

Depression in older patients: Pharmacotherapeutic considerations

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Roles

- **Research**
 - *Schlegel Research Chair in Geriatric Pharmacotherapy.*
 - *Alzheimer's disease and related disorders*
- **Clinical Geriatric Pharmacologist**
 - *CFFM Memory Clinic*
- **Teaching**
 - *UW School of Pharmacy*
 - *AHS Health Studies & Gerontology*
 - *McMaster School Of Medicine*



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Astra-Zeneca-adherence
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Ad board: Purdue

Geriatric Depression

- ▶ 87 yo female, lives alone, referred for evaluation of memory problems.
- ▶ History taking reveals:
 - Forgets to take medicines, doesn't know what they are for.
 - Has trouble concentrating.
 - Anxiety, sadness, lack of reactivity, motor retardation, decreased energy, apathy, decreased self esteem, "I've lived long enough".
- ▶ Comorbidities:
 - Hyperlipidaemia (pravastatin 20mg daily, ASA 81 mg daily)
 - Hypothyroidism (T₄ 175 ug daily)

Geriatric depression

- ▶ 66 yo female complains of:
 - Word finding difficulty, forgets passwords, forgets details of conversations, misses appointments, decreased ability to multitask.
 - Lack of energy, lack of interest in usual pleasurable activities, social withdrawal, hypersomnia.
- ▶ Cognitive testing nominal
- ▶ Comorbid conditions:
 - Sleep apnea
 - Migraines
 - Urge and stress incontinence

Epidemiology

- ▶ Depressive symptoms in those >65 years in community:
 - ~ 15%
- ▶ Prevalence of major depression in
 - Community: ~ 5%
 - Nursing home: ~15-25%
- ▶ More common in those w the three Cs:
 - CNS Dx, CVD, CA
- ▶ 2X as many women as men are affected.
- ▶ ***NOT a normal consequence of ageing***
 - *Lebowitz BD, et al. JAMA 1997;278:1186-1190.*

Under-recognised & undertreated

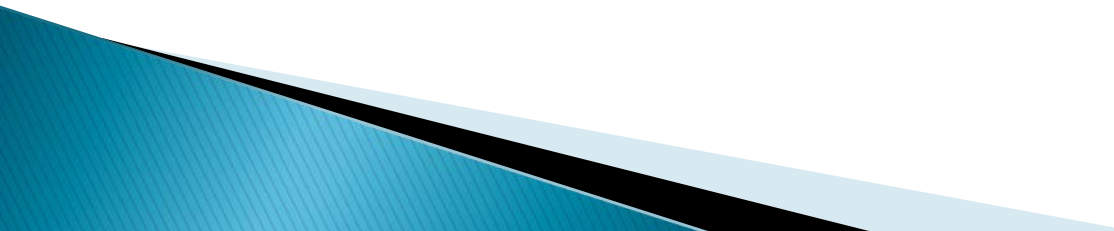
- ▶ Nursing Homes: 10.9% prevalence
 - 55% receiving antidepressants.
 - 32% at inadequate dose.

- ▶ Home Care: 13% prevalence
 - 22% receiving antidepressants.
 - Correct identification by NPs in 37%.

- ▶ Primary care
 - 42% receiving antidepressants.
 - 32% at inadequate dose.

Brown MN et al. J Am Geriatr Soc 2002;50:69-76, Bruce ML et al. Am J Psychiatry 2002;159:174, Brown EL, et al. J Am Geriatr Soc 2004;52:995-999, Unutzer J, et al. J Am Geriatr Soc 2003;51:505-514.

Clinical presentation

- ▶ May be very different in older people.
 - ▶ Patient and health professionals often do not recognize presenting symptoms as depression.
 - ▶ “Old people who are...morose, petulant, ill-tempered, and hard to please– these are faults of character not of age.” 43 BC
- 

Somatic complaints may be the focus of an encounter w HCP

- ▶ Headaches, pain or discomfort, stomach cramps, constipation, heavy feeling in abdomen, palpitations, burning upon micturition.
- ▶ Often leads to polypharmacy



Clinical presentation

▶ Anhedonia



- ▶ *Early AM awakenings (3–4AM) (vs. trouble falling asleep in anxiety)*



Clinical presentation

- ▶ Preoccupation with guilt, feelings of worthlessness or hopelessness & thoughts of suicide



Clinical presentation

- ▶ Anorexia, weight loss
- ▶ Anergia, anxiety, anger
- ▶ Subjective memory complaints
- ▶ Hoarding
- ▶ Complicated grief
- ▶ Self-neglect
- ▶ Frailty
- ▶ Fear of falling
- ▶ Irritability
- ▶ Hostility
- ▶ Anxiety symptoms
 - Worry
 - Obsessive ruminations
- ▶ Exacerbation of underlying diseases

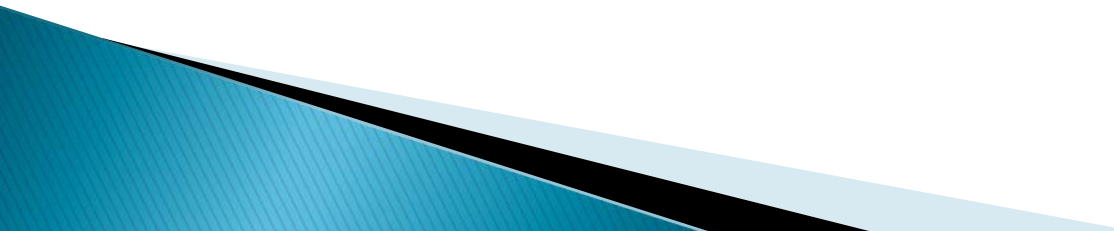
Clinical presentation

Cognitive symptoms

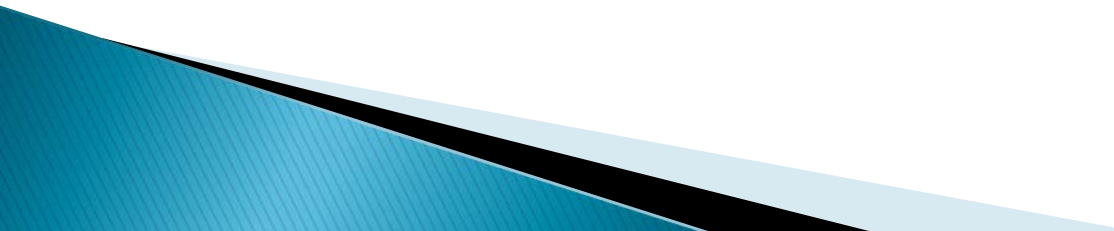
1. ↓ selective attention
2. ↓ working memory/retrieval
3. ↓ new learning
4. ↓ processing speed
5. ↓ executive function

How would this present in a patient?
i.e., how is this operationalised?

Burden of Depression

- ▶ Impairs recovery from stroke, hip #s, pulmonary disease
 - ▶ May lead to functional impairment & NH placement
 - ▶ Increased physician & ER visits
- 

Burden of Depression

- ▶ Increased medication use
 - ▶ **Increased mortality** overall, and in post-MI patients [also the case for minor depression in older men].
 - ▶ **Successful suicide [esp in older males]**
- 

DSM-IV-TR[®] Diagnostic Criteria for MDD

- ▶ The presence of one or more major depressive episodes

- ▶ ≥ 5 of the following have been present during the same 2-week period and are a change from previous function
 - Depressed mood
 - Loss of interest or pleasure
 - Significant weight loss or gain (>5% in 1 month)
 - Hypersomnia or insomnia
 - Fatigue or loss of energy
 - Psychomotor agitation or retardation
 - Feelings of worthlessness or excessive/inappropriate guilt
 - Diminished ability to think or concentrate
 - Recurrent thoughts of death or suicidal

DSM-IV-TR[®] Diagnostic Criteria for MDD

- ▶ At least one of the symptoms is depressed mood or loss of interest or pleasure.
- ▶ Differential diagnosis to rule out other psychiatric disorders, general medical conditions, or substance/treatment-related disorders
- ▶ From the point of view of DSM-IV/V, there is no such thing as “Geriatric depression”
- ▶ The same can be said of Health Canada or FDA

Screening

- ▶ Geriatric Depression Scale (GDS; validated)
15 item scale (≥ 5 points or positive responses is diagnostic)
 - ▶ 15 or 30 item, self-report
 - ▶ Eliminates somatic and vegetative symptoms
 - ▶ Validity decreases with cognitive impairment
- ▶ Cornell Scale for Depression in Dementia
 - Scoring system:
 - >8 suggestive of depression
 - >12 means probable depression

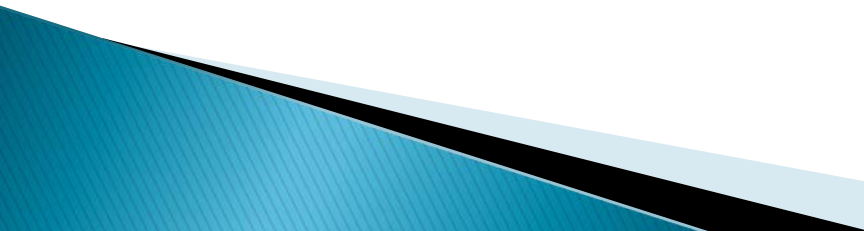
Screening

- ▶ Two item scale (PHQ-2):
 - During the previous 2 weeks.....
 1. Have you often been bothered by feeling down, depressed or hopeless?
 2. Have you often been bothered by having little interest or pleasure in doing things?

(“Yes” answer to either is considered positive)
- ▶ Sensitivity: 100%; Specificity:77%; PPV: 14%

NEJM: 357:22; 11/29/07

Differential Diagnosis

- Ordinary Unhappiness, Adjustment Disorder, Grief
 - **Medical Problem vs. Depression**
 - **Dementia vs. Depression**
 - Executive dysfunction may predict a poor or delayed response to antidepressants
 - Personality Disorder vs. Depression
 - Substance Abuse vs. Depression
 - Other major mental illness vs. depression
 - Comorbid (depression + one of the above)
 - **Iatrogenic depression (rare)**
- 

Differential Diagnosis

DEPRESSION

- ▶ Subacute onset
- ▶ Family recognition early
- ▶ Rapid progression
- ▶ Impairment inconsistent over time
- ▶ **Pt admits deficits**

- ▶ **Appears depressed**

- ▶ Anhedonia

- ▶ **Abstract thought usually normal**

- ▶ “I don’t know” response to questions
- ▶ Pt often unconcerned

DEMENTIA

- ▶ Insidious onset
- ▶ Delayed family recognition
- ▶ Slow progression
- ▶ Impairment consistent; slow, gradual decline
- ▶ **Pt denies/unaware of deficits**

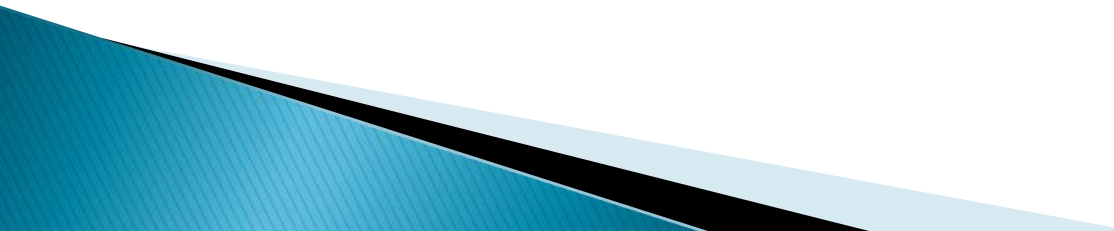
- ▶ **Not depressed**

- ▶ Can experience pleasure

- ▶ **Abstract thought impaired**

- ▶ Near miss answers
- ▶ Pt tries to cover up

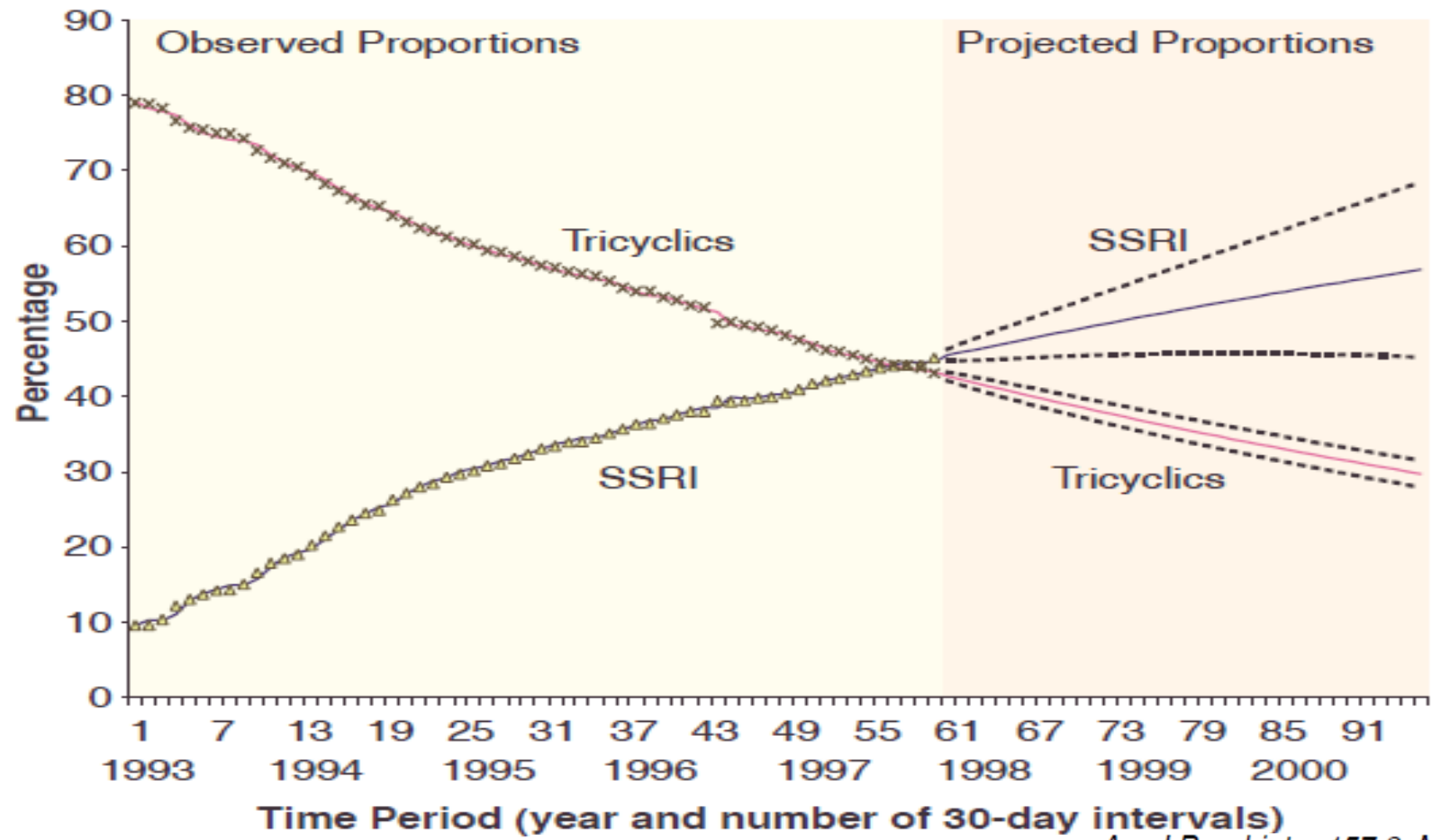
Checking in

- ▶ Depression is a normal part of ageing.
 - ▶ Depression is more common in NH settings.
 - ▶ Most common sx's: hypersomnolence, increased appetite, or impaired concentration?
 - ▶ Suicide is more or less common?
- 

Epidemiology of AD use in older people

- ▶ Overall use by >65 is $\sim 2-5\%$
- ▶ ADs can be used for other indications
 - Pain, anxiety, sleep disorders

FIGURE 2. Changes in the Proportions of Antidepressant Prescriptions Attributable to SSRIs and to Tricyclic Antidepressants in a Population-Based Study of Elderly Ontario Residents, 1993–1997^a

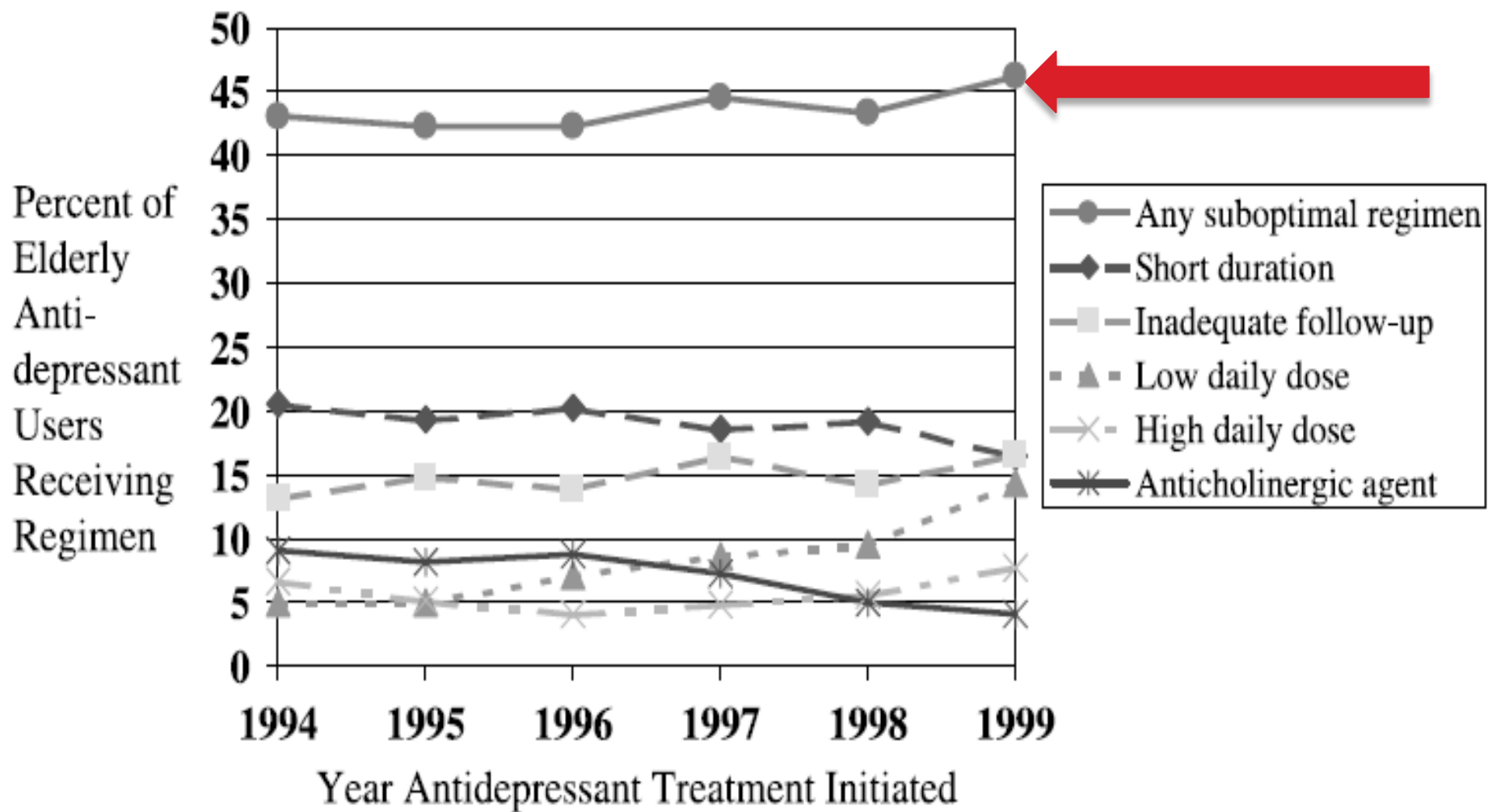


Am J Psychiatry 157:3, March 2000

^a Solid lines to the right of the vertical division represent the best estimate of the projected proportions after 1997. The dotted lines represent 95% CIs around these projected estimates.

Suboptimal antidepressant regimens

Potentially hazardous regimens	11.9
Anticholinergic tricyclic	7.3
High daily dosage	5.3
Low-intensity regimens	34.8
Low daily dosage	7.6
Short duration (<1 mo)	19.3
Inadequate follow-up	14.8
Any suboptimal antidepressant regimen	43.3



Goals of therapy

▶ Response?

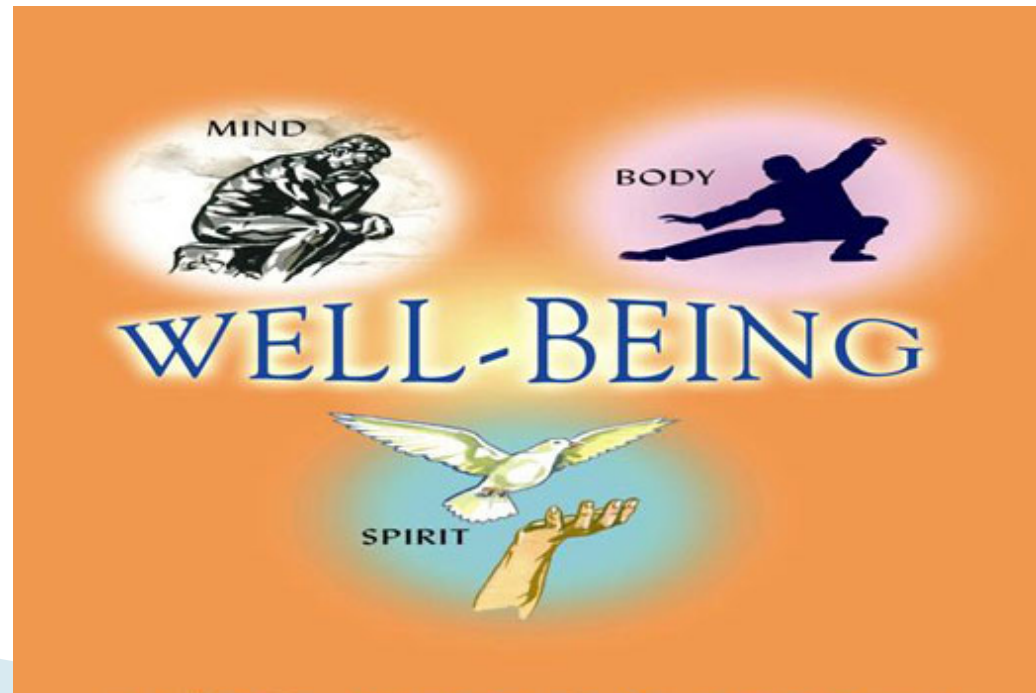
- Typically defined as $\geq 50\%$ decrease in depression score.
- Not good enough

▶ *Remitters have better outcomes than responders for:*

- *QoL*
- *Functional status*
- *Overall well being*
- *Health care costs*
- *Productivity*

Remission

- Gold standard
- Defined as euthymia.
- May be difficult to achieve.
- Never give up....



Consider:

Response Rates

Drug: 35–72%

Placebo: 30–52%

Remission Rates

Drug: 28–44%

Placebo: 18–38%

Antidepressant selection issues

1. ~ 50% of studies do not separate from placebo.
2. When used in *appropriate* doses there is no convincing evidence that any antidepressant is superior to another.
3. One must consider toxicity, drug–disease interactions & drug–drug interactions when selecting drug.

Drugs to avoid in older people

- ▶ Fluoxetine (t $\frac{1}{2}$ & weight loss)
 - ▶ DDIs: CYP 2D6

- ▶ Fluvoxamine (nausea)

- ▶ Paroxetine
 - Anticholinergic properties
 - Potential for DDIs: CYP 2D6

Drugs to avoid

▶ TTCAs

▶ WHY?

- Anticholinergic effects– CNS & peripheral effects, falls, functional impairment.
- Cardiovascular effects (↓bp, arrhythmias)
- ↓ elimination– renal & hepatic

JAMA 1997;278:1186-90,

Arch Intern Med 1997;157:1531-36,

CMAJ 1997;157:1061-7

Generally useful drugs

- ▶ Sertraline, citalopram, escitalopram
- ▶ Mirtazapine, venlafaxine, duloxetine
- ▶ Desipramine, nortriptyline

Rojas-Fernandez C. CPJ 2012;145:128-35.

Rojas-Fernandez CH. Res Gerontol Nurs. 2010 Jul;3(3):176-86

Pros and cons of select antidepressants

Mirtazapine

- Mild anticholinergic & antihistaminic properties
- Can contribute to weight gain
- Sedating
- Low potential for drug interactions

Citalopram

- Mild antihistaminic properties
 - Low potential for drug interactions
- 

Pros and cons of select antidepressants

Venlafaxine

- Low potential for drug interactions
- Nausea (may be less tolerable in frail older people)
- Increased blood pressures at higher (> 150mg/day) doses

Pros and cons of select antidepressants

Bupropion

- May be useful for
 - Apathy, amotivation, hypersomnia, parkinson's disease
- Not a good choice for:
 - Co-morbid anxiety, concomitant loss of appetite and/or weight loss, concomitant seizure disorder

Clinical use of antidepressants

- ▶ **Start with low doses**
 - e.g., sertraline 25mg od, citalopram 5–10mg daily
- ▶ Titrate slowly
- ▶ **Do not under dose!**
- ▶ Baseline & f/u lab monitoring:
 - **Sodium** (SIADH: more common in older people)

Common & infrequent side effect of SRIs

▶ Common side effects

- Nausea, anorexia, diarrhea
- Insomnia or somnolence
- Tremor, sexual dysfunction

▶ Infrequent

- SIADH, EPS, hypofrontal syndrome, bleeding

Additional considerations


- ▶ Methylphenidate (10–20mg daily) & rapid response (within one week)
 - Wallace AE. Am J Psychiatry 1995;152:929–31.
- ▶ Trazodone as hypnotic, even for those taking other antidepressants—not likely result in serotonin toxicity.
 - Gillman PK. Biol Psychiatry 2006;

Additional considerations

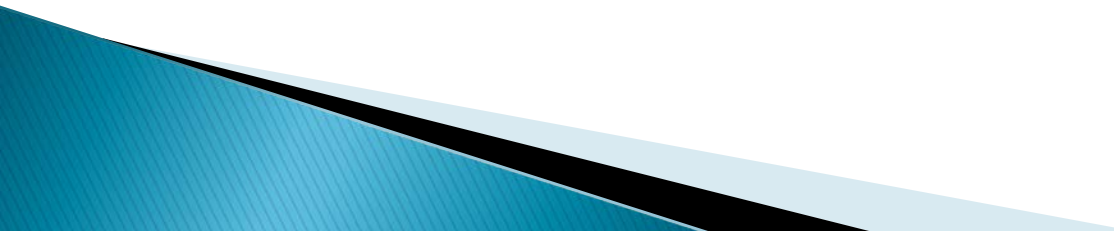
- ▶ **Weight issues and appetite**
 - Useful drugs:
 - Mirtazapine
 - Nortriptyline
 - ? Methylphenidate

- ▶ **Nortriptyline, desipramine & pain syndroms**
 - Even these drugs may be difficult to use
 - Koenig et al. J Gen Intern Med 1989;4:498-05.

Patient counselling

- ▶ Physical symptoms tend to improve first (1–3 weeks)
 - ▶ Cognitive symptoms take longer (4+ weeks) and may not fully resolve.
 - ▶ Functionality may take longer to return.
 - ▶ Importance of adherence & not stopping drug suddenly to avoid withdrawal symptoms
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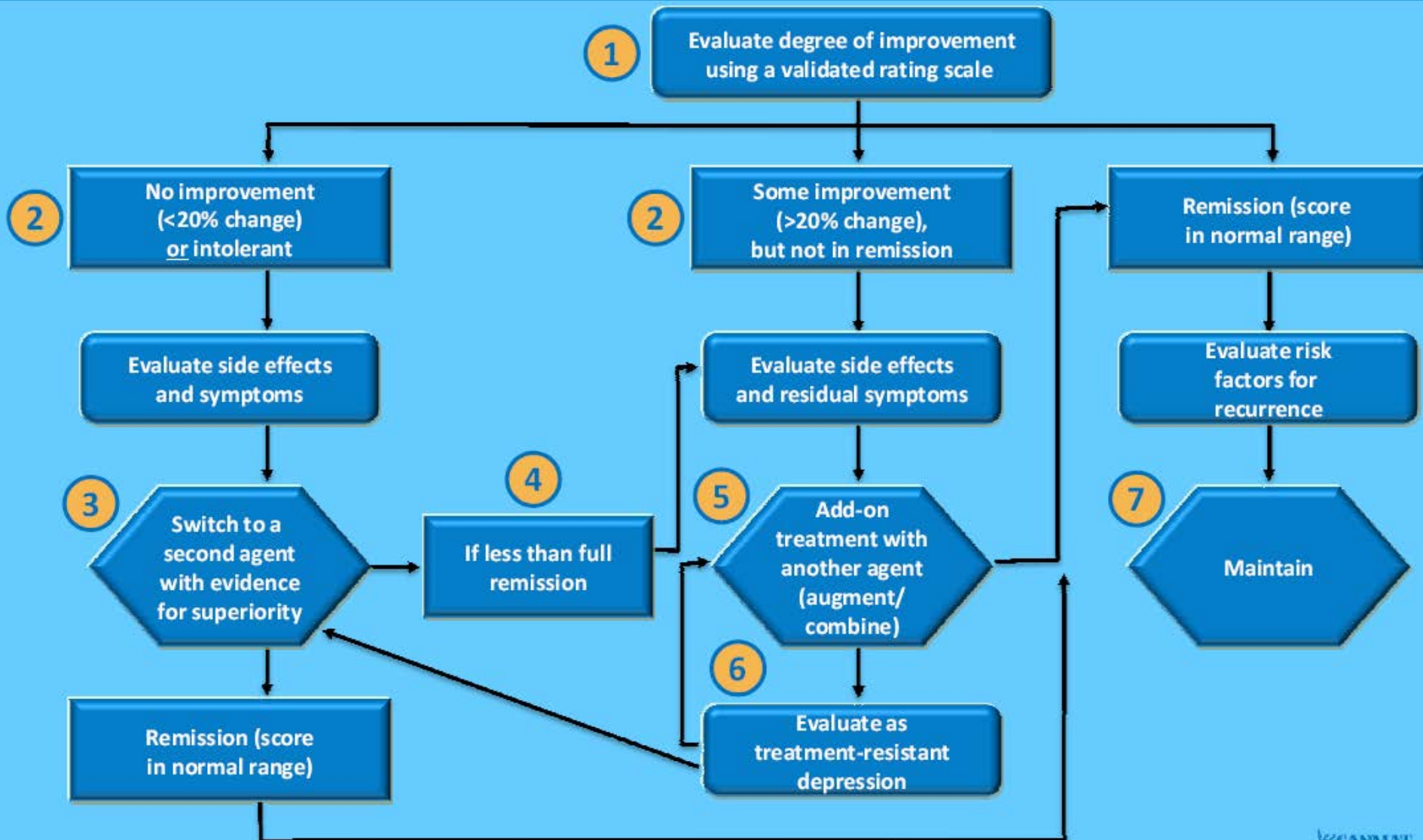
Partial or non-response: what to do?

1. Assess reversible causes:
 - Subtherapeutic dosing
 - Non-adherence
 - Drug-drug interactions
 - Alcohol or other substance abuse
 1. If no response whatsoever: switch drugs
 2. Partial response: See slides that follow
- 

Partial or non-response: what to do?

- ▶ **NB: Early response predicts later response and vice versa.**
 - See: V. Henkel et al. *Journal of Affective Disorders* 115 (2009) 439–449.

Algorithm for Managing Limited Improvement with a First-line Antidepressant



Rationale for Adjunctive Treatment to Antidepressant Therapy

- ▶ Help improve clinical efficacy by treating unresolved symptoms^{1,2}
- ▶ May increase the spectrum of activity to different neurotransmitters by targeting additional receptors^{3,4}

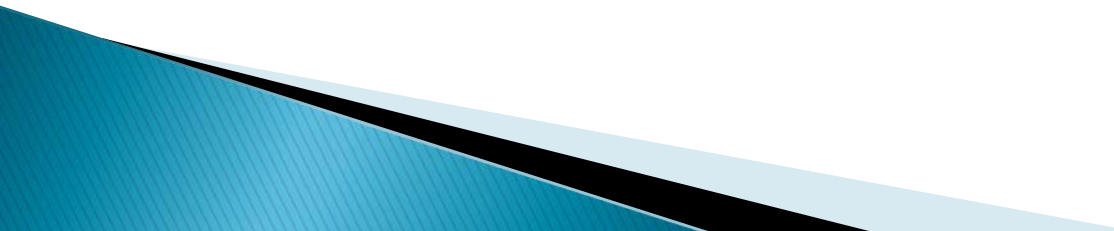
1. Trivedi MH et al. *N Engl J Med*. 2006;354:1243-1252.

2. Nierenberg AA et al. *Am J Psychiatry*. 2006;163:1519-1530.

3. de la Gandara J et al. *Acta Psychiatr Scand Suppl*. 2005;(428):11-13, 36.

4. Blier P. *J Clin Psychiatry*. 2001;62 (suppl 4);7-11.

Adjunctive Treatment Categories

- ▶ Lithium
 - ▶ T3 or T4
 - ▶ Mirtazapine
 - ▶ Modafinil
 - ▶ Lamotrigine
 - ▶ Buspirone
 - ▶ Bupropion
 - ▶ Folate / Methylfolate
 - ▶ Atypical Antipsychotics– aripiprazole, quetiapine
- 

New findings challenge us...



FDA Drug Safety Announcement

- ▶ [8-24-2011] The FDA is informing healthcare professionals and patients that the antidepressant **citalopram (Celexa) should no longer be used at doses greater than 40 mg per day because it can cause abnormal changes in the electrical activity of the heart.** Studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day.

FDA Data Summary

Table 1: Increase in the Corrected QT Interval for Citalopram (FDA Analysis)

Citalopram dose	Increase in QT Interval (ms)	90% Confidence Interval (ms)
20mg/day	8.5	(6.2,10.8)
60mg/day	18.5	(16.0,21.0)
40mg/day	12.6*	(10.9,14.3)*

*Estimate based on the relationship between citalopram blood concentration and QT Interval

FDA Information for Healthcare Professionals

- ▶ **Citalopram should no longer be prescribed at doses greater than 40mg per day**
- ▶ It should not be used in patients with congenital long QT syndrome
- ▶ Patients with heart failure, bradyarrhythmias or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs, are at higher risk of developing TdP
- ▶ **Hypokalemia and hypomagnesemia should be corrected before administering citalopram**

FDA Information for Healthcare Professionals

- ▶ Consider more frequent **ECG monitoring** in patients with heart failure, bradyarrhythmias or patients on concomitant medications that prolong the QT interval.
- ▶ **20mg per day is the maximum** recommended dose for patients with hepatic impairment, **who are greater than 60 years old**, who are CYP 2C19 poor metabolizers or who are taking concomitant cimetidine (Tagamet) because these factors lead to increased blood levels of citalopram, increasing the risk of TdP.

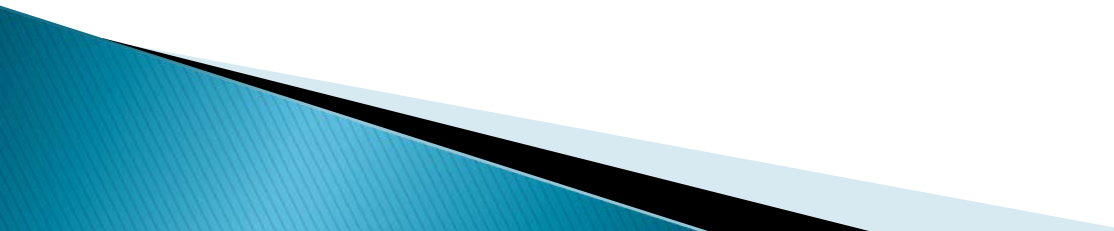
Other considerations

- ▶ Available cases of TDP have **confounders**
 - E.g., other drugs, diseases.
- ▶ C_p CIT in aged (73–90) given 5–20mg are comparable to younger people given 40mg, i.e., increased exposure to drug.
- ▶ C_p vary by **more than 2 fold**, as does $t_{1/2}$.
- ▶ QT increases are **not linearly** related to TDP risk.


Geriatric depression

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 - Word finding difficulty, forgets passwords, forgets details of conversations, misses appointments, decreased ability to multitask.
 - Lack of energy, lack of interest in usual pleasurable activities, social withdrawal, hypersomnia.
- ▶ Cognitive testing nominal
- ▶ Comorbid conditions:
 - Sleep apnea
 - Migraines
 - Urge and stress incontinence

Conclusions

- ▶ Depression is NOT part of normal ageing
 - ▶ Depression can be successfully treated
 - ▶ Presentation may be different in older people
- 

Conclusions

- ▶ Despite increasing antidepressant use, many patients do not achieve remission.
 - ▶ The goal of therapy is REMISSION...never give up.....
 - ▶ Pharmacotherapy must be *carefully tailored* to individual patient's needs
 - ▶ Geriatric depression is often an interplay of various factors (e.g., depression, cognitive impairment, etc)
- 

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Additional resources

- ▶ www.nimh.nih.gov
- ▶ www.aagpgpa.org
- ▶ Impact-uw.org
- ▶ www.healthinaging.org
- ▶ <http://www.cpa-apc.org/index.php>

