Hepatic encephalopathy (HE) is a common complication in patients with hepatic cirrhosis. Ammonia from intestinal overgrowth with bacteria is the main cause of HE symptoms. Treatment of intestinal bacterial overgrowth with antibiotics that have low gastrointestinal absorption demonstrates the most benefit. However, increasing gastrointestinal motility is another integral part of treatment and currently used antibiotics, such as neomycin, lack this ability. To date, no treatment modalities treat bacterial overgrowth and increase motility. Erythromycin is an oral antibiotic that has been used as a prokinetic agent and has the potential to work on both aspects of HE.

Erythromycin was studied in a randomized, controlled, double blind trial in patients with HE. This study provided head-to-head comparison between erythromycin and neomycin in patients with cirrhosis who presented with HE. Thirty patients were randomized to receive either 1000 mg neomycin or 250 mg erythromycin four times daily. All patients were managed with the same care regarding diet and treatment of precipitating factors. The primary endpoint was the number of in-hospital days and was analyzed on an intent-to-treat basis.

The study groups did not differ in HE etiology, severity, or laboratory characteristic. The only significant differences between the treatments were a reduction in ALT levels (3.20 ± 8.54 U/L vs. 3.71 ± 7.12 U/L, p = 0.026) and fewer in-hospital days (median 3.0 days, IQR 2.25-4.00 days vs. 5.0 days, 3.25-11.25 days, p=0.032). There was also a significant correlation between hospital days and Glasgow Coma Scale scores (p=0.007), HE Index scores (p=0.015), HE grade (p=0.028), and C-reactive protein levels (p=0.015). All thirty patients finished the study, and no adverse effects were attributed to the test medications. The authors concluded that the use of erythromycin in HE patients decreased hospitalization duration and decreased ALT level compared to neomycin. However, the small number of patients and the severity of the patients in the study (20 patients were HE grade ≥2) limit the generalizability of the results.

CONCLUSION: In patients with cirrhosis presenting with hepatic encephalopathy, a medication with the ability to treat both the bacterial overgrowth and the decreased intestinal motility would be beneficial. Erythromycin, along with its antibiotic uses, has been used as a prokinetic agent. In this study, use of erythromycin resulted in shorter hospital stays and reduced ALT levels compared to neomycin. Larger studies are needed to further investigate these findings.


By Brent Dion, Pharm.D. Candidate
Enzalutamide (Xtandi®) in Prostate Cancer after Chemotherapy

Prostate cancer is an androgen-dependent disease with a high occurrence of progressive resistance to current antiandrogen therapies.\(^1\) Recently completed preclinical models of prostate cancer have suggested that continued disease progression is attributable to androgen-receptor signaling, due to androgen receptor over-expression. Enzalutamide (Xtandi®; formerly MDV3100) is an androgen-receptor-signaling inhibitor that inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment. It was granted approval on August 31, 2012 by the FDA.\(^2\) This new medication has a greater affinity for the androgen receptor with no agonistic effects, which makes enzalutamide distinct from other currently available antiandrogen agents. Enzalutamide is indicated for patients who have received and failed a docetaxel-containing regimen for castration-resistant prostate cancer.\(^2\) Approval was based on a phase I/II study and the phase III AFFIRM.\(^2\)

The phase I/II study enrolled patients with a histologically confirmed diagnosis of progressive castration-resistant prostate cancer.\(^3\) A total of 140 subjects were enrolled and received dosages of 30 mg (n=3), 60 mg (n=27), 150 mg (n=28), 240 mg (n=29), 360 mg (n=28), 480 mg (n=22), and 600 mg per day (n=3). The primary objective was to identify the safety and tolerability (including maximum tolerable dose) of enzalutamide. Antitumor effects occurred at all doses with significant androgen receptor blockade at doses from 60 mg to 480 mg per day (range 20-100%). However, the maximum tolerable dose over an extended period of time, defined as ≥28 days of continuous treatment, was 240 mg/day. The most common grade 3/4 adverse event was dose-dependent fatigue (11% of patients), which resolved after dose reduction. Due to the demonstrated efficacy and safety of enzalutamide in this patient population, the phase III AFFIRM trial was performed.\(^1\)

The AFFIRM study was a randomized, double-blind, placebo-controlled trial that was conducted at 156 sites in 15 countries.\(^1\) One thousand, one hundred and ninety-nine men with progressive castration-resistant prostate cancer who had been previously treated with docetaxel were recruited. Subjects were stratified in a 2:1 ratio to enzalutamide 160 mg orally once daily or matching placebo groups according to disease progression and severity using the Eastern Cooperative Oncology Group (ECOG) performance status. The primary endpoint was overall survival, defined as the time to death due to any cause. Secondary endpoints included measures of response and progression. Baseline demographics were similar between both groups with no significant differences. A predefined interim analysis revealed that enzalutamide treatment reduced the risk of death by 37% compared to placebo (HR 0.63; 95% CI, 0.53-0.75; p<0.001). Study subjects were unblinded after the interim analysis. The placebo group was offered the enzalutamide, and monitoring was continued. Mean duration of treatment was 8.3 months and 3.0 months in the enzalutamide and placebo groups, while median overall survival was 18.4 months (95% CI, 11.3-15.8), respectively. The overall survival benefit was consistent across all subgroups, and enzalutamide was superior to placebo in all secondary endpoints (p=0.001).\(^1\)

The rate of adverse events in the AFFIRM trial was similar between the two groups; however, the incidence of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache was higher in the enzalutamide group than placebo.\(^2\) Grade 3 or higher adverse events were more frequent in the placebo group (53.1%) than in the enzalutamide group (45.3%). The median time till the first adverse event was 12.6 months and 4.2 months, respectively. Five (0.6%) subjects in the enzalutamide group experienced seizures; four of these subjects had predisposing conditions or concomitant treatments for seizure. The authors concluded that enzalutamide increased the survival time of men with castration-resistant prostate cancer.\(^2\)

The usual dose of enzalutamide is 160 mg (four 40 mg capsules) orally once daily with or without food.\(^2,4\) Because of the increased incidence of seizures in enzalutamide-treated patients in the AFFIRM trial, enzalutamide may lower the seizure threshold in patients who are already predisposed to seizure.\(^2\)

Enzalutamide significantly improved the mortality in men with metastatic castration-resistant prostate cancer who were previously treated with a docetaxel-containing regimen compared to placebo. A multinational study of enzalutamide in chemotherapy-naïve patients with progressive metastatic prostate cancer is currently ongoing, with an expected completion date of September 2014.\(^5\)

**REFERENCES:**


**By Alex Pfeiffer, PharmD Candidate**
Vitamin K antagonist therapy is considered standard oral anticoagulation treatment and requires monitoring of INR to determine if patients are in therapeutic range. Patients outside the therapeutic range are at risk for developing a clot or a bleed depending if they are below or above the desired range. Eliquis® (apixaban) is a new oral anticoagulant that works as a direct factor Xa inhibitor and requires no laboratory monitoring. Currently, apixaban is approved to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation. In the following trials, apixaban was first compared to aspirin in patients who did not qualify for vitamin K antagonist therapy and to the current standard of therapy, warfarin. Apixaban 5 mg twice daily was compared to aspirin in a double-blind, double-dummy, randomized controlled trial. Patients with documented atrial fibrillation and a low risk of bleeding were randomized to receive either apixaban or aspirin and were followed for an average of 1.1 years. The dose of aspirin ranged from 81-324 mg daily depending on the discretion of the investigator. A total of 5599 patients were included in the trial. The primary efficacy outcome was the occurrence of stroke or systemic embolism, and the primary safety outcome was occurrence of major bleeding. The study was terminated early as investigators found patients treated with apixaban were significantly less likely to have stroke or systemic embolism compared to those taking aspirin (p = 0.000002) in the interim analysis. The final data was collected three months after the termination of the study. There were 51 patients in the apixaban group who experienced the stroke or systemic embolism compared to 113 of patients taking aspirin (HR 1.13, 95% CI 0.74-1.75; p = 0.57). The most common adverse event was bleeding, and there was no significant difference between the two groups. The authors concluded that, for patients who could not take vitamin K antagonist therapy, apixaban significantly decreased stroke risk without an increased risk of bleeding compared to aspirin. Limitations of this study include the variable aspirin dosing and the early termination of the trial which may overestimate the benefit of apixaban treatment.

In a second randomized, double-blind, double-dummy trial, the safety and efficacy of apixaban was compared to warfarin in patients with atrial fibrillation or atrial flutter. A total of 18201 patients were randomized to receive either apixaban 5 mg twice daily or warfarin. The dose of warfarin was adjusted for patients to have an INR between 2.0 and 3.0. Follow up was an average of 1.8 years. The primary efficacy endpoint was the incidence of stroke or systemic embolism and the primary safety endpoint was the occurrence of major bleeding. The primary efficacy outcome occurred in 212 patients in the apixaban group and 265 patients in the warfarin group (p < 0.001 for noninferiority). Major bleeding occurred in both groups, but significantly fewer patients in the apixaban group reported this complication (p < 0.001). The most common adverse event was bleeding, but there were no significant differences between the two groups in the rates of adverse events. The authors of the study concluded that apixaban was superior in preventing stroke and blood clots compared to warfarin. However, this was a noninferiority study and the study results support that apixaban is noninferior, not superior, to warfarin in this patient population. Study patients had an average age of 70 years and only 35% were women, so these results may not be extrapolated to other populations.

To prevent stroke and clots in patients with atrial fibrillation, apixaban should be dosed at 5 mg twice daily. A dose adjustment to 2.5 mg twice daily is recommended in patients with impaired renal function who are either ≥80 years or weigh ≤60 kg. Adverse events reported with this medication include bleeding and hemorrhage. Hypersensitivity reactions to apixaban have also been reported. Patients should monitor themselves for these potential adverse events and report any unusual findings to their provider.

Apixaban has shown efficacy in preventing stroke and clots in patients with nonvalvular atrial fibrillation. Its advantage compared to standard therapy is that it requires no laboratory monitoring. Apixaban currently has one approved indication, and more studies are being done to evaluate the use of apixaban in other conditions requiring anticoagulation.

By Alexis Anderson, PharmD Candidate

REFERENCES:
Academic Entitlement in Pharmacy Education

Academic entitlement is generally defined as an attitude that a student should receive high grades or preferential treatment without investing significant time or effort. Published literature is filled with accounts of disappointment resulting from students’ consumeristic view of their own education. Lack of personal responsibility was first described in medical students and centered around five facets. First, that knowledge is a right and should require minimal exertion. Entitled students typically expect to be catered to throughout their higher education. Commonly expected is an education that is convenient and requires little personal effort. Second, instructors should provide all the necessary information and guidance required. Third, the instructor, not the student, is responsible for failure or success. Faculty members often cite a lack of personal responsibility as a core characteristic for entitled individuals. Fourth, students should receive equal recognition regardless of individual effort. Fifth, aggressive confrontations are acceptable if expectations are not met. These attitudes also stem from student consumerism. This is the idea that the student is an education consumer and employs the “customer is always right” position. Consumeristic students often have statements like, “I pay $X in tuition, I deserve Y treatment.”

Many of factors leading to the feeling of academic entitlement are personal in nature. Published studies have found that this outlook is more prevalent in males than females and may correlate with low self-esteem. Narcissism is also cited as a characteristic of these individuals. The millennial generation (1980-2000) has been accused of being the most narcissistic in recent history, although this may be due to older generations’ tendency to describe subsequent generations as arrogant or disrespectful. The idea of outside forces influencing success or failure results in students less inclined to work hard for their success. Parental over-engagement and pressure to succeed is also common.

Personal factors are not the only culprits leading to this sense of entitlement. Society also plays a large role in academic entitlement. The rise in for-profit higher education establishments increases a student’s options for advancement. If a student is not happy, they can simply take their tuition dollars elsewhere, leading to establishments catering to students to improve retention. The decline in state funding also increases institutional competition. For example, a degree from a professional school may be marketed as a means to a lucrative career placing the emphasis on an economic end rather than education.

An important question is the implication of entitlement/consumerism on pharmacy education. Grade inflation is perhaps one of the most significant possible results. Professors may be inclined to meet student demands to avoid poor evaluations, which creates unprepared students. Placating students may also lead to student incivility, which manifests as sarcastic remarks, arguing, talking, tardiness, or cell phone use, which affect classroom morale. Academically entitled students may be aggressive, obtrusive, or empowered to make demands of the professor. All of this can lead to professors tailoring education because of the fear of reprisal in evaluations. Cynicism toward individual students or the entire pharmacy education process may result from faculty not feeling valued or respected.

Based on these implications, some recommendations can be made for pharmacy education professionals. First, revise recruitment and admissions practices. Instead of promoting pharmacy education as a means to a lucrative future, focus the recruiting message toward the pharmacist’s role as an accessible healthcare professional. Required skill sets should be highlighted at the outset and should reflect the maturation of pharmacy from a drug-centered profession to a patient-centered one. Pre-pharmacy interviews should be one-on-one without the involvement of parents. Using multiple mini-interviews can help gauge altruism, empathy, self-awareness, and commitment to care. Revise instructor evaluation so that student input is only one piece of the process. Teaching portfolios, peer evaluations and professional development in the areas of emphasis should also be included in the instructor evaluation process. Lastly, increasing student accountability through milestone assessments helps evaluate the student’s ability to integrate learning over time.

In summary, personal and societal factors help breed academic entitlement and student consumerism. Entitled students want to control their education leading to conflicts with faculty and deficits in education quality. Although academic entitlement is a likely detriment to the education system, steps can be taken to alleviate the problem. It must be noted that discussion on this topic is mostly subjective and anecdotal, which necessitates future research and studies in pharmacy education settings.


By Brent Dion, Pharm.D. Candidate
Acute mountain sickness (AMS) is associated with hypobaric hypoxemia, and a high altitude headache (HAH) is required for diagnosis. Prior studies assessing the prophylactic treatment of AMS suggest there is an inflammatory aspect that nonsteroidal anti-inflammatory drugs (NSAIDs) are capable of treating. Ibuprofen is an inexpensive, over-the-counter NSAID that may be an appropriate alternative to the current standard of therapy acetazolamide. However, the analgesic properties of ibuprofen may be masking the HAH required to diagnose AMS.

This randomized, double-blind study was conducted to compare ibuprofen to placebo in preventing AMS and HAH. Healthy non-Nepali males and females, 18 to 65 years of age who were traveling between either of two villages (4380 m/4328 m) to the summit (4928 m) of Mount Everest, were enrolled between October to November 2009. Symptoms of AMS were self reported using the Lake Louise AMS Questionnaire (LLQ) and visual analog scale (VAS). Potential subjects who were excluded had exhibited >2 AMS symptoms per the LLQ, had an acute infection, had slept above 4500m, or had recently taken NSAIDs or acetazolamide. Study subjects were sequentially randomized and given study medication (600 mg ibuprofen or visually identical placebo) with instructions to take one dose three times daily with a minimum of three doses prior to beginning the ascent. Compliance was defined as traveling from baseline to the summit, missing fewer than two doses, and abstaining from non-study medication. LLQ and VAS scores were taken the night of arrival to the summit and the morning after arrival. A total of 294 subjects were enrolled. One hundred eleven either broke protocol (n=49) or were lost to followup (n=62), which resulted in 183 subjects completing the study (IBU: n=110; placebo: n=73). The primary endpoint was the incidence of AMS per LLQ at study’s end. Secondary endpoints included AMS severity, HAH severity and incidence per LLQ and VAS, and pulse oximetry readings (SpO₂).

There was no statistically significant difference demographically between the groups. In the intent to treat analysis, ibuprofen treatment resulted in statistically significant benefit verses placebo in the incidence of HAH, AMS, severity of HAH, and endpoint SpO₂; however, in the compliant subpopulation, statistical significance in all categories was lost. This was theorized to be due to the loss of the sickest subjects requiring further treatment. Relatively few side effects were experienced (n=11).

**CONCLUSION:** Ibuprofen was effective in treating AMS in the intent-to-treat population. Limitations of the study include the potential for subjects to be partially acclimated at baseline and the possibility that the analgesic properties of ibuprofen may have masked the cerebral swelling of AMS.


By Alex Pfeiffer, Pharm.D. Candidate