Overview of Antipsychotic Use in LTC Patients

Should we use brexpiprazole (Rexulti) for Dementia with Behaviors?

First rule of medicine… *including* antipsychotics

Protect patients from unnecessary risks.

"Primum non nocere"…

First, DO NO HARM

Format for JC Today…
A Deviation from the Norm

1. My conclusions
2. Data / reasoning behind this

FDA Fast Track Drug Approval

- The FDA's Fast Track program is a process that expedites the development and review of drugs that treat serious conditions and fill unmet medical needs
- **Purpose**: To get new drugs to patients faster
- **Eligibility**: Drugs must treat serious or life-threatening conditions, or address unmet medical needs
- **Request**: Drug companies must submit a request with supporting documentation
- **Decision**: FDA must decide within 60 days of receiving request
- **Benefits**: Includes the possibility of a "rolling review" and close collaboration with the FDA throughout the testing process

PRO: Yes, we should use it

1. The 3rd Brexipiprazole Trial showed statistically it *may* work in the right patients and statistically met criteria for being better than placebo
2. **Required CMAI* Factor 1 aggressive behavior, which included…**
   - hitting, kicking, scratching, grabbing, pushing, hurting self or others, throwing things, tearing things or destroying property and biting

   But also included…
   - cursing or verbal aggression, spitting or screaming
3. The FDA has approved it for this indication, so we have some legal "cover"

** Cohen-Mansfield Agitation Index*

CON: **NO!** We should not use it!

1. The 1st & 2nd Brexipiprazole Trials did **not** show that it was better than placebo
2. 3rd Trial was only a **12-week study**. The CATIE-AD Trial showed that Risperdal and Zyprexa (*though not Placebo or Seroquel*) worked for **22-26 weeks**
   - **Only had 345 patients**
     - 11-13% dropped out = **302 patients**
     - **Spread across 7 countries / 68 sites!** = 4.4 patients / site
     - 45% living in a care facility (NH / ALF) = **136 patients in LTC**
   - 95% of enrollees were caucasian
   - Qualifying behaviors included cursing or verbal aggression, spitting or screaming which would not qualify under CMS regs to be treated – data did not cull this out

CON: **NO!** We should not use it!

3. Excluded dementia other than Alzheimers and those with any clinically significant neurologic or psychiatric *(some exceptions)* or unstable medical condition
   - *How many of the patients we treat would fit this exclusion?*
4. Only worked at the 2 and 3 mg qd groups
5. Limited use of benzodiazepines allowed for first 4 weeks (19.5% brexipiprazole vs 14.7% placebo)
   - ie, 1/3 of the study was confounded by an unknown amount of benzodiazepine use

CON: **NO!** We should not use it!

6. Carries same BOX Warning about increased risk of death as other antipsychotics
7. It is MUCH more expensive than Risperdal or Zyprexa
8. Only showed efficacy in 1/3 of the limited number of patients to whom it was given

So what about Rexulti?

Results from **3rd** trial are encouraging - it *may* work in the right patients

Who are the right patients?

- White
- MMSE 5-22 with a previous MRI or CT diagnosis consistent with AD
- A test documenting whether a person is experiencing cognitive impairment
- Those who exhibit the type, frequency, and severity of agitation behaviors that require medication
- 51 to 90 years of age
- Not on antipsychotics, mood stabilizers or anticonvulsants

So what about Rexulti?

- The overall effect size is small **(worked in only 30 in LTC, as <1/3 responded**), but could make a difference for some individuals
- For patients who meet the threshold to justify a trial of an antipsychotic, consider risperidone, olanzapine or aripiprazole depending on comorbidities and compliance
- If someone demands to try it (*maybe they believe the marketing campaign*), consider it after going over the BOX warning and potential side effects
- Given its high cost, limited time of the trial, so few patients (*especially in LTC*), most of the trial done in other countries with very few patients / facility, still a black box warning for use in dementia, and **no** head-to-head trials which compare it to other atypicals…

I would not prescribe it

Now, for those who want to stay,
it is time for the details...

Why do we use so many antipsychotics in dementia patients ?

- Behaviors often look psychotic or inappropriately aggressive
- Limited training of providers about dementia
- Distressing behaviors over a long period of time leads to frustration among families, nurses and providers willing to "*try anything!*"
- Fraudulent pharmaceutical marketing really does sell drugs

Antipsychotic side effects

SERIOUS

- QT Prolongation (ie, heart rhythm abnormalities)
- Low WBC Counts (decreased ability to prevent/fight infections)
- Cardiovascular Events (eg, MI, CVA)
- NMS (Mental Status, Fever, Rigidity, Orthostasis, HTN…)
- Confusion
- Falls / Fractures
- **Death**
- EPS / TD
- Pneumonia
- Arrhythmias / Sudden Death
- Seizures
- Hepatic Impairment

Antipsychotic side effects

COMMON

- EPS (Shuffling gait, stiff, slow)
- Dystonia (Tachycardia, Orthostasis, HTN, Constipation, Diarrhea, Sweating)
- Somnolence
- Blurred Vision
- Akathisia
- Insomnia / Lethargy
- Anxiety
- Impaired Body Temperature Regulation
- Falls / Fractures
- High Blood Sugars / Diabetes

Antipsychotic FDA BOX warning

(*read it at least once and periodically to remind yourself of this*)

Increased Mortality in Elderly Patients with Dementia–Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at **an increased risk of death** compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. **[THIS DRUG] is not approved for the treatment of patients with Dementia-Related Psychosis**.

Basic Pharmacology

Half Life: the time it takes for the concentration of a drug in the plasma or the total amount in the body to be reduced by 50%

Therapeutic Range: the medicine levels in blood known for some agents that are in a **range** that is clinically helpful, but not dangerous

Therapeutic Life: less well defined, but as a first approximation this is often about 1.5X the half-life once a drug reaches steady state

Steady State: That point where serum drug levels of the drug are relatively stable *and* therapeutic. The time taken to reach steady state is about 5 times the half-life of a drug. Drugs with a *long* half-life take longer to reach a steady state than those with a short half-life and concomitantly take longer to eliminate / drop out of steady state

Practical Applications of these Concepts

A drug with a short **half-life** (eg, 4 hours) will…

- Achieve **Steady State** quickly **if** it is given every 6 hours (its **Therapeutic Life**)
- Be eliminated quickly if the dosing interval is too long, eg, if only given qd, it drops out of the **Therapeutic Range** in 8-10 hours

Practical Applications of these Concepts

A drug with a long **half-life** (eg, 24 hours)…

- Takes longer to achieve **Steady State**. 5 Half-lives = 5 days if given qd
- Has a Therapeutic Life of about **36 hours** per dose
- Is eliminated slowly, ie, it takes about a week to drop out of the **Therapeutic Range** *(give GDRs time!)*

Giving it more frequently than qd *does* ***NOT*** *make it work any faster*, it just increases cost, pills and nursing time, eg…

Zyprexa has a **Half-Life** of 25-50 hours, so…

- **Steady State** is not achieved for 7-10 days if given qd
- Does not get to a therapeutic range *or* steady state any faster if the dose is given 2 or 3 (or 10) times daily

Cohen-Mansfield Agitation Index - Short

WHAT IS AGITATION?

Agitation was operationally defined by Cohen-Mansfield and Billig (1986) 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 agitated individual.

Agitation is not a diagnostic term, but rather a term used by clinicians for a group of symptoms that may reflect an underlying disorder.

Agitated behavior is always socially inappropriate and can be manifested in 3 ways:

- It may be abusive or aggressive toward self or others
- It may be appropriate behavior performed with inappropriate frequency, such as constantly pacing or asking questions
- It may be inappropriate according to social standards for the specific situation, as in taking off clothes in the activity room

CMAI

The purpose of the CMAI is to assess the frequency of manifestations of agitated behaviors in elderly persons. It was developed for use in the nursing home.

Though originally developed for research purposes, it has been used for clinical purposes, such as deciding whether withdrawal of psychotropic medication resulted in an increase in agitation in elderly persons. The CMAI may be self-administered by a caregiver or completed by interviewing staff.

The CMAI is a caregivers' rating questionnaire consisting of 29 agitated behaviors, each rated on a 7-point scale of frequency. Ratings pertain to the 2 weeks preceding administration of the CMAI

Cohen-Mansfield Agitation Inventory (CMAI)[1] – Short

Instructions: For each of the behaviours below, check the rating that indicates the average frequency of occurrence over the last 2 weeks.

	1- Never	2- Less than once a week	3- Once or twice a week	4- Several times a week	5- Once or twice a day	6- Several times a day	7- Several times an hour
Physical / Aggressive							
1. Hitting (including self)	1	2	3	4	5	6	7
2. Kicking	1	2	3	4	5	6	7
3. Grabbing onto people	1	2	3	4	5	6	7
4. Pushing	1	2	3	4	5	6	7
5. Throwing things	1	2	3	4	5	6	7
6. Biting	1	2	3	4	5	6	7
7. Scratching	1	2	3	4	5	6	7
8. Spitting	1	2	3	4	5	6	7
9. Hurting self or others	1	2	3	4	5	6	7
10. Tearing things or destroying property	1	2	3	4	5	6	7
11. Making physical sexual advances	1	2	3	4	5	6	7
Physical / Non-Aggressive							
12. Pace, aimless wandering	1	2	3	4	5	6	7
13. Inappropriate dress or disrobing	1	2	3	4	5	6	7
14. Trying to get to a different place	1	2	3	4	5	6	7
15. Intentional falling	1	2	3	4	5	6	7
16. Eating / drinking inappropriate substance	1	2	3	4	5	6	7
17. Handling things inappropriately	1	2	3	4	5	6	7
18. Hiding things	1	2	3	4	5	6	7
19. Hoarding things	1	2	3	4	5	6	7
20. Performing repetitive mannerisms	1	2	3	4	5	6	7
21. General restlessness	1	2	3	4	5	6	7
Verbal / Aggressive							
22. Screaming	1	2	3	4	5	6	7
23. Making verbal sexual advances	1	2	3	4	5	6	7
24. Cursing or verbal aggression	1	2	3	4	5	6	7
Verbal / Non-aggressive							
25. Repetitive sentences or questions	1	2	3	4	5	6	7
26. Strange noises (weird laughter or crying)	1	2	3	4	5	6	7
27. Complaining	1	2	3	4	5	6	7
28. Negativism	1	2	3	4	5	6	7
29. Constant unwarranted request for attention or help	1	2	3	4	5	6	7

Other Scales Commonly Cited

Clinical Global Impression of Severity is rated on a 7-point scale from 1 (normal) to 7 (extremely ill)

Clinical Global Impression of Improvement is rated on a 7-point scale from 1 (very much improved) to 7 (very much worse)

Clinical Global Impression of Change (CGIC) is a subjective rating by the clinician of change after an intervention, better or worse

Neuropsychiatric Inventory Nursing Home Version (NPI-NH)

A tool used to assess neuropsychiatric symptoms and behavioral changes in dementia patients in nursing homes. Used by professional caregivers to characterize a patient's psychopathology & measure impact of treatments

Based on original NPI with modifications – questions were rephrased to account for the fact caregivers didn't know the patients before the illness

Caregiver distress questions were rephrased to assess how disruptive the patient's behaviors are for caregivers

To administer, caregiver rates severity & frequency of each behavior on a scale:

- **Frequency**: Rarely, sometimes, often, or very often
- **Severity**: Mild, moderate, or severe

Total score is calculated by multiplying frequency & severity ratings for each item, then adding up scores for all behavioral domains

Neuropsychiatric Inventory Nursing Home Version (NPI-NH)

10 Behavioral areas…

- Delusions
- Hallucinations
- Agitation/Aggression
- Depression/Dysphoria
- Anxiety
- Elation/Euphoria
- Apathy/Indifference
- Disinhibition
- Irritability/Lability
- Aberrant Motor Behavior

and 2 types of Neurovegetative changes:

- Sleep and Nighttime Behavior Disorders
- Appetite and Eating Disorders

Remember… rated by Frequency (Rarely, sometimes, often, or very often) and Severity (Mild, moderate or severe)

Scoring the NPI–NH

Frequency is rated as:

1. Rarely – < once / week
2. Sometimes – about once / week
3. Often – several times / week, but < qd
4. Very often – >/= 1 qd / essentially continuously present

Severity is rated as:

1. Mild – produces little distress in the patient
2. Moderate – more disturbing to the patient but can be redirected by the caregiver
3. Severe – very disturbing to the patient and difficult to redirect

The score for each domain is: domain score = frequency x severity

Occupational Disruptiveness is scored as:

0. Not at all
1. Minimally (almost no change in work routine)
2. Mildly (some change in work routine but little time rebudgeting required)
3. Moderately (disrupts work routine, requires time rebudgeting)
4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

A total NPI-NH score can be calculated by adding the first 10 domain scores together. All 12 domain scores can be summed in special circumstances where the neurovegetative symptoms are of particular importance

Antipsychotic Use in Dementia: The Early Days

(For us, this involves only those living in a nursing home)

How did the "inappropriate antipsychotic" movement emerge?

Catie – ad trial (2006)

- 42 Sites, 421 patients with Alzheimer's Dementia (MMSE 5 – 26, Average = 15)
- 60% on Cholinesterase Inhibitors
- Symptoms: **Delusions** (80%), **Hallucinations** (42-57%), **Aggression** (85%) or **Agitation** that disrupted functioning nearly daily for >1 week
- Excluded: Primary Psych disorder, delirium, Non-Alzheimer Dementia
- Study Drugs titrated up or down for effect: **Risperdal, Zyprexa, Seroquel, Placebo**

Findings:

1. **Time to DC Drug** (*any reason*): **No Statistically Significant Difference**
2. **Median time to dc drug for lack of efficacy:** Favored Zyprexa & Risperdal
   - *(22-27 weeks for Zyprexa & Risperdal vs 9 for Seroquel & Placebo)*
3. **DC drug due to adverse event or death: Favored Placebo**
4. **CGIC Scale**: **No Statistically Significant Difference**
   (21% of Placebo patients improved)

Schneider, L, et al; Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease. 355: 1525-38; 10/12/06

Applied common sense for providers, staff & families

Education and acceptance that there are **NO** pills that…

- ✓ **Fix personality disorders**
- ✓ Make people stop cursing or disrobing in public
- ✓ Improve nasty, belligerent, uncooperative behaviors
- ✓ Get patients to stop yelling, screaming or perseverating
- ✓ Keep patients from continually coming to a nursing station
- ✓ Make them sleep 8 hours at night (*and stay awake all day*)

or…

- ✓ Stop them from getting angry when they are in pain, can't hear or see or are simply scared of a world they don't understand

From a regulatory perspective…
when can Antipsychotics be used?

When a patient has unprovoked psychotic behaviors (delusions, hallucinations or paranoia) or aggressive / assaultive behaviors that pose a significant clinical risk to the patient or to others

Note:

- Does not include “staff” if the inappropriate behaviors occur during their interactions or provision of care
- The FDA Box warning should be reviewed with the responsible party and a consent detailing potential clinical risks should be explicitly documented prior to initiation

Explicit Documentation

1. What is the diagnosis for use of the medication?
   - *Does it match the drug chosen?*
2. What behaviors are being addressed or are intended to be improved?
   - *Do they meet the previously noted CMS criteria?*
3. Anticipated timeframe to see the improvement?
4. Potential Risks verses Intended Benefit(s)
   - *Were these discussed with the patient's decision-maker?*
   - *Was the conversation documented? (Date, Names, Content, Decisions)*
   - *Did the conversation note there will be a time for Mandatory GDRs?*
5. Drug chosen – *why this one?* Is it being dosed correctly?

Assessing Success

1. Did the explicitly targeted behaviors improve meaningfully?
2. Did improving the target behavior(s) improve the **patient's** condition, ie, not just make it a more pleasant environment?
3. Are all reasonable nonpharmacologic options still being used?
   - *PRNs must have 2 nonpharmacologic interventions tried, given time to work and documented prior to giving prn psychoactive meds except in extreme situations*
   - *PRN Psychoactive agents must be limited to 14 days and require a face-to-face visit before renewing with documentation to support why they are still necessary*
4. "Failed Tapers" should have reason(s) for the failure documented and need to meet the same criteria required for initiating the drug
5. Tapering psychoactive drugs too quickly will result in both physiologic and psychologic withdrawal symptoms that can easily be misinterpreted as a 'failed' taper

Comparing Antipsychotics: **Dosing Intervals**

DRUG	HALF-LIFE (hours)	THERAPEUTIC LIFE
Abilify	75 or 146*	112.5 (4.5 days) / 219 (9 days)
Zyprexa	21 – 54 hours	32 – 81 hours (1-3 days)
Risperdal	**20 hours**	**30 hours**
Risperdal Consta	9 – 11 days	14 – 18 days
Haldol	21 – 24	32 – 36
Haldol Decanoate	21 days	32 days
Geodon	7 hours	10 hours
Seroquel or XR	**6 – 7 hours**	**9 – 10 hours**
Clozaril	4 – 66 hours	6 – 100 hours
Rexulti	**90 hours**	135 hours (5 1/2 days)

**About ½ of the population are fast and ½ are slow metabolizers*

QUESTIONS? / DISCUSSION