Taking Another Look at Antipsychotics

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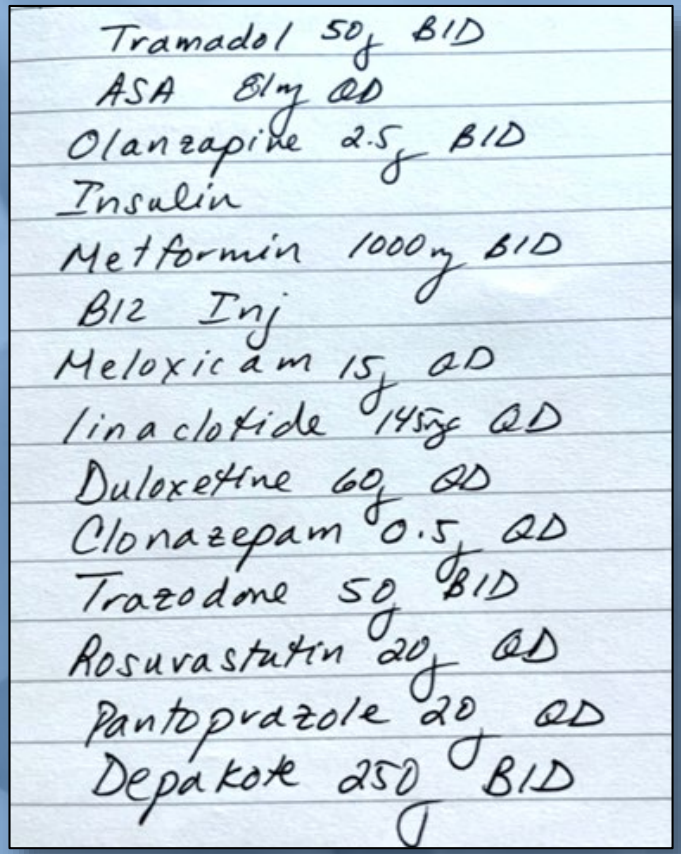
Tramadol 50g BID
ASA 81mg QD
Olanzapine 2.5g BID
Insulin
Metformin 1000mg BID
B12 Inj
Meloxicam 15g QD
Linaclotide 145mcg QD
Duloxetine 60g QD
Clonazepam 0.5g QD
Trazodone 50g BID
Rosuvastatin 20g QD
Pantoprazole 20g QD
Depakote 250g BID

How Do Antipsychotics Work?

- The original antipsychotic drug, chlorpromazine, was developed as a surgical anesthetic.
- The drug was regarded as a non-permanent pharmacological lobotomy.”
- Antipsychotics are broadly divided into two groups:
  - Typical or first-generation antipsychotics
  - Atypical or second-generation antipsychotics

How Do Antipsychotics Work?

- Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences and decreased dopamine release in the prefrontal cortex are associated with psychotic episodes in schizophrenia and bipolar.
- Typical antipsychotics (first generation) block dopamine D2 receptors, which means that dopamine released has less effect. These drugs have higher side effects because they are not selective of where they work.
- Atypical antipsychotics (second generation) also block dopamine receptors, but most also act on serotonin receptors. Some only bind long enough to elicit antipsychotic effects, but not long enough to cause EPS and other side effects.

Antipsychotics by Type

Typical/1st Generation

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Perphenazine
- Prochlorperazine
- Thorazine

Atypical/2nd Generation

- Aripiprazole
- Clozapine
- Ziprasidone
- Paliperidone
- Lurasidone
- Olanzapine
- Risperidone
- Quetiapine
- Olanzapine

Not Completely Clear

- The role of dopamine in psychosis is clear, though the link between the neurobiological and pharmacologic “brain-level” findings and the “mind-level” nature of psychosis and its resolution is somewhat unclear.
- An antipsychotic improves symptoms more in the first 2 weeks of treatment than in any other 2-week period.
- In the initial stage of the antipsychotic response, the patient experiences a “detachment” from symptoms (the delusions and hallucinations are relegated to the back of the mind rather than complete erasure).

Antipsychotic Prescriptions

	2013	2018
People with at least one antipsychotic prescription	5 Million	6 Million
Average total expense of antipsychotic prescription	$ 390	$ 269

Source: AHRQ, Medical Expenditure Panel Survey Statistical Brief #534: *Comparison of Antidepressant and Antipsychotic Utilization and Expenditures in the U.S. Civilian Noninstitutionalized Population, 2013 and 2018*. https://meps.ahrq.gov/data_files/publications/st534/stat534.shtml

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Case

- 78-year-old male LTR of facility with med hx: CVA, dysphagia, HTN, a-fib, dementia, seizures
- Meds: alprazolam 0.5mg qhs, duloxetine 30mg qd, levetiracetam 500mg bid, olanzapine 2.5mg po qhs, metoprolol 25mg bid, hydrocodone-acetaminophen 5/325mg po bid, tamsulosin 0.4mg po qd
- Pharmacy consultant recommends GDR of olanzapine to 1.25mg qd and it is ordered. A few weeks later the olanzapine is stopped. Resident is documented as being combative with care or having verbal outbursts 3-4 times/month.

Case – 2 Weeks Later…

- Note: Resident has proceeded with aggression and verbal outbursts this AM. resident was refusing care and hitting at CNA while yelling " get out of here you dirty b****..." resident continued with behavior while AM care was attempted to be performed. Support and encouragement given.
- Nurse contacted on-call provider about above events and order given to restart olanzapine 1.25mg po qhs

Antipsychotics

- Carry a black-box warning for use in the elderly with dementia-related behaviors as they may increase mortality in the elderly.
- There is only one antipsychotic approved by the FDA for the use in agitation associated with dementia (brexpiprazole).
- Are often used for insomnia (in the outpatient and inpatient settings).
- Do carry side-effects that can be mistakenly thought of as symptoms of another disease process.

Brexpiprazole

Incidence of Adverse Events of Special Interest Across all 12-week Phase 3 Studies

AE of Special Interest	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	Placebo (N=388)
Extrapyramidal Symptom Related Events	5 (3.2%)	9 (6.8%)	10 (4.7%)	4 (2.6%)	12 (3.1%)
Akathisia	-	4 (3.0%)	1 (0.5%)	2 (1.3%)	1 (0.3%)
Dizziness, Syncope, or Orthostatic Hypotension Related Events	4 (2.5%)	9 (6.8%)	12 (5.6%)	5 (3.3%)	9 (3.6%)
QT Prolongation	4 (2.5%)	1 (0.8%)	3 (0.8%)	-	2 (0.5%)
Somnolence	2 (1.3%)	9 (6.8%)	7 (3.3%)	6 (3.9%)	7 (1.8%)
Accidents and Falls	5 (3.2%)	2 (1.5%)	5 (2.3%)	3 (2.0%)	16 (4.1%)
Cardiovascular Events	7 (4.5%)	7 (5.3%)	9 (4.2%)	1 (0.7%)	9 (2.3%)
Cerebrovascular Events	2 (1.3%)	1 (0.8%)	-	-	1 (0.3%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety Report and adae.xpt dataset

Note: *Extrapyramidal symptoms* include: extrapyramidal disorder, dyskinesia, muscle spasms, musculoskeletal stiffness, bradykinesia, bradyphrenia, gait disturbance, hypertonia, hypokinesia, muscle rigidity, parkinsonism, and tremor; *Akathisia* includes: akathisia, psychomotor hyperactivity, and restlessness; *Dizziness* includes: balance disorder, dizziness, hypotension, loss of consciousness, orthostatic hypotension, presyncope, syncope, and vertigo; *Somnolence* includes: sedation and somnolence; Accidents and Falls includes: buttock injury, contusion, fall, femur fracture, head injury, hip fracture, humerus fracture, limb injury, patella fracture, rib fracture; *Cardiovascular events* include: atrial fibrillation, atrioventricular block, bundle branch block, electrocardiogram QT prolonged, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, angina pectoris, myocardial ischemia, cardiac failure, pulmonary edema; *Cerebrovascular events* include: cerebrovascular accident, intracranial hemorrhage, lacunar infarction, subdural hematoma, and transient ischemic attack

https://www.fda.gov/media/167066/download

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Brexpiprazole Safety Findings

- “The most common AE (> 2% in the All BREX group and higher than placebo) included nasopharyngitis, urinary tract infection, dizziness, somnolence, and insomnia.”
- “Due to the evidence that the use of antipsychotics to treat dementia-related behavioral disorders (i.e., psychosis and agitation) results in higher mortality, the Boxed Warning should remain to adequately inform health care providers.”

https://www.fda.gov/media/167066/download

Antipsychotic Side Effects (1st and 2nd Generation)

- Dry mouth
- Constipation
- Blurred vision
- Urinary retention
- Shuffling gait
- Drooling
- Motor stiffness
- Extrapyramidal side-effects
- Stroke
- Weight gain
- Extrapyramidal side-effects (not as common as 1st generation)
- Life threatening agranulocytosis
- Anticholinergic effects
- Sexual dysfunction
- Hyperlipidemia
- Hyperglycemia

Antipsychotics Started in the Hospital

- Cohort study of 5,835 patients aged 65 and older who were admitted for infection-related diagnosis January 1, 2004, to May 31, 2022.
- Patients had no prior psychiatric diagnosis.
- All patients had either haloperidol or an atypical antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone, etc) initiated during their hospital stay to treat delirium.
- Researchers followed these patients to determine discontinuation rates over time.

Zhang Y, Wilkins JM, Bessette LG, York C, Wong V, Lin KJ. Antipsychotic Medication Use Among Older Adults Following Infection-Related Hospitalization. *JAMA Netw Open.* 2023;6(2):e230063. doi:10.1001/jamanetworkopen.2023.0063

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Results

- 790 patients were prescribed haloperidol, 5,045 patients were prescribed at atypical antipsychotic.
- 52.1% of patients prescribed haloperidol had the medication discontinued at 30 days.
- 11.4% of patients prescribed atypical antipsychotics had the medication discontinued at 30 days.
- Why was haloperidol discontinued at such a higher rate at 30 days compared to atypical antipsychotics?

Adverse Side Effects That May Be Related to Resident's Medication Regimen

- Anorexia/unplanned weight changes
- Behavioral changes
- Sedation, changes in alertness
- Insomnia or sleep disturbance
- Rash, pruritis
- Bleeding or bruising
- Falls
- Decline of activities of daily living (ADLs)

Adverse Side Effects (Continued)

- Respiratory changes
- Fall, dizziness, headaches
- Muscle pain/nonspecific pain/unexplained movements
- Dehydration or swallowing difficulty
- Bowel dysfunction, urinary retention, incontinence

ASPE
ASSISTANT SECRETARY FOR PLANNING AND EVALUATION

ISSUE BRIEF

March 8, 2022

ANTIPSYCHOTIC MEDICATION PRESCRIBING IN LONG-TERM CARE FACILITIES INCREASED IN THE EARLY MONTHS OF THE COVID-19 PANDEMIC

KEY POINTS

- Prescriptions dispensed for antipsychotics in nursing homes and assisted living facilities increased since the beginning of the pandemic, with 20.8 million dispensed in 2020 compared to 20.5 million in 2019. This represents a 1.5% increase in total prescriptions since the beginning of the pandemic despite lower resident census levels in long-term care facilities (LTCFs).
- In 2020, the highest increase in the number of prescriptions dispensed occurred during the first quarter of the pandemic, with an increase of 7.4% compared to the first quarter of 2019. After this initial increase, the quarterly number of prescriptions for antipsychotic medications dropped close to pre-pandemic levels, despite a declining nursing home resident census and likely a declining LTCF resident census overall.

https://aspe.hhs.gov/sites/default/files/documents/c7cded0bf6f55567b55d78ef9e56687d/antipsychotic-medication-ltcf.pdf

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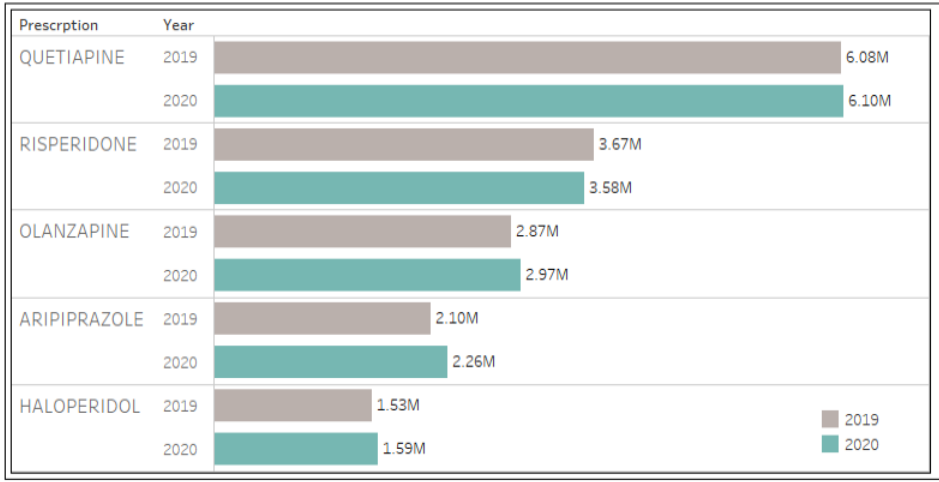
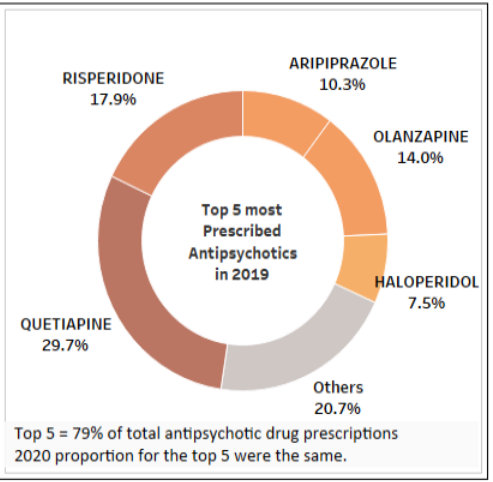
Figure 2. Share of Top 5 Prescribed Antipsychotics in LTCFs in 2019 and 2020





Top 5 = 79% of total antipsychotic drug prescriptions
2020 proportion for the top 5 were the same.

SOURCE: Internal ASPE analysis using IQVIA National Prescription Audit, 2015-2021.

https://aspe.hhs.gov/sites/default/files/documents/c7cded0bf6f55567b55d78ef9e56687d/antipsychotic-medication-ltcf.pdf

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Antipsychotic Trends as a Result of the Pandemic

- Prescriptions dispensed for antipsychotics in nursing homes and assisted living facilities increased during the COVID-19 pandemic when prescriptions dispensed in 2020 were compared to those dispensed in 2019.
- There was a 1.5% increase in total prescriptions since the beginning of the pandemic despite lower resident census levels in long-term care facilities.
- The highest increase in the number of prescriptions dispensed occurred during the first quarter of the pandemic with an increase of 7.4%.

Quetiapine

- Quetiapine carries the risk of serious adverse reactions including tardive dyskinesia, hyperglycemia, dystonia, and hypotension.
- A study of 93 patients with Alzheimer's dementia and clinically significant dementia compared the use of quetiapine to rivastigmine or placebo.
- Neither quetiapine nor rivastigmine were effective in the treatment of agitation in people with dementia.
- Quetiapine was associated with significantly greater cognitive decline compared with placebo.

Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R, Jacoby R. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 2005 Apr 16;330(7496):874. doi: 10.1136/bmj.38369.459988.8F. Epub 2005 Feb 18. PMID: 15722369; PMCID: PMC556156.

Common Medications With Psychotic Side-Effects

- Anticholinergics
- Antivirals
- Baclofen
- Benzodiazepines
- ß-blockers
- Cephalosporins
- Clonidine
- Corticosteroids
- Digoxin
- Metronidazole
- Opioids
- Quinolones
- Calcium channel blockers

Casagrande Tango R. Psychiatric side effects of medications prescribed in internal medicine. Dialogues Clin Neurosci. 2003 Jun;5(2):155-65. doi: 10.31887/DCNS.2003.5.2/rcasagrandetango. PMID: a22034468; PMCID: PMC3181628.

F757 Unnecessary Medications

An unnecessary medication is any medication that is:

- In excessive dose (including duplicate therapy)
- For excessive duration
- Without adequate monitoring
- Without adequate indications for its use
- In the presence of adverse consequences, which indicate the dose should be reduced or discontinued
- Any combination of the reasons above

If an Antipsychotic is Ordered

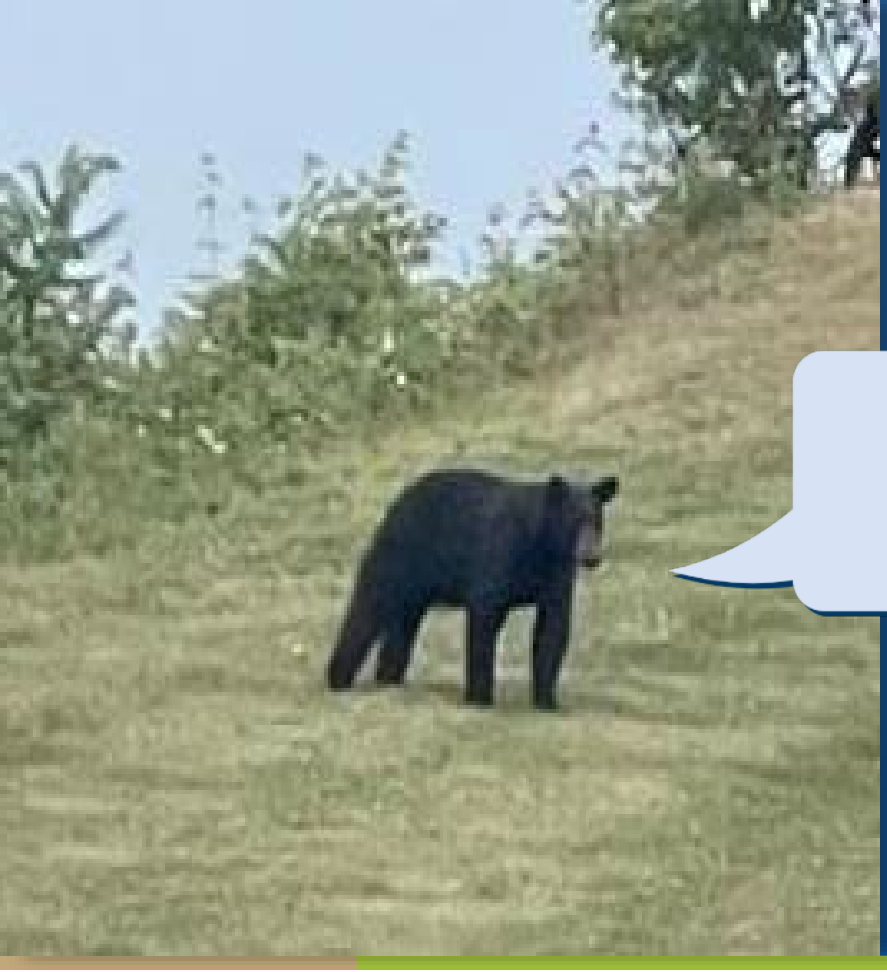
- A GDR is required, unless clinically contraindicated, within the first year that a resident is admitted or after the facility has initiated an antipsychotic.
- The facility must make a GDR attempt in 2 separate quarters with at least one month between attempts in the first year.
- A GDR attempt must be made at least annually after the first year.
- I think it is important to note that it is not necessary to “wait” until a GDR is due to reduce or eliminate an antipsychotic.

Cholinesterase Inhibitors and Memantine

- A 12-week, double-blind, randomized, placebo-controlled trial studying 148 patients with moderate AD showed combination therapy was beneficial in reducing disinhibition symptoms.[1]
- A study of 532 patients with dementia and agitation demonstrated reduced agitation with use of the medication combination compared to cholinesterase inhibitors alone.[2]

1. Youn H, Lee KJ, Kim SG, Cho SJ, Kim WJ, Lee WJ, Hwang JY, Han C, Shin C, Jung HY. The Behavioral Effects of Combination Therapy of Memantine and Acetylcholinesterase Inhibitors Compared with Acetylcholinesterase Inhibitors Alone in Patients with Moderate Alzheimer's Dementia: A Double-Blind Randomized Placebo-Controlled Trial. Psychiatry Investig. 2021 Mar;18(3):233-240. doi: 10.30773/pi.2020.0329. Epub 2021 Mar 10. PMID: 33685036; PMCID: PMC8016683.

2. Memantine Added to Background Cholinesterase-Inhibitors Raeduces Agitation and Neuropsychiatric Symptoms in Alzheimer's Disease (P3.082) Alireza Atri, George Grossberg, Suzanne Hendrix, Noel Ellison, Merrilee R. Johnstone, John Edwards Neurology Apr 2017, 88 (16 Supplement) P3.082.



Questions?

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