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Pharmacy Column

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Is a new symptom an adverse drug reaction?

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In the years I have written this column I have often mentioned various "mantra's" of geriatric drug therapy. The word mantra is a noun defined as either a word or formula chanted or sung as an incantation or prayer. It is also defined an often-repeated word, formula, or phrase, often a truism.[1] This is the operative definition that I am referring to in this article.

For example, the mantra "Start low and go slow" is a commonly-repeated phrase in geriatric drug therapy. "Start low" refers to starting medications (drugs) at the low-end of the normal dosage range to reflect age-related changes in body physiology and/or function. "Go slow" refers to a gradual upward dosage titration so as not to exceed the proper dosage for the patient. Another less commonly used geriatric drug therapy mantra is "Any drug can cause any side effect." Admittedly, this is a rather grand generalization that is probably not entirely accurate but it reflects situations that are occasionally observed when older individuals take prescription or non-prescription drugs. That is, sometimes drug side effects, or adverse drug reactions (ADR), are unexpected and not apparently related to the desired pharmacologic effect of the drug. For example, antihistamines, such as diphenhydramine (brand name example Benadryl®) will often cause drowsiness. This is a well-known side effect of diphenhydramine that is actually often used for therapeutic benefit by helping individuals sleep. However, individuals taking diphenhydramine may also less commonly experience excitation, irritability and euphoria, the opposite of what we would normally expect from this drug.[2] Other examples of expected vs. unexpected adverse side effects include quinolone antibiotics which commonly cause nausea, dyspepsia and vomiting but less commonly can cause tendinitis and tendon rupture.[3]

In the clinical setting the development of new symptoms is obviously a routine occurrence. These symptoms could be due to progression or exacerbation of one or more existing diagnoses or it could indicate that a new health condition has developed. Another possibility is that the new symptom(s) could be the result of one or more drugs the individual is taking. It is obviously critical to differentiate between disease-related symptoms and symptoms that could be the result of one or more ADRs. Depending on the situation, the action(s) taken may be in direct opposition. If due to a medical condition, it may be appropriate to add a drug or increase the dosage of one that is already being used while if the symptom is an ADR it might be appropriate to discontinue the offending drug or decrease its dosage. In some cases of symptomatic ADRs it may also be in the patients' best interest to add another drug such as adding prednisone when there is a severe allergic reaction.

In fact, differentiating between symptoms of disease vs. ADRs is a key aspect of clinical practice. As a pharmacist, one of my responsibilities is to play an important role in the identification of medication-related problems including ADRs. This role is a natural one for pharmacists because, while pharmacists are not formally trained in medical diagnosis, we are well aware of common symptoms of disease and are highly-trained in all aspects of pharmacotherapy including likely and unlikely ADR's.

Determining the probability of whether a clinical event is an ADR is usually based on clinical judgement. Without a more formal, systematic method of establishing causality a large variability in assessment between different health professionals exists. One study found that when a group of physicians and pharmacists were asked to identify ADRs and classify them as either definite, probable, possible or doubtful agreement was only about 50%.[4] Clearly, that lack of agreement is not sufficient for high-quality patient care. In 1981 a team of health professionals developed a method to categorize whether the likelihood that an event was actually an ADR. When using this method agreement increased dramatically to the range of approximately 80% to 90%.[4]

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There are a variety of computer programs and other methods to help us identify ADRs but I will devote the rest of this column to the method referred to above.

Another important mantra is "Correlation does not imply causation." This is often used in discussions of statistics but in relation to pharmacology this means that the simple presence of a symptom, perhaps occurring sometime after a new drug is added to an individual's therapeutic regimen, does not mean that the symptom correlates with being an ADR but, it MIGHT be an ADR. The short answer is that this is rarely a black and white situation. There are various shades of gray. The method that I am referring to is the Naranjo algorithm which was developed to help clinicians determine the likelihood of a symptom being an ADR. It consists of 10 relatively direct questions which are listed below. Each of the questions requires a response of either "Yes", "No" or "Do not know" and each item has its own scoring value listed below each item.[4]

1. Are there previous *conclusive* reports on this reaction?
   Yes +1, No 0, Do not know 0
2. Did the adverse event appear after the suspected drug was given?
   Yes +2, No −1, Do not know 0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?
   Yes +1, No 0, Do not know 0
4. Did the adverse reaction reappear when the drug was re-administered?
   Yes +2, No −1, Do not know 0
5. Are there alternative causes (other than the drug) that could have caused the reaction?
   Yes −1, No +2, Do not know 0
6. Did the reaction reappear when a placebo was given?
   Yes −1, No +1, Do not know 0
7. Was the drug detected in any body fluid in toxic concentrations?
   Yes +1, No 0, Do not know 0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
   Yes +1, No 0, Do not know 0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?
   Yes +1, No 0, Do not know 0
10. Was the adverse event confirmed by any objective evidence?
    Yes +1, No 0, Do not know 0

When the cumulative score for all the items is totaled the number indicates the likelihood that the occurrence was the result of an ADR according to the following scale: <1 doubtful, 1 to 4 possible, 5 to 8 probable, >+ 9 definite.

The nomogram is available in manuscript format as well as online.[5] After applying patient-specific data to the nomogram the cumulative score may still need some interpretation. Let's use a quick case study to demonstrate: An 85 yof is mistakenly given methotrexate 10 mg once daily rather than once weekly. On day 21 of therapy she died and it was found that she had pancytopenia with an overwhelming infection. In answering the Naranjo questions we find that items #1, 2 and 10 can be answered in the affirmative and 5 in the negative yielding a score of 6 which classifies this as a *probable* ADR. In my opinion, the outcome of this inadvertent use of methotrexate given daily rather than weekly is classically fatal but since only these four items applied the cumulative score was only 6 indicating a probably ADR. Based on my professional experience I would argue that this is a *definite* ADR but still, categorizing it as *probable* directs us to the likelihood that in this case the ADR and the outcome not only correlate but demonstrate that the methotrexate was the cause of this very unfortunate outcome. Patients who experience an adverse reaction that first occurs after drug administration and then resolves after the drug is discontinued and re-appears upon re-challenge with the drug are most likely to be classified by the Naranjo algorithm as *probable* or *definite* ADRs. In reality, however, in most cases where we suspect that a symptom is related to that particular drug such a re-challenge does not occur so the actual the Naranjo score is subject to additional interpretation based on each unique, patient-specific, situation.

The availability of a systematic method like the Naranjo algorithm does not substitute for clinical experience and judgement but in combination can greatly assist clinicians in sorting out the often difficult task of determining whether a new symptom is due to a disease or is the result of an ADR.

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