health in primary care
  - Patient, family, socio-economy.
- Terminology
- Brief description of the disorder

- Advances in Neuroscience
- Treatment

Mental Health is for **Everyone**

Challenges in Primary Care:

- Impairment and disability for patients.
- Burden of care to caregivers.
- Direct cost.

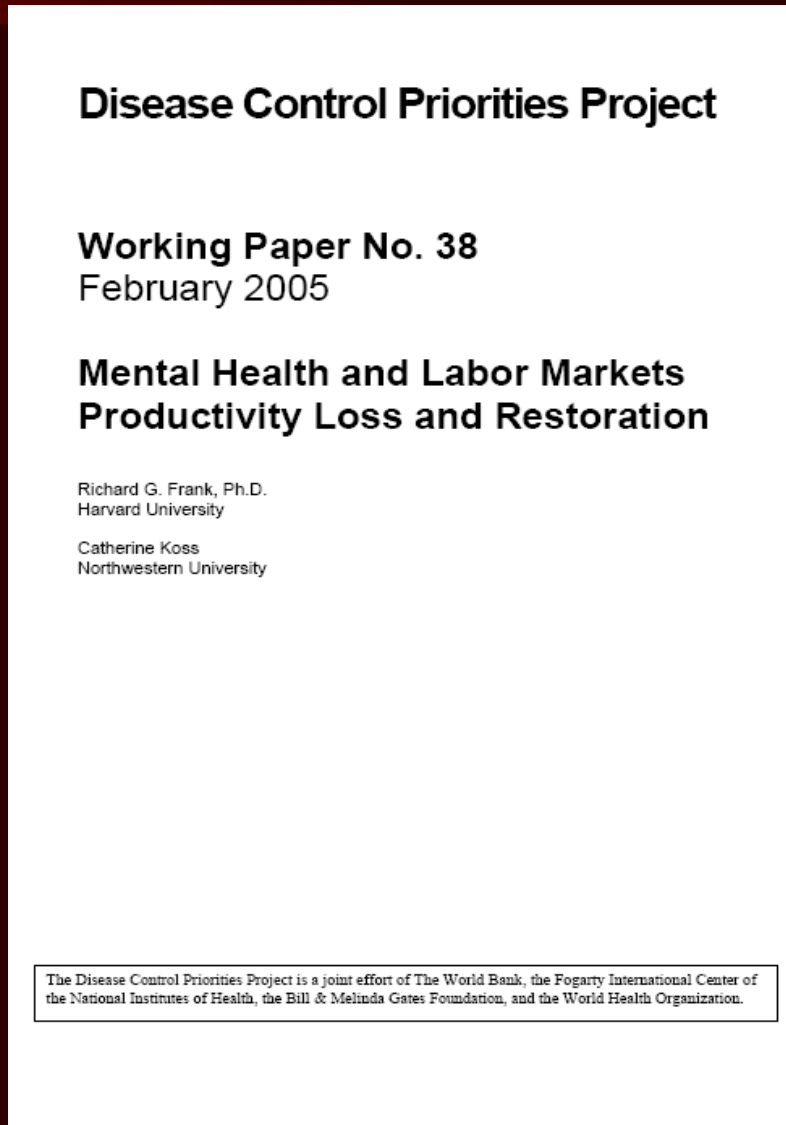
Cost and Effects of a Specified Mental Health Care Package

	World Bank region					
	Sub-Saharan Africa	Latin America and the Caribbean	Middle East and North Africa	Europe and Central Asia	South Asia	East Asia and the Pacific
Total effect (DALYs averted per year per 1 million population)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	254	373	364	353	300	392
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	312	365	322	413	346	422
Depression: proactive care with newer antidepressant drug (SSRI: generic)	1,174	1,953	1,806	1,789	1,937	1,747
Panic disorder: newer antidepressant drug (SSRI; generic)	245	307	287	307	284	330
Total effect of interventions	1,985	2,998	2,779	2,8625	2,867	2,891
Total cost (US$ million per year per 1 million population)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	0.47	1.81	1.61	1.32	0.52	0.75
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	0.48	1.80	1.23	1.39	0.62	0.95
Depression: proactive care with newer antidepressant drug (SSRI: generic)	1.80	4.80	3.99	3.56	2.81	2.59
Panic disorder: newer antidepressant drug (SSRI; generic)	0.15	0.27	0.21	0.23	0.16	0.20
Total effect of interventions	2.9	8.7	7.0	6.5	4.1	4.5
Cost-effectivness (DALYs averted per US$1 million expenditure)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	544	206	226	267	574	522
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	647	203	262	298	560	446
Depression: proactive care with newer antidepressant drug (SSRI: generic)	652	407	452	502	690	675
Panic disorder: newer antidepressant drug (SSRI; generic)	1,588	1,155	1,339	1,350	1,765	1,649

Source: Hyman, S., D. Chisholm, R. Kessler, V. Patel, and H. Whiteford. 2006. "Mental Disorders." In Disease Control Priorities in Developing Countries, 2nd ed., ed. D. T. Jamison, J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, P. Jha, A. Mills, and P. Musgrove, table 31.7. New York: Oxford University Press.

Challenges in Primary Care:

- Initial onset of mental illnesses occur at later part of adolescence and young adulthood.
  - vs other medical conditions.
- Chronic and recurrent.
- Indirect cost: loss of productivity



Disease Control Priorities Project

Working Paper No. 38
February 2005

Mental Health and Labor Markets
Productivity Loss and Restoration

Richard G. Frank, Ph.D.
Harvard University

Catherine Koss
Northwestern University

The Disease Control Priorities Project is a joint effort of The World Bank, the Fogarty International Center of the National Institutes of Health, the Bill & Melinda Gates Foundation, and the World Health Organization.

July 2006

Mental and Neurological Disorders

About 13 Percent of the Global Disease Burden Stems From These Illnesses, But Stigma and Lack of Resources Often Prevent Their Diagnosis and Treatment

Mental and neurological disorders affect more than 450 million people globally, causing substantial disability rates and suffering and making major contributions to the world's total disease burden. About 13 percent of disability-adjusted life years (or DALYs, a measure of the amount of health lost due to a particular disease or condition) are due to mental and neurological disorders.

These disorders bring significant economic hardship not only to those who suffer from them, but also to their caregivers—who are very often the patient's family, given the lack of health resources often found in developing countries. The costs are devastating—loss of gainful employment, the requirement for caregiving, the caregivers' loss of family income, the cost of medications, and the need for other medical services.

The absence of these disorders from lists of the leading causes of death has contributed to their long-term neglect by both donors and policymakers in developing countries. As a result, 90 percent of people with epilepsy and more than 75 percent of people with major depressive disorder in developing countries are inadequately treated. The stigmatization and discrimination associated with these illnesses also remain substantial obstacles to diagnosis and treatment.

The immediate challenge for developing countries is generating sufficient resources for primary mental health care to ensure correct diagnosis and treatment of these disorders.

For mental disorders such as schizophrenia, bipolar affective disorder, major depressive disorder, and panic disorder, the proper drugs and counseling can be cost-effective interventions. For neurological disorders such as dementia, epilepsy, Parkinson's disease, and acute ischemic stroke, interventions are inexpensive and effective, with the added benefit that they can be applied on a large scale through primary care.

Mental Disorders

Cost-Effective Interventions Are Available

The four leading contributors to mental disorders are schizophrenia and related nonaffective psychoses; bipolar affective disorder (manic-depressive illness); major depressive disorder; and panic disorder. Less than 10 percent of the disease burden for schizophrenia and bipolar disorder currently is being averted, while current levels of effective coverage avert only 3 percent to 8 percent of the existing disease burden for depression and panic disorder. But the implementation of combined interventions at a scaled-up level of coverage could avert from 14 percent to 22 percent of the burden of schizophrenia, from 17 percent to 29 percent of the burden of bipolar disorder, and at least 20 percent of the burden of disease for both depression and panic disorder.

- The most cost-effective strategy for averting the burden of *psychosis* and *severe affective disorders* in developing countries would be a combined intervention of first-generation antipsychotic or mood-stabilizing drugs along with psychosocial treatment delivered through a community-based outpatient service model.

- This combined approach would avert more than 500 DALYs per $US1 million expenditure in Sub-Saharan Africa and South Asia, and 200 DALYs in Latin America and the Caribbean. Currently, the high price of second-generation antipsychotic drugs makes their use in developing regions questionable on efficiency grounds, although this situation can be expected to change as these drugs come off patent.

- For more common mental disorders treated in primary-care settings (*depressive and anxiety*

Challenges in Primary Care:

- More than 450 million people in the world:
  - About 10% of the population
- 13% disability-adjusted life years.

WORLD HEALTH ORGANIZATION
EUROPE

Fact shee
Copenhagen, Vienna, 8 Se

Mental health in the WHO European Region

Mental health issues have had an outdated image and mental disorders have
considered not only rather rare but also sinister and shameful. New knowledge and e
are revealing the true picture. In fact, mental health problems are quite common: ar
million people worldwide currently suffer from such conditions, placing mental disorder
the leading causes of ill health. One in four families has at least one member with a
disorder at any point in time. Moreover, the spread of mental illnesses is increasing: fro
12% of the total burden of disease, projections for 2020 reach 15%. The most eloquent ex
is depressive disorders, the fourth leading cause of disease and disability, which are expec
rank second by 2020. In Europe, one in five persons will develop a depression during
lifetime. *The world health report 2001. Mental health: new understanding, new hope* states
"one in four people in the world will be affected by mental or neurological disorders at so
point in their lives". Add to this the increasing problems among youngsters and young adu
which have doubled in some developed European countries since 1990.

No country is immune to mental health problems. In the WHO European Region,[1] menta
disorders figure among the leading causes of disease and disability. The following are some
figures for the number of individuals suffering from a mental disorder in this Region.

- According to a recent calculation, stress-related conditions count for more than half of all disability in a northern European country.
- Life expectancy has in one decade decreased by 10 years in some Member States, much due to stress and conditions related to mental ill health.
- Mental health problems account for up to 30% of consultations with general practitioners in Europe.
- Over a lifetime, slightly over 3 million adults (or 7 out of 1000 people) in the WHO European Region are affected by schizophrenia, with onset in adolescence in 33% of cases.
- Some 33.4 million people in the WHO European Region suffer from major depression in any given year.
- Depression is a condition that shows a genuine increase. It is also increasingly affecting adolescents. In a recent European investigation, 8% of all girls and 2% of all boys aged 16,

[1]Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, the Netherlands, Norway, Poland, Portugal, the Republic of Moldova, Romania, the Russian Federation, San Marino, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, the United Kingdom and Uzbekistan.

in the country studied, fulfilled the criteria for severe depression; 14% of girls and about 5% of boys were found to be moderately depressed. Increasing problems also related to depression are violence, suicide, addiction and behavioural disturbances.

One in four European adolescents shows one or more mental symptoms.

- About 41 million adults are estimated to be abusing or dependent on alcohol. In a northern European country, 45% of men who committed suicide were alcohol abusers. In one of the Baltic states, 40% of traffic accidents are alcohol-related. Despite the severity of these problems about 66% of people are untreated. In a western European country, the economic costs of alcohol reached 1.4 % of gross domestic product (GDP) in 2000.
- Suicide is a major cause of death in adolescents and young adults, but also in risk populations such as farmers in changing societies. Suicide rates range widely from 2 to 44 per 100 000 population; the highest rates in the European Region are also the highest in the world. Certain populations are at particular risk, such as males in eastern Europe. In western Europe, however, adolescents and women are at increasing risk.

Resource allocation and gaps

According to the United Nations development index, WHO European Member States are amongst the richest and the poorest in the world. There is a huge difference in GDP per capita ranging from US$ 500 to over US$ 30 000 per year. The percentage of GDP spent on health care differs widely too, from 2% to 11%, with the poorest countries often allocating the smallest share. The percentage of the health care budget spent on mental health varies hugely, from no budget allocation at all in some countries, to over 20% in others. Although the consequences of mental ill health can easily account for a third or more of all health care costs, many countries in the European Region spend less than 3% of their health budgets on mental health care.

The treatment gap is considerable.

- In the WHO European Region, about 47% of people suffering from major depression remain untreated.
- The estimated percentage of people with untreated schizophrenia ranges from 36% to 45%.
- In European countries, 10% of all children and adolescents suffer severely from mental disorder and need treatment. Even in countries with well developed services, three quarters of those remain untreated.
- In some European countries, the untreated percentage of epilepsy is over 60%.
- Thirteen countries of the WHO European Region have neither initiated the reform process leading to community-based care, nor stated their will to start. Twenty five countries have initiated a partial reform and only thirteen have established it in full.
- One feature of community-based care is the availability of beds in general hospitals for those who need hospital treatment. The proportion of psychiatric beds in general hospitals in the Region (10%) falls inexplicably below the world average (16%).
- Some eastern European countries face over-hospitalization, with 60% of all patients treated in large psychiatric institutions of over 500 beds. Some of these hospitals have high mortality because of unacceptable conditions of care and shortcomings in human rights and integrity.
- In Europe, as in other parts of the world, many people with mental health complaints contact primary health care services. Yet, these are inadequately integrated with mental

Challenges in Primary Care:

- World Health Report 2001
  - 1:4 people in the world.
- 1:4 families has at least 1 member with mental disorder.
- In Europe:
  - Stress-related conditions = more than half of all disability in a northern European country.
  - Mental health problems = up to 30% of consultations with GPs.

Why is mental health important?

- **The W.H.O (World Health Organization):**

The 10 leading sources of DISEASE BURDEN in established Market Economies.

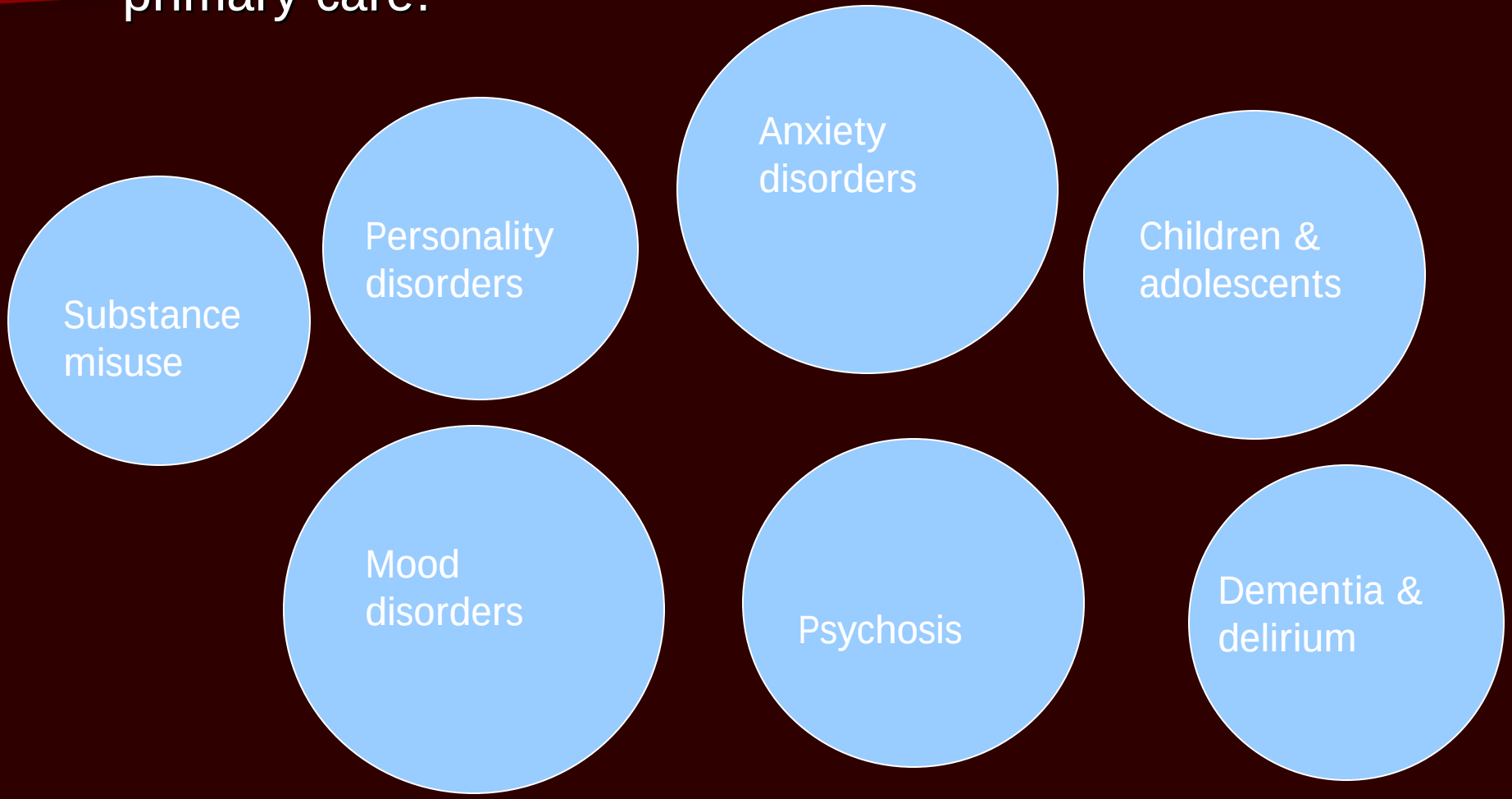
- Ischemic Heart Disease
- **Unipolar Major Depression**
- Cardiovascular Disease
- **Alcohol Use**
- Road Traffic Accidents
- Lung Cancers
- **Dementia & Degenerative CNS Diseases**
- Osteoarthritis
- Diabetes
- Chronic Obstructive Pulmonary Disease

Challenges in Primary Care:

- A leading cause of Global Burden of Disease.
- Projected to be number 2 worldwide by 2020.
- Future challenges in:
  - Anxiety disorders
  - Depressive disorders
  - Substance misuses
  - Suicide

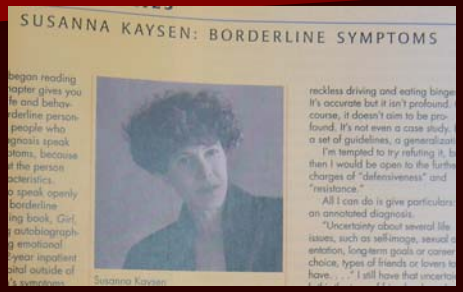
Terminology:

A few of the groups of mental disorders commonly seen in primary care:

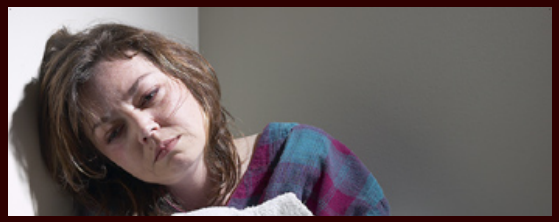


Terminology:

A few of the major groups of mental disorders (DSM-IV):

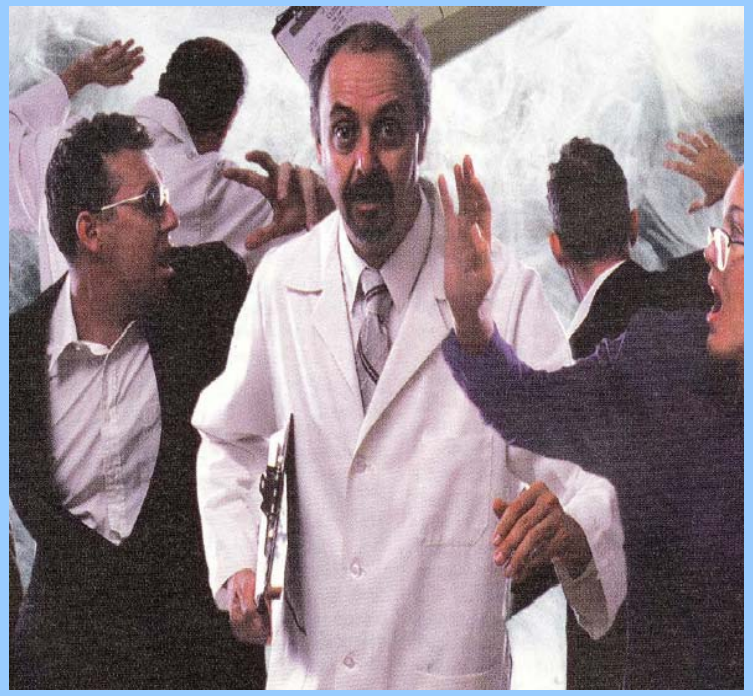

SUSANNA KAYSEN: BORDERLINE SYMPTOMS

Anxiety disorders

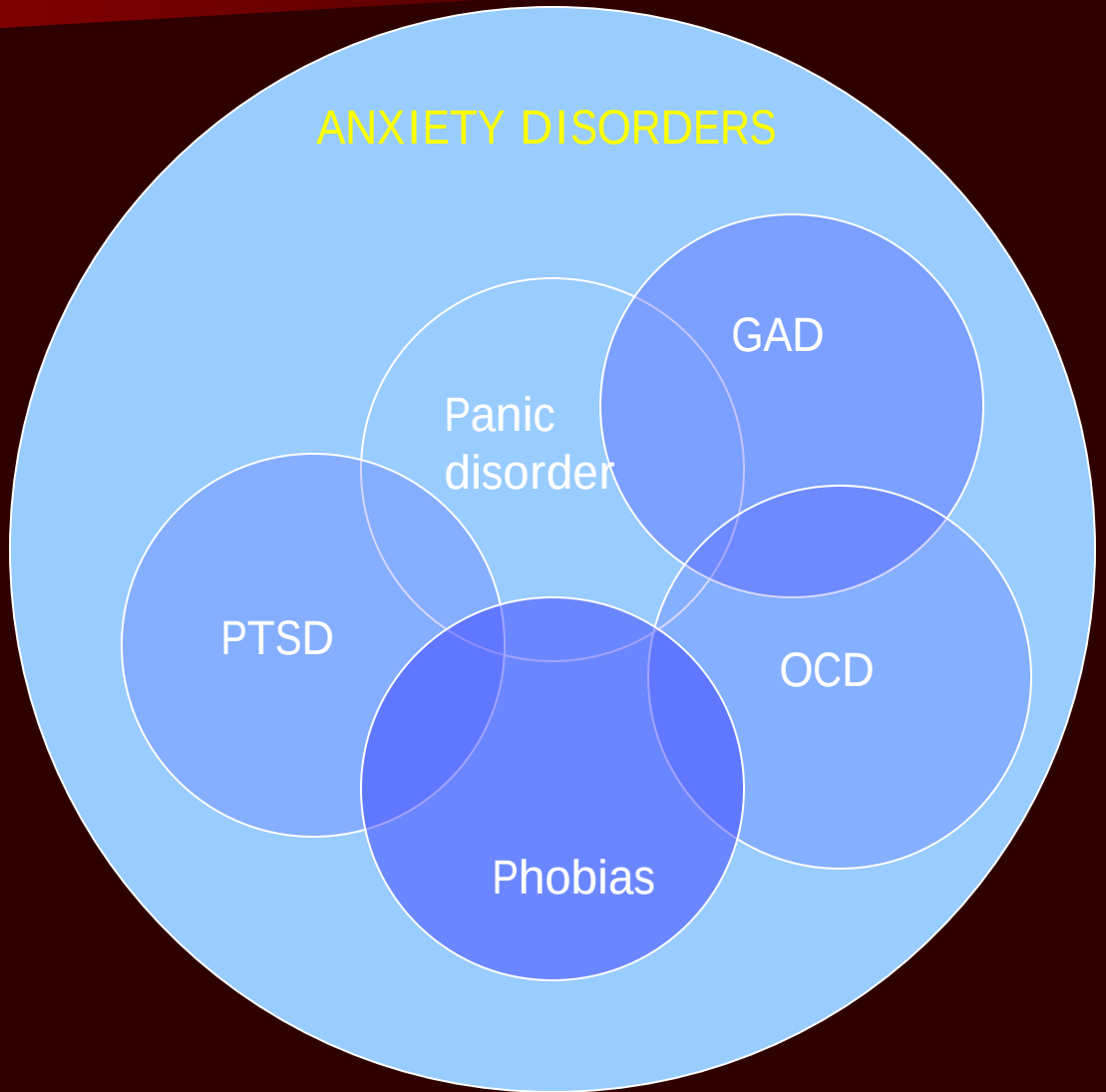


Terminology:

ANXIETY DISORDERS



Terminology:



Terminology:

- The term ‘neurosis’:
  - used in DSM-III, ICD-10, literature.
  - dropped from DSM-IV.
  - broad-vague.
  - ?politically incorrect.

- Anxiety disorders:
  - Core element is anxiety reaction due to maladaptive human behavioral patterns.

Description:

- One of the most common groups.
- National Comorbidity Study:
  - 1:4 met diagnostic criteria for at least 1 anxiety disorder.
  - Prevalence (12-months) = 17.7%
  - Lifetime prevalence in women = 30.5%
  - Lifetime prevalence in men = 19.2%

Description:

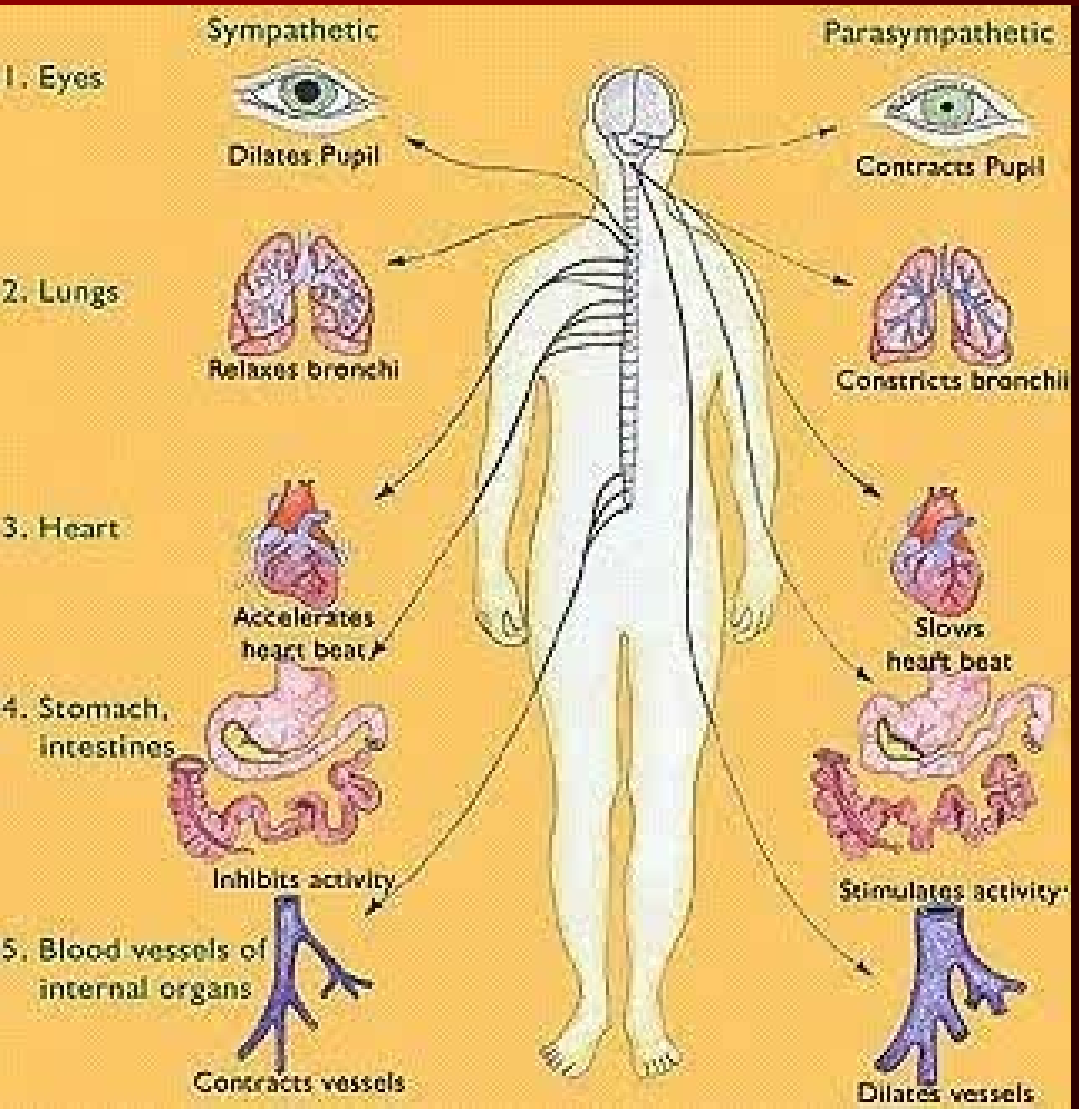
- Signs & symptoms:
  - Excessive feeling of anxiety & tension
  - Dizziness, fainting spell
  - Palpitations
  - Chest discomfort
  - Choking sensation
  - Shortness of breath
  - Abdominal distress, nausea
  - Sweating

Description:

- Trembling
- Numbness
- Derealization, depersonalization
- Fear of losing control
- Fear of ‘dying’

- Irritable
- Insomnia
- Hyperarousal

Description:



Patients may persistently worry of:

Stroke

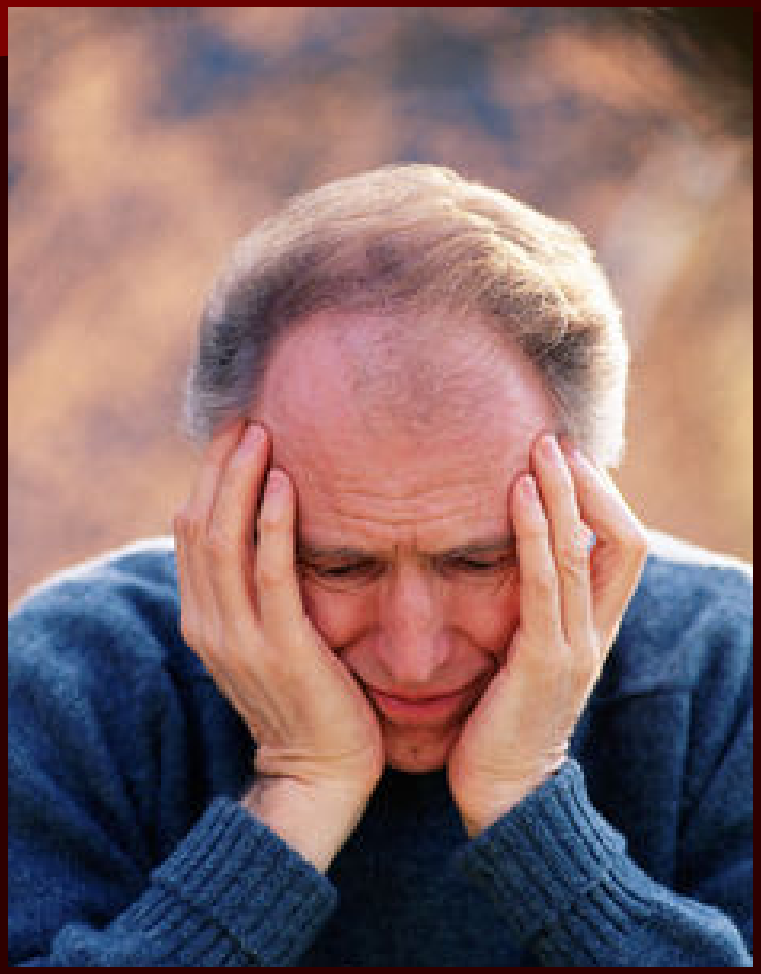
Asthma

Heart attack

Gastritis

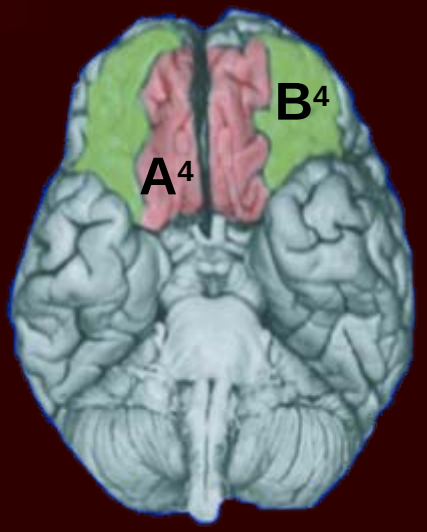
~despite no evidence from investigations.

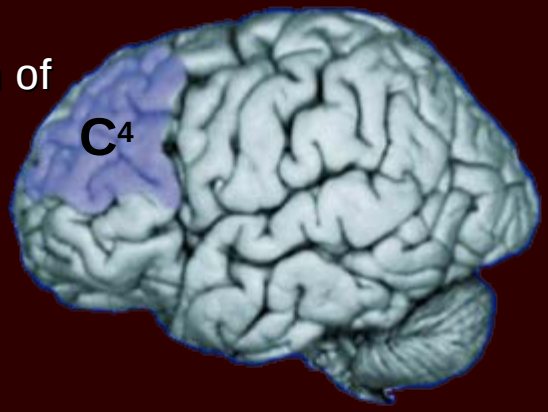
Advances in Neuroscience



Neuroanatomy

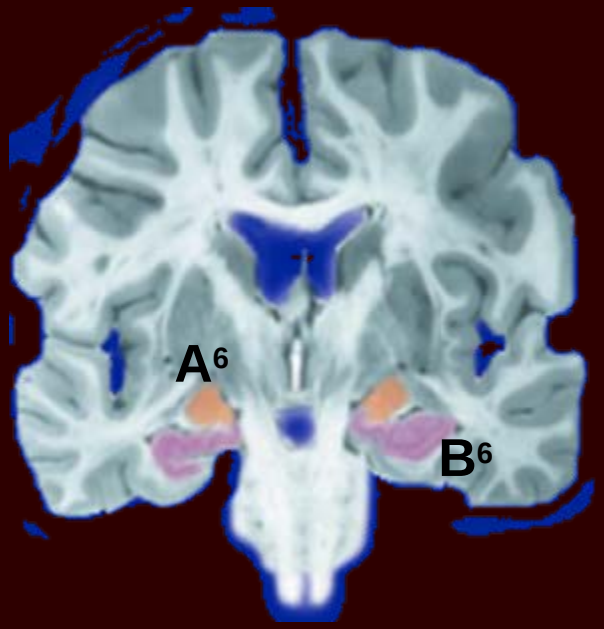
- (A) Ventromedial prefrontal cortex (VMPFC)[1]
  - Modulates pain and aggression, and sexual and eating behaviors
  - Regulates autonomic and neuroendocrine response
- (B) Lateral orbital prefrontal cortex (LOPFC)[2]
  - Activity is increased in depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and panic disorder
  - Corrects and inhibits maladaptive, perseverative, and emotional responses
- (C) Dorsolateral prefrontal cortex (DLPFC)[3]
  - Cognitive control, solving complex tasks, and manipulation of information in working memory
  - Hypoactivity of DLPFC in depression has been associated with neuropsychological manifestation of depression



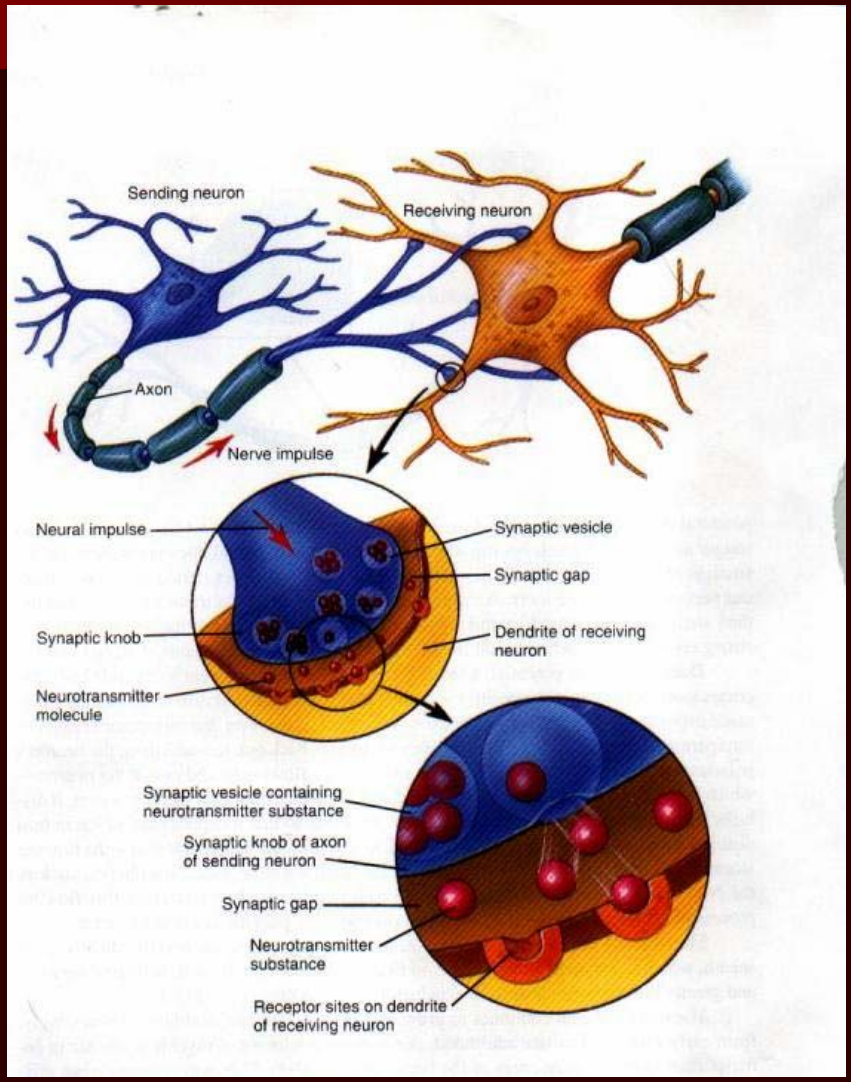


1. Öngür D, Price JL. *Cereb Cortex.* 2000;10(3):206-219.
2. Drevets WC. *Annu Rev Med.* 1998;49:341-361.
3. MacDonald AW III, et al. *Science.* 2000;288(5472):1835-1838.
4. Davidson RJ, et al. *Annu Rev Psychol.* 2002;53:545-574.

- (A) Amygdala: regulates cortical arousal and neuroendocrine response to surprising and ambiguous stimuli[1]
  - Role in emotional learning and memory
  - Activation of amygdala correlates with degree of depression[2]
  - Implicated in tendency to ruminate on negative memories[2]
- (B) Hippocampus: has a role in episodic, contextual learning and memory[3,4]
  - Rich in corticosteroid receptors[5]
  - Regulatory feedback to hypothalamic-pituitary-adrenal axis
  - Hippocampal dysfunction may be responsible for inappropriate emotional responses



1. Davidson RJ. *Psychophysiology.* 2003;40(5):655-665.
2. Drevets WC. *Curr Opin Neurobiol.* 2001;11(2):240-249.
3. Squire LR, Knowlton BJ. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences*; 2000:765-779.
4. Fanselow MS. *Behav Brain Res.* 2000;110(1-2):73-81.
5. Reul JM, De Kloet ER. *J Steroid Biochem.* 1986;24(1):269-272.
6. Davidson RJ, et al. *Annu Rev Psychol.* 2002;53:545-574.

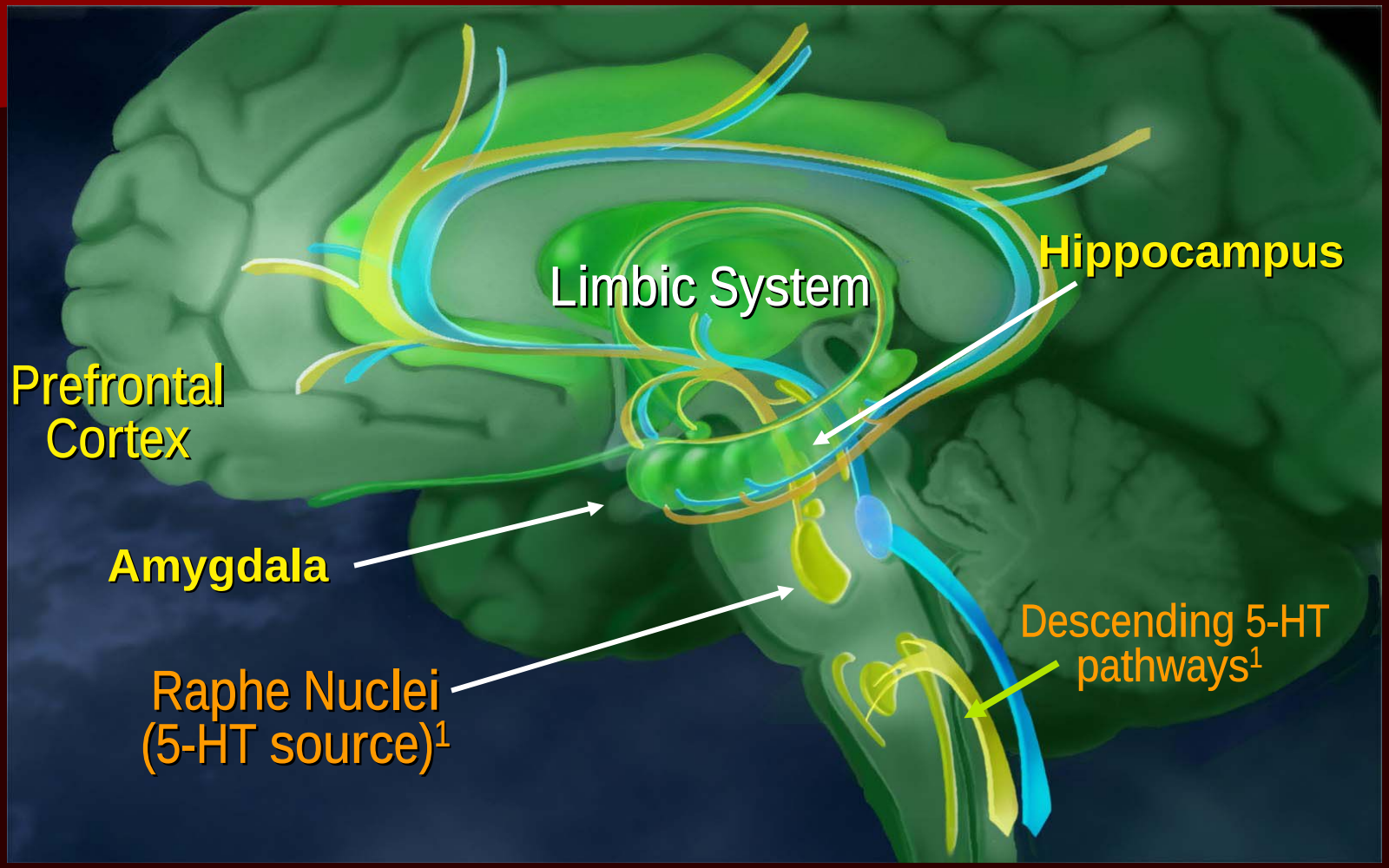

Sending neuron
Receiving neuron
Axon
Nerve impulse
Neural impulse
Synaptic vesicle
Synaptic gap
Synaptic knob
Dendrite of receiving neuron
Neurotransmitter molecule
Synaptic vesicle containing neurotransmitter substance
Synaptic knob of axon of sending neuron
Synaptic gap
Neurotransmitter substance
Receptor sites on dendrite of receiving neuron

Neurochemistry:

- Serotonin
- Norepinephrine
- GABA etc.

SEROTONIN

Serotonin (5-HT) pathways in the human brain

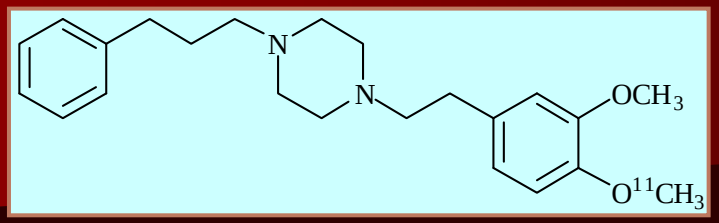


Based on: Cooper JR, et al. *The Biochemical Basis of Neuropharmacology*. 8th ed. New York: Oxford University Press; 2003.

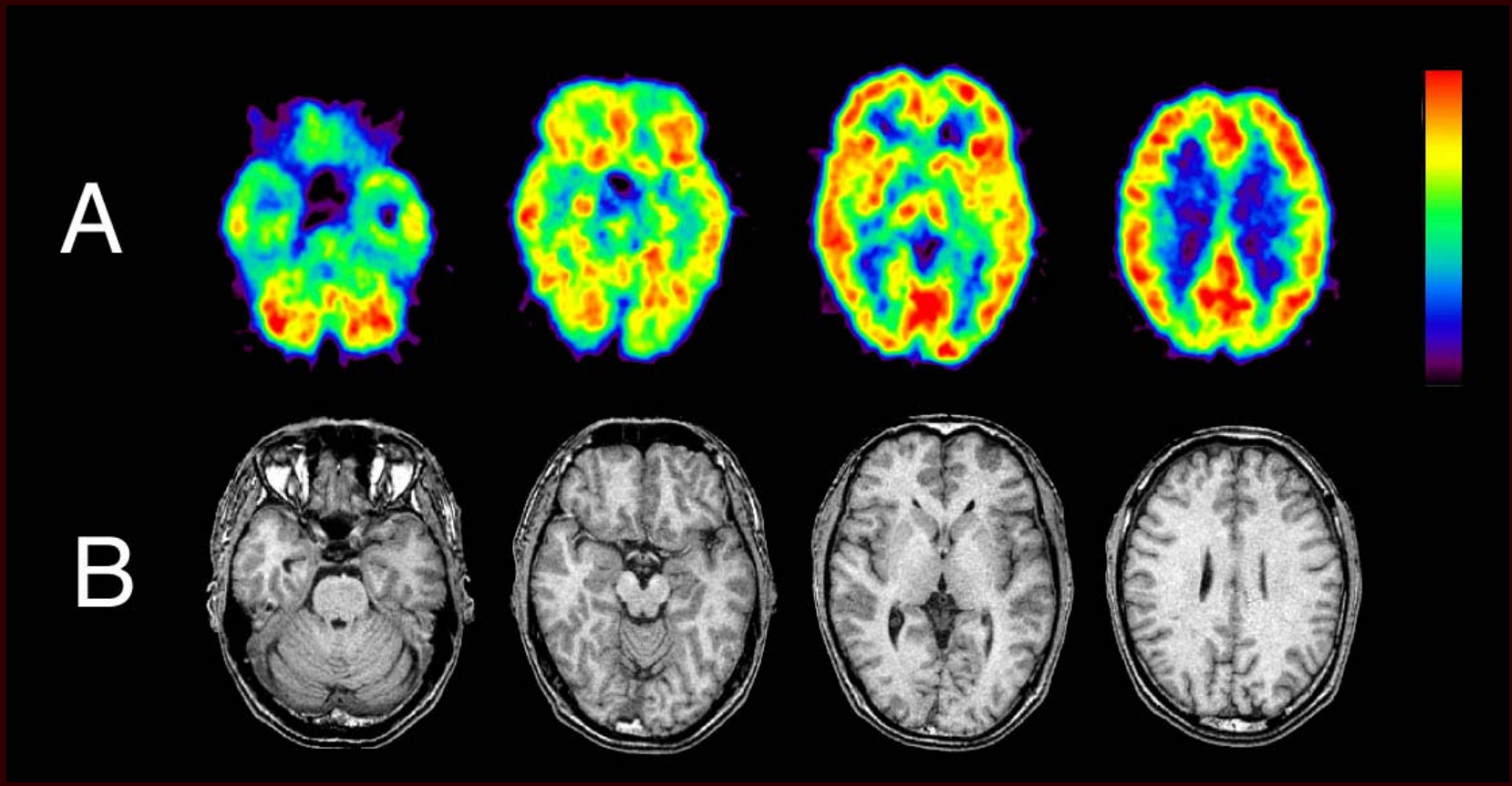
- Synthesized in dorsal & median raphe.
- Axons traveled throughout forebrain.
- Implicated in:
  - Anxiety
  - Mood
  - Impulse control
  - Appetite
  - Neuroendocrine regulation
  - Sleep
  - Sexual function

- Pre & postsynaptic 5-HT1A, 5-HT2, 5-HT3 and 5-HT1B/D receptors.

- Hypothesis:
  - On-going researches.
  - Specific functional/ anatomical pathways + different 5-HT® subtypes -> clinical expression of distinct forms of anxiety.



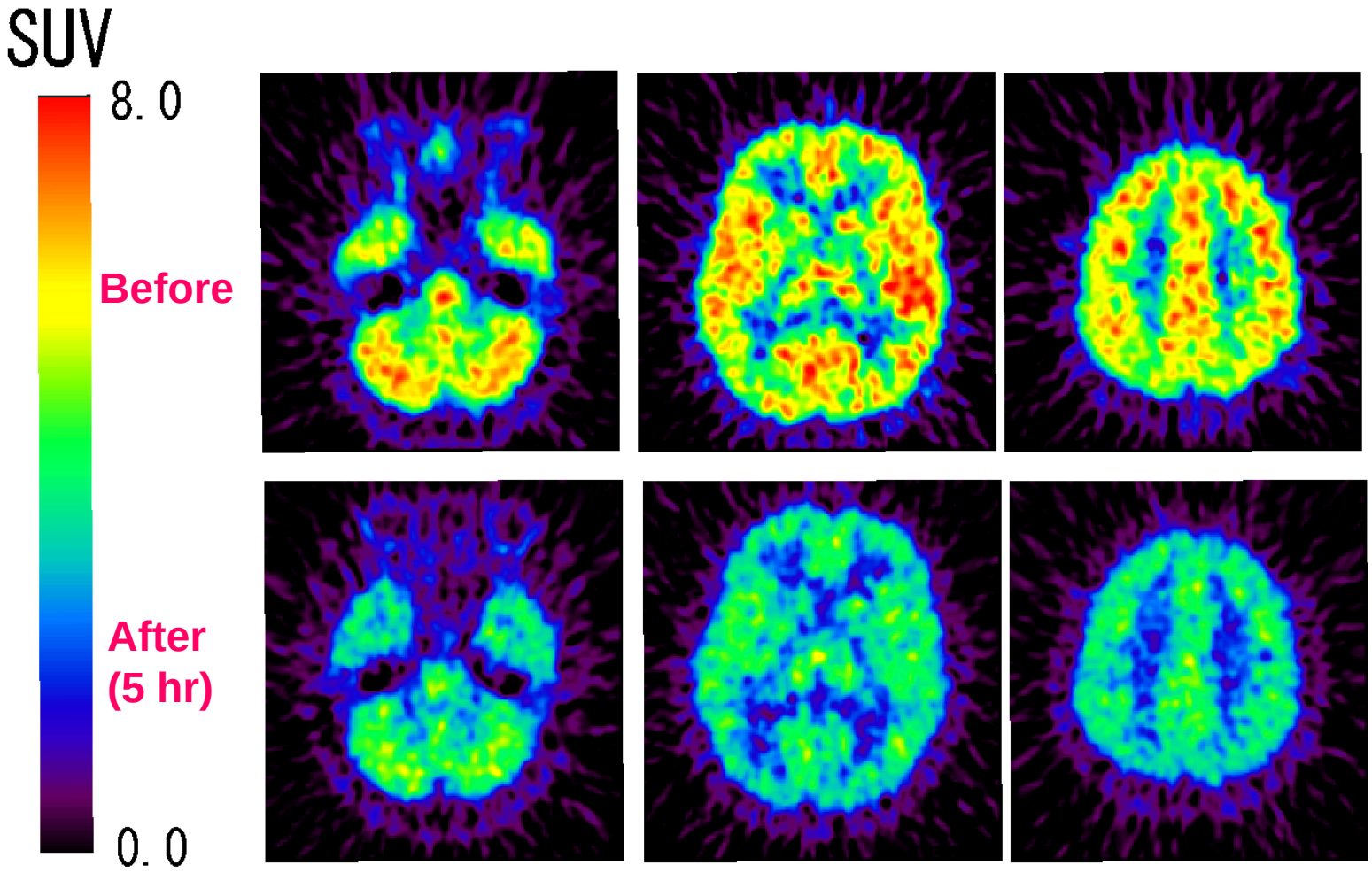
Imaging of Sigma-1 Receptors In Human Brain Using [^{11}C]SA4503 & PET



Male Control Subject

(From Drs. K. Ishi and K. Ishiwata)

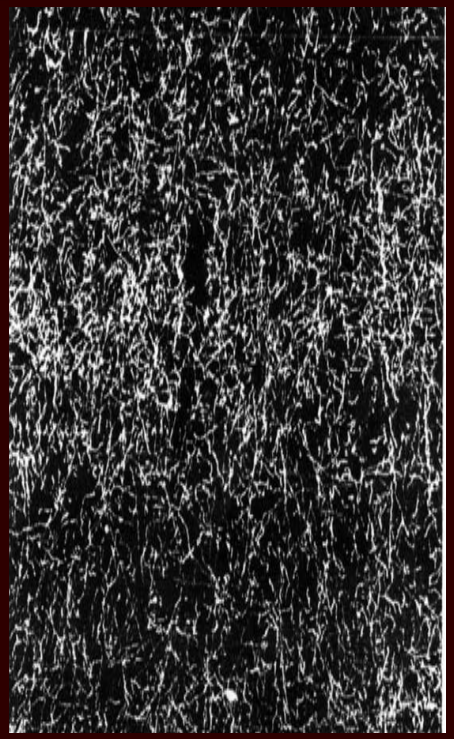
Occupancy of Sigma-1 receptors in Human Brain after Administration of Fluvoxamine (50 mg)

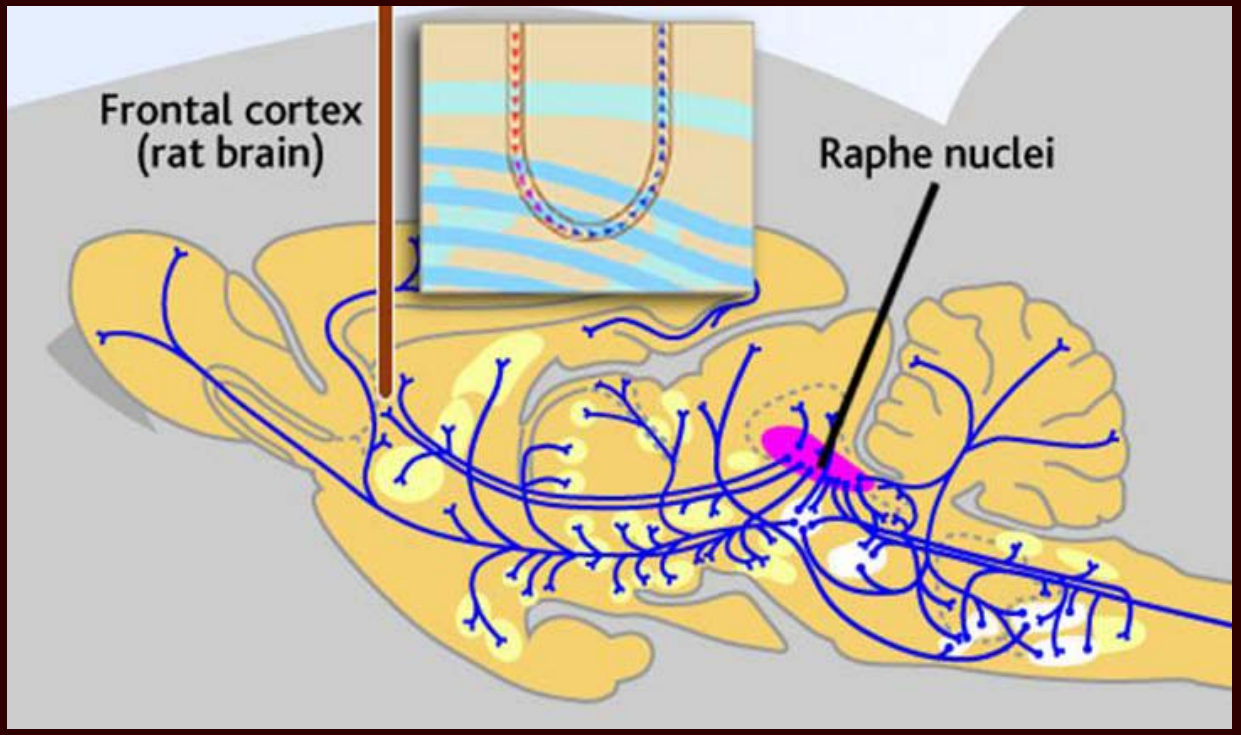


Male Control Subject

Serotonin projections in the brain (animal model)

Diffuse distribution in cortex

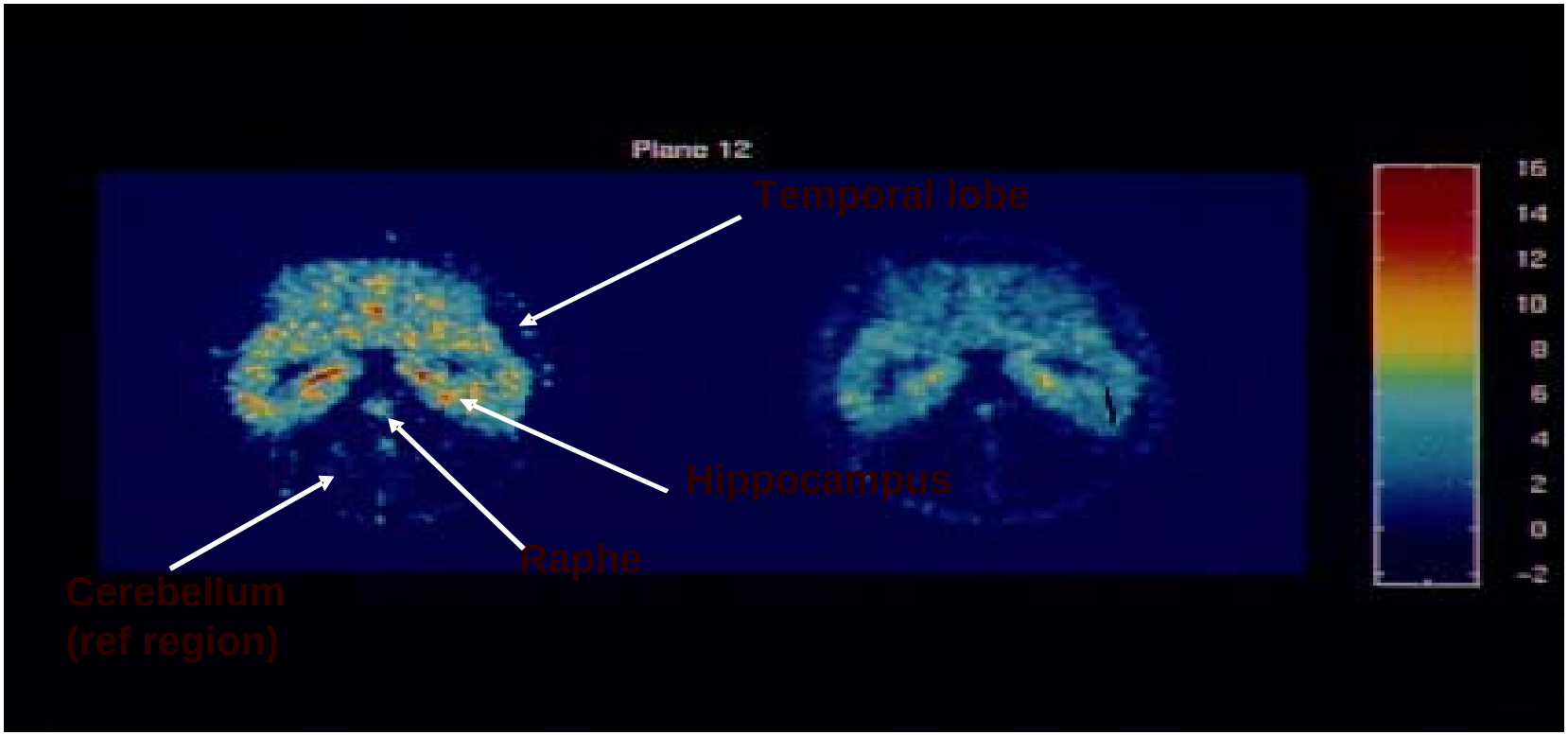




Microdialysis = animal model for measuring 5-HT release in rat brain – not easy to do in humans, but there are alternatives!

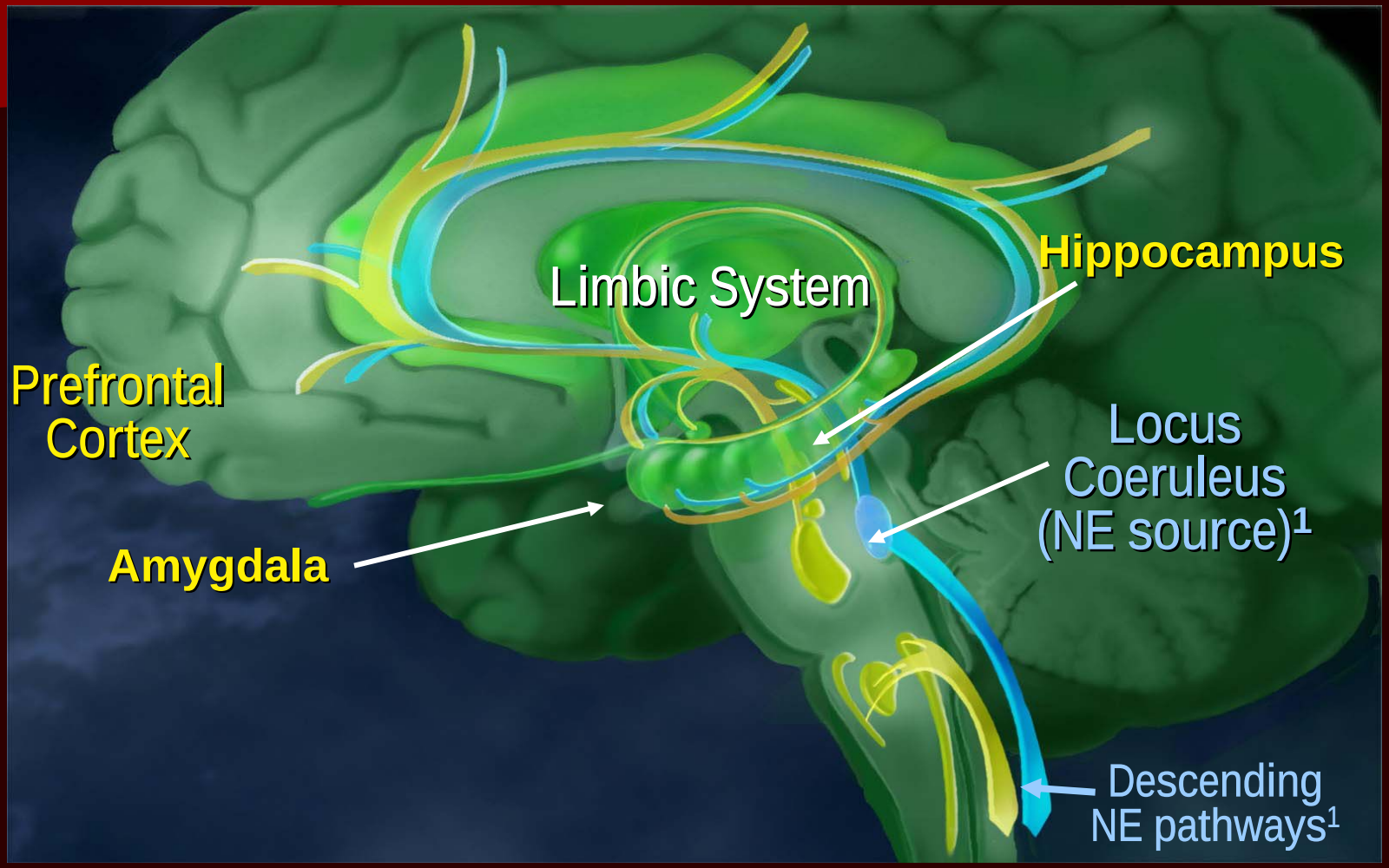
Steinbusch & Nieuwenhuys, 1983.
In: Chemical Neuroanatomy, (Ed. PC Emson), pp 131–207. Raven Press, New York

PET tracers can provide exquisite definition of 5-HT_{1A} receptors



NOREPINEPHRINE

Norepinephrine (NE) pathways in the human brain



Based on: Cooper JR, et al. *The Biochemical Basis of Neuropharmacology*. 8th ed. New York: Oxford University Press; 2003.

- NE neurons originate mainly from locus coeruleus -> forebrain.
- Receptors: alpha2 (CNS), beta (PNS)

- Presynaptic alpha2®:
  - Supersensitivity of ® at locus coeruleus.
- Postsynaptic alpha2®:
  - Hyposensitivity of ®
- PNS beta ®:
  - Cognitive misinterpretation of peripheral symptoms.

GABA

- GABA = main inhibitory transmitter in brain.
- GABA-A receptor ® is linked with anxiety, memory, muscle relaxation, control of convulsions.
- Agonist of GABA-A ® = anxiolytic:
  - Benzodiazepines
  - Endozepines
  - Neurosteroids

- Hypothesis:
  - Abnormal benzodiazepine ® functioning
  - Down-regulated
  - Resulting in decreased function of the endogenous transmitter
  - Expressed anxiety behavior.

Molecular/ Genetic factor

- [A common single-nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene, a methionine (Met) substitution for valine (Val) at codon 66 (Val66Met), is associated with alterations in brain anatomy and memory, but its relevance to clinical disorders is unclear. In an animal model experiment, a variant BDNF mouse (BDNFMet/Met) that reproduces the phenotypic hallmarks in humans with the variant allele is generated. BDNFMet was expressed in brain at normal levels, but its secretion from neurons was defective. When placed in stressful settings, BDNFMet/Met mice exhibited increased anxiety-related behaviors.]

- A variant BDNF may thus play a key role in genetic predispositions to anxiety and depressive disorders.
- Predispose the sensitivity of receptors.
- Anxious traits in personality.

TREATMENT

- Studies and researches in:
  - Benzodiazepine
  - Imipramine, clomipramine
  - SSRI: fluvoxamine, escitalopram, fluoxetine, sertraline, paroxetine
  - Venlafaxine, mirtazapine
  - Beta-blocker
  - Anticonvulsants/ mood stabiliser etc

CLINICAL GUIDELINES

- In general:
  - Anxiety spectrum disorders are chronic.
  - May occur as psychiatric disorder per se, or comorbid with another psychiatric disorder, or as consequence of a physical illness, or drug-induced (eg. caffeine).
  - SSRI:
    - Preferred first choice.
    - Start low. Onset from few weeks to months.
  - Benzodiazepines

CLINICAL GUIDELINES

licensed doses

- Escitalopram
  - 5-20mg/d
- Fluoxetine
  - 20-60mg/d
- Fluvoxamine
  - 100-300mg/d
- Paroxetine
  - 10-50mg/d
- Sertraline
  - 25-200mg/d

- Venlafaxine (XL)
  - 75mg/d
- Benzodiazepines
  - Alpraxolam
  - Lorazepam
  - Clonazepam
  - Diazepam
    - Rapid symptom relief.
    - Indicated for severe, disabling, distressing cases.
    - Short term 4wks/ prn

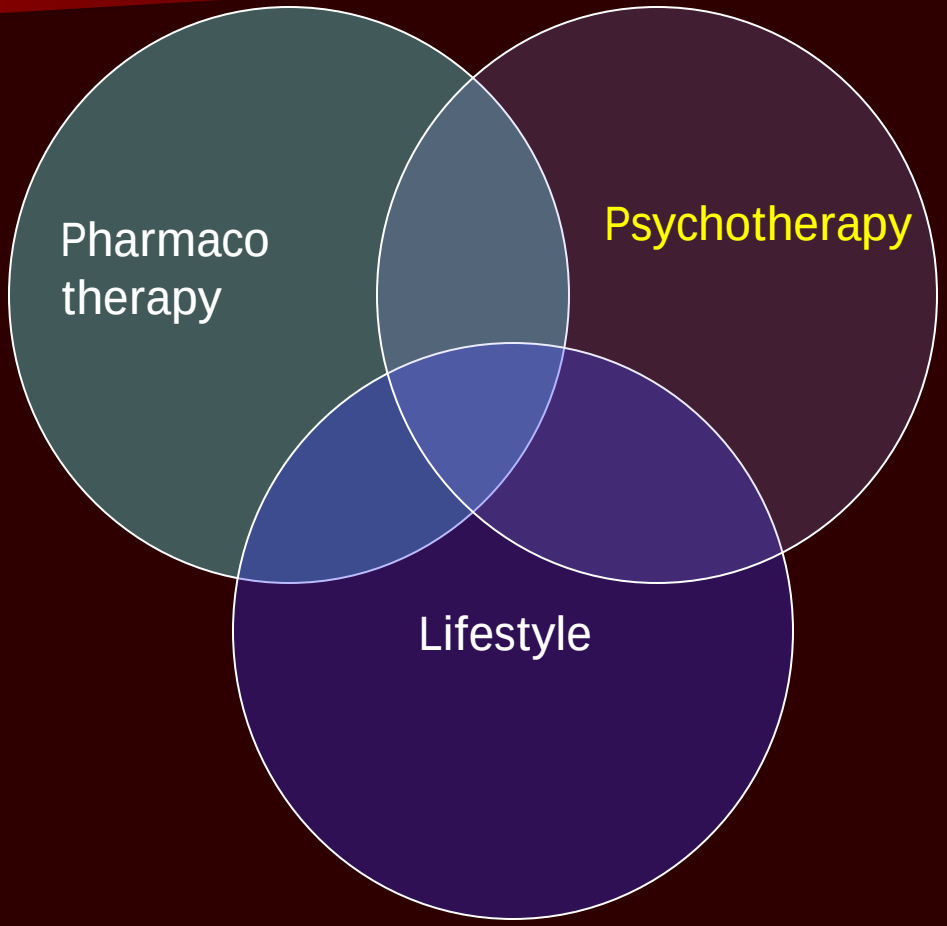
Holistic treatment

Holistic treatment

SSRI

BZD

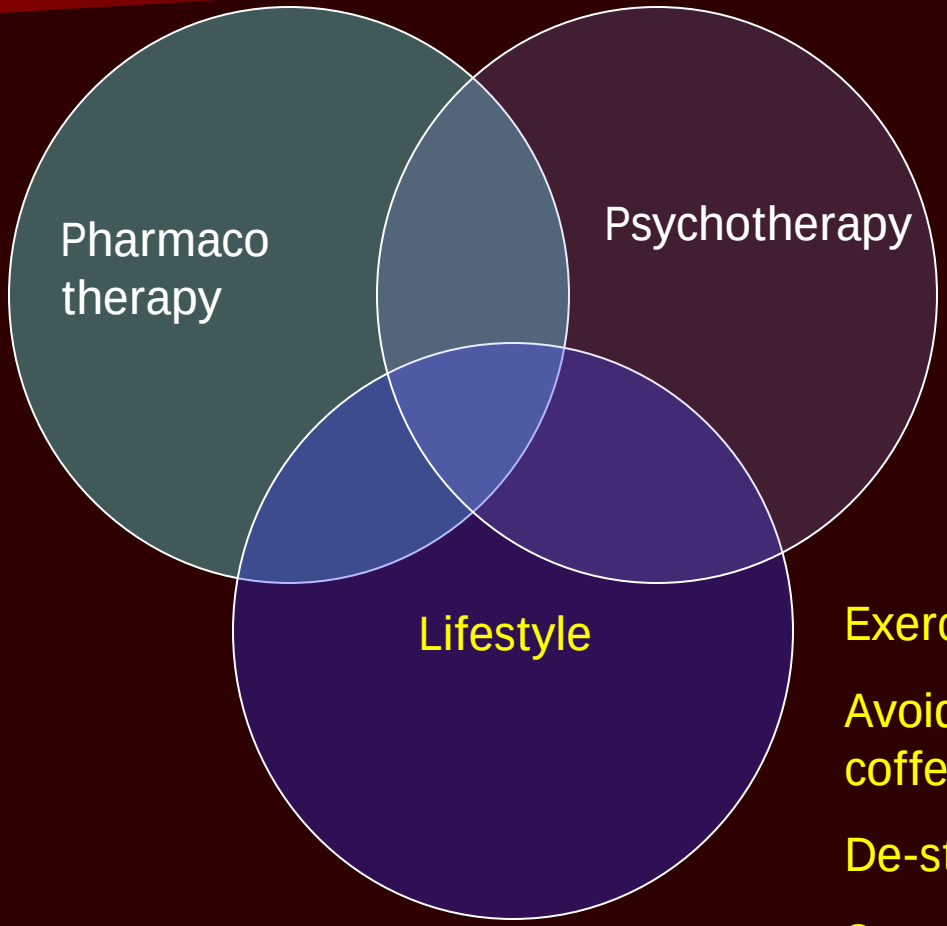
Holistic treatment



Cognitive behavioral therapy

Psychoanalytic therapy

Holistic treatment



Exercise

Avoid alcohol, coffe, tea

De-stress

Supports

Thank You