

DOSE, DELIVERY, DEPOSITION, & DISTRIBUTION

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I have always had a "thing" for using the proper terminology in respiratory therapy. It really bugs me when people use a wrong or imprecise term to refer to a device, procedure or concept. Of course, I also have separate drawers for my black, blue and brown socks; but that's another story. In this story, we are going to talk about what we call things. And we are probably going to become progressively obsessive-compulsive as we develop the story line. So don't say I didn't warn you. Because this is a column about aerosols in medicine, the nomenclature we are concerned with is that used for referring to different aspects of aerosol therapy. This is one of my pet peeves because of the confounding prevalence of so many "D-words." I don't know whether people are lazy and just don't care if they use the correct terminology or not, or whether all the D-words manage to confuse everyone. Let's try to find out. Let me challenge the readers with an admittedly trick question:

When we give an aerosol medication treatment, what is the Dose (first D-word)? Is it: (1) The amount of drug the physician prescribes? (2) The amount of drug in the "unit dose" ampoule? (3) The amount of drug that you place in the nebulizer? (4) The amount of drug that is nebulized? (5) The amount of drug that is inhaled or "delivered" (second D-word)? (6) The amount of drug that is "deposited" (third D-word)? Or (7), does it have anything to do with the "distribution" (fourth D-word)? Well, I think we can rule out answer (7), but we'll talk about it in its proper context later.

Speaking of context, perhaps the answer to the above question depends on context. For the prescribing physician, the task at hand is to write an order, or a prescription; and the dose is a required component of a prescription. So, in the context of a prescription, dose is the amount of drug the physician prescribes. However, as we well know, the amount of medication the physician prescribes, or that we place in the nebulizer, or is emitted by an MDI, is not the amount that the patient inhales. For the practicing therapist, the context may be altogether different; the "dose" may be the particular strength of the medication in the ampoule (think Xopenex®, 0.32mg, 0.63 mg, or 1.25 mg). But wait a minute, isn't that the same as what the doctor ordered? The aerosol scientist or device developer is going to look at this issue in an entirely different context. Generally speaking, the aerosol scientist is primarily concerned with either the device's performance (amount of drug emitted from the device) or the amount of drug inhaled by a simulated breathing pattern in the lab. Clearly, context is important when a word such as "dose," with so many potential meanings, is used to discuss aerosol drug delivery.

All too often I have taken note of practitioners who describe the "dose" of medication they place in the nebulizer in terms of its volume rather than its mass. For example, I have seen notes in the medical record written thusly: "Administered SVN TX w/3 cc albuterol." That note does not tell me what the mass of albuterol was. It gives me no hint whatsoever as to the dose, regardless of whether we agree on the definition of dose. I could assume the writer meant that he administered 2.5 mg of albuterol in a total volume of 3 cc. But I could be wrong. When it comes to aerosol therapy, which is already somewhat imprecise, we should not assume anything. Aerosol scientists always express medication measurements in terms of mass. Virtually all inhalable medications, regardless of whether they are given by nebulizer or inhaler, can be expressed in either milligrams or micrograms.

Getting back to the word "dose," I have considered advocating the ban of the word as it pertains to aerosol therapy because of the aforementioned confusion regarding context. I frequently find myself misusing the word. I know better. But the word often slips off my tongue before I have had a chance to think and to conjure up a more suitable term for the particular context. I guess this is habit. Banning the word won't work. We all need to pay more attention to our use of the word dose.

In addition to "dose," there are 3 more "D" words in our aerosol therapy vocabularies that we really need to use more precisely: delivery, deposition and distribution. I like the word "delivery" to describe the act of administering an aerosol treatment. We are delivering the medication to the patient. The device we use to do so is an aerosol drug delivery device, just as a syringe is a delivery device for a parenteral medication and a tablet is a delivery device for an oral medication. Amusingly, but aptly, a cigarette has been defined as a delivery system for nicotine. The drug that has passed the threshold of the airway opening has been delivered. The amount of drug that has been delivered could be called "delivered dose," but it has been termed

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Inhaled Mass by the aerosol scientists. The important thing to remember about Inhaled Mass is that it expresses only the amount (mass) of drug that has been delivered to the respiratory system; it does not tell us how much of that delivery was actually retained in the respiratory tract or where it went. We have two other D-words for that.

The first of which is "deposition," which readily slips off the tongue of many practitioners who use it generously to describe anything having to do with the administration of aerosols. But, as we have just noted, the term delivery describes the amount of drug that is inhaled. Deposition is a very precise word, or at least it should be, because it describes only the amount of drug that is retained. In fact, the term "deposition fraction" is frequently used by aerosol scientists to describe the amount retained (deposited) as a percentage of the amount inhaled (delivered).

The last D-word is "distribution." Distribution pertains to the location in the respiratory tract that aerosol particles are deposited. We typically have no accurate idea about the distribution of aerosol particles when we administer a treatment. Arguably, it is important. For example, if we were trying to deliver and deposit an antibiotic aerosol in the endobronchial regions of the lungs, we would have failed if, for example, the majority of the distribution was to the trachea and mainstem bronchi. The converse is probably true; distribution of a bronchodilator aerosol to the alveoli, instead of major upper and middle airways probably will not help to relieve bronchospasm. Distribution is difficult to determine and must be estimated by in vivo techniques, usually by deposition lung imaging using radiolabeled aerosols that emit gamma rays that can be detected by a gamma scintillation camera positioned externally adjacent to the chest. This is a technique within the realm of Nuclear Medicine known as "lung scanning." Through the use of contemporary computerized lung scanning methodologies, regions of interest (ROI) can be defined on the lung scan, and the amount of gamma energy in each region can be determined as an index of the distribution of the delivered and deposited aerosol. Bluntly, it tells us where the aerosol went. Typical methods for describing distribution involve defining ROIs then comparing the gamma energy of one ROI to another. For example, central-to-peripheral, upper-to-lower, and right-to-left or, more specifically, a diseased area compared to the rest of the lung.

In summary, more precise usage of all 4 of the aerosol D-words would help us to say what we mean and mean what we say when it comes to describing aerosol therapy.

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"You call it doing my homework, I call it intentional infliction of emotional distress"

used due to the lack of available, FDA approved drugs or standard of care guidelines many years ago with the rationale and hope of sedating the patients to the point of not experiencing the restless legs. In essence these agents may mask RLS symptoms but do not treat the underlying cause. Tolerance seems to develop fairly quickly and there is a significant risk of abuse and daytime sedation. Despite these negatives, these agents may be beneficial in combination therapy for patients that cannot fall asleep despite relief of sensory symptoms. Common medication in this category include Clonazepam (Klonopin), Temazepam (Restoril), and Lorazepam (Ativan). Non benzodiazepines in this group include Zaleplon (Sonata), Zolpidem (Ambien), and Eszopiclone (Lunesta).

Third class of medications used for RLS are the anticonvulsants. Most common agents used are Gabapentin (Neurotin) and Carbanazepine (Tegretol). Gabapentin is usually preferred for tolerability and safety. Gabapentin is recommended as second or third line therapy but patients who report pain as a major symptom it can be a first line treatment. The last group of medications commonly used in RLS are the Opioids. Agents in this category include Propoxyphene (Darvocet), Hydrocodone (Vicodin) and Oxycodone (Percocet). Considered effective second or third line agents for patients who report frequent or nightly symptoms or first line if there is a significant pain component. Dependence and tolerance may occur.

One of the most common problem observed with treatment for RLS is Augmentation. Augmentation is by definition exacerbation of RLS symptoms, attributable to a specific therapeutic intervention. Common features include shift on onset of daily RLS symptoms to a time period that is equal or greater than 2 hours earlier than was typical before beneficial stable treatment and absence of any other medical, psychiatric, behavioral or pharmacologic factor that explains RLS symptoms exacerbation.

Atypical features of Augmentation include: Increased intensity temporally related to increased daily medication dose, decreased intensity temporally related to decreased daily medication dose and symptoms extended to previously unaffected body parts.

However, it is important to keep in mind there are certain symptoms that mimic augmentation, such as natural progression of RLS, temporary symptoms worsening due to external factors (sleeplessness, alcohol, caffeine.), medication (dopamine receptor blockers, antidepressants), tolerance and end of dose rebound.

Augmentation is primarily seen with dopaminergic agents. No reported cases with opiates, anticonvulsants, or other non-dopaminergic drugs.

As with many chronic diseases, it is important to empower the patients with education and resources. For RLS, these websites are recommended - The Restless Legs Foundation (www.rls.org), National Institutes of Health (www.ninds.nih.gov) and Worldwide Education and Awareness of Movement Disorders(www.wemove.org)

Look forward to the day a cure is found and the name Nightwalkers is a euphemism for couples on a romantic rendezvous during the night.

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