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Can Medicines Unintentionally Change Our Behavior?

By Chuck Dinerstein, MD, MBA — January 16, 2020

With vanishingly few exceptions, we do not understand the underlying causes of dementia. A new study adds evidence to the hypothesis that unintended side-effects of anticholinergics may be involved.

Image courtesy of Gerd Altmann on Pixabay [1]

A bit of background

Acetylcholine is a neurotransmitter responsible for sending "signals" throughout our body. Cholinergic receptors involve many aspects of our unconscious behavior, heart rate, muscle contractions in the bowel and bladder, as well as respiratory functions. There are any number of medical conditions in which drugs that block the effect of acetylcholine, anticholinergic drugs are useful, nausea, urinary incontinence, to dilate airways, even acting as antidepressants. Anticholinergics are ubiquitous.

Roughly 10% of adults over age 50 are using anticholinergic medications, frequently more than one. And some experts believe that as we age, we produce less acetylcholine, so that those drugs may exert a greater effect as we age. The Beer's Classification of medicines that may be inappropriate for use in the elderly includes a number of these anticholinergics.

Like all medications, anticholinergics have "off-target" effects, side effects like dry mouth, or low blood pressure. In some individuals, anticholinergic drugs have been associated with memory

problems, confusion, and subsequent agitation. Another line of research has shown that cholinergic neurons "are particularly susceptible" in Alzheimer's Disease, which would make anticholinergics a bio-plausible cause of some forms of dementia.

The Study

Let's get the caveats out of the way first; the data came from records of general practitioners, so the diagnosis of dementia, which is often a constellation of findings, not one measure, was not wholly accurate. More importantly, dementia takes time to develop, and some early symptoms, like depression, treated with anticholinergics, are part of that constellation, not a separate problem – making for a chicken-egg dilemma. Finally, the dosages of anticholinergics taken by the patients came from prescription records, not what the individuals swallowed. It was an observational study, so the usual association, not causality rule apply

"One of the key difficulties in examining medication exposure as a risk factor is untangling the effects of the medication from the reason why the medication was prescribed. Observational data cannot determine whether anticholinergic medications or the conditions, such as depression, parkinsonism, and urge incontinence are leading to the increased risk of dementia." Raj C. Shah, MD - associate professor in the family medicine and Rush Alzheimer's Disease Center at Rush University Medical Center in Chicago

Roughly 59,000 patients with dementia were matched by age and gender with 226,000 controls, with approximately two-thirds of the identified causes being Alzheimer's disease and the other third, vascular dementia. Patients with other conditions associated with dementia, such as Parkinson's, were excluded. The exposure to anticholinergics predated the diagnosis by one to eleven years, and total standardized daily doses (TSDD) [1] recorded.

The most frequently prescribed anticholinergics were antidepressants, antivertigo/antinausea medications, and agents to control bladder spasms in both dementia patients and controls.

- Roughly 50% of patients in both groups had dementia without any history of anticholinergic use – so anticholinergics are not the "smoking gun" to explain dementia.
- Compared with no use, use of these agents for roughly 3 years (1095 TSDDs) resulted in a 50% increase in the risk of developing dementia.
- When stratified by the indication for the anticholinergics, the increases were associated with drugs used for depression, Parkinson's, psychosis, seizures, and bladder spasms – depression and Parkinson's disease have known associations with dementia and may represent the prodrome.

"It's also possible, the authors note, some conditions, like depression, may be early harbingers of cognitive decline. It's possible, for example, that some people taking antidepressants might actually be being treated for what will turn out to be an early symptom of dementia, so it's their depression that goes along with an increased risk of dementia — not the medicine they are taking to treat it."

- There was no increase with the use of "antihistamines, bronchodilators, muscle relaxants or medications for stomach spasms or heart arrhythmias."
- ***"…if this association is causal, the population-attributable fractions indicate that around 10% of dementia diagnoses are attributable to anticholinergic drug exposure."***

That final finding may put the whole study into a clearer perspective. Dementia with aging global demographics and the vast resources necessary for its treatment is a slowly growing catastrophe. With no drugs genuinely effective, the "Hail Mary" hope is that some forms of dementia have modifiable risk factors. As the authors go on to state, "This proportion is sizeable and is comparable with estimates for other modifiable risk factors for dementia, such as 5%for midlife hypertension,3%for diabetes, 14%for later life smoking, and 6.5% for physical inactivity."

The study adds to the plausibility of anticholinergics having a role in some cases of dementia. It is an issue on the radar of gerontologists, physicians specializing in the care of the elderly, for some time. The study is not a reason to panic, it is just a part of the conversation we need to have when we begin any medication.

[1] TSDD, the total dosage is the number of mg prescribed daily divided by the standard dosage and added over time. For a 25 mg pill prescribed daily for a month, with a standard dose of 25 mg, the standardize daily dose is 1, and TSDD would be 30; if the standard dose were 50 mg, the standardized daily dose would be 0.5, and TSDD would be 15 for the same time period.

Source Anticholinergic Drug Exposure and the Risk of Dementia A Nested Case-Control Study JAMA Internal Medicine DOI: 10.1001/jamainternmed.2019.0677

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