DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX – MANAGEMENT OF MEDICATION-INDUCED SIALORRHEA

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

I. Purpose:

A. To increase awareness of the different classes of medications which can induce sialorrhea which increases the risk for aspiration pneumonia.

B. To provide guidance on what treatments are available to address sialorrhea based on cause/mechanism.

C. To improve patient's treatment adherence and chances for illness improvement/remission by ameliorating this medication-induced adverse effect.

II. Background:

A. Sialorrhea (a.k.a., hypersalivation or drooling) results from either increased production of saliva or failure of mechanisms that clear and remove saliva from the oral cavity.

B. Uncontrolled drooling can be due to various medical conditions. Some examples include:

- Parkinson's disease
- amyotrophic lateral sclerosis
- cerebral palsy
- carcinoma of upper digestive tract
- posttraumatic/iatrogenic salivary sialoceles
- post-op cysts/salivary fistulas
- Frey's Syndrome
- hyperhidrosis

C. Sialorrhea can be an adverse effect of a number of medications. Swallowing is a complexly orchestrated, orderly progression of muscle contractions resulting in the wave motion of the esophagus known as peristalsis. Any disruption of this would hinder a person's ability to swallow and increase the associated risk for choking. This complex muscle activity is sensitive to disturbances in central nervous system dopaminergic activity.

1. Benzodiazepines. Excessive drooling can also be seen with patients prescribed excessive amounts of benzodiazepines, which can cause an ataxia of the pharyngeal muscles leading to an impairment of esophageal peristalsis.

2. Dopamine antagonism/blockade. The excessive drooling seen with dopamine blockade results from impaired swallowing with saliva buildup. A robust D2 antagonist might cause dystonia of pharyngeal muscles and impede a person's

ability to swallow, resulting in subsequent pooling in the posterior pharynx of saliva that is produced in physiologically normal amounts.

3. Clozapine. Clozapine induces sialorrhea via cholinergic stimulation. Although clozapine's muscarinic antagonism contributes to the intestinal hypomotility which can lead to constipation and possible small bowel obstruction, the leading hypothesis for the mechanism by which clozapine causes sialorrhea involves the muscarinic agonist effects of its metabolite norclozapine on the M1 receptors found in salivary glandular tissue.

D. Patients who are prescribed clozapine are predominantly those who have treatment-resistant illness (psychosis or bipolar mood disorder). If inadequately treated, sialorrhea can lead to adverse medical consequences and social embarrassment. The latter can deter patients from medication adherence where the patient requests switching medications to less effective antipsychotic therapy, leading to psychiatric destabilization and consequently a more elevated risk for aggression and violence.

III. Approach to Treatment:

A. Sialorrhea Secondary to Excess Benzodiazepines

1. Unless the patient has catatonia, which requires high-dose benzodiazepines for an extended period of time, tapering benzodiazepines to discontinuation is the recommended treatment course.

a. While benzodiazepines may initially help promote sedation, nearly 100% tolerance to the sedating effect occurs after 4 – 6 weeks. Specifically, this class of drugs would not promote sedation after a month to month and a half of use. Moreover, benzodiazepines can be disinhibiting and lead to behavioral acting out.

b. If sedation is desired, note that the antihistamine hydroxyzine is sedating and does not result in the same tolerance seen with benzodiazepines. Further, hydroxyzine is not anticholinergic, does not induce withdrawal, and does not increase the long-term risk for suicide like benzodiazepines.

B. Sialorrhea Secondary to Dopamine Antagonism

1. For any of the dopamine antagonist antipsychotics, dystonia is a dose-dependent adverse effect of dopamine blockade in the basal ganglia. Potential treatments are dose reduction or amantadine.

a. Dose reduction

i. If lowering the dosage/plasma concentration of the dopamine antagonist results in exacerbation or re-emergence of psychotic symptoms, then titration back to the dosage at which the patient was stable is recommended and addition of amantadine (addressed below) is recommended.

ii. Notably, the risk of dystonia is decreased with use of a decanoate antipsychotic preparation as a result of its gradual increase in plasma concentration and significantly diminished peak when compared to oral equivalent antipsychotic doses. This may be less true of fluphenazine decanoate, as it has a first post-injection peak that is higher than that of haloperidol decanoate. Nevertheless, such a peak is less problematic than daily peaks associated with oral dosing.

b. Amantadine

i. Amantadine has been shown to be helpful in reducing both dystonia and tardive dyskinetic movements. Because sialorrhea induced by dopamine antagonist antipsychotics is due to the identical mechanism by which cervical and extremity dystonia and dyskinesias occur, amantadine would be helpful for dystonic adverse effects in the pharyngeal muscles.

Amantadine could be initiated at 100 mg QAM for three days and increased to 100 mg BID. If adverse antipsychotic affects persist after three days of amantadine 100 mg BID, consider a dose increase to 200 mg BID. If the patient experiences post-dose nausea, a nonformulary request could be submitted for an extended-release formulation.

ii. It is important to note that sialorrhea secondary to pharyngeal dystonia is a result of dopamine antagonism. This type of drooling results from impaired swallowing rather than overproduction of saliva. Hence, topical and systemic anticholinergic agents would not be helpful. Similarly, treatment modalities targeting the salivary glands would not be helpful.

C. Sialorrhea Secondary to Clozapine

1. Topical anticholinergic agents

a. Atropine 1% ophthalmic drops

i. The patient should receive no more than 3 drops of atropine maximum in the mouth. Let the topical agent sit for about 15 seconds, take in 5mL (about a teaspoon) of water, swish that mixture around for another 15 seconds, and then spit it all out. This procedure can be administered from once to four times per day.

b. Ipratropium bromide 0.06% nasal spray (The 0.03% solution tends to be ineffective.)

i. The typical dose is 1 – 3 sprays of ipratropium in the mouth where it should sit for about 30 seconds. Then, the patient should take in

5 mL (about a teaspoon) of water, swish that mixture around for another 15 seconds, and then spit it out. This procedure can be administered from once to four times per day.

2. IncobotulinumtoxinA (Xeomin®) (IncobotulinumtoxinB also has been used but is more antigenic.)

    a. The National Institute of Health has issued a consensus statement that this drug is effective and safe in treating sialorrhea based on extensive supporting data from studies in neurological patients (e.g., patients who have drooling as a symptom of their Parkinson's disease, amyotrophic lateral sclerosis, cerebral palsy, Frey's syndrome, etc.). This is one of the safest and most effective methods of controlling clozapine-induced sialorrhea.

    b. Using anatomical landmarks to locate the parotid and submandibular glands, the physician injects 30 units to each parotid gland and 20 units to each submandibular gland. The frequency of injections depends on each patient's response and can vary from every 6 to 20 weeks.

3. Systemic anticholinergic agent – Treatment of Last Resort

    a. Glycopyrrolate, a systemic anticholinergic medication, is considered the treatment of last resort for sialorrhea because concomitant prescription with clozapine roughly doubles the risk for ileus. It is the preferred systemic anticholinergic medication because it does not cross the blood brain barrier.

    b. Glycopyrrolate can be initiated at 1 mg BID and titrated every 1 – 2 weeks up to a maximum of 8 mg total daily (or, 4 mg BID) *provided that constipation is adequately managed*. Please refer to Chapter 38: Appendix – Management of Medication-Induced Constipation.

4. The alpha-2 adrenergic receptor agonist (clonidine) and alpha-1 antagonists (e.g., tamsulosin and terazosin) have not generally been effective in addressing sialorrhea.

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