Bipolar disorder in older people

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LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

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Lithium salts enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if pieces of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution.

Guinea-pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1-25 millilitres per ounce of body weight. When 0-5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

To determine whether lithium salts per se had any discernible effects on guinea-pigs, animals were injected...
Methodological limitations

- no consistent age cut off to distinguish young vs older, or EO vs LO
- small sample sizes
- retrospective reviews
- overemphasis on inpatients
- dearth of longitudinal data
Is age at onset bimodal?
Or trimodal?
Probably neither
National Comorbidity Survey Replication (NCS-R) 2005

Lifetime prevalence

- Anxiety
- Substance
- MDD
- Bipolar

- Age groups: 18-29, 30-44, 45-59, 60+
Australian National Mental Health Survey 1997

12 mth prevalence

- 18-24
- 25-34
- 35-44
- 45-54
- 55+
Is prevalence underestimated in older people?

- Counterintuitive
- Increased mortality
- Sample frame exclusion (homeless or institutionalized)
- Misdiagnosis
- Misattributed diagnosis
- Atypical presentations in old age
Why counterintuitive?

- Depressive episodes precede mania by years
- Diagnostic change from depression to bipolar low (Angst et al. 2005)
  - Risk for bipolar I (1% patients/yr) > bipolar II (0.5%/yr)
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Bipolar & risk of dementia (Da Silva et al. 2013)
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‘Misattribution’ hypothesis

- Expect age related increase in rate of “organic mania” (AKA secondary mania & disinhibition syndromes)
- Cerebral pathology (TBI, epilepsy, encephalitis, tumours) commonly described, but publication bias & small case series
- “Vascular mania” (Wijeratne & Malhi 2007) - tentative association between mania and vascular risk factors + cerebrovascular disease
- Medications & ECT
  - antidepressants, prednisolone, dopamine agonists
- Rate of organic mental disorder 0.8% (Almeida & Fenner 2002)
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- Atypical clinical presentations in old age
Clinical features

- no significant diff between younger & older bipolar I patients in symptoms of depression (except distractibility), or (hypo)mania, incl psychosis & irritability (Al Jurdi et al. 2012)

- Older patients more likely to present with depressive polarity (vs mania in younger) (Nivoli et al 2014)
  - Tendency to melancholia (vs atypical depression in younger)

- 11% with mania (YMRS 18+) experienced mixed symptoms (at least mod. depression) (Sajatovic et al. 2011)
Clinical features - comorbidities

- Lower rate substance use disorder (8.3% cf 38% young & 28% middle aged) (Depp et al 2005)
- Anxiety disorders 15% vs 9% for substance abuse (Sajatovic & Kales 2006)
- Medical co-morbidity (3-4 conditions) common (Lala 2012)
  - Similar to older people with unipolar depression but higher BMI & greater burden from metabolic syndrome, endocrine & cardio-respiratory conditions (Gildengers et al. 2008)
EO vs LO

- 16,330 veterans aged 60+ with bipolar (Sajatovic et al. 2005)
- EO group (mean age 70) more likely to be divorced or separated than LO group (mean 71 yrs)
- EO hospitalised more for mania, bipolar I > II or NOS
- no diff in hospitalisation for depression or substance abuse
- EO received more outpatient care, incl medical care
- EO received more mood stabilisers & atypical antipsychotics
Regional brain volume changes

- Hippocampus, amygdala & interconnections in frontal lobe play key role in pathogenesis
  - amygdala associated with affective cognition
  - hippocampus with regulation of mood & emotional behaviour
- Volumetric heterogeneity
  - associated with sex (females - smaller hippocampi)
  - lithium use (assoc. with larger volumes) (Hallahan et al 2011)
Regional brain volume changes

- Smaller hippocampal & right amygdala volumes in older group (Wijeratne et al. 2013)
  - smaller hippocampal vol associated with duration of mood episodes
- Lower total GM & hippocampal volumes related to longer duration of bipolar & longer exposure to antipsychotics, after controlling for age & stroke risk/burden (Gildengers et al. 2014)
- Structural abnormalities greater in chronic & recurrent bipolar > early (Berk et al. 2010)
- Bipolar may be neuroprogressive disorder
Neurocognition

- Significant differences (effect sizes 0.61-0.88) from controls on attention, digit span, delayed recall, serial learning, cognitive flexibility & verbal fluency (Semame et al 2013)

- Older euthymic subjects (mean age 65) worse on attention, declarative memory, executive function, language than HCs (Schouws et al. 2012)
  - Comparable vascular risk factors
  - Number of hospitalisations predicted language decline
  - No greater decline over two years than HCs (2/3 on lithium - ?neuroprotective ? tolerance marker of overall health)
Treatment trials

- Drug trials
  - Only one designed exclusively for older people (GERI-BD) - yet to report
  - Open trials
  - Secondary analyses
  - Small cohorts 50-100

- Psychosocial trials
  - Medication adherence skills training (Depp et al. 2007)
  - Medical care model (Kilbourne at al. 2008)
Treatment outcome (STEP-BD)

- 3,364 patients < 60 yrs vs 246 patients 60 yrs + (Al Jurdi et al. 2008)
- 78% older “recovered” vs 67% younger
- Recovered patients administered mean two psychotropics (no diff)
- Lithium administered to 30% older vs 38% younger (yet 42% older recovered with lithium monotherapy vs 21% younger)
  - sodium valproate 39% vs 34%
  - atypical antipsychotics 31% vs 33%
  - antidepressants 47% vs 43%
  - benzodiazepines 22% vs 20%
EMBLEM study (Oostervink et al 2015) found older (age > 60) patients did not differ from younger (age < 50) in mean duration of hospitalisation, or number achieving remission, recovery, relapse

- more older patients experienced recurrence (40% vs 23%) more quickly (mean 7 weeks earlier)
- higher cycle frequency (more frequent antidepressant use)

GERI-BD study (Beyer et al. 2014) - shorter duration of mania associated with fewer mixed symptoms, older age, close social interactions & support
Acute mania

- **Quetiapine** (QTP) monotherapy 400-800mg daily in 59 patients (mean age 63) (Sajatovic et al. 2008)
  - signif. better than placebo
  - effects apparent as early as day 4

- **Lithium**
  in four open-label studies (137 older patients), mania improved in 66% (Young et al. 2004)

- **Sodium valproate**
  in five open-label studies (137 older patients), mania improved in 59% (Young et al. 2004)
Acute bipolar depression

- **Lamotrigine** 12 wk open trial in 57 patients (Sajotovic et al. 2011)
  - Mean age (66.5) & mean lamotrigine dose 151mg
  - 57% remission & 65% response; 33% dropped out (4/19 due to rash)
  - Lamotrigine most effective in those with high cardio-metabolic risk & fewer mixed features (Glidengers et al 2012)
    - Lamotrigine acts primarily on neuroprogressive pathways involving oxidative stress, neurotrophins & inflammation
    - Effects on shared vulnerability factors in bipolar & medical illness
How long should mood stabilisers be maintained?

- Risk of recurrence remains constant over 30-40 year period after onset, up to age of 70 yrs + (Angst et al 2003)
  - risk for bipolar (0.4 episodes/yr) > depression (0.2 episodes/yr)
  - slightly higher risk for bipolar II > I
Secondary analysis of two placebo controlled RCTs (Sajotovic et al 2005)

Initial 8-16 week open label phase with lamotrigine (194 older pts)

98 responders aged 55+ (mean age 61) randomised for 18 months

Significant delay in time to intervention, compared with placebo

- for any mood episode - lamotrigine, but not lithium
- for depression - lamotrigine, but not lithium
- for mania - lithium, but not lamotrigine
Adverse effects - lithium

- incidence of ARF 1.5% per person-year (Rej et al. 2012)
  - risk factors - concurrent loop diuretic & ACE inhibitor use
- prevalence of CRF 1.2% to 34%
  - risk factors - age, previous lithium intoxication, polyuria, previous impaired renal function, decreased urine osmolality
- prevalence of NDI 1.8% to 85%
  - risk factors - lithium duration, dose, level, slow-release formulation
- no compelling evidence to suggest that lithium should be avoided in elderly patients for fear of renal side effects
Lithium & dementia risk

- Lithium reduced relative risk by 62% (Kessing et al. 2008)
- Continuous lithium exposure (301-365 days) associated with 23% reduction dementia risk (Gerhard et al. 2015)
  - No association for shorter exposure or any exposure to anticonvulsants
- Lithium inhibits GSK-3
  - Implicated in pathogenesis of neurodegenerative disorders
Adverse effects - atypical antipsychotics

- 4717 Veterans 65yrs + with bipolar disorder (Bhalerao et al 2012)
- Six month mortality rate differed by psychotropic class & agent
  - risperidone (11.8 per 100 person yrs)
  - quetiapine (5.3)
  - valproate (4.6)
Summary

- Studies of older bipolar disorder patients essentially survivor cohorts
- No evidence of a sub-group with “very late onset”
- Clinical symptoms similar to younger, but probably less severe
- Neuroimaging & other findings may represent neuroprogression of disease & chronicity rather than true aetiological effects
- Risk of dementia even higher than in unipolar depression
- Limited evidence for lamotrigine & lithium as safe & effective prophylactic agents, with probable neuroprotective effects
  - Neurotoxic effects of antipsychotics
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