

TABLE OF CONTENTS

• Short-term Safety of Antipsychotics for Dementia	1-2
• Preoperative Statins and Effects on Mortality	2-4
• Hormone Replacement Therapy and Risk of Venous Thromboembolism	4-5
• P&T Committee Formulary Action	5

Short-term Safety of Antipsychotics for Dementia

Safety concerns regarding use of antipsychotic medications present a distinct challenge in the geriatric population. Nevertheless, conventional and atypical antipsychotic medications are widely used short-term to control psychiatric and behavioral symptoms of dementia, including psychosis, agitation, and aggression. Up to 40% of patients with Alzheimer’s disease experience psychotic symptoms and even more experience behavioral disorder. Recently, prescribing habits have favored atypical antipsychotics because of concerns regarding the safety of conventional agents.

Previously, there was little randomized, controlled trial evidence supporting use of most antipsychotics for this indication. Recently, the National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease (CATIE-AD), a large-scope study designed to examine efficacy and outcomes in atypical antipsychotic use in Alzheimer’s patients, reported results indicating some of these agents do provide benefit in reducing certain symptoms of dementia (e.g., anger, aggression, and paranoid ideas) although their overall effects on quality of life were minimal. The CATIE-AD trial studied 421 outpatients with Alzheimer’s disease and either psychosis or behavioral disorders; it is part of a larger study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which also examines these agents in schizophrenia. These results suggest that atypical antipsychotics will continue to be utilized in geriatric patients to reduce dementia symptoms.

However, complicating the use of these agents is the recent Food and Drug Administration (FDA) black box warning cautioning prescribers about the risk of mortality associated with atypical antipsychotics in patients with dementia. This warning is based on findings from placebo-controlled studies, involving over 5000 elderly patients, with dementia that reported increases in mortality with antipsychotic treatment over placebo. Causes of

death included cardiovascular events (heart failure and sudden death) and infections (primarily pneumonia). In June 2008, the FDA expanded this warning to include conventional antipsychotics after results of 2 large epidemiologic studies showed an increased risk of mortality among elderly patients with dementia in association with conventional antipsychotic use. Neither conventional nor atypical antipsychotics are indicated for treatment of dementia in elderly patients.

In addition to the 2 studies used as the basis for the FDA recommendations, a third large, observational study was conducted that evaluated the safety of antipsychotic use in patients with dementia.

Retrospective study on antipsychotic use in dementia

To investigate the safety associated with short term use of both conventional and atypical antipsychotics in geriatric patients with dementia, Rochon and colleagues initiated the Antipsychotic Therapy and Short-term Serious Events in Older Adults with Dementia trial in 1997. Serious adverse events were only measured for acute care (i.e., up to 30 days), a treatment principle suggested in the current dementia guidelines. In addition, this study assessed antipsychotic use in the outpatient as well as nursing home populations. This study analyzed the effect of these medications on a number of adverse events associated with antipsychotic use in geriatrics; the primary endpoint was occurrence of a composite endpoint of any serious event including death, hospitalization, falls, hip fractures, cerebrovascular events, and extrapyramidal symptoms (EPS) identified within 30 days of cohort entry.

Patients in this population-based retrospective cohort study were divided into 2 groups, based on whether the patient resided in the community or in a nursing home. Patients with recent history of schizophrenia, tics, Huntington disease, and dialysis were excluded. Patients who had a history of the major adverse effects being

assessed (including parkinsonism, EPS, or hip fracture) as well as any conditions that may lead to an event were also excluded.

Each of the 2 resulting cohorts was then divided into 3 treatment groups using case-control matching based on antipsychotic use (none, atypical, or conventional). The final cohorts included 20,682 patients from the community and 20,559 patients from nursing homes. The community cohort included 6,894 patients in each of the 3 treatment groups and the nursing home cohort included 6,853 patients in each of the 3 treatment groups. The most common antipsychotic agents used are presented in Table 1.

	Community Cohort (n[%])	Nursing Home Cohort (n[%])
Atypical	n = 6894	n = 6853
Risperidone	5051 (72.0%)	5310 (73.1%)
Olanzapine	1405 (20.0%)	1469 (20.2%)
Quetiapine	564 (8.0%)	486 (6.7%)
Conventional	n = 6894	n = 6853
Haloperidol	4087 (58.6%)	3780 (52.9%)
Loxapine	1242 (17.8%)	1726 (24.2%)
Thioridazine	745 (10.7%)	830 (11.6%)

Study results

Within the community cohort, 13.9% of patients in the atypical antipsychotic group and 16.0% of patients in the conventional antipsychotic group experienced a serious adverse event as defined in the primary endpoint. The distribution of events was similar among the 2 treatment groups; EPS, cardiovascular events, and falls and hip fractures were very low while hospitalization for other causes and death were high. Patients in the atypical antipsychotic group were 3.2 times more likely to exhibit a serious event than the group receiving no antipsychotic (95% CI 2.77-3.68). Patients in the conventional antipsychotic group were 3.8 times more likely to exhibit a serious event than the group receiving no antipsychotic (95% CI 3.31-4.39). Within the nursing home cohort, 9.4% of patients in the atypical antipsychotic group and 11.6% of patients in the conventional antipsychotic group experienced a serious adverse event. The distribution of events was similar among the 2 treatment groups and consistent with the results from the community cohort. Patients in the atypical antipsychotic group were 1.9 times more likely to have a serious event than the control group (95% CI 1.68-2.21). Patients in the conventional antipsychotic group were 2.4 times more likely to have a serious event than the control group (95% CI 2.08-2.72). Table 2 lists the frequency of occurrence of the individual adverse events.

	Community Cohort			Nursing Home Cohort		
	N = 20,682			N = 20,559		
	Conv	Atyp	None	Conv	Atyp	None
Any serious event (%)	16.0	13.9	4.4	11.6	9.4	5.6
Death	4.6	2.7	1.2	6.5	5.2	3.3
EPS	0.2	0.3	0.0	0.1	0.1	0.0
Cardio-vascular	0.6	0.7	0.2	0.2	0.2	0.1
Fall/hip fracture	1.2	1.2	0.4	1.2	1.0	0.5
Other	11.7	11.0	3.2	5.2	4.5	2.5

Conv=conventional antipsychotics; Atyp=atypical antipsychotics; EPS=extrapyramidal symptoms.

Summary

This article confirms that any antipsychotic use, even short-term exposure, is associated with serious adverse events among elderly patients with dementia. However, due to its design and patient baseline characteristics, it is uncertain whether antipsychotic use itself was the sole cause of these events. This article highlights the importance of cautious use of these agents, especially considering that the increased monitoring in the nursing home environment seems to decrease serious adverse events when compared to a community setting. However, the study would have had more of an impact by clearly addressing a comparison between atypical and conventional antipsychotics. Because the results of the CATIE-AD trial may lead to continued or increased prescribing of atypical antipsychotics, stronger comparative data would be beneficial.

Preoperative Statins and Effects on Mortality

In many well designed studies, HMG Coenzyme A reductase inhibitors (also known as “statins”) have been shown to effectively lower serum cholesterol, slow the formation of atherosclerotic occlusive disease, and reduce the risks of death, myocardial infarction, stroke and other adverse cardiovascular events. Additionally, several large studies have shown that treatment with statins prior to cardiac surgery and some non-cardiac surgeries can significantly reduce postoperative morbidity and mortality. There are, however, some mixed conclusions and conflicting studies regarding this benefit, with some studies showing a decrease in mortality and major cardiovascular events in the short-term and other failing to show benefit. As such, though existing guidelines suggest using therapy to aggressively lower lipids in high-risk populations, statin use is only at about 40% for patients preparing to undergo cardiac surgery.

In previous studies that sought to elucidate the benefits of preoperative statins, a major limitation was the retrospective nature of the study designs. Controlling

for confounding variables such as baseline patient characteristics and medication use is more difficult in retrospective studies. The published systematic reviews and analyses designed to bring clarity to the possible benefits of preoperative statins have also been limited, mainly by potential bias and insufficient power. To further investigate the effects of preoperative statin use, Liakopoulos conducted a large meta-analysis involving over 30,000 patients undergoing cardiac surgery.

Meta-analysis design

The primary objectives of the meta analysis were to determine if preoperative statins reduce early all-cause mortality and decrease the incidence of major adverse post-operative events. Additionally, the authors sought to quantify the magnitude of the treatment effects. The secondary objective was to identify confounding factors that may limit the estimated treatment effects on the endpoints. The analysis included 19 unique studies published between 1999 and 2007; the total number of patients included was 31,725. Of those, 17,201 (54.2%) were given preoperative statin therapy and 14,524 (45.8%) were not.

The inclusion criteria allowed for randomized prospective clinical trials and observational studies published between 1966 and 2008 reporting the effects of preoperative statin therapy on postoperative outcomes in adult patients undergoing cardiac surgery. Trials included in this analysis met the following criteria: the use of a statin at any dose or duration prior to cardiac surgery, a comparison of patients who received preoperative statin therapy with those who did not, and data on clinical endpoints of early all-cause mortality, myocardial infarction, atrial fibrillation, stroke, and renal failure.

Of 1197 studies identified, 33 were reviewed and 19 met the inclusion criteria; 3 were randomized controlled trials (RCT), 3 had a prospective design, and 13 a retrospective design. All 19 used a study population of patients undergoing CABG, some with valve surgery and some without. The dose and duration of statins given were variable between studies. All studies used in the analysis were examined for methodological quality using the Jadad score for RCT and the Downs and Black checklist for RCT and observational trials, with an overall rating of good quality.

Meta-analysis findings

The clinical endpoints assessed are defined in Table 1. For the endpoint of early or short-term mortality, the overall incidence was 2.9%. This endpoint was included in 15 studies (28,517 patients), and in one that reported mortality after a 60-day follow-up. Between patients receiving preoperative statins and those not receiving preoperative statins, the absolute risk reduction with statin use was shown to be 1.5% (mortality rates of 2.2% vs. 3.7%, respectively, $p < 0.0001$); or a relative reduction of 43% for short-term mortality (odds ratio

[OR] 0.57, 95% CI: 0.49-0.67, $p < 0.0001$).

For the endpoint of myocardial infarction, the overall incidence was 4.1%. This endpoint was included in 10 studies (14,330 patients). Between groups there was no significant reduction of myocardial infarction risk (4.2% vs. 3.9%, $p = 0.373$; OR 1.11, 95% CI: 0.93-1.33, $p = 0.25$).

For the endpoint of post-operative atrial fibrillation (AF), the overall incidence was 26.9%. This endpoint was included in 7 studies (7,643 patients), and 3 studies reported new onset AF. Between the 2 groups of patients (statin vs. no statin treatment), the absolute risk reduction with statin use was 4.3% (24.2% vs. 29.2%, $p < 0.0001$). These results gave a relative reduction of 33% for post-operative AF (OR 0.67, 95% CI: 0.51-0.88; $p < 0.0001$).

For the endpoint of stroke, the overall incidence was 2.4%. This endpoint was included in 7 studies (16,390 patients). Between the 2 groups of patients, the absolute risk reduction was shown to be 0.8% (2.1% vs. 2.9% for statin vs. no statin use, $p < 0.001$). These results gave a relative reduction of 26% for post-operative stroke (OR 0.74, 95% CI: 0.60-0.91; $p < 0.004$).

Finally, for the endpoint of renal failure, the overall incidence was 4.1%. This endpoint was included in 5 studies (6,408 patients). Between groups there was no significant reduction of renal failure risk (3.9% vs. 4.5%, $p = 0.275$; OR 0.78, 95% CI: 0.46-1.31, $p = 0.34$).

Table 1. Clinical endpoint definitions
Short-term mortality: <ul style="list-style-type: none"> Any-cause death during hospitalization or within 30 days of surgery
Myocardial infarction: <ul style="list-style-type: none"> Elevations of perioperative markers of cardiac damage New ECG changes Clinical signs of myocardial ischemia Diagnosis at autopsy
Atrial fibrillation: <ul style="list-style-type: none"> Any postoperative atrial fibrillation (excluding atrial flutter or supraventricular tachycardia)
Stroke: <ul style="list-style-type: none"> Clinical or radiological neurologic deficit
Renal failure: <ul style="list-style-type: none"> Postoperative elevation of serum creatinine (>2.0 mg/dL) Need for postoperative dialysis

Summary

According to the authors of the meta-analysis, this review demonstrates a substantial benefit to patients and a clear basis to advocate for an intensified pre-treatment statin regimen and rigorous post-op regimen per existing guidelines for patients undergoing cardiac surgery who have multiple cardiac risks and coronary heart disease. The authors further concluded that although the analysis included an appropriately large sample size, it would be premature to suggest that all patients undergoing cardiac surgery receive preoperative statins.

Hormone Replacement Therapy and Risk of Venous Thromboembolism

Until recently, hormone replacement therapy (HRT) was commonly used for relief of symptoms associated with menopause in women. In addition, HRT was used for treatment of osteoporosis with additional evidence suggesting a role for cardioprotection. However, the Women's Health Initiative study, a randomized, controlled trial involving nearly 162,000 women, reported significant increases in the risks of serious adverse events, such as myocardial infarction, stroke, and venous thromboembolism (VTE), among a cohort of 16,608 women in one arm of the study. A number of other observational and interventional clinical trials have also evaluated the effects of hormone replacement therapy, including effects on the risk of VTE. However, many of these studies used oral conjugated equine estrogens (with or without medroxyprogesterone), the most widely used of the estrogen agents. Less information is available regarding the risk of VTE with other estrogen replacement therapies, including transdermal estrogen. In a recent issue of the British Medical Journal, Canonico and colleagues published the results of a meta-analysis conducted to evaluate the effect of several types of hormone replacement therapy on the risk of first episode VTE in postmenopausal women.

Meta-analysis results

The authors identified 111 articles related to estrogen use; of 24 articles they were eligible for inclusion, 17 met the criteria for the meta-analysis. Nine of these studies were randomized controlled trials and the remaining 8 were observational (primarily case-control) trials. In addition to the effect of HRT on the occurrence of VTE, the analysis included the effects of the type of estrogen, the route of administration (oral vs. transdermal), and duration of treatment. The major characteristics of the randomized controlled trials are given in Table 1; observational studies are described in Table 2.

Study	No. pts	Duration	Route/type of estrogen
PEPI 1995	847	3 y	Oral/CEE
HERS 1998	2763	4.1 y	Oral/CEE
EVTET 2000	140	1.3 y	Oral/Estradiol
ERA 2000	309	3.2 y	Oral/CEE
WEST 2001	664	2.8 y	Oral/17-beta estradiol
ESPRIT 2002	1017	2 y	Oral/estradiol valerate
WHI I 2002	16,608	5.2 y	Oral/CEE
WHI II 2004	10,739	7 y	Oral/CEE
WISDOM 2007	5692	0.99 y	Oral/CEE

HRT=hormone replacement therapy; CEE= conjugated equine estrogen.

Study	Study design	Exposed cases	Route/type of estrogen
Boston CDSP 1974	Case-control	3	Oral/CEE
Daly 1996	Case-control	42	Oral or transdermal/estradiol, estradiol valerate, or CEE
Jick 1996	Case-control	21	Oral/CEE or esterified estrogens
Nurse' Health Study 1996	Prospective cohort	68	Oral/CEE
Perez-Gutthann 1997	Case-control	27	Oral or transdermal/estradiol, estradiol valerate, or CEE
Smith 2004	Case-control	207	Oral/CEE or esterified estrogen
Douketis 2005	Case-control	39	Oral or transdermal/NA
ESTHER 2007	Case-control	124	Oral or transdermal/estradiol, estradiol valerate, or CEE

HRT=hormone replacement therapy; CEE=conjugated equine estrogen; NA=not available.

Pooled data from the various trials were analyzed by route

of administration as well as by type and duration of use. For observational studies, oral estrogen was associated with an increased risk of VTE, with a calculated odds ratio of 2.5 (95% CI, 1.9-3.4). Similar results were found for data from randomized controlled trials of oral estrogens—odds ratio of 2.1 (95% CI, 1.4-3.1) for oral estrogen use. However, for transdermal estrogen, the odds ratio for first episode VTE was 1.2 (95% CI, 0.9-1.7), indicating no significant increase with exposure. Previous exposure to any estrogen was assessed in 4 observational studies and was not found to increase the risk of VTE (OR 1.2; 95% CI, 0.9-1.7). Data were available from 6 observational studies on the use of unopposed and opposed oral estrogen; concurrent use of progesterone also had no effect on the risk of VTE. However, duration of treatment did have a significant effect on VTE risk, based on results of 5 case-controlled studies. Use of estrogen for less than 1 year was associated with an odds ratio for VTE of 4.0 (95% CI, 2.9-5.7); for more than 1 year of use, the odds ratio was 2.1 (95% CI, 1.3-3.8), a significantly lower risk ($p=0.046$ for comparison). Only 1 study evaluate the effects of different types of estrogen. In comparison to conjugated equine estrogen, esterified estrogen was not associated with an increased risk of VTE. Finally, as would be expected, the presence of pre-existing risk factors for VTE—increased body mass and prothrombotic mutations—increased the risk of VTE with oral estrogens.

Summary

The results of this meta-analysis confirm the effects of estrogen therapy on the risk of first episode VTE. Use of estrogen as part of hormone replacement therapy significantly increases the risk of first episode VTE, based on data from both randomized and observational trials. Although based on more limited data, transdermal estrogen did not show a similar effect. The authors suggested that transdermal estrogen, due to its lack of first pass hepatic metabolism, may not have the same effect as oral estrogen on plasma concentrations of prothrombin fragment 1+2 or of antithrombin. Use of transdermal estrogen may be of benefit in reducing the risk of VTE, especially among women with pre-existing risk factors, such as prothrombotic mutations and increased body mass index.

P&T Committee Formulary Action

Additions

Fomepizole - Use restricted to Toxicology Consult

Line extensions

Desmopressin tablet

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Deletions

Procainamide

Cochicine injection

Saquinavir mesylate

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