Antipsychotics in the treatment of neuropsychiatric symptoms in dementia

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ABSTRACT

The use of antipsychotics in the treatment of neuropsychiatric symptoms (NPS) in the geropsychiatric population is a controversial topic. Clinicians must be aware of current guidelines and best practices regarding antipsychotic use in long term care populations due to an associated risk of mortality. This article discusses and compares the guidelines regarding treatment of NPS published by the American College of Neuropsychopharmacology and the World Federation of Societies of Biological Psychiatry, and reviews the guidelines regarding gradual dose reduction in this population.

KEYWORDS

antipsychotic, neuropsychiatric symptoms, dementia

INTRODUCTION

One of the most controversial therapeutic topics in contemporary geropsychiatry is the use of antipsychotics in the treatment of neuropsychiatric symptoms (NPS). Much of the controversy centers around use of these agents without regard to FDA approved indications and the "black box" warning showing an increase in mortality in the geropsychiatric population. Unfortunately, this results in negative media and government attention. This article aims to give clinicians an overview of the controversy, discuss treatment guidelines in treating NPS, and reinforce the importance of the gradual dose reduction guidelines in treating patients with NPS in long term care facilities.

BACKGROUND

Neuropsychiatric symptoms can occur in up to 60% of community-dwelling dementia patients and 80% of dementia patients residing in long term care facilities. Secondary to the intensity and frequency of these events, antipsychotics have been commonly utilized to control the behavior of patients with NPS in long term care settings.[1]

On April 11, 2005, the FDA released a public health advisory associating deaths with antipsychotics use in the treatment of elderly patients with behavioral disturbances.[2] The FDA found in their retrospective analysis of both published and unpublished data from 5106 patients receiving olanzapine, risperidone, and quetiapine that atypical antipsychotics had an increase in mortality of 1.6 to 1.7 times compared to placebo. Analysis showed that specific causes of death were associated to heart related events or infections. At that time, the warning was issued to only the drugs classified as an "atypical antipsychotic". However, on June 16, 2008, after two observational studies showed an increase in mortality with conventional antipsychotics, the FDA issued a black box warning to all antipsychotic agents, regardless of classification.[3] In one of the cited observational studies from the FDA warning, Gill and colleagues found that conventional antipsychotics were associated with an even higher mortality than the second generation antipsychotics (adjusted hazard ratio, 1.31 [95% CI, 1.02 to 1.70]).[4] Interestingly, since the initial findings from the FDA, several other database analyses have consistently found similar findings with regards to antipsychotics causing an increase in mortality in various elderly and/or demented populations.[5-7]

Secondary to the FDA warning, antipsychotic utilization decreased from 17% to 14% in this population over the course of 3 years.[8] Despite the decrease in utilization, a disparity still existed between efficacy and safety of antipsychotics used in long term care settings. This eventually led to the involvement of the United States Congress and an investigation by the Office of the Inspector General (OIG) to evaluate the use of antipsychotics in the nursing home population.[9] In the OIG investigation, it was found that found 14% of nursing home patients were prescribed an antipsychotic, 88% of antipsychotics were used specifically for the treatment of NPS in dementia, and 22% of the antipsychotics administered were not in accordance with Center for Medicare and Medicaid Services (CMS) rules regarding unnecessary drug use (higher than recommended doses and lack of documentation for a trial of a gradual dose reduction). Eventually, the testimony and findings from

the OIG were presented to the United States Senate Special Committee on Aging on November 30, 2011 which continued to highlight and politicize the use of antipsychotics in long term care. Due to the increase scrutiny regarding antipsychotics use, clinicians must employ evidence based practices in order to optimize treatment while avoiding any medico-legal repercussions for using antipsychotics to treat NPS.

Table 1: Comparison of ACNP and WFSBP Guidelines

Intervention	ACNP White Paper	WFSBP Guidelines
Step 1	Determine etiology of symptoms	Assess for any underling factors for behavior
Step 2	General therapeutic interventions (nonpharmacological therapies)	Eliminate any precipitating factors
Step 3	Include patient and family for guidance on how to proceed	Psychosocial interventions
Step 4	Identify target symptoms	Drug therapy
Step 5	Choose specific pharmacotherapy	Reassess need for agent and maintain lowest effective dose if needed
Step 6	Dose agent at lowest effective dose	
Step 7	Monitor effectiveness	
Step 8	Monitor safety	
Step 9	Continue to educate patient and caregivers	
Step 10	Consider discontinuing or switching pharmacotherapy based on response	
Step 11	Coordinate care among other health care providers (this occurs at each step)	

TREATMENT GUIDELINES

Clinicians must be cognizant of current guidelines and best practices regarding antipsychotic use in long term care populations due to the associated risk of mortality. In the past couple of years, two sets of treatment guidelines and consensus statements have been published to help guide clinicians in the decision making process of treating NPS in a demented population.[1,10] In this section, we will highlight the general themes of the recommendations. Table 1 compares the two guidelines in their step by step approach in treating NPS.

ACNP: American College of Neuropsychopharmacology; WFSBP: World Federation of Societies of Biological Psychiatry

In many ways, the guidelines mirror each other in their approach to treatment of patients with NPS. The first step should attempt to determine the rationale for an escalation of the behavior, including biological factors, adverse events from current medication or illicit substances, psychosocial factors, and environmental factors.[10] It should be noted, one of the concerns in the OIG report was a lack of investigation into possible causes of the behavior, thus essentially skipping the first step in both treatment guidelines. Once assessment is complete, **nonpharmacological therapies should always be considered first line treatment of NPS.** There is an argument that nonpharmacological modalities lack evidence to support efficacy in treating NPS; however, because of the overall safety to the patient, these therapies are considered first line.[11] Only patient specific behavioral management techniques, de-escalation education to caregivers, and cognitive stimulation (music and Snoezelin therapies) have been shown to be consistently effective. Unfortunately, no guidelines give recommendations on how long nonpharmacological therapy should be tried once implemented, but clinically this would depend on the severity of the NPS. Once these techniques have been utilized and/or failed, drug therapy may be a possible option. This author would highly recommend that clinicians closely follow the ACNP white paper recommendations in assuring that any treatment decision is a shared decision among the patient's family, caregivers, and other health care professionals to minimize any potential medico-legal complications. Target behaviors must also be identified and documented in the treatment plan if any drug therapy is initiated. If the therapeutic goal is achieved, dose reduction or drug discontinuation must be considered in order to minimize likelihood of mortality with the antipsychotics and to comply with CMS guidelines for gradual dose reduction.

Neither set of guidelines from Table 1 specify a particular agent to use as first line treatment of NPS. Several conventional antipsychotics, along with risperidone, olanzapine, aripiprazole, and quetiapine all have randomized controlled trials of NPS in dementia prior to the black box warning.[12] The CATIE-AD study also prospectively studied olanzapine, quetiapine, and risperidone in outpatients with NPS in dementia.[13] Overall findings in the CATIE-AD study showed that all cause discontinuation was no different for any agent compared to placebo. However, risperidone and olanzapine did

show improvement in the NPI versus placebo in secondary analysis of the CATIE-AD.

In a meta-analysis conducted by Schneider and colleagues of over 15 clinical trials looking at atypical antipsychotics in NPS, small but statistically significant findings regarding efficacy were noted with both risperidone and aripiprazole. In a similar finding, the Agency for Healthcare Research and Quality (AHRQ) 2011 report for off-labeled uses of antipsychotics also found risperidone, olanzapine, and aripiprazole having more efficacy than placebo on the BEHAVE-AD, BPRS, and NPI scales for agitation in dementia.[14] For patients with psychosis and dementia, risperidone was statistically better than placebo, whereas aripiprazole did not reach statistical significance. In the end, AHRQ concluded that risperidone, aripiprazole, and olanzapine have efficacy supporting their use in this population and are considered first line agents when drug therapy is initiated. Despite which agent is chosen to treat NPS, the treatment guidelines are clear: the lowest effective dose must be utilized and dose reductions are mandatory in order to minimize adverse events. The next section will cover the gradual dose reduction guidelines in detail (Table 2).

TABLE 2: GRADUAL DOSE REDUCTION (GDR) GUIDELINES

Drug Class	Frequency of dose reduction within 1st year of admission to the LTC facility	Frequency of GDR after 1 year
Antipsychotics	Attempt a GDR in two separate quarters (with at least one month between the attempts)	A GDR should be attempted annually
Sedative/ Hypnotics	Quarterly	Continue quarterly reduction until discontinuation
Other CNS active medications (antidepressants, mood stabilizers)	Attempt a GDR in two separate quarters (with at least one month between the attempts)	A GDR should be attempted annually

There are instances when a GDR is not mandated; however, appropriate documentation is required. The documentation should state that the continued use is in accordance with relevant current standards of practice and that the physician has documented clinical rationale OR the resident's target symptoms returned or worsened after most recent GDR attempt within a facility and the physician has documented clinical rationale.[15] For example, if there is an elderly patient with a long history of schizophrenia in a nursing home doing well for years on a current antipsychotic, a GDR does not need to be conducted as long as the indication for the antipsychotic is clearly identified and the physician documents that continued use is in accordance to current standards of practice. Unfortunately, the latter documentation does not exist in many instances, thus putting the facility at risk for citation by not following the GDR guidelines. Ultimately, it is the physician's responsibility to assure that proper documentation is noted in the chart. However, pharmacists can play an important role in assuring that the GDR guidelines are followed, and if clinically contraindicated, that appropriate documentation is in place. By appropriately following the GDR guidelines, the pharmacist can have a significant impact on the patient's quality of care.

CONCLUSIONS

As described above in detail, the use of antipsychotics in treating NPS has become a very controversial and politicalized topic which has placed emphasis on appropriate management of dementia patients. To help navigate through the controversies and provide evidence based medicine, guidelines recommend a full patient assessment to rule out factors causing the behavior, employ nonpharmacological measures first, and drug therapy as a last resort. If antipsychotic therapy is started, risperidone, aripiprazole, and olanzapine have data to support their use in treating NPS in dementia. Once these drugs are started, gradual dose reductions must be made in order to comply with CMS and to minimize the adverse events of the antipsychotics in this population.

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