Commentary

A Comparison of Four Methods to Quantify the Cumulative Effect of Taking Multiple Drugs With Sedative Properties

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ABSTRACT

Background: Older people (ie, those aged >65 years) often use multiple drugs with sedative properties. These include drugs for intentional sedation and drugs that have sedation as an adverse reaction. Recent pharmacoepidemiologic studies have investigated the risks of multiple or combined sedative drug use.

Objective: The purpose of this commentary was to describe, compare, and discuss 4 previously published pharmacoepidemiologic methods used to quantify the cumulative effect of taking multiple drugs with sedative properties.

Methods: A MEDLINE literature search was conducted in January 2010 using Medical Subject Headings and the following search terms: *hypnotics, sedatives*, *benzodiazepines*, *GABA-A receptors, model, load, measurement, index, burden, system*, and *aged*. The search was limited to English language, humans, and the year 2000 until present. Reports of methods that involved simply counting the number of sedative or psychotropic drugs, or described sedative drug use in anesthesia, were excluded. The search identified 4 methods. Research articles that have cited the descriptions of the 4 methods were retrieved using MEDLINE, Google Scholar, Scopus, and the Web of Science.

Results: The literature search identified 14 studies describing the use of 4 different methods to quantify the cumulative effect of taking multiple drugs with sedative properties. The 4 methods are the sedative load model, the Sloane model, the Drug Burden Index, and the central nervous system drug model. The methods differed with respect to the specific drugs or drug classes considered, the sedative ratings assigned to each drug, the inclusion or exclusion of drug dose in the model, and each model's likely ease of use in clinical practice. Adverse outcomes associated with taking multiple drugs with sedative properties included impaired physical and cognitive function, and an increased risk of falls.

Conclusions: Evidence is accumulating in relation to a range of adverse outcomes associated with using multiple drugs with sedative properties. However, no studies have been conducted using >1 method to quantify the cumulative effect of taking multiple drugs with sedative properties. Each method has likely advantages and disadvantages. The usefulness of each method in clinical practice remains to be determined. The models must be validated in different populations of older people and may subsequently need to be refined. (*Am J Geriatr Pharmacother*. 2010;8:460–471) © 2010 Elsevier HS Journals, Inc.

Key words: hypnotics, sedatives, benzodiazepines, psychotropic drugs, pharmacoepidemiology, aged, sedation.

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INTRODUCTION

Older individuals, often defined as those aged >65 years, use a disproportionately large number of drugs, especially psychotropic medications, and rates of use are increasing.[1–4] Forty percent of community-dwelling older people use ≥1 drug with sedative properties.[5] The appropriateness of medication use among older people has been the subject of extensive pharmacoepidemiologic research in recent years.[6,7] This is important because there is a lack of evidence from clinical trials to guide medication use among older individuals with multiple comorbidities.[8]

One approach to evaluating the appropriateness of drug use is to quantify the cumulative effect of taking multiple drugs with sedative properties.[9–12] Instead of simply counting the number of psychotropic drugs, this approach involves developing indices of medication use based on the sedative potential of a drug regimen. Sedation refers to the depressant effects of drugs on the central nervous system (CNS). Although sedation may be considered clinically useful in certain circumstances (for preanesthesia or to reduce agitation and aggression), sedation is increasingly becoming recognized as therapeutically undesirable in the treatment of depression and psychoses.[13]

Drugs with sedative properties, including benzodiazepines, antipsychotics, antidepressants, and opioid analgesics, are frequently associated with adverse drug reactions (ADRs). Benzodiazepines have been associated with impaired functional status,[14–17] as well as with cognitive and memory impairment.[18–22] Adverse cognitive and psychomotor outcomes have also been associated with histamine H_1-receptor antagonists, olanzapine, second-generation antidepressants such as mianserin and mirtazapine, and, to a lesser extent, with selective serotonin reuptake inhibitors.[23–25] Furthermore, age-related pharmacodynamic changes mean that older people may be particularly sensitive to ADRs associated with CNS-active drugs, including benzodiazepines, anesthetics, and opioids.[26]

Quantifying the cumulative effect of taking multiple drugs with sedative properties is complicated because drugs with sedative properties do not have a common pharmacology. Sedation is mediated by multiple receptors in the CNS, including agonism of the benzodiazepine receptor in γ-aminobutyric acid-A complex, blockade of central histamine H_1-receptors, antagonism or agonism of α_1- and α_2-adrenergic receptors, and agonism of μ-opioid receptors.[13,27,28] Defining the term *sedation* is also complicated.[13,19,24] Definitions of sedation typically include both subjective feelings of drowsiness or sleepiness, and decreased psychomotor processing. Although drowsiness and psychomotor processing can be assessed experimentally using sedation tests,[19] consensus is lacking about how best to quantify sedative drug use in pharmacoepidemiologic research.

The objective of the present commentary was to describe, compare, and discuss 4 previously published pharmacoepidemiologic methods used to quantify the cumulative effect of taking multiple drugs with sedative properties.

METHODS

A MEDLINE literature search was conducted in January 2010 using Medical Subject Headings and the following search terms: *hypnotics, sedatives, benzodiazepines, GABA-A receptors, model, load, measurement, index, burden, system*, and *aged*. The search was limited to the English language, humans, and the year 2000 until present. Studies that described a model to quantify the cumulative effect of taking multiple drugs with sedative properties and designed to be used among older people were included. Reports of methods that involved simply counting the number of sedative or psychotropic drugs, or described sedative drug use in anesthesia, were excluded. Scales that were developed to assess anticholinergic drug use only were not considered for the review.[29–32] The full-text versions of articles were retrieved and read if it was unclear whether they met inclusion criteria from reading the abstract alone. The literature search yielded 631 hits. Reports describing 4 different methods were identified. Research articles citing these methods were retrieved using MEDLINE, Google Scholar, Scopus, and the Web of Science.

DESCRIPTION OF THE 4 METHODS

The literature search identified 14 studies describing the use of 4 different methods to quantify the cumulative effect of taking multiple drugs with sedative properties. The 4 methods were the sedative load model, the Sloane model, the Drug Burden Index (DBI), and the CNS drug model. Each method differed with respect to the specific drugs or drug classes considered, the sedative ratings assigned to each drug, the inclusion or exclusion of drug dose in the model, and their likely ease of use in clinical practice (**Table I**).

Sedative Load Model

The sedative load model was first published in 2003.[9] It was developed by reviewing the summary of product characteristics for all drugs available in Finland from 1998 to 2001. All drugs were then classified into 1 of