

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Volume XXXIX / July 2018 / Number 7

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Fluoroquinolone Warnings Strengthened

Most fluoroquinolone antibiotic labels carry warnings about potential blood sugar disturbances and psychiatric adverse effects. However, these warnings vary by individual drug within the class. The FDA is now requiring that the labels for all fluoroquinolones include a warning that hypoglycemia, which can lead to coma, is possible and occurs more frequently in elderly patients and those taking oral hypoglycemic medications or insulin for diabetes. In addition, the psychiatric adverse effects that will now be added or updated across all agents in the class include: disturbances in attention; disorientation; agitation; nervousness; memory impairment; and delirium. Prescribers are reminded that when other options are available, fluoroquinolones should not be used for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or uncomplicated urinary tract infection as the risks of these agents outweigh the benefits.

FDA MedWatch Alert: Fluoroquinolone antibiotics: FDA requires labeling changes due to low blood sugar levels and mental health side effects. Available at <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm612979.htm>.

Second-Line Diabetes Drugs and Mortality

According to results of a meta-analysis of clinical trials, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists are associated with reduced mortality outcomes compared with placebo. The third class of second-line glucose-lowering medications, dipeptidyl peptidase 4 (DPP-4) inhibitors, was not

superior to placebo with regard to mortality outcomes.

Background: According to current international guidelines, escalation to any of the 3 drug classes is recommended in patients who do not achieve glycemic control with metformin (*Glucophage*). However, no randomized trials have directly compared the mortality effects of these 3 classes.

Methods: The network meta-analysis included randomized controlled trials of drugs from any of the 3 classes in patients with type 2 diabetes. Medications could be compared with placebo, no treatment, or each other. The primary outcome of the analysis was all-cause mortality. Secondary outcomes included cardiovascular mortality and several cardiovascular endpoints.

Results: The network meta-analysis included 236 publications with a total of >176,000 participants. The analysis of all-cause mortality was based on 97 studies with >134,000 participants. Nine trials, which comprised nearly half of study participants, were cardiovascular outcome trials in patients with or at risk for cardiovascular disease.

Compared with placebo or no treatment, all-cause mortality was significantly reduced with SGLT-2 inhibitors (hazard ratio [HR],* 0.80) and GLP-1 agonists (HR, 0.88), but not with DPP-4 inhibitors. There was no difference between SGLT2-inhibitors and GLP-1 agonists in overall mortality, but both were superior to DPP-4 inhibitors (HRs, 0.78 and 0.86, respectively).

Results for cardiovascular mortality were similar to those for overall mortality, with HRs of 0.79 and

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0.85 for SGLT-2 inhibitors and GLP-1 agonists, respectively, compared with control treatments. With regard to individual cardiovascular outcomes, only SGLT-2 inhibitors were superior to control treatments for heart failure events (HR, 0.62) and MIs (HR, 0.86). GLP-1 agonists were superior to DPP-4 agonists (HR, 0.82) but not control treatments for heart failure. No treatment was superior to control at reducing strokes or unstable angina.

In an analysis of the likelihood of superiority to other treatments, SGLT-2 inhibitors were ranked best for all-cause and cardiovascular mortality, GLP-1 agonists second best, and DPP-4 inhibitors worst. SGLT-2 inhibitors also were most likely to rank best for heart failure and MI outcomes, and GLP-1 agonists ranked best for stroke outcomes.

Both DPP-4 inhibitors and SGLT-2 inhibitors were associated with a higher rate of hypoglycemia than controls. SGLT-2 inhibitors were associated with a lower risk of serious adverse events than control treatments, and GLP-1 agonists had the highest rate of withdrawal for adverse events.

Discussion: The present analysis suggests SGLT-2 inhibitors may be preferable to incretin-based therapies, based on both lower mortality and a more favorable adverse-event profile. However, it is noteworthy that efficacy and safety was evaluated by drug class, rather than by individual agent. While this increases statistical power to detect treatment effects, within-class treatments may not be interchangeable.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Zheng S, et al: Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2018;319 (April 17):1580–1591. From Imperial College Healthcare NHS Foundation Trust, London, U.K.; and other institutions. **Funded by the British Heart Foundation; and other sources. One of 7 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Depression as Medication Adverse Effect

Use of medications that have depression as a potential adverse effect is common and increasing, according to a longitudinal series of surveys of American adults. Use of ≥ 3 of these medications was associated with simultaneous depression.

Methods: The authors analyzed 5 waves of data from the U.S. National Health and Nutrition Examination Survey, an in-person audit of a representative sample of community-dwelling adults, which is conducted in 2-year cycles. The final sample included $>26,000$ persons interviewed between 2005–2006 and 2013–2014. Participants showed interviewers containers for all prescription medications taken in the past 30 days. Information about the relationship of drugs to depression and suicidal thoughts or behavior was obtained from Micromedex, an online database that lists FDA-labeled adverse events. Depression was assessed using the Patient Health Questionnaire 9 (PHQ-9).

Results: Use of any medication with depression as a listed potential adverse effect increased from an estimated 35% of the population in 2005–2006 to 38% in 2013–2014. Concurrent use of ≥ 3 of these medications increased from 7% to 9.5%, and use of medications with suicidal symptoms as a potential adverse effect increased from 17% to 23.5%. Overall, antidepressants with depression as a labeled adverse effect were the most widely used medication class, and use increased significantly between the study waves, from 11% to 15% of surveyed patients ($p=0.001$). Use of gastrointestinal agents (in particular proton pump inhibitors and histamine H_2 antagonists), anxiolytics and sedative/hypnotics, and anticonvulsants also increased significantly ($p\leq 0.01$ for all). Use of depression-related anti-hypertensives, analgesics and muscle relaxants, hormonal contraceptives, and hormone replacement therapy was frequent but did not increase over the 10 study years.

The estimated prevalence of depression increased from 4.7% in patients taking no medications with depression as a labeled adverse effect to 6.9% in those taking 1 medication ($p=0.002$), 9.5% for those taking 2 ($p<0.001$), and 15.3% for those taking ≥ 3 medications ($p<0.001$). A similar trend was seen for patients taking increasing numbers of medications with suicidal symptoms as potential adverse effects. Most of the combinations associated with depression involved the beta-blockers atenolol or metoprolol, the narcotic hydrocodone, or the anticonvulsant gabapentin. Use of multiple medications without depression as an adverse effect was not associated with depression risk, compared with no medication use. The associations persisted in analyses that excluded users of psychotropic drugs, suggesting

the association was not dependent upon the underlying psychiatric diagnosis.

Discussion: The study population reported using >200 different drugs with depression or suicidal symptoms as a labeled adverse effect. Some of these drugs, including proton pump inhibitors and emergency contraceptives, are also available over the counter, and product labeling does not always include full information about adverse effects. Furthermore, commonly used screening instruments for depression do not include evaluation of prescribed medications that have depression as a potential adverse effect.

Qato D, Ozenberger K, Olfson M: Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA* 2018;319 (June 12):2289–2298. doi 10.1001/jama.2018.6741. From the University of Illinois College of Pharmacy, Chicago; and other institutions. **Funded by the Robert Wood Johnson Foundation; and other sources. Two of 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names: atenolol—*Tenormin*; gabapentin—*Neurontin*; hydrocodone—*Hysingla*, *Zohydro*; metoprolol—*Lopressor*

Anticholinergics and Dementia Risk

Exposure to anticholinergic antidepressant, antiparkinsonian, and urological drugs was associated with an increase in the incidence of dementia in a population-based study. Increased risk for several other anticholinergic categories could not be ruled out.

Methods: The study was based on data from the U.K.'s Clinical Practice Research Datalink, which contains primary-care records for >11 million patients. Case patients were aged ≥65 years and had received a diagnosis of dementia between 2006 and 2015. Each was matched with up to 7 control patients based on gender, age, and other factors. An anticholinergic drug exposure period was defined as a prescription lasting ≥1 year and ending ≥4 years before the date of dementia diagnosis. Anticholinergic drugs were classified according to the 3-point Anticholinergic Cognitive Burden (ACB) scale, based on serum anticholinergic activity, blood-brain penetration, and known associations with delirium. Drugs with serum anticholinergic activity or affinity for muscarinic receptors, but without known clinically relevant negative cognitive effects, are assigned an ACB score of 1 (possibly anticholinergic). Drugs with established and clinically relevant anticholinergic

effects are assigned a score of 2, and drugs that meet those criteria and also have reported associations with delirium are assigned a score of 3. Drugs were further classified according to indication, and exposures were quantified by the defined daily dose, based on average maintenance doses. The analysis was adjusted for covariates suspected to be linked to dementia incidence and many other factors.

Results: The study population consisted of nearly 41,000 patients with dementia and >280,000 controls. Patients had a median age of 83 years at the index date (diagnosis of dementia). The median drug exposure period was >7 years.

During the anticholinergic drug exposure period, 35% of cases and 30% of controls were given a prescription for a drug with an ACB score of 3. The most frequently prescribed ACB-3 drugs were amitriptyline (29%), dosulepin or dothiepin (16%), paroxetine (8%), oxybutynin (7%), and tolterodine (7%). Use of drugs with an ACB score of 2 was rare, and use of drugs with an ACB score of 1 was near-universal. After adjustment, each ACB category was associated with a significant increase in risk for dementia. (See table.) A dose-response relationship was evident for drugs with an ACB

Odds ratios* for dementia by ACB score			
ACB score	Incidence of dementia		Adjusted odds ratio [†]
	% of cases	% of controls	
0	10.5%	12.8%	1.00 (reference)
1	89.4%	87.1%	1.11
2	3.5%	2.8%	1.10
3	35.5%	30.4%	1.16
ACB-3 drug class			
Anti-depressant	21.6%	17.9%	1.13
Anti-parkinsonian	0.7%	0.3%	1.45
Urologic	8.0%	5.9%	1.23
[†] Odds ratios are adjusted for covariates present at start of the drug exposure period			

score of 2 or 3. When drugs were analyzed by indication, significant risk of dementia was associated with ACB-3 anticholinergics prescribed as antidepressants, antiparkinsonian agents, and urologic treatments. Associations were also positive for ACB-2 antiparkinsonian drugs and for ACB-1 antidepressants. Anticholinergic antidepressants were consistently associated with dementia across the board, and these associations persisted after controlling for the presence and severity of depression. Gastrointestinal drugs had a negative association with dementia.

Exposure times were also classified in 3 different periods: 4–10, 10–15, and 15–20 years before the index date. Associations for drug classes with an ACB score of 3 were consistent across all of these timespans, with no decrease when used 15–20 years in the past. In contrast, associations of dementia with drugs with an ACB-1 or 2 rating were more apparent closer to the index date.

Discussion: The study included a 4-year diagnostic lag designed to reduce the chances that the

anticholinergic drugs were prescribed for early or prodromal symptoms of dementia. The present findings suggest that the relationship of anticholinergic drugs to dementia is specific to the drugs, not the underlying conditions that they treat; however, a link to underlying disorders other than dementia cannot be ruled out. The observed class-specific effects may be related to differential ability of drugs to cross the blood-brain barrier.

Richardson K, Fox C, Maidment I, Steel N, et al: Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018; doi 10.1136/bmj.k1315. From the University of East Anglia, Norwich, U.K.; and other institutions. **Funded by the Alzheimer's Society. Four of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: amitriptyline (not available in the U.S.)—*Elavil*; dosulepin/dothiepin (not available in the U.S.)—*Prothiaden*; oxybutynin—*Ditropan*; paroxetine—*Paxil*; tolterodine—*Detrol*

*See Reference Guide.

Reference Guide

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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