Recognizing and Managing the Complications of Dementia:

Behavioral & Psychological Symptoms of Dementia (BPSD)

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Geriatric Psychiatrist
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ROBERT LUDLUM
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Objectives

Participants will be able to:

- Identify symptoms and clusters of behavioral disturbances in patients with dementia

- Plan treatment strategies of common behavioral disturbances in various settings: Home, LTC facility, inpatient unit or the ER

- Understand the role of pharmacological management in the treatment planning

What is BPSD?

- Occurs in all types of dementia
- Some types of dementias present with characteristic symptoms
  - e.g. Lewy Body - visual hallucinations
  - Frontotemporal dementia – disinhibition
- BPSD leads to earlier institutionalization, hospitalization, decreased quality of life

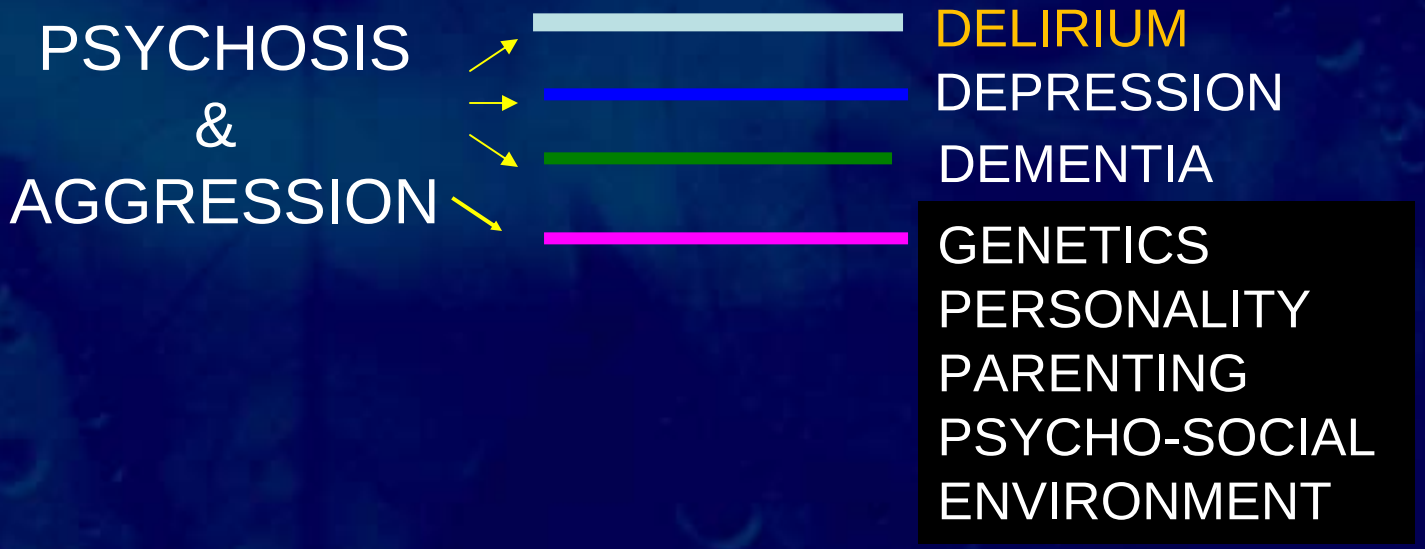
“Psychosis” in the elderly is a symptom, NOT a disorder

- Delirium
- Schizophrenia
- Delusional Disorder
- Mood Disorder
- Dementia
- Substance Abuse
- Drug-induced Psychosis
- Medical / Neurological Conditions

Presentation & Diagnosis: Highly variable
Key Principle: Comorbidity

Comorbidity is The Rule

DELIRIUM OFTEN
PRESENTS WITH
PSYCHOTIC / AGGRESSIVE BEHAVIOR



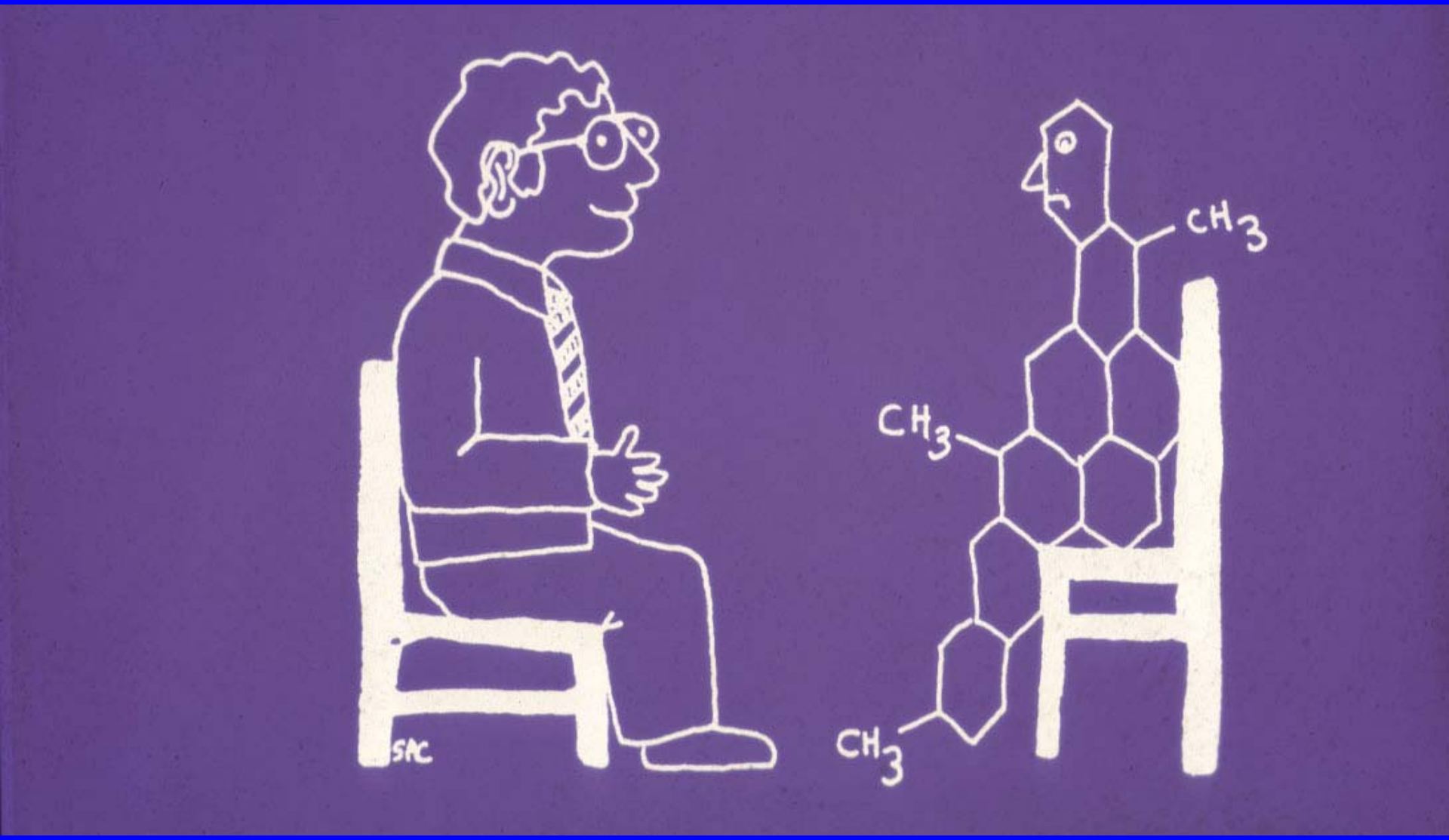
Psychosis & Aggression in the Elderly
Phases of Treatment

ACUTE → SAFETY → patient,staff,residents

MEDIUM → ASSESS → 1) rule out delirium
2) medicate or not?

LONG-TERM → **MAINTENANCE** → 1) on what?
2) how long?

DRUGS: NECESSARY BUT NEVER SUFFICIENT ALONE!!



JAMA 2002 Apr 10;287(14):1840-7

Placebo response in studies of major depression: variable, substantial, and growing.

Walsh BT, Seidman SN, Sysko R, Gould M.

Non-Pharmacological Interventions

Approach A kind, unrushed, non-confrontational, face-to-face approach may work better

Schedules Patient-centred care schedules

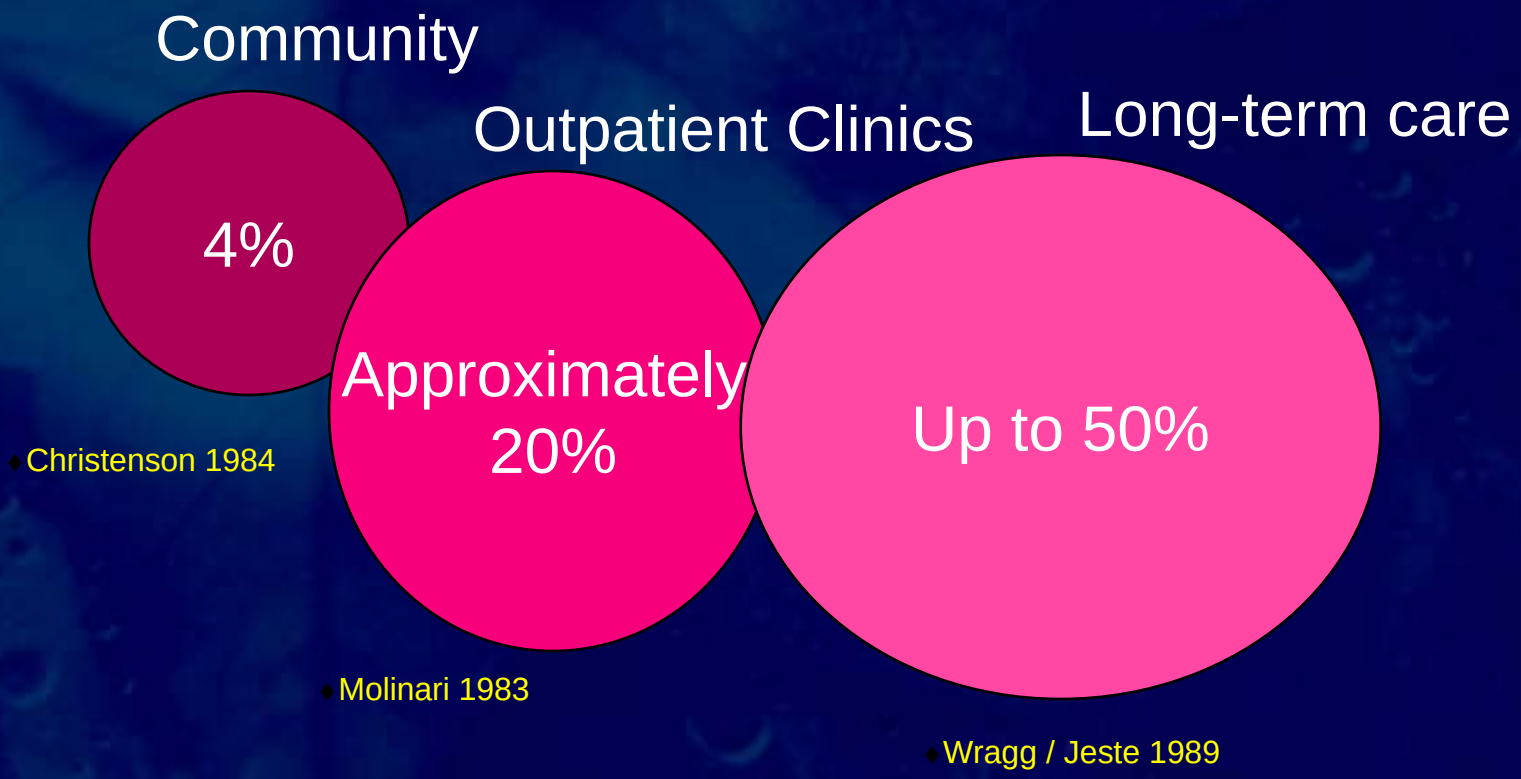
Demands Reduce demands on patient

Communication Communicate more effectively

Personal Care Meticulous attention to good personal care is essential

Activity and Environment Appropriate daytime activity and environment

Psychotic symptoms in Late Life
Prevalence by Setting



The top 10 most frequent drug events in long-term care by drug type

Use caution when prescribing atypical antipsychotics: They're often administered in error. A nine-month study of two large long-term care facilities found that 11% of adverse drug events involved atypical antipsychotics—second only to warfarin—and 12% of those were deemed preventable.

Drug class	% of total (n=815)	% preventable (n=338)
Warfarin	15%	12%
Atypical antipsychotic agents	11%	12%
Loop diuretics	8%	10%
Opioids	6%	8%
Antiplatelets	6%	7%
ACE inhibitors	6%	8%
Antidepressants (non-SSRI, nontricyclic)	5%	7%
Laxatives	5%	5%
Benzodiazepines (intermediate-acting)	5%	9%
Insulins	5%	5%

Source: American Journal of Medicine, March 2005.

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Last Updated: Tuesday, 9 March, 2004, 13:00 GMT

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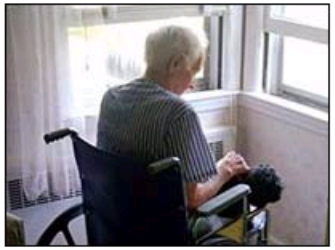
Expert warning on dementia drugs

Experts have ruled drugs used to treat schizophrenia should not be given to elderly patients with dementia.



The drugs were given to elderly patients

The antipsychotic drugs risperidone and olanzapine are used to control behavioural problems.

But the Committee on Safety of Medicines said patients with dementia were three times more likely to have a stroke if they were taking the drugs.

The CSM estimated that around 40,000 over-65s were prescribed the drugs last year.

Around 30,000 were given risperidone, and 9,000 olanzapine.

> **People with dementia are too frequently given powerful sedative and antipsychotic drugs**
>
> Professor Clive Ballard, Alzheimer's Society,

Both drugs are atypical antipsychotics, which are also used to treat agitation, anxiety, mania and aggression.

Some doctors prescribed the drugs for patients with dementia, even though they were not specifically licensed for that use, if they believed they could help the individual patient.

SEE ALSO:
- Dementia drugs put under spotlight
  21 Feb 02 | Health
- Care homes dispense 'chemical cosh'
  05 Dec 01 | Health
- Concern over sedative use
  23 Jul 01 | Health

RELATED INTERNET LINKS:
- MHRA
- Committee on Safety of Medicines
- Alzheimer's Society

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- TV daily limits call unrealistic
- New painful joint disorder found

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Risperdal

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Risperidone

Adverse Effects/ Potential Injuries:
Diabetes
Hyperglycemia
Stroke
Neuroleptic Malignant Syndrome
Tardive Dyskinesia

Practice Area(s):
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Parker & Waichman Files Claims Against Eli Lilly and Company on Behalf of Three Individuals Claiming Injuries Caused by Zyprexa; Plaintiffs Diagnosed with Serious Cases of Diabetes and Pancreatitis

Additional Claims vs. Eli Lilly & Co. Expected to be Filed

PRNewswire –

03/19/04 - Parker & Waichman LLP (www.yourlawyer.com) filed claims against Eli Lilly and Company (NYSE: LLY - News) on behalf of three individuals who claim to have sustained severe side-effects from Zyprexa. The claims were filed in Federal District Court in the Eastern District of New York. Two plaintiffs have been diagnosed with serious cases of diabetes, and another plaintiff has required lengthy intensive care hospitalization due to a diagnosis of acute pancreatitis. Zyprexa is currently the most popular atypical antipsychotic medication, and is Eli Lilly and Company's best-selling pharmaceutical. Zyprexa users can visit www.zyprexa-side-effects.com for more information on these claims.

The British Medical Control Agency and the Japanese Health and Welfare Ministry have both warned about the risk of diabetes in patients who are prescribed Zyprexa. In 2002, a study at Duke University showed a connection between Zyprexa and diabetes. This study documented nearly 300 cases of diabetes in people using Zyprexa. Only recently has Eli Lilly and Company added some language to their labeling in the United States concerning the risk of diabetes from Zyprexa.

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Other Names:
Risperidone

Adverse Effects/ Potential Injuries:
Diabetes
Hyperglycemia
Stroke
Neuroleptic Malignant Syndrome
Tardive Dyskinesia

Practice Area(s):
- Defective Drugs

News: Risperdal

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FDA Calls for Warning on Antipsychotic Drugs

Reuters -

04/11/05 - The U.S. Food and Drug Administration ordered new warnings on antipsychotic drugs, alerting physicians to a higher death rate when the medicines are prescribed for atypical use of treating dementia in elderly patients.

The black box warning affects Eli Lilly and Co.'s Zyprexa and Symbyax, AstraZeneca Pharmaceuticals LP's Seroquel, Johnson & Johnson's Risperdal, Novartis AG's Clozaril, Pfizer Inc.'s Geodon, and Bristol-Myers Squibb Co.'s and Otsuka America Pharmaceutical's Abilify.

The FDA said it is asking the companies to add the boxed warning to their labels describing the heightened risk and noting the drugs are not approved to treat symptoms of dementia in the elderly.

The FDA said after reviewing 17 studies of four drugs in the class, the death rate for elderly patients on the medication were 1.6 to 1.7 times greater than those on a placebo. Most of the deaths were either heart related or from infections, the FDA said.

Because the FDA believes it is a class effect, it is ordering the warnings on all drugs in the category, it said.

Eli Lilly spokeswoman Carole Copeland said the Zyprexa label

Dementia Drugs May be Risky

May 28, 2009 | Parker Waichman Alonso LLP

We have long been writing about the serious side effects associated with some popular dementia drugs. Now, ScienceDaily is reporting that these adverse effects could be placing the elderly at risk, citing Sudeep Gill, a geriatrics professor at Queen's University who is also an Ontario Ministry of Health and Long-term Care Career Scientist working at Providence Care's St. Mary's of the Lake Hospital in Kingston.

Aricept, Exelon, and Reminyl are in a class of drugs called cholinesterase inhibitors and are typically prescribed for Alzheimer's disease patients and patients with related dementias, said Science Daily, explaining that the drugs increase the brain chemical thought to aid in memory. The drugs also seem to decrease heart rates and prompt

BREAKING NEWS: Problems with "Hydraulic fracturing" causing more obstacles.

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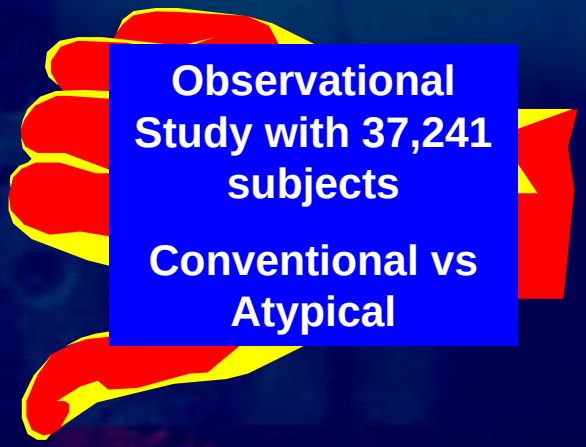
Aricept, Zantac, Detrol, other Anticholinergic Drugs Lined to Mental Impairment in Elderly

May 6, 2008 | Parker Waichman Alonso LLP

Two separate reports written by researchers at Wake Forest University School of Medicine support findings released recently concerning anticholinergic medications like Aricept, Zantac and Detrol. The studies found that anticholinergic drugs may be adversely affecting the thinking skills of older patients, a phenomenon not observed in those patients studied who do not take these medications. The studies also indicate that anticholinergics may cause older patients to experience a decrease in their daily physical activities.

Use of Antipsychotics in Elderly Dementia Patients: Benefits out-weighed by adverse events



Drugs for BPSD

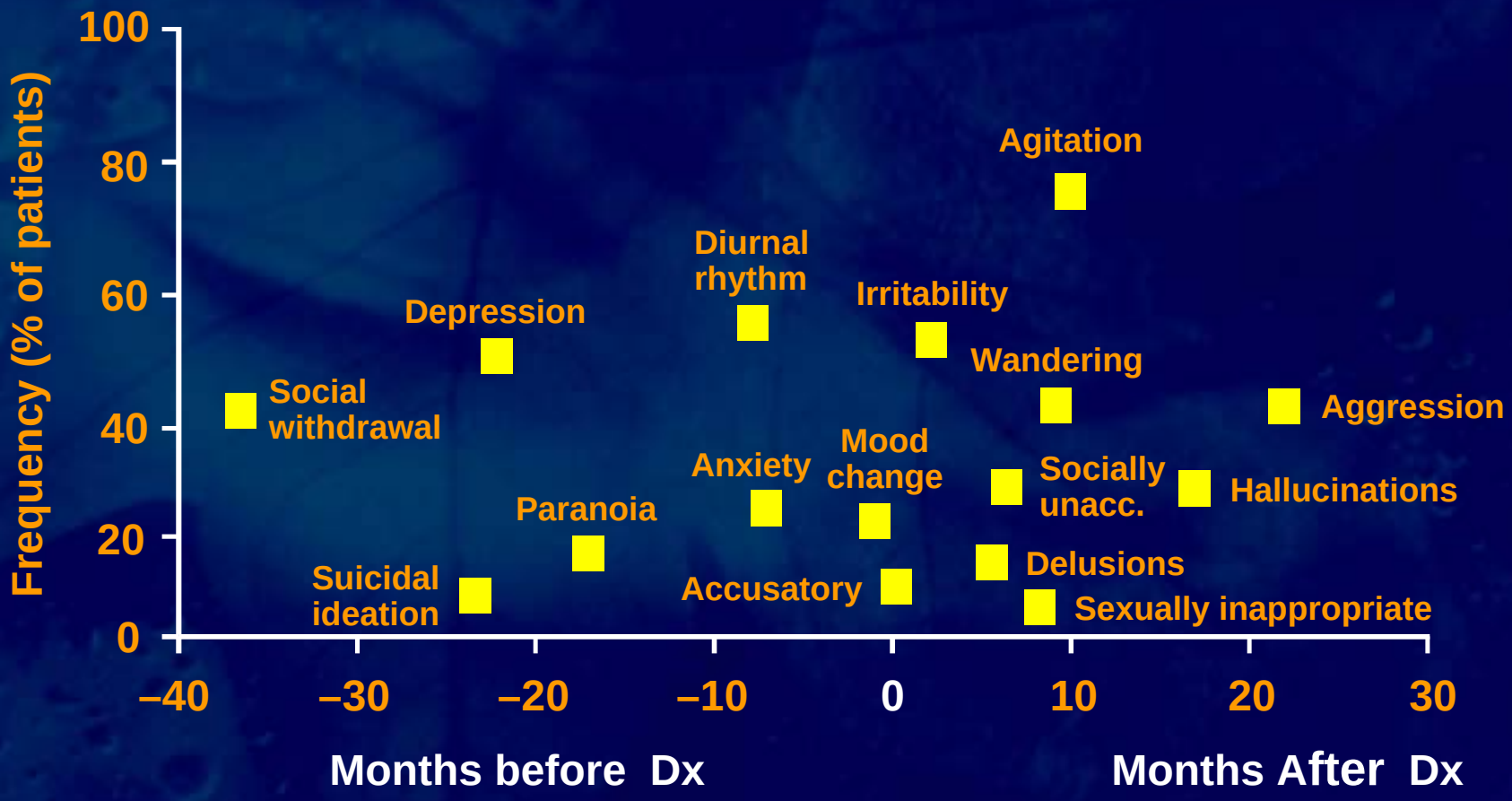
- If drugs are bad……..
- Why do we still use them?
- If we have to use them, how do we use them safely?
- Goal is to:
  - Maximize benefit
  - Minimize risk
  - Explain these to patient & family
  - Consent

CONCEPT:

1. SYMPTOMS

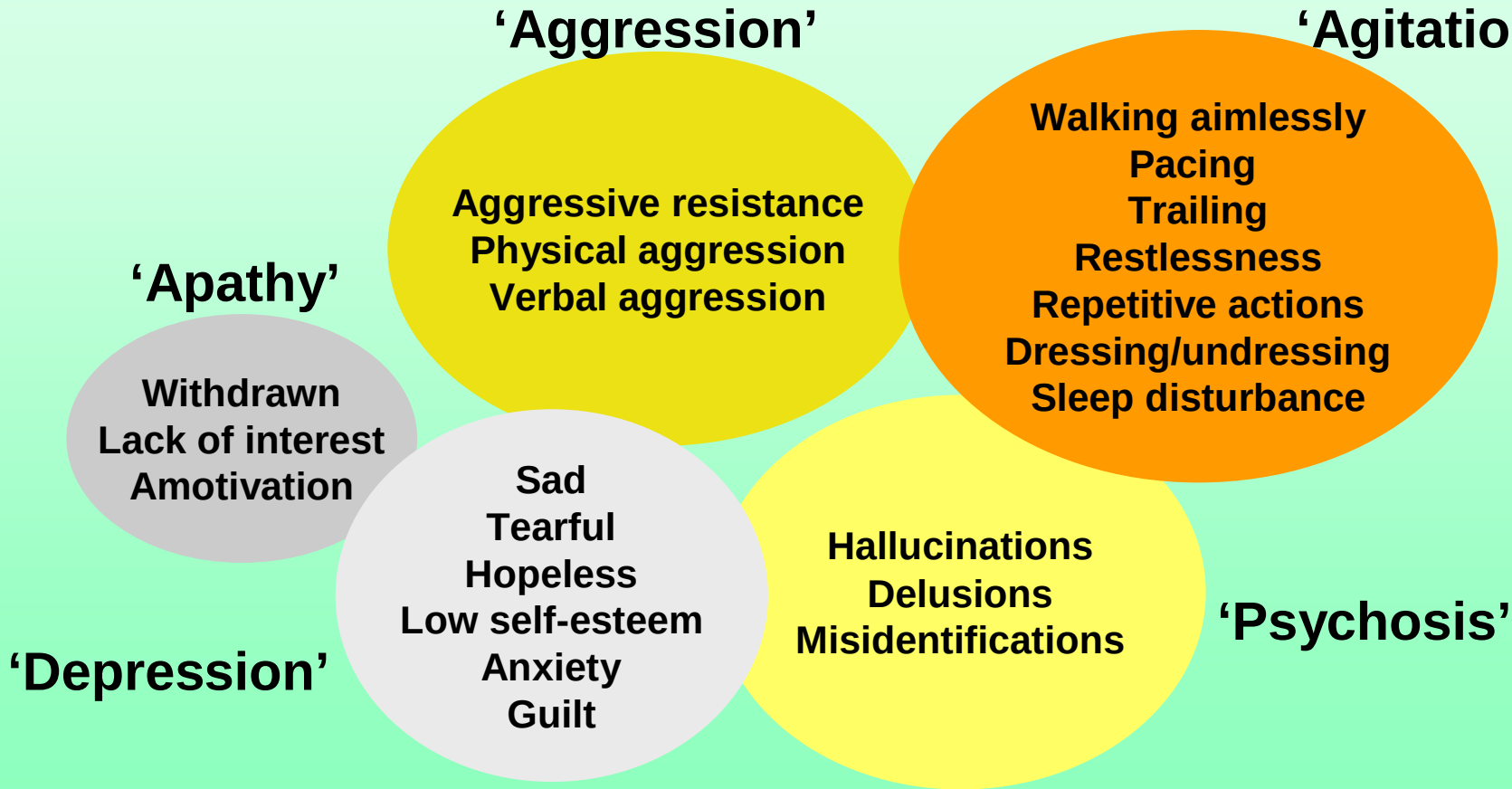
2. CLUSTERS OF SYMPTOMS

Symptoms of BPSD



Jost and Grossberg, 1996

Clusters of BPSD



Adapted from McShane R. Int Psychogeriatr 2000; 12(Suppl 1): 147–54

Measurement of vital signs

Identifying & Measuring BPSD

“Behavioural Vital Signs” or “BVS” Tool

Target
Symptoms & Clusters

- **Frequency**
- **Severity**
- **Impact**

BVS Tool: www.cagp.ca

- Click: “LINKS”
- Click: “ASSESSMENT TOOLS”
- Click: “BVS TOOL”

“Behavioral Vital Signs” Tool

BEHAVIOURAL·VITAL·SIGNS·(BVS)¶

1.→The·primary·caregiver·or·treatment·team·is·to·refer·to·each·target·symptom·listed·below.·¶
2.→Then·rate·their·overall·severity,·frequency·and·impact·and·chart·these·findings.¶
3.→Can·be·done·per·shift,·daily,·weekly·or·monthly·as·ordered.¶

Produced·by·¶
Dr·Kiran·Rabheru,·MD,·DABPN,·CCFP,·FRCPC¶
Chair,·Division·of·Geriatric·Psychiatry¶
University·of·Western·Ontario¶
London,·Ontario¶

Delusions·(of)¶ People·stealing·things¶ Not·recognizing·one's·own·house·or·surroundings¶ Not·recognizing·spouse·(or·other·caretaker)-"imposter".¶ False·belief·of·abandonment·(e.g.,·to·an·institution)¶ False·belief·of·infidelity¶ Suspiciousness·or·paranoia·other·than·above_____¶ Other·Delusions_____¶	**Hallucinations¶** Visual·¶ Auditory¶ Olfactory·¶ (false·perception·of·smell)¶ Haptic·¶ (false·perception·of·touch·or·surface·sensation)¶ Other·hallucinations¶ _____¶	**Depression·/·Anxiety¶** Anxious¶ Fear·of·being·left·alone¶ Constant·requests·for·attention¶ Pacing·/·restless¶ Preoccupied·with·physical·complaints¶ Negative¶ Sad·/·Depressed·mood¶ Does·not·participate·in·activity¶ Tearfulness¶ Sleep·problems¶ Loss·appetite·or·weight¶ Poor·energy¶ Poor·concentration¶ Hopeless·/·Helpless¶ Guilty¶ Suicidal¶ Others_____¶	**Manic·States¶** Elation/Euphoria¶ Disinhibition¶ Pressured·speech¶ Flight·of·ideas·/·Distractible¶ Inflated·self·esteem¶ Grandiose·ideas¶ Decreased·need·for·sleep¶ Irritability/lability¶ Socially·/·sexually·inappropriate·e.g.·foolish·spending,·business·investments¶ Other_____¶	**Sleep·/·Wake·Cycle·Disturbance¶** Difficulty·with:¶ Falling·asleep¶ Waking·up·in·middle·of·the·night¶ Waking·up·too·early¶ Drowsy·/·groggy·during·the·day¶ Wants·to·sleep·all·day¶ Other_____¶
Agitation¶ Physically·Aggressive¶ Hitting¶ Pushing¶ Scratching¶ Grabbing¶ Kicking¶ Biting¶ Spitting¶ Other_____	**Agitation¶ Verbally·Aggressive¶** Screaming¶ Cursing¶ Temper·outbursts¶ Aggressive·&·inappropriate·social·comments¶ Aggressive·verbal·sexual·advances¶ Other_____	**Agitation¶ Physically·Non-Aggressive¶** General·restlessness¶ Repetitive·purposeless·motor·activity¶ Pacing¶ Hiding·objects¶ Inappropriate·handling·of·objects¶ Shadowing¶ Exit·seeking¶ Inappropriate·dressing/undressing¶ Other_____¶	**Agitation¶ Verbally·Non-Aggressive¶** Negativism¶ Chanting¶ Repetitive·sentences¶ Constant·interruptions¶ Constant·requests·for·attention¶ Other_____¶	**Apathy¶** Appears·withdrawn¶ Lack·of·interest¶ Not·motivated¶ Sit·/·sleeps·all·day¶ Does·not·participate·in·activity¶ Other_____¶

Definition·of·Agitation¶

- Some·patients·have·symptoms·that·do·not·neatly·fit·into·the·better-defined·symptom·complexes·of·BPSD··(e.g.·psychosis,·depression·or·anxiety).¶
- These·symptoms·are·consigned·to·the·"grab-bag"·category·of·agitation.¶
- Agitation·can·be·defined·as·inappropriate·verbal,·vocal·or·motor·activity·that·is·not·judged·by·an·outside·observer·to·result·directly·from·the·needs·or·confusion·of·the·person.··

Behaviour Frequency (Rate 1-5)	**Severity** (Rate 1-5) **How much difficulty is it to distract or redirect the patient?**	**Impact** (Rate 1-5) **Potential harm to self / others**
5: Constant	5: Extreme (not directable)	5: Extreme (serious harm)
4: Several times a day	4: Intense (major problem)	4: Intense (significant harm)
3: At least once daily	3: Moderate (moderate problem)	3: Moderate (moderate harm)
2: At least once a week	2: Minimal (minor problem)	2: Minor (minor harm)
1: Less than once a week	1: Negligible (insignificant problem)	1: Negligible (no notable harm)
0: Almost never	0: None	0: None

Please place appropriate X, * or — symbols in chart below according to your assessment based on the above criteria.

Behavioural Rating Score Behaviour Frequency: **X** Severity: * Impact: —	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I	F	S	I
5																																							
4																																							
3																																							
2																																							
1																																							
0																																							
	1			2			3			4			5			6			7			8			9			10			11			12					

Time Frame

Choose Time Frame being Rated: ☐ Shift ☐ Day ☐ Week ☐ Month

Approach to BPSD:

The *SMART* Approach:

- Safety: remove patient to safe environment
- Medical: organic workup to treat reversible causes; reduce medication load
- Assess Competency: personal care decisions, financial, driving; protect assets
- Rest, nutrition, hydration; pain ambulation, vision, hearing, constipation
- Trial of medication: cholinesterase inhibitor / antipsychotic / antidepressant/ mood stabilizer

Rabheru K. Can Family Physician Vol 49 March 2003 pg. 389

Algorithm For Management of Psychosis In Late-Life

Identify and document target cluster(s) / symptom(s); consider BVS Tool

↓

Rule out new medical and psychiatric causes
New onset behavioural problem = delirium until proven otherwise

↓

Implement caregiver-led non-pharmacologic interventions and monitor closely

↓

Initiate pharmacological treatment if target symptom(s) severe, persistent and disturbing or dangerous enough

↓

Start appropriate initial and maintainace pharmacotherapy
Monitor efficacy & side effects
If not meeting therapeutic goals, consider switching agents, adjunctive therapy or consult geriatric psychiatry

Adapted from Mintzer JE, Browman-Mitzer O. J Clin Psychiatry 1996:5(7):55-63

Antipsychotics for BPSD

- **Goal:**
  - Reduce psychotic symptoms & aggression.
  - Increase the safety & comfort for patient and caregiver.

- **Prerequisites:**
  - Monitor target symptoms / clusters.
  - Consider need for drug Rx only if risk is significant.
  - Monitor impact of Rx.

Evidence-Based Recommendation From AGS-AAGP Consensus Panel in 2002-2003

On improving the quality of mental health care in nursing homes:

*"Appropriate first-line pharmacological treatment of residents with **severe** behavioral symptoms with psychotic features, such as hallucinations and delusions that are **causing distress**, consists of atypical antipsychotics."*

American Geriatrics Society, American Association for Geriatric Psychiatry. *J Am Geriatr Soc*. 2003; 51:1287-1298.

SPECIAL ARTICLE

Efficacy and Adverse Effects of Atypical Antipsychotics for Dementia: Meta-analysis of Randomized, Placebo-Controlled Trials

Lon S. Schneider, M.D., M.S., Karen Dagerman, M.S., Philip S. Insel, M.S.

Am J Geriatr Psychiatry 2006; 14:191–210

Objective: *Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease (AD) and other dementia. Several clinical trials have not shown efficacy, and there have been concerns about adverse events. The objective of this study was to assess the evidence for efficacy and adverse events of atypicals for people with dementia* **Methods:** *MEDLINE, the Cochrane Register of Controlled Trials, meetings, presentations, and information obtained from sponsors were used in this study. Published and unpublished randomized, placebo-controlled, double-blind, parallel-group trials in patients with AD or dementia of atypical antipsychotics marketed in the United States were studied.*

Schneider meta-analysis

- N= 16 trials AP vs. PBO
- 3,353 pts. On drug and 1,757 on PBO
- aripiprazole (k3), olanzapine (k5), quetiapine (k3), risperidone (k5)
- Variable reporting; 1/3 drop-outs
- Efficacy: aripiprazole and risperidone, but not for olanzapine
- Smaller effects for less severe dementia, outpatients, and patients selected for psychosis

Schneider meta-analysis

- A/E: somnolence & UTI / incontinence
- across drugs, EPS & abnormal gait with risperidone or olanzapine
- Cognition worsened
- No evidence for increased injury, falls, or syncope
- Significant risk for CVAEs, especially with risperidone. Increased mortality

The Lancet Neurology, 2009: Volume 8, Issue 2, Pages 151-157

THE LANCET Neurology

The Lancet Neurology, Volume 8, Issue 2, Pages 151 - 157, February 2009
doi:10.1016/S1474-4422(08)70295-3 Cite or Link Using DOI
Published Online: 09 January 2009

Editors' note: Antipsychotics do not improve cognitive or neuropsychiatric outcomes in most patients with dementia, and serious concerns have been raised about their side effects in the very old. Increased mortality rate and risk of cerebrovascular events have been reported by previous studies of relatively short duration (usually 12 weeks). In this article, the DART-AD investigators report long-term mortality rates among patients with Alzheimer's disease in residential care after 12-months of neuroleptic treatment, adding to the growing evidence against the use of antipsychotics in this vulnerable population.

The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

Clive Ballard MD [a], Maria Luisa Hanney PhD [b], Megan Theodoulou MRCPsych [c], Simon Douglas BSc [d], Rupert McShane MRCPsych [e], Katja Kossakowski BSc [a], Randeep Gill MBBS [a], Edmund Juszczak MSc [f], Ly-Mee Yu MSc [f], Robin Jacoby DM [c], for the DART-AD investigators

DART-AD RESULTS

- N=165
- 83 AP & 82 PBO

Survival:

- 70% vs 77% at 1 year
- 46 % vs. 72 % at 2 years
- 30% vs 59 % at 3 years
- Seek less harmful alternatives for the long-term treatment

Mortality: Atypicals vs. placebo

- Odds ratio of death all drugs pooled = 1.54 (1.06-2.23) vs PBO
- Black box warnings of death on atypicals: 4.5% vs 2.6% on PBO
- Causes: “cardiovascular, infection”.

Mortality: Typicals vs. Atypicals

- Typicals: higher mortality RR = 1.37
  - For every 100 patients treated with typicals….7 additional deaths….no black box warning for typicals
- Other medications have less evidence for efficacy or safety.
- Absence of evidence $\neq$ Evidence of absence

Cholinesterase Inhibitors for BPSD

- Treatment with cholinesterase inhibitors (ChEIs) has been reported to show behavioural benefits for AD patients in:
  - Mild-to-moderate AD[1-3]
  - Moderate-to-severe AD[4,5]
  - AD patients in nursing homes[6]
- Unlike most psychotropics[7], ChEIs appear to treat multiple behavioural symptoms (eg, affective and psychotic)[1-6]

[1]Holmes C et al. *Neurology*. 2004;63:214-9; [2]Cummings et al. *Am J Psychiatry*. 2004;161:532-8; [3]Finkel et al. *Int J Geriatr Psychiatr*. 2004;19:9-18; [4]Feldman H et al. *Neurology*. 2001;57:613-21; [5]Gauthier S et al. *Int J Psychogeriatr*. 2002;14:389-404; [6]Hatoum et al. *J Am Med Dir Assoc*. 2005;6:238-45; [7]Lee et al. *BMJ*. 2004;329:75; [8]Pratt et al. *Int J Clin Prac*. 2002;56:710-7.

Review Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2009;27:164–172
DOI: 10.1159/000200013

Accepted: December 16, 2008
Published online: February 5, 2009

Memantine Therapy of Behavioral Symptoms in Community-Dwelling Patients with Moderate to Severe Alzheimer's Disease

George T. Grossberg[a] Vojislav Pejović[b] Michael L. Miller[b] Stephen M. Graham[c]

[a]Department of Neurology and Psychiatry, Saint Louis University School of Medicine, St. Louis, Mo.,
[b]Prescott Medical Communications Group, Chicago, Ill., and [c]Forest Research Institute, Jersey City, N.J., USA

Dement Geriatr Cogn Disord 2009;27:164–172

Key Words

Memantine · Alzheimer's disease · Behavioral disturbances ·

a reduced severity or emergence of specific symptoms, particularly agitation and aggression. Prospective, well-de-

MEMANTINE:

Mild to moderate: very small advantage over placebo. Individuals may consider….little risk.

In moderate to severe: evidence & indication given upto 6 months (APA) with or without a ChEI

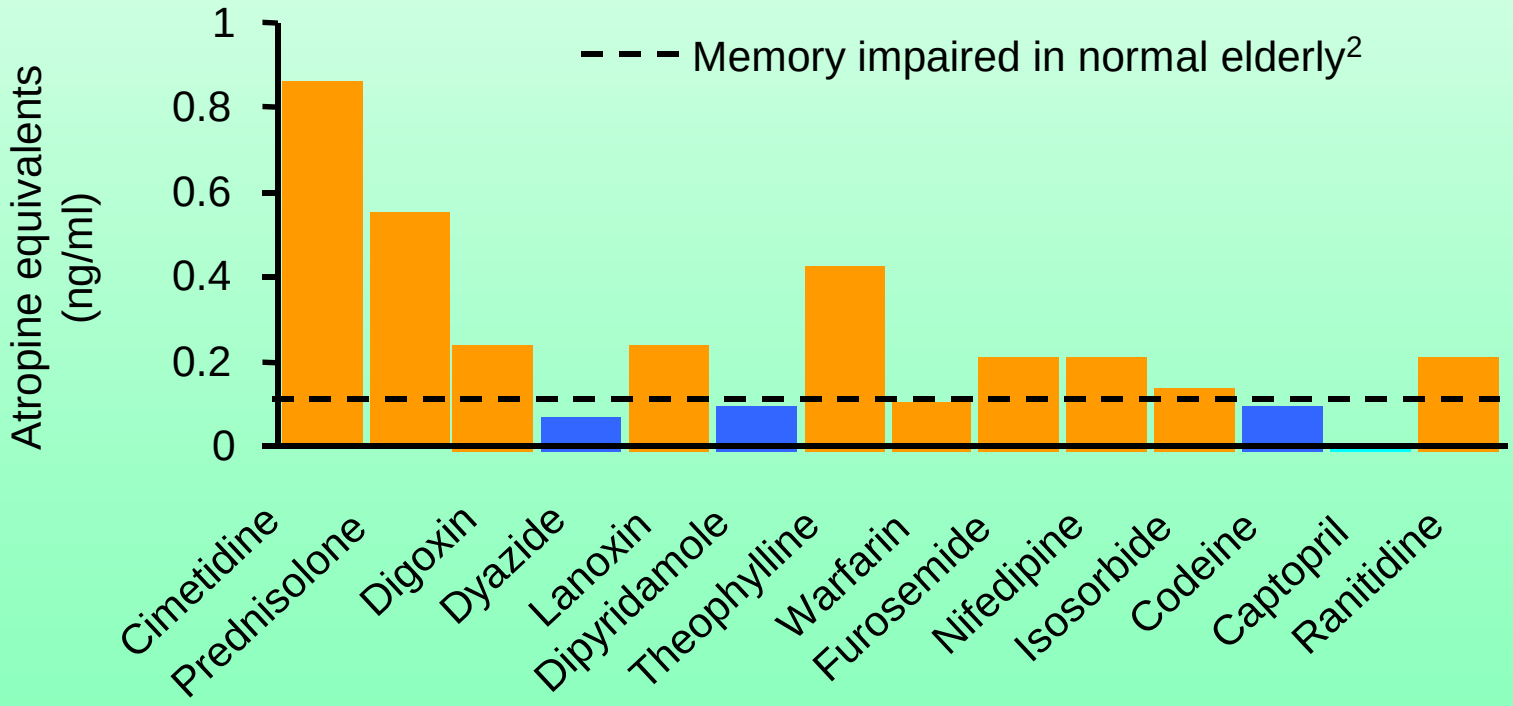
Memantine in moderate to severe Alzheimer's disease
Barry Reisberg, M.D., *et al.*
The New England Journal of Medicine April 2003

Memantine treatment in patients with moderate to severe AD already receiving donepezil
Pierre Tariot, M.D., *et al.*
JAMA, January 2004

Memantine in severe dementia:
Results of the M-BEST study
(Benefit and Efficacy in Severely Demented Patients During Treatment with Memantine)
Bengt Winblad, M.D., Ph.D., *et al.*
International Journal of Geriatric Psychiatry, 1999

Common Medical drugs with Anticholinergic Effects

- 14/25: detectable anticholinergic activity[1]
- 10/25: activity with the potential to impair memory[2]



1. Tune L *et al.* Am J Psychiatry 1992; 149: 1393–4
2. Miller PS *et al.* Am J Psychiatry 1988; 145: 342–5

Common Drugs Potentially Worsening Cognition

1.	Anticholinergic	Lomotil, ditropan, detrol
2.	Antidepressants	Elavil, sinequan, prozac, lithium
3.	Antipsychotic	Haldol, stelazine, mellaril
4.	Antihypertensives	Betablockers, alpha-antagonists, calcium channel
5.	Antibiotics	Cipro, flagyl, keflex
6.	Anticonvulsants	Dilantin, tegretol, Velproic acid
7.	Antiemetics	Antivert, phenergan, gravol
8.	Antiparkinsonian	Cogentin, artane, sinemet, parlodel
9.	Antihistamines	Benadryl, cough & cold preparations (OTC)
10.	Narcotics	Codeine, demerol, talwin
11.	H_2 Receptor Antagonists	Cimetidine, ranitidine
12.	NSAIDs	Motrin, naprosyn, indocid
13.	Benzodiazepines	Valium, dalmane, ativan, halcion

AHCPR Clinical Practice Guidelines # 19 publication #97-0702

Washington – Dept. of Health and Wellness Services Nov 1956

Depression in Dementia

- No clear established & validated criteria
- citalopram, sertraline, venlafaxine, mirtazapine, & bupropion
- Treatment may help other neuropsychiatric symptoms eg. aggression or psychosis
- Rule out: alcohol, sedative-hypnotics, other drug dependence, CNS pathology, and medical problems eg hypothyroidism

JAMA. 2005;293:596-608

Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia

A Review of the Evidence

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Karen F. Holden, MD
Kristine Yaffe, MD

Context Neuropsychiatric symptoms of dementia are common and associated with poor outcomes for patients and caregivers. Although nonpharmacological interventions should be the first line of treatment, a wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms; therefore, concise, current, evidence-based recommendations are needed.

Objective To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia.

Evidence Acquisition A systematic review of English-language articles published from 1966 to July 2004 using MEDLINE, the Cochrane Database of Systematic Reviews, and a manual search of bibliographies was conducted. Inclusion criteria were double-blind, placebo-controlled, randomized controlled trials (RCTs) or meta-analyses of any drug therapy for patients with dementia that included neuropsychiatric outcomes. Trials reporting only depression outcomes were excluded. Data on the inclusion criteria, patients, methods, results, and quality of each study were indepen-

Up to 50% of community-dwelling elderly individuals older than 85 years have dementia, with Alzheimer disease (AD), vascular dementia, and dementia with Lewy bodies accounting for most cases.[1,2] Although cognitive deficits are the clinical hallmark of dementing illnesses, noncognitive

JAMA Review

- **No first-line** recommended drug treatment for agitation without delusions

- **Typical antipsychotics**:
  - No clear evidence that typical AP are useful.
  - Haloperidol with aggression: too many adverse effects.
- **Serotonergics**: recommended only for depression.
- **Anticonvulsants**: Carbamazepine, Valproate: **Not recommended**
- **Cholinergic medications**:
  - Statistical significance of small magnitude & questionable clinical significance.
  - Only mild BPSD symptoms in all trials except two.

Benzodiazepines

- Better vs. PBO
- Equal IM olanzapine at 2 hours but inferior at 24 hours. No data beyond 8 weeks
- Sedation, ataxia, amnesia, confusion , delirium, paradoxical anxiety→ falls, respiratory suppression.
- All are dose related
- With alcohol: may cause disinhibition or withdrawal

Benzodiazepines

- Useful if anxiety is prominent, occasional PRN s, procedures
- Use low dose, short t1/2,
- Clonazepam has longer t1/2…use with caution as ….falls …increase
- Start SLOWLY…monitor…..taper very slowly.

Pharmacologic Options in Dementia

Possibly Prevent Emergence of BPSD

- ✓ Consider Cholinergic medication early in AD & Mixed AD /CVD

Mild/Moderate Agitation

- ✓ Consider Trazodone & Consider SSRIs

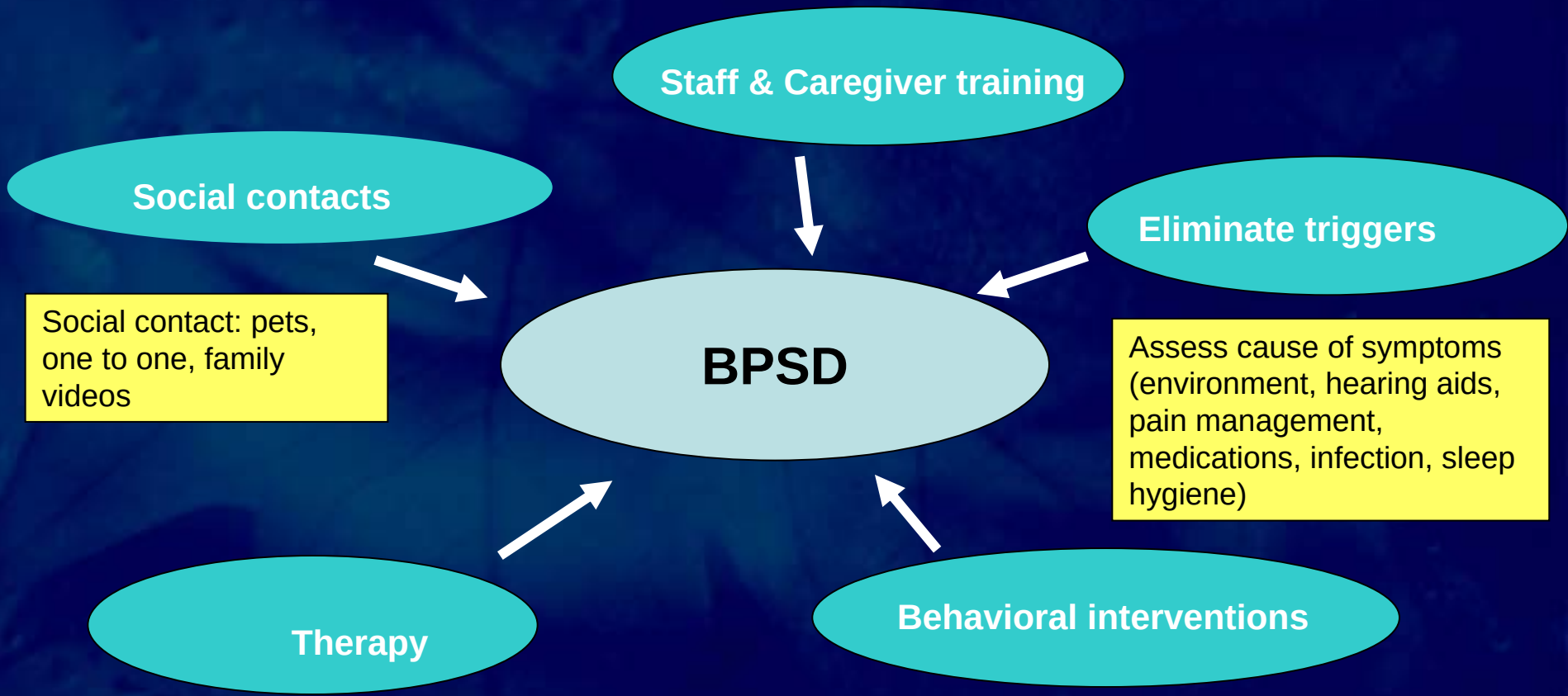
Aggressive / Psychotic

- ✓ Consider Atypical antipsychotics

CAUTION: AVOID LONG-TERM USE OF BENZODIAZEPINES

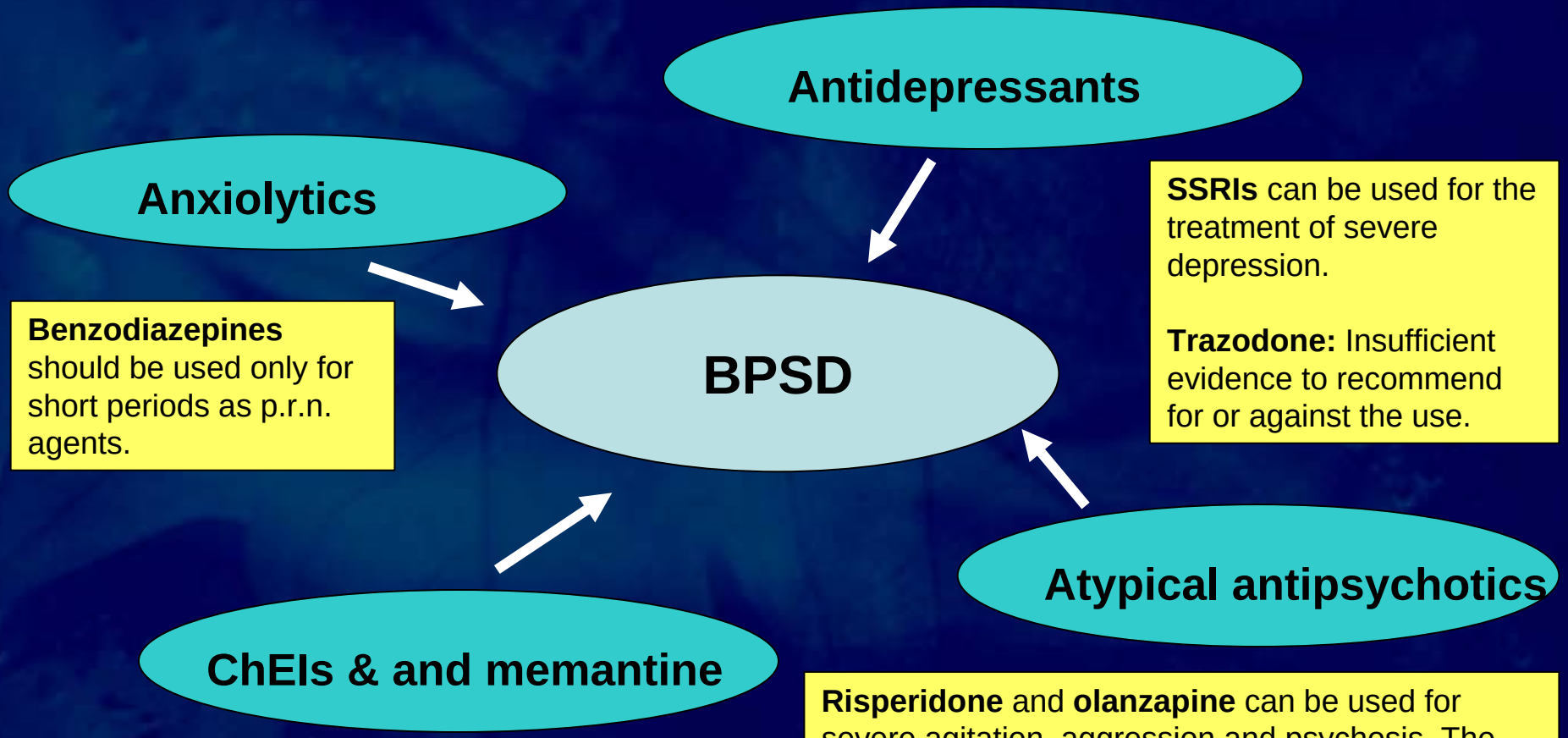
ROBERT LUDLUM
THE BOURNE SUPREMACY

Non-Pharmacological Options for the Treatment of BPSD



Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Alternative Pharmacological Options for the Treatment of BPSD



SSRIs can be used for the treatment of severe depression.

Trazodone: Insufficient evidence to recommend for or against the use.

Benzodiazepines should be used only for short periods as p.r.n. agents.

Risperidone and **olanzapine** can be used for severe agitation, aggression and psychosis. The potential benefit of all antipsychotics must be weighed against the potential risks such as cerebrovascular adverse events and mortality.

A trial of a **cholinesterase inhibitor** and/or memantine can be considered

Canadian Consensus Conference on Diagnosis and Treatment of Dementia

CATIE-AD Study
NEJM, Oct 12 2006

- Multi-site, double-blind, placebo-controlled
- 421 outpatients with moderately severe Alzheimer Disease complicated by agitation, aggression, or psychosis
- Randomly assigned to olanzapine, risperidone, quetiapine, or placebo

CATIE Study

- Outcome Measures:
  - Time to discontinuation for any reason
  - At least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks
- Results:
  - No significant differences among treatments

CATIE Study

- “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.”

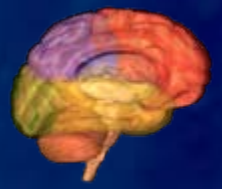
Outcome - Results

- The median time to the discontinuation of treatment due to a lack of efficacy:
  - olanzapine 22.1 weeks
  - risperidone 26.7 weeks
  - quetiapine 9.1 weeks
  - Placebo 9.0 weeks

Pharmacokinetics & Clinical Potency of Atypical Antipsychotic Agents

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
Drug class	Dibenzo-diazepine	Benzio-xazol	Thienoben-zodiazepine	Dibenzo-thiazepine	Benziso-thiazolyl piperazine
Potency	50	1	4.0	80	20
Time to peak plasma conc. (hrs)	3	1.5	5	1.5	4
Protein binding (%)	92 - 95	90	93	83	98 - 99
Active metabolites	No	Yes	No	No	No
Metabolism	CYP1A2, CYP3A4	CYP2D6	CYP1A2, CYP2D6	CYP3A4	CYP3A4
Elimination half-life (hrs)	10 - 100	6 - 24	20 - 70	4 - 10	3 - 10[1]

MD Jibson. J Psychiatric Research 32 (1998) 215-228

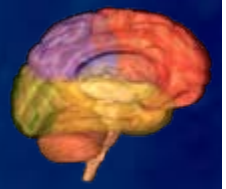


Antipsychotic Agents
Side Effect Profiles

0 = none; + = mild; ++ = moderate; +++ = severe

	Conventional antipsychotics	Atypical Antipsychotics			
		Clozapine	Risperidone	Olanzapine	Quetiapine
EPS	+/+++	0	0/+	0/+	0
TD	+/+++	0/+	0/+	0/+	0/+
Seizures	0/+	+++	0	0	0
Sedation	+/+++	+++	+	++	++
Anticholinergic effects	+/+++	+++	0	0/+	0

Adapted from Masand PS et al. Handbook of Psychiatry in Primary Care 1998



Antipsychotic Agents
Side Effect Profiles *(cont'd)*

0 = none; + = mild; ++ = moderate; +++ = severe

Atypical Antipsychotics

	Conventional antipsychotics	Clozapine	Risperidone	Olanzapine	Quetiapine
Hypotension	+/+++	+++	0/+	0/+	++
Liver transaminase increase	+	+	0	+	+
Antihistaminic effects	+/+++	+++	0	+	++
Prolactin increase	+/++	0	++	+	0
Weight gain	+	+++	+	++	+

Adapted from Masand PS et al. Handbook of Psychiatry in Primary Care 1998

Suggested Treatment in Acute/urgent Situations for Psychosis in Late Life with Atypical Antipsychotics

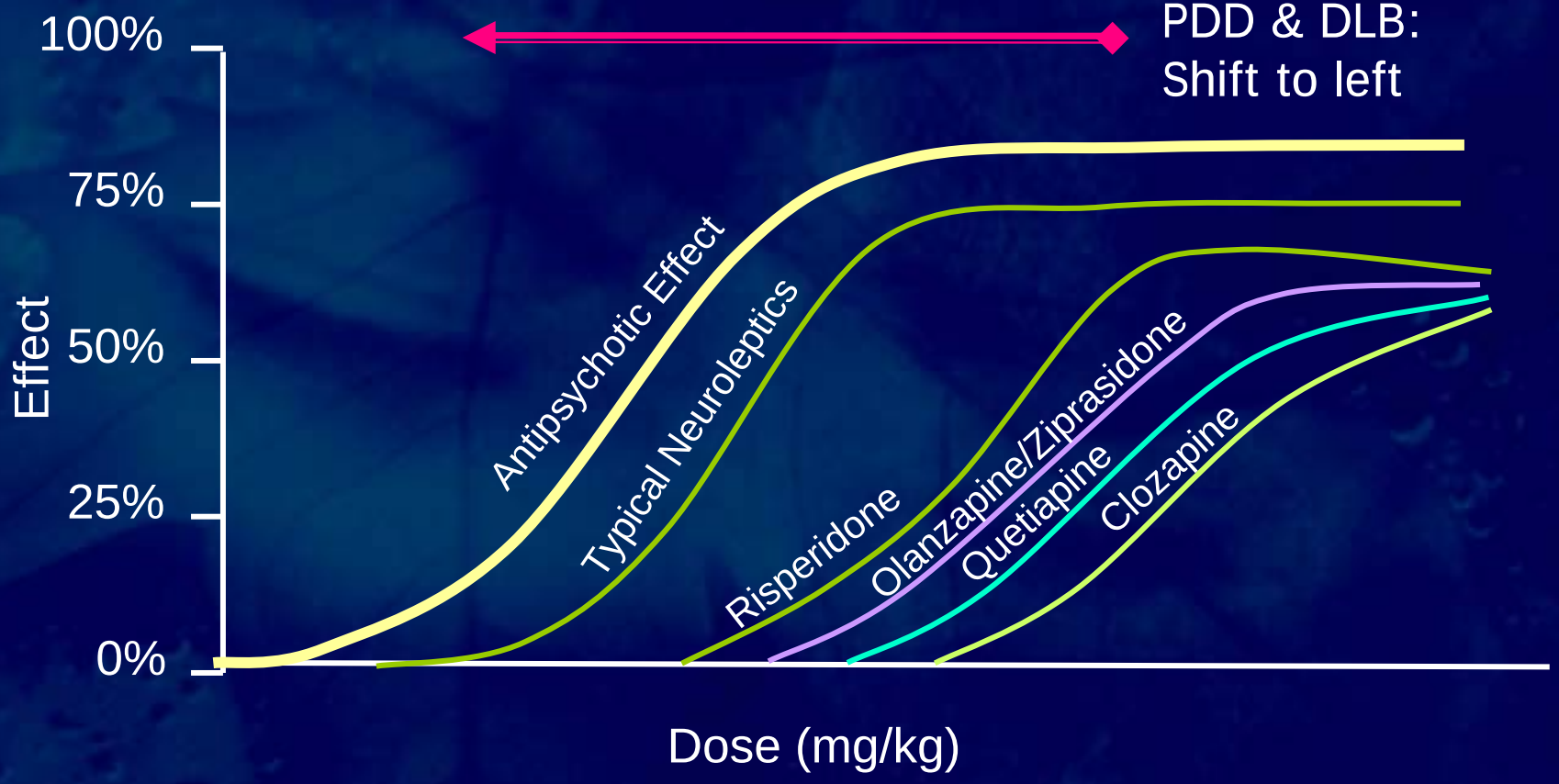
Atypical Medication	Usual dose and formulation	Usual frequency	Maximum dose / 24 hours
Risperidone	0.25-1 mg, PO Tabs or Liquid / M-tab	Q2-4 hours as needed and tolerated	2 mg for many dementia patients Not DLB / PD May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.
Olanzapine	2.5-5 mg PO Tabs /Zydis Note: IM formulation is available but there is little experience with its use in Canada with the elderly dementia population. Dosage 2.5 mg-5 mg IM, max 10 mg/24 hours. Not given IV.	Q2-4 hours as needed and tolerated	10 mg for dementia patients May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.
Quetiapine	12.5 – 25 mg BID		75.0 mg BID (150.0 mg tab split = 2 X 75.0 mg)

Guidelines for Maintenance Therapy of Psychosis in Late-Life with Atypical Antipsychotics

Atypical Antipsychotic	Starting Dose (mg/day)	Usual Daily Dose (mg/day)	Maximum Dose
Risperidone	0.25 mg In very old, frail or LBD or PD patients Usual starting dose is 0.5 mg May be increased Q3 -5 days by 0.25 mg – 0.5 mg as tolerated	1 mg/day for most dementias - not for LBD/PDD May be given as single dose or divided dose, as tolerated	2.0 mg/day for most dementias - not for DLB/PDD Doses may be higher (e.g. schizophrenia) or lower (e.g. LBD, PD) Official indication for BPSD in Canada
Olanzapine	1.25 -2.5 mg In very old, frail or LBD or PD patients Usual starting dose is 2.5 – 5 mg May be increased Q3-5 days by 1.25-2.5 mg as tolerated	5-10 mg/day for most dementias – not for LBD/PDD May be given as single dose or divided doses as tolerated	10 mg/day for most dementias – not DLB/PDD Doses may be higher (e.g. schizophrenia) or lower (e.g. LBD or PDD)
Quetiapine	6.25 – 12.5 mg In very old, frail or LBD or PD patients Usual starting dose is 12.5 – 25 mg May be increased Q3-5 days by 25-50 mg as tolerated	100 mg/day for most dementias – may be lower for LBD/PDD Wide range of dosing May be given as single dose or divided doses as tolerated	150 mg/day – some dementia patients need higher doses Wide range of dosing Consider first with LBD or PDD patients Doses may be higher (e.g. for schizophrenia) or lower (e.g. LBD or PDD)

Antipsychotic & EPS: DLB & PDD

Litmus Test for neuroleptic sensitivity: Dose Response Curves
Conventional antipsychotics contraindicated



MD Jibson. J Psychiatric Research 32 (1998) 215-228;
Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms.J Clin Psychiatry. 2004;65 Suppl 11:16-22 .Baskys A.

2004 Alexopoulos Guidelines

Recommended Treatments

Psychotic Major Depression

ECT → first line Rx or AD + risperidone 0.75-2.25 mg/day

Olanzapine 5-10mg/day or quetiapine 50-200 mg/day

Duration of antipsychotic use: 6 Months

Delusional Disorder

Antipsychotic is the only treatment recommended

Risperidone 0.75-2.5 mg/day preferred

Olanzapine 5-10mg/day or quetiapine 50-200 mg/day

Duration of treatment: 6 months-indefinitely at the lowest effective dose

Late-life Schizophrenia

Risperidone (1.25-3.5 mg/day) preferred

Quetiapine (100-300 mg/day), olanzapine (7.5-15 mg/day) are high second line

Duration of treatment: indefinite treatment at the lowest effective dose

2004 Alexopoulos Guidelines

Recommended Treatments

For Mild Geriatric Non-psychotic Mania

Mood stabilizer alone; D/C Antidepressant

For Severe Non-psychotic Mania

First: Mood stabilizer alone; D/C Antidepressant

Next: Add an antipsychotic / add or change mood stabilizer

For Psychotic Mania

Treatment of choice is a mood stabilizer plus an antipsychotic

Risperidone (1.25-3.0 mg/day) and olanzapine (5-15 mg/day) are first-line options in combination with a mood stabilizer for mania with psychosis

Quetiapine (50-250 mg/day) high second line

Duration: Mania with psychosis, 3 months

2004 Alexopoulos Guidelines

Recommended Treatments

Diabetes, dyslipidemia, or obesity:
Avoid clozapine, olanzapine, and conventional antipsychotics (especially low- and mid-potency).

Parkinson's disease
Quetiapine is first line for a patient with Parkinson's disease

QTC prolongation or congestive heart failure:
Avoid clozapine, conventionals (especially low- and mid-potency) and ziprasidone antipsychotics

For patients with cognitive impairment, constipation, diabetes, diabetic neuropathy, dyslipidemia, xerophthalmia, and xerostomia
Risperidone, with quetiapine high second line