Lithium and Chronic Kidney Disease

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Life can be difficult…..

Lithium and CKD can be difficult....

Complex

Costly

Consensus guidelines?

Common

Consent

1 Lithium recap

Lithium recap – the pros

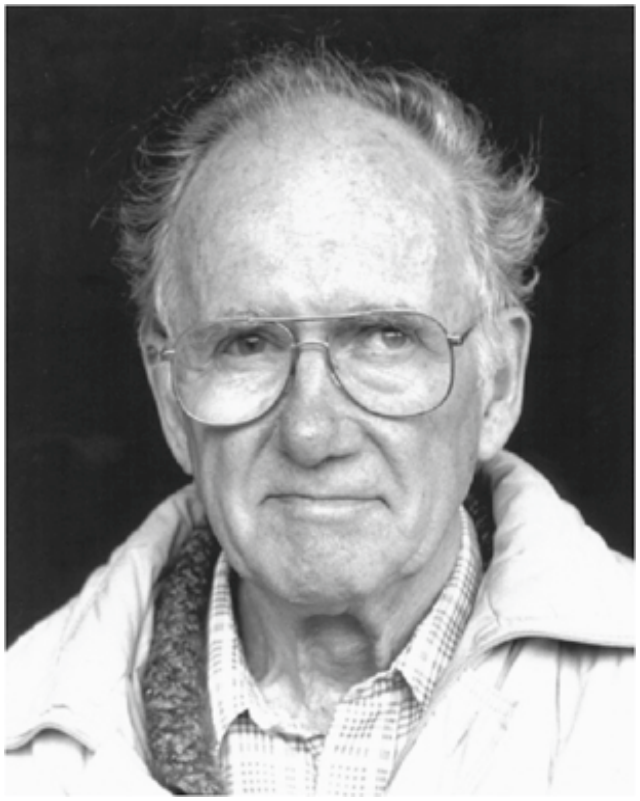
1960s:
bipolar prophylaxis (Schou's "normothymotic agent")

1970s:
↓ suicide and ECT (Coppen)

1980s:
AD agmentation (Heninger)

Confirmatory studies:

- BALANCE trial 2010: bipolar prophylaxis
- Severus et al 2014: bipolar prophylaxis
- Cipriani et al 2013: suicide prevention
- Bauer et al 2014: unipolar depression augmentation



Morgans Shou
1918-2005

Lithium recap – the pros

	PHASE	NICE National Institute for Health and Care Excellence	BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY
BIPOLAR	Acute Hypo/Mania	3rd line	1st line option
	Acute Depression	-	Augmentation/ TRD cover
	Prophylaxis	1st line (manic/depressed/mixed)	1st line (if adherent)
UNIPOLAR	Depression	Augmentation esp post ECT	Augmentation (esp elderly)/ post ECT
	Rx of Recurrence	Augmentation esp post ECT	Augmentation (↓suicide)/ consider (not routinely) as 2nd line to ADs
	Prophylaxis	Augmentation esp post ECT	If prior success with acute phase augmentation, post ECT,↓suicide

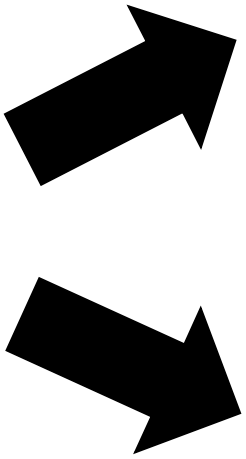
Lithium recap – the cons

Action of therapeutic/ adverse effects

remain opaque

Side effects:

↓TFTs x6 risk (rarely ↑)
↑ PTH/Ca x100 risk
↑ weight
Nausea/ diarrhoea
Tremor/ sedation
Psoriasis/ acne/ hair loss
ECG changes
Teratogenic
Toxicity
and.....



ALL ↑NON-ADHERENCE

Try:
- ↓dose
- night time dosing
- controlled release
- avoid caffeine
- with food
- symptomatic medication
- amiloride

Lithium recap – the cons

Renal impairment:

- Nephrogenic Diabetes Insipidus (NDI)

- CKD

Also: distal tubular acidosis and nephrotic syndrome (rare)

2 CKD

CKD – overview

Abnormal kidney structure or function

Common

Often asymptomatic

Progresses to ESRD/GFR cat 5 in small but significant number

CKD – categorisation

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	>90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

* Relative to young adult level

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate

Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

CKD – aetiology

DM (25%)

Glomerulonephritis (15%)

Hypertension (15%)

Pyelonephritis (15%)

Polycystic disease (10%)

Obstructive uropathy (5%)

Interstitial nephritis eg **lithium**, sarcoidosis, myeloma (**<5%**)

Post-AKI (<5%)

Amyloidosis (1%)

Idiopathic (10%)

CKD - impact

- £1.5billion/ yr: >50% for 2% on RRT (≈20000 pts)

- Haemodialysis £80K/yr; peritoneal £55K/yr; transplant £15K; CKD £8K/yr

- Exponential ↑ all cause mortality; 7000 CVAs, 12000 MIs, falls etc

3 Lithium and the kidney

Hestbech 1977 – Li + chronic change

Seminal Danish study

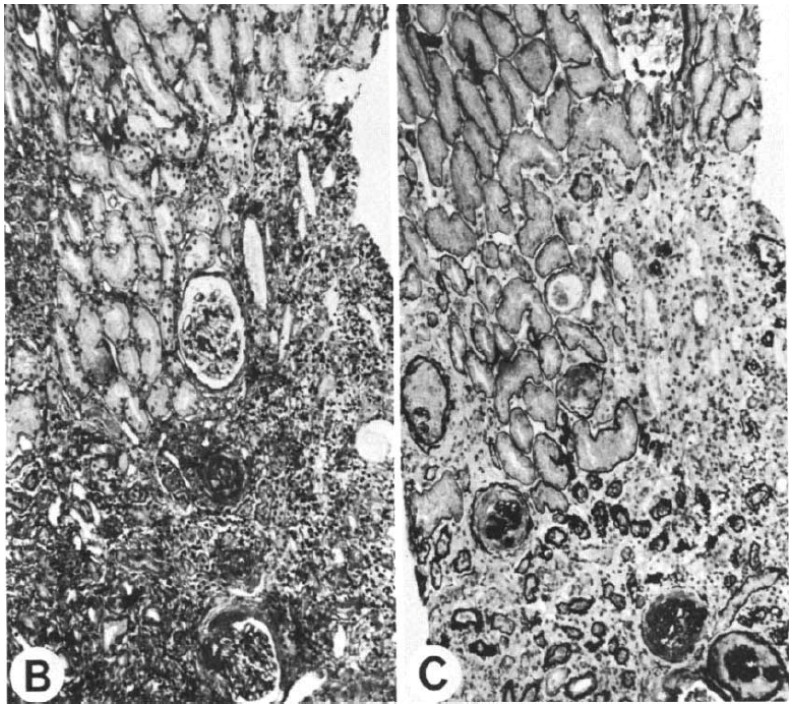
14 pts on long-term (2-15yrs) Li with NDI/ toxicity

Biopsied – rarely done in prior studies

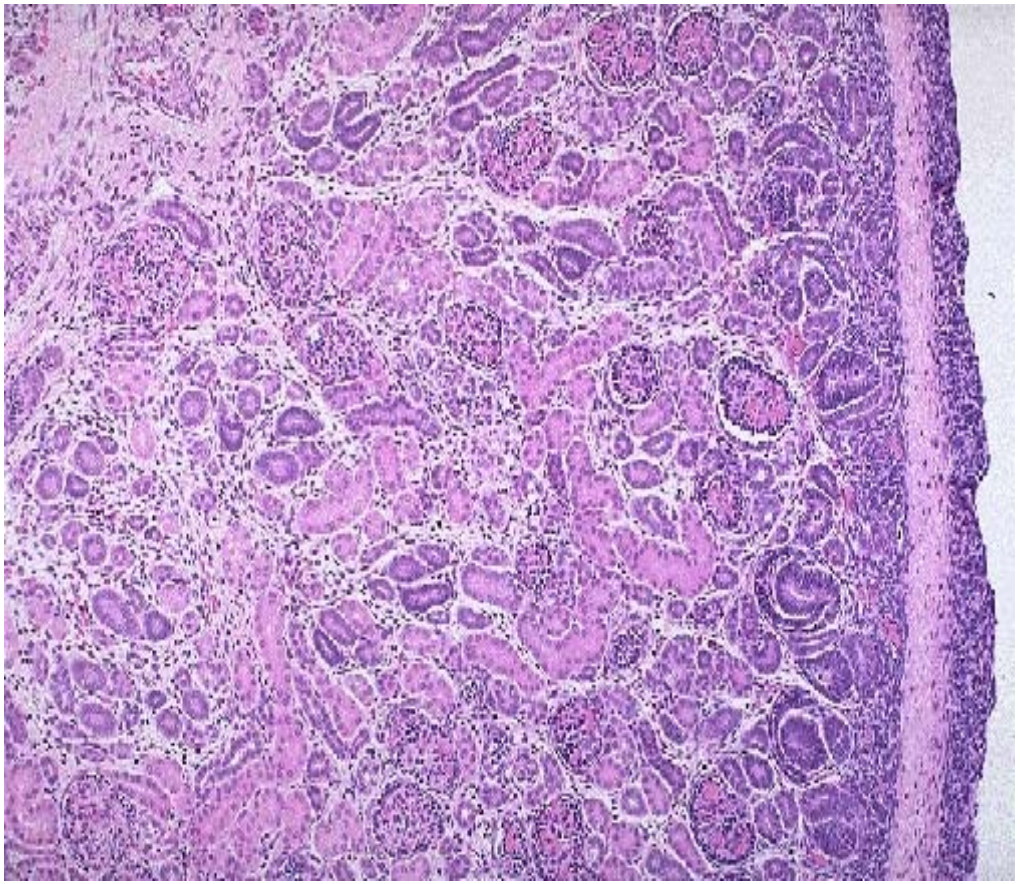
No acute lesions but....13/14 had chronic changes:

- macroscopic granular scarring/ cysts
- ↑ interstitial fibrosis
- tubular atrophy
- sclerotic glomeruli

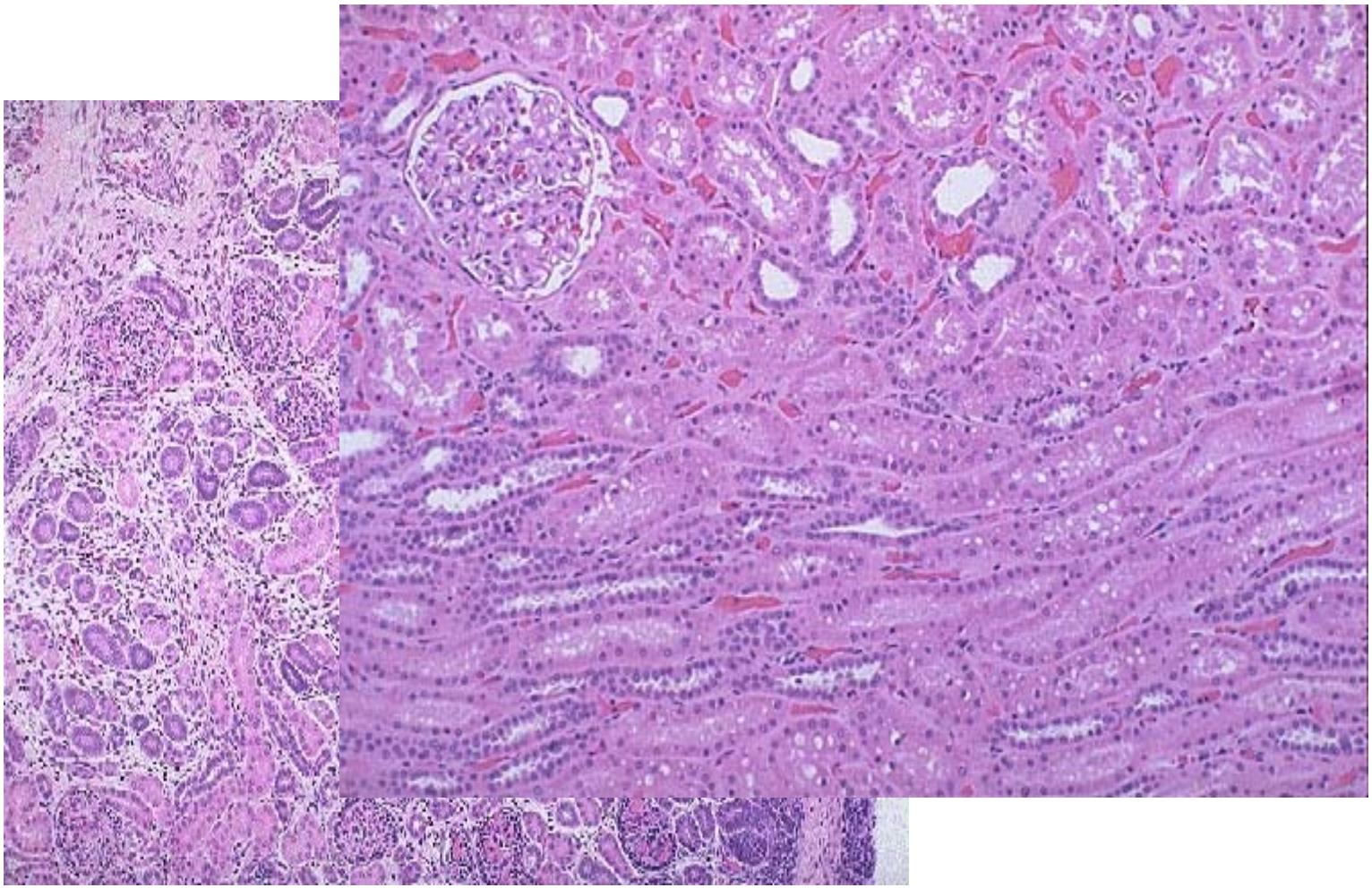
3 had persistent ↓creatinine clearance



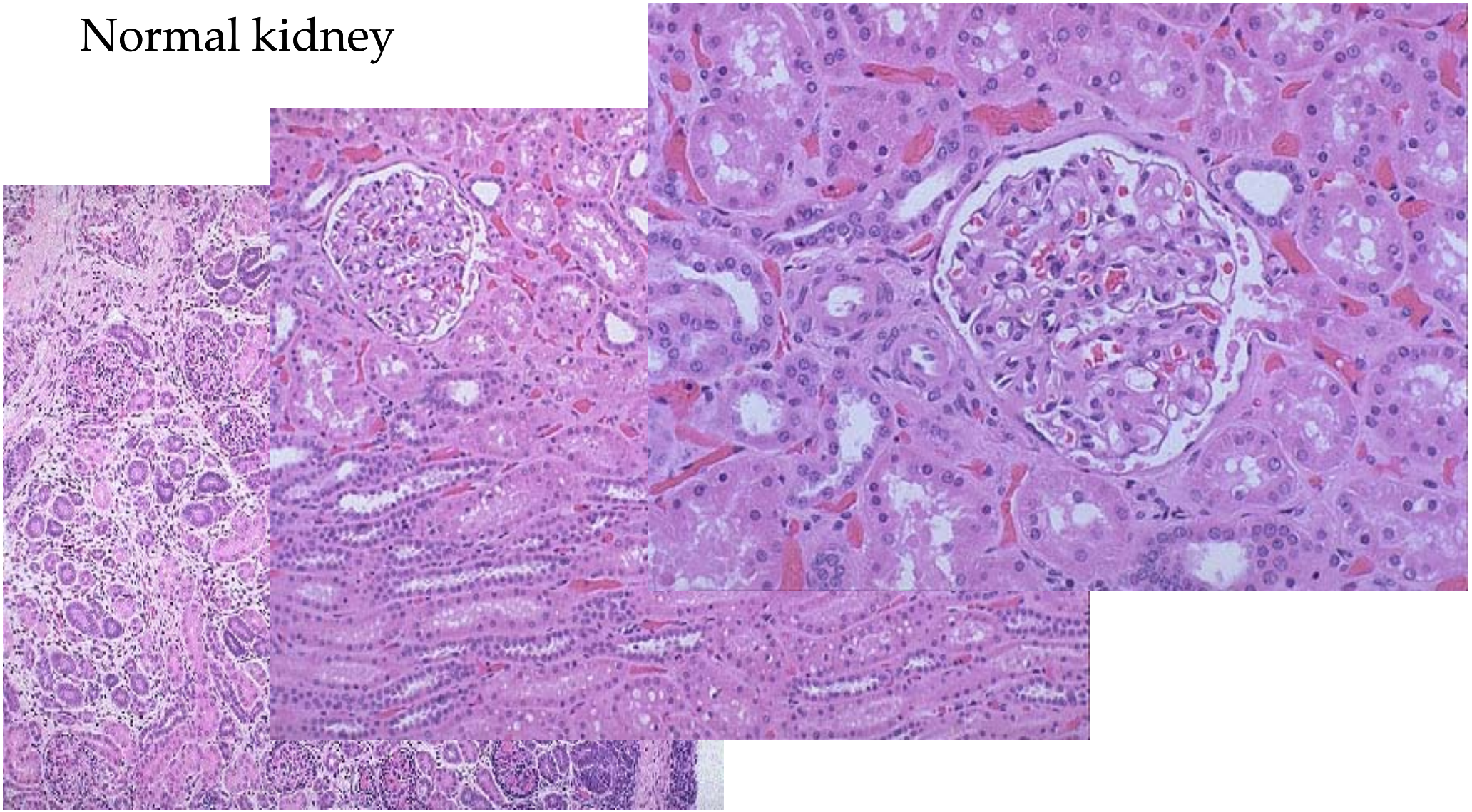
Normal kidney



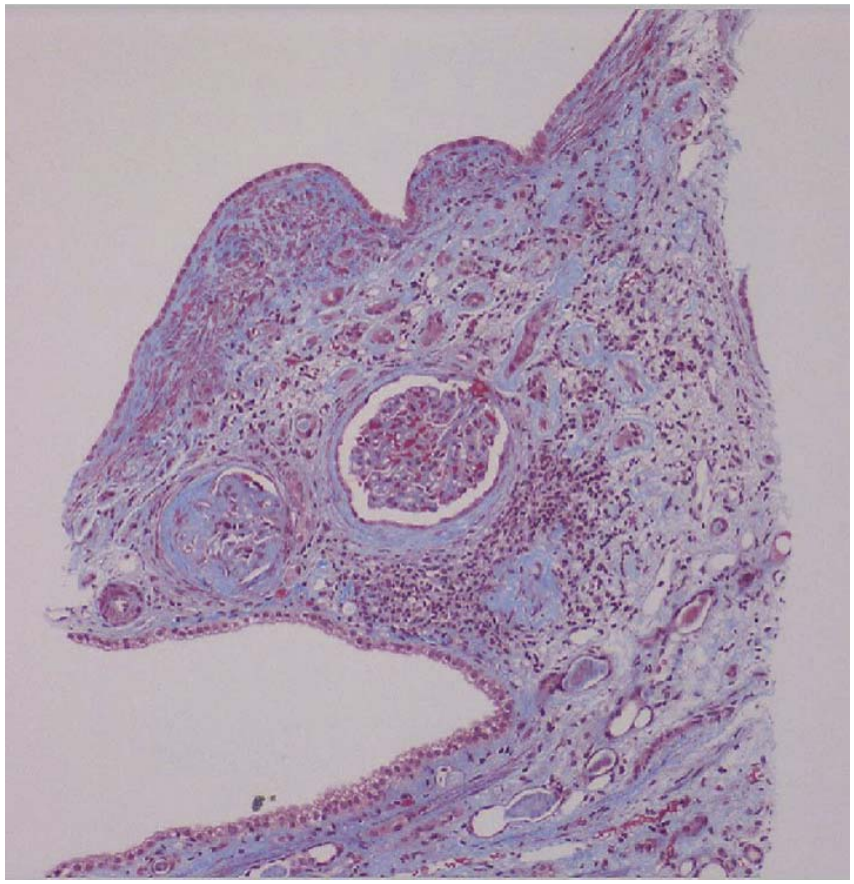
Normal kidney

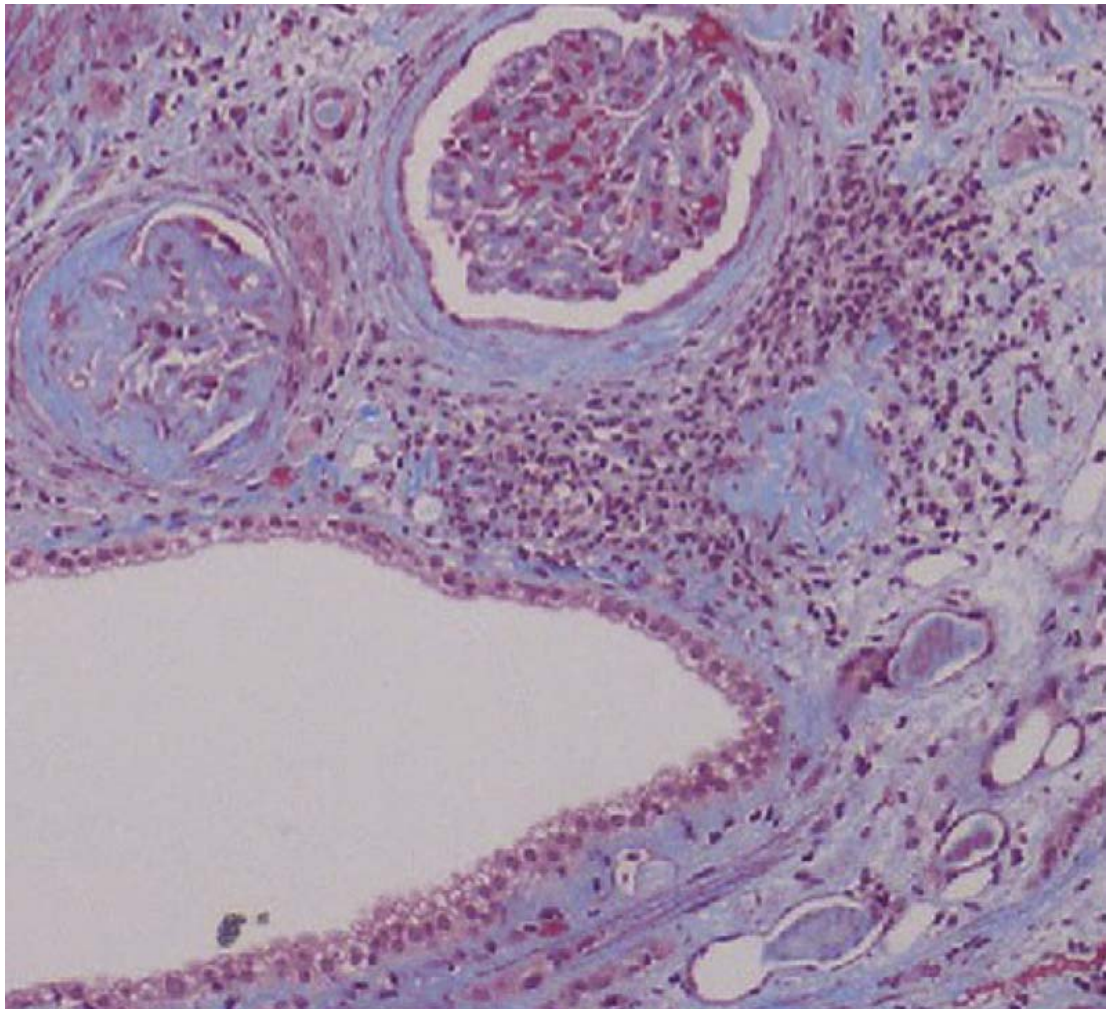


Normal kidney

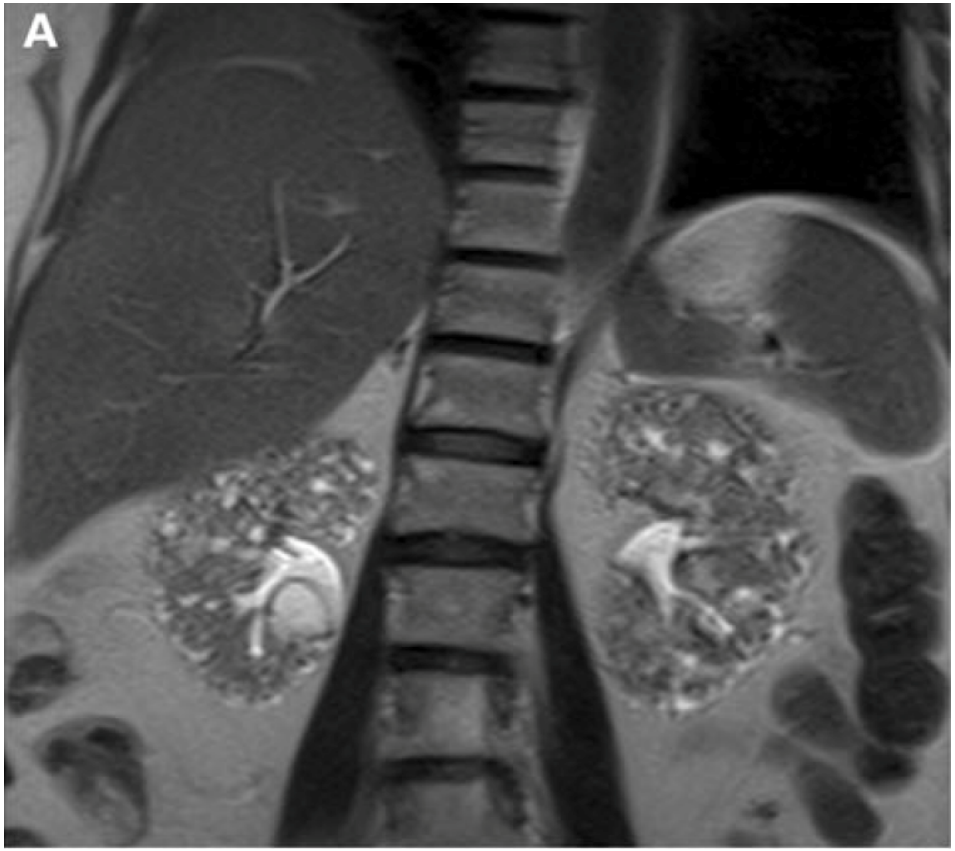


Lithium-induced chronic tubulointerstitial nephritis (CTIN)





Fogo, *Am J Kidney Dis*, 2017



Lithium induced renal cysts – MRI

Roque et al, *Abdominal Imaging*, 2012

Lithium induced renal cysts – US

Di Salvo et al, J Ultrasound Med, 2012

Aurell 1981 - confirmation

9 pts on long-term Li (3-13yrs)

All biopsies:

- cortical fibrosis
- dilated tubules
- microcysts

3/9 GFR<60mls/min, normal prior to lithium

Li induced renal damage?

In vulnerable pts?

Further studies

Hetmar 1991: 19 pts, 10 yr f/u, mean 0.8mmol/L
- ↓GFR correlated with age

Kallner and Patterson 1995: 207 pts. 1-30yrs Li Rx, 0.6-0.8mmol/L
- no sig change in GFR

Bendz 1994: 142 pts, 15yrs Rx, mean 0.65mmol/L

- 21% ↓GFR

Further studies

Walker et al 1996: 20 pts, 20yrs Rx
- 20% ↓GFR

Bendz 1996: 13pts, 18yrs Rx. Li stopped, Ax after 9 weeks.
- GFR no different to controls

Presne 2003: 25pts stopped Li..
- When cessation GFR>40mls/min 5/7 improved. <25mls/min all deteriorated.

Paul et al 2010 – meta-analysis

23 studies

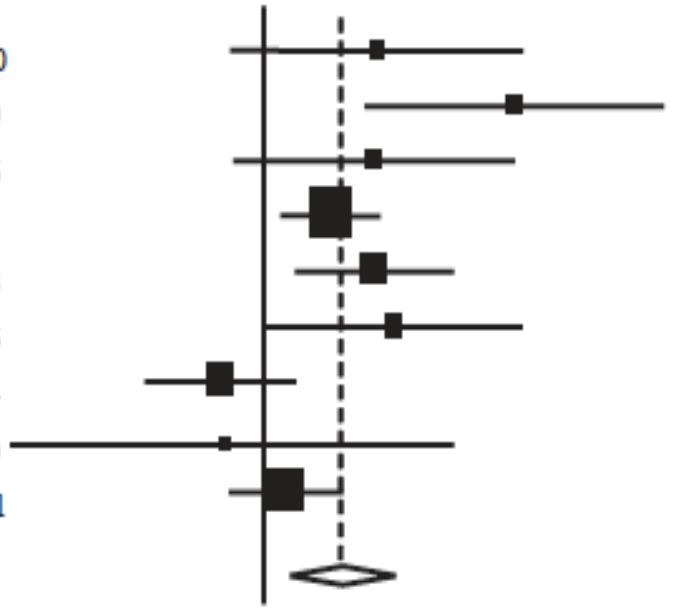
Creatinine levels

Age- and sex-matched

Aim: significant change? If so at what Rx stage?

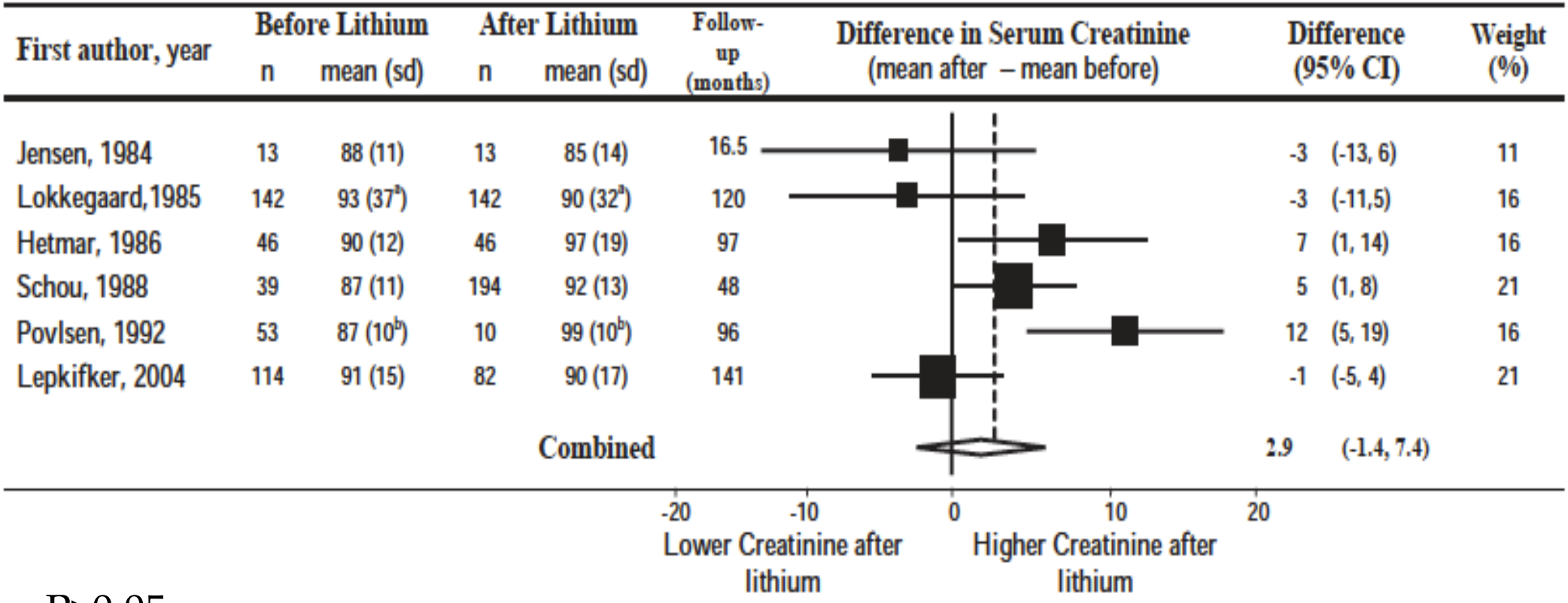
Paul et al 2010 – cross-sectional studies

First author, year	Control group n	Control group mean (sd)	Lithium group N	Lithium group Mean (sd)	Treatment duration (months)	Difference (95% CI)	Weight (%)
Hullin, 1979	30	84 (15)	30	93 (29)	100	9 (-3, 21)	9
Walker, 1982	19	80 (20*)	25	100 (20*)	60	20 (8, 32)	9
Khandelwal, 1983	15	97 (18)	40	106 (19)	56	9 (-2, 20)	9
Decina, 1983	190	110 (19)	190	115 (21)	61	5 (1, 9)	17
Gelenberg, 1987	44	85 (16)	220	94 (20)	38	9 (2, 15)	13
Hetmar, 1987	53	87 (30)	46	99 (20)	96	10 (0, 20)	9
Coskunol, 1997	29	85 (17)	107	81 (14)	54	-4 (-10, 3)	13
Turan, 2002	10	78 (27)	10	75 (16)	80	-3 (-22, 16)	4
Lepkifker, 2004	94	88 (14)	82	90 (17)	141	2 (-3,6)	17
				Combined		**5.7 (1.7, 9.9)**	



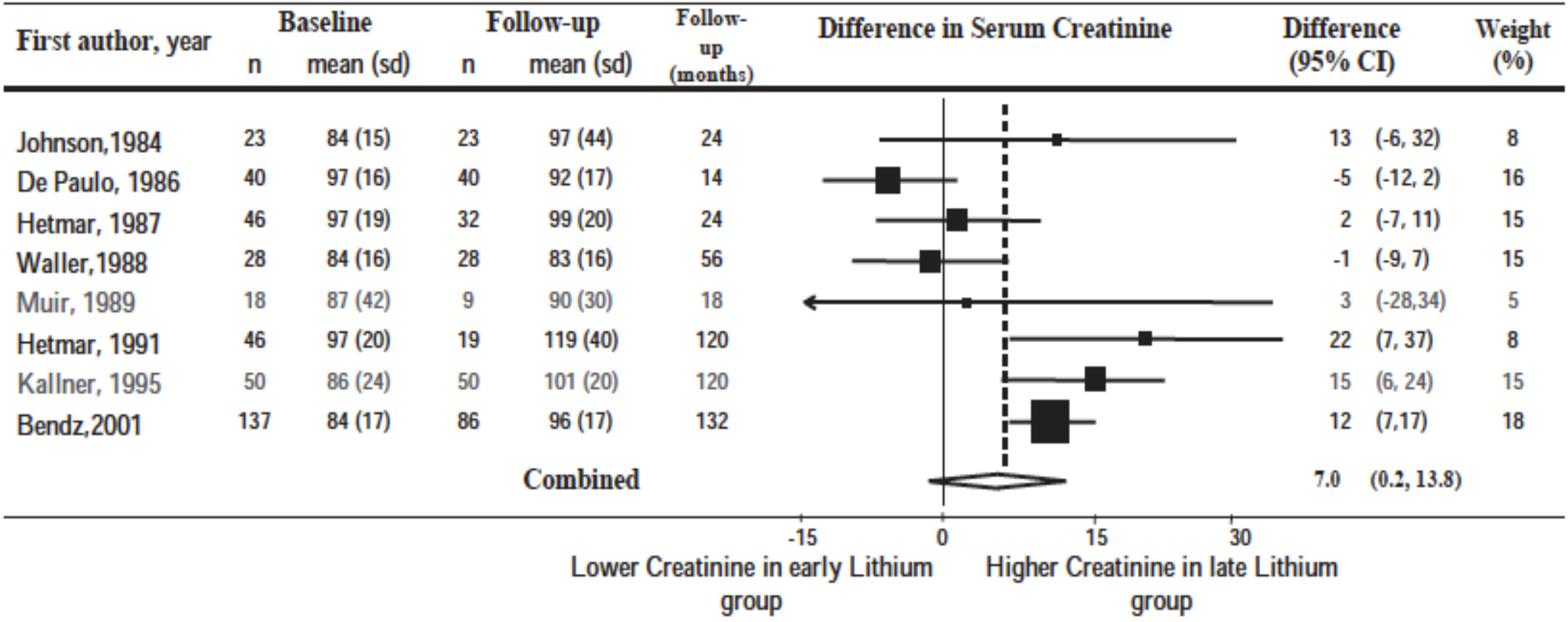
p=0.005

Paul et al 2010 – new starters



P>0.05

Paul et al 2010 – long-term Rx



p=0.045

Paul et al 2010 – meta-analysis

+ves: Large studies+/- long f/u

-ves: Small no of studies, high drop out, many short-term studies, I_2 59-75%

Small long-term effect of “questionable clinical significance”

Change in renal function more often due to age/toxicity/concurrent illness

McNight 2012 – meta-analysis

9 case-controlled studies

Effort to quantify risks

Over 1 yr f/u: ↓GFR 6.2mls/min (p=0.14)

Possible risk of Li-induced renal failure but "absolute risk was small" – 0.5% vs 0.2%

But: 1° data poor quality, heterogeneous, not powered for dose/age/other meds

Due to higher rates of CVD/DM in bipolar disorder?

Bendz 2010 – Swedish cohort study

2.7m population

Li pts in RRT: 18/3369

Av 23 yrs Li Rx, 10 stopped Li 10 yrs prior to ESRD

Prevalence CKD (excl RRT) in Li pts: 1.2% - no effect from Li levels/ diagnosis

Prevalence RRT in Li pts: 5.3% (0.8% in background pop)

Prevalence RRT in Li Rx>15yrs: 12.2%

Li-ESRD: “uncommon but not rare”

Aiff 2014 – monitoring effect

32 Li-ESRD RRT pts

Same Swedish population as Bendz

All started on Li 1965-80

1980: stricter monitoring, 0.5-0.8mmol/L

Monitoring or general Li effect?

Lower serum Li levels and stopping before “irreversible” damage removed Li-induced ESRD?

Tsermpini 2017 – CKD vulnerability

Genetic vulnerability – heritability up to 0.53

70 pts, BD type I, eGFR 50-90mls/min, 10-20 yrs Li Rx

Model with rs378448 SNP (ASIC gene CC allele) = best prediction of ↓ eGFR

However: 'exploratory' study, small nos, lots of SNPs, mechanistic targets

4 Li-CKD Management

Prevention/Early stage CKD

- Li levels 3/12ly if: risk of renal impairment/ U and Es↑/eGFR↓ twice

- U+Es/ eGFR 6/12ly: more often if renal impairment

- Lithium >0.8mmol/L and twice daily dosing ↑ CKD risk: consider dose reduction/single night time dose

- Ax rate of renal deterioration.....

Renal referral*, NICE CG182

- sustained ↓ eGFR of 25% over 3 tests/ >90 days and change in CKD category in last year **

- sustained yearly ↓ eGFR of >15mls/min **

- eGFR<30mls/min

- albumin:creatinine (ACR) >70mg/mmol

- ACR>30mg/mmol with haematuria

* Some authors recommend referral when GFR<60mls/min, or >60mls/min with significant proteinuria (Severus and Bauer, 2013; Gupta, 2013)

** NICE definition of CKD 'progression'

CKD

Joint Mx plan - 1º/2º (close) f/u

Provide info: risk factors + support

Exclude nephrotoxic medication

BP<140/90mmHg (130/80mmHg if DM) – ACEi/ AIIRBs

Consider: statins, antiplatelets, vit D, bisphosphonates, bicarbonates

Monitor for ↑K+

PTH/Ca^{2+}/PO_4^{3-} when eGFR<30mls/min

Lithium

- renal effects generally mild, minority progress to ESRD
- may progress after stopping Li
- relapses after stopping Li often more severe
- balance risks/benefits of Li vs alternatives and renal/CVD background risks
- consider advance directive wrt relapse if stopping Li

- **collaborative** (with pt, GP, renal team, RADS etc)
- **clinical judgement**

5 Conclusions

Current knowledge

- Li the most effective bipolar prophylactic/ ↓ suicide risks

- Unclear whether Li causal in ↓ eGFR

- Rx duration α nephropathy

- ↑ elderly bipolar cohort/ 'diabesity' effects

Future work

- Large epidemiological studies
- Delineate dose/ Rx duration/ episodes of toxicity/ age/ gender/ other medication
- Mechanism of eGFR ↓
- Vulnerability factors
- More precision medicine/ quantifiable risks
  (Joshua Gordon: *Nature*, 2016, Nov 3;539(7627):18-19)

Joshua Gordon
Director NIMH

Recommended resources

NICE, https://www.nice.org.uk

BAP, http://www.bap.org.uk

The Renal Association (UK), http://www.renal.org

Patient View, https://www.patientview.org

RenalMed, http://www.renalmed.co.uk

RCPhys (London), https://www.rcplondon.ac.uk

National Kidney Foundation (US), https://www.kidney.org

Thanks