

# “To Use or Not to Use—That is the Question”

## Atypical Antipsychotics in the Treatment of Aggression & Agitation related to Dementia



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- Nothing to disclose
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# Key Learning Objectives

1. Nonpharmacological 1<sup>st</sup> line
2. Evidence for and “controversy” over atypical antipsychotic use
3. Medication alternatives
4. Case
5. Balancing indications and risks

# Background: BPSD

## Behavioural & Psychological Symptoms of Dementia

Ubiquitous Clinical Problem in Dementia:

- **Behavioural**- *agitation, aggression, restlessness, wandering, repetition, disinhibition, insomnia*
- **Psychological**- *delusions, hallucinations, personality changes, depression, mania, apathy*

# Impact: Caregivers

- Individual behavioural symptoms with the most significant impact on caregivers:

Aggression, agitation and irritability

- Reference: Matsumoto N et al. Caregiver burden associated with behavioural and psychological symptoms of dementia in elderly people in the local community. Dement Geriatr Cogn Disord 2007; 23 (4): 219-24

# Nonpharmacological Management – First Line Approach

Newer guidelines are all recommending that the first approach to BPSD be nonpharmacological wherever possible...

# What do you need to know?

- Research on nonpharmacological interventions complex & expensive
- Translating research interventions into the real world much more difficult than with pharmaceuticals
- Successful interventions are individually designed – one size doesn't fit all.
- Informed person-centered dementia care is the key preventative strategy

# Range of Behavioural Approaches

- Adhere to schedules/ routines (sleep)
- Avoid over-stimulating situations
- Use diversion tactics (vs. confrontation)
- Use of simple/ non-verbal communication
- Maintain bowel routine/ hygiene
- Regular physical and/or social activities
- Developmentally appropriate recreation therapy
- Use of music therapy/ aromatherapy/ massage

Ref: Dianne Rossy, RN, BPSD Symptoms of AD in Practical Issues in Alzheimer's Disease, 2009

# What Do You Need to Know?

- Has a careful systematic analysis of behavioral needs been completed? (A,B,C's)
- Is there an individualized care plan...& more importantly is it being carried out consistently?
- P.I.E.C.E.S.
- Are you asking/ being asked to prescribe because of:
  - Inadequacy of staffing levels?
  - Inadequacy of staffing skill?
  - Inadequacy of leadership?
  - The institutional model of care?.....or.....
  - Because it will benefit the patient?

# Most recent studies of relevance

- **Nonpharmacological Treatment of Agitation: A controlled trial of systematic individualized intervention**
  - Cohen-Mansfield, Libin, & Marx 2007  
Journal of Gerontology: Med Sci. 62A:908-916
- **An Individualized psychosocial approach for treatment resistant behavioral symptoms**
  - Davison, Hudgson, McCabe et al 2007  
International Psychogeriatrics 19:859-873
- **Tailored Activities to Manage Neuropsychiatric Behaviors in Persons with Dementia and Reduce Caregiver Burden: Randomized Pilot Study**
  - Gitlin, Winter, Burke et al 2008  
AJGP 16:229-239

# **Part II: Antipsychotics – The evidence behind the controversy**

# Tx of BPSD with Atypical Antipsychotics – When?

## Severe Agitation and Psychosis in Dementia: Best Evidence: Novel Antipsychotics<sup>a,b,c</sup>

### Cochrane review:<sup>c</sup>

- Mostly severely demented, institutionalized patients

## Risperidone & olanzapine reduce aggression:

- Risperidone also efficacious in psychosis
  - Quetiapine: only 1 study analyzed- no effect
- **Modest efficacy, clinically significant**

a) Hermann N, CAGP Bulletin 2004; b) Ranco KN et al. J Am Med Dir Assoc 2006; 7(3):201-2; c) Ballard C et al. Cochrane Database Syst Rev 2006; CB003476

# Tx BPSD with atypical antipsychotics – How much?

## Dosage Range:

- Risperidone 0.5-2 mg/d
- Olanzapine 2.5-15 mg/d
- Quetiapine 25-200 mg/d

Ballard C et al. Cochrane Database Syst Rev 2006; CB003476

# So What is the Controversy?

Atypical  
Antipsychotic  
*Side Effects*

# Atypical Antipsychotics in Cochrane Review (Ballard 2006): Adverse Effects

- Somnolence
- EPS, Abnormal gait
- Falls
- Urinary incontinence
- URTI (risperidone)
- UTI (risperidone)
- Peripheral edema (risperidone)
- Metabolic risks and ? prolonged QT

# Atypicals increase Stroke Risk in Dementia Patients

## Risperidone:

- 4 placebo-controlled trials
- Elderly patients w dementia
- Stroke rates:  
RSP: 3.3%  
PLB: 1.1%

**RR=3.30 (95% CI: 1.43–7.70)**

[http://www.fda.gov/medwatch/  
SAFETY/2003/risperdal\\_PI.pdf](http://www.fda.gov/medwatch/SAFETY/2003/risperdal_PI.pdf)

## Olanzapine:

- 5 placebo-controlled trials
- Elderly patients w dementia
- Stroke rates:  
OLZ: 1.3%  
PLB: 0.4%

**RR=3.04 (95% CI: 0.70–13.3)**

[http://www.hc-sc.gc.ca/hpfb-dgpsa/  
tpd-dpt/zyprexa\\_hpc\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/zyprexa_hpc_e.html)

Research by Brodaty 2005 & Kryszhanovskaya 2006  
Slide from Dr. David Gardner, Pharmacologist, Dalhousie

# Background: Controversy

Atypicals: Increased risk of death

Schneider et al.<sup>a</sup>

- Meta-analysis, 15 trials (9 unpublished)
  - Death rate: 3.5% atypicals, 2.3% placebo (OR 1.54, 1.06-2.23)

a) Schneider LS et al., JAMA October 2005, 294:1934-43

# Atypical increase risk for death in elderly with dementia

FDA Warning: April 11, 2005

Use: behavioral symptoms in elderly with dementia

Aripiprazole  
Olanzapine  
Quetiapine  
Risperidone  
*Clozapine*  
*Ziprasidone*

- 17 RCTs
- n=5106
- placebo
- ~10 week

Rate of death in RCTs:  
1.6-1.7 x placebo

Atypical: 4.5%  
Placebo: 2.6%

All antipsychotics?

# Background: Controversy

Warnings from FDA (April 2005)\*:

- Atypical antipsychotics nearly double risk of death compared to placebo
- Also in Europe

**\*Warnings not extended to conventionals**

# Background: Controversy

- Health Canada Black Box Warning\*:
  - Risperidone (October 2002)- Increased risk of stroke in older pts treated for BPSD
- Health Canada Black Box Warning \*
  - All atypicals (June 2005) - Use of atypicals in elderly pts with dementia is associated with increased risk of death (risperidone, quetiapine, olanzapine)
  - Death- Cardiac events or infections

**\*Warnings not extended to conventionals**

# So...what about conventional antipsychotics?

1990 Meta-analysis<sup>a</sup>: 33 studies of conventionals:

- Efficacy > placebo
- **18% benefit over placebo (small effect size)**
  - Helps hallucinations, co-operation during care
  - Side effects found in > 80% (EPS, TD, anticholinergic sedation)
- 6 studies (Thioridazine), 5 studies (Haloperidone) compared with another neuroleptic: no differences between drugs

2006 Review<sup>b</sup>: **Conventionals not effective, some harm**

a) Schneider L et al. JAGS 1990; 38 (5): 553-63 b) Franco KN et al. J Am Med Dir Assoc 2006 Mar; 7 (3): 201-2

# So....what about conventional antipsychotics?

## Cochrane Review- Haloperidol<sup>a</sup>

### 5 RCT's

- Lower aggression, higher adverse events vs. placebo
- Conclusions:
  - Little evidence to support use of Haldol for other manifestations of BPSD including agitation in dementia except for aggression
  - Haldol should not be used routinely in dementia for BPSD

a) Cochrane Database, 2002, Loneragan E et al, ab002852

# Conventionals vs. Atypicals

Antipsychotics in Dementia (Gill et al.)<sup>a</sup>:

- **Ischemic stroke:** 1.6% atypical; 1.5% conventional (HR 1.01, 0.81- 1.26) ns
- **No difference in stroke risk between atypicals/ conventionals**

a) Gill S et al, BMJ 2005; 330:445-51

# Conventionals vs. Atypicals

## Conventionals significantly greater risk of death vs. atypicals

Wang et al<sup>a</sup>: Retrospective cohort study using pharmacy data bases (22,890: 1994-2003)

- Death within 180 days of treatment
- **37% higher dose-dependent risk of death**

Hollis et al<sup>b</sup>: 16634 patients -Veteran pharm. database 2003-04

- 2 yr follow-up., risk of death
- **Haloperidol highest risk: 2.26** compared to Olanzapine

Ray W. et al<sup>c</sup>: Retrospective cohort chart review compared atypicals to typicals (93,300: 1990 to 2005)

- Rate sudden cardiac death 2x with conventionals vs. controls, but similar with atypicals
- **Dose-dependent increase in both typicals and atypicals**

a)Wang P S et al. ,NEJM 2005; 353:22:2335-41

b)Hollis et al. Am J. Geri Psych 2008; 15:11

c) Rat W et al. N Eng J Med 2009; 360: 225-35.

# Background: Controversy

## Flaws in warnings on strokes and death:

- Warnings not extended to conventionals
- Conventional antipsychotics are at least as likely as atypicals to increase risk of death<sup>a</sup> or stroke<sup>b,c</sup>
- **Conventionals should NOT replace novels**

a) Wang PS et al, NEJM 2005; 353: 2335-41;

b) Gill S et al, BMJ 2005 225; 330:445-51;

c) Hermann N et al AJP 2004 161 (6):1113-5

Slide from presentation by Dr. Kathy Hickey and Susan Bowles

# Background: Warnings

- Increased risk of stroke confined to:
  - Subjects with vascular or mixed dementia, or with cerebrovascular risks
- Flaws in the evidence on strokes and mortality:
  - CVAEs not formally defined, or reliably measured
  - Inadequate control of influential variables
  - Temporal relationship missing
  - Based on pooled analyses, not peer-reviewed journals
  - Derived from unsophisticated statistical analysis

# Background: Warnings?

**“Warnings Without Weighing”<sup>a</sup>** -Nathan Hermann

- Best evidence “by far” for severe BPSD is with risperidone and olanzapine
- Conventionals NOT good substitutes
- Important to consider caregiver burden, severity of symptoms, and lack of alternatives
- Costs of BPSD<sup>b</sup>- \$30.00/month per 1 pt on NPI

a) Hermann N Bulletin of CAGP 2004; Vol 11, 1

b) Hermann N et al Int J Geri Psych 2006; Oct 2: 972-6.

# More Controversy: CATIE- AD Trial

## *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 12, 2006

VOL. 355 NO. 15

### Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H.,  
John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S.,  
J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D.,  
and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group\*

# CATIE-AD: Summary

## Methods:

- 42 sites, DBPC trial
- 421 outpatients with AD, psychosis and aggression or agitation
- Randomly assigned to:
  - Olanzapine (mean dose 5.5 mg/d)
  - Quetiapine (mean dose 56.5 mg/d)
  - Risperidone (mean dose 1.0 mg/d)
  - Placebo

# CATIE-AD: Summary

- Doses adjusted as needed
  - Followed to maximum 36 weeks
  - Discontinue after 2 weeks, then enter Phase II
- Main outcomes were:
  - 1) Time to discontinuation of treatment **for any reason** (side effect or ineffective) and
  - 2) Number of patients with at least minimal **improvement on the CGIC** scale at 12 weeks

# CATIE-AD: Authors' Conclusions

- Findings: No significant diff in groups, higher dropout rate in drug group from intolerability, lower rate of discontinuation due to ineffectiveness in active groups
- Conclusions: “Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression or agitation in patients with Alzheimer’s disease.”

# Main Findings vs. Conclusions

## Main Findings Appear to Be:

- 1) Median time to remain on treatment due to efficacy was significantly longer for 2 atypicals compared to placebo:
  - 26.7 weeks (risperidone) and 22.1 weeks (olanzapine), vs 9 weeks (placebo) ( $p < 0.002$ )
- 2) Risperidone (at dose used) seemed to be slightly favoured, considering balance of duration of use versus tolerability

# CATIE- AD: Our Conclusions



- Significantly more effective than placebo:
  - Risperidone slight advantage over olanzapine in effectiveness vs. side effects balance
  - Quetiapine not effective at 25% equivalency
- 5-7 point improvement on NPI with treatment
- Community- based sample, mild symptoms: not informative re. severe BPSD in NH settings
- Underpowered to assess stroke/death, ns difference from placebo

# Most Recent News: Antipsychotics

- Ballard et al.: Dementia Antipsychotic Withdrawal Trial (DART-AD)
- 165 AD patients from 2001-2004 randomized to continue antipsychotic (4 typicals, risperidone) x12 months or change to placebo, F/U at 12 & 24 months
  - 12 months- 70% survival with treatment vs 77% in placebo group; **24 months- 46% survival with treatment vs. 71 % with placebo**

Ref: Ballard C et al. Lancet Neurol. 2009 Jan 8

# Key Learning Objectives

1. Nonpharmacological strategies 1<sup>st</sup> line
2. Evidence for and “controversy” over atypical antipsychotic use  
3. Medication alternatives
4. Case
5. Balancing indications and risks

# Most Recent News: Alternatives for BPSD

- AchEI's
- Memantine
- Citalopram
- Aripiprazole
  
- Potential alternatives
- Not well-studied in more severe populations

# Recent News: Cognitive Enhancers and BPSD

- AchEI's
  - Pivotal trials RCT's show improvements esp. in:
    - Hallucinations, apathy, anxiety, aberrant motor behaviour
  - Negative RCT's
    - Donepezil (Howard, NEJM 2007, 12 wk trial)
    - Rivastigmine (Ballard, BMJ 2006, 26 wk trial)

Reference: Passmore, Rabheru, et al. "Alternatives to Atypical Antipsychotics for the Management of Dementia-Related Agitation" *Drug Aging* 2008; 25(5).

# Recent News: Cognitive Enhancers and BPSD

- Memantine
  - RCT's for cog. enhancement show modest benefit
  - May worsen agitation or halluc in some, esp LBD<sub>a</sub>
- Gauthier et al.<sup>b</sup>
  - Pooled analysis of 1829 pts with mod to severe AD memantine vs. placebo
  - At 12 & 24 weeks, memantine improved NPI scores and items: delusions, hallucinations, agitation/aggression, irritability/ lability

a) Passmore, Rabheru, et al. "Alternatives to Atypical Antipsychotics for the Management of Dementia-Related Agitation" Drug Aging 2008; 25(5); b) Gauthier S et al, Int J Geriatr Psychiatry 2007

# Recent News: Citalopram vs. Risp. in BPSD

- 12 wk RCT, hospitalized due to BPSD
- N=103 patients
- 44% overall completers
- Mean dose:
  - Risperidone: 1.25 mg/d
  - Citalopram: 30 mg/d

Ref: "A double-blind comparison of citalopram and risperidone for the treatment of BPSD associated with dementia" Pollock et al. Am J. Geri Psych. Nov 2007

# Citalopram vs. Risp. in BPSD

**TABLE 1. Baseline Participant Characteristics**

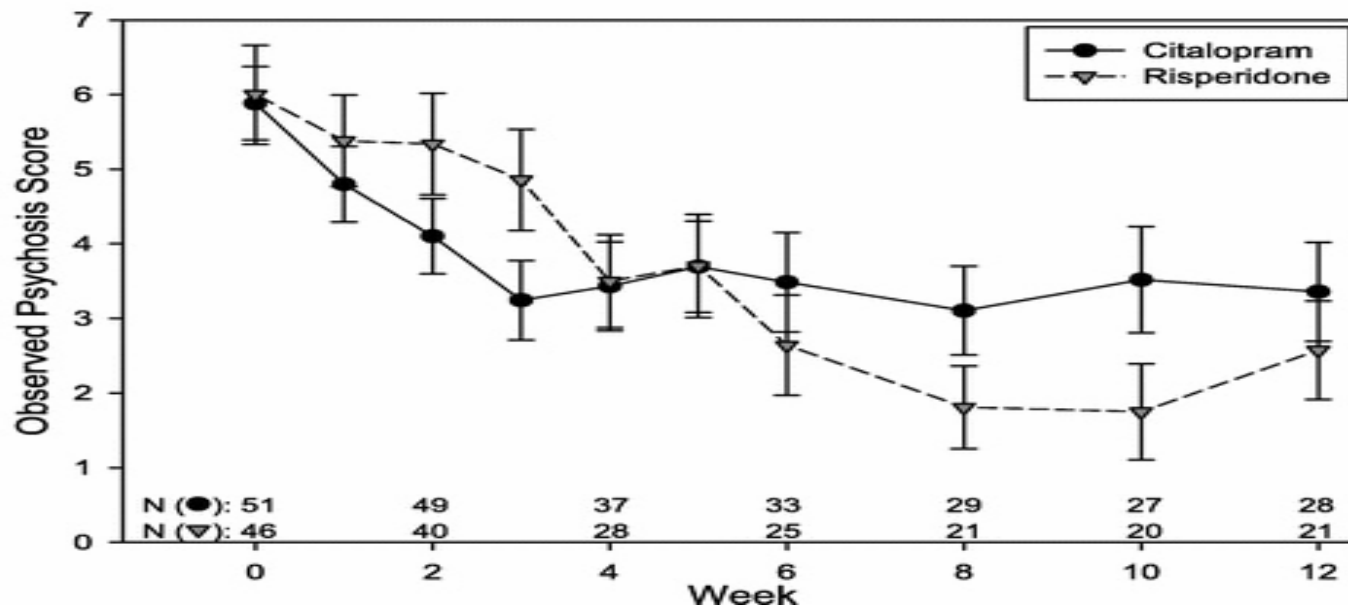
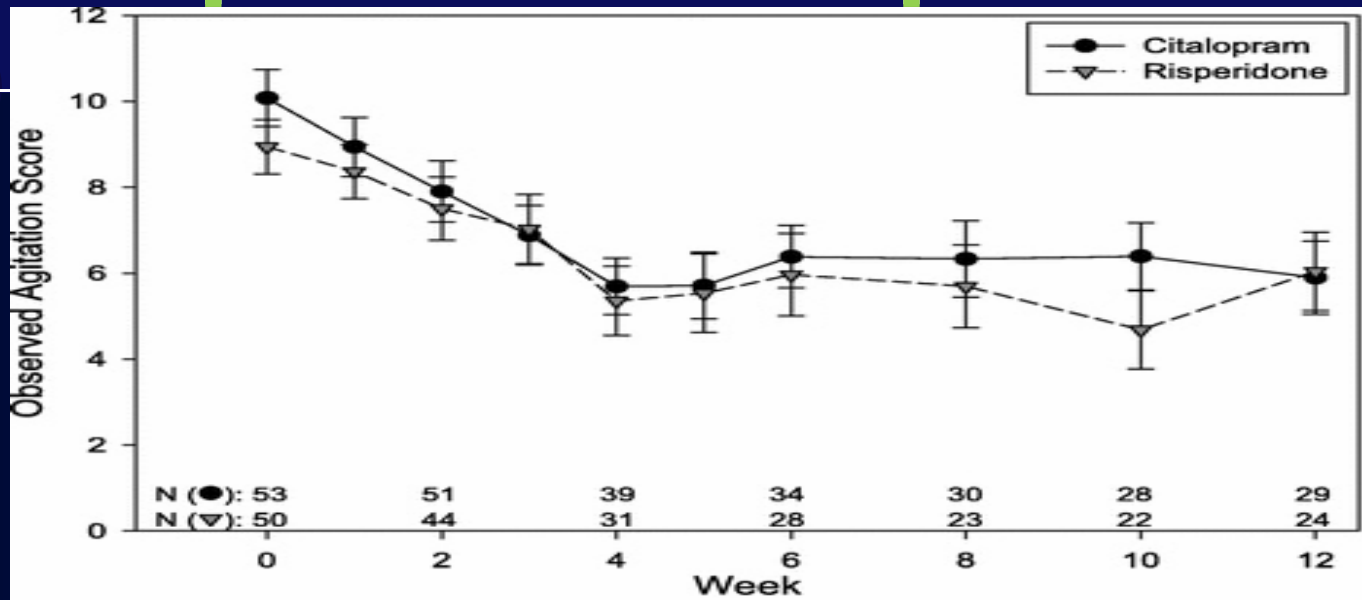
Characteristic	Citalopram	Risperidone
N	53	50
Age (years)	82.0 (7.3)	81.5 (9.2)
Female, % (N) <sup>a</sup>	47.2 (25)	76.0 (38)
White, % (N)	81.1 (43)	82.0 (41)
Cumulative Illness Rating Scale-Geriatrics score	9.6 (3.0)	9.5 (4.5)
Mini Mental State Examination score	9.8 (8.5)	11.9 (8.4)
Median	7	11.5
Interquartile range	2-18	4.5-19.5
Severe Impairment Battery	63.9 (35.5)	71.4 (29.3)
Cornell Scale for Depression in Dementia	10.7 (11.8)	13.3 (16.2)
Delusions or hallucinations, % (N)	35.8 (19)	40.0 (20)
NBRS total score <sup>b</sup>	60.3 (16.8)	53.6 (15.6)
NBRS agitation score (items 8, 11, and 14)	10.1 (4.8)	8.9 (4.5)
NBRS psychosis score (items 16, 18, and 20)	5.9 (3.5)	6.0 (4.5)
NPI total score	40.8 (23.1)	34.4 (21.1)
UKU total score	13.7 (5.2)	12.1 (4.1)

*Notes:* Data are means (SD) unless noted.

<sup>a</sup>Significant difference between treatment groups:  $\chi^2 = 9.00$ ,  $df = 1$ ,  $p = 0.003$ .

<sup>b</sup>Significant difference between treatment groups:  $t = 2.04$ ,  $df = 94$ ,  $p = 0.044$ .

# Citalopram vs. Risp. in BPSD



# Recent News: Citalopram vs. Risperidone for BPSD

- Conclusions:
  - Equivalent efficacy in agitation AND psychosis
  - HOWEVER: No placebo grp, high dropouts limit interpretation
  - Risperidone had more side effects (somnolence) but not more EPS compared to citalopram

Reference: Pollock et al. Am J. Geri Psych. Nov 2007

(Slide from Dr. Peter Chan)

# Recent News: Aripiprazole for BPSD

- Psychosis in AD (2<sup>nd</sup>ary aggression, agitation)
  - DBPCT, n= 131 vs. 125 placebo
  - 10 weeks, mean dose 9 mg/d: starting at 2 mg -> increased up to 5, 10 or 15 mg prn)
- **Results:** No diff in psychosis or primary measures (NPI psychosis, CGI) BUT improvements on NPI total, BPRS, Cohen Mansfield and Cornell Depression; SE: somnolence
- **Conclusions:** Improved agitation, anxiety & mood but not psychosis, well-tolerated

Reference: Streim J et al. Am J Geriatr Psych 16;7, July 2008

# Part III: Case

# Mrs. B. Ware

- 84 year old widow living at home
- Hearing voices threatening to damage her home, drown her in boiling oil
- She attributes voices to new neighbours
- Started as background noise in her bedroom 6 months ago
- Now (X 6 weeks) throughout the house, louder, and she is responding

# Mrs. B. Ware

- No previous psych history
- CVA 3 yr ago, 3 probable TIAs since; mild HTN; 3 sibs with Alzheimer's
- **Meds:** ECASA, Colace
  - didn't tolerate Plavix, HCTZ
- **Cog testing:** visuospatial deficits, mild perseveration, moderate STM impairment
- **CT Head:** severe generalized atrophy and extensive microangiopathic changes

# Q's for Discussion

- What would be your first choice for medication intervention?
- To what extent does her cardiovascular history factor into your decision?
- How would you disclose the potential risks to the patient / decision-maker?

# What if.....?

- ....she was later on in her illness, living in a facility, and had recently become very resistive to getting dressed, bathing, & other personal care?
- ....the voices were a sudden onset and you suspected a delirium?
- How might these scenarios change your approach to atypical antipsychotic usage?

# Summary

- BPSD prevalent
- Major cause of caregiver burden
- Some will benefit from atypicals
- Range of situations, risks and potential benefits to consider
- Difficult to predict who will benefit and who will suffer side effects

**What to do?**

# Conclusions: What To Do?

## “Warnings Without Weighing”<sup>a</sup>

-Nathan Hermann

- Best evidence “by far” for severe BPSD is with risperidone and olanzapine
- Important to consider caregiver burden, severity of symptoms, and lack of alternatives
- Costs of BPSD<sub>b</sub>- \$30.00/month per 1 pt on NPI

a)Hermann N Bulletin of CAGP, Vol 11, 1 (2004);

b) Hermann N et al Int J Geri Psych 2006; Oct 2: 972-6.

# Warnings With Weighing

- Modest Efficacy
- Balance of Risk: Benefit Ratio
  - Numbers Needed to Treat (NNT) to benefit = 6-10
  - Numbers Needed to Harm (NNH) = 45-111 (for stroke); 52 (for death)
  - 1 patient death for every 9-25 who benefit (Schnieder, JAMA, 2005)

# Warnings With Weighing

- Balance of Risk: Benefit Ratio
- Compare to Other Medications\*:
  - NNT vs. NNH worse for bisphosphonates in preventing hip fractures, warfarin in atrial fibrillation, anticoagulants in preventing stroke or treating MIs
- Palliative care model of dementia. Consider:
  - Severity of disease and symptoms
  - Cost of not treating
  - Impact on caregivers

\* Verbal discussion with Susan Bowles, Pharmacist, Geriatric Medicine Dalhousie University

# What to do?

## Suggestions:

- Consider other options 1<sup>st</sup>: nonpharm, ?other class
- Continue to use atypical antipsychotic medications for carefully targeted symptoms in severe BPSD (psychosis and aggression in dementia, severe distress/ harm to self or others)
- Consider the risks:
  - Document baseline EPS, CV & metabolic risks<sub>a</sub>
  - Caution in Lewy Body Disease & Dementia Secondary to Parkinson's Disease
- Be vigilant re: informed consent & documentation
- Monitor target symptom outcomes
- Trial of discontinuation after 3 month period of stability<sub>b</sub>

a) Hermann N, Lanctot, K. Can J Psy, 2007 52(10) 630. Ballard, CG et al; J Clin Psychiatry 2004 65:114-119

# Key Learning Objectives

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Q & A

## Case 2: Sister

- 87 year old nun, worked as OR nurse
- Primary progressive aphasia Dx 2003
- Colon ca with resection – 2004
- TAH - endometrial adeno Ca - 2006
- Now generalized dementia

# Sister

- Lives in LTC setting
- Meticulously straightens others' belongings
- Wanders into others' rooms, some hoarding
- Worst after nap, 4-8pm, sleeps well at night
- Physically aggressive to 1 nun in particular, whom she pushes and beats with her own cane

# Sister

- Staff utilizing distractions for high risk time periods
- Galantamine ER 8mg added Feb 2008 -  
> behaviours progressed
- Increased to 16mg July 08 – behaviours worsened

# Q's for Discussion

- What factors might be influencing her behaviour? Do you use a particular model to consider these?
- What pharmacological options would you be considering at this time?
- How would you follow up? Are there particular tools that you use?

## Case 3: Mr. D

- 93 year old married man living in LTC X 2 years
- Dx: Mixed Dementia – 2005
- Moved to secure unit 1 month ago
- Staff there report steadily increasing suspiciousness since he arrived
  - Believes family members are stealing money from his bank account
  - Suspects staff are “colluding” with family by removing bank books from his room

# Mr. D

- He sleeps poorly and has been entering other residents' rooms during the night
- Recently he has begun to refuse assistance with bathing and staff feel he can be threatening when approached for care
- House physician added memantine to his cholinesterase inhibitor 2 weeks ago. He has continued to worsen

# Mr. D

- Staff voice fears that he will be the target of physical aggression because he is intrusive. They want him removed to hospital “for his own safety”
- Chart review shows UTI’s X 3 in past year - all treated with ABx
- His son, a chemist, has been researching medications online. He has issued a dictum to staff that they never give his father any of the neuroleptics

# Q's for Discussion

- Does the possibility of delirium make you more comfortable with antipsychotics?
- How do you approach a dictum of no-antipsychotic use in a situation where safety issues are significant?
- How do you deal with the staff's insistence that he be sent to hospital?