

**Acute Hallucinations: Where Did That Come From?
A Unique Case of Acute Onset Hallucinations**

Tracy Boschee, DO PGY III
Wellmont Family Medicine Residency

INTRODUCTION:

Acute onset hallucinations in the elderly have a wide differential diagnosis. New medications, unusual symptoms, non-acute lab and imaging results, and benign physical exam findings of this 82 year old male patient with acute intermittent auditory and visual hallucinations of four days duration adds complexity to the diagnostic process.

Here we discuss this interesting case of acute onset hallucinations that occurred in an 82 year old male in September 2013 after starting Amlodipine Besylate for elevated blood pressure. A literature and internet review will aid in the differential diagnosis, clinical decision making, and other complex considerations in this unique case.

THE CASE:

Eighty two year old male with a past medical history significant for diastolic CHF, syncopal episode vs. vertiginous fall with transient confusion 4/2011, very small left occipital CVA 4/2011, seizure disorder (Grand Mal seizure in his 60's, Dilantin therapy in the past, but not currently being treated and with no recent seizures), subclinical hyperthyroidism, dizziness, arthritis, HTN, anxiety, BPH, and hearing loss. Home medications included Flomax, Celexa, Lisinopril, Coreg, Mobic, Singulair, Aspirin, and Vitamin D.

9/14/2013: Patient presented to the ER with a chief complaint of elevated blood pressure for the past two days. Blood pressure was 176/86. He denied headaches, blurry vision, chest pain and palpitations. Physical exam was benign, with mental status showing patient alert and oriented to person, place, and time. Labs, EKG (RBBB & LAD), and chest x-ray were non-contributory. He was given Amlodipine 5mg orally x1 dose and HCTZ 25mg orally x1 dose. He was discharged home with a prescription for Amlodipine Besylate 5mg po daily.

9/20/13 Morning: Patient presented to his primary care physician's office for an ER follow-up visit and with the complaints of new onset visual and auditory hallucinations, dizziness, and shortness of breath. He also was experiencing decreased hearing.

The hallucinations appeared to have started the day after he began taking the Amlodipine he was prescribed. One hallucination he described was seeing the president in his home. The hallucinations and confusion were intermittent in nature. Patient states he knew the auditory and visual hallucinations were not real. Vitals showed his blood pressure to be 146/88. Physical exam was once again benign and UA was negative. The Amlodipine Besylate was discontinued and his current Lisinopril dose was increased for treatment of his hypertension.

9/20/13 Evening: Patient presented to a tertiary care hospital with the chief complaint of confusion. Vitals and physical exam were benign. Only possible contributory lab was a TSH that was low at 0.11 microunits/ml, although this was unchanged from prior labs (clinic labs had shown a TSH of 0.106 microunits/ml and a Free T4 of 1.29 mcg/dl in May 2013). A CT scan of the head showed cerebral atrophy, microvascular disease, and a chronic appearing lacunar infarct of the left centrum semiovale (which was new since 2011 scan, but chronic in appearance), but

no acute abnormality was seen. The patient was admitted to the hospital for observation the morning of 9/21/13.

Hospital work-up included a bilateral carotid duplex which showed no significant stenosis. A MRI showed no acute infarct and clear sinuses, but severe progressive microvascular disease. Patient was discharged home the following day (9/22/13).

The hallucinations stopped 9/22/13.

9/25/13: Follow-up office visit for the patient's recent hospitalization revealed he had no further hallucinations. He complained his dizziness and hearing loss seemed to be worsening. On Mini Mental Status Exam patient scored 26/28. Orthostatic blood pressures were negative. He was sent to ENT for further evaluation of hearing loss and dizziness. Chest x-ray from hospitalization had revealed a left paratracheal mass thought to be a goiter. U/S of thyroid was ordered and results showed a multi-nodular goiter. Vitamin B12 level was ordered and found to be borderline low at 212.

10/1/13: Patient's family called the primary care physician's clinic stating his dizziness continued. They requested a neurology referral. Neurology appointment was made.

10/2/13: Patient's daughter called the primary care physician's clinic and stated patient was again having auditory and visual hallucinations. Appointment was scheduled for 10/7/13.

10/2/13: Patient was seen by ENT and referral was made to audiology.

10/7/13: Clinic appointment for repeated hallucinations reported by patient's daughter showed the patient to be doing well except for the complaint of multiple falls at home without loss of consciousness. His dizziness and hearing loss had improved. He and his wife reported no hallucinations since his last visit (9/25/13) in contradiction to the daughter's report. Thyroid function studies were ordered. Results showed low TSH with normal free T4.

10/9/13: Audiometry and vestibular testing showed sensorineuroal hearing loss and right-sided benign paroxysmal positional vertigo. He was scheduled for PT for repositioning.

10/22/13: Neurology referral revealed gait imbalance to likely be multifactorial. Some peripheral neuropathy with sensory loss in both feet was noted.

11/11/13: Follow-up appointment with primary care physician revealed dizziness had improved and patient continued to deny any further hallucinations.

11/15/13: EEG obtained by neurology showed slowing of the background consistent with degenerative disease, but no epileptiform activity was identified.

LITERATURE, TEXTBOOK, and INTERNET REVIEW:

Prescribing information for Norvasc (Amlodipine Besylate) states adverse reactions include edema, dizziness, flushing, palpitations, fatigue, nausea, abdominal pain, and somnolence. Other events which occurred in less than 2% of trials and marketing experience included arrhythmia, bradycardia, syncope, hypoesthesia, peripheral neuropathy, paresthesia, tremor, vertigo, asthenia, hot flushes, malaise, arthralgias, myalgias, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, and abnormal vision. (*Norvasc U.S. Physicians Prescribing Information*, 2013)

Amlodipine Besylate is extensively metabolized by the liver and CYP450, 3A4 substrate. The patient's home medications of Flomax, Singulair, Mobic, Coreg, and Celexa also are metabolized by the 3A4 substrate of CYP450. His other home medications of Lisinopril, Aspirin, and Vitamin D are also metabolized by CYP450, but not specifically by the 3A4 substrate. According to the InteractionCheck by Epocrates, there are no interactions of Amlodipine Besylate with the patient's home medications. (*Epocrates*, 2013)

In research by Naina Mohamed, et al., reasons for discontinuation of amlodipine included dizziness, peripheral edema, headache, fatigue, and vivid dreams, but did not mention hallucinations. (Naina Mohamed, Helms, Simpson, Milne, & McLay, 2011)

An eight week multicenter, prospective, randomized, double-blind, parallel-group clinical trial that assessed effects of Amlodipine Camsylate versus Amlodipine Besylate in Korea adults with mild to moderate hypertension reported adverse events of Amlodipine Besylate to include dizziness, headache, paresthesias, facial flushing, lower extremity edema, palpitations, and dyspnea, but again did not make any mention of hallucinations. (Kim, et al., 2007)

In assessing tolerability of the fixed-dose combination Olmesartan and Amlodipine, Bramlage, et al., noted adverse drug reactions of eye disorders, nervous system disorders, and psychiatric disorders although they do not go into specifics. (Bramlage, et al., 2010)

In researching this topic, other papers found that included adverse reactions to amlodipine also included many of the reactions stated before, but once again, did not mention hallucinations. (Khurshid, Agil, Alam, Kapur, & Pillai, 2012) (Barrios et al., 2008)

In an internet article based on a July 8, 2002 issue of *The Medical letter on Drugs and Therapeutics*, several reports of delirium, confusion, psychosis, and mania were reported in the use of calcium channel blockers such as Amlodipine. (Drug Induced Psychiatric Symptoms, 2002) Another website notes hallucinations, agitation, and erratic behavior as rare side effects of Amlodipine. (Amlodipine: Dihydropyridine, 2013) Yet another website names hallucinations as a common side effect of Norvasc. (Norvasc, 2012) One blog site tells the story of a female who had hallucination as reactions to both Lisinopril and Norvasc at separate times. (Carol, 2007)

An eHealthMe study from FDA reports noted that of the 75,743 people reporting side effects when taking Norvasc, 389 people reported hallucinations. Of those that had hallucinations, 83.53% were over 60 years of age. The report noted that the numbers were

approximations only and that some reports may have had incomplete information. The report also was based on active ingredients and brand names and may not have included generic medications that had the same active ingredient. This was an observational report that was not supported by scientific studies or clinical trials. (eHealthMe, 2013)

DISCUSSION:

Although hallucinations do not appear to be a common adverse reaction to Amlodipine Besylate, this case raises concern for the possible rare occurrences of the reaction. The fact that this patient's auditory and visual hallucinations began just a day or two after starting the medication and stopped two days after cessation of the medication with no further recurrence makes this a plausible cause and effect relationship.

Factors considered in reaching a differential diagnosis for this patient included medications and their possible interactions, infection, history of seizures, subclinical hyperthyroidism, metabolic disturbances, microvascular disease, and dementia.

Issues related to generic vs. brand name medication may have played a role in the possible adverse reaction. The difference in the dose of the active ingredient or the mix of inert ingredients in the generic form may have played a role in the unusual findings in this patient.

Could the patient have had a brief psychotic event or acute delirium brought on by stress or a change in environment (emergency room visit and overnight hospitalization)? These are possibilities which are difficult to rule out.

Infectious disease was considered in the differential diagnosis of this patient's acute hallucinations. Urinalysis ruled out urinary tract infection and chest x-ray and physical exam ruled out pneumonia.

Neurologic causes such as focal seizures were also considered, but the negative EEG and discontinuation of the hallucinations without an anti-seizure medication disfavor this.

Microvascular dementia was deemed to be less likely the cause of the acute hallucinations in the patient due to the short duration of the hallucinations and their complete resolution. The Mini Mental Status Exam findings also contributed to placing this diagnosis lower on the differential.

The patient required close follow-up and monitoring for any recurrence of hallucinations. He has done well since discontinuation of the Amlodipine Besylate. In treatment of acute hallucinations it is important remove any possible reversible causes, protect the patient from potential harm caused by the hallucinations, and prevent further hallucinations.

CONCLUSIONS:

There are many diagnoses to consider in the event of acute hallucinations in an elderly patient. We have reviewed some common and not-so-common differentials brought to light by this unusual case. Further studies on adverse effects of generic vs. brand name medications and rare side effects of medications may contribute to a better understanding of new onset symptoms after starting a new medication.

As in much of medicine, a definitive cause is not always found for acute hallucinations.

REFERENCES

- Amlodipine: Dihydropyridine. (2013). Retrieved from <http://www.library.everyonehealthy.com/library/drug/Amlodipine>
- Barrios, V., Escobar, C., De La Figuera, M., Honorato, J., Llisterri, J.L., Segura, J., & Calderon, A. (2008, Mar 18). High doses of lercanidipine are better tolerated than other dihydropyridines in hypertensive patients with metabolic syndrome: results from the TOLERANCE study. *International Journal of Clinical Practice*, 62(5): 723-728. Retrieved from <http://onlinelibrary.wiley.com/doi/10.0000/j.1742-1241.2008.01736.x/full>
- Bramlage, P., Wolf, W., Stuhr, T., Fronk, E., Erdlenbruch, W., Ketelhut, R., & Schmieder, R. (2010, Sept 7). Effectiveness and tolerability of a fixed-dose combination of olmesartan and amlodipine in clinical practice. *Vascular Health and Risk Management*, 6: 803-811. Retrieved from <http://europepmc.org/articles/PMC2941791?sessionid=bBhOEDSsfWbIBsOON1bW.50>
- Carol. (2007, Dec 3). Nighttime Hallucinations After Taking Norvasc. Retrieved from <http://seidlweb.com/public/b.og/191402>
- Drug Induced Psychiatric Symptoms: Worst Pills, Best Pills News. (2002). Retrieved from <http://fqframes.org/fqframes/News/Psychiatric/area.htm>
- eHealthMe study from FDA reports. (2013). Retrieved from <http://www.ehealthme.com/pring/ds16252134>
- Epocrates Rx Pro*. (2013, Jan 28).
- Khurshid, F., Agil, M., Alam, M.S., Kapur, P., & Pillai, K.K. (2012, Sept 10). Monitoring of adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi. *DARU Journal of Pharmaceutical Sciences*. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3555729/>
- Kim, S.H., Kim, Y.D., Lim, D.S., Yoon, M.H., Ahn, Y.K., On, Y.K., . . . Kim, H.S. (2007, May 15). Results of a Phase III, 8-week, Multicenter, Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial to Assess the Effects of Amlodipine Camsylate Versus Amlodipine Besylate in Korean Adults with Mild to Moderate Hypertension. *Clinical Therapeutics*, 29, 1924-1936.
- Naina Mohamed, I., Helms, P.J., Simpson, C.R., Milne, R.M., & McLay, J.S. (2011, Jan 10). Using primary care prescribing databases for pharmacovigilance. *British Journal of Clinical Pharmacology*, 71: 224-249. Retrieved from <http://onlinelibrary.wiley.com/doi/10.0000/j.1365-2125.2010.03816.x/full>
- Norvasc U.S. Physicians prescribing Information*. (2013). Retrieved from <http://www.pfizer.com/products/product-detail/norvasc>
- Norvasc. (2012). Retrieved from <http://www.bad-drug.net/bad-drug/norvasc>