Tabula Rasa HealthCare Position Paper on the Public Health Risk of Strongly Anticholinergic Over-the-Counter Products

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Executive Summary

In the United States, over-the-counter (OTC) products are consumed by millions of people to self-medicate and, thereby, take an active role in their health care. However, despite public belief, not all OTCs are safe for all people. Over-the-counter products containing drugs with strong anticholinergic properties, such as chlorpheniramine and diphenhydramine, are ubiquitous and can cause myriad side effects, particularly for older Americans. Some anticholinergic side effects can be temporarily severe and disabling. But, more disturbing is the fact that anticholinergic drugs can cause insidious, permanent cognitive and physical dysfunctions, such as dementia, which may not manifest for years after [repeated] consumption. Consequently, OTC products with strong anticholinergic properties pose a threat to the health and well-being of our nation's older adult population. The silent epidemic of anticholinergic-induced side effects and dysfunctions amongst older Americans requires immediate action.

As a national organization that advocates for patient safety and focuses on mitigating medication risks, Tabula Rasa HealthCare calls on Norman E. Sharpless, M.D. (Commissioner) to request that the U.S. Food and Drug Administration (FDA) mandate that manufacturers of OTC products with strong anticholinergic properties place warnings about anticholinergic-induced side effects and dysfunctions on their product labels. Such a directive would inform the public,

notably older adults, about the risks associated with consuming these OTCs. In turn, these consumers can make better-informed decisions about their health care.

Background

Drugs with anticholinergic properties (also known as anticholinergics) block acetylcholine from binding to muscarinic and nicotinic receptors in the central and peripheral nervous systems.[1,2] The potency of this blocking activity, in large part, determines the strength of the drug's anticholinergic properties. These properties make anticholinergic drugs, especially the strongest ones, useful for treating a wide variety of medical conditions, including movement disorders, seasonal allergies, and overactive bladder. Drugs with anticholinergic properties are commonly prescribed to older adults who ordinarily suffer from multiple medical conditions.[1,2]

In addition to prescription anticholinergics, many OTCs contain drugs with strong anticholinergic properties. Currently, there are eight drugs contained in various OTC products on the U.S. market that are considered by most experts, including the American Geriatrics Society,[3] to be **strongly anticholinergic** and preferentially avoided for use in older adults. These drugs include, in alphabetical order: (1) brompheniramine, (2) chlorpheniramine, (3) clemastine, (4) dimenhydrinate, (5) diphenhydramine, (6) doxylamine, (7) meclizine, and (8) oxybutynin.[4-7] These strongly anticholinergic drugs are contained in cough and cold products (e.g., Vicks® NyQuil™), motion sickness products (e.g., Dramamine®), and sleep aid products (e.g., Tylenol® PM). These products are ubiquitous and consumed by hundreds of thousands of older Americans each year.

Despite their widespread availability and proven benefits, strongly anticholinergic OTCs pose undue risks to older adults who consume them. Further, older adults self-medicate with OTCs containing strongly anticholinergic drugs without knowing the unintended effects and

potentially debilitating risks associated with these drugs. As a result, the unnoticed and often insidious risks could be unnecessarily contributing to deteriorating health among our nation's most vulnerable populations. Without knowing the risks, OTC products containing strongly anticholinergic drugs pose a subtle but very real danger to those who consume them.

Risks Associated with Strongly Anticholinergic Drugs

Anticholinergic-induced side effects are among the most common drug-related problems that occur in older adults.[8,9] These side effects often are poorly tolerated by older adults and commonly overlooked by healthcare professionals. Drug-related anticholinergic side effects can be characterized as central and peripheral effects, and can even cause severe and disabling effects, most notably cognitive and physical dysfunctions.

Central and Peripheral Side Effects

Central side effects of drugs with strong anticholinergic properties include agitation, attention deficits, confusion, delirium, dizziness, fatigue, gait instability, and hallucinations.[1,2,8,9] Peripheral side effects of these drugs include abdominal pain, constipation, dry eyes, dry mouth, hypohidrosis, nausea, tachycardia, taste disturbances, and urinary retention.[1,2,8,9] Individually, anticholinergic side effects can lead to severe medical problems (e.g., anorexia, paralytic ileus) or even life-threatening consequences (e.g., cardiac arrhythmias, hyperthermia), especially in older adults.[2] Collectively, anticholinergic side effects accumulate in the body, increasing the risk for dysfunctions.

Cognitive and Physical Dysfunctions

In addition to the troublesome side effects, strongly anticholinergic drugs can cause temporary short-term impairment in cognition, including attention and reaction time.[10] Over

the past decade, mounting evidence suggests that use of these drugs also is associated with long-term cognitive dysfunction, namely dementia. One systematic review of 27 studies found an association between strongly anticholinergic drugs and either cognitive impairment or dementia.[11] Another systematic review of 46 studies found significantly declining cognitive function associated with increasing anticholinergic burden.[12] Since 2015 to present, the number of studies that have found similar associations has intensified.[13-19] A pivotal study published in the journal *JAMA Internal Medicine* this week revealed that strongly anticholinergic drugs (e.g., bladder antispasmodics, certain antidepressants) are tied to nearly 50% higher dementia risk in older adults.[20] These infringements on cognitive function and brain health pose significant burdens on older Americans and the U.S. healthcare system.

Similar to cognitive dysfunction, an increasing amount of evidence has emerged associating strongly anticholinergic drugs with physical dysfunction, including falls, injuries (not exclusively as a result of falls), and impaired activities of daily living.[2,21-30] Researchers have found a significant decline in physical function among users of drugs with strong anticholinergic properties.[12] Moreover, the decline was inversely related to anticholinergic burden; in other words, the higher the anticholinergic burden, the lower the physical functioning.[12] Overall, these findings are important because a decline in physical function might predict disability and frailty, which are major threats to independent living and often necessitate institutionalization among older adults.

Changes to OTC Product Labeling are Needed to Protect the Public from Anticholinergics

Much research has highlighted the importance of reducing exposure to anticholinergic drugs in older people. Yet, sales of OTC products and, thus, exposure to drugs with strong

anticholinergic properties, have been steadily increasing. In the United States, sales of OTCs rose from $29.7 billion in 2013 to $32.8 billion in 2015.[31] Sales of OTC sleep aids alone, which contain strongly anticholinergic drugs, rose from $402 million in 2013 to $428 million in 2015.[31] The number of allergy sufferers who used OTC products, including antihistamines with moderate to strong anticholinergic properties, increased from 66% in 2009 to 75% in 2015.[31] While older adults make up roughly 13% of the U.S. population, they account for more than 30% of all OTC sales.[32]

To preserve the health of the public and protect thousands of older people from the malevolent consequences of strongly anticholinergic drugs, FDA needs to take immediate action. As a national organization that advocates for patient safety and focuses on mitigating medication risks, Tabula Rasa HealthCare calls upon FDA to mandate that manufacturers of OTC products containing active ingredients with strong anticholinergic properties place warnings about the serious side effects and dysfunctions associated with using these drugs on their product labels. Such a directive is an ideal way to inform Americans, notably older adults, about the risks associated with consuming these OTC products. In turn, these consumers can make better-informed decisions about their health care.

Changes to product labeling have been effective in the past for increasing public awareness of potentially harmful effects of OTC drugs and to make these products safer. A fairly recent precedent was established with acetaminophen. In 2009, FDA issued guidelines for all manufacturers of acetaminophen-containing OTCs to provide more specific label warnings about the risk of liver injury and the importance of avoiding the concurrent use of multiple products containing acetaminophen. In 2011, FDA asked drug manufacturers to limit the

strength of acetaminophen in prescription drug products to 325 mg. Then, in 2014, the agency announced its intent to take steps to withdraw approval of prescription combination drug products containing more than 325 mg of acetaminophen. Continued surveillance and additional years of data are needed to quantify more fully the impact of these risk mitigation efforts.[33]

Summary

Despite their advantages, OTCs can be harmful to people who consume them. OTC harm risk is particularly pronounced in older adults, who tend to consume more OTCs and have higher rates of medical conditions and multiple drug use than other age groups. While FDA mandates that OTC labels contain some critical information designed to minimize harms, the failure to warn about potential harms from strongly anticholinergic drugs is problematic, particularly for older consumers.

Anticholinergic side effects can mimic medical conditions and cognitive and physical dysfunctions frequently associated with aging. Of particular concern is the insidious effect of dementia. However, drugs as a contributing factor may be overlooked by healthcare professionals and by older adults who self-medicate with OTC products that they presume to be safe. Tabula Rasa HealthCare calls upon FDA to mandate that manufacturers change the labeling of OTC products with strong anticholinergic properties. These changes are necessary to combat the hidden threat that is plaguing our country.

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References

1. Bostock CV, Soiza RL, Mangoni AA. Association between prescribing of antimuscarinic drugs and antimuscarinic adverse effects in older people. *Expert Rev Clin Pharmacol.* 2010;3(4):441-452.
2. Collamati A, Martone AM, Poscia A, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. *Aging Clin Exp Res.* 2016;28(1):25-35.
3. The American Geriatrics Society. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
4. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health.* 2008;4(3):311-320.
5. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med.* 2008;168(5):508-513.
6. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol.* 2006;46(12):1481-1486.
7. The American Geriatrics Society. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
8. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry.* 2001;62 Suppl 21:11-14.
9. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. *J R Soc Med.* 2000;93(9):457-462.
10. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging.* 2012;29(8):639-658.
11. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging.* 2009;4:225-233.
12. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing.* 2014;43(5):604-615.
13. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med.* 2015;175(3):401-407.
14. Campbell NL, Perkins AJ, Bradt P, et al. Association of anticholinergic burden with cognitive impairment and health care utilization among a diverse ambulatory older adult population. *Pharmacotherapy.* 2016;36(11):1123-1131.

15. Chatterjee S, Bali V, Carnahan RM, Johnson ML, Chen H, Aparasu RR. Anticholinergic medication use and risk of dementia among elderly nursing home residents with depression. *Am J Geriatr Psychiatry.* 2016;24(6):485-495.
16. Pfistermeister B, Tumena T, Gassmann KG, Maas R, Fromm MF. Anticholinergic burden and cognitive function in a large German cohort of hospitalized geriatric patients. *PLoS One.* 2017;12(2):e0171353.
17. Yang YW, Liu HH, Lin TH, Chuang HY, Hsieh T. Association between different anticholinergic drugs and subsequent dementia risk in patients with diabetes mellitus. *PLoS One.* 2017;12(4):e0175335.
18. Campbell NL, Lane KA, Gao S, Boustani MA, Unverzagt F. Anticholinergics influence transition from normal cognition to mild cognitive impairment in older adults in primary care. *Pharmacotherapy.* 2018;38(5):511-519.
19. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ.* 2018;361:k1315.
20. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med.* 2019;doi: 10.1001/jamainternmed.2019.0677. [Epub ahead of print].
21. Aizenberg D, Sigler M, Weizman A, Barak Y. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study. *Int Psychogeriatr.* 2002;14(3):307-310.
22. Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs Aging.* 2013;30(5):321-330.
23. Dauphinot V, Faure R, Omrani S, et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. *J Clin Psychopharmacol.* 2014;34(5):565-570.
24. Richardson K, Bennett K, Maidment ID, Fox C, Smithard D, Kenny RA. Use of medications with anticholinergic activity and self-reported injurious falls in older community-dwelling adults. *J Am Geriatr Soc.* 2015;63(8):1561-1569.
25. Spence MM, Karim FA, Lee EA, Hui RL, Gibbs NE. Risk of injury in older adults using gastrointestinal antispasmodic and anticholinergic medications. *J Am Geriatr Soc.* 2015;63(6):1197-1202.
26. Sura SD, Carnahan RM, Chen H, Aparasu RR. Anticholinergic drugs and health-related quality of life in older adults with dementia. *J Am Pharm Assoc (2003).* 2015;55(3):282-287.
27. Marcum ZA, Wirtz HS, Pettinger M, et al. Anticholinergic medication use and falls in postmenopausal women: findings from the women's health initiative cohort study. *BMC Geriatr.* 2016;16:76.
28. Clarke CL, Sniehotta FF, Vadiveloo T, Donnan PT, Witham MD. Association between objectively measured physical activity and opioid, hypnotic, or anticholinergic medication use in older people: data from the physical activity cohort Scotland study. *Drugs Aging.* 2018;35(9):835-842.
29. Kose E, Hirai T, Seki T. Anticholinergic drugs use and risk of hip fracture in geriatric patients. *Geriatr Gerontol Int.* 2018;18(9):1340-1344.

30. Villalba-Moreno AM, Alfaro-Lara ER, Rodriguez-Perez A, et al. Association between drug burden index and functional and cognitive function in patients with multimorbidity. *Curr Pharm Des.* 2018;24(28):3384-3391.
31. Consumer Healthcare Products Association. Statistics on OTC Use. 2019; https://www.chpa.org/MarketStats.aspx. Accessed July 7, 2017.
32. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med.* 2016;176(4):473-482.
33. Major JM, Zhou EH, Wong HL, et al. Trends in rates of acetaminophen-related adverse events in the United States. *Pharmacoepidemiol Drug Saf.* 2016;25(5):590-598.