Late and very late onset psychosis

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Conflicts of interests

VJP:

McGill psychiatry resident, geriatric psychiatry subspecialty, McGill.

No financial conflict of interest

SR:

Faculty: Soham Rej

Relationships with financial sponsors:

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- **Other:** Aifred Health – Shareholder in a company that a McGill Psychiatry Resident founded, Unrelated to this Presentation

Objectives

- Learn about the differential diagnosis of psychosis in older populations
- Better differentiate various presentations of psychosis (related to MNCD vs primary psychotic disorders vs other medical causes)
- Manage psychosis in older populations safely and based on available evidence

Outline

Definition and epidemiology

DDx

Management

- Non-pharmacological
- Pharmacological

Definition/Epidemiology

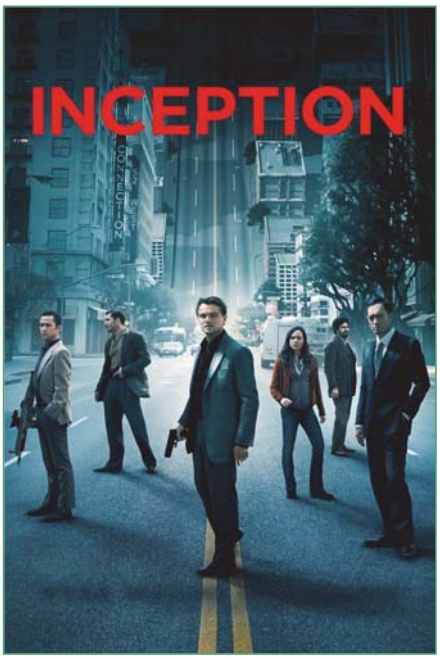
Definition (1)

Primary psychotic disorder

scz/scza, Delusional d/o, MDD, BAD

vs secondary

MNCD, delirium, CNS pathology, etc.



These terms are simpler than they appear

Definition (2)

Psychosis: DSM V, crit A of Scz, 2+ of (for >6 mo):

- Delusions,
- Hallucinations,
- Disorganized speech/behavior (incl catatonia),
- negative sx

DSM V; Tampi (2019)

Definition (3)

Late onset psychosis (LOP)/ Late life psychosis

- Onset between 40-60 y-o
- Some sources :45-60 y-o

Very Late Onset Psychosis (VLOP)

- 65+ up to 85+

Does not include older adults who presented with psychosis earlier in their lives

DSM V; Tampi (2019)

Epidemiology- secondary causes (MOST COMMON)

- Account for 40-60% of presentations of psychosis
- Mostly MNCD
  - AD: 40% psychosis
  - Vasc: 15%
  - Mostly persecutory delusions
  - LBD; bvFTD
- Delirium
  - 40% psychotic ft

Iglewiscz (2011) Tampi (2019) Ducharme (2020)

Epidemiology- primary causes- psychotic disorders

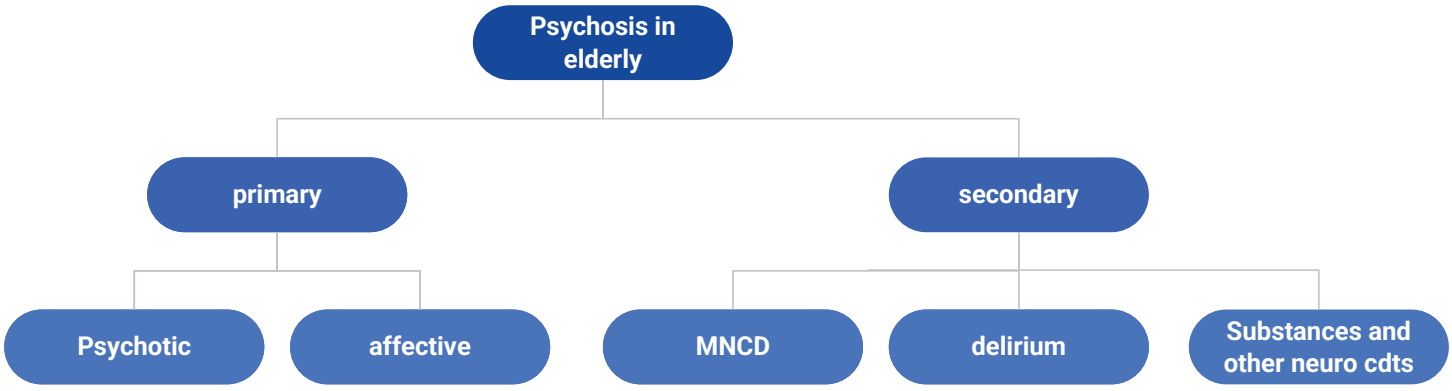
Late life schizophrenia majority of **primary** psychotic d/o in elderly:

- 0.5% (or 0.5-1%) of older adults
- In scz:
  - 20-25% LOP VLOP
  - vs 75% EOS

Tampi (2019) Iglewiscz (2011) Solmi (2019) Maglione (2014)

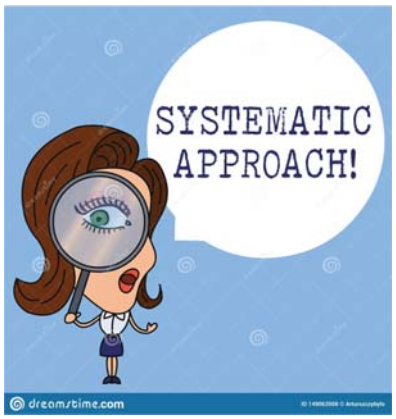
DDx

Summary



Iglewiscz (2011) Tampi (2019)

How to differentiate :Systematic approach



Thorough history (personal and family)

- Psychiatric AND MNCD
- Substance use Hx (think withdrawal and increasing rates)

Psychiatric and neurological clinical assessments

Collateral (timeline)

Scales

- Disease specific (FTD vs PPD) or MMSE, MoCA

Tampi (2019); Durcharme (2020)

Systematic approach (2)

Brain imaging (MRI, FDG PET, CT)

- DAT scan, TAU imaging

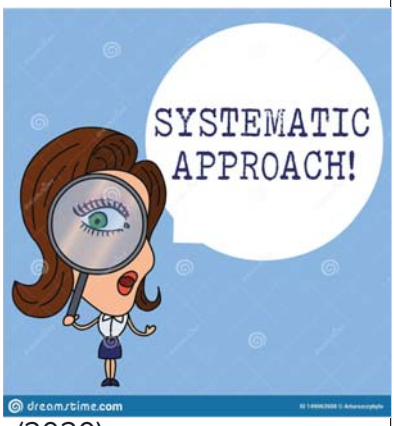
Complete physical exam and neurological

- Frontal release signs

Routine labs (CBC, B12, TSH, Electrolytes, glucose, VDRL HIV)

- Eventually neurofilament light chains (?); genetics..

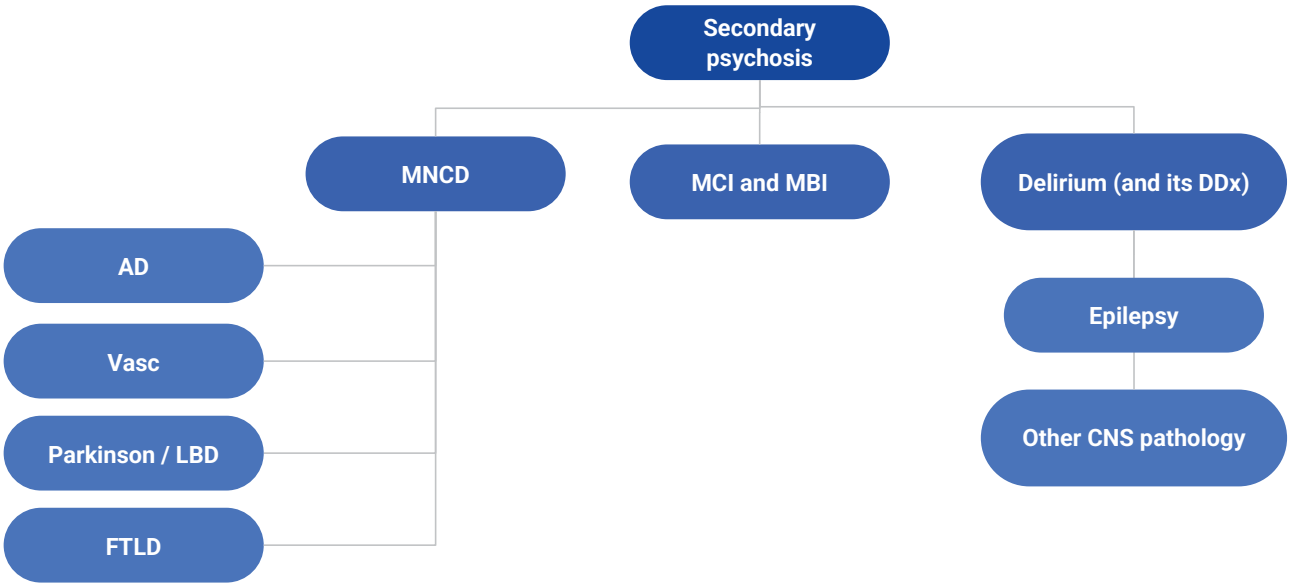
Careful selection of neuropsychological assessments



Tampi (2019); Durcharme (2020)

Secondary (More Common)

Distinguishing secondary causes



An overview of psychosis in AD

Review of 55+ articles

- Psychotic sx: 41%
  - Delusions: 36% (non-bizarre, paranoid, related to memory loss (theft, mienditification))
  - Hall: 18% (more often visual)
  - Tend to be less prominent after 1 yr of sx
- More prevalent
  - Inpatient settings
  - Older patients
  - Longer illness

Ropacki (2005) Iglewiscz (2011)

Vasc

Not uncommon (less well studied) - up 50%

Depends on location(s) of lesions

PDD/LBD

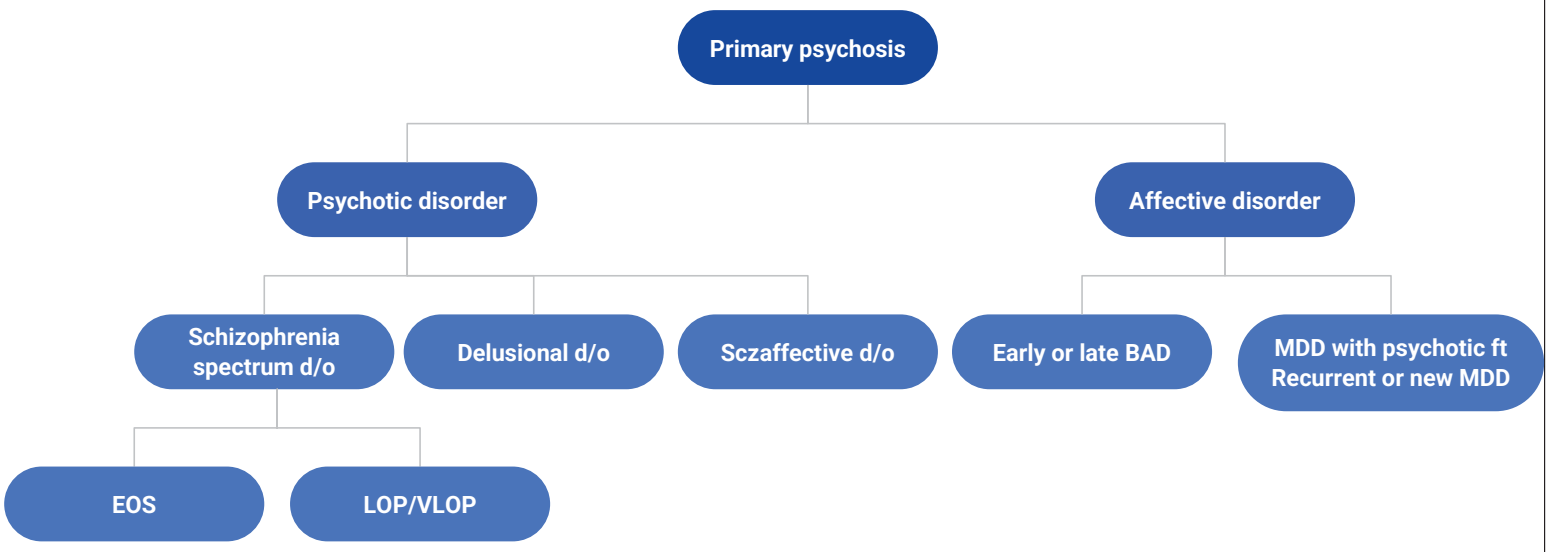
Continuum between mild benign VH and frightening in more advanced MNCD

Up to 60% psychotic sx over 12 yr obs. VH most freq.

Iglewiscz (2011)

Primary

Distinguishing primary (psychiatric) causes



Management

Non-pharmacological (strongest evidence for most patients)

- Optimizing known RF
  - MNCD... and comorbidities
- Supported employment/rehabilitation (>vocational rehab)
- Social skills training
- Cognitive behavioral skill training (CBSST)
  - Group cognitive and behavioral coping skills
  - Compensate neuro deficits
  - Sustained 1 yr benefits in skills and perceived functioning
  - Decreases hopelessness
- FAST: functional adaptation skill training
  - organization, transportation, social skills, finances, Rx management

Iglewiscz (2011) Tampi (2019)

Non-pharmacological (strongest evidence for most patients)

- SW - support, additional food/cleaning at home, residence, taxes,
- OT - activities you can do, functioning - like I had an RN who went on the bus with the patient, after that she was good for a long time
- PIT-A/TIP-OA - volunteer phone support
- Engaging families,
  - where present, is powerful

Pharmacological - in MNCD

Black box warning (FDA, 2008)

- findings in dementia (AR death 1-2%- CVA/inf)

CATIE-AD (n=421; duration: 36 wks): Risk>benefits

- Biggest non-sponsored RCT for psychosis/agitation in AD
- Risp vs Olanz vs Quet vs placebo
- All equal in time until discontinuation for any reason between (all<10 wks)
- Looking at the subgroup who discontinued due to lack of efficacy Olanz+Risp>placebo
  - stuck longer before deciding not useful
- HOWEVER, higher SE of Risp and Olanz

FDA (2008) Iglewiscz (2011) Tampi (2019); Howard (2000); Rej (unpublished data), Steinberg (2013) Schneider (2006)

Pharmacological - psychosis in MNCD

So which ATP to choose?

- No definite evidence for one SGA over the other
- Mild eff: Risperidone (0.25-2), Olanzapine (1.25-10), Abilify (1-10)
- Less so quetiapine (exception for PDD, LBD, still not ideal)
- ACHeI VH in LBD
- Consider side effect profile

? antidepressant (RCT evidence for citalopram and sertraline agitation and psychosis)

Different risk when patients are hospitalized FOR psychosis (with or without MNCD)

- lower mortality
- **Soham's clinical Pearl:** 1) risperidone 0.5 hs is a nice compromise efficacy/side effects; 2) after age 60, survivor effect - even with olanzapine, cardiovascular burden of some wt gain isn't as bad as when age 30-50
- Controversy about THC, Nabilone, and CBD oil?

FDA (2008) Iglewiscz (2011) Tampi (2019); Howard (2000); Rej (unpublished data), Steinberg (2013) Schneider (2006)

Pharmacological - in primary psychotic d/o

Antipsychotics are the mainstay for LOP VLOP

Less data geriatric populations (mix of VLOP and old age scz)

Lower doses as patients age (½- ¼); also for LAI

Shorter duration if possible

FDA (2008) Iglewiscz (2011) Tampi (2019); Howard (2000)

Pharmacological- General aspects

Greater propensity for TD (1st)

- Overall, esp affective d/o
- when we suddenly stop AP-
  - sometimes even if you restart it doesn't go away

Common side effects (2nd)

- Sedation; hypotension, antichol, cardiovasc (QTc), NMS, hyperPRL, metabolic...

Generally: start low, go slow.. Expect slower response

Consider liquid form for dysphagia

Stahl, 2013; Maglione (2014); Guerrero (2015); Tampi (2019); Iglewiscz (2011)

Pharmacological- General aspects

Lower doses - receptor sensitivity

- Monitored dose reduction over 3 mo
- n=35; up to 40% decr in Risp/Olanz
- D2/D3 occupancy decr from 70% to 64%
  - (putamen, caudate, striatum)
  - 2 wks post stable dose
- ass. w good outcome in most pt (PANSS, BPRS); fewer SE
- EPS at lower occupancy (60%) -typically over 80% in adults

Stahl, 2013; Maglione (2014); Guerrero (2015); Tampi (2019); Iglewiscz (2011)

Pharmacological - Psychotic disorders (2)

Cochrane review (2012) does not favor any Rx for LLS

Specific recommendations (few available) -mostly expert opinion.

- Risperidone and paliperidone*
  - Most studies (Risp: 1.25-3.5 per day; average 2; start at 0.25-0.5 daily)
  - Paliperidone: 3-12 mg daily
- Olanzapine
  - Second most (7.5-15)
- Amisulpride*
  - Not available Canada: 100 mg in primary; 50 in secondary
- Aripiprazole
  - 15-30 die
- Quetiapine
  - 100-300 die; good w EPS
- **Clozapine**
  - Limited date in elderly, multiple SE (HypoTN, sedation, agran)
  - good for EPS, TD and PDD, LBD

*2 blinded RCT (vs placebo) of Amisulpride (VLOP) and paliperidone (old age scz)
Expert opinion(n=48): Risp>Quet>Olanz>Aripiprazole

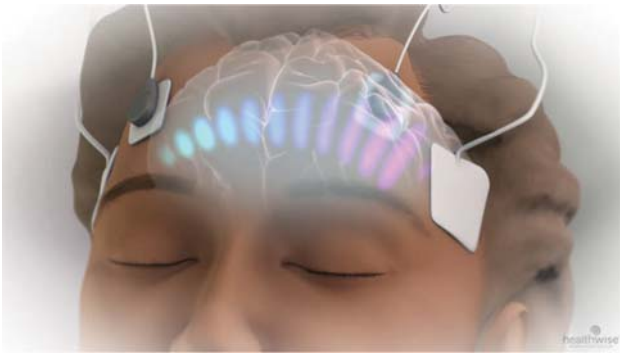
Iglewiscz (2011) Tampi (2019); Essali (2012)

Other tx - ECT

ECT in older OES or LOS/LOP minimally studied.

Better when agitation, catatonia

need quick resp due to suicidality



PRIDE study: Maintenance ECT is an option in geriatric TR-depression

- With fewer side effects

Iglewiscz (2011) Tampi (2019); PRIDE

Pharmacological - MDD w psychosis

ECT

ATD+antipsychotics (together) (update)

- In Europe, ECT is first-line for psychotic depression

Suggestion based on small samples (n=110) that ECT might be related to less relapse in older age MDD (w/o psychotic ft) (OR: 0.32)

https://pubmed.ncbi.nlm.nih.gov/31429896/

CCSMH (2021); Margot (2021); Flint (2019)

Pharmacological -BAD

Similar effectiveness as in younger adults

- Most data: Li and VPA lit
- some data for lamotrigine
- less for atypical APs

No RCTs except for GERI-BD (still in-press)

Monotherapy ideal, but cautious low-dose polypharmacy often needed (and used- up to 81%)

Bipolar: CANMAT algorithm (2018)

	Acute mania	Bipolar depression	Maintenance
First line	Lithium (2) Divalproex (2)	Quetiapine (2) Lurasidone (2) Lithium (4)* Lamotrigine (4)*	Recommended: Lithium (2) Lamotrigine (2) Divalproex (3) Continue what has been effective in the acute phase
Second line	Quetiapine (2)		
Third line	Asenapine (4) Aripiprazole (4) Risperidone (4) Carbamazepine (4)	Divalproex (4) Aripiprazole (4)	
Treatment resistance	Clozapine (4) ECT (4)	ECT (4), also for patients who are suicidal or with inadequate PO intake	

*Could be tried first based on efficacy in adults, given concerns about side effects of antipsychotics.

Despite controversy and lack of evidence, antidepressants are frequently used (40+%). SSRIs or bupropion could be used in combination with mood stabilizers.

Rej et al. In Press – J Clin Psych, Oostervink et al. 2013 – IJGP Al-Jurdi et al. 2008 – Am J Geri Psych,Beyer et al. 2014 – *IJGP,* , Young et al. *In Press;* CANMAT (2018)
Table by Dr. Friedland (DH, MUHC)

Pharmacology LOBAD (2)

Li levels and eGFR should be closely monitored, esp. if:

- low eGFR (<60), Nephrogenic diabetes insipidus, Acute kidney injury
- new diuretics, ARBs, ACEI, NSAID

Use Li Levels <0.8mmol/L,

- when possible (goal 0.4-0.6 depression, 0.5-0.8 mania/hypomania).

Once-daily dosing best

Start at 150mg/day – often 150-450mg/day is sufficient to get therapeutic geriatric levels

Juurlink et al. 2004 - *JAGS;* Close et al. 2014- *PLOS one;* Rej et al. 2015 – *Drugs and Aging;* Rej et al. 2014 – *Aging and Mental Health, Am J Geri Psych;* Rej et al. 2013 – *Drugs and Aging, Int J Geri Psych*

extra

Antipsychotics and Mortality

- Antipsychotic (AP) use controversial in both non-dementia and dementia populations, even though main treatment for psychotic disorders.
- FDA and Health Canada black box warnings for use in dementia for their potential for premature mortality.
- Very little safety data - *whether or not APs associated with mortality in late-life psychosis?*

Health Canada

Lenzer 2005 –*BMJ*, Kales 2012 – *Am J Psychiatry*

Methods

- We conducted a province-wide cohort study.
  - Patients were older adults aged ≥66 between April 1st, 2008 and March 31st, 2016 from Ontario, Canada.
- Patients were included into a:
  - sensitive cohort (n= 22,314, any physician diagnosis of psychosis)
  - specific cohort (n=6,498, hospitalization for psychosis).

Methods (cont.)

- Main exposures were Antipsychotic Use (vs. Not)
- The main outcome was Mortality. Patients were followed up to 5 years.
- Cox regression analyses compared adjusted hazard ratios (aHRs) for mortality in AP users and non-users, after controlling for important covariates that differed between groups (including health care/other medication use).

Results

- In the specific cohort, where 24.8% of patients not using APs:
  - atypical AP monotherapy associated with reduced mortality in
    - non-dementia (aHR 0.49 (0.42-0.58), p= 0.004) and
    - dementia (aHR 0.38 (0.32-0.45), p<0.001) late-life psychosis populations.
  - Similar results in sensitive cohort, typical AP monotherapy, and AP polypharmacy.

Results - Cox regression APs and Mortality Over 5-year follow up, specific cohort (N=6,498)

Characteristics	Hazard Ratios (95% CI)	P-Value
Typical Monotherapy vs. None	0.62 (0.49-0.78)	<0.001
Atypical Monotherapy vs. None	0.44 (0.39-0.50)	<0.001
Polypharmacy vs. None	0.47 (0.39-0.56)	<0.001
Oral Olanzapine equivalents		
Low-Medium vs. None/Low	0.52 (0.45-0.61)	<0.001
Medium-High vs. None/Low	0.56 (0.45-0.70)	<0.001
High vs. None/Low	0.45 (0.40-0.52)	<0.001

- * Adjusted for age (categorized); sex; ADG total score (continuous); and recent mental health diagnoses of dementia, substance-related, mood and anxiety disorders** Adjusted for above variables* plus Ontario Marginalization index average score (continuous); prior comorbidities of diabetes mellitus, COPD and CHF; ECT therapy; number of unique non-AP medication; recent exposure to antidepressants, mood stabilizers, benzodiazepines and anticholinergic medication; Rudolph anticholinergic risk score; and total number of family physician visits, psychiatrist visits, mental health ED visits, non-mental health ED visits, mental health hospitalizations and non-mental health hospitalizations

Results - Cox regression APs and Mortality Over 5-year follow up, specific cohort (N=4,841) – Non-Dementia Only

Characteristics	Hazard Ratios (95% CI)	P-Value
Typical Monotherapy vs. None	0.62 (0.46-0.82)	0.001
Atypical Monotherapy vs. None	0.49 (0.42-0.58)	<0.001
Polypharmacy vs. None	0.46 (0.37-0.58)	<0.001
Oral Olanzapine equivalents		
Low-Medium vs. None/Low	0.55 (0.45-0.68)	<0.001
Medium-High vs. None/Low	0.66 (0.49-0.87)	0.004
High vs. None/Low	0.48 (0.41-0.57)	<0.001

- * Adjusted for age (categorized); sex; ADG total score (continuous); and recent mental health diagnoses of dementia, substance-related, mood and anxiety disorders** Adjusted for above variables* plus Ontario Marginalization index average score (continuous); prior comorbidities of diabetes mellitus, COPD and CHF; ECT therapy; number of unique non-AP medication; recent exposure to antidepressants, mood stabilizers, benzodiazepines and anticholinergic medication; Rudolph anticholinergic risk score; and total number of family physician visits, psychiatrist visits, mental health ED visits, non-mental health ED visits, mental health hospitalizations and non-mental health hospitalizations

Results - Cox regression APs and Mortality Over 5-year follow up, specific cohort (N=1,657) – Dementia Only

Characteristics	Hazard Ratios (95% CI)	P-Value
Typical Monotherapy vs. None	0.61 (0.41-0.91)	0.016
Atypical Monotherapy vs. None	0.38 (0.32-0.45)	<0.001
Polypharmacy vs. None	0.46 (0.35-0.60)	<0.001
Oral Olanzapine equivalents		
Low-Medium vs. None/Low	0.49 (0.40-0.61)	<0.001
Medium-High vs. None/Low	0.46 (0.33-0.64)	<0.001
High vs. None/Low	0.40 (0.32-0.49)	<0.001

- * Adjusted for age (categorized); sex; ADG total score (continuous); and recent mental health diagnoses of dementia, substance-related, mood and anxiety disorders** Adjusted for above variables* plus Ontario Marginalization index average score (continuous); prior comorbidities of diabetes mellitus, COPD and CHF; ECT therapy; number of unique non-AP medication; recent exposure to antidepressants, mood stabilizers, benzodiazepines and anticholinergic medication; Rudolph anticholinergic risk score; and total number of family physician visits, psychiatrist visits, mental health ED visits, non-mental health ED visits, mental health hospitalizations and non-mental health hospitalizations

Pharmacotherapy of Late-Life Bipolar Disorder

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Geriatric Psychiatry Research Fellow, University of Toronto
Co-Lead, Geri-PARTy Research Group, Jewish General Hospital, McGill University, Montreal

Medical Health Utilization, Mortality not different w/ late-life BD pharmacoTx (n=1,388)

- 1-year Acute Med Hospitalizations and ER visits very similar across medication groups

Outcomes	Lithium Users (n=279)	Valproate Users (n=452)	Non-Lithium, Non-Valproate Users (n=657)
Inpatient medical hospitalization, N (%)	58 (20.8%)	96 (21.2%)	151 (23.0%)
Medical ER visit, N (%)	98 (35.1%)	167 (36.9%)	270 (41.1%)

- Time-to-hospitalization not independently affected by lithium, valproate, atypical APs

	Univariate Hazard Ratio (HR) [95% CI]	Multivariate Hazard Ratio [95% CI]
Lithium Use	0.93[0.7-1.24]	0.88[0.65-1.2]
Valproate Use	0.93[0.73-1.19]	0.92[0.71-1.19]
Concurrent Antipsychotic Use	0.85 [0.66-1.09]	0.92 [0.71-1.19]

- Mortality did not differ significantly (3.5%/yr)

Rej et al. 2015 – *Gen Hosp Psychiatry*

Principles in Action: Preventing + Treating CKD in Lithium Users

Li levels and eGFR should be closely monitored, esp. if:

- low eGFR (<60), Nephrogenic diabetes insipidus, Acute kidney injury
- new diuretics, ARBs, ACEI, NSAID

Use Li Levels <0.8mmol/L, when possible (goal 0.4-0.6 depression, 0.5-0.8 mania/hypomania).

Once-daily dosing best, start at 150mg/day – often 150-450mg/day is sufficient to get therapeutic geriatric levels

Control DM2, HTN, and Cardiovascular Factors

Lithium d/c may not resolve renal problems and can worsen psychiatric condition

Medical risks and psychiatric benefits of lithium need to be weighed in older Li users

Juurlink et al. 2004 - *JAGS;* Close et al. 2014- *PLOS one;* Rej et al. 2015 – *Drugs and Aging;* Rej et al. 2014 – *Aging and Mental Health, Am J Geri Psych;* Rej et al. 2013 – *Drugs and Agirg, Int J Geri Psych*

What medications are actually being used in late-life BD?

- Canadian inpatient BD sample aged ≥66(n=1433)
  - Psychotropic polypharmacy highly prevalent (>81%)
    - Mean of 2.65 psychotropic medications (similar to outpt)
  - Most common medications on psychiatric discharge:
    - Atypical antipsychotics (75.3%)
    - Benzodiazepines/zopiclone (42.3%)
    - Antidepressants (38.5%)
    - Valproate (35.4%) and lithium (23.4%).
    - 1.4% of patients on lithium monotherapy,
    - 4.4% and 15.7% on antidepressant or atypical monotherapy.
    - 8.9% using ≥2 atypical antipsychotics.
    - 6% lamotrigine, 4% carbamazepine

Rej et al. *In Press – J Clin Psych,* Oostervink et al. *2013 – IJGP*

Patient Pharmacotherapy Preferences in Late-Life BD

Independently of other factors, geriatric lithium users have more positive attitudes towards BD pharmacotherapy compared to non-lithium users

- In spite of high rates of moderate self-reported side effects (e.g. polyuria)!
- Positive drug attitudes are associated with better treatment adherence

Rej et al. *In Press – Int Psychogeriatrics*

Pharmacotherapy in Late-Life BD – Clinical Punch Lines

Lithium works!

- **Lithium is effective**! Up to 40% of older adults with BD can be stabilized on Li monotherapy.
  - Li also associated with Improved Cognition, found helpful by pts
- Average pt is often on 2-3 agents
  - **Almost half** of late-life BD1 patients in Ontario (and likely in rest of Canada) are on Antidepressants – controversial and not first-line
  - 75-80% of pts on Atypical APs (other than lurasidone) – not necessarily effective vs. BD depression, major issue in late-life
- Serious medical problems about the same regardless of Li, Val, APs, perhaps slightly favoring Li (mortality, cognition, DM2)
- When prescribing in late-life – start low, go slow
  - E.g. Target Li Dose 0.4-0.8, start at 150mg/day and titrate up

Al-Jurdi et al. 2008 – *Am J Geri Psych,* Beyer et al. 2014 – *IJGP,* , Young et al. *In Press,* Rej et al *In Press – J Clin Psych,* Yatham 2013 –*Bipolar Disorders,* Rej et al. 2014 – *Drugs and Aging*