Managing Behavioral and Psychological Symptoms of Dementia (BPSD) in the Era of Boxed Warnings

American Association for Geriatric Psychiatry (AAGP)
Thursday, July 1, 2021, 6:00 pm-7:00 pm
Pallavi Joshi, DO, MA (Chair)
Rajesh R. Tampi, MD, MS, DFAPA, DFAAGP
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1

Objectives

Objective One:	To describe the epidemiology of BPSD
Objective Two:	To elucidate the neurobiology and assessment of individuals with BPSD
Objective Three:	To discuss the management of individuals with BPSD
Objective Four:	To elaborate on the controversies in the treatment of individuals BPSD

2

Disclosures

- There are no FDA approved medications for the treatment of behavioral and psychological symptoms of dementia and hence all medications discussed today are “Off Label” in their use
- We have no conflicts of interest to disclose for this presentation

3

Pallavi Joshi, DO, MA

4

Behavioral and Psychological Symptoms of Dementia

- These are a heterogeneous range of psychological reactions, psychiatric symptoms and behaviors that may be unsafe, disruptive and impair the care of the patient in a given environment

Barucha et al, CNS Spectrum, 2002

5

Prevalence

- **Community**
  - ➢ 65% have at least 1 disruptive behavior
  - ➢ 40% have at least 3 disruptive behaviors
- **Nursing Homes**
  - ➢ 90% have at least 1 disruptive behaviors
  - ➢ 45% have at least 4 disruptive behaviors
- These behaviors are often chronic with different symptoms emerging as the illness progresses.
- They also fluctuate with Psychomotor Agitation being the most persistent.

Tampi et al, Clinical Geriatrics, 2011

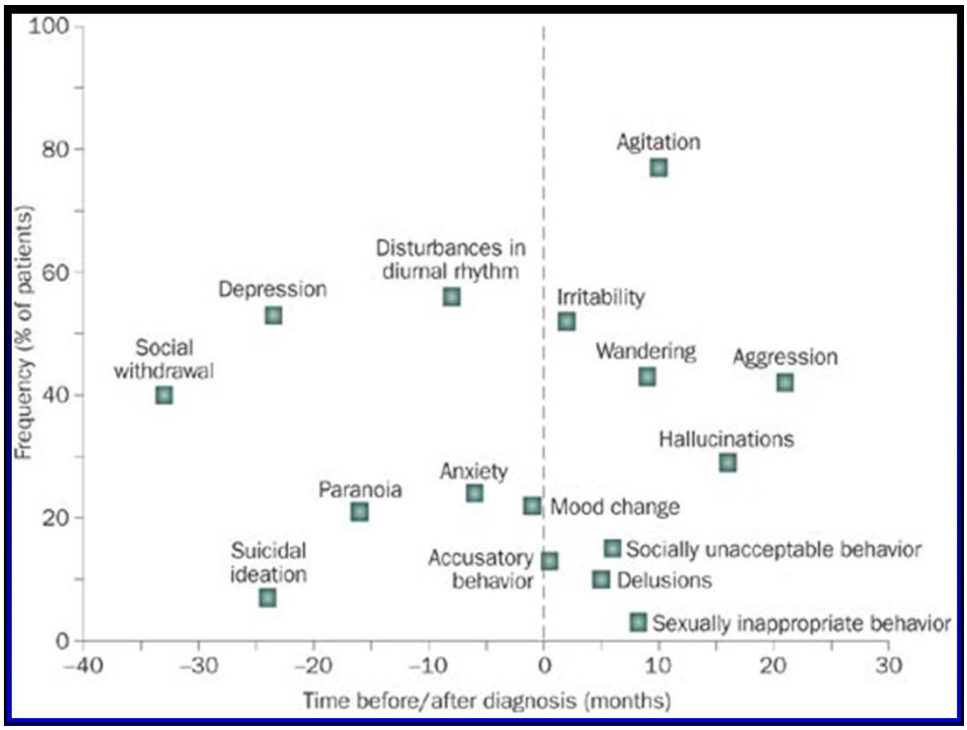
6

Classification

Phenomenological	Etiologic
1. **Affective:** depression, anxiety, agitation, apathy, mania	1. **Primary:** not due to any known etiology
2. **Psychotic:** delusions, hallucinations	2. **Secondary**: due to an underlying medical or psychiatric disorder
3. **Sleep-Wake cycle disturbance**	
4. **Behavioral:** agitation, aggression, verbal disruption, impulsivity	

Tampi et al, Clinical Geriatrics, 2011

7



8

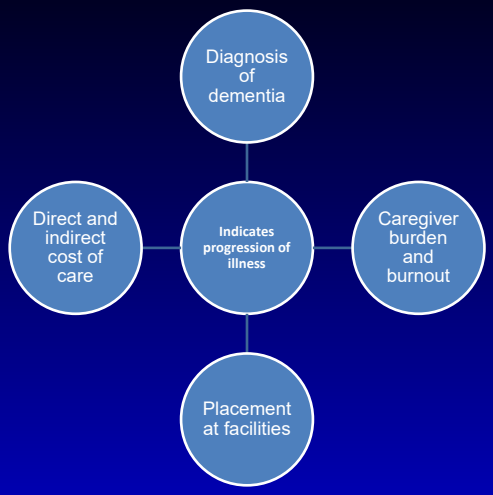
Common BPSD

Type of behaviors	Prevalence
Anxiety	21% to 60%
Apathy	48% to 92%
Delusions	16% to 70%
Depression	30% to 50%
Disinhibition/Impulsivity	30% to 35%
Hallucinations	4% to 76%
Inappropriate sexual behaviors	7% to 25%
Mood lability	30% to 40%
Sleep disturbance	20% to 25%
Stereotyped behaviors	12% to 84%
Weight loss	15% to 20%

Tampi et al, Clinical Geriatrics, 2011

9

Impact of BPSD



Tampi et al, Clinical Geriatrics, 2011

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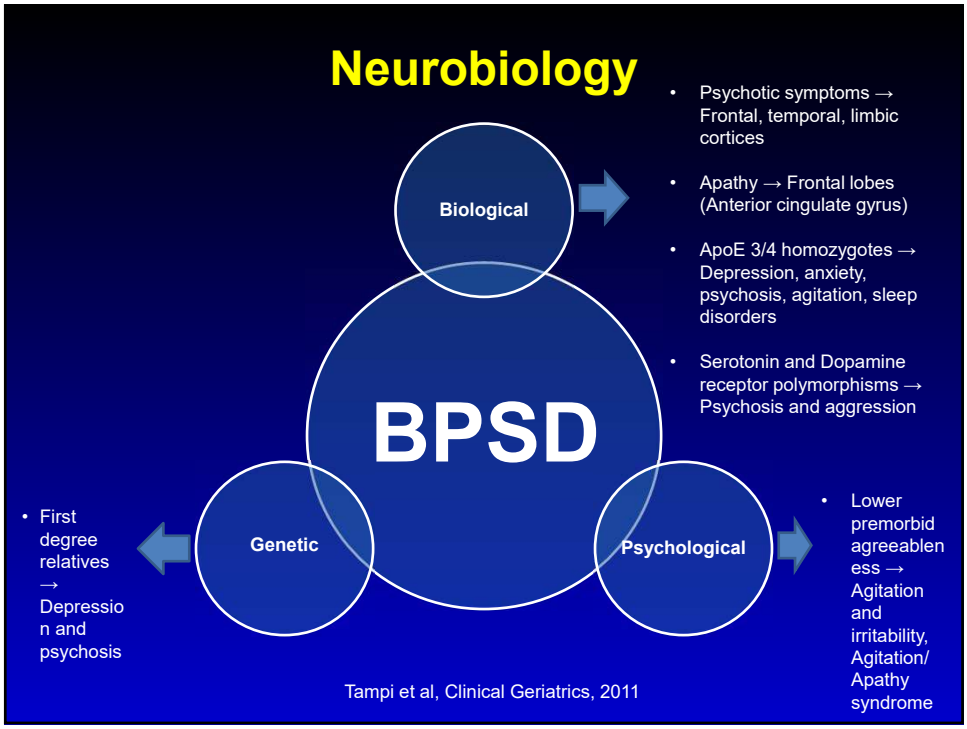
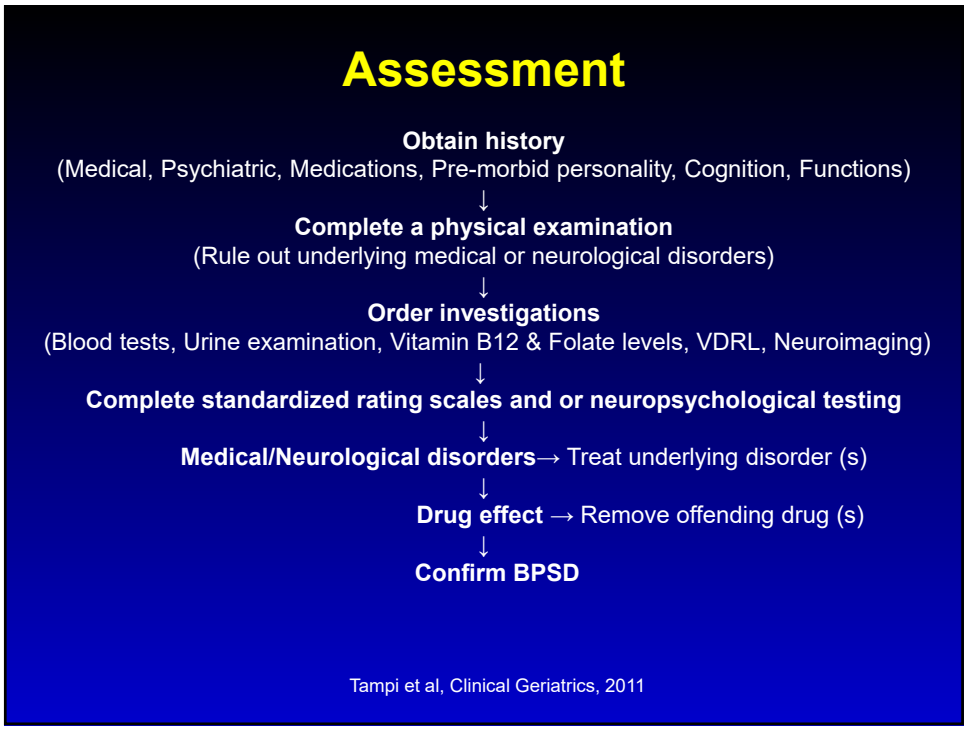

Neurobiology
Biological
BPSD
Genetic
Psychological
• Psychotic symptoms → Frontal, temporal, limbic cortices
• Apathy → Frontal lobes (Anterior cingulate gyrus)
• ApoE 3/4 homozygotes → Depression, anxiety, psychosis, agitation, sleep disorders
• Serotonin and Dopamine receptor polymorphisms → Psychosis and aggression
• First degree relatives → Depression and psychosis
• Lower premorbid agreeableness → Agitation and irritability, Agitation/ Apathy syndrome
Tampi et al, Clinical Geriatrics, 2011

11

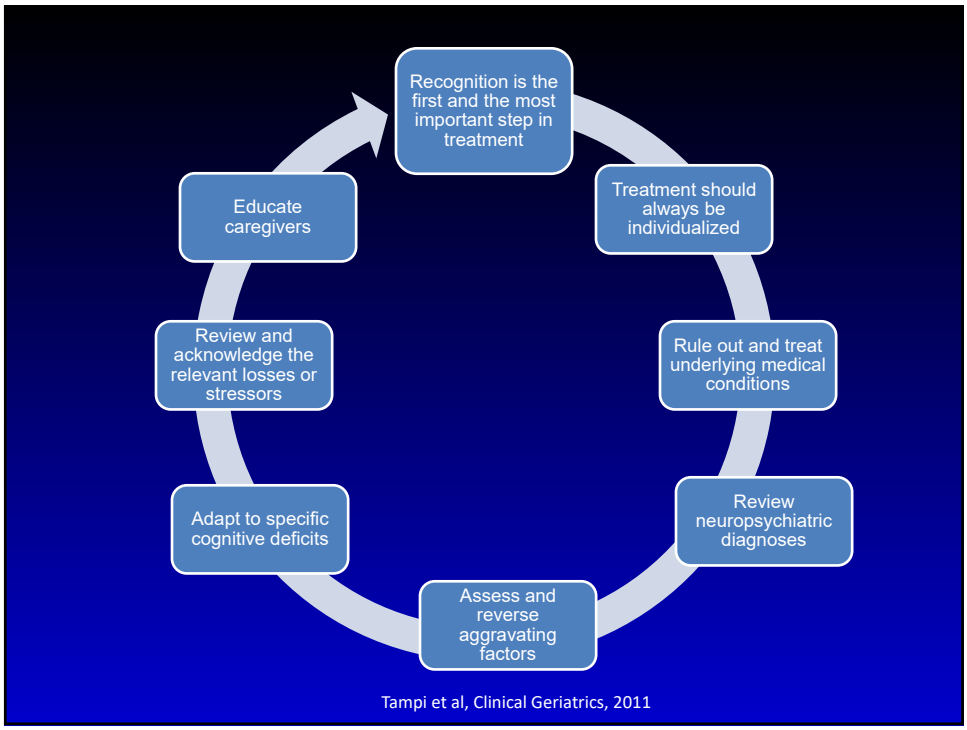

Assessment
Obtain history
(Medical, Psychiatric, Medications, Pre-morbid personality, Cognition, Functions)
↓
Complete a physical examination
(Rule out underlying medical or neurological disorders)
↓
Order investigations
(Blood tests, Urine examination, Vitamin B12 & Folate levels, VDRL, Neuroimaging)
↓
Complete standardized rating scales and or neuropsychological testing
↓
Medical/Neurological disorders→ Treat underlying disorder (s)
↓
Drug effect → Remove offending drug (s)
↓
Confirm BPSD
Tampi et al, Clinical Geriatrics, 2011

12

Management of Individuals with Behavioral and Psychological Symptoms of Dementia

Rajesh R. Tampi, MD, MS, DFAPA, DFAAGP

13



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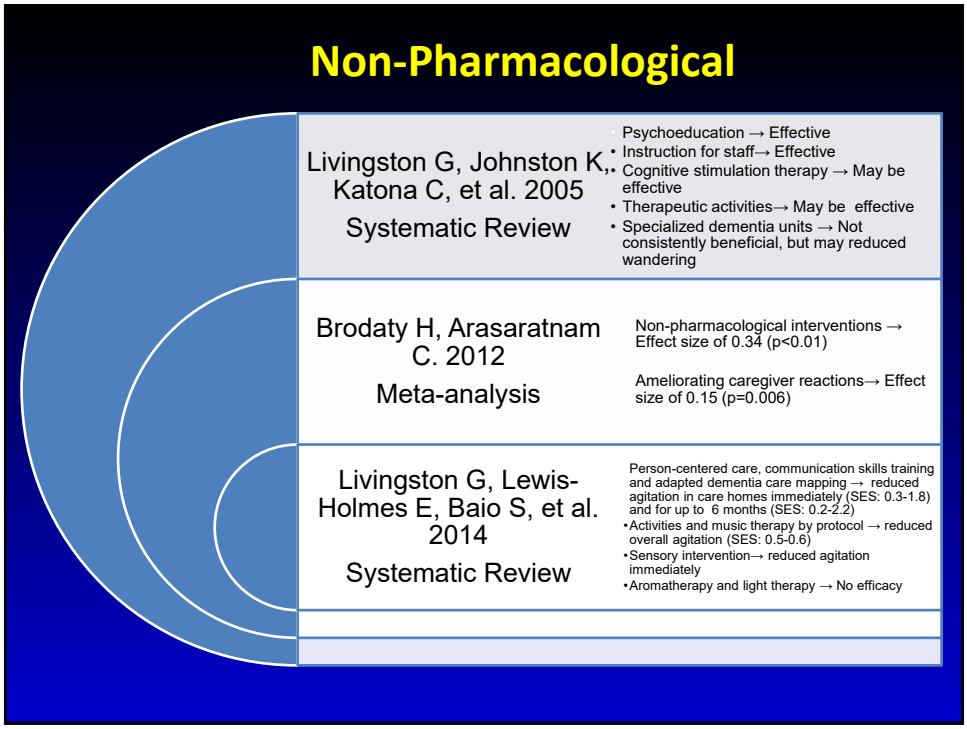
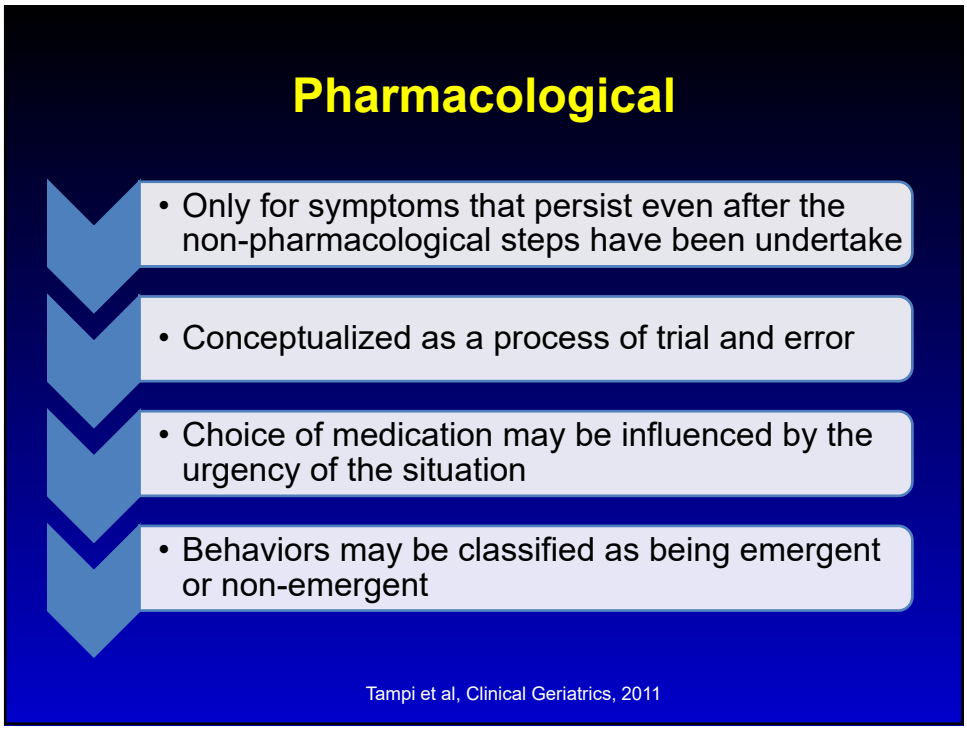
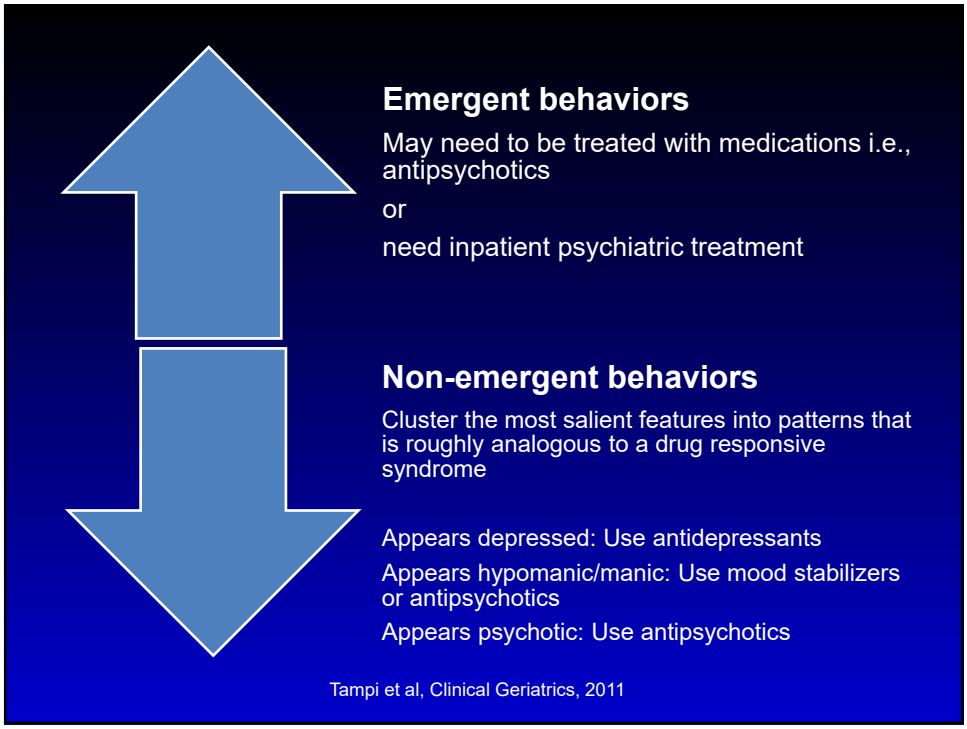

Non-Pharmacological
Livingston G, Johnston K,. Katona C, et al. 2005
Systematic Review
• Psychoeducation → Effective
• Instruction for staff→ Effective
• Cognitive stimulation therapy → May be effective
• Therapeutic activities→ May be effective
• Specialized dementia units → Not consistently beneficial, but may reduced wandering
Brodaty H, Arasaratnam C. 2012
Meta-analysis
Non-pharmacological interventions → Effect size of 0.34 (p<0.01)
Ameliorating caregiver reactions→ Effect size of 0.15 (p=0.006)
Livingston G, Lewis-Holmes E, Baio S, et al. 2014
Systematic Review
Person-centered care, communication skills training and adapted dementia care mapping → reduced agitation in care homes immediately (SES: 0.3-1.8) and for up to 6 months (SES: 0.2-2.2)
• Activities and music therapy by protocol → reduced overall agitation (SES: 0.5-0.6)
• Sensory intervention→ reduced agitation immediately
• Aromatherapy and light therapy → No efficacy

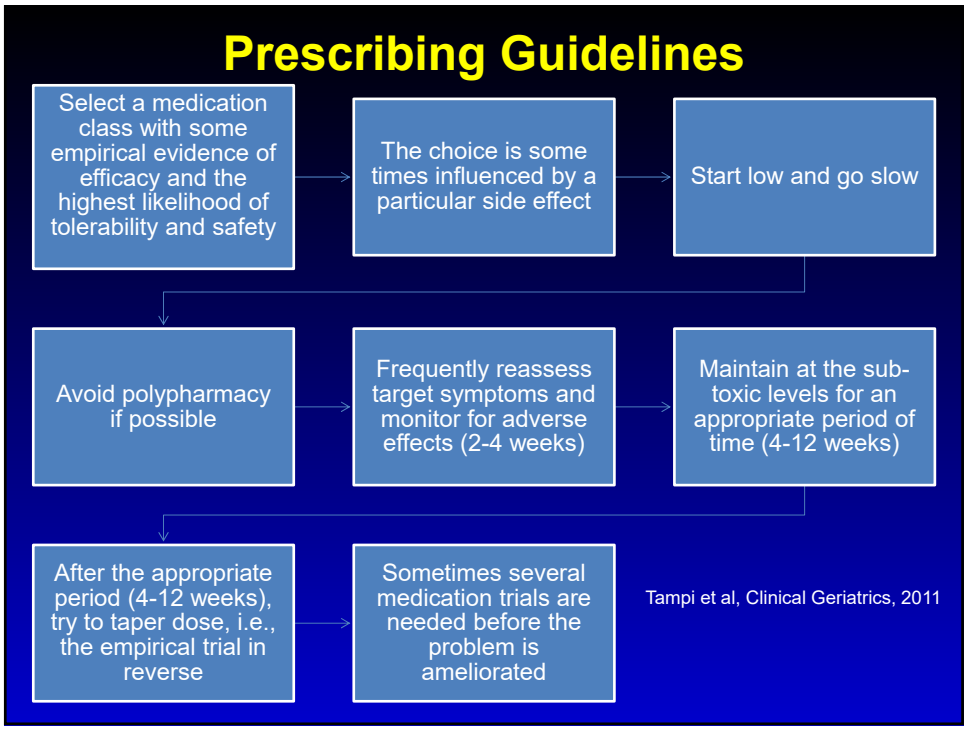
15


Pharmacological
• Only for symptoms that persist even after the non-pharmacological steps have been undertake
• Conceptualized as a process of trial and error
• Choice of medication may be influenced by the urgency of the situation
• Behaviors may be classified as being emergent or non-emergent
Tampi et al, Clinical Geriatrics, 2011

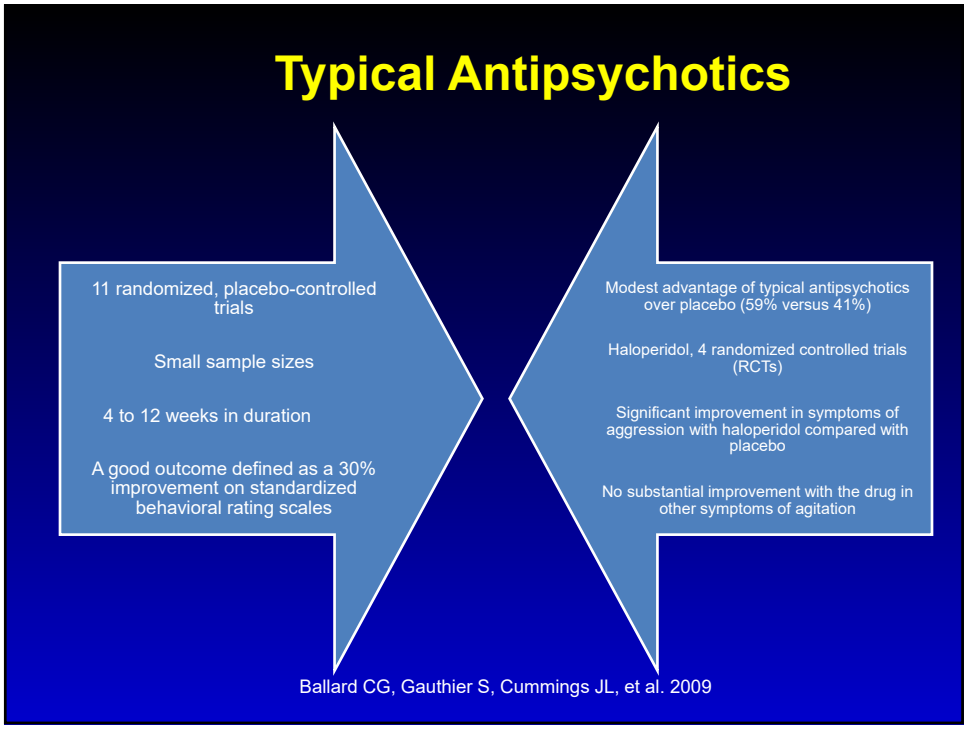
16


Emergent behaviors
May need to be treated with medications i.e., antipsychotics
or
need inpatient psychiatric treatment
Non-emergent behaviors
Cluster the most salient features into patterns that is roughly analogous to a drug responsive syndrome
Appears depressed: Use antidepressants
Appears hypomanic/manic: Use mood stabilizers or antipsychotics
Appears psychotic: Use antipsychotics
Tampi et al, Clinical Geriatrics, 2011

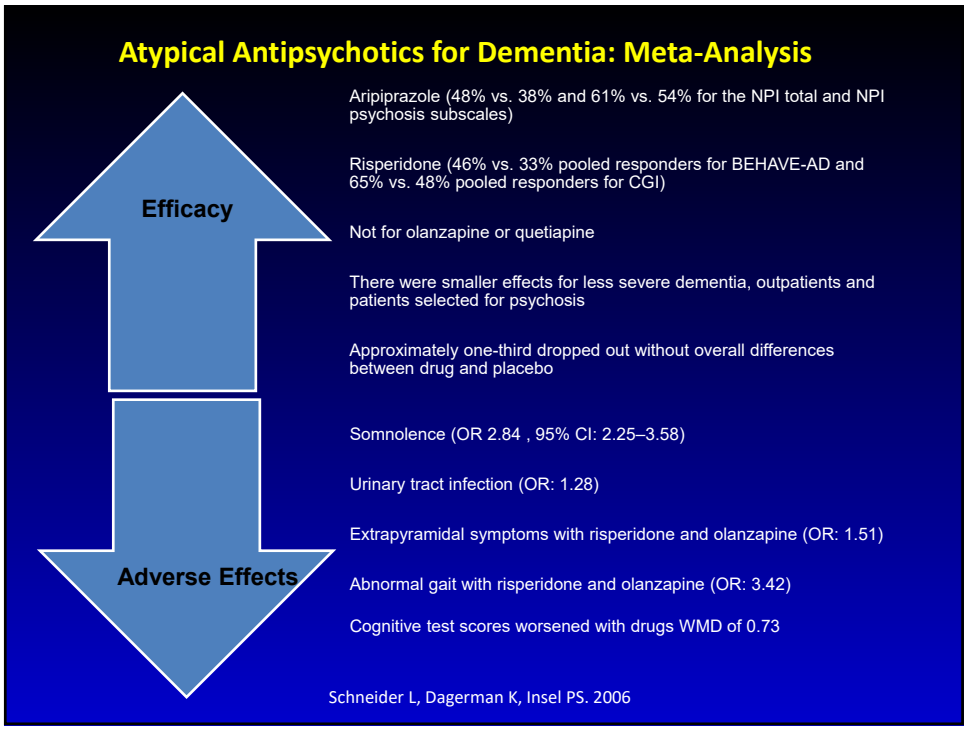
17


Prescribing Guidelines
Select a medication class with some empirical evidence of efficacy and the highest likelihood of tolerability and safety
The choice is some times influenced by a particular side effect
Start low and go slow
Avoid polypharmacy if possible
Frequently reassess target symptoms and monitor for adverse effects (2-4 weeks)
Maintain at the sub-toxic levels for an appropriate period of time (4-12 weeks)
After the appropriate period (4-12 weeks), try to taper dose, i.e., the empirical trial in reverse
Sometimes several medication trials are needed before the problem is ameliorated
Tampi et al, Clinical Geriatrics, 2011

18


Typical Antipsychotics
11 randomized, placebo-controlled trials
Small sample sizes
4 to 12 weeks in duration
A good outcome defined as a 30% improvement on standardized behavioral rating scales
Modest advantage of typical antipsychotics over placebo (59% versus 41%)
Haloperidol, 4 randomized controlled trials (RCTs)
Significant improvement in symptoms of aggression with haloperidol compared with placebo
No substantial improvement with the drug in other symptoms of agitation
Ballard CG, Gauthier S, Cummings JL, et al. 2009

19


Atypical Antipsychotics for Dementia: Meta-Analysis
Efficacy
Adverse Effects
Aripiprazole (48% vs. 38% and 61% vs. 54% for the NPI total and NPI psychosis subscales)
Risperidone (46% vs. 33% pooled responders for BEHAVE-AD and 65% vs. 48% pooled responders for CGI)
Not for olanzapine or quetiapine
There were smaller effects for less severe dementia, outpatients and patients selected for psychosis
Approximately one-third dropped out without overall differences between drug and placebo
Somnolence (OR 2.84 , 95% CI: 2.25–3.58)
Urinary tract infection (OR: 1.28)
Extrapyramidal symptoms with risperidone and olanzapine (OR: 1.51)
Abnormal gait with risperidone and olanzapine (OR: 3.42)
Cognitive test scores worsened with drugs WMD of 0.73
Schneider L, Dagerman K, Insel PS. 2006

20

Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease.

42-site, double-blind, placebo-controlled trial for 36 weeks

421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation

Randomly assigned to receive:

Olanzapine (mean dose, 5.5 mg per day)

Quetiapine (mean dose, 56.5 mg per day)

Risperidone (mean dose, 1.0 mg per day)

Placebo

- Time to the discontinuation of treatment for any reason no different for drugs compared to placebo (P=0.52)
- The median time to the discontinuation of treatment due to lack of efficacy placebo =quetiapine; risperidone and olanzapine >placebo
- 3-5 times more individuals discontinued the drugs due to side-effects when compared to placebo (P=0.009)
- Improvement on the CGIC scale no different between drugs and placebo (P=0.22)

The main outcomes were:

1. The time from initial treatment to the discontinuation of treatment for any reason.
2. The number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

- No significant differences between antipsychotics and placebo on functioning, care needs, or quality of life
- Cognitive function declined more in patients receiving antipsychotics on multiple cognitive measures
- Treatment groups had significantly higher costs
- There were no cerebrovascular events or deaths that could be attributable to the drugs

CATIE: Dementia study

21

Brexpiprazole

- Two 12-week, randomized, double-blind, placebo-controlled, parallel-arm studies

Study 1	Study 2
• 81 sites in 7 countries	• 62 sites in 9 countries
• 433 randomized	• 270 randomized
• Brexpiprazole 2 mg/day, brexpiprazole 1 mg/day, or placebo (1:1:1) for 12 weeks	• Brexpiprazole 0.5-2 mg/day or placebo (1:1) for 12 weeks
• Cohen-Mansfield Agitation Inventory (CMAI) and Clinical Global Impression - Severity of illness (CGI-S)	• Cohen-Mansfield Agitation Inventory (CMAI) and Clinical Global Impression - Severity of illness (CGI-S)
• On CMAI, at 12 weeks ➢ Brexpiperazole 2mg/day > placebo (P=0.04) ➢ Brexpiperazole 1 mg/day = placebo (P=0.90)	• On CMAI, at 12 weeks ➢ Brexipiperazole 0.5-2 mg/day = placebo (P= 0.15) ➢ Maximum brexpiprazole dose of 2 mg/day > placebo (P=0.012)
• On CGI-S ➢ Brexpiperazole 2mg/day = placebo (P=0.16)	• On CGI-S ➢ Brexpiprazole 0.5-2 mg/day > placebo (P=0.016)
• Treatment-emergent adverse events (TEAEs) with incidence ≥5% among patients receiving brexpiprazole 2 mg/day vs placebo: ➢ Headache (9.3% vs 8.1%) ➢ Insomnia (5.7% vs 4.4%) ➢ Dizziness (5.7% vs 3.0%) ➢ Urinary tract infection (5.0% vs 1.5%)	• Treatment-emergent adverse events (TEAEs) with incidence ≥5% among patients receiving brexpiprazole 0.5-2 mg/day vs placebo: ➢ Headache (7.6% vs 12.4%) ➢ Somnolence (6.1% vs 3.6%)

Grossberg GT, Kohegyi E, Mergel V, et al. Am J Geriatr Psychiatry. 2020 Apr;28(4):383-400.

22

Pimavanserin

PUBLICATION 1	PUBLICATION 2
• 181 participants, ≥50 years, Nursing homes • Pimavanserin 34 mg/day vs placebo, 12 weeks • Jadad score: 4/5 • **Primary outcome**: • **At week 6:** ➢ **NPI-NH psychosis score:** Pimavanserin (mean change was -3.76 points) vs placebo (mean difference -1.84, P=0.045) without negative effects on cognition or motor function ➢ **Response (≥ 30% improvement):** Pimavanserin (55%) vs placebo (37%) ➢ **NPI-NH<12 subgroup:** Pimavanserin (-0.58) vs placebo (-0.16), Cohen's d =–0.77, P=0.694 • **At week 12:** ➢ Pimavanserin vs placebo [treatment difference -0.51, P=0.561]. • **Adverse events** (pimavanserin vs placebo) ➢ Agitation (21% vs 14%) ➢ Aggression (10% vs 4%) ➢ Falls (21% vs 21%) ➢ Urinary tract infection (20% vs 25%) ➢ Peripheral edema (8% vs 2%) ➢ Weight loss (-0.7 kg vs -0.1 kg) ➢ QTc prolongation (9.4 ms vs -0.2 ms) ➢ Death (4 vs 4)	• **Primary outcome**: • **At week 6** ➢ NPI-NH psychosis score: Pimavanserin (-3.76) pimavanserin vs Placebo (-1.93) (Cohen's d =-0.32, P=0.045) ➢ NPI-NH scores>12: Pimavanserin (-10.15) vs placebo (–5.72) (Cohen's d effect size of -0.73, P= 0.011) ➢ In the more severe subgroup, pimavanserin was superior to placebo for treating both hallucinations (P=0.046) and delusions (P=0.034) ➢ 66.7% of those in the pimavanserin group improved to an NPI-NH psychosis score < 6 *vs* 32.0% of those in the placebo group (difference = 34.7%) • **At week 12** ➢ 45.5% of both pimavanserin and placebo-treated patients had an NPI-NH psychosis score<6 ➢ Proportion with a baseline NPI-NH psychosis score ≥12 achieving a response was significantly (P< 0.05) greater with pimavanserin vs placebo • Aggression: 14.3% in the severe psychosis subgroup vs 10.0% in overall population • Agitation: 17.9% in severe psychosis subgroup vs 21.1% in general population

Srinivasan S, et al. World J Psychiatry. 2020 Jul 19;10(7):162-174.

23

Cognitive Enhancers

Authors	Type of Study	Outcomes
Rodda J, Morgan S, Walker Z. 2009	Meta-analysis	• 14 studies were identified • 9 were of donepezil, 3 of galantamine and 2 of rivastigmine • Median study treatment length was 24 weeks • Four studies were specifically designed to assess behavioral outcomes • Three studies found statistically significant but modest (2.1 to 6.2), differences in the change of NPI total score between drug and placebo
Maidment ID, Fox CG, Boustani M, et al. 2008	Meta-analysis	• 6 randomized, parallel-group, double-blind studies • Five of the 6 studies identified had NPI outcome data • 868 patients were treated with memantine and 882 patients were treated with placebo • Patients on memantine improved by 1.99 on the NPI scale compared to the placebo group

24

Mood Stabilizers

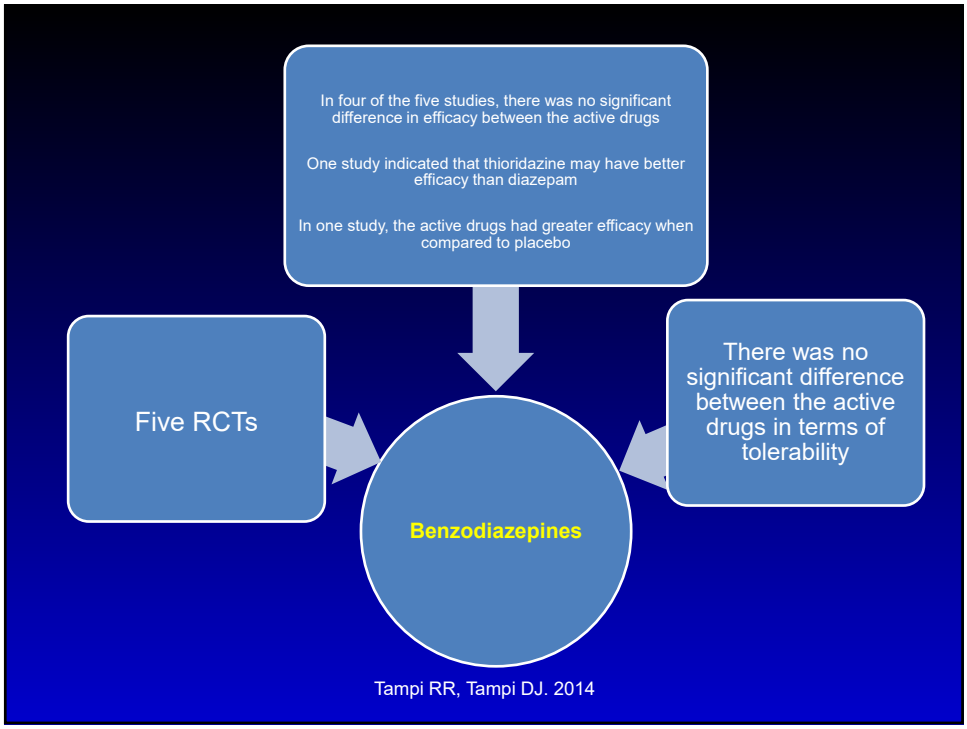
Authors	Outcomes	Bottom-line
Lonergan E, Luxenberg J. 2009	• Total of 3 RCTs • 2 were included in the meta-analysis	• Valproate preparations are ineffective in treating agitation among demented patients • Valproate therapy is associated with an unacceptable rate of adverse effects
Konovalov S, Muralee S, Tampi RR. 2008	• Total of seven RCTs • 2 for carbamazepine and 5 for valproate • 1 study showed statistically significant improvement • 5 studies showed no significant differences • 1 study showed statistically significant worsening • Majority of the studies reported significantly more frequent adverse effects in the medication group	• Although clearly beneficial in some patients, anticonvulsant mood stabilizers cannot be recommended for routine use in the treatment of BPSD at the present time
Kim Y, Wilkins KM, Tampi RR. 2008	• 11 case reports, 3 case series and 1 retrospective chart review; no controlled studies	• Well tolerated and effective treatment • Less well tolerated in patients with dementia with Lewy bodies

25

Antidepressants

Authors	Type of Study	Outcomes
Martinon-Torres G, Fioravanti M, Grimley EJ. 2004	Meta-analysis	• Two studies were included, comprising 104 participants with dementia • 16 and 6 weeks duration, trazodone from 50 to 300mg daily • Compared to placebo, no statistically significant benefit for behaviors, cognition or function • No difference between placebo and trazodone for adverse effects
Seitz DP, Adunuri N, Gill SS, et al. 2011	Meta-analysis	• 5 studies compared SSRIs to placebo • 2 studies were combined in a meta-analysis • In 2 studies sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo • No effect on trazodone compared to placebo and equal efficacy to haloperidol • Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics
Henry G, Williamson D, Tampi RR. 2011	Literature review	• 19 placebo controlled trials • 11 trials, 8 using a selective serotonin reuptake inhibitor (SSRI) compound and 3 using trazodone showed benefit in the treatment of BPSD • The antidepressant drug was well tolerated in at least 14 of the 19 trials

26



27

Analgesics

Tampi RR, Hassell C, Joshi P, Tampi DJ. Analgesics in the management of behavioral and psychological symptoms of dementia: a perspective review. Drugs Context. 2017 Nov 22;6:212508. doi: 10.7573/dic.212508.	• 3 unique RCTs • 6 published papers • All 3 RCTs identified some benefit for the use of analgesics in reducing BPSD • The analgesics appeared to be well tolerated in the included studies. • Major study limitations ➢ Data exclusively from published RCTs ➢ English language publications ➢ No statistical methods used

28

Melatonin

Jansen SL, Forbes DA, Duncan V, Morgan DG. Melatonin for cognitive impairment. Cochrane Database. 2006 Jan 25;(1):CD003802Me	• Improvement for melatonin compared with placebo in behavioral and affective symptoms: • Measured by the ADAS non-cognitive scale in a study of 20 patients (-3.48 [-4.89, -2.07]) • Neuropsychiatric Inventory (NPI) following treatment with 2.5 mg/day (SR) melatonin (1.60 [-3.63, 0.43]), but not with 10mg/day (IR) melatonin in a larger study of 157 patients

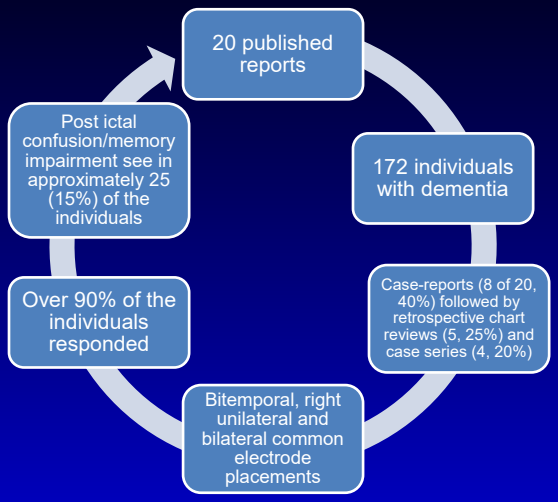
29

Cannabinoids

Tampi RR, Young JJ, Tampi DJ. Cannabinoids for the treatment of behavioral and psychological symptoms of dementia. Neurodegener Dis Manag. 2018 Jul 24. doi: 10.2217/nmt-2018-0019.	• 8 reports • 117 individuals with a dementia (67 with AD, 8 with VD and 42 with unspecified dementia) • 5 of the 8 reports used dronabinol, 2 reports used THC and 1 study used nabilone (synthetic cannabinoid) • 7 of the 8 studies indicate symptomatic improvement • Behaviors that were improved were agitation, aggression, impulsivity, nocturnal restlessness, wandering, and poor sleep • 4 of 8 eight studies did not report any significant adverse effects • Sedation was the most commonly reported adverse effect followed by delirium, urinary tract infection and confusion

30

Electroconvulsive Therapy



Tampi et al, 2019

31

Confirm behavioral and psychological symptoms of dementia

↓

Assess the severity of dementia
(MMSE, ADAS-Cog, SIB, FAST)

↓

Treat with AchEIs* ←Mild to Moderate Moderate to Severe→ Treat with AChEIs and memantine

↓

Plus

Initiate psychological/behavioral treatments
(Specific types of caregiver and residential care staff education and cognitive stimulation)

↓

Define symptomatology

↓	↓	↓	↓
Depressed/Anxious	Hypomanic/Manic	Psychotic	Agitation/Aggression

↓

Initiate (after obtaining informed consent)

↓	↓	↓	↓
SSRI** antidepressants	Carbamazepine/Divalproex sodium Atypical antipsychotics	Atypical antipsychotics	SSRI antidepressants Carbamazepine Divalproex sodium Trazodone

↓

If monotherapy fails, use judicious combination of medications (e.g., antidepressants with antipsychotics or with mood stabilizers)

↓

Reinforce psychological/behavioral techniques
Use within prescribed dosage ranges
Frequently assess efficacy and side-effects of these medications
Control modifiable cerebrovascular and cardiovascular risk factors (Atrial fibrillation/ Diabetes/Hyperlipidemia/ Hypertension)
Initiate taper off the medications if possible after 3-4 months of symptom free period

*AchEIs (Acetylcholinesterase Inhibitors)
**SSRI (Selective Serotonin Reuptake inhibitors)

Tampi RR, et al. Clinical Geriatrics. 2011

32

APA Practice Guideline

- Use antipsychotics only if the benefit outweigh the risks
- Initiated treatment at a low dose and titrate to the minimum effective dose as tolerated
- If adverse effects occur, risks vs. benefits should be reviewed to determine if taper and discontinuation of the medication is indicated
- If there is no response after a 4-week trial on an adequate dose, then the medication should be tapered and discontinued
- When there is a positive response the decision to possibly taper the medication should be discussed with the patient and/or the surrogate decision maker
- When there is adequate response, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment unless there is a recurrence of symptoms with previous attempts at tapering the medication
- While tapering the medication assess symptoms at least every month during the taper and for at least 4 months after the medication discontinuation
- In the absence of delirium, haloperidol should not be used as a first-line agent
- Long-acting injectable antipsychotic medication should not be used unless for a co-occurring chronic psychotic illness

Reus et al, 2016

33

Controversies in the Treatment of Individuals with BPSD

Shilpa Srinivasan, MD, DFAPA, DFAAGP

34

FDA Boxed Warning (2005)

- 17 placebo controlled trials
- Involved olanzapine, aripiprazole, risperidone, or quetiapine
- Enrolled a total of 5106 patients
- 15 trials showed numeric increase in mortality (1.6-1.7 fold)
- Death was mainly due to cardiac events (e.g., heart failure, sudden death) or infections (mostly pneumonia)
- Warning extended to clozapine, ziprasidone and combination olanzapine, fluoxetine
- FDA subsequently added a similar warning to older antipsychotic medications (2008)

35

Schneider L, Dagerman K, Insel PS. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43

Medication	No. events in treatment group	No. events in placebo group	Odds ratio, 95% CI
Aripiprazole	21/603	6/348	1.73, 0.70-4.30
Olanzapine	31/1184	6/478	1.91, 0.79-4.59
Quetiapine	21/391	7/246	1.67, 0.70-4.03
Risperidone	45/1175	22/779	1.30, 0.76-2.23
Overall	**118/3353 (3.5%)**	**41/1851 (2.3%)**	**1.54, 1.06-2.23 P=0.02**

36

- Death occurred more often over the first 8 to 12 weeks of treatment,118 [3.5%] vs 40 [2.3%]
- Likelihood of harm versus help (LHH) indicates that for every 9 to 25 persons helped, there will possibly be 1 death
- Excess mortality was not due to any particular atypical antipsychotic and it could only be appreciated when this class of medications were examined as a whole
- Subgroup analysis did not reveal differences between patients of lower cognitive function, psychosis of AD or inpatients versus outpatients

37

Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. 2005 Dec 1;353(22):2335-41.

Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.*

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.51 (1.43–1.59)
Adjusted analysis†	
Use of any conventional APM	1.37 (1.27–1.49)
Low dose of conventional APM (<median)	1.14 (1.04–1.26)
High dose of conventional APM (>median)	1.73 (1.57–1.90)
Adjusted analysis of death†	
<40 Days after beginning therapy	1.56 (1.37–1.78)
40–79 Days after beginning therapy	1.37 (1.19–1.59)
80–180 Days after beginning therapy	1.27 (1.14–1.41)
Adjusted analysis of patient subgroups†	
With dementia	1.29 (1.15–1.45)
Without dementia	1.45 (1.30–1.63)
In a nursing home	1.26 (1.08–1.47)
Not in a nursing home	1.42 (1.29–1.56)

* APM denotes antipsychotic medication, and CI confidence interval.
† Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.

38

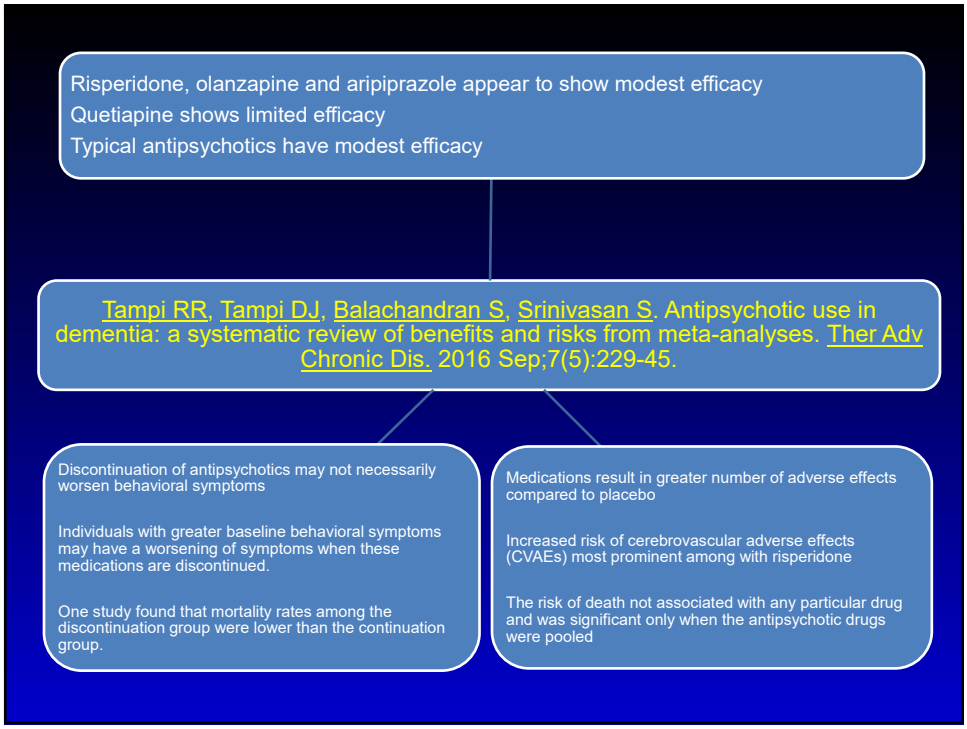
Herrmann N, Lanctôt KL. Do atypical antipsychotics cause strokes? CNS Drugs. 2005;19(2):91-103.	• 11 studies: 6 risperidone, 5 olanzapine • 48 out of 2187 (2.2%) drug-treated subjects experienced CVAEs vs. 10 out of 1190 (0.8%) placebo treated subjects • The combined relative risk was 2.7 (95% CI, 1.4-5.3) • Numerically more risperidone-treated patients (33 of 1009 [3.3%]) experienced CVAEs compared with olanzapine-treated patients (15 of 1178 [1.3%]) • The weighted relative risk was statistically significant for risperidone (3.2, 95% CI, 1.4-7.2), p=0.004 but not for olanzapine (1.8, 95% CI, 0.5-6.3), p=0.36

39

Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly demented patients when treated with antipsychotic medications: A Literature Review of Evidence. Am J Alzheimers Dis Other Demen. 2011 Feb;26(1):10-28.

Cerebrovascular Adverse Event (CVAEs)	Death
• 22 studies, only two were placebo controlled trials	• 14 studies, only three were placebo controlled trials
• 1.3-2.0 times higher in the drug treated group	• 1.2-1.6 times higher in the drug treated group
• Atypical antipsychotics = Typical antipsychotics	• Atypical antipsychotics = Typical antipsychotics
• Risks: • Higher than median doses • Older age • Vascular dementia • Comorbid atrial fibrillation	• Risks: • Older age • Male gender • Severe dementia • Functional impairment
• Risk remains elevated for about 20 months	• Risk is elevated in the first 30 days and possibly for 2 years

40



41

Algorithm For Treating Emergent Agitation

- Offer Risperidone: 0.25 mg-1.0 mg dose
- Or Aripiprazole 2.0-5.0 mg dose
- Or Olanzapine 2.5 mg-5 mg dose
- Or Quetiapine 25 mg-50 mg dose
- May repeat dose in 0.5-1 hour if needed
- May need 1-2 repeats before the patient responds. **Avoid Benzos!**

- **If patients is refusing PO medications and is severely agitated or aggressive**
- Give IM Aripiprazole: 1.875 mg-7.5 mg dose
- Or IM Olanzapine: 2.5 mg-5.0 mg dose
- Or IM Haloperidol: 0.5 mg-2.0 mg dose (extreme agitation

- Can repeat dose in 0.5-1 hour if needed.
- May need 1-2 repeats before the patient responds. **Avoid Benzos!**

42

Treatment Algorithm For Non-Emergent Agitation

- Start treatment with a cholinesterase inhibitor
- Add memantine if the patient has moderate to severe dementia
- If agitation persists, consider trial of SSRI antidepressant
- If SSRI (antidepressant) response is suboptimal, consider trazodone
- For persistent agitation, consider risperidone/ aripiprazole
- Consider quetiapine
- If trial fails, use olanzapine
- If olanzapine trial fails, use either divalproex or carbamazepine
- **Consider combination therapy ONLY if monotherapy trials suboptimal***
- **Avoid benzodiazepines!**

Severity

43

Class of Medication	Name of Medication and Dosages
Antipsychotics	Aripiprazole: 2 mg-10 mg/day Olanzapine: 2.5 mg-10 mg/day Quetiapine: 25 mg-200 mg/day Risperidone: 0.25 mg-2 mg/day
Antidepressants	Citalopram: 10 mg-20 mg/day Escitalopram: 5 mg-20 mg/day Mirtazapine: 7.5 mg-45 mg/day Sertraline: 25 mg-200 mg/day
Mood stabilizers	Carbamazepine: 200 mg-400 mg/day Divalproex sodium: 250 mg-1000mg/day Oxcarbazepine: 300 mg-600 mg/day
Cognitive Enhancers	Donepezil: 5 mg-10 mg/day Galantamine: 8 mg-24 mg/day Rivastigmine: 3 mg-12 mg/day Memantine: 10 mg-20 mg/day

44

Thank you!

45