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In this Issue...

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Varenicline (Chantix™; Champix™): A New Aid for Smoking Cessation

Learning Objectives:

1. Present an overview of efficacy studies of varenicline used in the treatment of tobacco dependence.
2. Explain the mechanism of action of varenicline in smoking cessation.
3. Identify patients for whom varenicline dose adjustment is needed.
4. List potential varenicline adverse effects.
5. Highlight the extent of the causal relationship between smoking, cancer and other diseases.

Introduction

According to the U.S. Surgeon General's 2004 Report, evidence is sufficient to infer a causal relationship between cigarette smoking and the following diseases: bladder cancer, cervical cancer, esophageal cancer, kidney cancer, laryngeal cancer, leukemia, lung cancer, oral cancer, pancreatic cancer, stomach cancer, abdominal aortic aneurysm, atherosclerosis, cerebrovascular disease, coronary heart disease, chronic obstructive pulmonary disease, pneumonia, respiratory effects in utero, respiratory effects in childhood and adolescence, respiratory effects in adulthood, fetal death and stillbirths, reduced fertility in women, low birth weight, pregnancy complications, cataracts, hip fractures, low bone density, and peptic ulcer disease.[1] The list of diseases that the evidence is sufficient to infer a causal relationship has grown so extensive that the Surgeon General reports that smoking affects nearly every organ of the body. In the United States alone, an estimated 438,000 or 1 of every 5 preventable deaths occur each year as a consequence of smoking.[2, 3]

Smoking cessation is important not only for the health of the smoker but for nonsmokers as well. Fifty different carcinogens have been identified in the smoke exhaled by smokers and burning tobacco.[4] Secondhand smoke has been positively linked to lung cancer, coronary heart disease and sudden infant death syndrome.[4] In 2005, an estimated 3,000 nonsmokers died from lung cancer, 46,000 from coronary heart disease and 430 from sudden infant death syndrome, all linked to exposure of secondhand smoke.[4] People living with a smoker have a 20-30% greater chance of lung cancer and a 25 to 30% increased risk of coronary heart disease.[4] No level of exposure to secondhand smoke is considered risk-free.[4]

Therapy options

The odds are against the person who says they are going to "quit on their own" as self-help methods have been shown to be ineffective when trying to stop smoking.[5] Counseling, behavioral therapy, and pharmacotherapy have been proven effective in helping smokers kick the habit.[5] Research suggests that a combination of pharmacotherapy and counseling may offer the best chance for success.[6] Bupropion sustained-release (SR), nicotine gum, nicotine inhaler, nicotine nasal spray and nicotine patch are considered first-line therapies for smoking cessation.[6] Clonidine and nortriptyline have also been effective and may be used if first-line therapies do not work or are incompatible.[5, 6]

In 2006, varenicline, a new molecular entity with a new pharmacologic mechanism, was approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Evaluation Agency (EMEA) as an aid to smoking cessation under the trade names Chantix™ and Champix™.

Mechanism of Action

The nicotine dependence that often accompanies cigarette smoking is considered to be a consequence of genetic susceptibility influenced by environment.[7] Nicotine dependence begins with the binding of nicotine to nicotinic acetylcholine receptors (nAChRs) in the central nervous system.[8] The withdrawal symptoms smokers experience when trying to quit are thought to be related to low dopamine levels in the mesolimbic area of the brain due to the lack of nicotine binding to nAChRs.[9] In developing varenicline, investigators at Pfizer based their research on the belief that nicotine dependence in part, results from nicotine binding to α4ß2 neuronal nAChRs resulting in the release of dopamine in the nucleus accumbens and prefrontal cortex.[10] Varenicline is a partial neuronal nicotinic receptor agonist with high affinity for the α4ß2 neuronal nicotinic receptor subtype acting like nicotine in inducing a moderate and sustained release of mesolimbic dopamine.[11] By antagonistically competing with nicotine for receptor sites, varenicline may also reduce the satisfaction or reward derived from smoking.[12]

Efficacy

A Cochrane evidence-based review based on 4 published[13-16] and 1 unpublished randomized smoking cessation trials and 1 relapse prevention trial[17] concluded that varenicline treatment increased the odds of quitting by 3 times, compared to placebo, and was safer and more effective than bupropion.[9] There were nearly 5000 participants in these trials, of which 2451 patients received varenicline.[9] Mild to moderate nausea that subsided over time was the most common side effect in varenicline treated patients. Further independent comparison trials of varenicline with placebo, bupropion and nicotine replacement therapy were recommended as all the published trials reviewed had been funded by Pfizer.[9]

Results from 30 clinical trials and 3 then ongoing trials were submitted by Pfizer to the FDA with the new drug application for Chantix™.[12] Six controlled clinical efficacy trials submitted to the FDA by Pfizer provided evidence of efficacy of varenicline.[12] Analysis of evidence of safety and efficacy of varenicline focused on 5 randomized controlled clinical trials involving varenicline treatment for 12 weeks or more.[12] In these trials, 40-51% of varenicline treated patients achieved the 4-week Continuous Quit Rate primary efficacy criterion compared to 30% of bupropion SR (Zyban®, GlaxoSmithKline) patients and 12-18% of placebo patients.[12] Because of the substantial evidence of efficacy and superiority to bupropion SR and placebo, varenicline was given priority review status by the FDA.[12]

Inclusion and exclusion criteria were similar across all the studies. The average participant in these studies was a white male or female, 43-years of age who had smoked 25 years and smoked 21 cigarettes per day. Of note, 79-95% of the subjects in these studies were white.[12] While not uncommon for clinical trials, the exclusion criteria were extensive and included anyone with diabetes, history of seizures, history of cancer, cardiovascular disease, uncontrolled hypertension, history of clinically significant allergic, hematologic, renal, endocrine, pulmonary, hepatic, gastrointestinal or neurologic disease, alcohol or other drug abuse, major depression, history of panic disorder, psychosis or bipolar disorder, history of anorexia or bulimia and anyone less than 18 years of age.[12] The efficacy of varenicline in the types of patients excluded is not likely to be substantially different, although that is technically unknown at this time. The potential safety issues of the use of varenicline are perhaps more relevant in these excluded groups and should be watched closely for new reports of adverse events.

Varenicline titrated to 1 mg twice daily (BID) for 12 weeks was the most common dose but varenicline 0.3 mg once daily (QD), 0.5 mg BID and 1.0 mg QD were also studied.[12] Bupropion SR standard dosing, titrated to 150 mg BID and placebo were the comparators. Participants were instructed to quit smoking on day 7 of treatment. Abstinence rates were self-reported and confirmed by an exhaled carbon monoxide (CO) test of CO ≤ 10 ppm at weekly clinic visits during the treatment period. Besides the study medication, subjects were given an educational booklet on smoking cessation and were provided with up to 10 minutes of counseling at each weekly office visit. The 4-week Continuous Quit Rate (CQR) for the last 4 weeks of treatment was the primary efficacy measurement. Subjects who completed 12 weeks of therapy and had stopped smoking were often then entered into a 40-week non-treatment follow-up phase for weeks 13 to 52.

In the *FDA Approval Package* for varenicline, studies A3051028 and A3051036 were considered the pivotal Phase III studies comparing varenicline 1 mg BID to bupropion SR 150 mg BID and placebo.[12] Study A305103612 was funded by Pfizer and published by Jorenby et al.[14] Jorenby et al reported that 23% of varenicline subjects remained abstinent at week 52 versus 10.3% of placebo subjects and 14.6% of bupropion SR subjects ($p < .001$).[14] Study A305102812 was also funded by Pfizer and published by Gonzales et al.[13] Gonzales et al[13] reported a continuous abstinence rate at week 52 for 21.9% of varenicline subjects, 8.4% of placebo subjects, and 16.2% of bupropion SR subjects ($p = .057$). The 4-week CQR for varenicline, confirmed by reviewers for the FDA, was superior to placebo and bupropion SR and virtually the same for both study A3051028 and A3051036: 44% for varenicline, 18% for placebo and 30% for bupropion SR ($p < .0001$).[12] FDA reviewers concluded that the pivotal Phase III studies of varenicline provided "substantial evidence of efficacy of varenicline 1 mg BID as an aid to smoking cessation, and substantial evidence of the 1-mg BID dose's superiority to Zyban®…"[12]

Study A305103512, funded by Pfizer and included in the *FDA Approval Package* for varenicline, was also published by Tonstad et al.[17] Study A3051035 was a maintenance of efficacy study that examined whether 24 weeks of varenicline 1 mg BID increased long-term smoking abstinence.[12, 17] After a 12 week open-label phase in which all subjects received varenicline 1 mg BID, participants that had not smoked in the past 7 days were randomized to an additional 12 weeks of varenicline 1 mg BID or placebo. This was equal to ~63% (1210/1927) of the patients that had received open-label varenicline. This study also included a non-treatment follow-up of smoking status up to week 52. The primary efficacy measure was the continuous abstinence rate from week 13 through week 24. The long-term quit rate at week 52 was a secondary efficacy measurement. Tonstad et al reported a 70.5% continuous abstinence rate at week 24 for varenicline subjects versus 49.6% of those receiving placebo ($p <.001$).[17] At week 52, the long-term continuous abstinence rate was 43.6% for varenicline versus 36.9% for placebo ($p = .02$). FDA analysis of this same data submitted by Pfizer confirmed the results of Tonstad et al with little discrepancy.[12] Based on this study, Pfizer and FDA reviewers concluded that 6 months of varenicline treatment is better than 3 months for maintaining smoking abstinence.[12]

While the labeling for varenicline recommends varenicline 1 mg BID, studies A3051002, A3051007 and A3051016 showed that lower doses were also effective with fewer dose-dependent side effects.[12, 18] Reviewers for the FDA noted that "incremental efficacy" was gained by using the higher dose as well as a higher number of adverse events.[12] Studies A3051002 and A3051007 were also funded by Pfizer and published by Nides et al[15] and Oncken et al[16], respectively. The CO confirmed week 4-7 quit rate reported by Nides et al was 14%, 25% ($p = .002$), 31% ($p < .001$) and 41% ($p < .001$) for placebo, varenicline 0.3 mg QD, 1 mg QD and 1 mg BID, respectively.[15] Oncken et al found that titrated or non-titrated varenicline 0.5 mg BID or 1 mg BID were all more effective than placebo ($p < .001$).[12,16] The 4-week CQR for weeks 9-13 for the 0.5 mg BID non-titrated and titrated groups were 47.3% ($p < .001$) and 40.8% ($p < .001$), respectively and 44.2% ($p < .001$) and 54.6% ($p < .001$) for the 1.0 mg BID non-titrated and titrated groups respectively, versus 11.6% for the placebo group.[16]

Study A3051016 was a flexible dosage study.[12] Subjects took varenicline 0.5 mg QD or placebo for 3 days, then 0.5 mg BID for 4 days. After day 7, subjects were allowed to decrease or increase their own daily dose to a minimum of varenicline 0.5 mg QD to a maximum of 1 mg BID for a total of 12 weeks. Subjects could adjust their dose as often as they liked and for whatever reason, e.g. side effects or lack of efficacy. During week 2 of treatment, 62% of the varenicline group and 75% of the placebo group had self-titrated to the maximum dose but in each subsequent week, the percentage of subjects using the maximum varenicline dose fell with a low of 29.46% by week 12.[12] This suggests that given the choice, people would not choose the 1 mg BID dose recommended by Pfizer. The pooled 4-week CQR for Weeks 9-12 was 40% for varenicline subjects versus 15% for placebo subjects ($p < .0001$).

Similar efficacy and safety results for varenicline were reported for Japanese, Korean and Taiwanese smokers in two randomized controlled trials.[19, 20] Tsai et al[20] found a 59.5% 4-week CQR for varenicline 1 mg BID treated patients verus 32.3% for the placebo group at the end of 12 weeks ($p < .001$). The continuous abstinence rate 12 weeks post-treatment was 46.8% for varenicline patients and 21.8% for placebo patients ($p < .001$). Nakamura et al[19] reported significantly higher continuous abstinence rates after 12 weeks of therapy for all doses of varenicline compared to placebo: varenicline 0.25 mg BID (54.7%), 0.5 mg BID (55.5%), 1 mg BID (65.4%) and placebo (39.5%) ($p < .001$).

Safety

Mild to moderate nausea was reported in 28-52% of varenicline treated patients compared to 8-15% of placebo patients and 7-13% of bupropion patients.[13-16] A dose response relationship for nausea was noted, with titration and dosage levels affecting both the severity and incidence.[15, 16] Besides nausea, some gastrointestinal and psychiatric adverse events appeared to be dose related.[21] Insomnia, abnormal dreams, and headache were other notable side effects reported. Electrocardiograms collected during eight Phase II/III efficacy studies and twenty-four Phase I studies indicated no QT prolongation potential for varenicline.[21] Atrial fibrillation, chest pain, transient ischemic attack and cataracts were the only serious adverse events that were possibly or probably attributed to treatment with varenicline.[9]

The combined exposure response analysis of studies A3051007, A3051028, A3051036, and A3051037 showed that the incidence of nausea was related to gender and dose of varenicline.[21] These studies included titrated and non-titrated subjects. For females the incidence of nausea was 13% (57/423) for placebo, 18% (23/130) for 0.5 mg BID and 42% (242/582) for 1.0 mg BID.[21] For males, the incidence of nausea was 7% (35/509) for placebo, 10% (13/123) for 0.5 mg BID and 22% (133/618) for 1.0 mg BID.[21] Females appeared to be more susceptible to nausea than males.[12] Women who do not tolerate the 1 mg BID dosing may benefit by reducing the dose to 0.5 mg BID.[21]

A 5-day psychotic relapse was attributed to varenicline in a 42-year old schizophrenic woman after she started taking varenicline 2 mg.[22] The woman had been maintained on thiothixene for 17 years with periodic psychotic episodes each year. The woman's psychotic episode coincided with the initiation of varenicline. The psychotic episode remitted after 5 days. Varenicline was then stopped and she had no further exacerbations. Varenicline was also reported to induce a manic episode in 63-year old man with bipolar disorder who had been stable the previous 5 years while receiving valproic acid.[23] One week after starting varenicline 1 mg BID he started experiencing manic symptoms. The patient was admitted to the hospital and varenicline was discontinued. He continued to receive valproic acid and olanzapine was started. Within 1 week, he was euthymic with no psychotic or manic symptoms.

Weight gain while quitting smoking is often a concern of many smokers. Weight gain was noted during the clinical trials but was not necessarily related to the study drug or comparators. The weight gain in varenicline subjects ranged from 0.8 kg to 3.62 kg, versus 1.51-4.0 kg for placebo and 1.32-1.88 kg for bupropion SR.[13-17]

Pharmacokinetics

Clinical Pharmacology reviewers for the FDA based their population pharmacokinetic evaluation on plasma varenicline data pooled from four Phase I, two Phase II and three Phase III studies involving a total 1878 smokers.[21] Of these 1878 subjects, 954 were male, 924 female, 81% Caucasian, 12.6% Black, 1.2% Asian and 5.2% other ethnic origins with an age range of 18-76 years. Reviewers for the FDA determined that no dose adjustment for varenicline is required based solely on age, gender, race, body weight or hepatic dysfunction.[21] In a randomized trial comparing a single dose of varenicline 0.5 mg or 1.0 mg or placebo in 22 adolescent smokers, varenicline exposure, as assessed by AUC (0-∞) and renal clearance of varenicline, was comparable to that of an adult population.[21]

Following repeated daily or twice daily dosing, steady state levels of varenicline are reached after 4 days with a 2.5-3 fold accumulation, compared to a single dose.[21] Pharmacokinetics of varenicline were not affected by administration in the morning versus the evening.[21] Administration with food did not change the bioavailability of varenicline.[21] The elimination half-life of varenicline is ~20 hours. Varenicline is absorbed with a Tmax of ~3 hours with 10-20% plasma protein binding.[21]

Varenicline undergoes very little metabolism and is excreted mainly by the renal route.[21] Renal function, specifically glomerular filtration rate (GFR), does significantly influence varenicline pharmacokinetics, and a dose reduction is recommended in patients with severe (estimated creatinine clearance <30 mL/min) and end-stage renal disease.[18, 21] Results of pharmacokinetic study A3051008 showed a 1.5-2.7 fold increase in Cmax and AUC in patients with moderate (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min) to severe to end-stage renal disease compared to healthy subjects at steady state.[21] Based on pharmacokinetic studies, varenicline clearance is predicted to decrease from 10.4 L/hr for a subject with normal renal function and GFR = 100 mL/min, to 4.4 L/hr for a subject with severe renal impairment and estimated GFR = 20 mL/min.[21]

Drug Interactions

Small drug interaction studies with varenicline were done with cimetidine, metformin, digoxin, warfarin, bupropion SR and transdermal nicotine. Study A3051010, a single-dose, non-randomized study of 12 healthy smokers, 19-41 years of age, found that co-administration of cimetidine 300 mg four times a day (QID) and varenicline 2 mg resulted on average in a 29% increase in plasma varenicline exposure.[21]

Thirty healthy, predominantly white, smokers participating in study A3051038, a randomized, open-label, crossover study, received varenicline 1 mg BID or metformin 500 mg BID or varenicline 1 mg BID and metformin 500 mg BID. No significant differences were noted in the pharmacokinetics of varenicline or metformin.[21]

An 11.3% increase in renal clearance of digoxin with no apparent effect on systemic digoxin exposure was found in study A3051031.[21] Eighteen healthy smokers, 18-55 years of age, received concomitant digoxin 0.2 mg QD and varenicline titrated to 1 mg BID for 14 days in a randomized, placebo-controlled crossover study. Overall, it was determined that varenicline had no effect on the steady-state pharmacokinetics of digoxin in healthy smokers.[21]

The effect of single dose warfarin on steady-state varenicline was examined in study A3051032.[21] Twenty-four healthy smokers, 18-55 years of age, were randomized to receive placebo or varenicline 1 mg BID for 13 days with concomitant warfarin 25 mg administered on day 8. Varenicline had no effect on the single-dose pharmacokinetics or pharmacodynamics of racemic warfarin in healthy smokers, however, the effect of varenicline on the pharmacokinetics and pharmacodynamics of multiple dose warfarin is not known.[21]

Forty-two healthy smokers participated in study A3051034, a randomized, 2-way crossover, for approximately 7 weeks.[21] The study evaluated the pharmacokinetics of co-administered bupropion SR and varenicline. Varenicline 1 mg BID had no clinically relevant effect on the pharmacokinetics of bupropion SR150 mg BID. Study A3051033 was a randomized, placebo-controlled crossover study in which 24 smokers using 21/mg/24 hr nicotine transdermal patches also received varenicline 0.5 mg QD to 1 mg BID or placebo during two 14 day periods.[21] Transdermal nicotine and varenicline were found to be safe when administered together with no clinically relevant effects on the pharmacokinetics of transdermal nicotine.

A possible interaction between varenicline and immediate-release amphetamine-dextroamphetamine, resulting in the ineffectiveness of varenicline, was reported in an 18-year old man with attention-deficit hyperactivity disorder.[24] After 1 week of varenicline he stopped smoking and was smoke-free for 17 days. During the same time, he had also been taking amphetamine-dextroamphetamine (Adderall®, Shire US Inc.) 15-30 mg daily. Forty-eight hours after increasing his dose of Adderall® to 30 mg twice daily, he again started smoking. With intensive counseling, a second attempt with varenicline was initiated while the patient remained on Adderall®. He was unable to stop smoking and stated that he did not feel the benefits of varenicline as he had in the beginning. The authors postulated that substances, such as amphetamines that increase dopamine concentrations in the CNS, may interfere with the efficacy of varenicline.

Dosing

The recommended dosing schedule for otherwise healthy smokers is varenicline 0.5 mg once daily on days 1-3, 0.5 mg twice daily on days 4-7 and then 1 mg twice daily for 11 weeks.[18] An additional 12 weeks of therapy is recommended to increase the long-term success rate in patients who have successfully stopped smoking after the initial 12 weeks of therapy. If adverse effects are a problem, the daily dose may be lowered temporarily or permanently.

No dosing adjustment is necessary for persons with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min) but it may be necessary in subjects with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min) if they do not tolerate the regular dose for healthy subjects.[18, 21] For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline 0.5 mg QD is the recommended starting dose and may be titrated to a maximum of 0.5 mg twice daily as needed. Varenicline 0.5 mg QD is the maximum dose for patients with end-stage renal disease or on dialysis.[18]

Safety and effectiveness of varenicline has not been proven for patients under 18 years of age, and the drug is therefore not recommended for anyone in that age group.

Conclusion

Nicotine dependence is a chronic disease, and relapses and remissions do occur.[25] When patients relapse or fail, healthcare workers should continue to encourage and assist their patients in their efforts to quit this preventable, life-threatening condition. Counseling alone, and combined with pharmacotherapy, has been proven effective in aiding smokers to quit, and should be a part of any smoking cessation attempt.[5] Counseling and weekly check-ins were an aspect of all the clinical trials of varenicline. Anyone starting a smoking cessation regimen be it varenicline, bupropion SR or nicotine replacement should not depend solely on the medication but utilize some sort of counseling or support. Advice on how to quit smoking is available at http://smokefree.gov and toll free in the U.S. at 1-800-QUIT-NOW (800-784-8669).[26] Realizing the necessity of counseling, Pfizer offers patients taking Chantix™ a 52-week support program through its GETQUIT™ Support Plan that offers a toll-free support hotline for up to 1 year (www.chantix.com).

Like most new drugs, the safety and effectiveness of varenicline in the general public is yet to be determined. A chief complaint of the efficacy studies is the lack of a diverse population, e.g. 79-95% of the patients were Caucasian. In the United States, in 2006, American Indians and Alaska Natives had the highest prevalence of smoking at 32.4% followed by 21.9% of non-Hispanic whites, 23.0% non-Hispanic blacks, 15.2% Hispanics and 10.4% Asians.[26] Persons with psychiatric illnesses are another population that was not represented in varenicline clinical trials. This population is known to have a high percentage of smokers with a low success rate in smoking cessation programs.[5] Studies in adolescents, an age group when smoking often begins, are also needed. Varenicline was shown to be superior to bupropion SR in several clinical trials but little or no evidence is available directly comparing varenicline to nicotine replacement.[13-17] The question of whether combining varenicline with other approved treatments for smoking cessation will safely increase the success rate is also yet to be answered.

Varenicline may be the newest FDA approved therapy for smoking cessation but research continues. Some day quitting smoking may be as simple as getting a shot in the arm. In fact, there are several new drugs in Phase I-III trials including a nicotine vaccine in Phase II trials that is hypothesized to induce antibodies that bind to nicotine and inhibit its actions.[27] Regardless of how it is accomplished, the more people that can "kick the habit" the more lives that will be saved.

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ASSESSMENT QUESTIONS

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Title of Educational Activity

VARENICLINE (CHANTIX™;CHAMPIX ™): A NEW AID FOR SMOKING CESSATION

NAME ____

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Social Security Number (optional)___________________

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I hereby certify that I have taken this test:

____

Signature/Date

(circle the correct answer)

1. According to the U.S. Surgeon General's 2004 Report there is enough evidence to infer a causal relationship between smoking and:
   a) cancer of the pancreas and the cervix
   b) reduced fertility in women and neonatal low birth weight
   c) atherosclerosis and coronary heart disease
   d) all the above

2. All of the following statements are true except:
   a) In 2005 in the U.S., 46,000 people died from coronary heart disease associated with passive smoke.
   b) Exposure to secondhand smoke has been linked to up to a 30 % increased risk of lung cancer and coronary heart disease.
   c) There is evidence of passive smoke causing pulmonary cancer, coronary heart disease and sudden infant death syndrome but no carcinogens have been identified in secondhand smoke.
   d) Approximately 500 cases of sudden infant death syndrome in the U.S. in 2005 were related to exposure to secondhand smoke.

3. Which one of the following is the recommended dose of varenicline for smoking cessation in healthy adult smokers?
   a) 1 mg twice a day for 12 weeks without titration
   b) 0.5 mg twice a day for 1 week followed by 1 mg daily for 11 weeks
   c) 0.5 mg daily for 3 days, followed by 0.5 mg twice a day for 4 days then 1 mg twice a day for 11 weeks
   d) 0.5 mg twice a day for 7 days then 1 mg twice a day for 11 weeks

4. The dose of varenicline should be adjusted in smokers with severe renal impairment. What is the maximum recommended dose for smokers with end stage renal disease on dialysis?
   a) 0.5 mg daily
   b) 0.5 mg twice a day
   c) 1 mg daily
   d) 0.25 mg daily

5. Which one of the following statements is true regarding smoking prevalence in the U.S. in 2006?
   a) Non-Hispanic Whites had the highest prevalence of smoking.
   b) Non-Hispanic Blacks had the lowest prevalence of smoking.
   c) American Indians and Alaska Natives had the highest prevalence of smoking.
   d) The estimated smoking prevalence among Asians is 30%.

6. Varenicline dose adjustment is recommended in smokers with moderate to severe renal dysfunction. According to reviewers for the FDA, the recommended dose of varenicline should also be adjusted in:
   a) elderly smokers with normal renal function
   b) female smokers
   c) overweight smokers
   d) none of the above

7. Mild to moderate nausea has been reported with varenicline. All of the following statements are true except:
   a) The incidence of nausea with varenicline is dose related.
   b) Varenicline induced nausea occurs more often in males.
   c) The severity of nausea induced by varenicline is dose related.
   d) Dose titration helps decrease the incidence and severity of varenicline induced nausea.

8. Which one of the following statements is true regarding varenicline drug interactions?
   a) In smokers, varenicline plasma concentrations decreased by approximately 10% when cimetidine was administered with varenicline.
   b) No clinically significant interaction was observed when varenicline was given together with either bupropion SR 150 mg BID or transdermal nicotine 21 mg/24 hr.
   c) Food decreases varenicline bioavailability.
   d) Adderall® (dextroamphetamine-amphetamine) is contraindicated in patients on varenicline therapy.

9. Which one of the following statements is not true regarding nicotine dependence and varenicline mechanism of action?
   a) Nicotine dependence is related to the binding of nicotine to nicotinic acetylcholine receptors in the nucleus accumbens and prefrontal cortex, causing release of dopamine.
   b) Varenicline is a complete neuronal nicotinic acetylcholine receptor agonist with high affinity for the $\alpha 4 \beta 2$ neuronal nicotinic receptor subtype.
   c) Varenicline induces slow, moderate and sustained release of dopamine from the mesolimbic area of the brain.
   d) Genetic factors have a role in nicotine dependence risk.

10. Serious side effects "possibly or probably" associated with the use of varenicline include all the following except:
    a) atrial fibrillation
    b) cataracts
    c) kidney stones
    d) transient ischemic attacks

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Forms should be mailed to:

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PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				Disagree
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Molecular Entities & Biologicals

FDA Approvals
August 2007 – October 2007

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name ***Trade Name*** **(Review Classification)**	**Sponsor** **(Approval Date)**	**Valid *IDIS* Drug Term** **Drug Number** **(*IDIS* Citations)**	**Indication/Use** **Dosage Form**	**Valid *IDIS* Disease Term** **Modified ICD-9-CM Number**
Ammonia, N-13 *Ammonia N 13* (S)	Feinstein (Aug. 23, 2007)	AMMONIA, N-13 78040186 (173 citations)	PET (Positron Emission Tomography) imaging in patients with CAD (Coronary Artery Disease) for evaluation of myocardial blood flow. Intravenous injection	Radioisotope Scan, Cardiovas 92.05
Doripenem *Doribax* (S)	Johnson and Johnson (Oct. 12, 2007)	DORIPENEM 8122945 (1 citation)	Complicated intra-abdominal and complicated urinary tract infections, including pyelonephritis. Injection	Infection, Kidney NEC 590. Peritonitis 567. Infection, Urinary Tract 599.0
Ixabepilone *Ixempra* (P)	Bristol Myers Squibb (Oct 16. 2007)	IXABEPILONE 10120214 (27 citations)	Breast cancer. Intravenous infusion	Neop, MGN-Female Breast 174.
Lanreotide Acetate *Somatuline Depot* (SO)	Beaufour Ipsen (Aug. 30, 2007)	LANREOTIDE 10120119 (145 citations)	Acromegaly. Subcutaneous injection	Acromegaly and Gigantism 253.0
Nilotinib *Tasigna* (O)	Novartis Pharma (Oct. 29, 2007)	NILOTINIB 10120856 (13 citations)	Chronic myeloid leukemia (CML). Oral capsule	Leukemia, Myeloid, Chronic 205.1
Raltegravir Isentress (P)	Raltegravir (Oct. 12, 2007)	RALTEGRAVIR 8180892 (8 citations)	Treatment of human immunodeficiency virus (HIV)-1 infection, in combination with other antiretroviral agents. Oral tablet	Syn-Acq Immune Deficiency 042.

Review Classification:
S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs
AA = Accelerated Approval
FT = Fast Track
P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease
BIO = Biological
O = Orphan drug

Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

Selected Bibliography

Doripenem
Rice LB. Challenges in identifying new antimicrobial agents effective for treating infections with Acinetobacter baumannii and Pseudomonas aeruginosa. *Clin Infect Dis.* 2006; 43:S100-S105. (*IDIS* Article Number 560246)
This review highlights problems of drug resistance in nosocomial infections caused by the two gram-negative pathogens, Acinetobacter baumannii and Pseudomonas aeruginosa. Doripenem is featured as a new antimicrobial with activity against both gram-positive and gram-negative organisms, as well as showing the lowest percent of drug resistant organism strains after use.

Ixabepilone
Perez EA, Lerzo G, Pivot X, Thomas E, et al. Efficacy and safety of ixabepilone (BMS-247550) in a Phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol*. 2007; 25:3407-3414. (*IDIS* Article Number 582369)
Safety and efficacy of ixabepilone were assessed in this Phase II case series study of 126 breast cancer patients who received the study drug in doses of 40 mg/m^2 in intravenous infusions over a 3-hour period on the first day of a 21-day cycle. Of the 113 patients who were assessable for response, investigators found the objective response rate was 11.5% (95% CI, 6.3%-18.9%) and 50% of patients achieved stable disease, while 14.3% achieved stable disease lasting at least 6 months. Side effects included peripheral sensory neuropathy (14%), fatigue (13%), myalgia (8%), and mucositis/stomatitis (6%).

Lanreotide Acetate
Attanasio R, Baldelli R, Pivonello R, Grottoli S, et al. Lanreotide 60 mg, a new long-acting formulation: effectiveness in the chronic treatment of acromegaly. *J Clin Endocrinol Metab.* 2003; 88:5258-5265. (*IDIS* Article Number 509883)
Ninety-two patients with acromegaly were included in this multicenter, open study in which lanreotide was given by intramuscular injection every 28 days for three injections, and was then individually tailored for each patient. After a median follow-up of 24 months (range, 6-48 months), investigators found insulin-like growth factor-I (IGF-I) was normalized in 65% of patients from 199 +/-8% to 87 +/-4% (given as a percentage of the upper limit of normal range), p<0.0001. Growth factor (GF) also decreased to less than 2.5 mcg/liter in 63% of patients, and to less than 1 mcg/liter in 25%, p<0.0001.

Nilotinib
Kantarjian H, Giles F, Wunderle L, Bhalla K, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med.* 2006; 354:2542-2551. (*IDIS* Article Number 564558)
In this Phase I non-randomized, dose escalation study, 119 patients with chronic or acute lymphoid leukemia resistant to treatment with imatinib received oral nilotinib in once daily doses of 50, 100, 200, 400, 600, 800, and 1200 mg, or twice daily doses at 400 and 600 mg. Results from the study showed that 13 of the 33 patients with blastic phase disease experienced a hematologic response and 9 had a cytogenic response, and of the 46 patients with accelerated phase disease, 33 had a hematologic response and 22 had a cytogenic response, while 11 of the 12 patients with chronic phase disease had a complete hematologic response. Side effects included myelosuppression, rash, and transient hyperbilirubinemia.

Raltegravir
Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a Phase II randomised controlled trial. *Lancet.* 2007; 369:1261-1269. (*IDIS* Article Number 572887)
This was a randomized, multicenter, triple-blind dose ranging study of 179 HIV patients whose disease had become resistant to at least one nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor. Raltegravir was given orally in doses of 200, 400 or 600 mg twice a day. Results assessed at 24 weeks showed that the mean change from baseline of the viral load in the 200 mg group was -1.80 (95% CI -2.10 to -1.50)log_{10} copies per ml, in the 400 mg group the change was -1.87(-2.16 to -1.58) log_{10} copies per ml, and in the 600 mg group it was -0.35 (-0.61 to -0.09) log_{10} copies per ml, with side effects similar to placebo in all groups.

Exciting News!

As you may have already noticed, full-text articles from 1995 and 1996 are now available in *IDIS*/Web. When you perform a search now, complete articles from these years are available for retrieval. Pre-1995 articles will be added in the near future. We are interested in finding out how valuable this is to you and how far back you usually go when conducting a search. Please let us know your thoughts by e-mailing a quick note to donna-brus@uiowa.edu. We appreciate your input on this subject as we strive to make our database the most useful tool for meeting your drug information needs.

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