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Re-evaluating the Use of Second Generation Antipsychotics

A VA Clinician's Guide

VA Academic Detailing Service

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Re-evaluating the Use of Second Generation Antipsychotics in Our Veterans

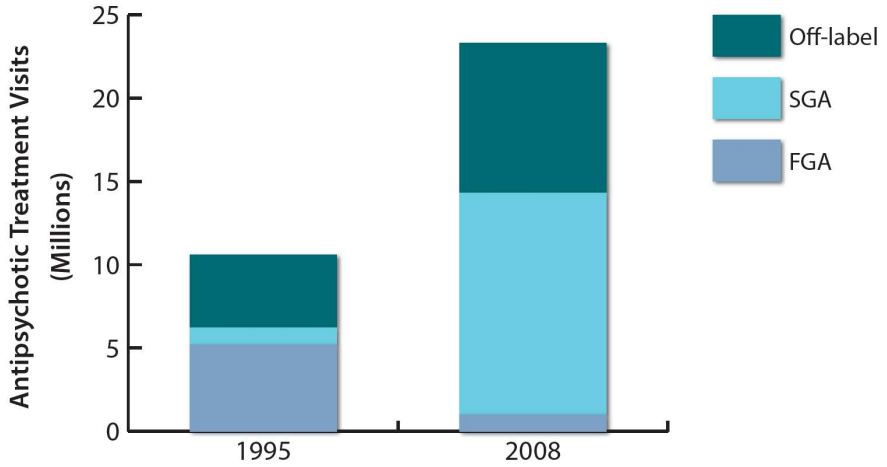
Have we been sold on *hype*, *hope* and *aggressive marketing*?

With the advent of the second generation antipsychotics (SGA), we have seen a significant increase in antipsychotic use. They are being used to treat an array of conditions for which there is little to no evidence of effectiveness.[1–3]

Why Are SGAs So Popular?

- ➔ **Hype** that they are safer than the earlier generation of drugs
- ➔ **Hope** that they will work for a variety of ailments when other treatments have not
- ➔ **Aggressive marketing** by drug companies to prescribers and patients

Figure 1. Overall Trends of Antipsychotic Use[1]



National data includes patient visits where a first generation antipsychotic (FGA) or second generation antipsychotic (SGA) was reported. From 1995 to 2008 there was a shift in antipsychotic prescribing from first-generation antipsychotics (84% of all antipsychotic visits) to second-generation antipsychotics (93% of all antipsychotics visits). Off-label use has increased from 4.4 million visits in 1995 to 9 million visits in 2008.

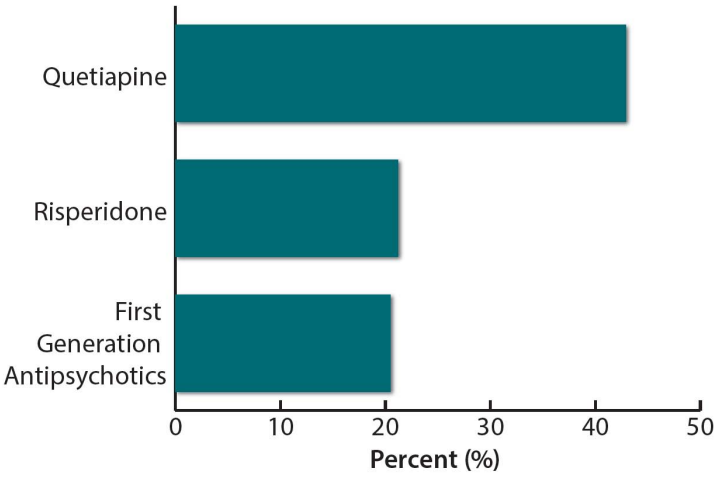
Re-evaluate the Use of Antipsychotics[3,4]

Off-label antipsychotic prescribing is concerning due to the lack of scientific evidence supporting this practice.

Re-evaluate the use of antipsychotics in Veterans:

- ➔ With:
  - ❖ Dementia
  - ❖ Post-Traumatic Stress Disorder (PTSD)
  - ❖ Insomnia
  - ❖ Anxiety
  - ❖ Personality Disorder
  - ❖ Substance Use
  - ❖ Eating Disorders
- ➔ On lower than recommended dosing
- ➔ On higher than recommended dosing
- ➔ On multiple antipsychotics

Figure 2. Proportion of Off-Label Antipsychotics Used in Veterans Affairs[3]



60.2% of the 279,778 patients in FY2007 received antipsychotics for off-label uses. None of these patients had a diagnosis of schizophrenia or bipolar disorder; however, 40% had a PTSD diagnosis. Quetiapine was the antipsychotic with the largest proportion of off-label use followed by risperidone and first generation antipsychotics considered as a class.

Table 1. FDA-Labeled Indications for Atypical Antipsychotics[5,6]

	Schizophrenia		Bipolar				MDD
	Treatment	Agitation	Acute Episode		Maintenance	Agitation	Adjunct
			Manic or mixed	Depression			
Aripiprazole	√‡	∫	√¶		√¶	∫	√¥
Asenapine (NF)	√		√¶				
Clozapine	√*						
Iloperidone (NF)	√						
Lurasidone	√			√¶			
Olanzapine	√‡	∫	√¶	√º	√	∫	√º
Paliperidone (NF-Oral)	√‡						
Quetiapine	√XR		√XR	√XR	√XR¶		XR¥
Risperidone	√‡		√		√‡		
Ziprasidone	√	∫	√		√¶		

NF = Not currently on VA National formulary; √ = oral regular formulation; ∫ = short acting injectable formulation; XR = extended-release oral formulation also approved but not currently on VA National formulary; * = treatment resistant or reducing suicidal ideation in patients with schizophrenia; ‡ = long-acting injectable formulation also approved; ¥ = used in adjunct with antidepressant; º = used in combination with fluoxetine; ¶ = as monotherapy or in adjunct with lithium or valproate.

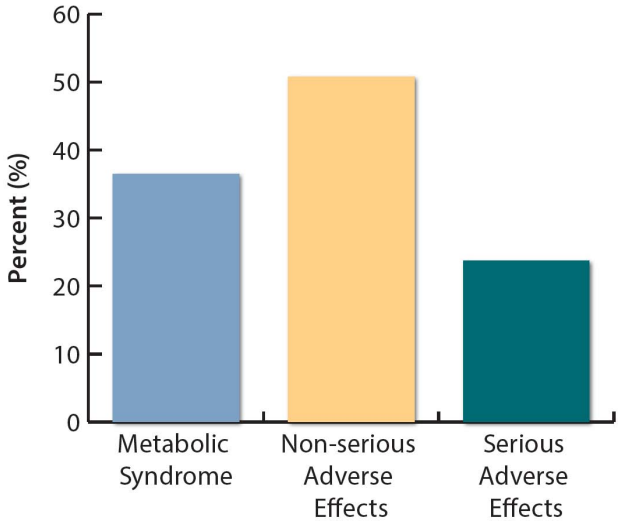
Antipsychotic Use and Substantial Risks

➔ Mortality in dementia related psychosis[5,6,7,8]

➔ Extrapyramidal symptoms and potentially irreversible tardive dyskinesia[5,6]

➔ Cardiovascular and metabolic morbidity[5,6,9]

Figure 3. Longer-Term Safety of SGA in Patients Over Age 40[9]



A study of 332 patients over the age of 40 receiving SGAs (aripiprazole, olanzapine, quetiapine, and risperidone) for up to 2 years revealed a high incidence of metabolic syndrome (36.5%), non-serious adverse events (50.8%) and serious adverse effects (23.7%) including deaths, hospitalizations, and emergency room visits.

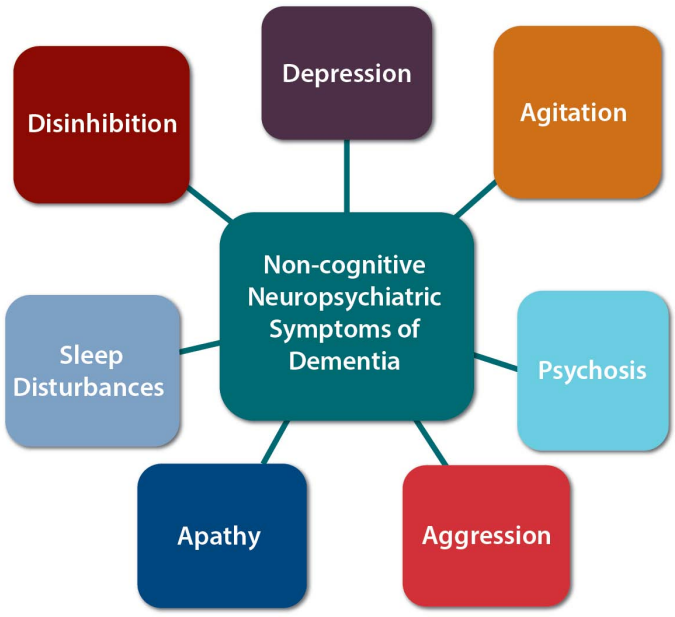
Antipsychotic Use and Dementia

WEIGHING THE BENEFITS VERSUS RISKS

Neuropsychiatric symptoms of dementia typically wax and wane.[10]

A discontinuation trial should be seriously considered in patients who remain relatively asymptomatic on an antipsychotic for 3–6 months.[10]

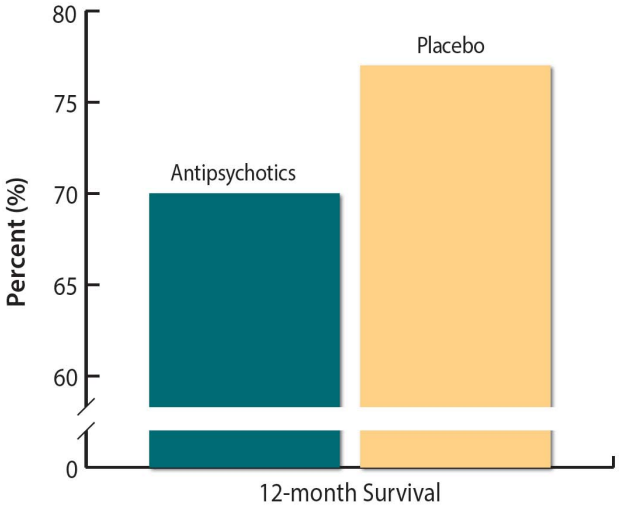
Figure 4. Non-cognitive Neuropsychiatric Symptoms of Dementia[11]



CATIE-AD AND DART-AD: WHAT DID WE LEARN?

- ➔ No improvement was seen on measures of functional abilities, quality of life, or caregiving time necessary[12]
- ➔ Efficacy data for all SGAs reveals mixed evidence for neuropsychiatric symptoms in dementia[10]
- ➔ Increased long-term risk of mortality in patients with Alzheimer's Disease who were prescribed antipsychotics compared to placebo[13]

Figure 5. Reduced Survival in Patients with Alzheimer's Disease[13]



This randomized, placebo-controlled, parallel, two-group treatment discontinuation trial in 165 patients with Alzheimer's Disease randomly assigned participants to continue antipsychotic treatment or switch their medication to placebo. There was a reduction in survival time in the participants who continued to receive antipsychotics compared with those who were switched to placebo at 12 months (70% vs. 77%, p = 0.03).

Antipsychotics are not approved for behavioral symptoms of dementia and have a **black box warning** addressing this use.

- ➔ When antipsychotics are used in elderly patients with dementia, risk of death increases up to 4-fold.[18]
- ➔ Risks associated with use of Antipsychotics in Dementia:[14–17]
  - ❖ Death
  - ❖ Cerebrovascular event
  - ❖ Extrapyramidal symptoms
  - ❖ Fall/hip fracture
  - ❖ Acute care hospital admission

Figure 6.

For every 100 patients with dementia treated with an antipsychotic:[19,20]

- **9-25 patients benefit**
- **1 patient dies**

Antipsychotic medications should be avoided in patients with dementia. Consider using non-drug approaches instead of medications.

RECOMMENDED MANAGEMENT OF BEHAVIORAL SYMPTOMS RELATED TO DEMENTIA

Nonpharmacologic strategies are recommended as the preferred first-line treatment approach for non-cognitive neuropsychiatric symptoms of dementia, except in emergency situations when these symptoms could lead to imminent danger or otherwise compromise safety.[11]

Consider non-drug approaches in all dementia patients with behavioral symptoms[21,22]

Reorient: ***gently remind of person, place, time***
Calm: ***offer exercise, music, massage, aromatherapy***
Comfort: ***address temperature, lighting, hunger, thirst***
Reduce distress: ***reduce noise, correct hearing/vision, provide structure, allow time to respond***
Supervise: ***provide companionship, observation, reduce choices, provide simple activities***

Antipsychotic Use and Post-Traumatic Stress Disorder (PTSD)

It is extremely important to distinguish PTSD symptoms from a primary psychotic disorder in order to optimize PTSD treatment and minimize the risks associated with inappropriate use of antipsychotic medications.

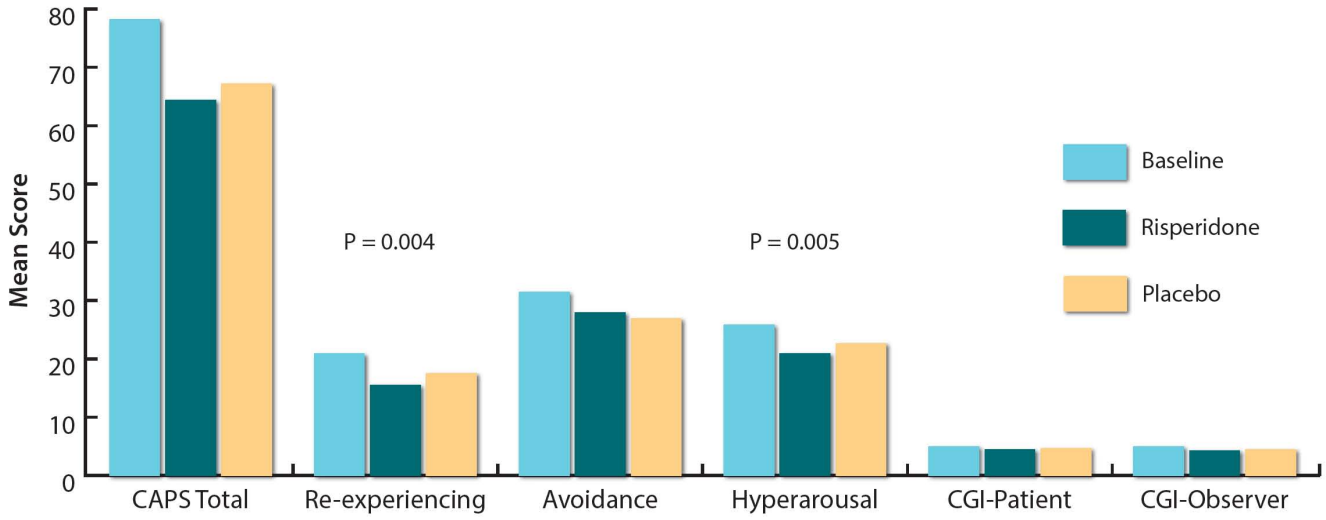
Table 2. Differentiating PTSD Symptoms from Psychosis

Comprehensive assessment of psychotic symptoms
Observe for concurrent thought disorder
Assess affect
Rule out substance use, intoxication, withdrawal
New onset psychosis requires full evaluation including medical workup
Consider referral for specialized care

LIMITED BENEFITS

Most clinical trials for antipsychotic use in PTSD are small, have high placebo response rates and questionable clinical significance[23,24,25,26,27]

Figure 7. Risperidone vs. Placebo in Veterans with Chronic Post-Traumatic Stress Disorder[28]



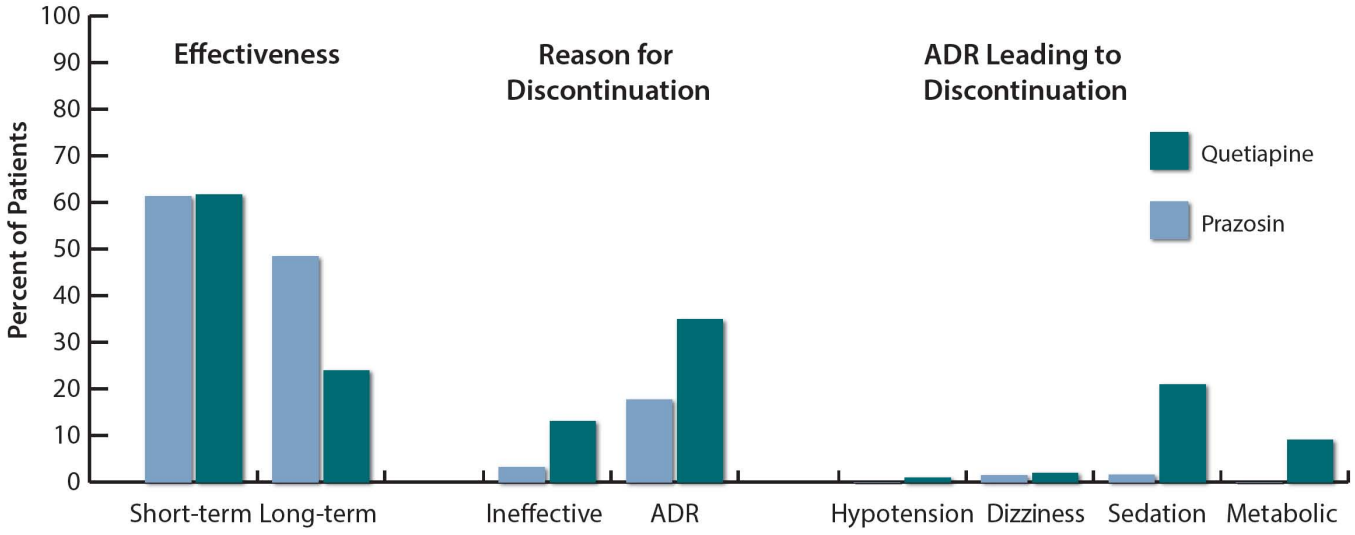
No difference was found at 6 months between adjunctive risperidone (n = 133) and placebo (n = 134) for reducing CAPS total score in Veterans with treatment resistant PTSD. In addition, risperidone did not reduce symptoms of depression, anxiety, or patient and observer rated CGI. In post hoc analysis it was found that there was statistical improvement in the re-experiencing and hyperarousal symptom clusters; however, these differences have a small effect size and questionable clinical significance. This study cannot rule out the possibility that risperidone treatment addresses a real clinical need for some patients. CGI = Clinical Global Improvement; CAPS = Clinician-Administered PTSD Scale.

SUBSTANTIAL RISKS

➔ Cardiometabolic risks of antipsychotics are at least as equivalent if not higher in PTSD as they are in other mental health disorders[29]

➔ Patients prescribed quetiapine for PTSD-related nighttime symptoms were more likely than those receiving prazosin to discontinue quetiapine due to side effects or ineffectiveness[30]

Figure 8. Prazosin vs. Quetiapine for Night-time PTSD Symptoms[30]



This retrospective chart review (n = 237) found that prazosin and quetiapine had similar short-term (<6mo) response rates. However, patients that were given prazosin were significantly more likely to continue their therapy ($p < 0.001$). More patients discontinued quetiapine therapy because of ineffectiveness ($p = 0.003$) and side effects, including sedation ($p < 0.001$) and metabolic changes ($p = 0.014$). ADR = adverse drug reaction.

Figure 9. Recommended Treatment of PTSD[23]

SSRI = Selective Serotonin Reuptake Inhibitor,
TCA = Tricyclic Antidepressant

There is limited evidence for the use of SGAs in PTSD and they can potentially cause significant harm, thus they cannot be recommended at this time.[23,24–28]

Antipsychotic Use and Insomnia

LIMITED BENEFITS

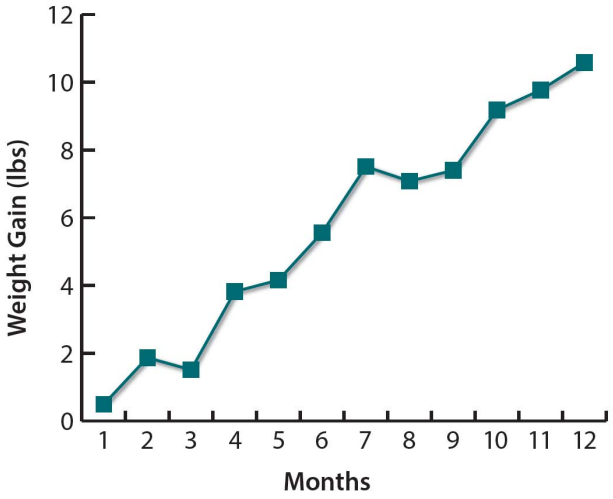
Minimal evidence currently available to support use in insomnia[25,32–34]

- ➔ Limited by small sample sizes and poor study design
- ➔ Questionable clinical significance

SUBSTANTIAL RISKS[34]

- ➔ Cardiometabolic effects
  - ❖ Significant weight gain even at low doses[35]
- ➔ Tardive dyskinesia, orthostasis, constipation, dry mouth[35,36]
- ➔ Case studies report somnambulism, periodic leg movements, lack of REM sleep and nighttime combativeness[33,35,36]

Figure 10. Weight Gain with Low Dose Quetiapine ≤100 mg/day Over 12 Months



At 6 and 12 months of treatment with quetiapine ≤100 mg/day, there was a significant increase in weight compared to baseline values ($p<0.001$ for both time points).[35]

RECOMMENDED MANAGEMENT OF INSOMNIA

- ➔ It is important to first thoroughly evaluate the Veteran's complaint of insomnia and rule out or manage underlying causes of sleep disturbance.
- ➔ Psychological and behavioral interventions such as cognitive behavioral therapy for insomnia (CBT-I) should be recommended 1st line for the treatment of insomnia.[37]
- ➔ If the patient still suffers from insomnia after being offered CBT-I and basic principles of sleep hygiene, pharmacotherapy options may be considered.

Table 3. Pharmacologic Agents to Consider by Comorbidity

Substance Use Disorder	PTSD or Anxiety Disorder	No Comorbidities	Depression	Pain
Amitriptyline	Amitriptyline	Amitriptyline	Amitriptyline	Amitriptyline
Antihistamines	Antihistamines	Antihistamines	Antihistamines	Antihistamines
Doxepin (NF*)	Doxepin (NF*)	Doxepin (NF*)	Doxepin (NF*)	Doxepin (NF*)
Gabapentin	Melatonin	Melatonin	Melatonin	Gabapentin
Melatonin	Mirtazapine	Mirtazapine	Mirtazapine	Melatonin
Mirtazapine	Prazosin (if nightmares)	Ramelteon (NF)	Ramelteon (NF)	Mirtazapine
Ramelteon (NF)	Ramelteon (NF)	Temazepam	Trazodone	Ramelteon (NF)
Trazodone	Trazodone	Trazodone		Trazodone
	Zolpidem	Zolpidem		

Medications are listed in alphabetical order. Medications listed may not be approved for insomnia or strongly supported by evidence. Medications recommendations are guided by clinical experience and based on risks vs benefits analysis; use clinical judgment.
NF = not currently on VA National formulary; NF*= Not currently on VA National Formulary at FDA-Approved dose for Insomnia (3–6 mg).
Doxepin 10 mg can be considered as an alternative to the NF product based on clinical judgment. Medications with anticholinergic activity should be avoided in elderly patients, please refer to Academic Detailing Insomnia module for more information on risks and benefits of specific medications.

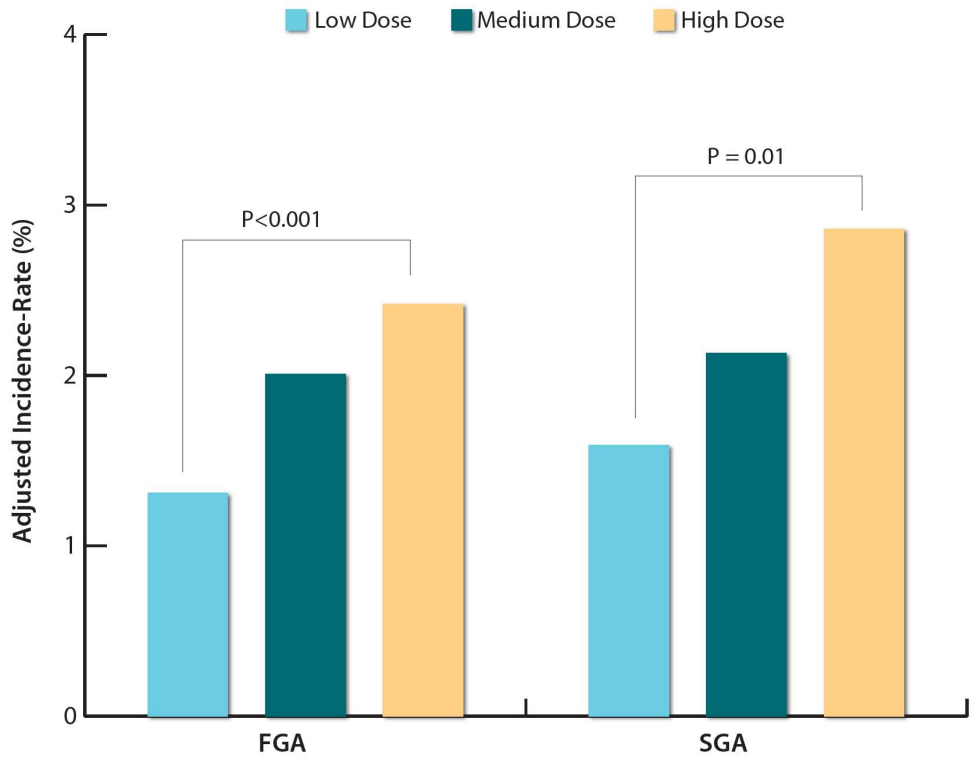
Avoid using low dose antipsychotics for sleep as the risks outweigh the benefits at this time.

Use of Antipsychotics at Higher Than FDA-approved Doses

Potential Concerns with Exceeding Maximum Dose

- ➔ Reviews of dose-response effects have revealed no evidence supporting increasing doses above accepted licensed ranges[38,39]
- ➔ Risks include:
  - ❖ ↑ mortality,
  - ❖ ↑ side effects,
  - ❖ ↑ risk of non-adherence[40,41,42,43,44]

Figure 11. Adjusted Incidence-Rate of Sudden Cardiac Death Among Current Antipsychotic Users[40]

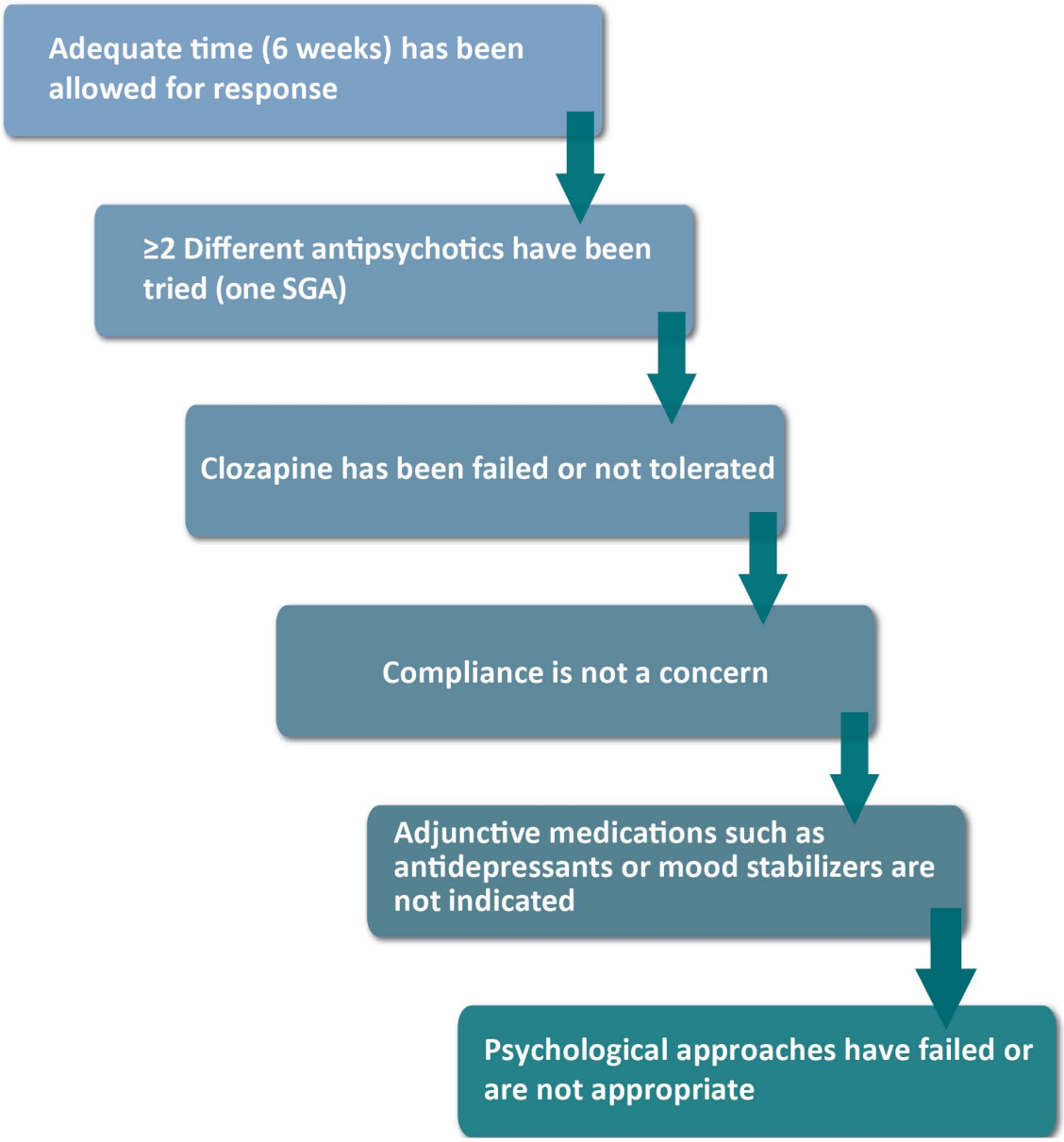


Analysis included 44,218 FGA and 46,089 SGA subjects and compared them to 186,000 matched controls with schizophrenia. Patients on antipsychotic medications had a higher incidence of sudden cardiac death compared to non-users and the risk of sudden cardiac death was found to be dose related for both FGA and SGAs.

Low Dose: <100 mg chlorpromazine (CPZ);
Medium Dose: 100–299 mg CPZ;
High Dose: ≥300 mg CPZ.

Trials of an alternative antipsychotic or augmentation with other psychotropic agents should be tried prior to exceeding maximally effective doses. If the patient is suffering from treatment refractory schizophrenia, **clozapine** is the only antipsychotic that has been found to be superior to both first and second generation antipsychotics.[45,46,47]

Figure 12. Factors to Consider Prior to Exceeding Maximum Recommended Dose of Antipsychotics[48]



High dose antipsychotics have unknown efficacy and known risks. Only use high dose antipsychotics when standard treatment options have failed.

Is Use of More than 1 Antipsychotic Desperation or Evidence-Based?

Evidence is lacking for the effectiveness of multiple antipsychotics and studies indicate an increased side effect burden.[49,50]

Additionally, studies indicate that patients do as well or better on one antipsychotic vs. multiple antipsychotics.[44,51–53]

LIMITED BENEFITS

A higher proportion of patients who had an antipsychotic added (19%) rather than switched to an alternative antipsychotic (9%) received inpatient psychiatric care ($p = 0.033$) 3 months after the change.[51]

SUBSTANTIAL RISKS

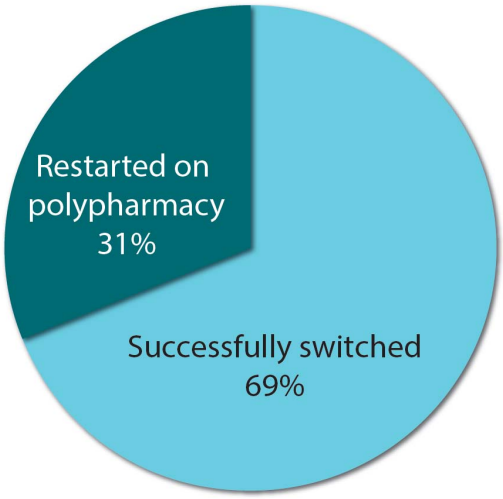
➔ Increased sedation, prolactin, glucose, heart rate, metabolic syndrome, and hospitalizations; decreased working verbal memory.[41,42,43,51,53]

Switching from Multiple Antipsychotic Use to Monotherapy

➔ Psychiatrists who converted to an alternative antipsychotic perceived more effectiveness than psychiatrists who prescribed additional antipsychotics.[51]

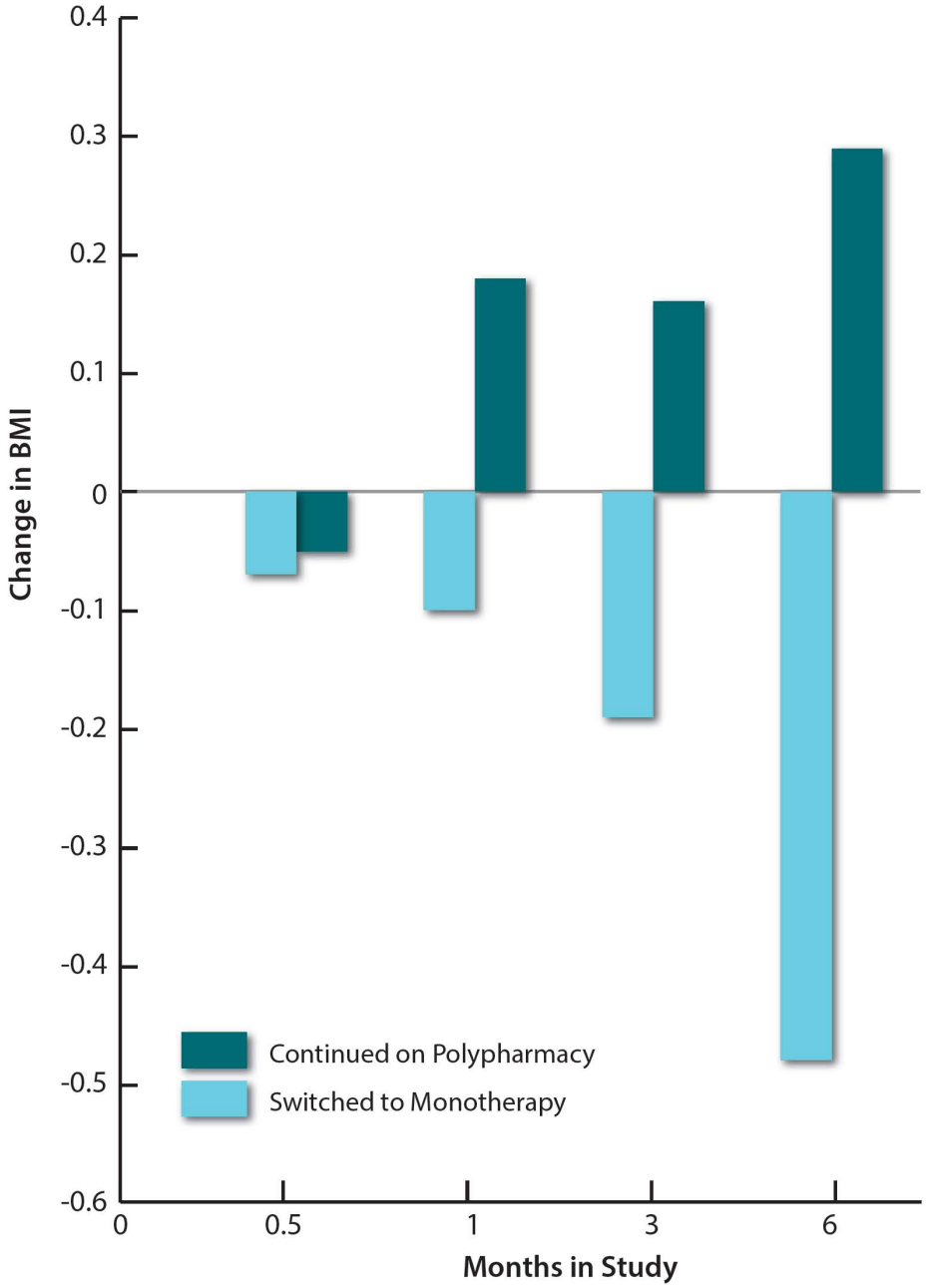
➔ Switching to monotherapy resulted in a weight loss of 0.5 BMI units over 6 months.[44]

Figure 13. Effectiveness of Switching from Polypharmacy to Monotherapy



Approximately two-thirds of the patients switched from polypharmacy (2 antipsychotics) to monotherapy did so successfully. No differences were seen in psychiatric symptoms or hospitalizations between those switched to monotherapy and those who continued on polypharmacy.[44]

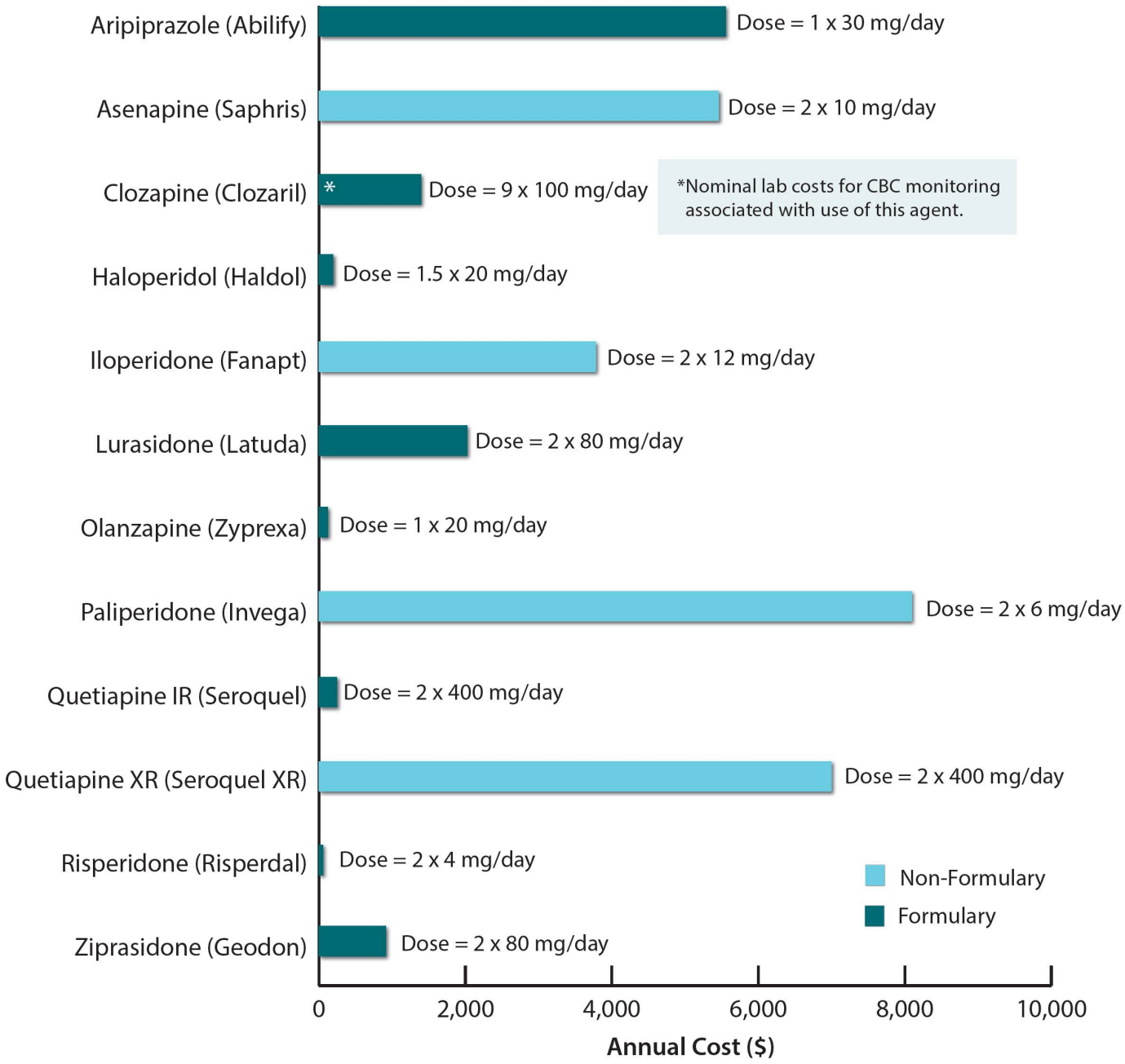
Figure 14. Difference in Body Mass Index[44]



Due to insufficient evidence, only consider the use of multiple antipsychotics after failure of clozapine, or in patients for whom clozapine is contraindicated.

Figure 15

Annual Cost of Oral Therapy per Patient Based on Maximum FDA Recommended Daily Dose (July 2015)



Drug costs were derived from the National Pharmacy Cube from July 2015.
Annual costs assume 12 fills of 30 day supplies.

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VA Academic Detailing Service

Real Provider Resources
Real Patient Results

U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint.

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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