POST-SSRI'S SEXUAL DISORDERS (PSSD)

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SSRI's: Indications & Use

- Depressive disorder
- Anxiety disorder
- OCD
- Panic attacks
- PTSD
- PE

- Prevalence: up to 7% of US population
- SSRI's are the 3rd most often prescribed medication in US
- In NL: 3% of population use SSRI

Ekhart CG, Tijd Psychiatry 2014
Mojtabai R, Health Aff 2011

SSRI's: Sexual Side-Effects

- Decreased libido
- Erectile dysfunction/decreased lubrication
- Ejaculatrory diosorders (Delayed)
- Delayed/Anorgasmia

- Anesthesia of genitals
- PGAS

- Depression or SSRI ?

- SSRI side-effect

Clayton A, Postgrad Med 2014;
Dutch Pharmacovigilance Center Lareb 2012
Leiblum SR. J Sex Marital Ther 2008

- Prevalence up to 70%
- Due to activation of the 5-HT_{2A} receptors
- Endure for the duration of treatment, assume to be resolved upon discontinuation

Clayton A, Postgrad Med 2014;
Dutch Pharmacovigilance Center Lareb 2012

Desire, Arousal & Depression

- Depression - **Decreased** desire in
  - 40 % of men
  - 50% of women (variability up to 70%)
- Depression – **Increased** desire in
  - 23% of men
  - 9 % of women
- Increased risk of
  - OR-3.4 for erctile dysfunction
  - OR-2.3 for vaginal dryness
- Nocturnal penile tumescence is decreased in 40% of men with depression

Laurent. Clinical Psychology rew. 2009:29;573-85
Zemishlany. Adv Psychosom Med.2008:29;89-106
Kennedy. J.Clin.Psycho.Pharmacol. 2009:29:157-164

Ejaculation, Orgasm & Depression

- 15-25% increased risk of premature or delayed ejaculation
- 40 % of women report orgamic problems
- Large variability in studies

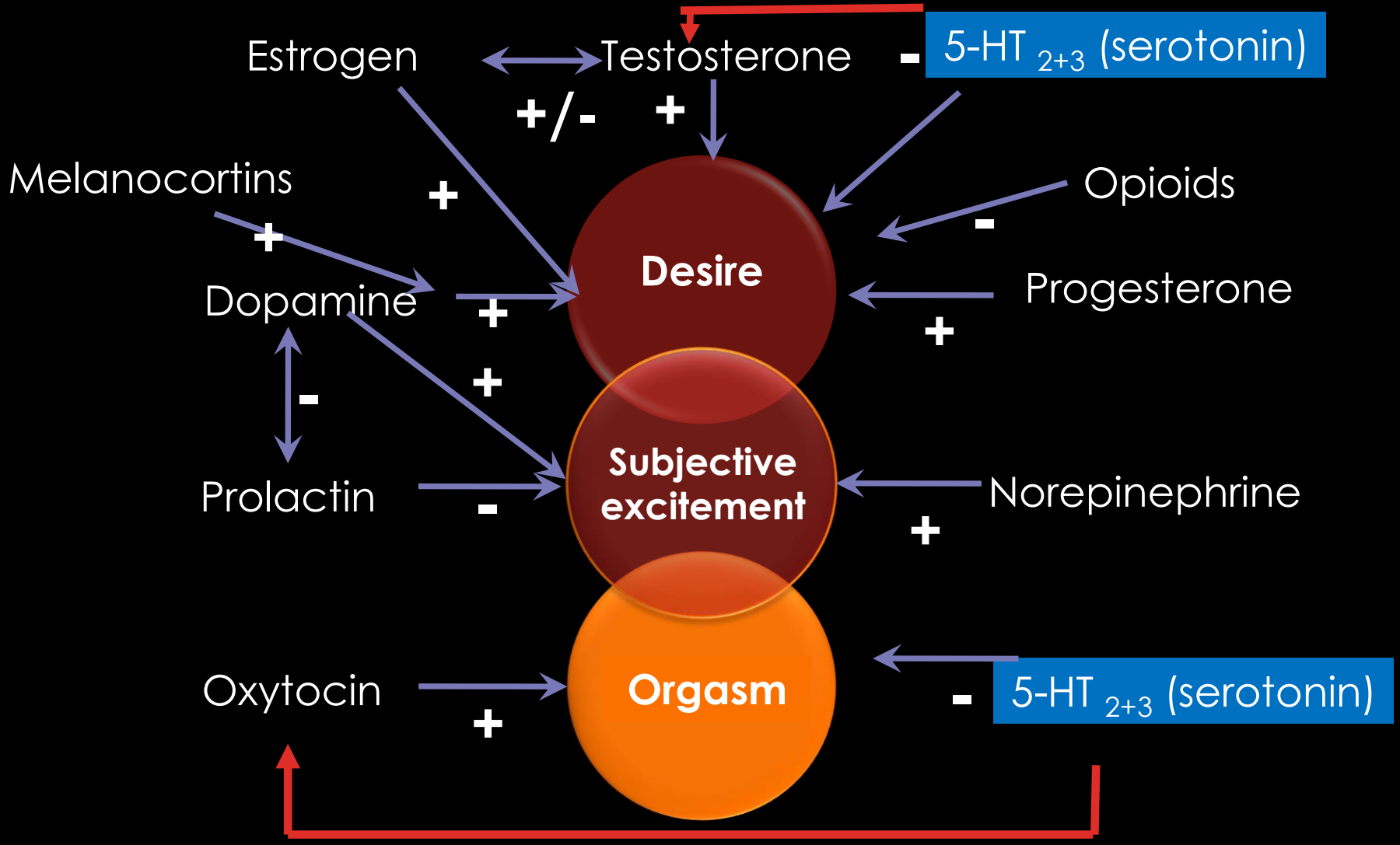
Laurent. Clinical Psychology rew. 2009:29;573-85
Zemishlany. Adv Psychosom Med.2008:29;89-106
Kennedy. J.Clin.Psycho.Pharmacol. 2009:29:157-164

The Effect of Psychopharmaca on Sexual Function

- Unspecific:
  - Overweight, tiredness
- Specific effect on CNS neurotransmitters:
  - serotonin, noradrenaline, dopamin, NO, cholinergic system
- Direct hormonal effect:
  - Prolactin
- Indirect hormonal effect
  - SHBG & metabolic syndrome

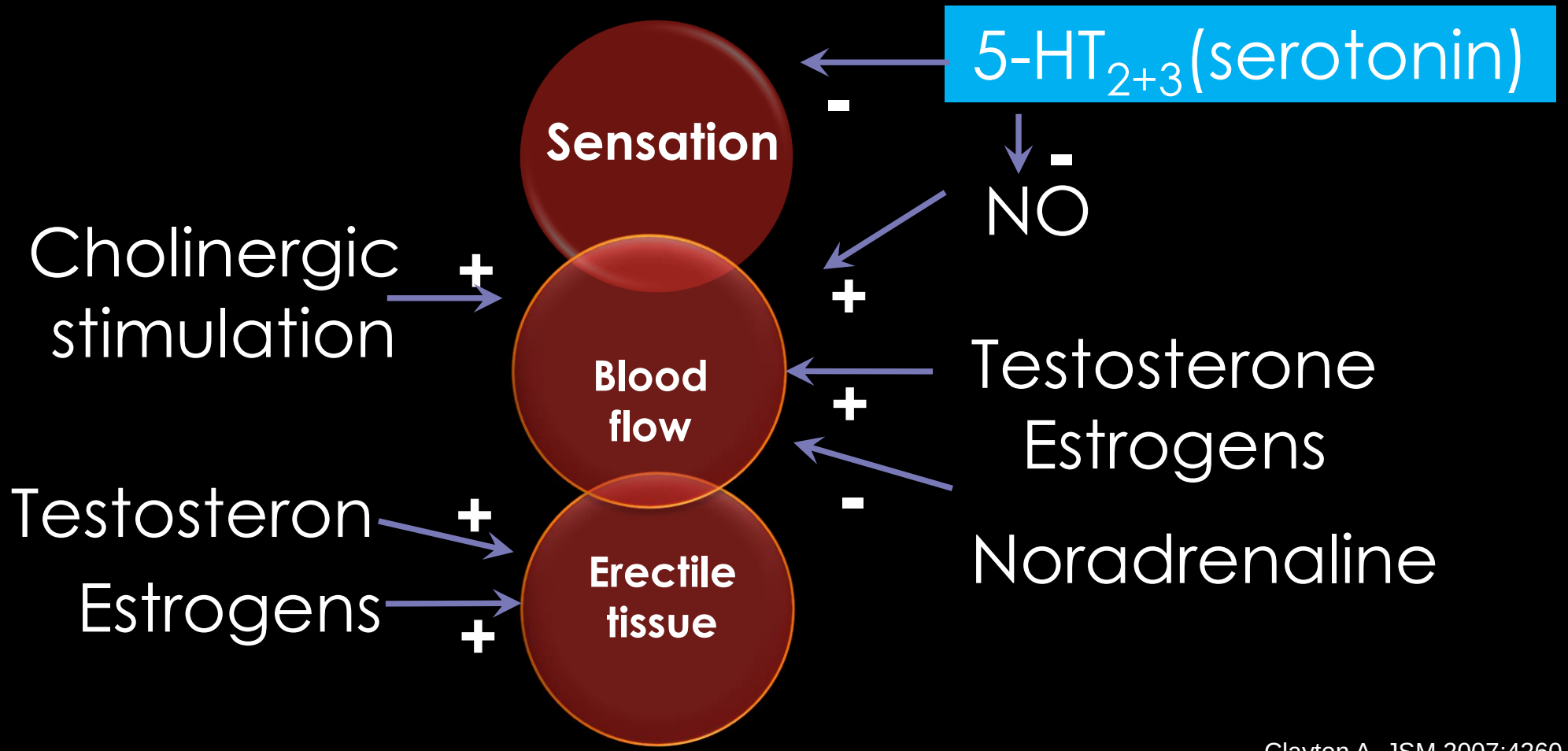
Segraves 1989
Corona G. Eur Endocrin 2008

Central Effects of Neurotransmitters & Hormones on Sexual Functioning



Clayton A. JSM 2007;4260-268

Peripheral Effects of Neurotransmitters & Hormones on Sexual Functioning



Clayton A. JSM 2007;4260-268

More about Anti-depressant & Sexual Dysfunction

- Sexual dysfunction, sleeping problems and weight gain are major reason for stopping anti-depresant treatment (60-75% of patients)
- 90% of patients stop prematurely with the medication
- Side effects early in reatment can decline, decrease or persist – but it will rarely dissapear
- Sex is important for patients

Nurnberg 2003 & 2008

Treatment Of Medication Induced SD

- Wait for tolerance(10%)
- Dose-reduction
- Change of drug / Drug with less side effects
- ”Drugholiday”
- Change sexual habits
- Pharmacological treatment of SD
  - PDE5-inhibitors
  - Antidote treatment
- Information/ couple therapy

ANTIDOTES

- Bupropion (Zyban®) — *dopamin & noradrenalin agonist*
- Buspiron (Buspar®) — *5-HT_{1A_A} partiel agonist*
- Mirtazapin (Remeron®) — *adrenerg antagonist & $5HT_3$ & $5HT_{2A}$ antagonist*

- Sildenafil (Viagra®) — *PDE5 inhibitor*
- Granisetron (Kytril®) — *$5HT_{3_3}$ antagonist*
- Apomorfin SL — *dopaminagonist*
- Cyproheptadin — *serotonin antagonist*
- Yohimbin — *adrenerg α_2 antagonist*
- Neostigmin — *cholinerg agonist*
- Amantadin — *dopamin agonist*
- Dextroamfetamin — *dopamin agonist*

- Emerging evidence that in some patients these SD side-effects persist after cessation of SSRi's >> **PSSD**

- No-one know what withdrawal syndrome and **PSSD** actually are !!!

- What is the treatment / How to manage ???

PSSD

- Difficult to diagnose
- Difficult to treat
- Difficult to cure

Frustration for patient & physician

What Is The Evidence

- Lareb database[1]:
  - 140,000 registrations, 44,000 about SSRI
  - 19 reports of PSSD
  - 13 ♂ : 6 ♀
  - Mean age 30 years (20-59)
    - SSRI use: 9 days – 10 years
    - PSSD: 2 months – 2 years
  - Paroxetine, Sertraline, Venlafaxine, Citalopram, Fluoxetine, Fluvoxine, Esitalopram
  - DE, Libido decrease, ED, Orgasmic disorders, reduced sensitivity

- Csoka[2]:
  - 3 males (20, 28 and 44 years old)
  - After use of SSIR's for different period (4-24 months)
  - Libido loss, ED, genital anesthesia

- Csoka & Shapro[3]:
  - 2 ♂ & 1♀
  - 24 – 30 years
  - Libido loss, ED, numbness

➢ **Diminshed Physical Capacity to Experience Sexual Pleasure**

- Bolton[4]:
  - 26 years ♂
  - Genital anesthesia, libido loss and orgasmic dysfunction
  - 6 years after Sertraline

- Kaufman[5]
  - 32 years ♀
  - genital anesthesia and anorgasmia persist 1 year after Citalopram

- No relationship problems or Sexual complains prior to SSRI
- SD after start medication
- Depression in remission, no CVD risk factors
- Normal Serum T, LH, FSH, Cortisol, ACTH, Estrogen & Serotonin

[1] Dutch Pharmacovilligance database 2012
[2] CSoka AB, J Sex Med 2008
[3] Csoka AB Psychoth Psochosom 2006
[4] Bolton JM, J Sex Mart Therp 2006
[5] Kaufmann

Possible Theories

- Serotonine increase in hypothalamus - down regulation receptors - Testosteron decrease
- Epigenetics: Serotonine transmission: single Nucleotide Polymorfism (SNP)
- Sodium chanals changes – decrease in Oxytocine release
- Transient Recptor Potentia Chanales (TLPR)
- Change in brain structures with SSRI (Amygadala,)
- Endocrine: SSRI & OAC more side effects, decreased Dopamine

Markman 2016
Bishop JR 2006
Yamada 2005
Scala 1987
Baird AD 2004
Rosen RC 1999

Contributing Factors

- Psychological
- Concomitant medical disorders
- Medications

WHAT WE SHOULD DO?

- Registration and longer follow-up
- Informed consent before treatment
- When possible - avoid SSRI's
- Assess Sexual function before, during and after treatment
- When side effect:
  - Drug holiday
  - Reduce doses
  - Change to drug with less Sexual side effects (Bupropion, Mirtazapine, Nefazodone)*

*Clayton A, 2007 &2012
Ben-Sheetrit 2015

- Multidisciplinary approach
  - Other contributing factors/ Psycho-pathology
- History and Physical examination
- Routine Laboratory and Hormones (TSH, LH, FSH, Testo, PRL, Estrogen)
- Support & addressing the fear of permanent problem

- Sleep, Nutrition, Physical activity, Routine
- Avoiding of Alcohol & Drugs

Anecdotal evidence

- Fenylethylamine (Wine, Choclate, Chees) & Sofran
  - Reducation of symptoms severity
- Imipramine & Amineptine
  - increase dopamine transmission. Improvement of ejaculation
- Pramipexol (Dopamine agonist)
- Methylphenidole (Ritalin) –
  - Increase dopamine transmission
- Trazodone (5HT2 antagonist)
  - Reducation of SD sevirity
- Low-power laser irradiation for genital anesthesia

Montejo 1999
Stacey J 2009
Waldinger 2015
Kahani 2013

Thank you

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