

# Lithium in Older Adults: A Double Edged Sword

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## Mania in older adults: special features

- ▶ Late age of onset
- ▶ Neurologic co-morbidity
- ▶ Cognitive impairment
- ▶ ↑ Mortality

## Determinants of mania in older adults

- ▶ Affective vulnerability
- ▶ Aging
- ▶ Heterogeneous cerebral pathology
- ▶ Lesion localization

## Cerebrovascular risk and bipolarity

- ▶ Framingham Stroke Risk Score
- ▶ ↑ In late onset older bipolars
- ▶ ↑ Risk of stroke

Jin et al (2007)

Subramanian et al (2007)

## Assessment of bipolarity in older adults

- ▶ Neurologic and cognitive exam
- ▶ Neuroimaging
- ▶ Screening for CVRFs
- ▶ Management of CVRFs



**Select an element from the periodic table.**

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Period	1	2																	2
1	H																		He
2	Li	Be											B	C	N	O	F		Ne
3	Na	Mg											Al	Si	P	S	Cl		Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br		Kr
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I		Xe
6	Cs	Ba	*	Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	**	Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub	Uut	Uuq	Uup	Uuh	Uus	Uuo
*Lanthanoids	*		57	58	59	60	61	62	63	64	65	66	67	68	69	70			
**Actinoids	**		89	90	91	92	93	94	95	96	97	98	99	100	101	102			

## Serendipity

The faculty of making fortunate discoveries by accident

‘The Three Princes of Serendip’

## History of lithium therapy

- ▶ 1800's observation
  - ▶ • urate bladder stones dissolve in solutions of lithium salts
- ▶ Uric acid diathesis
  - ▶ • gout, migraine, GI disorders etc.
  - ▶ • included mood disorders

## History of lithium therapy Late 1800's

### Faculty logic

- ▶ Lithium dissolves urate stones
  - ▶ Eliminates uric acid
  - ▶ Mood disorders are caused by ↑ uric acid
  - ▶ Lithium may be an effective Rx for mood disorders
- Case reports (Denmark)

## History of lithium therapy

1949

- ▶ John Cade – Rx of acute mania
- ▶ Lithium as salt substitute → fatalities
- ▶ 1960's
- ▶ 1970's
- ▶ 1990 - 2010

## What is a mood stabilizer?

Rx of acute mania

Rx of acute depression

Prevention of mania

Prevention of depression

("two by two definition")

Bauer & Mitchner (2004)

## Evidence-based treatment guidelines

### Lithium remains a first line treatment

American Psychiatric Association

<sup>a</sup>British Association for Pharmacology

<sup>b</sup>Expert Consensus Guidelines Series

<sup>c</sup>Texas Medication Algorithm Project

<sup>d</sup>CANMAT

a – Goodwin et al (2003)  
b – Sachs et al (2000)  
c – Suppes et al (2002)  
d – CANMAT et al (2009)

## BALANCE study – relapse prevention bipolar I

- ▶ Randomized, open-label, 3 groups
- ▶ Up to 24 months follow-up
- ▶ Mean age 43
- ▶ 1° outcome – new intervention for emergent mood disorder

Lancet, January 30, 2010

## BALANCE study

### Conclusions

- ▶ Lithium + valproate > valproate
- ▶ Lithium > valproate

Lancet, January 30, 2010

## Old age psychiatrists preferences

	Acute Mania %	Prophylaxis %
Lithium	35.1	69.7
Valproate	28.2	13.3

Ephraim & Prettyman (2009)

## Old age psychiatrists concerns

	Efficacy %	Safety %	Drug Interactions %
Lithium	4.3	49.5	17
Valproate	11.2	1.2	2.1
Cbz	10.6	10.1	19.7
Lamotrigine	7.5	1.6	2.7

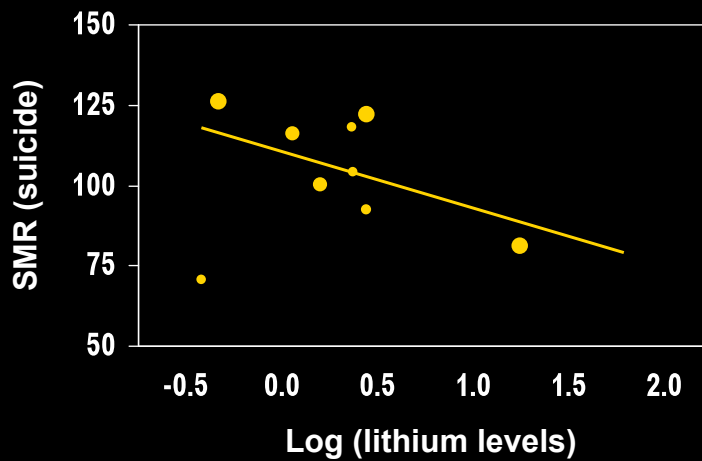
Ephraim & Prettyman (2009)

## Risk of suicide attempts and death divalproex vs lithium

Divalproex vs Lithium	
	RR
Suicide attempts in emergency department	1.8 (1.4-2.2)
Suicide attempts resulting in hospitalization	1.7 (1.2-2.3)
Suicide deaths	2.7 (1.1-6.3)

Goodwin et al. (2003)

## Lithium levels in drinking water



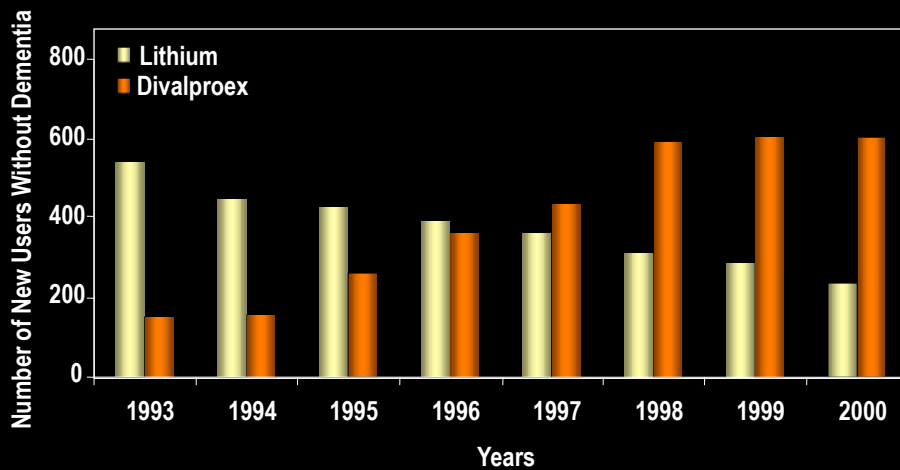
Oghami, et al. (2009)

## Changing Prescription Patterns for Lithium and Divalproex

Chronic Disease NET Program (ICES)

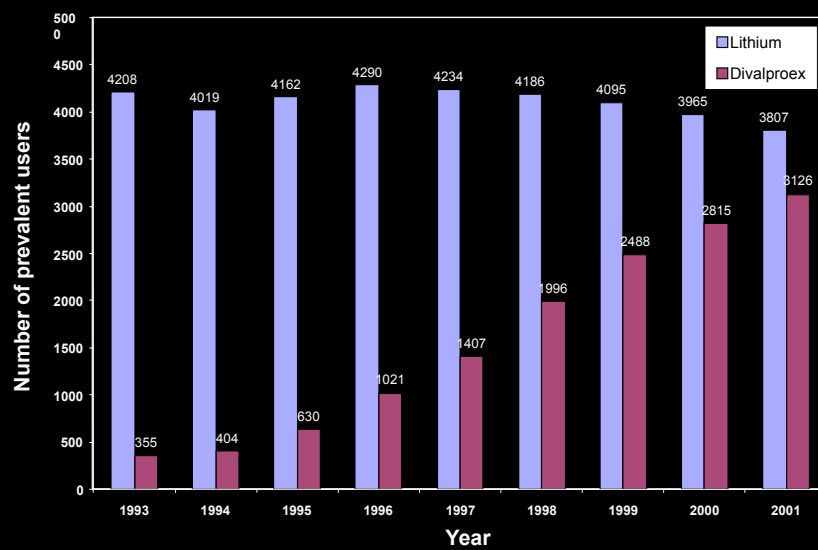
CIHR=Canadian Institutes of Health Research.

## New elderly users of divalproex and lithium in Ontario (1993-2000) without dementia

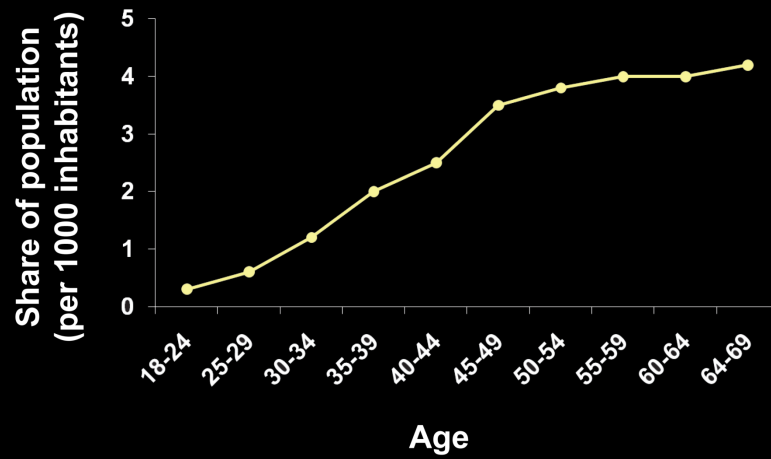


Shulman KI, et al. *BMJ*. 2003;326(7396):960-961.

## Prevalence of lithium and divalproex use among older adults (1993 to 2001)

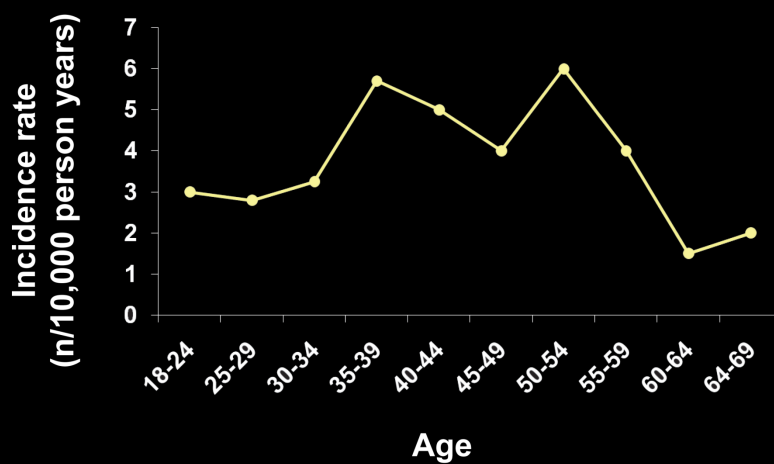


## Prevalence of lithium Rx by age group



Bramness et al. (2009)

## Incidence of lithium Rx by age group



Bramness et al. (2009)

## Special considerations for lithium carbonate in older adults

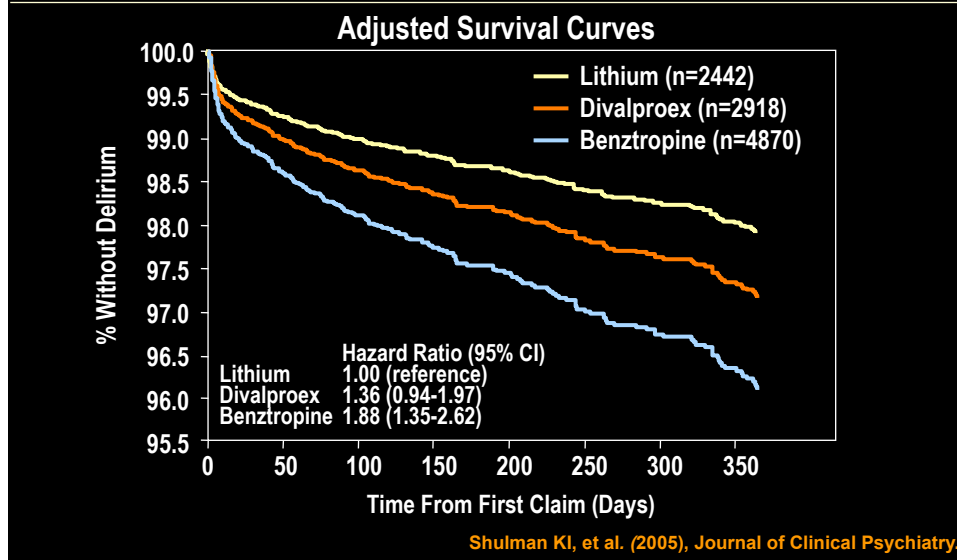
- ▶ Altered pharmacokinetics
- ▶ Narrow therapeutic range (? geriatric levels)
- ▶ Renal effects
- ▶ Drug interactions
- ▶ Toxicity/delirium
- ▶ Hypothyroidism

## Hospitalization for lithium toxicity and use of other medications

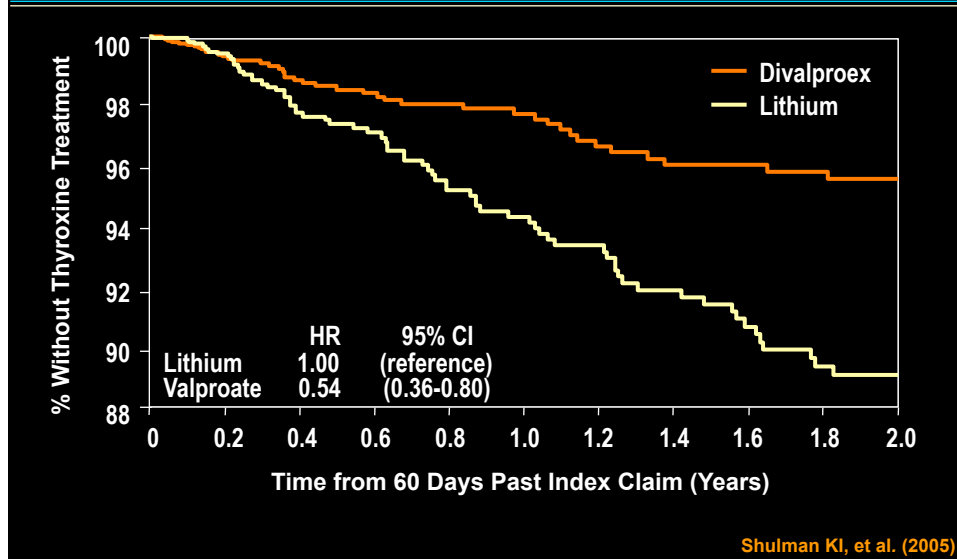
Dispensed within 28 days			
	Cases (n=413)	Controls (n=1651)	Relative Risk
	%	%	
Thiazide diuretics	3.9	2.2	1.8 (1.0-3.3)
Loop diuretics	13.1	4.3	3.4 (2.3-5.0)
ACE inhibitors	15.3	6.7	2.5 (1.8-3.5)
NSAIDS	15.3	11.3	1.4 (1.0-1.9)

Juurink et al. (2004)

## Incidence of delirium with new users of lithium or divalproex (older adults)



## Kaplan-Meier curves of time to thyroxine treatment



## Pharmaco-epidemiological conclusions:

- ▶ Lithium use decreasing
- ▶ Divalproex use increasing
- ▶ Lack of efficacy or effectiveness data
- ▶ Lithium orphaned by marketing

## Lithium and neuroprotection

### Glycogen synthase kinase (GSK)

- ▶ Lithium → ↓GSK 3
- ▶ ↓GSK 3 → ↓β amyloid ↓tangles
- ▶ ↓GSK 3 → ↓cell apoptosis

Gould et al. (2004)

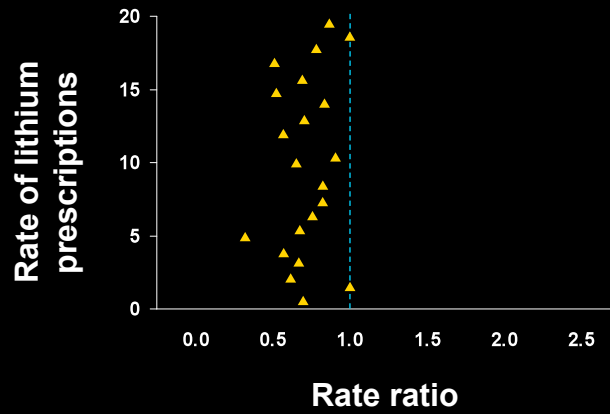
## Glutathione and neuroprotection

- ▶ Glutathione – brain anti-oxidant
- ▶ Li + VPA inhibit oxidative damage in rat
- ▶ Chronic Li + VPA → ↑ glutathione

## Lithium and neuroprotection Hypothesis

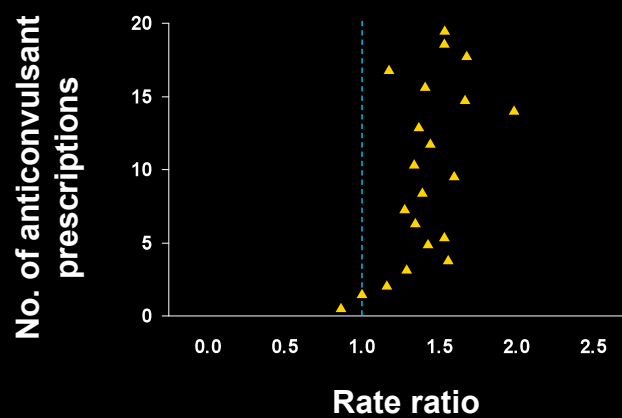
- ▶ ↓ GSK 3
  - ▶ ↑ BDNF
  - ▶ ↑ Glutathione
  - ▶ synergistic with VPA
- } ↓ Dementia

## Rate of dementia related to number of lithium prescriptions



Kessing et al (2008)

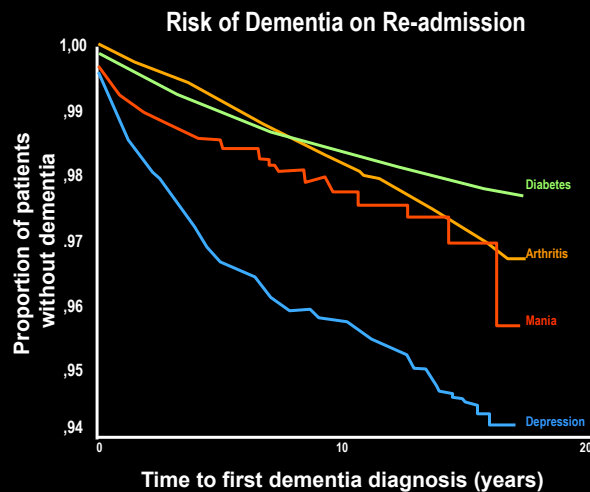
## Rate of dementia related to number of anticonvulsant prescriptions



Kessing et al (2008)

## Relationship between bipolar illness and dementia

- ▶ Individuals with bipolar disorder may develop dementia at a greater rate than elderly individuals without bipolar illness



Kessing LV, et al. *J Affect Disord.* 2003;73(3):261-269

## Summary

- ▶ Good evidence for effectiveness of lithium
- ▶ Concerns regarding lithium treatment in older adults (toxicity, renal, thyroid)
- ▶ Dramatic change in prescription patterns without evidence
- ▶ Evidence for neuroprotection
- ▶ Need for studies in old age, especially combination treatments

## Delirium in old age: case example

What's Lithium got to do with it?

## Delirium in old age:

- ▶ 86-year-old widow living independently
- ▶ Background
  - ▷ Family history
    - ▶ Uncle (psychiatric institution)
    - ▶ Son (schizoaffective)
    - ▶ Grandson (suicide)
  - ▷ Lifelong bipolarity: refused treatment
  - ▷ Last 7 years: stabilized by GP with lithium 600 mg
  - ▷ Previous episode of lithium toxicity 3 years ago
    - ▶ Fell, 1 month to recover

## Medical history

- ▶ Hypertension
- ▶ Type II diabetes
- ▶ Coronary bypass
- ▶ Medicines
  - ▷ Amlodipine besylate
  - ▷ ASA
  - ▷ Atorvastatin calcium
  - ▷ Hydrochlorothiazide
  - ▷ Ramipril

## History of present illness

- ▶ 2-day history of delirium
  - ▷ Concomitant with lethargy, diarrhea, confusion
- ▶ Urinary tract infection
  - ▷ Increase in white blood cell count
  - ▷ Possible sepsis
- ▶ Lithium continued for 2 weeks
- ▶ CT and MRI: negative
- ▶ Na–170 mmol/L (nephrogenic DI)
- ▶ Lithium discontinued: desmopressin acetate

## Follow-up

- ▶ 1 month after lithium discontinuation
  - ▷ Manic symptoms emerge
  - ▷ Olanzapine given as treatment
  - ▷ Persistent cognitive impairment
- ▶ 2 months later
  - ▷ Manic symptoms and cognitive impairment clear significantly
  - ▷ Mild residual cognitive impairment
- ▶ What is the psychopharmacological treatment?