TITLE: Administering Drugs with Anticholinergic Effects to Patients with Alzheimer’s Disease Who Are Currently Taking Cholinesterase Inhibitors: Clinical Effectiveness and Guidelines

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RESEARCH QUESTIONS:

1. What is the clinical effectiveness of administering drugs with anticholinergic properties to patients with Alzheimer’s disease who are currently taking cholinesterase inhibitors?

2. What are the evidence-based guidelines for the combination therapy of drugs with anticholinergic properties and cholinesterase inhibitors in patients with Alzheimer’s disease?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2005 and January 2010. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

RESULTS:

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, controlled clinical trials, observational studies, economic evaluations, and evidence-based guidelines.

Three observational studies regarding the clinical effectiveness of administering drugs with anticholinergic properties to patients with Alzheimer’s disease currently taking cholinesterase inhibitors were identified. No relevant evidence-based guidelines for the combination therapy of...
drugs with anticholinergic properties and cholinesterase inhibitors in patients with Alzheimer’s disease were identified from the literature search results. Additional articles of potential interest can be found in the appendix.

**Health technology assessments**
No literature identified

**Systematic reviews and meta-analyses**
No literature identified

**Randomized controlled trials**
No literature identified

**Controlled clinical trials**
No literature identified

**Observational studies**


   PURPOSE: Cholinesterase inhibitors (CEIs) have been subsidised in Australia since February 2001 for cognitive decline associated with mild to moderate Alzheimer disease. The number of people with Alzheimer disease is expected to increase, with a continuing increase in the number of people receiving CEI’s. Many anticholinergic drugs (ACDs) are also prescribed to people receiving CEIs and concerns about the impact of the interaction have been raised. The aim of this study was to describe co-prescribing of a group of important ACDs in patients initiating treatment with CEIs in Australia.

   METHODS: Pharmacy claim data for Australia (Pharmaceutical Benefits Scheme) was examined for the period 1 April to 30 June 2006. All selected prescriptions supplied for patients receiving their first supply of any CEIs (initiators) were extracted for 14 weeks prior to and post the first date of supply. The numbers of initiating people co-administering CEIs and ACDs was examined.

   RESULTS: 5797 persons received their first prescription for CEIs between 1 April and 30 June 2006. Thirty-two per cent of these also received prescriptions for at least one ACD. There was a statistically significant increase in the number of initiators receiving an ACD. The significant increase was in patients receiving atypical antipsychotics. There was a trend towards an increase in patients receiving oxybutynin. CONCLUSIONS: Extent of co-administration of ACDs and CEIs is similar to other international studies however the most significant increase is seen in patients receiving atypical antipsychotics. The implications of adding atypical antipsychotics are potential for worsening disease, increasing adverse effects and increased health resource utilisation in this vulnerable group.

BACKGROUND: Although cholinesterase inhibitors are used for the treatment of Alzheimer’s disease, the clinical benefits of these drugs are being questioned. Anticholinergic drugs have the opposite pharmacological action to cholinesterase inhibitors, and may antagonize the effects of cholinesterase inhibitors. Therefore, this drug combination should be avoided. Nevertheless, high rates of concurrent use of anticholinergic drugs and cholinesterase inhibitors have been reported in the US. To the authors’ knowledge, use of this inappropriate drug combination has not been studied outside North America. 

OBJECTIVE: To investigate (i) whether anticholinergic drug use is more common among users than non-users of cholinesterase inhibitors, and (ii) which factors are associated with use of anticholinergic drugs among users of cholinesterase inhibitors. 

METHODS: We analysed data on age, sex, type of residential area (urban/rural) and drugs dispensed for patients aged ≥75 years registered in the Swedish Prescribed Drug Register from October to December 2005 (n=731,105). The prevalence of use of anticholinergic drugs in users of cholinesterase inhibitors was compared with that in non-users of cholinesterase inhibitors and logistic regression was used to study the association between use of cholinesterase inhibitors and anticholinergic drugs. Logistic regression was also used to analyse whether age, sex, type of residential area or number of dispensed drugs was associated with use of anticholinergic drugs among users of cholinesterase inhibitors (n=18,326). 

RESULTS: Anticholinergic drug use was more common among cholinesterase inhibitor users than non-users, particularly in men, of whom 9% who were taking cholinesterase inhibitors were dispensed anticholinergic drugs compared with 5% who were not taking cholinesterase inhibitors. Use of cholinesterase inhibitors was associated with use of anticholinergic drugs in men (odds ratio 1.23; 95% CI 1.13, 1.35), after adjustment for age, type of residential area and number of dispensed drugs. Male sex and use of many drugs were independently associated with concurrent use of anticholinergic drugs and cholinesterase inhibitors. 

CONCLUSION: Anticholinergic drug use is more common among cholinesterase inhibitor users than non-users, even though anticholinergic drugs may antagonize the effect of cholinesterase inhibitors. Hence, if the true clinical effects of cholinesterase inhibitors are to be accurately assessed, they need to be studied in the absence of anticholinergic drugs.


BACKGROUND: The prescribing cascade model involves the misinterpretation of an adverse reaction to 1 drug and the subsequent, potentially inappropriate prescription of a second drug. We present a new example of the prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs used to manage urinary incontinence. 

METHODS: A population-based retrospective cohort study was carried out in Ontario, Canada. Participants included 44,884 older adults with dementia (20,491 were dispensed a cholinesterase inhibitor and 24,393 were not), enrolled between June 1, 1999, and March 31, 2002. Subjects were observed until they received an anticholinergic drug, stopped the cholinesterase inhibitor treatment, died, or the study period ended (March 31, 2003). The main outcome measure was receipt of an anticholinergic drug to manage urinary incontinence. RESULTS: After adjusting for
potential confounding factors, we observed that older adults with dementia who were dispensed cholinesterase inhibitors had an increased risk of subsequently receiving an anticholinergic drug (4.5% vs 3.1%; P<.001; adjusted hazard ratio, 1.55; 95% confidence interval, 1.39-1.72), relative to those not receiving cholinesterase inhibitors. This finding was consistent in a series of subgroup analyses. CONCLUSIONS: 

**Use of cholinesterase inhibitors is associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence.** The use of an anticholinergic drug in this setting may represent a clinically important prescribing cascade. **Clinicians should consider the possible contributing role of cholinesterase inhibitors in new-onset or worsening urinary incontinence and the potential risk of coprescribing cholinesterase inhibitors and anticholinergic drugs to patients with dementia.**

**Guidelines and recommendations**
No literature identified

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**Administering Drugs with Anticholinergic Effects to Patients with Alzheimer’s Disease Currently Taking Cholinesterase Inhibitors**
APPENDIX – FURTHER INFORMATION:

Observational studies


OBJECTIVES: To evaluate the extent of concomitant use of anticholinergic and cholinesterase inhibitor medications in Medicaid recipients with dementia residing in nursing homes. DESIGN: Cross-sectional survey of medical claims data. SETTING: Indiana Medicaid claims for 2004. PARTICIPANTS: Indiana Medicaid recipients continuously eligible for Medicaid in 2004 aged 65 and older with dementia who were residing in nursing homes and taking cholinesterase inhibitors. MEASUREMENTS: Rates of concomitant anticholinergic and cholinesterase inhibitor use, number of days residents experienced concomitant use, and concomitant use according to therapeutic class and level of anticholinergic activity were determined. RESULTS: A large proportion (46.7%) of 3,251 Medicaid beneficiaries living in nursing homes and taking cholinesterase inhibitors received anticholinergics concomitantly. Anticholinergics designated as Level 3, or having markedly anticholinergic adverse effects, accounted for most of the concomitant anticholinergic use. More than half (58.1%) of the individuals with concomitant anticholinergic use had 100 or more days of such use. CONCLUSION: Nearly half of Indiana Medicaid recipients with dementia residing in nursing homes who were taking cholinesterase inhibitors in 2004 were using anticholinergics concomitantly. Patterns of concomitant use in the population examined may assist practitioners in reviewing their prescribing decisions for this vulnerable population.


BACKGROUND: Inappropriate or contraindicated use of medications in elderly patients is common and associated with poor outcomes. An important risk factor for adverse drug events is the increased sensitivity to drug effects on the central nervous system (CNS). There is a high rate of use of CNS-active drugs in patients with cognitive impairment, despite the fact that these medications may worsen cognition and be a possible "reversible" cause of memory loss. OBJECTIVES: The goals of this study were to establish the prevalence of these contraindicated medications in a population of elderly patients referred to a memory disorders clinic for evaluation and to determine if those individuals receiving contraindicated medications had specific characteristics. This included determining how many patients were concurrently being prescribed a Cholinesterase inhibitor. METHODS: The review included new patients consecutively evaluated for cognitive complaints in a memory disorders clinic between June 2003 and August 2004. Each patient underwent a comprehensive evaluation by a multi-disciplinary team during a 3-hour clinic appointment. A thorough history of cognitive deficits and associated symptoms was obtained by the physician, who also performed a comprehensive neurologic examination. All patients underwent neuropsychologic testing.
with an extensive cognitive battery. In addition, patients' electronic medical records were reviewed to determine a list of prescribed and over-the-counter medications at the time of the initial referral. Contraindicated medications were identified using the updated Beers criteria of medications that should be avoided in older patients with cognitive impairment or that have high CNS adverse effects. RESULTS: A total of 100 patients (91 men, 9 women; mean [SD] age, 75.8 [9.7] years; 73% white) were included in the study. Eighty-six patients were determined at the time of evaluation to have some kind of cognitive impairment. They were mildly impaired, with a mean (SD) Mini-Mental State Examination score of 22.9 (5.1), based on a scale of 0 to 30. Twenty-two patients were taking > or =1 contraindicated medication that could potentially affect their cognition; the most frequently prescribed were benzodiazepines, oxybutynin, amitriptyline, fluoxetine, and diphenhydramine. Twenty-eight of the 100 patients were being treated with a Cholinesterase inhibitor at the time of their evaluation; of these, 4 (14%) were also taking > or =1 medication with Anticholinergic properties. CONCLUSIONS: Despite research evidence and recommendations to avoid these CNS-active medications because of their adverse effects, they continue to be prescribed in elderly patients with cognitive impairments. Further research is needed to determine strategies that will help reduce their administration in this population.

Review articles

   Note: see Contraindications, page 466

   Note: see Cognitive Impairment


Additional references

   Note: see section Co-Prescribed/Concomitant Therapies, page 15