

# WYOMING DRUG UTILIZATION REVIEW

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## Gabitril (tiagabine) and Off-Label Uses

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The FDA recently identified the off-label use of tiagabine as a risk for seizures. A black box warning was added to the package insert and a letter sent to prescribing physicians on the 18<sup>th</sup> of February 2005. Today the Food and Drug Administration announced that a **Bolded Warning** will be added to the labeling for Gabitril (tiagabine) to warn prescribers of the risk of seizures in patients without epilepsy being treated with this drug. Gabitril has been approved since 1997 for patients 12 years of age and older as adjunctive therapy (used in addition to other medications) for partial seizures. Recently, the Agency has become aware of reports of the occurrence of seizures in more than 30 patients prescribed Gabitril for conditions other than epilepsy. Most of these uses were in patients with psychiatric illnesses. Such so-called off-label prescribing is a common practice among physicians. Because of the risk of seizures, however, in addition to adding the **Bolded Warning** to product labeling, **the sponsor has agreed to undertake an educational campaign targeted to healthcare professionals and patients in which such off-label use will be discouraged<sup>1</sup>.**

**Indication.** GABITRIL (tiagabine hydrochloride) is indicated by the Food and Drug Administration (FDA) as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.

**Mechanism of Action.** Tiagabine's proposed mechanism of action is as a selective GABA reuptake blocker. It has little affinity for the other neuroreceptors.

**Metabolism.** It is metabolized by P450 (CYP3A) and is secreted in the urine and feces. The ½ life is 7-9 hours but can be decreased by 50-65% in hepatic enzyme induced patients.

**Wyoming MEDICAID data.** A search of the Wyoming MEDICAID patient population revealed 72 patients currently taking tiagabine. 85% of the use was for an off-label indication. (Sleep 46%, Mood 21%, ADHD 7%, other psychiatric conditions 4%, anxiety 5.5%, and 1.5% headaches).

**Literature search.** I accomplished a MEDLINE search and contacted the manufacturer to identify randomized controlled trials (RCT's) of tiagabine.

- **Sleep:** There are no published randomized controlled trials on the use of tiagabine for insomnia. Two unpublished studies revealed no significant effect on the primary outcomes<sup>2,3</sup>. Secondary benefits were noted in stage 3 and 4 sleep levels but no benefits in subjective measurements of sleep quality.
- **Pain:** One phase II trial revealed no significant benefit over placebo of an extended release tiagabine<sup>4</sup>. No randomized controlled trials of immediate release tiagabine have been

published<sup>5,6</sup>. One open label trial revealed no significant benefit over placebo<sup>7</sup>.

- **Mood disorders:** No randomized controlled trials have been published. Several reviews from 1999 through 2005 could not identify any studies suggesting tiagabine may be useful in Bipolar Disorders<sup>8,9</sup>. One review concluded that tiagabine is unlikely to have any beneficial effects and is poorly tolerated when the dose is rapidly increased<sup>10</sup>.
- **Anxiety:** One phase III randomized placebo controlled trial was identified; the company has not released the results of that study except as a poster presentation<sup>11</sup>. There was no significant benefit of tiagabine over placebo in that study.
- **Post Traumatic Stress Disorder:** One randomized placebo controlled trial was identified. The company has failed to publish the study but report that tiagabine had no significant benefit over placebo after 12 weeks<sup>12</sup>.

**Conclusions.** There are no placebo controlled trials suggesting a benefit in the off-label use of tiagabine. With a known risk (seizures) and lack of benefit tiagabine's off-label use is probably harmful to the health of patients.

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# The Link Between Respiratory Secretions and Antimicrobial Resistance

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In recent years, antimicrobial resistance (AMR) has developed into a serious public health crisis, causing many infectious disease experts to predict that we will soon be entering a “post-antibiotic” era<sup>1</sup>. Despite its recent attention, AMR is by no means a new phenomena. The “golden age” of antimicrobial therapy began in the 1940s when Alexander Fleming’s 1928 discovery of penicillin was first introduced to medicine. Penicillin was immediately successful in treating the then life-threatening infections: pneumonia, meningitis, syphilis, and rheumatic fever; however, resistance to penicillin quickly followed its introduction. *Staphylococcus aureus* was the first known organism to develop resistance to penicillin. In 1941, *S. aureus* was susceptible to penicillin G, but by 1944, almost all strains of *S. aureus* had developed resistance to penicillin through their production of  $\beta$ -lactamase, an enzyme, which destroys many antibiotics with a  $\beta$ -lactam ring in their structure<sup>2</sup>. Since then, many microbial pathogens have developed resistance to the more commonly used antibiotics, and recently surveillance by the Wyoming Department of Health has revealed an increase in fluoroquinolone resistance among *Streptococcus pneumoniae*<sup>3</sup>.

AMR results from microbes changing in ways that reduce or eliminate the effectiveness of drugs or other agents to cure or prevent infections<sup>4</sup>. AMR develops naturally and quickly and is fostered by any antibiotic use, regardless of medical justification<sup>5</sup>. A strong association exists between recent antibiotic use and the development of antimicrobial resistant infections. For example, individuals with acute otitis media, pneumonia, or meningitis caused by resistant strains of *Streptococcus pneumoniae* are much more likely to have taken antibiotics within the previous 12 weeks than those infected with susceptible strains. Even when one considers other risk factors for invasive pneumococcal disease such as recent hospitalization and immunosuppression, recent antibiotic use remains the single most predictive factor for an infection with resistant pneumococci<sup>6</sup>.

The single most important factor in the emergence of AMR is antibiotic exposure<sup>7</sup>. In outpatient primary care, over 75% of all antibiotics prescribed are for acute respiratory infections (ARIs)<sup>8</sup>. While most ARIs are viral in etiology, antibiotics are prescribed over 50% of the time for all outpatient ARIs and over 65% of the time for acute bronchitis<sup>9,10</sup>.

Inappropriate antibiotic prescribing for ARIs is a complex phenomena resulting from a host of patient, clinician, and system factors. For example, patients and parents often expect and/or demand antibiotics for ARIs<sup>11</sup>, and clinicians admit that they sometimes prescribe antibiotics against their better judgement in order to “satisfy” patients<sup>12</sup>. Furthermore, it is traditional in western healthcare for patients to receive a written prescription for a pharmaceutical agent at the end of a clinician office visit. This prescription legitimizes the patient’s visit to a provider and officially designates him or her as “sick”<sup>13</sup>.

In addition to the psychosocial factors, the presence of discolored nasal secretions and/or purulent sputum are also strongly associated with antibiotic prescribing for ARIs. Studies have shown that patients are more likely to pursue antibiotics for ARIs when discolored nasal secretions and purulent sputum are present<sup>14</sup>, and clini-

cians are more likely to prescribe antibiotics when patients report these secretions<sup>15</sup>. However, discolored or purulent secretions are poor predictors of bacterial infection<sup>16</sup> and result from the presence of inflammatory cells or sloughed mucosal epithelial cells, which occur with both viral and bacterial infections<sup>17</sup>.

In 2003, the Wyoming Department of Health conducted a survey to assess clinicians’ attitudes and beliefs regarding antibiotics and ARIs<sup>18</sup>. Surveys were mailed to all licensed physicians, physician assistants (PAs), and nurse practitioners (NPs) in the state (n=627) and were returned by 297 (47.4%) of them. While the majority of survey items focused on clinician attitudes related to ARIs, two items specifically assessed clinician beliefs about the value of respiratory secretions:

Does each of the following factors influence the likelihood that you will prescribe an antibiotic for an acute respiratory infection when the etiology (viral vs. bacterial) is uncertain?

- a) Presence of purulent nasal discharge?  
\_\_ Influence \_\_ Some influence \_\_ No influence
- b) Productive cough with purulent sputum?  
\_\_ Influence \_\_ Some Influence \_\_ No influence

Most respondents (>80%) indicated that the presence of purulent nasal discharge or sputum had an influence (22.8% and 31% respectively) or some influence (59.1% and 52.8% respectively) on whether they would prescribe an antibiotic for an ARI, and there were no significant difference in responses by practitioner type. While this survey did not assess actual antibiotic prescribing patterns, it is clear that many Wyoming clinicians may be prescribing antibiotics for ARIs based upon incorrect or outdated diagnostic criteria.

Current CDC-endorsed guidelines for acute sinusitis in otherwise healthy adults and children advise against the use of nasal secretions as a diagnostic tool for distinguishing between viral versus bacterial rhinosinusitis<sup>19,20</sup>. According to the pediatric guidelines, a clinical diagnosis of bacterial sinusitis requires either nonspecific upper respiratory signs and symptoms (e.g., cough, nasal congestion) with no improvement after 10-14 days or severe signs (e.g., fever  $\geq 39$ , facial swelling, facial pain) of rhinosinusitis<sup>20</sup>. The adult guidelines encourage clinicians to reserve the diagnosis of acute bacterial rhinosinusitis for patients with symptoms lasting 7 or more days or for patients who have severe maxillary pain or tenderness in the teeth (especially when unilateral) with swelling, and/or fever<sup>19</sup>. In addition, both sets of guidelines discourage the use of sinus radiography in the diagnostic workup of acute rhinosinusitis, as sinus radiographs are often abnormal in patients with viral rhinosinusitis, thus the results do not help clinicians distinguish between bacterial and viral infections<sup>19,20</sup>.

Current CDC-endorsed guidelines for acute bronchitis (or cough illness) in otherwise healthy adults and children encourage clinicians not to consider cough productivity in their diagnostic workup of patients presenting with an acute cough. As well, both sets of guide-

lines recommend against routine antibiotic use for acute bronchitis regardless of duration and cite multiple studies where antibiotics were no more effective than placebo for the treatment of acute cough illnesses<sup>21,22</sup>. The adult guidelines encourage clinicians who are working up patients with acute cough illnesses to focus on ruling out more serious illnesses, such as pneumonia<sup>21</sup>. In addition, recognizing that *Bordetella pertussis* is associated with 12-32% of acute cough illnesses in adults, clinicians should also consider testing for *B. pertussis* when patients present with prolonged cough (>2 weeks) and at least one of the following symptoms: paroxysmal coughing, inspiratory whoop, or posttussive vomiting. Laboratory criteria for diagnosis include a positive *B. pertussis* culture or a positive polymerase chain reaction (PCR) for *B. pertussis*<sup>23</sup>. The pediatric guidelines for acute cough illnesses are similar to the adult guidelines. However, they also stress that fever is often present in acute cough illnesses and is not in and of itself indicative of bacterial infection. Additionally, the pediatric guidelines encourage clinicians to consider *B. pertussis* and *Mycoplasma pneumoniae* infection when children present with prolonged (>10 days) cough illnesses<sup>22</sup>.

AMR is a naturally occurring microbial process that will continue to occur as long as antibiotics are used. However, we can slow the rate of AMR development by reducing the amount of antibiotics consumed. In fact the CDC estimates a 40% drop in total antibiotic usage if clinicians were to begin to follow the adult and pediatric CDC-endorsed guidelines for ARIs<sup>24</sup>.

Discolored respiratory secretions, whether from the nose or the bronchi, are not an indication for antibiotic therapy. Clinicians can help reduce the rate of AMR development by basing their antibiotic prescribing decisions for acute bacterial sinusitis and bronchitis on current evidence-based guidelines, which downplay the significance of respiratory secretions. You can download full-text copies of these and other ARI guidelines at <http://www.cdc.gov/drugresistance/community/>.

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