

## DRUG TREATMENT OF LATE LIFE DEPRESSION

October 11, 2011

Glen L. Stimmel, PharmD, BCPP  
Professor of Clinical Pharmacy / Psychiatry  
University of Southern California  
School of Pharmacy and Keck School of Medicine

## MY PERSPECTIVE

Psychiatric pharmacist for 39 years:

- 30 yrs practice in variety of psychiatric settings (hosp, clinics)
- 9 yrs in primary care clinics – depression consult service in rheumatology & geriatrics primary care clinic at Los Angeles County/USC Medical Center

## LAC/USC GERIATRICS CLINIC

~400 new admissions/year; ~1200 open cases

Mean age – 75yo (28% in 60s; 44% in 70s; 23% in 80s; 5% 90s & 100s)

~20% diagnosed with major depression

~20% taking an antidepressant drug  
psychotherapy available in clinic

14% cognitive disorder

## QUESTION

For which one of the following depressive conditions in the elderly is antidepressant drug treatment appropriate?

- Bereavement
- Major depression
- Adjustment disorder
- All of the above

## ANTIDEPRESSANTS – OVERUSED ?

Too many pts who do not meet criteria for major depression or dysthymia receive longterm low dose antidepressants for years

Situational depression, bereavement, adjustment disorder with depressed mood are not indications for antidepressant drugs

## Psychiatric Pharmacist Consult Service

New patients referred for antidepressant initiation in a rheumatology clinic:

- 20% did not need antidepressant drug therapy
- 40% referred to mental health (psychotherapy indicated; bipolar, psychotic sx, anxiety dx)
- 40% kept in rheum clinic and treated

In first year, found many pts on sertraline 50 mg for years – often no valid indication for Rx

### ANTIDEPRESSANTS – UNDERUSED?

- ~25% of all adults in U.S. will have a major depressive episode sometime in their life
- 50% of pts with major depression are not identified in primary care settings

### OVERUSED or UNDERUSED?

Both are true

Some pts on antidepressant should not be; some pts who could benefit from an antidepressant have not been identified

Goal – get the correct patients on antidepressant drug therapy

### QUESTION

A 72yo male experiences his first major depressive episode 3 months after a stroke that left him with significant left-sided permanent paralysis. Would an antidepressant drug be indicated?

YES

NO

### COMORBIDITIES STROKE

Post-stroke major depression (PSD) occurs in 20-30% of pts within one year of the stroke

Peak prevalence 3-6 mo after stroke

Clinicians and family must be vigilant for signs of depression, and get treatment

Antidepressants are just as effective for PSD

### CAN ANTIDEPRESSANTS PREVENT PSD ? (NO)

Escitalopram vs group therapy x 1 year in non-depressed stroke patients (Robinson JAMA 2008)

Depression developed in 22% of placebo pts, 12% in group therapy, 9% in escitalopram

“Pts on placebo were 4.5x less likely to develop depression with drug than placebo” (drug company hype)

This data also says - 88% of stroke pts do not develop depression – will we give 88% of patients an antidepressant for no reason?

Another study – 50mg sertraline not effective in preventing PSD 6mo after stroke (Almeida J Clin Psychiatry 2006)

Better idea – be vigilant for 6-12 mo after stroke for major depression

### COMORBIDITIES DEMENTIA

Is it **dementia** or **depression**? Both share common symptom of cognitive impairment

But often there are differences in behavior – constant negative spin on everything (depression) vs. trying to hide or give excuses for difficulties (dementia)

Language & motor difficulties are common in dementia (can't remember simple things, pen, or how to tie laces) while in depression language & motor function often remains intact

## COMORBIDITIES DEMENTIA

When in doubt, assume depression and initiate antidepressant since depression is treatable, dementia is not

This differential dx is sometimes not so critical, since depression and dementia often co-exist

## ANTIDEPRESSANT DRUG THERAPY

What is the best antidepressant drug for an elderly patient?

POOR question!

There is NO best antidepressant for any group of patients

There is only a best drug for an **individual** pt

## SSRI Antidepressants

Fluoxetine	(Prozac)	5-HT
Sertraline	(Zoloft)	5-HT
Paroxetine	(Paxil)	5-HT
Fluvoxamine	(Luvox)	5-HT
Citalopram	(Celexa)	5-HT
Escitalopram	(Lexapro)	5-HT

## FLUOXETINE

Usually should NOT be used in elderly

- Most activating SSRI – so AM dosing activation can be good or bad, but older patients more often have anxiety as part of their depression
- VERY long  $t_{1/2}$  - 3 days / 9 days, even longer in the elderly – ss levels in 2 mo!

## PAROXETINE

Usually should NOT be used in elderly

- A more sedating SSRI – HS dosing – usually good
- The most **anticholinergic** SSRI – very bad cognitive effects, constipation, urinary retention
- Greatest weight gain among SSRIs – usually good
- Most sexual dysfunction among SSRIs – bad (contrary to popular belief, sex does not end at 60)
- No active metabolites – w/d worse if d/c abruptly

## CITALOPRAM

Excellent choice in many elderly AM or HS dosing OK

Least likely SSRI to have P450 drug-drug interaction concerns

Many of our pts take 10 - 20 drugs

Recent QT concern re doses >40mg; liver/>60yo = 20mg/d maximum

No info yet if escitalopram is any safer

## Other Antidepressants

Bupropion	(Wellbutrin)	DA, NE
Venlafaxine	(Effexor)	5-HT, NE
Desvenlafaxine	(Pristiq)	5-HT, NE
Mirtazapine	(Remeron)	NE, 5-HT-1
Duloxetine	(Cymbalta)	NE, 5-HT
Trazodone	(Oleptro) 2010	5-HT, 2AC-
Vilazodone	(Viibryd) 2011	5-HT, 1A+/-

## MIRTAZAPINE

Excellent choice for many elderly  
Unique mechanism minimizes GI effects and sexual dysfunction  
Sedation & weight gain – bad in young, often a major benefit in the elderly – improves appetite & avoids use of hypnotic for sleep disturbance

## MIRTAZAPINE - Sedation

Inversely related to dose

5-10 mg	54%
20 mg	15%

Thus can choose degree of desired sedation - initial dose of 15 or 30 mg

## MIRTAZAPINE – Wt Gain

Weight gain (> 7% of body weight)

**8% of patients** (US) vs 1% in Europe

Inversely related to dose? uncertain

Often unwanted in younger patients, but often beneficial in elderly

Minor increased cholesterol, related to wt gain

## BUPROPION (Wellbutrin, Zyban)

- Mild dopamine agonist, metabolite is NE reuptake inhibitor (no direct 5-HT effect)
- Activating – anxiety, restlessness, insomnia
- Seizure risk – divided doses except XL
- GI, sexual dysfunction very low
- Concern in pts with psychotic sx

## TRAZODONE (Desyrel)

SSRI + 5-HT<sub>2A/C</sub> antagonist effect

Effective antidepressant at 300-600 mg/d

Prominent sedation & orthostasis

Priapism – rare but serious

Common use as hypnotic – 25-50 mg HS, most studies as adjunct to activating antidepressants

## TRAZODONE (Oleptro)

Extended release formulation, approved 2010  
Start at 150mg HS, go up to 375mg/d  
Sedation 46%; dizzy 25%; dry mouth 25%; nausea 21%;  
fatigue 15% (worse initially)  
Sexl dysfn ~5%, much less than SSRIs  
No comparison trials vs other antidepressants  
Relies on CYP4503A4 for metabolism, so caution if used  
with 3A4 inhibitors

## VILAZODONE (Viibryd)

SSRI + partial agonist of 5HT1A receptors  
(SSRI with built-in buspirone) ; 10-40mg/d  
Probably no dose adjustment in older pts  
Nausea, diarrhea, sedation/insomnia (?)  
Response rates ~40%; remission rates ~27%  
5 early studies - failed efficacy trials

Rickels K et al, J Clin Psychiatry 2009;70(3):326-333

Kahn A et al, J Clin Psychiatry 2011; 72 (4), 441-7

## VENLAFAXINE (Effexor)

Potent SSRI; NE effect **only** at higher doses ( $\geq$   
225 mg/day)  
Common: GI, sexual dysfunction  
Increased diastolic BP ( $\geq$  90 mmHg):  
100-300 mg/d 3-7%  
> 300 mg/d 13% **Monitor BP!**

## Desvenlafaxine (Pristiq)

Active metabolite of venlafaxine  
Doses > 50mg/d  $\rightarrow$  nausea in 50% of pts  
Rec dose for all pts – 50 mg/d  
Pure fantasy that the same dose will be  
effective for all patients !  
Only difference between desven and ven -  
desven is more expensive

## ADVERSE EFFECTS

Many are also commonly caused by other  
factors – what is actually due to the drug?  
Establish baseline before drug therapy  
begins: sexual function, sleep, weight,  
GI effects, vital signs  
Then monitor for **changes** in those findings  
Will lead to better management options  
Drugs too often wrongly blamed

## SEDATION - - ACTIVATION

**Most sedating**  
mirtazapine > paroxetine  
**Usually neutral**  
sertraline, citalopram, duloxetine  
**Most activating**  
bupropion > fluoxetine  
Match drug choice to patient's symptoms

## WEIGHT GAIN

**Most-** mirtazapine > paroxetine > other SSRIs

**Least -** bupropion, trazodone

What is drug effect vs improved appetite due to improved depressive symptoms?

? Mirtazapine vs prednisone ?

Atypical antipsychotic drugs - **much** worse

## SSRI SEXUAL EFFECTS

If a patient is sexually active, must counsel about antidepressant drugs and their potential for affecting sexual function

We usually warn pts about common possible side effects of drugs – those that occur in at least 5-10% of pts (GI effects & SSRIs; sedation with mirtazapine, etc)

What about drug-induced sexual dysfunction?

## SSRIs & ORGASM

	Delayed (%) men	Anorgasmia (%) men & women
Fluoxetine	51	34
Fluvoxamine	57	31
Sertraline	46	37
Paroxetine	59	48

If you don't ask, patient won't tell

Montejo-Gonzalez 1997

## BEST ANTIDEPRESSANT

“What is the best antidepressant drug for an elderly patient?”

Best drug is the one that a patient will actually take

Drug choice much less important vs. using a drug to its full benefit

## INDIVIDUALIZING DRUG SELECTION

Any past hx of antidepressant drug use?

Efficacy & adverse effect hx? Drug, dose, duration of Rx?

Pt attitude, + & - toward particular drugs?

Co-morbid diagnoses & meds

Presenting sx's – insomnia/anxiety/lethargy

## ANTIDEPRESSANT DRUG OF CHOICE

#1: Major depression and c/o insomnia

First & manage reasons for insomnia – pain, increased urination (BPH, DM), ...

Sedating antidepressant preferred over non-sedating drug plus hypnotic drug

## HYPNOTIC DRUGS IN THE ELDERLY

**Risks** are very high (cognition, falls)

**Benefits** are very limited

Most older patients with sleep complaints do not need a hypnotic drug

LAC/USC Geriatrics Clinic – among ~250 pt vists/month, < 10 are using a hypnotic drug

## REALISTIC EXPECTATIONS

WHAT IS NORMAL SLEEP ?

It is NOT immediate unconsciousness that lasts 8 hours without interruption every night

## NORMAL SLEEP IS

- Some nights –  
sleep onset takes a little longer
- Some nights –  
occasional interruptions in sleep
- Some nights –  
5 or 6 rather than 8 hrs of sleep

## REALISTIC EXPECTATIOINS

Good sleep hygiene practices or drug therapy will FAIL unless the patient understands that normal sleep means a return to a pattern of natural variations of occasional delayed sleep onset and nighttime awakenings

## ANTIDEPRESSANT DRUG OF CHOICE

#2: Major depression and 12 other drugs

Avoid CYP450 inhibitor antidepressants (most SSRIs), so consider citalopram or mirtazapine, or second-line escitalopram or venlafaxine

## ANTIDEPRESSANT DRUG OF CHOICE

#3: Major depression and already on amitriptyline 25mg for chronic pain  
Increase ami dose, or add an antidepressant?  
Ami's antidepressant dose is 150-300mg/day!  
Sedation, antichol, orthostatic hypotension, very poor pt adherence, cardiotoxic/lethal in OD of only 2 Grams

## QUESTION

After successful treatment of a first major depressive episode in a 68yo female with mirtazapine 30 mg/day x 2 months, how long should her drug treatment be continued?

- Can discontinue now
- 4 more months
- 10 more months
- Lifetime treatment is needed

## IDEAL DRUG THERAPY FOR MAJOR DEPRESSION

**Acute Phase** - **symptom remission**

6-8 weeks at full therapeutic dose

**Continuation Phase** - **prevent relapse**

4-5 months at **full** dose for all patients

**Maintenance Phase** - **prevent recurrence**

lifelong if 3+ episodes within 5 years

lifelong if first episode is  $\geq$  60 yo

## LIFELONG Rx FOR FIRST EPISODE IN ELDERLY

21 pts > 60yo successfully treated for 1<sup>st</sup> episode of major depression for 2 years had antidepressants discontinued

Over the next 2 yrs, 61% had relapse, 11/12 who relapsed resumed antidepressant, 10 had positive response

Relapse risk is higher in elderly, so recommend lifelong Rx after 1<sup>st</sup> episode

Flint Am J Psychiatry 1999

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- 15 mg/d
- 30 mg/d

## ANTIDEPRESSANT DOSE: ALL OR NOTHING

Acute dose = maintenance dose

Lower maintenance doses = relapse

The dose that gets you well is your maintenance dose, unless side effects are severe

## QUESTION

After successful treatment of a first major depressive episode in a 68yo female with citalopram 30 mg/day x 2 months, what should be her maintenance daily dose?

15 mg/d  
**30 mg/d**

## ONSET OF CLINICAL EFFECT

Physical symptoms (sleep, energy, appetite) may improve in first 1-2 weeks

Mood sx (dep mood, anhedonia, S/I) may take 3-4 weeks to show improvement

Don't wait 4 weeks to increase the dose – no change in physical sx after 1-2 weeks, increase dose

## WHAT IS AN ADEQUATE DRUG TRIAL ?

6-8 weeks at a given dose will allow assessment of the efficacy of that dose

Up to 12 weeks needed in **geriatric** patients

Drug judged to be ineffective **only** if adequate duration at top end of dosing range

12 wks citalopram 10 mg is **not** an adequate trial – just means 10 mg didn't work

## USUAL CARE IN PRIMARY CARE

Chart note: "Depression" or "crying"  
rarely see target sx of depression

Sertraline 25 mg QD #30, 2 refills

Next appointment - 3 months

## USUAL CARE IN PRIMARY CARE

3 mos later – typical patient comments:

"Sertraline helped a little, I take it once or twice a week."

"I took it for a week but it didn't work, so I stopped it."

"It worked really well, but my sister said it is addicting so I stopped it."

## USUAL CARE IN PRIMARY CARE

Starting doses continued for years, dose is never titrated upward

Starting doses often inadequate

So, many patients are *better*, but not *well*

Is half-treating a disorder appropriate?

Find all your pts still on their starting dose & reevaluate if they are in remission

## WHY ANTIDEPRESSANTS FAIL

Wrong indication –  
bereavement, adjustment disorder  
Inadequate dose or Rx duration  
Inadequate counseling  
“Treatment resistant depression” usually  
is inadequately treated depression

## KEYS TO MAXIMIZING ANTIDEPRESSANT OUTCOMES

- Individualize drug of choice
- Treat to full symptom remission
- Identify and manage adverse effects
- Ensure adequate dose and duration
- Adequately educate patient, set appropriate expectations

## CHOOSING A SECOND ANTIDEPRESSANT DRUG

Must identify why first drug is being stopped  
lack of efficacy?  
adverse effects?  
Answer dictates second drug of choice, and  
how quickly to switch

## CHOOSING A SECOND ANTIDEPRESSANT DRUG

Lack of Efficacy:  
More rapid switch needed – don't leave pt  
untreated any longer than necessary  
Assess relative adverse effect differences of  
first and second drug – eg. sedation  
Assess mechanism differences to determine  
if cross titration or rapid D/C is  
indicated

## SEROTONIN WITHDRAWAL SYNDROME

Dizziness, insomnia, fatigue, anxiety, nausea,  
headache, sensory disturbances  
Onset 2-3 days after D/C drug (but not  
fluoxetine), can last 2-3 weeks unless  
restart drug and taper more slowly  
Many pts skip doses, or SWS is a concern if  
giving drug holidays for sexl dysfunction  
But can't have w/d if substitute another  
serotonin agonist drug

## SEROTONIN SYNDROME

Possible when co-administer 5-HT drugs  
eg. SSRI + MAOI; SSRI + buspirone  
  
Anxiety, shivering, myoclonus,  
diaphoresis, tremor, hyperthermia;  
case reports of fatalities

## CHOOSING A SECOND ANTIDEPRESSANT DRUG

When switching drugs, abrupt D/C or slow taper?

paroxetine → mirtazapine Abrupt  
 sertraline → bupropion Slow  
 fluoxetine → bupropion Abrupt  
 fluoxetine → paroxetine VV Slow

## CHOOSING A SECOND ANTIDEPRESSANT DRUG

Switch due to adverse effects:

Chose a drug that does not cause the adverse effect of concern

Compliance with second drug is the primary concern

Egs. GI, sexual dysfunction, anxiety

Slower cross titration if 1<sup>st</sup> drug effective

## CASE # 1

## ANTIDEPRESSANT DISCONTINUATION RATES

WA primary care patients with major depression given newly prescribed antidepressants:

1 month	28%	
2 months	35%	
3 months	44%	
4 months	51%	Lin et al 95

## WHY PATIENTS STOP THEIR ANTIDEPRESSANTS

62%	disliked side effects
56%	believed treatment was no longer needed
50%	felt better
32%	felt treatment ineffective

Lin 1995

## TREATMENT ADHERENCE

Non-adherence to antidepressants in geriatric depression approaches 60%

Factors: (Wetherell, CNS Spectr 2003)

Lack of information	Cognitive impairment
Misperceptions	Adverse effects
Stigma	Cost
Lack family support	Lack transportation

## TREATMENT ADHERENCE

If a patient is non-adherent, find out WHY :

Adverse effects?      Fear, misinformation?  
Sx improvement?      Family pressure?  
Cognitive impairment? Cost?

Strategies to solve nonadherence will differ depending on the cause

Preaching, or scaring patient is not useful

## MEDICATION COUNSELING: ANTIDEPRESSANTS

5 KEY things pts must know:

Delay in onset of effect

Need for continued treatment after symptoms resolve

No concern about addiction or dependence

Adverse effects and management

Advise regarding use of alcohol

## COUNSELING ABOUT SIDE EFFECTS

Find positives when possible:

“Might make you sleepy, which is why you take it at bedtime so it can help you sleep”

“Take with food to reduce the risk of stomach upset” vs “This might upset your stomach”

## SSRIs and

## SEXUAL DYSFUNCTION

“This drug causes CHANGES in sexual functioning in some patients. Let me know if you notice any changes, since it can be treated if it occurs.”

Want to communicate that the drug may cause changes, but they can be treated

No need for patient to discontinue drug

## COUNSELING ABOUT ALCOHOL USE

**“Don’t drink if taking this drug”**

Forces patient to be non-compliant

Rather, **explain the consequences:**

effect on mood

additive effects – sedation, dizzy

**“Best not to drink, but ...”**

## EXPECTATIONS

Patients often bring preconceived ideas and incorrect expectations about their disorder and chosen drug therapy

Patients either expect too much from their drug or have excessive fears

We need to help set more appropriate Rx expectations → better Rx outcome

## HIGH EXPECTATIONS

When a first drug or drug class is approved for a disorder, there is great excitement, and usually excessive expectations – best e.g.:

Fibromyalgia

Pregabalin, Duloxetine, Milnacipran

ED & sildenafil

Panic disorder & alprazolam

## FIBROMYALGIA (FM)

First FM drugs with FDA approval; excitement & expectations high since previous Rx' efficacy often very limited

Patient view: If the FDA approves a new drug for fibromyalgia, it must be very effective

How much relief of pain do pts expect from a new FM drug? 100%, 50% ?

## FIBROMYALGIA Rx EXPECTATIONS

More than half of patients do not experience a 30% reduction in their pain

Studies with pregabalin, duloxetine, and milnacipran show that only 23 – 53% of patients experience a  $\geq 30\%$  reduction in pain scores

Drugs offer VERY modest pain relief for FM

## ANTIDEPRESSANT EXPECTATIONS

Drugs treat core depressive symptoms, not psychosocial stressors, coping skills, relationship issues, ...

Delay in onset of effect, worse before better

Initial dose is likely to be increased

Not addicting, not stimulants

If no response or intolerable side effects from the first drug, there are many other options

## CASE # 2