



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

PHYTOPHARMACEUTICALS

academic year 2018/19

LECTURE 4 – Preparations used to treat some disorders of CNS

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PHYTOPHARMACEUTICALS vs. CNS

- ▶ Psychostimulants
- ▶ Nootropics
- ▶ Sedatives
- ▶ Antidepressants
- ▶ (Analgesic drugs)



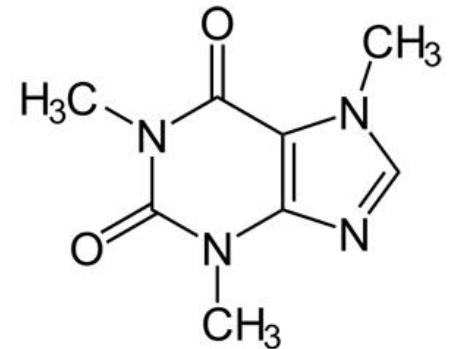
PSYCHOSTIMULANTS

- ▶ Indication/medical uses:
 - ▶ in case of tiredness, exhaustion, attention disorders, sleepiness
 - ▶ ADHD = attention deficit-hyperactivity disorder
 - ▶ for appetite-suppression (to reduce weight)
- ▶ natural compounds – used especially **methylxanthines** – **CAFFEINE** and its relative compounds

PSYCHOSTIMULANTS

CAFFEINE

- ▶ effects:
 - ▶ stimulating CNS, heart action, the centres (*in medulla oblongata*) that control blood pressure and respiration
 - ▶ diuretic, bronchodilator effect
- ▶ plant drugs contain caffeine
 - ▶ Coffeae semen – *Coffea arabica*, Rubiaceae
 - ▶ Theae folium – *Camellia (Thea) sinensis*, Theaceae
 - ▶ Colae semen – *Cola acuminata*, Malvaceae
 - ▶ Yerba mate (leaves) – *Ilex paraguariensis*, Aquifoliaceae
 - ▶ Guarana (seeds) – *Paullinia cupana*, Sapindaceae



CAFFEINE PLANT DRUGS



Coffeae semen
Coffea arabica



Theae folium
Thea sinensis



Yerba mate
Ilex paraguariensis leaves



Guarana
Paullinia cupana seeds



Colae semen
Cola acuminata

Phytopharmaceuticals – Psychostimulants

Extracts

▶ Guarana extract

- ▶ powdered extract
- ▶ tablets – content of extract: usually **800 mg/tablet**
content of *caffeine* – usually **10-30 mg/tablet**
- ▶ addition of pure substance of *caffeine*
- ▶ combination with other plant extracts, vitamins, amino acids,...
- ▶ used in herbal teas, energy drinks

- ▶ preparations with the pure substance (*caffeine*) only are not included into phytopharmaceuticals



Phytopharmaceuticals – Psychostimulants

Extracts

- ▶ powdered guarana extract
 - ▶ 100%, no additives
 - ▶ GEPA, Germany, the Fair Trade Company
 - ▶ bio-product
 - ▶ usage: ½-1 teaspoon a day, add to drink or meal
- ▶ herbal drops with guarana
 - ▶ composition: 10 % (m/V) extract of Guarana semen in alcohol 40 % (V/V)
 - ▶ usage: e.g. 20 drops into a glass of water twice a day



Phytopharmaceuticals – Psychostimulants

Herbal teas

- ▶ Herbal tea for better concentration (Megafyt Pharma)
 - ▶ **Theae folium** (40 %) - green tea
 - ▶ Menthae piperitae herba
 - ▶ Cymbopogonis herba
 - ▶ Menthae crispae folium
 - ▶ **Ilex paraguayensis folium** (8 %)
 - ▶ Liquiritiae radix
 - ▶ **Guaranae semen** (2 %)



NOOTROPICS



- ▶ „smart“ drugs, memory enhancers, cognitive enhancers,...
= preparations that improve mental function such as cognition, memory, intelligence, motivation, attention, concentration
- ▶ are thought to work by altering the availability of the brain's supply of neurochemicals (neurotransmitters, enzymes, hormones), by improving the brain's oxygen supply, or by stimulating nerve growth = **brain nutrients**

NOOTROPICS

▶ Ginkgo bilobae folium

Ginkgo biloba, Ginkgoaceae

- ▶ main active constituents are **terpene lactones** (*ginkgolides* A, B, C and *bilobalide*) and **flavonoids** (flavone glycosides, biflavonoids)
- ▶ Ginkgonis extractum siccum raffinatum et quantificatum Ph. Eur.
= Ginkgo dry standardized extract (contains 22.0-27.0 % flavonoids, 2.6-3.2 % *bilobalide*, 2.8-3.4 % *ginkgolides*), **EGB 761**
- ▶ **!!** limited content of toxic *ginkgolic acid* – not more than 5 ppm (0.0005 %)



NOOTROPICS

▶ Ginkgo bilobae folium

- ▶ Ginkgo has been used for improving blood flow, for improving memory/concentration due to certain brain disorders (e.g., Alzheimer's disease, dementia), also as anti-vertigo agent
- ▶ various phytopharmaceutical preparations – predominantly solid oral forms – tablets or capsules, or solutions, tinctures
- ▶ a component of complex preparations with other plant drugs
- ▶ **!!** Do avoid using products that contain fresh or roasted **ginkgo seeds**.
The seeds may contain a toxic chemicals (*ginkgotoxin*). Seizures and death have occurred in people who ate as few as 10 seeds. The risk is higher in case of children.



Ginkgo bilobae folium

▶ TANAKAN POR TBL FLM 30X40MG (Ipsen Ltd.)

- ▶ Ginkgo bilobae extr. sicc. normatum (EGb 761)
- ▶ contains 24 % of Ginkgo flavonoides and 6 % of terpenes in amount 40 mg in one tablet or in 1 ml of solution
- ▶ SUKL code : 0062914; OTC medicinal product
- ▶ ATC: N06DX02



▶ TEBOKAN POR TBL FLM 50X40MG (Dr. Willmar Schwabe GmbH & Co)

- ▶ EGb 761
- ▶ SUKL code: 0075124; OTC medicinal product
- ▶ ATC: N06DX02



Ginkgo bilobae folium

▶ tablets, capsules...

- ▶ content of extract: usually 40, 80 mg; also 120 mg
- ▶ producers, e.g.: Walmark, Dr. Müller Pharma, MedPharma, NefDesanté, Naturline...
- ▶ FAVEA Ginkgo – slow release tablets



Ginkgo bilobae folium

▶ herbal teas



▶ drops (guttae)

producers, e.g.:

- ▶ Aromatica
- ▶ Grešik – herbal drops (10% extract of *Ginkgo bilobae folium* in alcohol 40%)



Ginkgo bilobae folium

- ▶ composite preparations – addition of, e.g.:
 - ▶ lecithin
 - ▶ coenzyme Q10
 - ▶ magnesium
 - ▶ vitamins (e.g. pyridoxin B6)
 - ▶ other plant extracts (Ginseng radix, Guarana, Gotu kola,...)



- ▶ **Ginkgo-Stim (Walmark)**

- ▶ Ingredients:
 - Guarana 200 mg, Ginkgo biloba 200 mg, Gotu kola (*Centella asiatica* leaf) 250 mg



Ginkgo bilobae folium

Herbal teas

- ▶ **Ginkgo Tea**

(Dr. Popov)

- ▶ **Theae folium**

Ginkgo bilobae folium (20 %)

Cinnamomi cortex

apple fruit, rose flower



- ▶ **Tea for good memory**

(Apotheke)

- ▶ **Verbenae herba**

Rosmarini folium

Theae folium

Ginkgo bilobae folium

Callunae herba

Origani herba



Psychostimulants, nootropics

Other plant drugs

„adaptogens,,

- ▶ Ginseng radix – ginseng
 - ▶ *Panax ginseng*, Araliaceae
 - ▶ ginsenosids
- ▶ Eleutherococci radix – „siberian“ ginseng
 - ▶ *Eleutherococcus senticosus*, Araliaceae
 - ▶ eleutherosids
- ▶ Rhaponticae radix – „maral“ root
 - ▶ *Leuzea (Rhaponticum) carthamoides*, Asteraceae
 - ▶ ecdysteroids



Psychostimulants, nootropics

Other plant drugs

„adaptogens,,

- ▶ Schisandra – fruit
 - ▶ *Schisandra chinensis*, Schisandraceae
- ▶ Gotu kola – centella herb
 - ▶ *Centella asiatica*, Apiaceae
- ▶ Rose root, golden root,...
 - ▶ *Rhodiola rosea*, Crassulaceae
- ▶ „Brahmi“ herb
 - ▶ *Bacopa monnieri*, Plantaginaceae



Phytopharmaceuticals– Nootropics

Composite preparations

- ▶ **BRAIN ACTIVE**
(ADVANCE nutraceuticals)
- ▶ combination of 13 natural components for support of memory, concentration
- ▶ usage:
 - ▶ 1-2 capsules a day
 - ▶ do not use before sleeping
 - ▶ not suitable for children until 15y., for pregnant and lactating women



Active components	Content in 1 capsule
<i>Ginkgo biloba</i>	20 mg
<i>Bacopa monnieri</i>	100 mg
<i>Guarana</i>	100 mg
<i>Eleutherococcus senticosus</i>	30 mg
<i>Rhodiola rosea</i>	20 mg
<i>Schizandra chinensis</i>	20 mg
<i>Panax ginseng</i>	20 mg
<i>Cordyceps sinensis</i>	10 mg
DMAE	10 mg
caffeine	50 mg
taurine	50 mg
pantothenic acid (vitamin B5)	3 mg
pyridoxin (vitamin B6)	1 mg

Psychostimulants, nootropics

Preparations with essential fatty acids (EFAs)

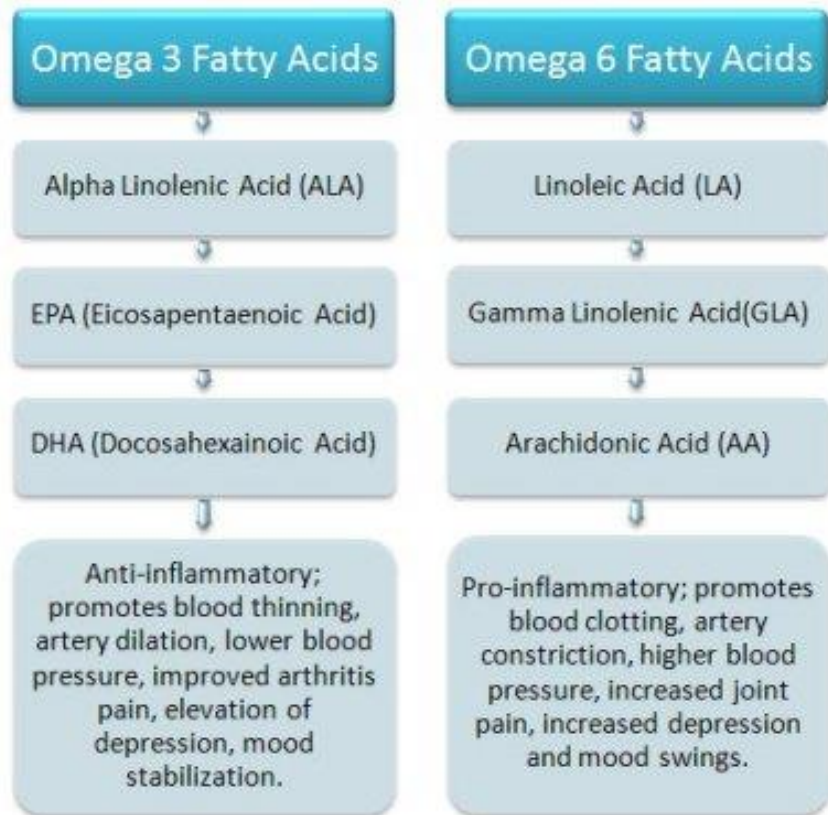
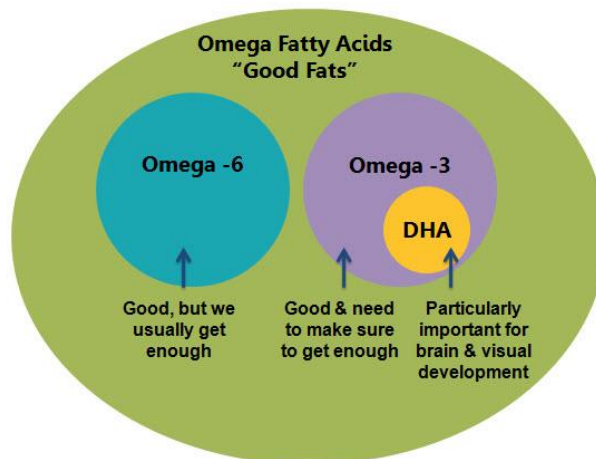
- ▶ the essential fatty acids start with the short chain polyunsaturated fatty acids (SC-PUFA):
 - ▶ ω (omega)-3 fatty acid – ALA = *α -linolenic acid* (18:3n-3)
 - ▶ ω (omega)-6 fatty acid – LA = *linoleic acid* (18:2n-6)
- ▶ These two fatty acids cannot be synthesized by humans. They form the starting point for the creation of longer and more desaturated fatty acids, which are also referred to as long-chain polyunsaturated fatty acids (LC-PUFA); not be synthesized by humans
 - ▶ ω -3 fatty acids: **EPA** = *eicosapentaenoic acid* (20:5n-3) and **DHA** = *docosahexaenoic acid* (22:6n-3)
 - ▶ ω -6 fatty acids: **GLA** = *gamma-linolenic acid* (18:3n-6), **DGLA** = *dihomo-gamma-linolenic acid* (20:3n-6) and **AA** = *arachidonic acid* (20:4n-6)

Psychostimulants, nootropics

Preparations with essential fatty acids (EFAs)

▶ Health effects

- ▶ mental health
- ▶ cognitive aging
- ▶ cardiovascular diseases
- ▶ inflammation
- ▶ developmental disorders
- ▶ cancer prevention



Psychostimulants, nootropics

Preparations with essential fatty acids (EFAs)

▶ Sources of ω -3 fatty acids

- ▶ oil of seeds and fruits – soyabeans, olives, sunflower seeds, nuts,...
- ▶ sea fish – trout, herring, salmon
- ▶ cereal grains
- ▶ vegetables (radish seeds, broccoli, alfalfa,...)

▶ Sources of ω -6 fatty acids

- ▶ vegetable oils – soyabean oil, corn oil, safflower oil (*Carthamnus tinctorius*), canola oil (*Brassica napus*, *Brassica rapa* subsp. *oleifera*), and other oils mentioned above



Psychostimulants, nootropics

Preparations with essential fatty acids (EFAs)

▶ **MOZKOVIT cps.**

(= „BrainVit“, vitamins for brain)

Dr. Müller Pharma

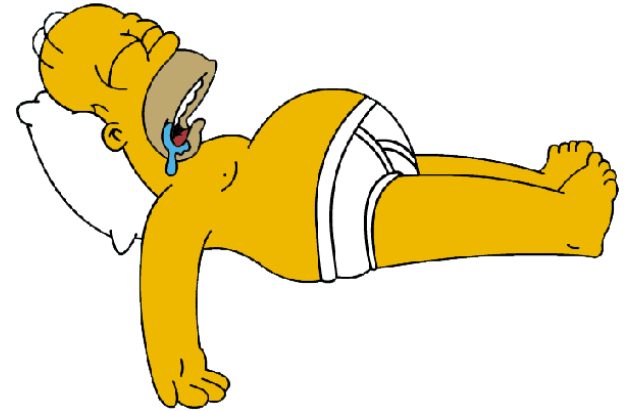
- ▶ DHA – effective dose is 250 mg
- ▶ *resveratrol* = polyphenolic compound found mainly in grapes, red wine,...
- ▶ B vitamins – play important role in normal function of nervous system



Active components	Content in 1 capsule
ω -3 fatty acids (DHA 250 mg, EPA 50 mg)	300mg
resveratrol	30 mg
Theae folium extract 70% (EGCG 52.5 mg)	75 mg
Vitamin B1 (thiamin)	1 mg
Vitamin B2 (riboflavin)	1 mg
Vitamin B5 (pantothenic acid)	5 mg
Vitamin B6 (pyridoxin)	3 mg
Vitamin E (DL- α -tocoferol)	10 mg
Folic acid	400 ug
Vitamin D (cholecalciferol)	5 ug

SEDATIVES

- ▶ or **tranquilizers**
= preparations that induce sedation by reducing irritability or excitement of brain.
- ▶ at higher doses they may act as **hypnotics** = to cause sleep.
- ▶ used for therapy of nervous tension and mild sleep disorders



SEDATIVES

- ▶ **Valerianae radix, valerian**
Valeriana officinalis, Valerianaceae
 - ▶ drug consists of rhizome and many greyish brown roots
 - ▶ characteristic odour (cat's root)
 - ▶ constituents: essential oils (mainly sesquiterpenes – e.g. *valerenic acid*), valepotriates (bicyclic iridoid monoterpenes – *valtrate*, *isovaltrate*,...), degradation products (*baldrinal*),...
- ▶ Mechanism of action: interaction of valerian constituents with the GABA neurotransmitter receptor system (inhibition of degradation of γ -aminobutyric acid)



Valeriana officinalis L.
©Thomas Schöpke
www.plant-pictures.com

SEDATIVES

- ▶ **Valerianae radix, valerian**
 - ▶ making the tea: pour boiling water over 3-5 g of the very finely cut drug, 10-15 min of infusion, then strain
 - ▶ mostly component of herbal tea mixtures
- ▶ Valerianae extractum aquosum siccum (Ph.Eur.)
- ▶ Valerianae extractum hydroalcoholicum siccum (Ph.Eur., ČL 2009)
- ▶ Valerianae tinctura (ČL 2009) – in a ratio of drug to alcohol 1:5 (m/V)



Other sedative plant drugs

- ▶ **Melissae folium, herba – lemon balm**
 - ▶ *Melissa officinalis*, Lamiaceae
- ▶ **Lavandulae flos – lavender flower**
 - ▶ *Lavandula officinalis*, Lamiaceae
- ▶ **Origani herba – oregano**
 - ▶ *Origanum vulgare*, Lamiaceae
- ▶ **Lupuli flos (Strobili lupuli) – hop flowers**
 - ▶ *Humulus lupulus*, Cannabidaceae
- ▶ **Hyperici herba – St. John's wort**
 - ▶ *Hypericum perforatum*, Hypericaceae
- ▶ **Passiflorae herba – passionflower herb**
 - ▶ *Passiflora incarnata*, Passifloraceae



Phytopharmaceuticals – SEDATIVES

Herbal teas

- ▶ Tea for restful sleep (Megafyt Pharma)

- ▶ Valerianae radix
- ▶ Melissa herba
- ▶ Passiflorae herba



- ▶ Species Nervinae (Leros)

- ▶ Melissa folium
- ▶ Valerianae radix
- ▶ Lupuli flos
- ▶ Hyperici herba
- ▶ Menthae piperitae herba
- ▶ Matricariae flos



- ▶ do not use in biliary disorders
- ▶ be careful about the content of Hyperici herba !

Phytopharmaceuticals – SEDATIVES

Herbal teas

▶ Children tea for sleep (Megafyt Pharma)

- ▶ Melissa herba (40 %)
Anisi fructus
Menthae piperitae herba
Lavandulae flos
- ▶ suitable for children from
6th month of age



▶ Children tea „Sweet dreams“ (Leros)

- ▶ Melissa herba
Tiliae flos
Origani herba
Rooibos
Liquiritiae radix
- ▶ suitable for children from
6th month of age



Phytopharmaceuticals – SEDATIVES

Herbal teas

▶ „Good night“ Tea

(Grešík – Devatero bylin)

- ▶ Origani herba
- Melissae herba
- Serpylli herba
- Lupuli flos
- Primulae flos
- Matricariae flos
- Leonuri herba
- Passiflorae herba
- Lavandulae flos



▶ „Calming tea“

Tea of Herbalist Pavel Váňa

- ▶ Serpylli herba
- Origani herba
- Melissae herba
- Hyperici herba
- Leonuri herba



Phytopharmaceuticals – SEDATIVES

Tablets, capsules

▶ PERSEN POR TBL OBD 40 (Sandoz)

- ▶ Valerianae extr. siccum
Melissae folii extr. siccum
Menthae piperitae folii extr.
sicc.
- ▶ SUKL code : 0075380
OTC medicinal product
- ▶ ATC: V11



▶ HOVA POR TBL FLM 20 (E&B Pharma)

- ▶ Valerianae extr. siccum 200 mg
Lupuli floris extr. siccum 45,5 mg
- ▶ SUKL code : 0030840
OTC medicinal product
- ▶ ATC: V11



Phytopharmaceuticals – SEDATIVES

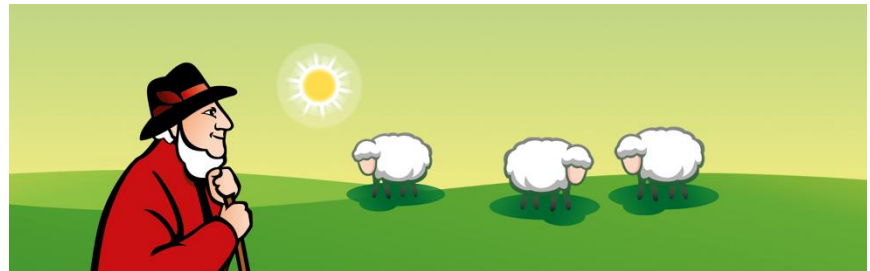
Tablets, capsules

▶ BALDRIPARAN TBL OBD 30 (Pfizer)

- ▶ high content of valerian extract, coated tablets (odor reduction)
- ▶ Valerianae extractum siccum 6,0-7,4:1, extracted by ethanol 70 % V/V

441,35 mg

- ▶ SUKL code: 0218346
OTC
- ▶ ATC: NO5CM09



SEDATIVES

Tablets, capsules



▶ Barny's HYPNOX Forte TBL 20 (Barnys - Biopol)

- ▶ Valerianae extr. 150 mg
- Lupuli extr. siccum 120 mg
- Passiflorae extr 120 mg
- Melissae extr. 50 mg
- vit. B6 (pyridoxin) 1.4 mg



▶ GS DORMIAN Rapid cps. (Green Swan Pharmaceuticals)

- ▶ Natural GABA Complex® = standardized extracts of:
 - Valerianae radix 100 mg
 - Melissae herba 50 mg
 - Lupuli flos 25 mg
 - Passiflorae herba 25 mg



SEDATIVES

Tablets, capsules

▶ **NEOSPAN FORTE 15 n. 45 tob.**
(Swiss)

▶ Content in 1 capsule:

Valerianae radix 200 mg

Melissae extr. siccum 65 mg

Passiflorae flos extr. siccum 50 mg

Lupuli flos extr. siccum 46 mg

Matricariae flos extr. siccum 37 mg

Mg (57 mg), vit. B6 (2 mg), B2 (0.6 mg), B1 (0.4 mg)



Phytopharmaceuticals – SEDATIVES

Drops, tinctures, syrups, medicinal solutions

- ▶ **NOVO-PASSIT sol.**
(IVAX-CR/TEVA)
 - ▶ **Herbarum extractum pro Passit fluidum 7,75 g:**
water extracts of Hyperici herba, Passiflorae herba Valerianae radix, Crataegi folium cum flore, Lupuli flos, Melissa herba, Sambuci flos
+ ! Guaifenesinum 4 g in 100 ml
 - ▶ SUKL code: 0088664, OTC product
 - ▶ ATC: N05CX (Hypnotics and sedatives in combination, except barbiturates)
 - ▶ also on foreign markets (solution, tablets)



Phytopharmaceuticals – SEDATIVES

Drops, tinctures, syrups, medicinal solutions

- ▶ **Passionflower drops (Topvet)**

- ▶ Content: 10 % (m/V) extract of *Passiflorae herba* in alcohol 40 % (V/V)

- ▶ **Drops for good sleep (Grešík)**

- ▶ Content: 10 % (m/V) extract of the mixture of plant drugs (*Lupuli flos*, *Melissae herba*, *Passiflorae herba*, *Lavandulae flos*) in alcohol 40 % (V/V)

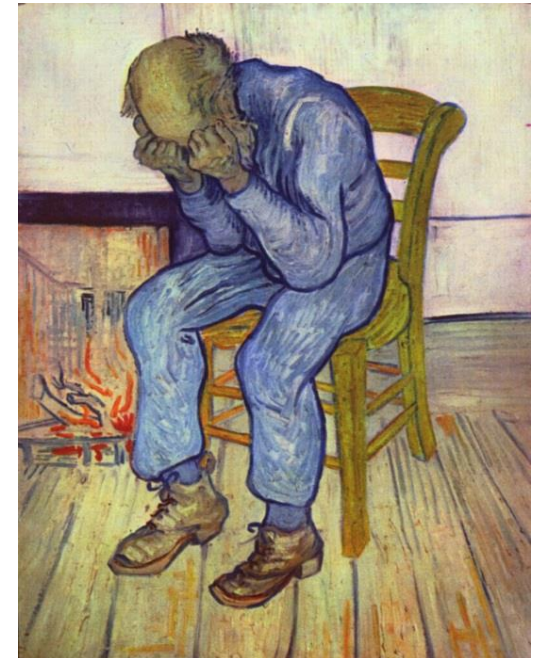
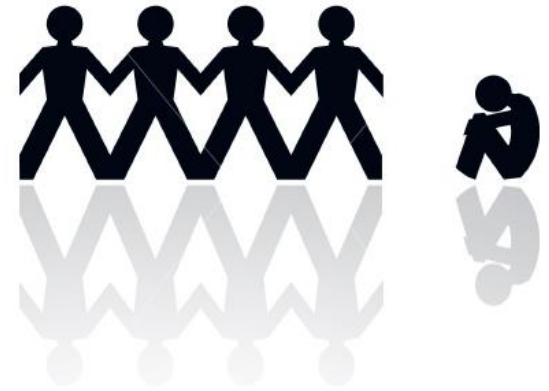
- ▶ **Herbal syrup with valerian and lemon balm (SILVITA)**

- ▶ contains extracts of *Valerianae radix* and *Melissae herba*



ANTIDEPRESSANTS

- ▶ = drugs used for the treatment of major depressive disorder (clinical depression)
- ▶ difficult diagnosis – various symptoms:
 - ▶ persistent low mood, loss of interest or pleasure - sadness, anxiety, sombre mood, „the blues“, fear, uneasiness
 - ▶ eating disorder, chronic pain, neuropathic pain, migraine, sleep disorders, tiredness, exhaustion
- ▶ **!** the risk of suicidal behaviour



Vincent van Gogh: *Old Man in Sorrow*
(*On the Threshold of Eternity*)

ANTIDEPRESSANTS

- ▶ the major cause of depressive disorders
 - lack of neurotransmitters in the brain
- ▶ effective synthetic drugs
 - ▶ SSRIs = selective serotonin reuptake inhibitors
 - ▶ SNRIs = serotonin-norepinephrine reuptake inhibitors
 - ▶ TCAs = tricyclic antidepressants
 - ▶ MAOIs = monoamine-oxidase inhibitors
- ▶ nowadays misuse of synthetic antidepressants



Plant antidepressants

- ▶ proven effect of *Hypericum perforatum*
= St. John's wort, *Hyperici herba*
- ▶ active constituents are **hyperforin**,
adhyperforin – can act as inhibitors of
reuptake of neurotransmitters (dopamine,
serotonin, norepinephrine, GABA,
glutamate)
- ▶ other constituents (*hypericin*,
procyanidines, flavonoids) may also
play a role in antidepressant effect



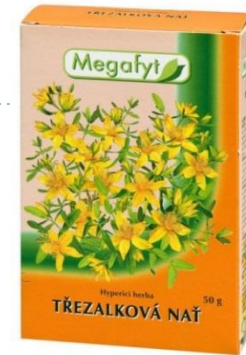
Hyperici herba

- ▶ quantified extract - Hyperici herbae extractum siccum quantificatum - St. John's wort dry extract (*hyperforin* max. 6.0 %; *hypericins* 0.1-0.3 %, flavonoids min. 6.0 %)
- ▶ antidepressive effect usually starts in 14 days – suitable for **mild** forms of depression, or for the treatment of sleep disorders
- ▶ **!!** interactions with other drugs – it may decrease efficacy of digoxin, theophylline, oral contraceptives, warfarin, cyclosporine; indinavir and other retroviral products (used in the treatment of HIV positive patients)
- ▶ **!!** interactions with some concurrently administered antidepressants
- ▶ **!!** photosensitive activity (*hypericin*)

- ▶ Hyperici herba is also used for other purposes (for digestive disorders; for external use – astringent, antiphlogistic activity)

Hyperici herba

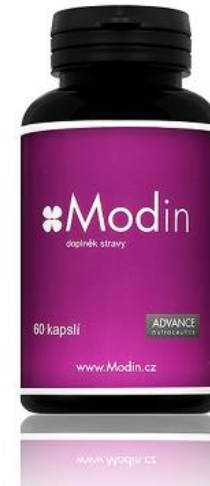
- ▶ herbal teas
 - ▶ monocomponent
 - ▶ polycomponent
 - ▶ e.g. LEROS Species nervinae, Pavel Váňa – Calming tea
- ▶ tablets, capsules...
 - ▶ Kneipp drg. (sugar coated pills)
 - ▶ MODIN cps.
- ▶ drops (guttae)
 - ▶ Grešík – herbal drops, 10 % (m/V) extract of Hyperici herba in alcohol 40 % (V/V)



Phytopharmaceuticals – ANTIDEPRESSANTS

Tablets, capsules

- ▶ **MODIN**
(ADVANCE nutraceutics)
- ▶ combination of natural components (extract of *Hypericum perforatum*) and amino acids, vitamins
- ▶ usage:
 - ▶ 1 capsule per day
 - ▶ break after 4 months of usage
 - ▶ not for children until 15 years, for pregnant and lactating women
 - ▶ photosensitivity, interaction with some other drugs (due to the content of *Hyperici herba* extract) !



Active components	Content in 1 capsule
<i>Hypericum perforatum</i> extract (content of hypericine 0.3%)	300 mg
L-tryptophane	50 mg
D,L-phenylalanine	50 mg
vitamin B3	16 mg
vitamin B5	6 mg
vitamin B6	2 mg

Phytopharmaceuticals – ANTIDEPRESSANTS

Tablets, capsules

▶ SAFRAMYL (3 Chênes)

- ▶ SATIEREAL® (24,5 %): extract of saffron (*Crocus sativus*) stigmatas – contains *safranal*
- ▶ *L-tryptophan, pyridoxin* (vit. B6)
- ▶ was clinically proven to naturally eliminate depression throughout the triple action on the neuromediator serotonin:
 - ▶ L-tryptophan (amino acid) indeed supports its production
 - ▶ SATIEREAL inhibits the recapture of serotonin
 - ▶ B6 vitamin supports the transfer of serotonin to neurons.
- ▶ usage:
 - ▶ 1 tablet once daily, before lunch

