Trends-in-Medicine

April 2005
by Lynne Peterson and Ed Susman

SUMMARY

The ASCPT meeting offered incremental but interesting new information on several drugs in development, including: Sanofi-Aventis's Ambien MR, MDS's transdermal fentanyl patch, Novartis's LAF-237 for diabetes, AstraZeneca's AZD-0865 (a potassium-competitive acid blocker that could be a first-in-class replacement for Nexium), Wyeth's desvenlafaxine-SR, and more.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS

March 3-5, 2005
Orlando, FL

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) is the largest scientific and professional organization serving the discipline of clinical pharmacology, and its annual meeting is an excellent opportunity to get a glimpse of various drugs in development. This year's meeting was no exception.

ASTRAZENECA

AZD-0865

Only rat and dog studies of this once-daily potassium-competitive acid blocker (P-CAB) were presented at ASCPT, but it is currently in Phase II, and first-in-man data will be presented in May 2005 at Digestive Disease Week (DDW). This is a follow-on to AstraZeneca's Nexium (esomeprazole) and Prilosec (omeprazole).

An AstraZeneca researcher said the company will seek an indication for the treatment of symptomatic GERD first, but eventually he believes AZD-0865 could replace Nexium. The key advantages of AZD-0865 over Nexium and Prilosec were described as:

- Faster onset of action.
- The full effect obtained after the first dose, so there is no build-up of effect over the first few days, as is the case with Nexium and Prilosec.

Researchers offered this information on AZD-0865:

- The minimum effect is not affected by repeat dosing.
- The maximum effect over a day is not dependent on the number of doses.
- In dogs (and in man) the onset of action is slightly greater with repeat dosing.
- Steady state (maximum effect) is reached in 2-4.5 hours.

Altana's soraprazan was described as the "main competitor." Soraprazan has a shorter half-life than AZD-0865 but may be able to be given at a higher dose. AstraZeneca researchers believe this is further ahead of AZD-0865, but suspect Altana may not be going forward with this drug and may have a different compound in development that is moving forward.

Exanta (ximelagatran)

A pharmacokinetic (PK) and pharmacodynamic (PD) study by AstraZeneca found that Exanta exposure was increased by co-administration with azithromycin (Pfizer's Zithromax) and, to a lesser extent, cefuroxime. Another PK-PD study found that Exanta was unaffected by amoxicillin, doxycycline, or ciprofloxacin.

BRISTOL-MYERS SQUIBB'S muraglitazar

A poster by Bristol-Myers researchers reported that this dual PPARα/γ agonist – in development to treat diabetes – does not affect the PK or PD of warfarin when the two drugs are administered concomitantly, and when a single dose of warfarin does not affect the steady-state concentrations of muraglitazar. A 10 mg dose of muraglitazar alone and with warfarin was reported to be safe and well-tolerated.

Another study found no PK interaction between muraglitazar 10 mg and fenofibrate 160 mg. Fenofibrate did not alter the PK of muraglitazar, and muraglitazar did not alter the PK of fenofibrate. Researchers concluded that co-administration of the two drugs is unlikely to result in clinically relevant PK drug-drug interactions.

CONJUCHEM'S DAC:GLP-1 (CJC-1131)

The company's GLP-1 clinical program was stopped due to excessive nausea and vomiting – described by a researcher as similar to that seen with Amylin's Exenatide (exendin). However, the drug was re-formulated and development resumed, and it is now in Phase II trials. A researcher said, "The way it is administered now is different. The company added a gel, which the company thinks has decreased the nausea by freeing the drug slower (delivering it slower)." CJC-1131 is administered either QD or once every two days.

A poster at ASCPT showed that adding metoclopramide did not decrease the nausea. A researcher described CJC-1131 as "promising," but wondered if it will succeed given the competition from Novartis's vildagliptin (LAF-237).

JERINI AG'S icatibant (JE-049)

This German pharmaceutical company presented a proof-of-concept poster on icatibant, a bradykinin B2 receptor antagonist to treat hereditary angioedema. The study found that icatibant was associated with:

- Rapid onset of symptom relief.
- Attacks of skin swelling and abdominal pain were shorter than without treatment.
- Rapid absorption after subcutaneous administration.
- Good safety and tolerability.

LILLY'S Cymbalta (duloxetine)

This drug was approved for depression, but Lilly withdrew the application for urinary incontinence because it appeared the FDA was going to turn it down, and the reason for the turndown was not clear. The posters at ASCPT did not shed any light on the reasons for this.

A Lilly-sponsored study looked at the co-administration of duloxetine and lorazepam, concluding:

- No PK interactions between the two drugs were observed.
- Steady-state duloxetine did not alter the amnesic effects of lorazepam.
- Objective (DSST) and subjective (alertness) sedation were detected with duloxetine on Day 4.
- Addition of lorazepam to steady-state duloxetine resulted in an increased number of reports of somnolence and postural tachycardia compared to lorazepam+placebo.
- Compared to lorazepam alone, the combination of duloxetine+lorazepam induced an increased sedation on subjective (alertness) and objective (DSST, MRT, and TRT) tests, with a peak effect at 3-6 hours on Day 5.
- Caution should be exercised when lorazepam and duloxetine are co-administered due to the potential for an increase in lorazepam-induced sedation.

Another study looked at combined duloxetine and fluvoxamine (Solvay's Luvox) dosing in CYP2D6 poor metabolizers. The study was done to assess duloxetine exposure and safety under the "worst case scenario" of maximal inhibition of both CYP1A2 and CYP2D6. Researchers reported that when the two drugs were administered together, duloxetine concentrations were substantially higher than when duloxetine was dosed alone, and metabolite concentrations were reduced, which is consistent with inhibition of metabolic enzymes responsible for their production. They also noted that CYP1A2 inhibition is the largest component of dual inhibition.

MDS PHARMA'S transdermal fentanyl patch

Researchers reported on a Phase I study that found this 100 µg/H transdermal fentanyl patch can safely be co-administered with 100 mg of oral naltrexone in healthy males. Oral naltrexone did not affect the PK of the fentanyl patch, and concomitant administration of the two drugs did not increase the opioid-induced adverse events. Most of the drug-related adverse events were due to mild patch irritation.

MDS's patch reaches peak steady state in ~72 hours, then plateaus. It is designed to be replaced every three days. The company is filing this as a 505(b)(2).

Researchers cited several advantages to this patch over the fentanyl patch already on the market, Johnson & Johnson's Duragesic:

1. Better adhesion to the body.
2. Drug delivery via membrane, so there is no leakage. The J&J patch is a reservoir patch.
3. Better control of drug release.
4. May be able to be used postoperatively, while the J&J patch can't.

MERCK'S L-791,515

The efficacy and tolerability of this next-generation Cox-2 inhibitor (at 50 mg and 100 mg) in treating postoperative dental pain were comparable to 400 mg ibuprofen. The 50 mg dose was the minimal dose providing maximal efficacy in this study. While this is a potential new Cox-2 inhibitor, the outlook is uncertain given the recent controversy over the cardiac safety of these drugs and the likely lengthy regulatory path for new agents.

MYLAN PHARMACEUTICALS/MENARINI RICERCHE/ JOHNSON & JOHNSON'S nebivolol

Nebivolol is a new, selective beta-1 blocker with vasodilation properties (through modulation of nitric oxide release that reduces peripheral vascular resistance). Johnson & Johnson owns the molecule, but it is marketed in Europe by Menarini, and will be marketed in the U.S. by Mylan, which must differentiate nebivolol from other beta blockers to be successful.

A researcher at ASCPT said the key advantages of nebivolol over other beta blockers are:

- **High B1 selectivity.** He said, "Perhaps in asthmatics it might be an advantage. We haven't looked at that yet, but it is possible."
- **Nitric oxide (NO) component.** He said, "Nebivolol is unique because it increases nitric oxide, so it may reverse endothelial dysfunction, but we only have in vitro data on that so far."
- **African-Americans.** An in vitro study to be published soon reportedly measured nitric oxides, super oxides, etc., and showed more efficacy of nebivolol in African-Americans. Mylan is unlikely to get a race-based label, but if there is a difference based on an NO test, that could lead to preferential use in a particular race.
- **No gender difference.** The researcher said a population PK analysis of the clinical data found no statistically significant difference in response to nebivolol based on gender.

Mylan presented at least nine posters at ASCPT, including:

- **Nebivolol+ACE inhibitor.** Co-administration of King Pharmaceuticals' Altace (ramipril) and nebivolol was studied in 12 patients who were extensive metabolizers (EMs) of CYP2D6 and three who were poor metabolizers (PMs) of CYP2D6. Researchers found changes in PK estimates but none that were considered to be significant and there were no drug interactions that affected the clinical profile of either drug upon co-administration.
- **Nebivolol+warfarin.** Researchers found no statistically significant changes in the pharmacokinetics of warfarin with co-administration of nebivolol.
- **Nebivolol+digoxin.** A study in 16 healthy adult volunteers found that concomitant administration of 10 mg nebivolol and 0.25 mg digoxin caused no PK changes in the rate or extent of digoxin absorption, no cardiac abnormalities, and no drug-related changes in lab tests.
- **Nebivolol+loop diuretic.** A study in 15 patients – 12 EMs and three PMs – found that co-administration of nebivolol and furosemide caused no drug interactions that affected the PK profile of either drug.
- **Nebivolol and CYP2D6 metabolism.** Twenty-five CYP2D6-genotyped healthy volunteers (17 EMs and 8 PMs) were studied to see if there are any PK differences in the metabolism of nebivolol. They found that nebivolol exposure in PMs is ~32-fold higher than EMs. Despite the PK differences, there was a lack of differences in adverse events, suggesting a similar degree of events for both populations.
- **Nebivolol in renally-impaired patients.** A study found total body clearance of nebivolol is decreased 53% in severely renal-impaired subjects. Thus, a reduction in the nebivolol dose may be required in these patients. Researchers reported that the pharmacokinetics of nebivolol appear to be affected by the degree of renal impairment, despite previous studies which demonstrated that nebivolol has no measurable renal clearance.
- **Nebivolol in hepatic-impaired patients.** A 16-patient study found AUC and C_{max} were increased ~3-4-fold in hepatic-impaired individuals given nebivolol, and researchers recommended reducing the nebivolol dose in patients with moderate hepatic impairment.

NOVARTIS'S vildagliptin (LAF-237)

There were only PK data on this oral DPP-4 at ASCPT. That poster found the 100 mg dose appeared the most effective, but the 25 mg dose might have utility, depending on the severity of the diabetes.

PFIZER'S lasoxifene

As part of the world-wide development plan for this next-generation selective estrogen receptor modulator (SERM), Pfizer presented a PK study in Japanese and Caucasian women given daily dosing for two weeks. The study found similar PK in Caucasian and Japanese subjects at both doses, that HDL was not consistently affected by lasoxifene, and reductions in LDL were similar in both the proposed clinical dose of 0.25 mg and double that dose.

Another PK study found that food had no effect on the PK of lasoxifene, no clinically relevant drug-drug interactions, but was associated with a small increase in drug exposure in subjects with moderate hepatic impairment.

Daily Lasoxifene in Japanese and Caucasian Postmenopausal Women

Measurement	Lasoxifene 0.25 mg		Lasoxifene 0.50 mg	
	Japanese	Caucasian	Japanese	Caucasian
C_{max}	1.9%	2.4%	1.6%	3.6%
T_{max}	4.0 hours	4.0 hours	8.0 hours	8.0 hours
AUC (ng-h/mL)	41.8	47.1	96.7	78.9
$t_{1/2}$	151	164	146	150
LDL (mg/dL) change from baseline at Day 14	-31	-37	-8	-25
HDL (mg/dL) change from baseline at Day 14	-7	0	-2	-9

SANOFI-AVENTIS'S Ambien MR (zolpidem extended/modified release)

Data from several new studies were presented at ASCPT.

Study 1

This was a 12-week, randomized, Phase I, double-blind, double-dummy, placebo-controlled, three-way crossover study evaluating the residual psychomotor and cognitive effects and safety of Ambien MR eight hours after a single nocturnal dose in 18 healthy adult volunteers, aged 22-38. Study medication was administered during three treatment periods, each separated by 21-day minimum washout periods.

Researchers reported:

- Ambien MR 12.5 mg and placebo demonstrated no significant difference in performance in CFF, CRT, WRi, WRd, and DSST, 8 hours post-dose.
- Only a significant increase in a secondary task in CTT (time reaction) which was half that found with flurazepam, was observed.

Ambien MR Phase I Study

Measurement	Placebo	Ambien MR 12.5 mg	Flurazepam 30 mg
Critical Flicker Fusion (CFF)	29.12 Hz	28.97 Hz	28.22 Hz
Total Choice Reaction Time (CRT)	618.87 ms	634.97 ms	662.47 ms
Mean response time on Compensatory Tracking Task (CTT)	469.5 ms	519.1 ms	565.4 ms
Immediate and Delayed Word Recall (WR_i, WR_d)	13.2 WR_i 10.3 WR_d	12.7 WR_i 8.9 WR_d	10.7 WR_i 5.9 WR_d
Digital Symbol Substitution Test (DSST)	63.6	63.7	59.7
Subjective evaluation of sleep by the Leeds Sleep Evaluation Questionnaire (LSEQ)			
Ease of getting to sleep	41.1	52.7	52.1
Quality of sleep	36.5	50.5	56.8
Awakening from sleep	48.3	46.4	42.7
Behavior after awakening	44.6	43.1	38.1

- Flurazepam significantly impaired performance vs. placebo in all tests except DSST.
- Unlike flurazepam, Ambien MR 12.5 mg had no residual effects on CNS integrative capacity, sensorimotor, or psychomotor performance, immediate and delayed memory recall, except for CTT mean reaction time compared to placebo. The increase in CTT mean reaction time was half that observed with flurazepam.

Study 2

This was a randomized, double-blind, placebo-controlled, single-center, Phase I, four-way crossover study similar to Study 1, but in 24 healthy elderly patients (age 65-78). Study medication was administered during four treatment periods, each separated by 28-day minimum washout periods. All subjects received each of the four treatments – Ambien MR 6.25 mg and 12.5 mg, flurazepam 30 mg, and placebo, given as a single, oral dose.

Ambien MR in Healthy Elderly Adults

Measurement	Placebo	Ambien MR 6.25 mg	Ambien MR 12.5 mg	Flurazepam 30 mg
CFF	28.03 Hz	28.22 Hz	27.6 Hz	27.29 Hz *
Total CRT	842.28 ms	841.16 ms	850.68 ms	890.48 ms *
Mean response time on CTT	655.49 ms	---	---	768.11 ms *
Word recall	9.2 WR_i 6.0 WR_d	8.8 WR_i 5.9 WR_d	8.5 WR_i 4.9 WR_d	6.4 WR_i 3.0 WR_d *
DSST	28.5	29.2	29.3	26.6
Subjective evaluation of sleep by the Leeds Sleep Evaluation Questionnaire (LSEQ)				
Ease of getting to sleep	38.8	55.5 *	57.9 *	58.7
Quality of sleep	35.4	56.9 *	56.7 *	68.6
Awakening from sleep	52.3	54.0	52.2	49.3
Behavior after awakening	46.5	54.9 *	52.4	45.3

*p<.05 vs. placebo

For Study 2, researchers reported:

- Neither Ambien MR dose demonstrated a significant difference in performance vs. placebo for CFF, CRT, total reaction time, CTT, WRi, WRd, and DSST, 8 hours post-dose.
- Flurazepam significantly impaired performance with respect to placebo on all tests.

In looking at both of these studies, researchers concluded:

➢ There were no residual effects on CNS integrative capacity, sensorimotor, psychomotor performance, or immediate and delayed memory recall compared with placebo with either Ambien MR dose.

- In PK studies, Ambien MR achieved plasma concentrations comparable to standard Ambien, maintained therapeutic plasma concentrations during the middle of the night (3-6 hours post-dose), and retained similar elimination characteristics compared to standard Ambien. The PK profile of Ambien MR should result in improved sleep maintenance without increased next-day residual effects.
- The LSEQ assessment showed no negative effects on awakening with Ambien MR in either study.
- Ambien MR was well tolerated at both doses.
- In contrast to flurazepam (30 mg), objective and subjective measurements of psychomotor and cognitive performance demonstrated that Ambien MR 12.5 mg resulted in no significant next-day residual effects except for one secondary parameter in the CTT (mean response time) in healthy adults as compared to placebo 8 hours post-dosing.

In healthy elderly subjects, neither Ambien MR 6.25 mg nor 12.5 mg caused significant next-day residual effects on psychomotor and cognitive performance 8 hours post-dosing compared with placebo.

Study 3

This was a 13-week, randomized, double-blind, placebo- and reference-controlled, single-center, 10-way crossover study in 36 healthy adult volunteers conducted in 2001. The study compared eight different doses of Ambien MR (up to 15 mg) and regular Ambien 10 mg vs. placebo. Each formulation featured a different combination of immediate- and delayed-release Ambien. Results were measured using polysomnography (PSG) in a traffic noise model to induce sleep-maintenance difficulties. PSG variables were recorded for 8 hours post-nocturnal dosing. Ambien medication was administered on one of two successive nights during 10 treatment periods, which were separated by washout intervals of 7 to 14 days. Psychometric testing and subjective sleep evaluation were conducted 8 and 9 hours post-nocturnal dosing.

Dose-Ranging Study of Ambien MR in Healthy Adults

Measurement	Placebo	Ambien 10 mg	Ambien MR 12.5 mg
Withdrawals	2 adverse events, 1 protocol deviation, 1 other		
Duration of awakenings	25.1	14.5 *	12.3 *
Total sleep time (TST, in minutes)	418	439 **	473 **
Number of stage shifts	141	128	132
Sleep efficiency index	87.3%	91.7% **	91.1% **
Early-morning awakenings	13.7 min.	9.09 min.***	9.66 min.
CFF (hz)	30.88	30.74	30.53
Total CRT	605.58	617.64	619.56
Mean response time on CTT	508.04	516.26	519.56
DSST	77.41	78.86	78.44
Mean number of awakenings	28.30	27.27	13.91

* p≤.001 vs. placebo, ** p<.01 vs. placebo, *** p<.05 vs. placebo

Researchers concluded that the 12.5 mg dose of Ambien MR best improved sleep maintenance in the middle of the night without compromising next-day psychomotor performance or sleep architecture. All Ambien MR formulations as well as regular Ambien were well tolerated, with no safety issues observed.

Researchers reported:

- **Arousals.** PSG scoring showed a significant overall treatment effect (p=.017) in the number of arousals (²10 seconds duration). Ambien MR 12.5 mg provided greater reductions in the mean number of arousals vs. both placebo (p=.016) and standard zolpidem (p=.010).
- **Awakenings.** Both the Ambien MR 12.5 mg and another formulation (H) significantly reduced awakenings (³15 seconds duration) vs. placebo (p=.0005 and p=.041, respectively). The 12.5 mg dose also significantly reduced the total number of awakenings vs. standard Ambien (p=.002). Mean number of awakenings and the total duration of awakenings (WASO) were significantly reduced with Ambien MR 12.5 mg.
- **Hourly Analysis of 30-Second Awakenings.** The mean number of awakenings was significantly reduced vs. placebo at 2 and 3 hours post-dose with standard Ambien, but at all time points up to 5 hours post-dose with Ambien MR 12.5 mg and another formulation (H), (p=.002 and p=.017, respectively). The 12.5 mg dose also significantly differed from standard Ambien at 4 and 5 hours post-dose (p=.029 and p=.054, respectively).
- **Psychomotor and Cognitive Tests.** Standard Ambien plus 3 MR formulations (12.5, A, and D) all had an impact similar to placebo on psychomotor test results obtained at 8 and 9 hours post-dose. Other MR formulations resulted in at least one test difference vs. placebo.
- **Sleep Architecture.** Very few modifications in sleep architecture were observed with any one formulation of Ambien MR. Slow-wave sleep duration was significantly greater for all Ambien MR formulations and for standard Ambien compared with placebo.
- **Subjective Sleep Evaluation.** All Ambien MR formulations and standard Ambien significantly improved "ease of getting to sleep" and "quality of sleep" versus placebo as measured by the LSEQ.
- **Safety and Tolerability.** Standard Ambien and all Ambien MR formulations were well tolerated, with no safety issues observed.

Study 4

This was a randomized, open-label, crossover study of the bioavailability and PK of two doses of Ambien MR (10 mg and 12.5 mg) vs. standard Ambien 10 mg in 10 healthy male volunteers (age 18-45). Researchers found absorption rapid with all doses, and no significant differences in T_{max}. However, C_{max} was "modestly" lower with both MR doses. Plasma concentrations were consistently higher from 2.5-8 hours post-dose with both MR doses vs. standard Ambien. The half-life of all three drugs tested was similar. The researchers concluded, "This study validated the pharmaceutical concept of an MR formulation with a sustained plateau of higher plasma concentrations compared to standard zolpidem between 3-6 hours post-dose while retaining the same rapid onset of action and mean terminal half-life.

Conclusions

Ambien has no claim for sleep maintenance, but the data at ASCPT suggest that Ambien MR may be able to get that claim. A researcher said patients get 1-1.5 hours more sleep per night with Ambien MR than with regular Ambien. According to researchers, the only advantage that Ambien MR has over regular Ambien is the extended sleep period, and the only advantage over Sepracor's Lunesta (eszopiclone) is that "it is a new formulation of a proven drug." Thus, the label is likely to look more like Ambien than like Lunesta.

TAP PHARMACEUTICALS' febuxostat (TMX-67)

Febuxostat 80 mg and 120 mg was submitted to the FDA in December 2004 for the management of hyperuricemia in patients with chronic gout. A study at ASCPT reported that febuxostat "mildly" inhibits metabolism of the tricyclic antidepressant despiramine, but, compared to other CYP2D6 inhibitors, the inhibitory effect of febuxostat on despiramine is not considered clinically significant and is not expected to require a despiramine dose adjustment when the two drugs are concomitantly administered.

Effects of Age and Gender on Febuxostat PK and Safety

Measurement	Young n=24	Elderly n=24	Male n=24	Female n=24
Change from baseline at Day 7				
Uric acid	-55%	-56%	-52%	-59%
Xanthine	+.094	+.118	+.118	+.112
Hypoxanthine	-.005	Same	-.016	-.011
Safety				
Subjects with at least 1 adverse event	25%	42%	13%	54%
Headache	8%	4%	0	13%
Constipation	13%	29%	4%	38%

Another study found that no adjustment in febuxostat dose is needed based on gender or age. However, the incidence of side effects was lower in males than females and lower in young subjects than in elderly subjects.

A third study found food causes a decrease in the absorption rate and extent of febuxostat in all food effect studies, but the decrease was not associated with a decrease in febuxostat PD effect (serum uric acid concentration) when evaluated in an 80 mg multiple-dosing study. Antacid decreased the absorption *rate* of febuxostat but had no effect on the *extent* of febuxostat absorption. Researchers concluded that febuxostat can be administered regardless of food or antacid intake.

VIROPHARMA'S maribavir

This benzimidazole compound, which was licensed from GlaxoSmithKline in August 2003, is intended as a replacement for ganciclovir in the treatment of CMV retinitis. Ganciclovir is fairly toxic; it is associated with bone marrow suppression, nausea, and vomiting. In earlier studies, maribavir side effects included taste disturbances, diarrhea, rash, sinusitis, neutropenia, and anxiety. However, a researcher said the major difference between maribavir and ganciclovir is not necessarily the toxicity but, more importantly, administration. Maribavir is an oral drug, and ganciclovir for acute CMV infection is intravenous.

Two poster presentations by Joseph Ma, Pharm D, a clinical pharmacology fellow at Bassett Research Institute in Cooperstown NY, looked at the pharmacology of maribavir and especially examined the interaction between maribavir and the CYP450 pathway. He said there were no red flags that indicated any unexpected toxicities or worrisome interactions. There appears to be interaction with the CYP2D6 pathway, which is also used by dextromethorphan, and the CYP3A pathway (used by midazolam), but the clinical significance of these interactions remains to be evaluated.

- **A randomized, double-blind, single and multiple dose PK study in 20 healthy women.** This study found repeated dosing with maribavir 400 mg BID for 10 days was well tolerated, with taste disturbance the most common adverse event.
- **A double-blind, placebo-controlled, multiple-probe drug interaction study in 20 adults** (16 on drug, 4 on placebo). Researchers reported that a 400 mg BID dose of maribavir showed a lack of equivalence for CYP2C19 and CYP2D6 activity and may decrease activity of both of these, but the clinical significance of this is unclear. Maribavir did not affect CYP1A2, CYP2C9, or CYP3A activity.

WYETH'S desvenlafaxine sustained-release (CVS-233-SR)

Wyeth's atypical antidepressant Effexor (venlafaxine) goes off patent in 2008, and sustained-release desvenlafaxine has to be meaningfully better if Wyeth is going to convert patients from Effexor/Effexor-ER (extended-release venlafaxine) to sustained-release desvenlafaxine before the patent expiration. Desvenlafaxine-SR also has to differentiate itself from Lilly's Cymbalta (duloxetine).

Nothing presented at ASCPT provided convincing data that desvenlafaxine-SR will be able to do either of these things, but a researcher cited these advantages to desvenlafaxine-SR over Effexor/Effexor-ER:

- **Higher dose with fewer side effects.**
- **Less nausea.**
- **Additional indication.** Wyeth is seeking approval for treatment of vasomotor symptoms (hot flashes) in postmenopausal women, which is not a labeled indication for Effexor or Effexor-ER.

In an open-label, randomized, crossover study of 35 healthy patients, Wyeth researchers compared the relative bioavailability of 75 mg and 150 mg Effexor-ER and desvenlafaxine-SR, concluding that nausea is less severe with desvenlafaxine-SR (at least at the 75 mg dose) than either Effexor-ER dose.

In another poster, Wyeth researchers looked at the various dosing levels of desvenlafaxine-SR and determined that:

- Nausea is the most common side effect, but subjects adjusted to the nausea after the first day in the 300 mg group and by Day 7 in the 450 mg group.
- The maximum tolerated dose was 450 mg, based on hypotension and tachycardia with the 600 mg dose, which resulted in that arm being discontinued.
- There were slight increases in supine systolic and diastolic blood pressure at all three dose levels (300 mg, 450 mg, and 600 mg), but the increases were deemed clinically unimportant.
- The mean half-life was 11-18 hours, with T_{max} at 5-8 hours post administration.

Ascending Multiple-Dose Study of Desvenlafaxine-SR

Measurement	300 mg BID n=9	450 mg BID n=9	600 mg BID n=9	Placebo n=9
Hypertension	55.6%	0	88.9%	11.1%
Postural hypotension	0	0	66.5%	0
Tachycardia	22.2%	44.4%	100%	33.3%
Anorexia	0	0	44.4%	0
Constipation	22.2%	33.3%	44.4%	0
Nausea	44.4%	66.7%	77.8%	11.1%
Abnormal dreams	0	0	44.4%	0
Dizziness	22.2%	11.1%	33.3%	0
Euphoria	0	0	33.3%	0
Twitching	11.1%	0	44.4%	0

Erythropoietic Growth Factors

A study by researchers at the University of Buffalo School of Pharmacy compared Johnson & Johnson's Procrit (epoetin) and Amgen's Aranesp (darbepoetin) use and outcomes, looking at changes in hemoglobin over 12 weeks in 108 adults. They found no difference in the effectiveness of the two erythropoietic growth factors for chemotherapy-induced anemia, but the effectiveness of both was lower than reported in clinical trials, due in part to underutilization of clinical guidelines and dose escalations. That hospital plans to implement a prospective monitoring program for the use of Procrit and Aranesp.

Comparison of Aranesp and Procrit

Measurement	Aranesp 200 mg EOW n=54	Procrit 40,000 U QW n=54	p-value
Baseline hemoglobin	10.2	10.0	0.3
Mean hemoglobin increase from baseline at Week 12	1.1	0.8	0.7
Overall clinical response at end of therapy	38.9%	35.2%	0.4
Dose changes	0	8 patients dose escalated	---

Open-Label, Randomized, Crossover Study of Desvenlafaxine-SR

Adverse events	75 mg Desvenlafaxine-SR n=18	150 mg Desvenlafaxine-SR n=17	75 mg Venlafaxine-ER n=18	150 mg Venlafaxine-ER n=17
Any adverse event	11.1%	41.2%	55.6%	41.2%
Headache	0	5.9%	0	0
Syncope	0	0	5.6%	0
Nausea	11.1%	35.3%	44.4%	35.3%
Vomiting	0	0	0	5.9%

Oral contraceptives

FDA researchers presented a survey of the labels of drugs that interact with oral contraceptives (OCs). The researchers identified drugs known or suspected to interact with OCs and looked at the labels. They concluded that labeling advice about interactions between OCs and other drugs is inconsistent. They also found that drug interactions between a drug and a specific OC may not apply to all OCs because of different progestins in the OCs. They recommended that:

- Standardized approaches to labeling of drugs that interact with OCs should be considered.
- When drug interaction studies are conducted with OCs, labeling should denote both positive and negative results.
- Drug and OC interactions in labeling should be clear and consistent.

Propofol

Breast-feeding women are usually advised to pump and discard their milk for 24 hours after surgery with propofol sedation because there are little data on the transfer of propofol into breast milk. To see if this is necessary, researchers from Northwestern University tested five women undergoing elective surgery under general anesthesia including propofol (2.5 mg/kg IV) for induction and a potent volatile anesthetic for maintenance. They found limited secretion of propofol into breast milk, due, at least in part, to its large V_{ss} and high CI_E. They concluded that the amount of propofol appearing in breast milk over 24 hours after propofol administration (0.05 mg) is unlikely to affect the child and is insufficient justification for the interruption of breast feeding. They advised that breast feeding may be resumed as soon after anesthesia and surgery as the mother is physically and mentally able.

Propofol in Breast Milk

Mean measurements	n=5
Propofol dose	188 mg
Milk volume	318 ml/24 hours
Propofol in milk	0.05 mg
Milk mg/dose mg	0.0003

Proton Pump Inhibitors (PPIs)

Researchers at Brigham & Women's Hospital reported on the clinical and economic consequences of formulary restrictions in British Columbia on PPI use. In 2003, PharmaCare of British Columbia listed Eisai/Johnson & Johnson's AcipHex (rabeprazole) as their preferred PPI. AstraZeneca's Prilosec (omeprazole), Wyeth's Protonix (pantoprazole), and TAP Pharmaceuticals' Prevacid (lansoprazole) were covered only after treatment failure on AcipHex. Researchers found the policy led to substantial utilization changes and savings without increasing non-adherence of clinical compliance:

- 45% of patients switched to AcipHex.
- There was no change in PPI discontinuation rates (~10%).
- 9% of AcipHex users switched back to their old PPI.
- There was no increase in GI bleed hospitalizations.
- Office visits increased slightly after three months, corresponding to switching back.
- PharmaCare saved $2.9 million in the first six months of this policy.

QT Prolongation

The FDA presented a poster on the preliminary results of the development of a QT database with analytic tools. The goal is to establish a central, all-accessible, user-friendly QT data management system (QTech) that grows over time. Currently, the results from 10 QT studies are entered into the data warehouse. The software under development appears to be working well and has assisted in efficient science-based QT risk evaluation and has revealed trends that may aid in designing future QT evaluation studies.

Statins

A study by Japanese researchers found that the SLCO1B1*15 gene is a risk factor for development of statin-induced myopathy in patients receiving either pravastatin (Bristol-Myers Squibb's Pravachol) or atorvastatin (Pfizer's Lipitor). They suggested that the results of genotyping of the mutation or SNPs that decrease the function of SLCO1B1 might supply useful information to predict myotoxicity of statins.

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