

# Somatische complicaties van farmacotherapeutische behandeling bij patiënten met een bipolaire stoornis

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# International Society of Bipolar Disorders (ISBD)

- The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments
- Richtlijn ter bevordering van patiënt en medicatieveiligheid gebaseerd op *veiligheidsrisico's van de meest gebruikte medicamenten* bij de behandeling van bipolaire stoornis alsmede op basis van *veiligheidsrisico's bij patiënten met een bipolaire stoornis*

# Doel richtlijn

- Bespreken preventie en behandeling meest ernstige veiligheidsrisico's
- Monitoren veiligheidsrisico's op basis van kosten-effectiviteit afweging
- Algoritme als basis voor vertaling naar nationale situatie en specifiek de eigen setting
  - Juridisch gezien gaat nationale richtlijn voor
  - Adherentie aan richtlijnen is een probleem
  - Dynamisch geheel; nieuwe ontwikkelingen

# ISBD werkgroep

- Michael Berk
- Felicity Ng
- Oomen K Mammen
- Ingeborg Wilting
- Gary S Sachs
- Nicol Ferrier
- Frederick Cassidy
- Serge Beaulieu
- Lakshmi N Yatham

The screenshot shows a web browser window displaying a PubMed search result. The browser's address bar shows the URL: [http://www.ncbi.nlm.nih.gov/pubmed/19689501?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPane](http://www.ncbi.nlm.nih.gov/pubmed/19689501?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPane). The page header includes the NCBI logo and the text "A service of the U.S. National Library of Medicine and the National Institutes of Health". The search bar contains the text "PubMed" and "for". Below the search bar, there are tabs for "Limits", "Preview/Index", "History", "Clipboard", and "Details". The "Display" section shows "AbstractPlus" and "Show 20". The search results section displays one result: "1: Bipolar Disord. 2009 Sep;11(6):559-95." The article title is "The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments." The authors listed are "Ng F, Mammen OK, Wilting J, Sachs GS, Ferrier IN, Cassidy F, Beaulieu S, Yatham LN, Berk M." The author's affiliation is "Discipline of Psychiatry, School of Medicine, University of Adelaide, SA, Australia." The abstract text begins with "OBJECTIVES: Safety monitoring is an important aspect of bipolar disorder treatment, as mood-stabilising medications have potentially serious side effects, some of which may also aggravate existing medical comorbidities. This paper sets out the International Society for Bipolar Disorders (ISBD) guidelines for the safety monitoring of widely used agents in the treatment of bipolar disorder. These guidelines aim to provide recommendations that take into consideration the balance between safety and cost-effectiveness, to highlight iatrogenic and preventive clinical issues, and to facilitate the broad implementation of therapeutic safety monitoring as a standard component of treatment for bipolar disorder. METHODS: These guidelines were developed by an ISBD workgroup, headed by the senior author (MB), through an iterative process of serial consensus-based revisions. After this, feedback from a multidisciplinary group of health professionals on the applicability of these guidelines was sought to develop the final recommendations. RESULTS: General safety monitoring". A "PubMed" logo with the text "Try the redesigned PubMed" is also visible. The browser's taskbar at the bottom shows the "start" button, several open applications, and the system clock showing "19:23".

# Opbouw richtlijn

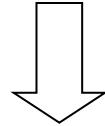
- Ernstige gezondheidsrisico's bipolaire stoornis
- Ernstige gezondheidsrisico's medicatie (bijwerkingen en interacties)
- Extra kwetsbare patiënten groepen
- Algoritme voor monitoren van veiligheidsaspecten:
  - Basis onderzoeken
  - Additionele onderzoeken per medicament

**“Basic” parameters for all patients prior to treatment implementation**

**History:** medical comorbidities (including CVD risk factors), smoking status, alcohol use, pregnancy status, family history of CVD risk factors

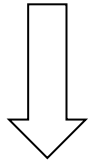
**Investigations:** waist circumference and/or BMI (weight & height), BP, FBC, EUC, LFT, fasting glucose, fasting lipid profile

Manage any identified  
medical conditions as  
appropriate

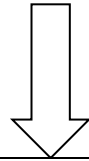


Selection of medication  
taking into consideration  
overall health risk profile

**“Add-on” parameters according to treatment selected**



**Lithium**  
Baseline  
TSH, ionised Ca  
Serum level  
2 levels to establish therapeutic  
dose, then every 3-6 months  
Longitudinal monitoring  
EUC 3-6 monthly  
Ionised Ca, TSH and weight after 6  
months, then annually



**Valproate & carbamazepine**  
Baseline  
Haematological and hepatic history  
Serum level  
2 levels to establish therapeutic dose, then as  
clinically indicated  
Longitudinal monitoring  
**Valproate:** weight, FBC, LFT, menstrual history  
3 monthly for first year, then annually; BP,  
fasting glucose and lipid profile if risk factors;  
bone densitometry if risk factors  
**Carbamazepine:** FBC, LFT, EUC monthly for  
first 3 months, then annually; alert to rash  
especially in first few months of treatment;  
bone densitometry if risk factors; review OCP  
efficacy where applicable



**Atypical antipsychotics**  
Longitudinal monitoring  
Weight monthly for first 3 months,  
then 3-monthly  
BP and fasting glucose every 3  
months for first year, then  
annually  
Fasting lipid profile after 3  
months, then annually  
ECG and prolactin level as  
clinically indicated  
\*Clozapine an exception

# Patiënt veiligheidsrisico's

- Veiligheidsrisico's bij patiënten met een bipolaire stoornis:
  - verhoogd voorkomen somatische comorbiditeit
    - cardiovasculaire risicofactoren: obesitas, diabetes mellitus, hypertensie, dyslipidemie, metabool syndroom
  - verhoogd voorkomen risicovollere levensstijl
    - Ongezond eten, lichamelijke inactiviteit, roken, alcoholabusus, drugsmisbruik
  - chronisch gebruik medicatie
  - frequent gebruik polyfarmacie

# Uitgangs veiligheidsrisico onderzoek

	<b>Recommendations</b>
<b><i>History</i></b>	<ul style="list-style-type: none"><li>▪ medical history</li><li>▪ cigarette smoking status and alcohol intake</li><li>▪ family history of cardio- and cerebrovascular disease, hypertension, dyslipidaemia and diabetes mellitus</li><li>▪ pregnancy and contraception (for women of childbearing age)</li></ul>
<b><i>Examination</i></b>	<ul style="list-style-type: none"><li>▪ waist circumference and/or body mass index (weight [kg]/height [m]<sup>2</sup>)</li><li>▪ blood pressure</li></ul>
<b><i>Investigations</i></b>	<ul style="list-style-type: none"><li>▪ full blood count</li><li>▪ electrolytes, urea, creatinine</li><li>▪ liver function tests</li><li>▪ fasting blood glucose</li><li>▪ fasting lipid profile</li><li>▪ pregnancy test (where doubt exists)</li></ul>

# Medicatie voor Bipolaire stoornissen

	Manie	Depressie	Onderhoud
1950	Klassieke a.p.	TCA-MAOI	
1960	Lithium	Lithium	Lithium
1970	Carbamazepine		CBZ
1980			
1990	Valproïnezuur	SSRI	VPA
2000	Atypische a.p.	lamotrigine	Ltg, atyp a.p.

# Veiligheidsrisico's medicatie besproken in ISBD- richtlijn

	Manie	Depressie	Onderhoud
1950	Klassieke a.p.	TCA-MAOI	
1960	Lithium	Lithium	Lithium
1970	Carbamazepine		CBZ
1980			
1990	Valproïnezuur	SSRI	VPA
2000	Atypische a.p.	lamotrigine	Ltg, atyp a.p.

# Lithium en interacties

Wat is veiliger?

- A) lithium met een NSAID combineren waarbij het NSAID langdurig in dezelfde dosis wordt gebruikt
- B) Lithium met een NSAID combineren waarbij het NSAID alleen als het echt nodig is wordt ingenomen

# Welke bijwerkingen leiden vaak tot staken van lithium

- A) patiënt geïnitieerd staken
- B) behandelaar geïnitieerd staken



1. A) tremor en cognitie, b) schildklier en nier problemen
2. A) tremor en cognitie b) hyperparathyreoïdie
3. A) misselijkheid braken, b) schildklier- en nierproblemen,
4. A) misselijkheid braken, b) hyperparathyreoïdie



# Lithium

- Bijwerkingen
  - Uitleg (speciale aandacht voor OTC-medicatie NSAID!, prodromale verschijnselen intoxicatie)
  - Monitoren bijwerkingen (nefrogeen, endocrien, intoxicatie), interacties (RAS-remmers, diuretica, NSAID)
- Monitoring aspecten lichamelijke conditie/co-medicatie die het veiligheidsprofiel van lithium kunnen beïnvloeden

# Lithium bijwerkingen

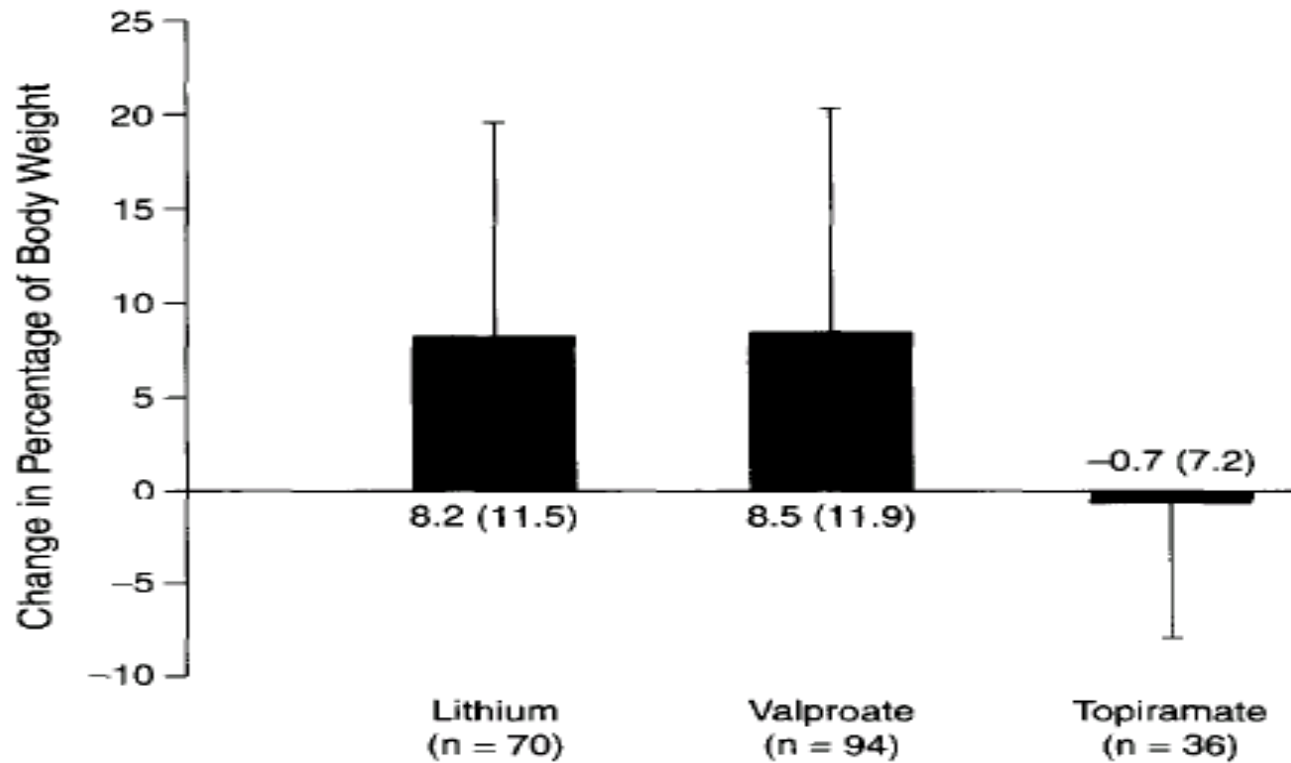
	Vroeg	Laat
Voorbijgaand	GI-effecten Diarree (6-30%) Misselijkheid/braken (5-10%) Vermoeidheid, spierzwakte Oedeem	
Persisterend	Gewichtstoename (11-65%) <b>Fijne tremor</b> (28-45%) <b>Cognitie en concentratie problemen</b> (10-43%) Leucocytose	<b>Polyurie</b> (15-40%)/ Polydipsie (38-70%)/ <b>NDI</b> (12%) <b>hypothyreoidie</b> (5-35%) Hyperparathyroïde (12-25%) Psoriasis/acne (7%) Droge mond/slechte smaak (25%) Oedeem (10%) Alopecia/dunner haar (19-28%)

# ISBD lithium veiligheidsrisico's

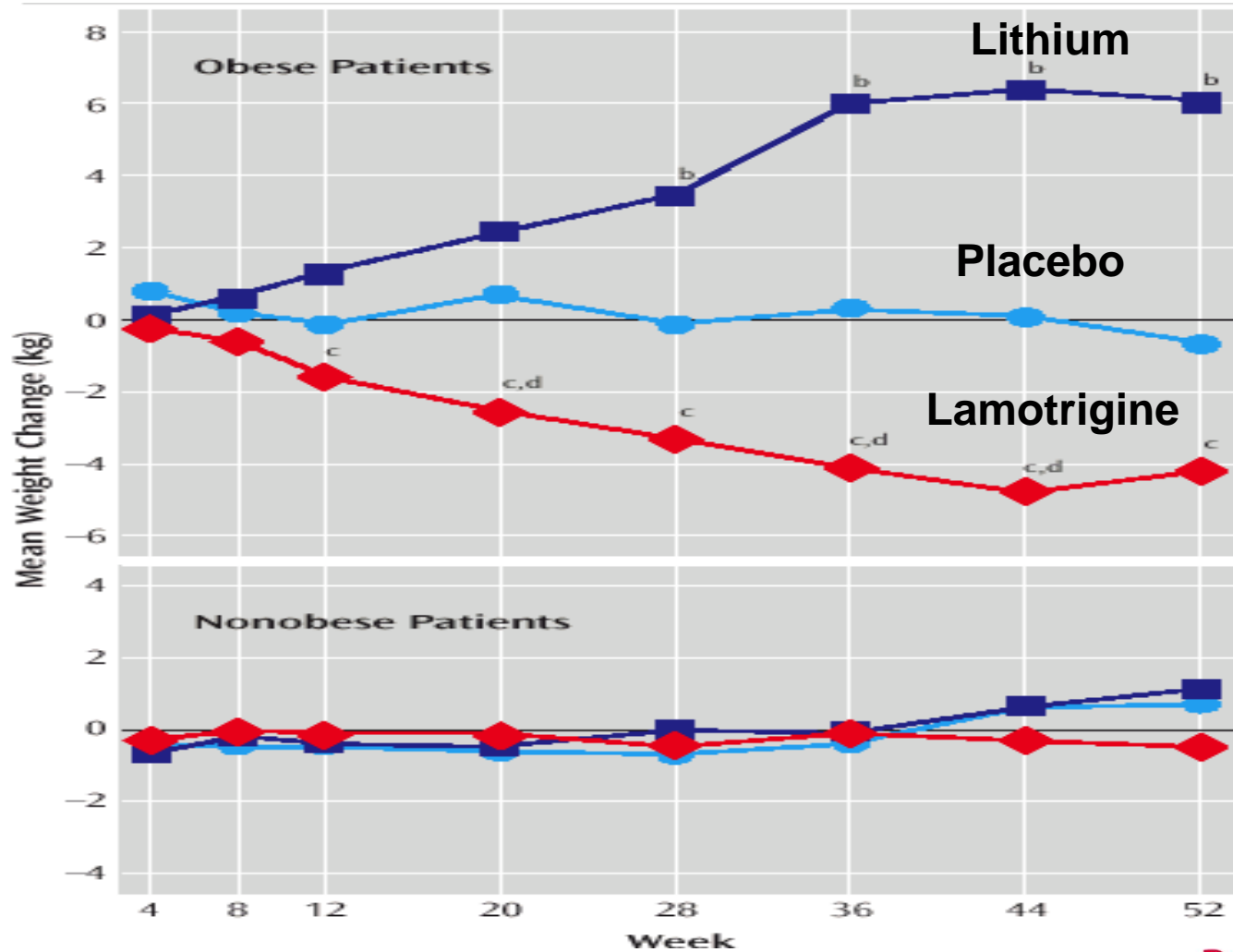
	<b>Recommendations</b>
<b><i>Baseline</i></b>	<ul style="list-style-type: none"><li>▪ thyroid stimulating hormone</li><li>▪ ionised calcium</li></ul>
<b><i>Serum levels</i></b>	<ul style="list-style-type: none"><li>▪ trough levels at steady state (&gt;5 days) on initiation of therapy, and after every dose change, until two consecutive levels within the therapeutic range are established</li><li>▪ 3-6 monthly at stable dosages for the duration of treatment</li></ul>
<b><i>Longitudinal</i></b>	<ul style="list-style-type: none"><li>▪ urea and creatinine 3-6 monthly for the duration of treatment</li><li>▪ serum ionised calcium, thyroid stimulating hormone and weight at 6 months, then annually</li></ul>

Investigations beyond these recommendations and consultation with the appropriate specialists may be required in patients with known renal, cardiac or thyroid disease.

# Gewichtstoename



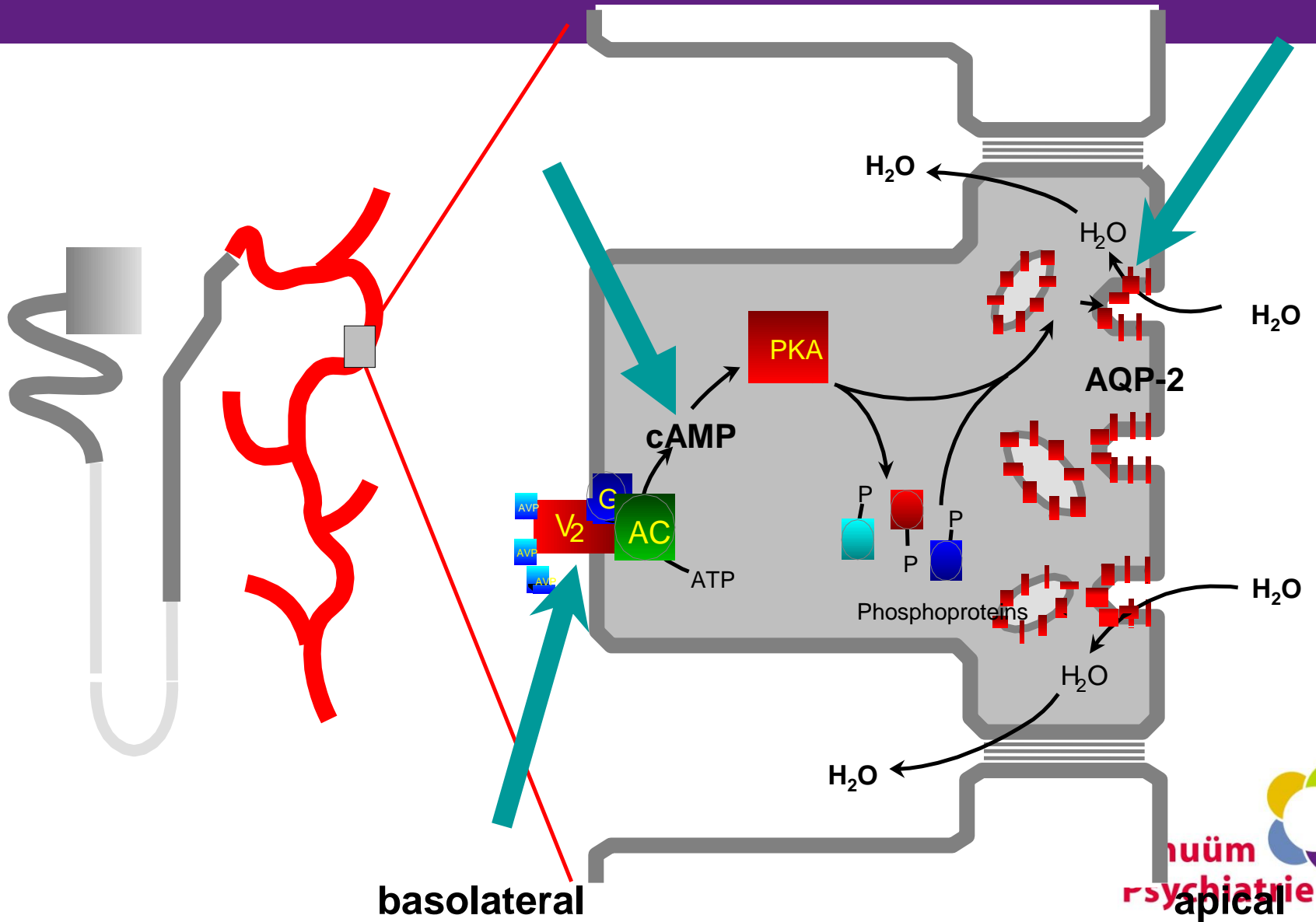
# Gewichtstoename



# NDI/ polyurie

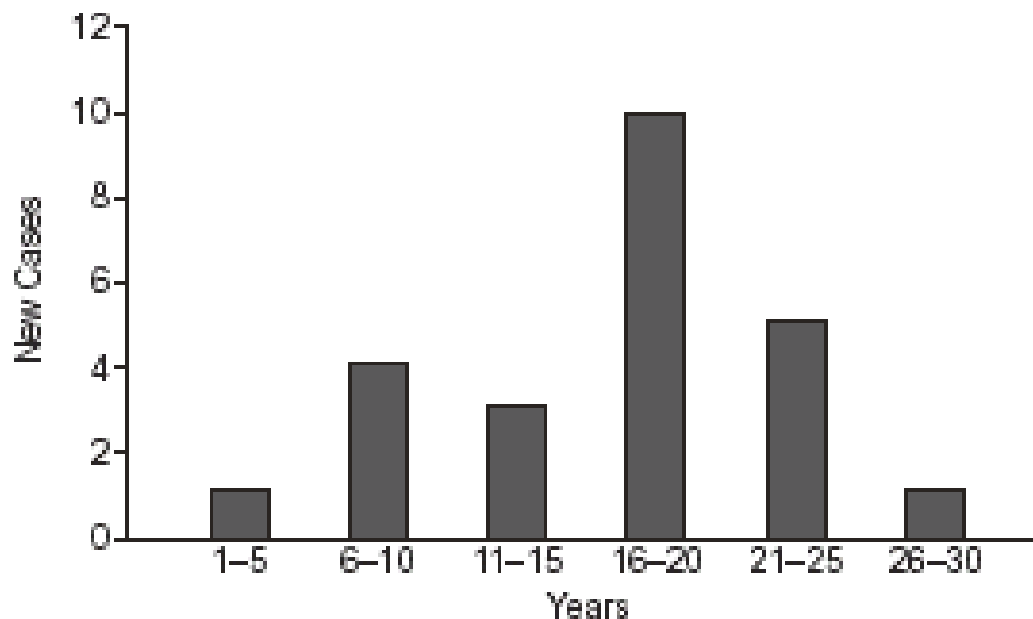
- Tijdens langdurig (maanden-jaren) van lithiumgebruik:
  - 15-40% polyurie ( $\geq 3\text{L}/24$  uur)
  - 54% afgenomen urine concentrerend vermogen
  - 12% NDI gedefinieerd als urine osmolaliteit  $< 300\text{mosm}/\text{Kg}$
- Risicofactoren:
  - Lithium serum spiegel, gebruiksduur, co-medicatie
- Meestal reversibel na staken lithium

# Mechanism NDI



# Nierinsufficiëntie

Figure 2. Number of New Onset Cases of Renal Insufficiency Among 114 Study Group Patients in 5-Year Periods



# Lamotrigine en orale anticonceptiva

Wat is waar?

1. Combineren van orale anticonceptiva en lamotrigine is niet mogelijk
2. Combineren van orale anticonceptiva en lamotrigine is alleen mogelijk bij continue gebruik (zonder stopweek) van orale anticonceptiva
3. Combineren van orale anticonceptiva en lamotrigine is mogelijk met behulp van spiegel monitoring in de stopweek

# Anticonvulsiva

- Bijwerkingen (hematologisch, lever, dermatologisch, bot, hyponatriemie, gewicht, PCOS, pancreatitis, hyperamioniemie)
  - Uitleg
  - Monitoren
- Monitoren interacties
  - Carbamazepine (autoinductie en inductie metabolisme andere medicamenten (anticonceptiva!))
  - Valproïnezuur en lamotrigine
- Extra aandacht voor vrouwen in de vruchtbare leeftijd

# ISBD AED safety monitoring

	Recommendations
<b>Baseline</b>	<ul style="list-style-type: none"><li>▪ <b>valproate and carbamazepine:</b> history of haematological or hepatic disease</li></ul>
<b>Serum levels</b>	<ul style="list-style-type: none"><li>▪ <b>valproate and carbamazepine:</b> 2 levels to establish therapeutic dose (separated by 4 weeks for carbamazepine), then as clinically indicated</li></ul>
<b>Longitudinal</b>	<ul style="list-style-type: none"><li>▪ <b>valproate*:</b> weight, FBC, LFT and inquiry of menstrual changes (for women of reproductive age) 3-monthly for the first year, then annually</li><li>▪ <b>carbamazepine:</b> monthly FBC, LFT and EUC for the first 3 months, then annually; review oral contraceptive efficacy</li><li>▪ <b>carbamazepine and lamotrigine:</b> remind patients to promptly withhold medications and seek medical attention within 24 hours of emergence of dermatological eruptions</li><li>▪ <b>valproate and carbamazepine:</b> advice on bone health</li></ul>

\*In those with cardiovascular risk factors, blood pressure, fasting glucose and lipid profile should be monitored in a similar fashion as described for atypical antipsychotics

# Gewichtstoename

Het meeste risico op gewichtstoename geven

1. Clozapine > olanzapine > risperidon  
> quetiapine
1. Olanzapine > clozapine > quetiapine  
> risperidon
1. Clozapine > olanzapine > quetiapine  
> risperidon
1. Olanzapine > clozapine > risperidon  
> quetiapine



# Atypische antipsychotica

- Bijwerkingen
  - Uitleg
  - Monitoren (preventief dietetist)
- Metabool syndroom
- Cardiale bijwerkingen
- Hyperprolactinemie
- Hematologische ADR
- EPS

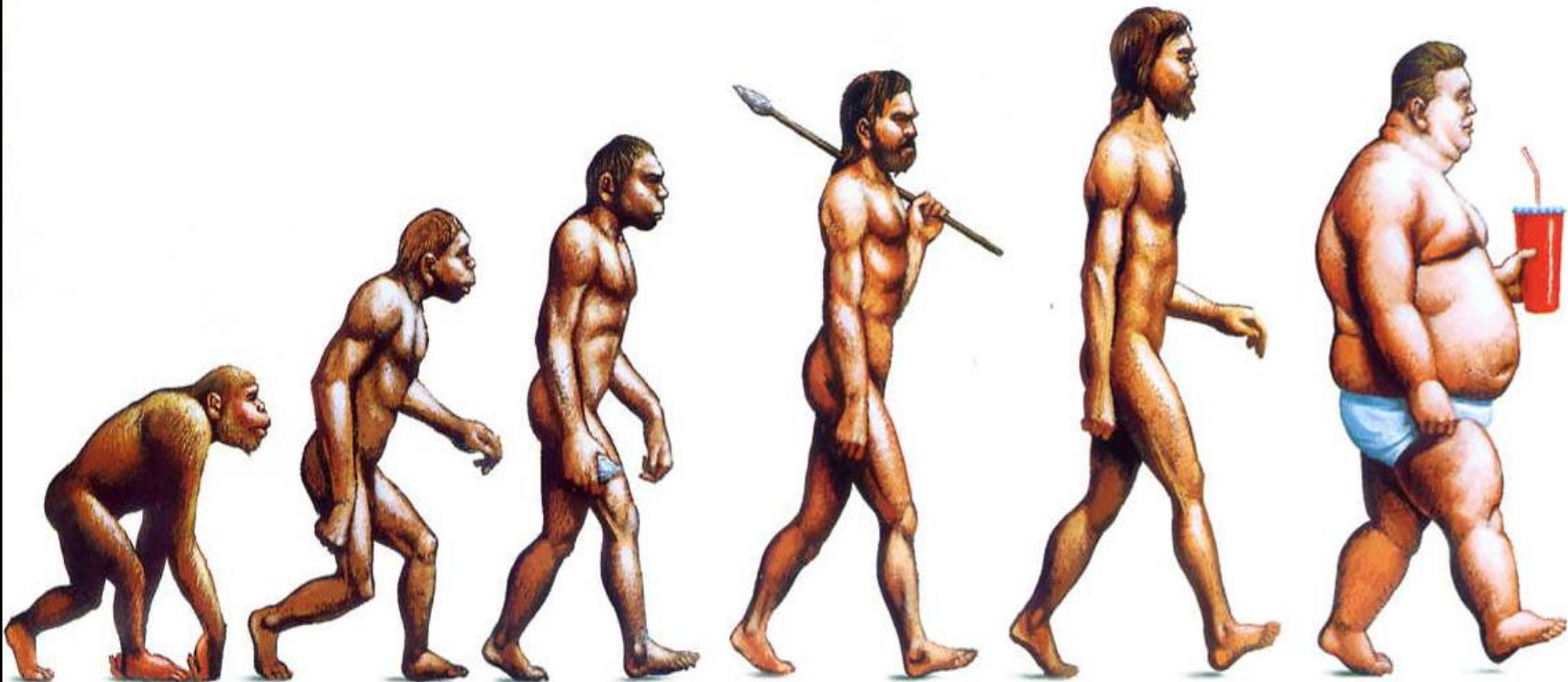
# ISBD atypische a.p. safety monitoring

	<b>Recommendations</b>
<b><i>Baseline</i></b>	<ul style="list-style-type: none"><li>▪ inquire about personal or family history of cardiac problems, including congenital long QT syndrome</li></ul>
<b><i>Longitudinal*</i></b>	<ul style="list-style-type: none"><li>▪ weight: monthly for the first three months, then 3-monthly measures for the duration of treatment</li><li>▪ blood pressure and fasting glucose: 3-monthly for the first year, then annually</li><li>▪ fasting lipid profile: at 3 months after initiating treatment, then annually</li><li>▪ ECT and prolactin levels are clinically indicated</li></ul>

Patients on clozapine should adhere to specific guidelines for its monitoring

\*Those with metabolic or cardiovascular risk factors may require more frequent and broader investigations

# Het metabool syndroom



# Focus van EPS naar andere bijwerkingen

## Side Effect Burden of Older Antipsychotics: *EPS Overwhelms All Others*



EPS = extrapyramidal symptoms; TD = tardive dyskinesia.  
Weiden PJ, et al. *J Clin Psychiatry*. 1998;59(suppl 19):36-49.

## Side Effect Burden of Atypical Antipsychotics: *Change in Focus Away From EPS*



- Focus of concern is moving away from EPS and towards other, non-EPS side effects

Weiden PJ et al. *J Clin Psychiatry*. 1998;59(suppl 19):36-49.

# Criteria voor diagnose 3 risicofactoren

NCEP III. Circulation 2002;106:3143-3421

International Diabetes Federation 2005 <http://www.idf.org/webdata/docs/MetS-def-FINAL.pdf>

Abdominal obesity	Waist circumference Men > 102 cm Women > 88 cm M EU >94cm W EU >80 cm
Triglycerides	> 150 mg/dl
HDL Cholesterol	Men <40 mg/dl Women <50 mg/dl
Blood pressure	>130/85 mm Hg
Fasting blood glucose	>110 EU >100 mg/dL

# NL richtlijn (Cahn et al)

	0	1 mnd	3 mnd	6 mnd	Jaarlijks
Familie anamnese	X	X			X
Gewicht (BMI)	X	X	X		x
Buikomvang	X	X	X	X	X
Bloeddruk	X		X		X
Glucose (n)	X	X	X	X	X
Lipiden profiel (n)	X		X		X
Volledig bloedbeeld	X		X	X	X
Na/K	X		X	X	X
Nierfuncties	X		X	X	X
Leverfuncties	X		X	X	X
TSH	X				

# Atypische antipsychotica

<b>Generieke naam</b>	<b>Gewichts- toename</b>	<b>Risico op diabetes</b>	<b>Verslechtering Lipidenprofiel</b>
<b>Aripiprazol</b>	<b>0</b>	<b>?</b>	<b>0</b>
<b>Clozapine</b>	<b>+++</b>	<b>++</b>	<b>++</b>
<b>Haloperidol</b>	<b>+/-</b>	<b>+/-</b>	<b>0</b>
<b>Levomepromazine</b>	<b>++</b>	<b>++</b>	<b>++</b>
<b>Olanzapine</b>	<b>+++</b>	<b>+</b>	<b>++</b>
<b>Risperidon</b>	<b>++</b>	<b>+</b>	<b>+/-</b>
<b>Quetiapine</b>	<b>+</b>	<b>+</b>	<b>+/-</b>
<b>Zuclopentixol</b>	<b>+/-</b>	<b>?</b>	<b>0</b>

# Extra kwetsbare groepen

- Kinderen:
  - Weinig evidence
  - Langdurig gebruik
  - Gevoeligheid bijwerkingen:
    - Cognitie/sedatie (schoolgaan)
    - Botbijwerkingen/metabool syndroom/PCOS (opgroeien)
- Zwangerschap/lactatie/vruchtbare leeftijd
- Ouderen
  - Kinetiek/dynamiek
  - Comorbiditeit (valrisico, cognitieve problemen) /Polyfarmacie

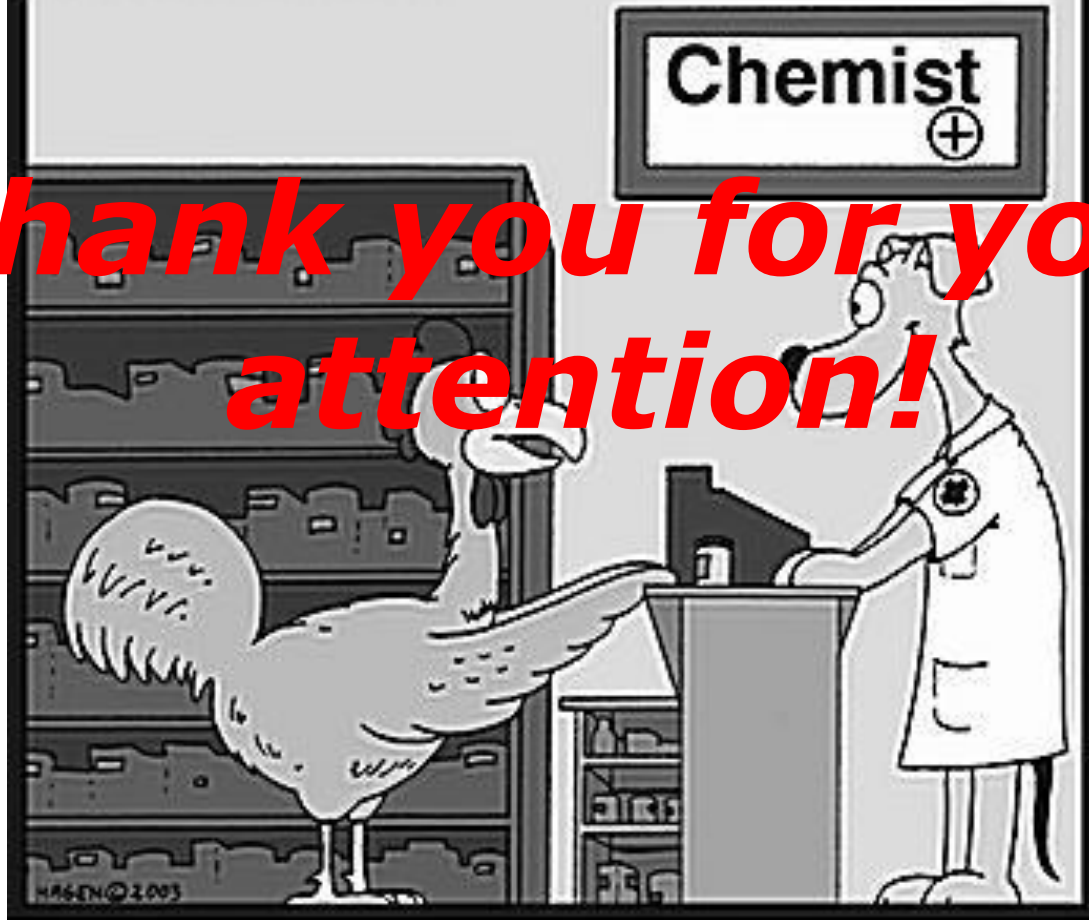
# Beperkingen

- Monotherapie-advies, bespreking beperkt aantal middelen
- Geen advies voor keuze op basis van risicoprofiel patiënt en geneesmiddel
- Geen duidelijke behandeling van bijwerkingen
- Geen adviezen in bepaalde omstandigheden zoals OK, patiënten die niet kunnen/willen slikken etc etc
- Beperkte evidence op basis van kosten-effectiviteit

# Take home messages

1. Bij de keuze van (toevoegen van) een middel moet het patiëntrisicoprofiel worden betrokken
2. Uitleg aan patienten over te verwachte bijwerkingen en over belang melden bijwerkingen aan behandelaar
3. Adherence aan veiligheidsmonitoring guidelines is essentieel dit kan mogelijk gefaciliteerd worden dmv clinical rules

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***Thank you for your attention!***

Are you sure it's non-drowsy?  
I cannot afford to oversleep...