Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Oxymetazoline

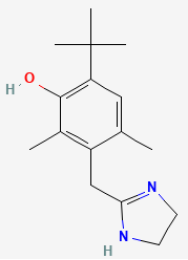
Evidence Summary

Short term use as a nasal decongestant is safe and effective. Chronic use can alter nasal cavity in a way that increases damage and the risk for drug-related adverse effects to the cardiovascular system.

Brain health risk: With chronic use at high doses, there is a risk for oxymetazoline to enter the CNS, and a risk for cerebral vasospasms which could trigger a stroke.

Aging and related health risk: Chronic use may damage the nasal mucosa and increase the risk for side effects. Individuals with cardiovascular risk factors and children may be at increased risk for an adverse event.

Safety concerns: Short-term use is safe. Chronic use at high doses can lead to rebound congestion, damage nasal mucosa, and increase systemic levels. Severe adverse events are rare, and usually with underlying risk factors present.

Availability: OTC (nasal spray); Rx (ophthalmic or topical preparations)	**Dose**: Oxymetazoline nasal spray (0.05%) 2-3 sprays per nostril every 12 hours (maximum 2X/day) for a maximum of 3 days	**Chemical formula:** $C_{16}H_{24}N_2O$ **MW**: 260.37 g/mol  Source: Pubchem
Half-life: 5-8 hours	**BBB**: Penetrant	
Clinical trials: It has been tested in numerous trials as a nasal spray for rhinitis/nasal congestion, in a topical form for rosacea, and an ophthalmic form for blepharoptosis	**Observational studies**: Case reports indicate that excessive use of nasal oxymetazoline can lead to adverse cardiovascular events if it gets into systemic circulation.	

What is it?

Oxymetazoline is an α-1 adrenoreceptor agonist, and also has affinity to α-2 adrenoreceptors, which are found on cells in the sympathetic nervous system, and thus acts as a sympathomimetic [1]. If it is present systemically, it can trigger a potent activation of the sympathetic nervous system. Due to its high lipophilicity, oxymetazoline can be rapidly absorbed by vessels and enter systemic circulation, which can lead to toxicity [2]. Consequently, all approved indications involve local administration, via nasal, topical, or ophthalmic preparations. It is most commonly used in OTC nasal decongestant nasal spray preparations, which will be the focus of this risk report. It is also approved by the FDA in a topical preparation, Rhofade®, for rosacea, which is marketed by EPI Health, and an ophthalmic (Upneeq®) formulation for blepharoptosis, which is marketed by RVL Pharmaceuticals.

Brain health risk: With chronic use at high doses, there is a risk for oxymetazoline to enter the CNS, and a risk for cerebral vasospasms which could trigger a stroke.

Types of evidence:

- 11 case reports/series of neurological adverse events
- Several laboratory studies

Human research to suggest risk for dementia, acceleration of decline, or impaired cognitive function:

Reversible cerebral vasoconstrictive syndrome: INCREASED RISK WITH POLYPHARMACY
Reversible cerebral vasoconstrictive syndrome (RCVS) involves a sudden constriction of blood vessels to the brain that presents as a 'beads on a string' like appearance to the cerebral arteries on vascular imaging [3]. It primarily presents as thunderclap headaches which can last from hours to days. Although the condition is reversible, and the majority of patients fully recover, some patients experience secondary events that lead to permanent neurological damage [4]. These include subarachnoid hemorrhage, intracerebral hemorrhage, seizures, and ischemic stroke. Women tend to be more susceptible to RCVS, and it is most common during the postpartum period. Aside from pregnancy, the largest risk factor involves exposure to vasoactive substances. In an analysis of 67 RCVS cases, the drugs most frequently tied to the risk of RCVS were cannabis, selective serotonin reuptake inhibitors (SSRIs), and nasal decongestants [4]. Consistent with these findings, there have been several case reports of RCVS with the use of oxymetazoline and the related drug xylometazoline. Notably, most of these cases involve the use of the nasal spray with another vasoactive drug, such as an SSRI.

Case reports
A 31-year-old woman presented with thunderclap headaches, nausea, vomiting, sonophobia, and photophobia, over the course of four days [5]. Her blood pressure and neurological exams were normal. Cerebral angiography revealed focal regions of vasospasm in the internal carotid artery, consistent with RCVS. She had used oxymetazoline-containing Afrin nasal spray (2-3 X/day) for six months. Two weeks prior to this event, she would get headaches 20 minutes after using the nasal spray. She was also taking an SSRI. Within six weeks of discontinuing use of the nasal spray, she was in complete remission.

A 52-year-old woman experienced two episodes of thunderclap headaches eight hours apart. CT angiography revealed multifocal mild to moderate narrowing of the intracranial artery, indicative of RCVS, as well as small areas of convexal subarachnoid hemorrhage [6]. She had been taking a xylometazoline-containing nasal spray, and had recently increased the dose from 1X to 2-3X/day. She was also taking an SSRI. She was tapered off both drugs. Within two weeks, the subarachnoid hemorrhage had resolved, and the intracranial arterial stenosis had improved.

A 53-year-old woman with a history of headaches presented with a thunderclap headache [7]. MRI revealed white matter lesions consistent with vasculitis, while angiography revealed narrowing of the middle cerebral and basilar arteries. She had been using oxymetazoline-containing Afrin nasal spray 3-

4X/day for many years, and this was thought to be a precipitating factor. Symptoms resolved within two weeks of discontinuing Afrin use.

Stroke: INCREASED RISK BUT RARE

There is evidence that the use of nasal decongestants may precipitate a stroke, particularly in those with underlying cardiovascular risk factors who are using higher than recommended doses. Most of the reported cases are related to the use of pseudoephedrine-containing products, however, there are a few reported cases associated with oxymetazoline [8].

A French pharmacovigilance study from 1985 to 2019 identified 52 cases of serious ischemic stroke associated with the use of nasal decongestants, most cases involved pseudoephedrine, occurred in men, and occurred in individuals with cardiovascular risk factors [9].

The primary mechanisms are thought to be sympathetic nervous system driven hypertensive crisis and vasculitis of cerebral arteries.

Case reports

A stroke registry identified 22 cases of stroke related to the use of sympathomimetics [8]. One of the cases involved an oxymetazoline-containing nasal spray. A 40-year-old man who had been using the oxymetazoline nasal spray daily for one-week experienced subarachnoid hemorrhage. He presented with a blood pressure of 160/110 and normal angiographic findings. He experienced a complete recovery.

There is a case report of a 54-year-old man who experienced an acute left lateral medullary infarct with left vertebral artery stenosis [10]. He had been using a xylometazoline-containing nasal spray (1 mg/ml) 3–4X/day for five to six years. The nasal spray was considered to be the driver of the cerebral vasospasm/RCVS-induced ischemic stroke in this case.

A 35-year-old man with no history or risk factors for cardiovascular disease presented with right paresis and hemisensory loss due to an ischemic infarct of the middle cerebral artery stemming from thrombotic occlusion of the left Silvian artery [11]. He had been using 15 mg of oxymetazoline-containing nasal spray every three days for 20 years, which was implicated as the driver of this stroke.

Psychosis: INCREASED RISK AT VERY HIGH DOSE WITH PSYCHIATRIC HISTORY

Due to its activity as a sympathomimetic, oxymetazoline exposure can induce simulant-related psychosis [12]. However, this effect is associated with the misuse of oxymetazoline, and has not been reported in

individuals following recommended usage of oxymetazoline-containing nasal sprays. Additionally, individuals in these cases typically have a history of psychiatric disorders. The ingestion or intravenous use of oxymetazoline-containing nasal sprays can lead to schizophrenic-like psychotic reactions.

Case Reports

A state of paranoid psychosis and acute delirium was reported in a 41-year-old woman who abused oxymetazoline (Vicks Sinex nasal spray) along with menthol and camphor (Vicks VapoRub) [13]. The psychosis was reversible with discontinuation.

A 41-year-old man who had previously undergone treatment for anxiety, obsessive compulsive disorder (OCD), and schizoid personality disorder experienced anxiety, hostility, and paranoia after dramatically increasing the use of his 0.05% oxymetazoline-containing nasal spray [12]. He used an entire 20 mL container, which should last two weeks, on a daily basis. The paranoia was mitigated with discontinuation, but returned with the resumption of high-dose nasal spray use. Due to its blood brain barrier (BBB) penetrance, it can exert effects in the CNS when used nasally at very high doses.

A 61-year-old man with a history of prior psychiatric hospitalization and borderline mental retardation had been experiencing visual and auditory hallucinations for over 20 years [14]. He had been using higher than recommended doses of nasal decongestants for nearly 40 years. At the time of medical evaluation, he was using Afrin nasal spray every 30 minutes, over eight bottles per month. The symptoms of psychosis and anxiety were alleviated following discontinuation of the nasal spray and use of an antipsychotic medication.

Due to the immaturity of the blood-brain-barrier in infants, young children are at increased risk for adverse CNS-related events following the use of oxymetazoline. A case series of convulsions, insomnia, and sedation has been reported in five infants exposed to oxymetazoline-containing nasal sprays [15]. Additionally, the use of oxymetazoline-containing nasal sprays in children under age six have been associated with reports of agitated psychosis, ataxia, and hallucinations (NICE UK).

Human research to suggest harm to patients with dementia:

There is no evidence to indicate that the use of oxymetazoline-containing nasal decongestants within the recommended guidelines worsen dementia symptoms or disease progression in dementia patients. Misuse of the sprays, resulting in higher than recommended doses, could increase the risk for the same

adverse neurological events described above. It has not been established whether, due to changes in BBB permeability or neurodegeneration, oxymetazoline gets into the brain at higher rates in patients with dementia. Dementia patients are likely at higher risk for adverse CNS events if oxymetazoline gets into the CNS in appreciable concentrations. It could potentially worsen agitation.

Mechanisms of action for neurological harm identified from laboratory and clinical research:

Due to its activity on adrenoreceptors, oxymetazoline acts as a sympathomimetic, and can impact the noradrenergic neurotransmitter system if it gets into the CNS. When administered locally to the nasal mucosa via nasal spray, it primarily acts locally to constrict blood vessels in the nasal cavity. With chronic use, it can lead to adaptations by the noradrenergic system, such that higher doses are needed to have the same vasoconstriction-mediated nasal decongestant effect [16]. This can lead to a form of nasal mucosa dependence, sometimes referred to as nasal decongestant addiction. As a result of these adaptations, the basal level of blood flow to the nasal vessels increases, resulting in a worsening of nasal congestion or rebound effect with drug discontinuation, called rhinitis medicamentosa. Rhinitis medicamentosa is considered to be a risk factor of oxymetazoline-related neurological and cardiovascular adverse events because it can lead to the use of higher than recommended doses and the enlarged nasal vasculature increases the ability of oxymetazoline to enter into the bloodstream, allowing it to induce effects systemically and within the CNS [6].
When administered into the nasal cavity, drugs can reach the CNS through two major routes [17]. Substances in the nasal cavity can go directly into the CNS vial the olfactory and trigeminal nerves. The drugs can be endocytosed and transported along the axons to the olfactory bulb, and then dispersed into connecting brain regions. The drugs can also be absorbed through the lamina propria of the olfactory epithelium via leaky passages or transcellular transport. Once in the lamina propria, the drugs can be absorbed by blood vessels into the systemic circulation, or by lymphatic vessels that drain into the cervical lymph nodes. The drugs can also potentially diffuse through perineural spaces to the cribriform plate, where it can potentially enter the cerebrospinal fluid.

The risk for systemic adverse events increases when oxymetazoline has increased access to these routes. Factors that can affect accessibility include drug formulation, spray administration, and the physiology of the nasal cavity.
The *formulation* of the drug affects its accessibility. Small lipophilic drugs, such as oxymetazoline, can readily utilize these pathways to be taken up into the brain and systemic circulation. Xylometazoline,

which is not approved in the United States, has even greater potential for absorption [18], and thus greater potential for systemic side effects, which is consistent with its case report profile.

The *nasal spray device* can influence the localization of the drug within the nasal cavity. A comparative analysis of nine oxymetazoline-containing nasal sprays found that different preparations showed different patterns of aerosol dispersion [19]. Afrin and Vicks Sinex had the most optimal particle size distribution and dispersion. A high percentage of very fine (1-5 um) particles is harmful for deep airways. This study did not, however, access the differential capacity of these preparations to enter the CNS. The orientation also affects exposure. The exposure is increased when the spray bottle is inverted and the body is in a supine position, and this can lead to higher systemic levels [20]. Administration from an upright position allows for a more controlled dose exposure.

The *integrity of the nasal epithelium* also influences the ability of oxymetazoline to get to the brain or blood. The level of drug absorption is increased when the mucosa is damaged. The loss of tight junctions in the vascular endothelium can also increase drug access. Preclinical studies suggest that chronic use of oxymetazoline-containing nasal sprays can damage the nasal mucosa [2; 21], which increases the risk for systemic adverse events.

APOE4 interactions: Not established

Aging and related health risk: Chronic use may damage the nasal mucosa and increase the risk for side effects. Individuals with cardiovascular risk factors and children may be at increased risk for an adverse event.

Types of evidence:

- 7 case reports/series of cardiovascular adverse events
- Several laboratory studies

Cardiovascular events: INCREASED RISK AT HIGH DOSE WITH UNDERLYING RISK FACTORS
As a sympathomimetic, oxymetazoline can impact the cardiovascular system if it is present systemically. A French pharmacovigilance survey from 1985 to 2019 identified 21 cases of myocardial infarction related to nasal decongestant use [9]. The majority of cases were in men with underlying cardiovascular risk factors. Pseudoephedrine was associated with the most cases, while oxymetazoline was second (n=4

cases). There have been a variety of case reports related to adverse cardiovascular events in association with the use of oxymetazoline nasal spray. The risks appear to be greatest in young children, individuals with cardiovascular risk factors, use of high doses, and use of multiple sympathomimetics.

Case reports

A 73-year-old man presented with dizziness and light-headedness leading to frequent falls [22]. He was found to have bradycardia (slow heart rate) and hypotension. He had been using oxymetazoline-containing (0.05%) Afrin nasal spray several times a day for about two months. The symptoms appeared following his use of the nasal spray, and resolved upon discontinuation. He had a reduced baroreflex due to cerebellar degeneration, which may have made him more susceptible to this effect.

An oxymetazoline-containing nasal spray was implicated in provoking fascicular tachycardia (elevated heart rate) in a patient in one case report [23].

A 64-year-old woman with a history of diabetes, hypertension, and smoking presented with chest pain [24]. The severe chest pain occurred within a minute of administering oxymetazoline-containing nasal spray two days in a row. She was diagnosed with non-ST-elevation myocardial infarction. She discontinued use of the oxymetazoline spray and was symptom-free within six months.

An otherwise healthy man in his early 30s was treated for acute nasal congestion with oral pseudoephedrine, paracetamol, and triprolidine for five days and then nasal oxymetazoline TID for three days [25]. Following use of nasal oxymetazoline, he presented with chest pain, ST-segment elevation, and a spasm on the anterior interventricular artery, leading to a diagnosis of acute coronary syndrome. The patient recovered completely.

A 54-year-old man with a history of hypertension and hyperlipidemia presented with chest pain (angina) three hours after starting use of oxymetazoline nasal spray following a tonsillectomy [26].

Children are at higher risk for cardiovascular adverse events related to systemic exposure of oxymetazoline following nasal administration [20]. This is because doses used in products targeted for adults are too high for children, and because oxymetazoline is more readily absorbed across the nasal mucosal membranes in children, and thus has easier access to the systemic circulation. Oxymetazoline-containing nasal sprays are used perioperatively in pediatric populations, and there are several case

reports of children experiencing adverse cardiovascular events following exposure to oxymetazoline [20]. These include instances of hypertension, bradycardia, and cardiac arrest.

Sinusitis: INCREASED RISK WITH CHRONIC USE (Preclinical)
Chronic use of oxymetazoline-containing nasal sprays may induce damage to the nasal mucosa in a manner which increases the risk for infections, based on results from preclinical studies. Male rats receiving oxymetazoline nasal spray 3X/day for four weeks showed evidence of focal inflammation, ischemia, arterial thrombosis, and necrosis in the affected region [2]. Similarly, rabbits exposed to 0.05% oxymetazoline nasal spray 2X/day for four weeks showed evidence of mild to moderate nasal ciliary loss and ulceration as well as inflammatory cell infiltration [21]. The rabbits also had increased rates of sinusitis. The damage to the nasal mucosa may increase the access to pathogens, while the decrease in blood flow may decrease the capacity to mount an effective immune response, leading to a heighted risk for sinus infections.

Safety concerns: Short-term use is safe. Chronic use at high doses can lead to rebound congestion, damage nasal mucosa, and increase systemic levels. Severe adverse events are rare, and usually with underlying risk factors present.

Types of evidence:

- 18 case reports/series of adverse events
- Several OTC drug databases
- Several laboratory studies

The most common side effects of oxymetazoline-containing nasal spray are temporary burning, stinging, dryness in the nose, runny nose, and sneezing (WebMD). However, if oxymetazoline gets into the systemic circulation it may lead to cardiovascular complications, including hypertension, tachycardia, and cerebral vasospasms. These may be indicated by changes to heart rate, light-headedness, headaches, dizziness, or weakness following administration of oxymetazoline (Drugs.com).

Due to its properties as a potent sympathomimetic, routes of administration that increase systemic levels, such as ingestion or intravenous injection can be fatal (Afrin data sheet). Children are at greatest risk, as the FDA reported 96 severe adverse events from 1985-2012 following accidental ingestion of oxymetazoline-containing nasal sprays or eye drops in children five and under (FDA.gov).

The risk for adverse events increases with dose, in terms of frequency of use. The recommended usage period is three days, due to the risk for rhinitis medicamentosa. However, this duration is controversial, as oxymetazoline has been safely used in a variety of studies for substantially longer periods of time (i.e weeks to months) without strong evidence of inducing this effect [27; 28]. It is likely that the duration is highly subjective, varying from person to person depending on their underlying physiology and pattern of use. Using it for longer than recommended periods of time may led to vascular adaptations resulting in rhinitis medicamentosa, and nasal decongestant dependency [16]. It can also lead to damage to the nasal mucosa. Rhinitis medicamentosa can lead to more frequent daily use, while the changes to the vasculature and nasal mucosa increase the ability of oxymetazoline to enter the CNS and systemic circulation. The levels of drug in the circulation and CNS are the primary factor related to risk for serious adverse events. Individuals with underlying cardiovascular and/or neurological risk factors may be especially vulnerable to adverse events stemming from elevated systemic oxymetazoline. Serious adverse events stemming from oxymetazoline use appear to be a rare occurrence; they primarily occur within people with underlying risk factors for the given event (cardiovascular, psychiatric, etc.) when taken at extremely high doses.

Drug interactions: According to Drugs.com, there are 48 drug interactions with oxymetazoline, six of which are major interactions. Most of the major interactors also constrict blood vessels and can lead to an elevation of blood pressure when combined with oxymetazoline. MAO Inhibitors could cause a serious drug interaction (WebMD). Blood pressure medications and antidepressants may also interact with oxymetazoline. The use of oxymetazoline with other sympathomimetics, such as pseudoephedrine, may also increase the risk for adverse events.

Sources and dosing:

Oxymetazoline (0.05%) is found in a variety of OTC nasal decongestant sprays. The most common brands are Afrin nasal spray, Neo-Synephrine 12-hour nasal spray, Dristan 12-hour nasal spray, Vicks Sinex severe nasal spray, and Zicam sinus relief nasal spray. The recommended dose for Afrin is 2-3 sprays per nostril once a day or, at maximum, twice a day, for up to three days (Afrin label). Use for longer than three days is not recommended, as it increases the risk for rhinitis medicamentosa and systemic side effects. Oxymetazoline is also available as a prescription in topical (Rhofade®) and ophthalmic (Upneeq®) formulations, for rosacea and blepharoptosis, respectively.

Research underway:

According to Clinicaltrials.gov, there are currently three active clinical trials specifically testing oxymetazoline. One trial is testing an oxymetazoline-containing nasal spray for nasal congestion with sleep apnea (NCT02630121). Two trials are testing ophthalmic preparations, one for presbyopia (NCT05006911) and one for eye appearance (NCT04831047).

Search terms:

Pubmed, Google: Oxymetazoline

- Dementia, brain, stroke, cardiovascular, adverse events, clinical trials, meta-analysis, safety

Websites visited for Oxymetazoline:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca

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