

# Wyoming Drug Utilization Review

## Interpretation of the Medical Literature

Scott Johnston, MD

Clinicians are often confronted with medical studies. Learning how to interpret and apply the medical study to patient care can be difficult. There are many levels of evidence that can be considered, but the double-blinded, randomized, placebo-controlled trial is the gold standard. Meta-analysis takes several smaller studies and combines them. Although these are sometimes beneficial, they can be misleading. The correct interpretation of a randomized double-blind placebo-controlled trial can be difficult. A simple approach is listed.

### Interpretation of a Double-Blinded, Randomized, Placebo-Controlled Trial (RCT)

RCTs have a wide range in quality and utility to the clinician. Primary outcome, length of the study, number of patients, study design, randomization, and inclusion of all patients have an

impact on the results and reliability of those results.

**Evidence of a Primary Outcome.** Lack of a primary outcome is a good indicator of a preliminary study. The primary outcome should be meaningful to the clinician. (A change in a lab value is of little benefit, but a change in mortality and morbidity is meaningful.)

**Length of the Study.** For chronic conditions the study should last at least 26 weeks. The study should be long enough to assure that the initial side effects of the medication are not confounding the results.

**Number of Patients.** A small number of patients is an indication of a preliminary study. To be meaningful, a small study should be followed with a larger study to demonstrate benefit in a wider range of patients.

**Design of the Study.** Studies should clearly state the reason for the primary outcome, length of the study, and pre-study analysis of the number of patients required to show a difference.

**Analysis of Randomization.** Analysis of randomization and a comparison that demonstrates the two populations are equal should be clear in the body of the study.

**Accounting for All Patients.** The study should account for all patients enrolled at the beginning of the study. The reason for dropouts should be analyzed and the final analysis should be based on intention to treat.

**Outcome Results Should Be Reported in Meaningful Terms.** Raw numbers, p-values, confidence intervals, and percent-improved can be confusing. Number needed to treat is both easy to understand and easy to explain to a patient.

**Example.** A good study evaluating a treatment for a chronic disease should be randomized, have a meaningful outcome, last at least 26 weeks, include at least 50 patients in the treatment arm, include a pre-study analysis, include all patients in the outcome, and report the results in a manner that is easy to understand.

### Searching the Medical Literature

**Start with a question.** The quality of the question is directly proportional to the outcome of the search. As an example; Which antiseizure medications are beneficial in treating painful diabetic neuropathy?

**Search the Literature.** FDA approval implies scientific evidence exists that the medication is effective. The off-label use of medications is the focus of this review. The literature search should include the published and unpublished literature.

**Published Literature.** A PUBMED search is fairly easy. Most libraries have access and PUBMED can be accessed via the Internet at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed>.

The search should be limited to human studies, published in the English-language and randomized controlled trials. PUBMED has checkboxes for each of these limits. A search box is located at the top of the web site. The prior example of painful diabetic neuropathy and antiseizure medications could be searched by entering the pharmaceutical name and painful diabetic neuropathy. Widening the search by just entering the pharmaceutical name will increase the likelihood of including all relevant randomized controlled trials.

**Unpublished Literature.** Recently The Pharmaceutical Research and Manufacturers of America (PhRMA) has developed a resource for unpublished studies. The PhRMA clinical study results database can be accessed via the Internet at <http://www.clinicalstudyresults.org>.

**Call the Manufacturer.** Pharmaceutical manufacturer phone numbers are available in the Physicians Desk Reference.

**Compile a List of Articles and Locate the Articles.** A list of references to each article is essential in locating the articles. Medical librarians are an excellent resource and enjoy helping the clinician in these searches.

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**Wyoming Drug Utilization Review**  
University of Wyoming  
School of Pharmacy  
Dept. 3375  
1000 E. University Ave  
Laramie, WY 82071  
307-766-6750

[www.uwyo.edu/DUR](http://www.uwyo.edu/DUR)  
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Edited by  
Aimee Lewis, PharmD  
Laura Miller, MS

**Analyze the Studies.** Analyze each article carefully. The abstracts can be misleading. The results of this analysis will yield an answer to most questions.

**Answer the Question.** Answers may include the following: 1) there is evidence that a medication works, 2) there is evidence that a medication does not work, 3) there is conflicting data (with the better studies revealing a benefit or lack of benefit), and 4) there is a lack of evidence. All four answers should be considered. The subdivision of conflicting data may be considered when the evidence favors benefit or lack of benefit.

Returning to our original question, which antiseizure medications are beneficial in treating painful diabetic neuropathy? All four answers are found. *There is evidence of a benefit for pregabalin (Lyrica®)<sup>1</sup>, carbamazepine (Tegretol®)<sup>2,3</sup> and valproic acid, divalproex, valproate sodium (Depakene®, Depakon®, and Depakote®)<sup>4</sup>. There is conflicting data with the better studies revealing a benefit for gabapentin (Neurontin®)<sup>5,6,7</sup>. There is conflicting data with the better studies revealing a lack of benefit for oxcarbazepine (Trileptal®)<sup>8,9</sup>, and topiramate (Topamax®)<sup>10,11,12,13,14</sup>. There is a lack of evidence for ethotoin (Preganone®), tiagabine (Gabitril®), levetiracetam (Keppra®), phenytoin (Dilantin®). There is evidence of no benefit for lamotrigine (Lamictal®)<sup>15,16,17,18,19</sup> and zonisamide (Zonegran®)<sup>20</sup>.*

On the basis of this review you would consider pregabalin (Lyrica®), carbamazepine (Tegretol®) and valproic acid, divalproex, valproate sodium (Depakene®, Depakon®, and Depakote®) to be good antiseizure medications to treat painful diabetic neuropathy. Gabapentin (Neurontin®) may be beneficial in treating painful diabetic neuropathy. The rest of the medications should be avoided because of the conflicting data. Lamotrigine (Lamictal®) and zonisamide (Zonegran®) should not be used because of a consistent lack of benefit in randomized controlled trials.

Two excellent books are available for those clinicians interested in learning more about the medical literature and evidence-based medicine.

1. Users' Guides to the Medical Literature, Essentials of Evidence-Based Clinical Practice. Guyatt, G and Rennie, D. AMA Press.
2. Users' Guides to the Medical Literature, A Manual for Evidence-Based Clinical Practice. Guyatt, G and Rennie, D. AMA Press.

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## New Manager for Wyoming Drug Utilization Review Program

The University of Wyoming School of Pharmacy is pleased to announce that Aimee Lewis, Pharm.D., was selected to be the new manager of the Drug Utilization Review program, effective August 14, 2006. Lewis graduated from the UW School of Pharmacy in 2000. She worked for the state of Wyoming in the Department of Health, Pharmacy Division, for many years. We look forward to associating with her and benefiting from her experience with the Department of Health.

Debra Devereaux, R.Ph., M.B.A., announced her resignation earlier this spring, effective July 1, 2006. We thank her for her many years of service to the School of Pharmacy, the Drug Utilization Review program, and the state of Wyoming. She had been manager of the Wyoming Drug Utilization Review program since its inception in 1992.

### Final Criteria for Use of Angiotensin II Receptor Blockers WY-DUR Board 7-20-06

*These criteria were changed to reflect comments from local providers. Thank you to those who provided feedback.*

Angiotensin II Receptor Blockers (A2RB): candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

A2RB combinations: candesartan/hydrochlorothiazide, eprosartan/hydrochlorothiazide, olmesartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, valsartan/hydrochlorothiazide

- Trial and failure of one ACE inhibitor
- Intolerance, adverse reaction or allergic reaction to one ACE inhibitor

## New Refill Too Soon Policy

A new Refill Too Soon policy will be implemented on October 1, 2006. The Refill Too Soon edit will post when a refill is requested at **80 percent** or less of the day supply of the previous fill, and when there is a **15 day** accumulation of the drug over a 180 day look back period. For **narcotics**, the new policy will require an edit to post when a refill is requested at **90 percent** or less of the day supply of the previous fill, and when there is **7 days** accumulation of the drug over a 180 day look back period. The application of this edit requires that the day supply information assigned to a claim be accurate.

If you receive a denied claim for Refill Too Soon (Edit 79) you must now call the ACS Prior Authorization Call Center at 1-866-556-9320. If the following criteria are met, the Prior Authoriza-

tion Call Center will enter the override via the prior authorization system. They will inform you if the override has been entered. You can then resubmit the claim that denied for Refill Too Soon.

Override criteria:

Dosage change

Lost prescription – 1 Refill Too Soon allowed per year

Trying to obtain overrides for reasons other than dosage change or lost prescription will result in an adjustment in which the reimbursement for the claim(s) are taken back from the pharmacy.

## Plan B Receives Over-the-Counter Approval

On August 24, 2006, the FDA gave Plan B emergency contraception OTC status for women 18 and older.<sup>1</sup> Plan B is intended to be a back-up method and should not be used as a regular form of contraception.<sup>2,3</sup> Plan B will continue to be stocked behind the pharmacy counter and will only be dispensed with a prescription or proof of age.

Plan B contains two tablets of levonorgestrel which, if taken correctly within 72 hours of unprotected sex, reduces the chance of pregnancy by 89% (from an 8% chance in an average cycle to a 1.1% chance).<sup>2,3</sup> The first dose should be taken as soon as possible within 72 hours, followed by the second tablet 12 hours later. Some experts recommend taking both tablets at once as it is equally effective.<sup>4</sup> For each 12 hours of delay in treatment, the efficacy decreases by 50%.<sup>3</sup> Failure rates for other birth control methods are listed in the table below.<sup>5</sup> Note that it is difficult to compare the efficacy of Plan B to other methods as efficacy for Plan B is not reported as a failure rate.

Since September 2005, Wyoming Medicaid has paid for 80 claims resulting in a cost of \$2,533. **As with other OTC medications, a prescription will be required for Medicaid coverage of Plan B regardless of age.**

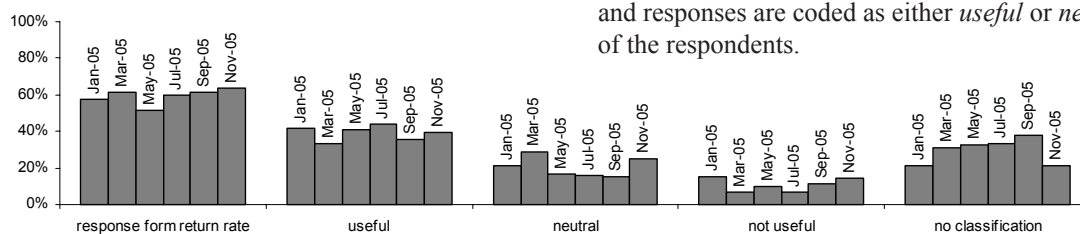
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Method	Failure rate with typical use within the first year
Spermicide	29%
Condom	
Female	21%
Male	15%
Diaphragm	16%
Oral hormonal birth control	8%
Injectable hormonal birth control	3%
Norplant	0.05%

## 2005 Education Letter Response Rate

The Wyoming Drug Utilization Review Program sends out 6 cycles of education letters to prescribers each year. Each prescriber who receives an education alert letter is asked to complete and return a response form. In the response form, we ask the prescriber to classify the information in the alert letter as *useful*, *neutral*, or *not useful*.



The graph below shows the following information: the return rate for prescriber response forms for 2005, the percentage of returned provider response forms that fall into each of the 3 classifications (*useful*, *neutral*, and *not useful*), and the percentage of *no classification*, which is assigned if the provider fails to classify the information in the alert letter. Response rates are over 50% and responses are coded as either *useful* or *neutral* by over 50% of the respondents.

Wyoming Drug Utilization Review  
University of Wyoming  
School of Pharmacy  
Dept. 3375  
1000 E. University Avenue  
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## Correction

The phone number for Partnership for Prescription Assistance was incorrect in the July 2006, April 2006, and October 2005 issues of the WY-DUR newsletter. The correct telephone number is 1-888-477-2669.

Partnership for Prescription Assistance (PPA) helps qualifying patients who lack prescription coverage get the medicines they need through a public or private program.