# EFECTELE ADVERSE INDUSE DE MEDICAȚIA PSIHOTROPĂ

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# Psihofarmacologie clinică – eficiență

- Integritatea structurală și funcțională a SNC
- Reacţii adverse
- Interacţiuni medicamentoase

# Particularităţi ale siguranţei şi eficacităţii terapiei în psihofarmacologie

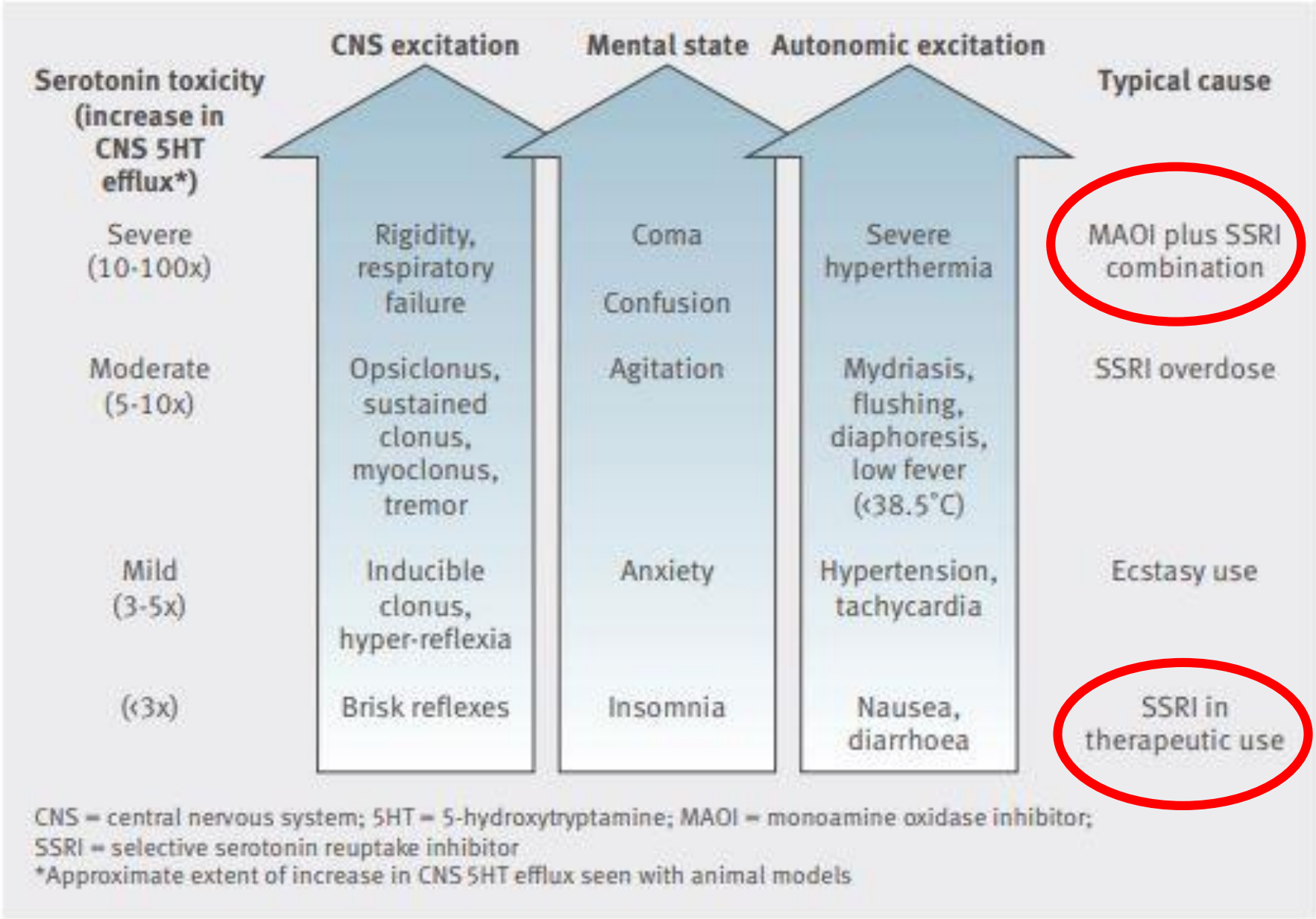
- Integritatea BHE
- Reacția inflamatorie, raportul neuron/activare microglială
- Calitatea perfuziei sangvine cerebrale
- Integritatea funcţională hepatică
- Suport metabolic cerebral
- Integritatea funcţională a pompei cardiace
- Integritatea funcţională renală
- Brain - gut microbioma axis
- Comorbidități
- Patologia dual

# SIGURANŢA TERAPIEI PSIHOTROPE ESTE DEPENDENTĂ DE:

Precocitatea diagnosticului
Corectitudinea diagnosticului
Calitatea şi completitudinea remisiunilor
Aderenţa şi complianţa la tratament

# EFECTE ADVERSE SEVERE CARE PUN ÎN PERICOL VIAŢA PACIENTULUI

- Sindromul serotoninergic
- Sindromul neuroleptic malign
- Hipotensiunea ortostatică
- Prelungirea intervalului QT, aritmii




*Serotonin syndrome, BMJ 2014, Buckley N, Dawson A, Isbister G*

# Drug-Induced Serotonin Syndrome

Dana Bartlett, RN, BSN, MSN, MA, CSPI

## Table 1 Agents that cause serotonin syndrome

| |
|---|
| Amphetamine |
| Buspirone |
| Cocaine |
| Dextromethorphan |
| Fentanyl |
| Linezolid |
| Lysergic acid diethylamide (LSD) |
| Monoamine oxidase inhibitors (MAOIs) |
| 3,4-Methylene dioxymethamphetamine (MDMA; ecstasy) |
| Methylene blue |
| Ondansetron |
| Selective serotonin reuptake inhibitors (SSRIs) |
| Serotonin-norepinephrine reuptake inhibitors (SNRIs) |
| St John's wort |
| Sumatriptan |
| Tramadol |
| Tricyclic antidepressants |
| Tryptophan |

## Table 2 Mechanisms of action of serotonin syndrome

| Mechanism | Example |
|---|---|
| Direct serotonin receptor agonism | Buspirone, LSD |
| Decreased serotonin breakdown | MAOIs, methylene blue |
| Decreased reuptake of serotonin | Duloxetine, fluoxetine |
| Increased formation of serotonin | Tryptophan |
| Increased release of serotonin | Cocaine, fentanyl |

Abbreviations: LSD, lysergic acid diethylamide; MAOIs, monoamine oxidase inhibitors.
Based on information from Hillman et al,[11] Ables and Nagubilli,[12] and Iqbal et al.[13]

## Table 3 Clinical situations in serotonin syndrome

| |
|---|
| Abuse of illicit drugs |
| Drug-drug interactions |
| Intentional overdose of a serotonergic medication |
| Therapeutic use of a serotonergic medication or medications |

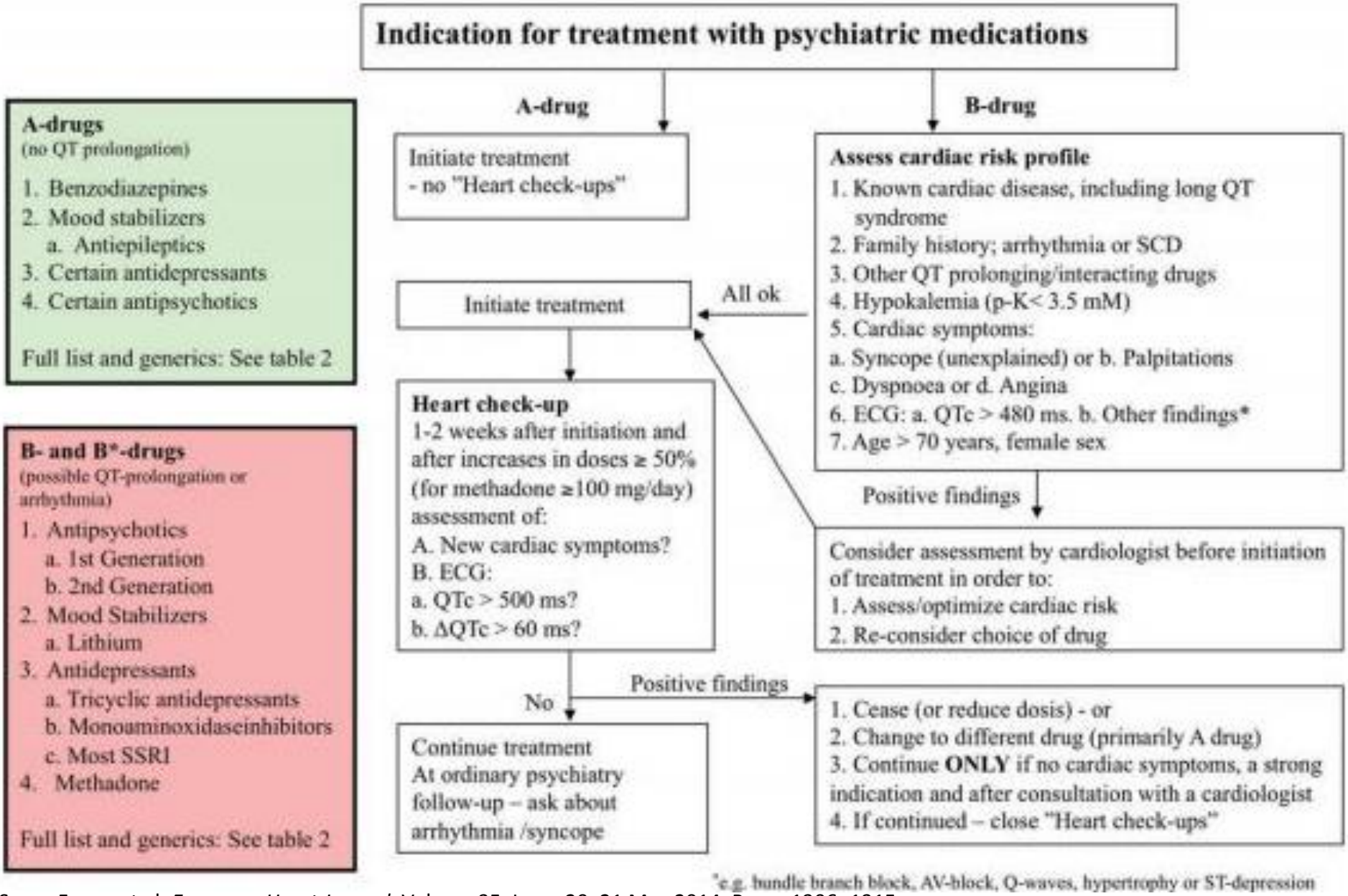
# Neuroleptic Malignant Syndrome

*Neuroleptic Malignant Syndrome: A Review from a Clinically Oriented Perspective, Lurdes Tse, Alasdair M Barr, Fidel Vila-Rodriguez, Current neuropharmacology 2015*

| Risk Factors | |
|---|---|
| **Category** | **Variable** |
| Pharmacological Treatment | Initial phases of treatment or, change of dosage<br>High dose of AP<br>Parenteral administration (i.v. or i.m.)<br>Polypharmacy<br>Antipsychotic treatment<br>Other compounds: AD, MS, aP |
| Environmental factors | Physical restraint<br>Dehydration<br>High temperature |
| Demographics | Age<br>Multimorbidities |
| Genetic liability | Previous NMS<br>Family history of Catatonic Syndrome<br>Muscle channelopathy |

*i.v.*, intravenous; *i.m.*, intramuscular; *AD*, antidepressants; *MS*, mood stabilizers; *AP*, antipsychotics; *aP*, antiparkinsonian

# Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management




Søren Fanoe et al, *European Heart Journal*, Volume 35, Issue 20, 21 May 2014, Pages 1306–1315

## Table 1

## Select Medications That Can Induce Orthostatic Hypotension

| |
|---|
| **Antihypertensives** |
| Thiazide diuretics |
| Loop diuretics |
| Clonidine |
| Methyldopa |
| Reserpine |
| ACE inhibitors |
| Diltiazem |
| Nifedipine |
| **Vasodilators** |
| Nitrates |
| Hydralazine |
| **Alpha-blocking agents** |
| Terazosin |
| Doxazosin |
| Prazosin |
| **Antidepressants** |
| Tricyclic antidepressants |
| Trazodone |
| Selective serotonin reuptake inhibitors |
| Venlafaxine |
| Monoamine oxidase inhibitors |
| **Antipsychotics** |
| Atypical antipsychotics |
| **Parkinson's disease drugs** |
| Levodopa |
| Bromocryptine |
| Pergolide |
| Selegiline |
| **Phenothiazine derivatives** |
| Chlorpromazine |
| Promazine |
| Thioridazine |
| **Miscellaneous** |
| Quinidine |
| Barbiturates |
| Alcohol |
| Narcotics |
| Insulin |
| Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) |
| Vincristine |

*ACE: angiotensin-converting enzyme.*
*Source: Adapted from references 19, 20, 43.*

*An Overview of Orthostatic Hypotension, Ivy Poon, US Pharm. 2006;12:HS32-HS41.*

# REACŢII ADVERSE CARE SEMNALIZEAZĂ EVOLUŢIA DEFAVORABILĂ ŞI RISCURILE EVOLUTIVE DISCOGNITIVE, DISMETABOLICE, NEURODEGENERATIVE ŞI COMPORTAMENTALE

# Selected Agents Associated with Drug-Induced Movement Disorders

## Acute and Tardive Akathisia

**Antiemetics**
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
**Antiepileptics**
Carbamazepine
**Psychotropics**
Lithium
Neuroleptics
Haloperidol
Molindone
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Thioxanthenes (e.g., thiothexene)
Reserpine
Selective serotonin-reuptake inhibitors
Tricyclic antidepressants

## Acute and Tardive Dyskinesia

**Antiemetics**
Metoclopramide
Prochlorperazine
**Antiepileptics**
Phenytoin
**Psychotropics**
Amoxapine
Haloperidol
Lithium
Molindone
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Olanzapine (high dosage)
Pimozide
Risperidone (high dosage)
Thioxanthenes (e.g., thiothexene)

## Acute and Tardive Dystonia

**Antiemetics**
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
**Psychotropics**
Amoxapine
Neuroleptics
Haloperidol
Molindone
Olanzapine (high dosage)
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Risperidone (high dose)
Thioxanthenes (e.g., thiothexene)

## Parkinsonism

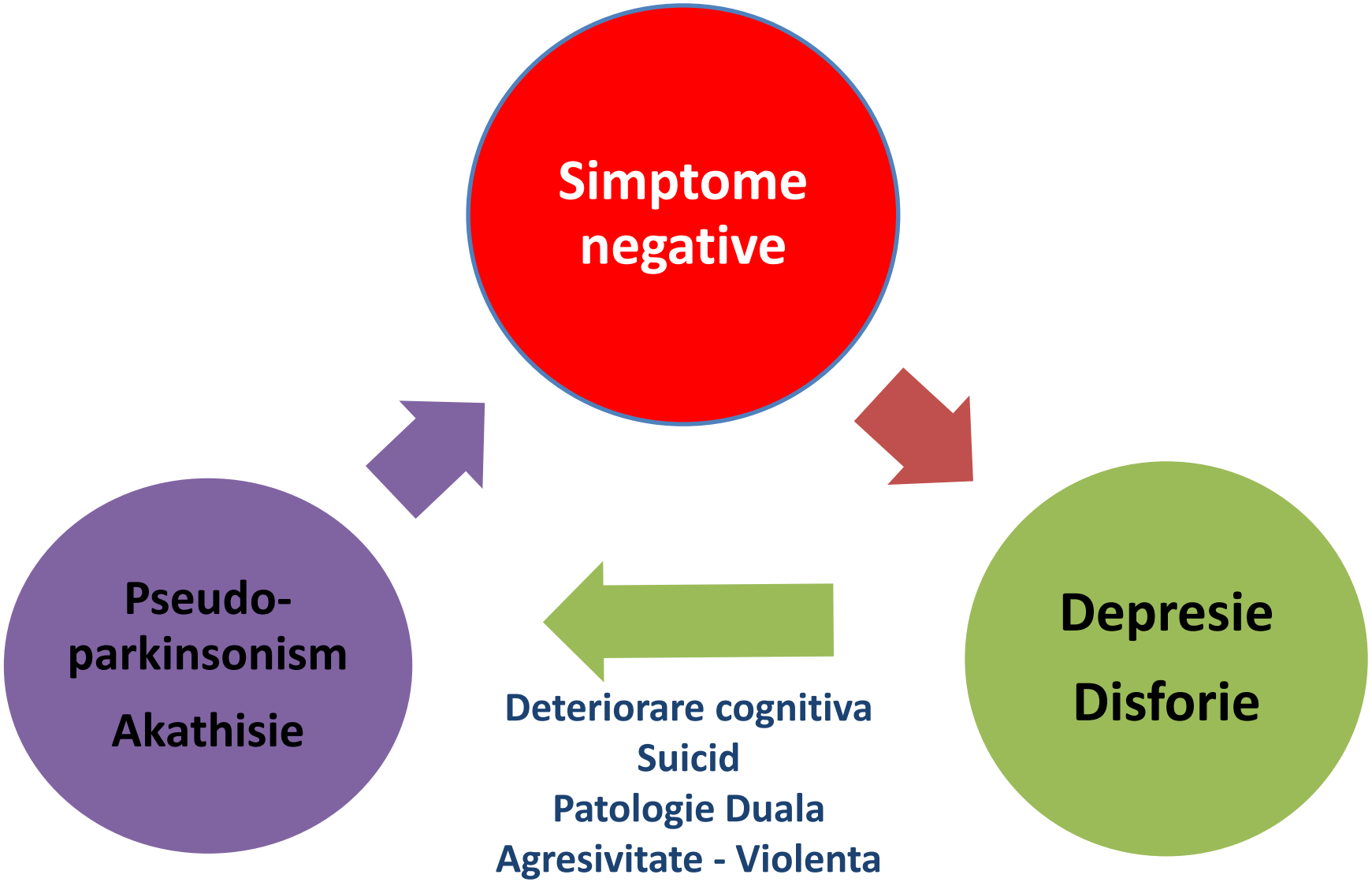
**Antiemetics**
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
**Antiepileptics**
Valproate
**Cardiovascular agents**
Alpha-Methyldopa
Reserpine
**Psychotropics**
Amoxapine
Neuroleptics
Haloperidol
Molindone
Olanzapine (high dosages)
Phenothiazines (e.g., chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Risperidone (high dosages)
Thioxanthenes (e.g., thiothexene)
**Vestibular sedatives**
Cinnarizine and Flunarizine*
**Miscellaneous**
Pimozide
Tetrabenazine*

*Drug-Induced Movement Disorders: A Primer*
*Jack J. Chen, 2007, US Pharm. 32(11)HS16-HS32*

# Reacţii adverse consemnate în ghidurile terapeutice

| Efecte adverse | AP convenţional | AP atipic |
|---|---|---|
| Simptome extrapiramidale | + + + | + |
| Prolactinemie | + + | + |
| Diskinezie tardivă | + + + | + |
| Hipotensiune ortostatică | + + | + |
| Prelungirea intervalului QT | + + + | + |
| Sindrom metabolic | + | + + + |
| Diabet zaharat | + | + + |
| Moarte subită | + + | + |
| Sindrom neuroleptic malign | + + + | + |
| Sindrom serotoninergic* | + - | + |
| Deteriorare cognitivă | + + + | + - |

* *risc amplificat de tratamente anterioare sau concomitente cu antidepresive serotoninergice.*




# RISC SUICIDAR

Pacientii cu schizofrenie au un risc de mortalitate precoce de pana la 40% prin doua cauze:

Suicid Moarte ne-naturala

(Kahyee Hor, 2010)

Pacientii spitalizati dupa primul episod de schizofrenie si care nu au luat in mod regulat medicatia antipsihotica (**aderenta scazuta**) au avut un risc de deces:

- de 12 ori mai mare, prin orice cauza
- de 37 ori mai mare, prin suicid.

(Tiihonen 2006)

**Suicidul este puternic corelat cu urmatorii factori de risc: varsta tanara, sexul masculin, nivelul educational inalt, depresia, tentativele anterioare de suicid, comorbiditatile somatice (Kahyee Hor, 2010).**

**There were 34 (30.9%) studies based on inpatient samples and outcomes.**

- The substance misuse domain was less strongly associated with violence risk, although it remained significant.

- The psychopathology and positive symptoms domains were more strongly associated with **violence risk**.

- The negative symptoms, neuropsychological, demographic, premorbid, **suicidality**, and treatment-related domains were associated with violence risk, but not significantly.

*Risk Factors for Violence in Psychosis Katrina Witt, Richard van Dorn, Seena Fazel*

Cel mai sever efect advers al medicaţiei psihotope este

NON-EFICACITATEA
şi/sau
NON-ADERENŢA LA TRATAMENT

*Frank H. Farky 2015*

# POTENŢIALE AFECŢIUNI COMORBIDE CORELATE CU TERAPIA ANTIPSIHOTICĂ ÎN TULBURĂRILE PSIHIATRICE MAJORE CARE INFLUENŢEAZĂ NEGATIV PROGNOSTICUL ŞI CRESC COSTURILE DE ÎNGRIJIRE:

- Diabet / hipoglicemie
- Afectiuni gastrointestinale
- Afecţiuni pulmonare cronice
- Alcoolism / patologie dual
- Patologie cardio-cerebro-vasculară
- Afecţiuni stomatologice cronice

## Table 2. Select Drug Categories and Drugs Associated With Hyperglycemia

- Antibiotics
  - Quinolone
    - Gatifloxacin (also associated with hypoglycemia)
    - Levofloxacin
- Atypical antipsychotics
  - Most Risky
    - Clozapine
    - Olanzapine
  - Intermediate
    - Paliperidone
    - Quietiapine
    - Risperidone
  - Least Risky
    - Aripiprazole
    - Ziprasidone
  - Unknown
    - Iloperidone
- β-blockers*
  - Atenolol
  - Metoprolol
  - Propanolol
- Corticosteroids
- Calcineurin inhibitors
  - Cyclosporine
  - Sirolimus
  - Tacrolimus
- Protease Inhibitors
  - Atazanavir
  - Darunavir
  - Fosamprenavir
  - Indinavir
  - Nelfinavir
  - Ritonivir
  - Saquinavir
  - Tipranivir
- Thiazide and thiazide-like diuretics
  - Chlorthiazide
  - Chlorthalidone
  - Diazoxide
  - Hydrochlorothiazide
  - Indapamide
  - Methyclothiazide
  - Metolazone

*Note: Carvedilol and nebivolol are not associated with the development of hyperglycemia.*

**Select Drug Categories and Drugs Associated With Hyperglycemia.**

Antibioterapie

Antipsihotice atipice

Beta blocante

Corticosteroizi exogeni

Ciclosporina

Antivirale – HIV

Diuretice tiazidice

**Abdur Rehman et al. Diabetes Spectr 2011;24:234-238**

Condiţiile comorbide metabolice determină modificări structurale cerebrale

- Hipoglicemia (diabet zaharat)
- Hipoxia
- Hipoperfuzia vasculară

Creşterea nivelului de glutamat declanşează reacţii asociate cu modelul comportamentului exploziv de tip epileptiform

# Comportamentul agresiv – crima

Pacientii cu psihoza au comis crime de 4 ori mai mult decat populatia generala

Factorii neurobiologici si psihofarmacologici care favorizeaza comportamentul criminal:

- Utilizarea medicatiei pentru afectiuni asociate
- Afectiuni comorbide de personalitate (personalitate antisociala)
- Lipsa aderentei la tratament
- Lipsa compliantei la tratament


1. Tuninger 2001
2. Jan Volavka Treatament approeaches to agressive behavior in schizophenia, cap 16 (2006) Crime and schizoprenia causes and cures

# Exista suficiente argumente neurobiologice si psihofarmacologice care sa permita preventia secundara a comportamentelor agresive sau suicidare !

Crima de la metrou.


http://www.gds.ro

Pacient ucis intr-un sanatoriu de neuropsihiatrie din Botosani. Agresorul nu poate fi pedepsit, deoarece e bolnav psihic


https://stirileprotv.ro

# Medicamentele care induc hipoglicemia cresc riscul comportamentelor violente şi suicidare

| | Clinical Setting |
|---|---|
| Ciabenzoline | Chronic and acute: few had diabetes and renal insufficiency |
| Clinafloxacin | Acute: pneumonia and sepsis |
| Gatifloxacin | Acute: various infections |
| Glucagon | Chronic: endoscopy patients |
| Indomethacin | Chronic: infants with patent ductus arteriosus |
| Pentamidine | Acute: infections in immunocompromised host |
| Quinine | Acute: malaria and cerebral malaria |
| Artesunate/artemisin/artemether | Acute: malaria and cerebral malaria |
| Chloroquineoxaline sulfonamide | Chronic: malignancy (mainly lung and colon) |
| IGF-I | Chronic: diabetes or isolated GH deficiency |
| Lithium | Chronic: postglucose hypoglycemia |
| Propoxyphene and | Chronic: renal insufficiency, few had |

**Drug-induced hypoglycemia**

**can be severe and cause significant morbidity. Prescribers should strive to avoid these adverse events particularly in elderly patients, patients with sepsis, renal or hepatic disease**

M. Hassan Murad et al, Drug-Induced Hypoglycemia: A Systematic Review, The Journal of Clinical Endocrinology & Metabolism, Volume 94, Issue 3, 1 March 2009,

# Drug-induced hypoglycemia

| Example | Mechanism of action |
|---|---|
| Insulin | Exogenous hyperinsulinaemia |
| Sulfonylureas | Increased insulin output |
| Meglitinides | |
| Salicylates | Impairment of gluconeogenesis |
| Pentamidine | β cell toxin |
| Quinine | Increased insulin output |
| Alcohol | Stimulates an exaggerated release of insulin by diverting blood flow to the endocrine part of the pancreas. Also impaired gluconeogenesis |

*Elora Mukherjee et al, Endocrine and Metabolic Emergencies: Hypoglycaemia, Ther Adv Endocrinol Metab. 2011 Apr; 2(2): 81–93.*

# Medicamentele care induc tulburări de tip (pseudo)psihiatric – posibilă sursă de erori de diagnostic şi tratament, cu scăderea siguranţei pacienţilor

# An approach to drug induced delirium in the elderly

## Box 1: Deliriants (drugs causing delirium)

**Prescription drugs**

- Central acting agents:
  - Sedative hypnotics (for example, benzodiazepines).
  - Anticonvulsants (for example, barbiturates).
  - Antiparkinsonian agents (for example, benztropine, trihexyphenidyl).
- Analgesics:
  - Narcotics (NB. meperidine*).
  - Non-steroidal anti-inflammatory drugs*.
- Antihistamines (first generation—for example, hydroxyzine).
- Gastrointestinal agents:
  - Antispasmodics.
  - $H_2$-blockers*.
- Antinauseants:
  - Scopolamine.
  - Dimenhydrinate.
- Antibiotics:
  - Fluoroquinolones*.
- Psychotropic medications:
  - Tricyclic antidepressants.
  - Lithium*.
- Cardiac medications:
  - Antiarrhythmics.
  - Digitalis*.
  - Antihypertensives (β-blockers, methyldopa)
- Miscellaneous:
  - Skeletal muscle relaxants.
  - Steroids.

**Over the counter medications and complementary/alternative medications**

- Antihistamines (NB. first generation— for example, diphenhydramine, chlorpheniramine).
- Antinauseants (for example, dimenhydrinate, scopolamine).
- Liquid medications containing alcohol.
- Mandrake.
- Henbane.
- Jimson weed.
- Atropa belladonna extract.

* Requires adjustment in renal impairment.

*An approach to drug induced delirium in the elderly, K Alagiakrishnan, C A Wiens, Postgrad Med J 2004;80:388–393.*

# Some possible mechanisms of drug-induced depression

| DRUG OR DRUG CLASS | POSSIBLE MECHANISM FOR DID |
|---|---|
| Nifedipine, other calcium channel blockers | Block slow influx of calcium into the cell, inhibiting calcium-dependent neurotransmitter release and reducing neurotransmitter amplification through the second-messenger system[20] |
| Benzodiazepines | Based on rodent studies: decreased release of serotonin in hippocampus (except with alprazolam)[23] |
| Exogenous corticosteroids | Based on rodent development studies: dexamethasone administration leads to deficits in the number and size of neural cells; reduced function of G-protein-coupled catecholaminergic or cholinergic receptors[24] |
| Varenicline | Displaces nicotine from acetylcholine receptors, produces low-to-moderate levels of dopamine release, and stimulates mesolimbic dopamine system. May upset the balance in cholinergic-adrenergic tone potentially leading to depression or mania[25] |

*Rogers & Pies, 2008*

# DRUG-INDUCED RHABDOMYOLYSIS

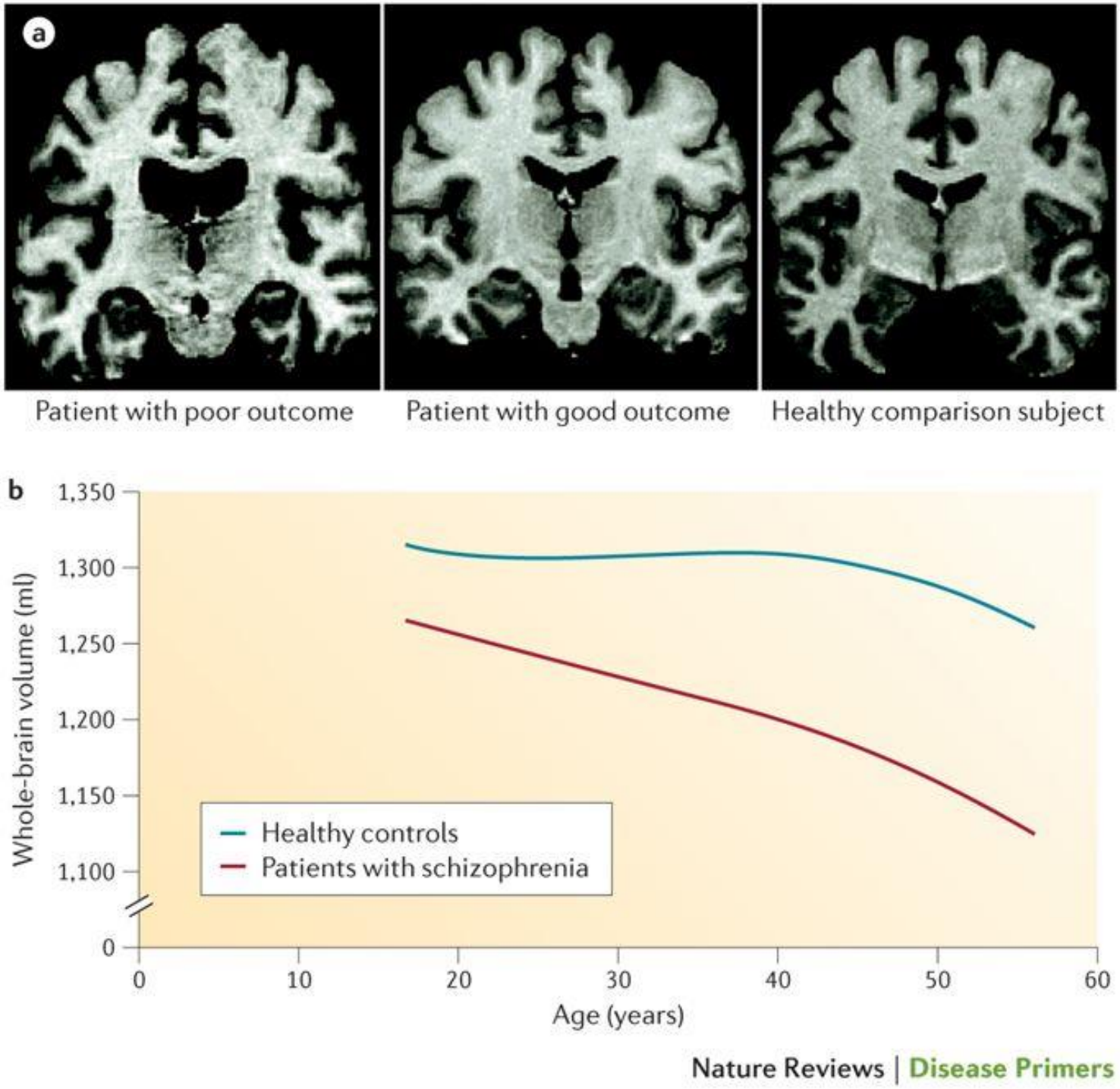
| Statins | Other Antilipid Agents | Psychiatric Agents | Abused Substances | Antihistamines | Other |
|---|---|---|---|---|---|
| Lovastatin | Ezetimibe | Amitriptyline | Alcohol | Diphenhydramine | Amphotericin B |
| Pravastatin | Bezafibrate | Amoxapine | Cocaine | Doxylamine | Arsenic |
| Simvastatin | Clozafibrate | Doxepin | Heroin/Opiates | | Azathioprine |
| Fluvastatin | Ciprofibrate | Fluoxetine | Amphetamines | | Carbon monoxide |
| Atorvastatin | Clofibrate | Fluphenazine | Methamphetamines | | Halothane |
| Rosuvastatin | Gemfibrozil | Haloperidol | Lysergic acid diethylamide | | Naltrexone |
| | | Lithium | Phencyclidine | | Quinidine |
| | | Protriptyline | | | Penicillamine |
| | | Perphenazine | | | Pentamidine |
| | | Promethazine | | | Propofol |
| | | Chlorpromazine | | | Salicylates |
| | | Trifluoperazine | | | Succinylcholine |
| | | Venlafaxine | | | Theophylline |
| | | Benzodiazepines | | | Terbutaline |
| | | Barbiturates | | | Thiazides |
| | | | | | Vasopressin |

*T.J. Coco, Therapeutics and toxicology, 2004*

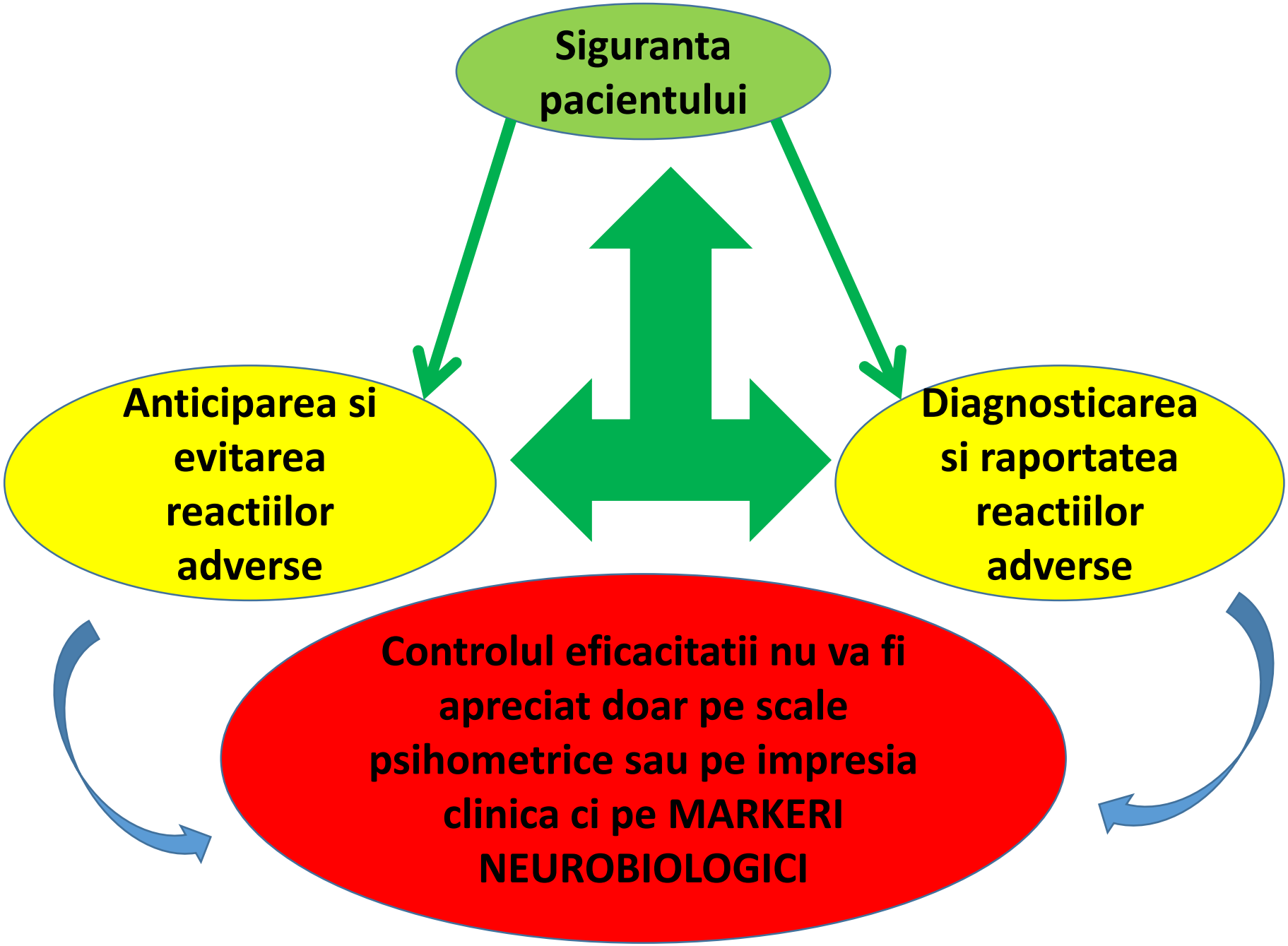
# Eficienţa medicaţiei şi lipsa reacţiilor adverse se corelează cu:

- Factorii genetici, farmacogenomica
- Integritatea funcţională hepatică – hepatosteatoza alcoolica şi non alcoolică
- Calitatea circulantă a proteinelor de legare a medicamentelor – hipoalbuminemia
- Integritatea funcţiei renale - clearance creatinină
- Integritatea BHE

**Lipsa eficacităţii medicaţiei şi prezenţa reacţiilor adverse se corelează cu neurotoxicitatea**




*Schizophrenia, Nature Reviews Disease Primers, Rene Kahn, 2015*


Siguranta pacientului
Anticiparea si evitarea reactiilor adverse
Diagnosticarea si raportatea reactiilor adverse
Controlul eficacitatii nu va fi apreciat doar pe scale psihometrice sau pe impresia clinica ci pe MARKERI NEUROBIOLOGICI