Trends-in-Medicine

June 2004
By Lynne Peterson

SUMMARY

The hot drug topics at this meeting appeared to be: ♦ Expanded use of AstraZeneca's antipsychotic Seroquel (quetiapine) – but at higher doses.
♦ Weight gain with Pfizer's pregabalin.
♦ Expected increases in use of both Bristol-Myers Squibb's Abilify (aripiprazole) and, to a lesser extent, Pfizer's Geodon (ziprasidone). These are both more activating (or less calming) than other atypical antipsychotics, but psychiatrists are finding them effective with less weight gain or metabolic syndrome.
♦ The potential of Corcept's Corlux (RU-486, mifepristone) in treating psychotic major depression, Aventis's Rilutek (riluzole) for major depression and bipolar depression, and Titan's Probuphine (depot buprenorphine) for opioid addiction (provided usage restrictions on buprenorphine are modified).
♦ Growing interest in other uses for GlaxoSmithKline's anticonvulsant Lamictal (lamotrigine).

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NEW CLINICAL DRUG EVALUATION UNIT (NCDEU)

Phoenix, AZ
June 1-4, 2004

This annual psychopharmacology meeting is sponsored by the National Institute of Mental Health (NIMH). It is not a meeting where a lot of new trial data is released, but it is an excellent forum to review psychopharmacology agents in development.

ASTRAZENECA'S Seroquel (quetiapine)

This atypical antipsychotic was one of the hot drugs at NCDEU. Usage both on-label and off-label is increasing, and sources expect that to continue. The average dose also is increasing. Seroquel is approved from 150 mg to 800 mg BID, but historically, doctors have started patients at a low dose and titrated them up. AstraZeneca is trying to educate doctors to titrate patients to a higher dose faster. An AstraZeneca official said, "I think doctors should titrate patients up to 600 mg BID, starting with 100 mg on Day 1, 200 mg on Day 2, 300 mg on Day 3, 400 mg on Day 4, and 600 mg by Day 6 or 7. The average dose today is 500 mg."

Seroquel is being used off-label for bipolar disorder (in which AstraZeneca has a registration development program) and for anxiety. Usage reportedly is branching out to mood disorders (especially bipolar disorder and depression) and addiction. A doctor said, "What's exciting about quetiapine is that it may be bimodal and could be used in bipolar disorder for either acute or maintenance depression…In bipolar disorder, there isn't any difference (in effectiveness) between the 300 mg and 600 mg doses; the higher dose does not add much benefit, and there is a possibility that a lower dose would work with possibly fewer dropouts." For depression, Seroquel is typically dosed QD at night.

Among the other points speakers made about Seroquel were:

- Seroquel was twice as effective as placebo in reducing suicidal thoughts, which a speaker said surprised him.
- Seroquel and Lilly's Zyprexa (olanzapine) are associated with excessive fatigue; lamotrigine with benign rash. However, in contrast to Zyprexa and Seroquel, there was no increased rate of dropouts due to side effects with lamotrigine.
- There is no "big time" added benefit of a higher dose of Seroquel.
- There is a need for studies of the combination of lamotrigine and Seroquel.
- An agent with bimodal activity (e.g., lithium) should be tried before Seroquel in bipolar disorder.
- Seroquel (but not Zyprexa monotherapy) possesses moderately large ***acute*** antidepressant effects. It also significantly reduces the core symptoms of depression, including suicidal thoughts.

AVENTIS'S Rilutek (riluzole)

This orphan drug is approved for ALS, but it is also being investigated by researchers – not by Aventis – for treating major depression and bipolar depression. A double-blind, placebo-controlled trial is planned, and funding has now been obtained for that trial. This was important because Aventis is not sponsoring the trial or providing free drugs, and the pills cost about $17 each and are administered twice-a-day, making the monthly cost $1,900. A speaker said, "Aventis could lose its orphan drug status by pursuing this indication, so they aren't."

In a small study of 19 treatment-resistant patients, all patients had statistically significant improvement at three weeks, and they maintained the effect for another three weeks.

- Mean dose – was 168.8 mg/day (range 50-200 mg/day)
- Mean age – 43.1
- Dropouts – 30%

In an ongoing, open label study in refractory bipolar depression, patients first go through a 7-14 day drug-free period, then get Rilutek 100-200 mg/day plus lithium (0.6-1.2 mEq/L) for eight weeks. Preliminary data on the first 14 patients was presented:

- 60% (8 of 14) completed all eight weeks. The reasons for discontinuation were: lack of response (3), increased liver enzymes (2), and kidney stones (1).
- The mean dose at last visit was 171 mg/day.
- Rilutek was well tolerated, with the most common adverse events being weight loss, decreased sexual drive, fatigue, and an asymptomatic increase in LFTs.
- A robust antidepressant effect was seen as early as one week in completers.
- 50% of patients had a response, and all of these were remitters.

In an NIH-sponsored study of treatment-resistant unipolar patients, six of 19 patients dropped out due to side effects. Another study in bipolar disorder had similar results. A double-blind, placebo-controlled trial as add on therapy to a mood stabilizer is starting in bipolar depression.

AXONYX'S phenserine

This third generation, highly selective acetylcholinesterase inhibitor (AChE-I) for Alzheimer's Disease has a dual method of action, reducing both amyloid precursor protein (APP) and amyloid peptide (amyloid-beta) formation in the brain.

BRISTOL-MYERS SQUIBB

➢ **Serzone (nefazodone).** This antidepressant was taken off the market in Europe after being linked to liver failure, and it also is being voluntarily removed from the U.S. market by the company. However, there was no discussion of this decision at NCDEU.

➢ **Abilify (aripiprazole).** Doctors said they expect Abilify to continue to pick up market share. Agitation is an issue with this agent – it is activating – but that is not considered a serious negative. A New York doctor said, "Abilify can be activating. I call it 'caffeinated.' It is an issue, but the vast majority of patients deal with it and get through it. It tends to be a temporary, solvable problem, but a problem." A Connecticut doctor said, "Any atypical antipsychotic can cause some agitation. It is a non-issue in clinical practice. It's just that those medications free of metabolic syndrome – Abilify and Geodon – often don't have the initial 'calming' effect." A Massachusetts doctor said, "Agitation is a real issue, but the rate is relatively low, and we haven't had patients quitting as a result." A Minnesota psychiatrist said, "Abilify works in some patients. Geodon and Abilify have some advantage in cognition." Another doctor added, "Abilify use is likely to increase, but Geodon use has stabilized."

CEPHALON'S Provigil (modafinil)

Provigil may be useful in treating drug addiction. An NIDA study was presented that indicated Provigil improves cocaine abstinence in cocaine addicts. Cephalon didn't fund the study, but it did provide the drug. A Phase III trial in 240 patients is underway, and another Phase III multicenter study of 240 patients is due to start in June 2004.

Phase II Trial of Provigil for Cocaine Abstinence

Time Frame	Placebo patients with clean urine	Provigil patients with clean urine
Week 1	~22%	~28%
Week 2	~26%	~36%
Week 3	~27%	~42%
Week 4	~24%	~43%
Week 5	~26%	~46%
Week 6	~24%	~47%
Week 7	~20%	~45%
Week 8	~24%	~43%

CORCEPT'S Corlux (mifepristone, RU-486,C-1073)

This drug is approved as an abortifacient, but it may also have value in treating psychotic major depression (PMD). The dose for PMD is seven times the dose needed as an abortifacient. A speaker said, "Psychotic patients tend to have cognitive defects. Increased cortisol activity is a hallmark of this disorder; psychotics have high cortisol levels…With Corlux, there is normalization of the cortisol rhythm…We did not see an effect on MADRS…It is really in the psychotic symptom domain that you see an effect…Mifepristone appears to reduce psychotic symptoms in PMD."

He said there are three reactions to Corlux:

1. Rapid responders – who show a response at both Day 7 and Day 28
2. Responders – who do show a benefit at Day 28 but not at Day 7
3. Non-responders

In early trials, patients responded, but side effects were an issue. A new dosing regimen – with patients getting Corlux for only seven days – appears to have resolved much of this. After this "shock" therapy, patients are then put on another drug. Whether or how often this Corlux shock therapy can be used has not been determined. A researcher said, "It is like a shock treatment, but the effect seems to last…It is an acute, intermittent therapy and it could possibly be a periodic treatment…We have repeated it in one patient – the first patient we treated, who relapsed at eight years, and we treated that patient successfully." The major side effects are rash (4%-10%) and some nausea, but there is no correlation between rash and response.

Treating Psychotic Major Depression with Corlux

Measurement	Corlux 600 mg/day for seven days n=95	Placebo n=122	p-value
One-Week Results			
Primary endpoint: 30% decrease in BPRS at both Day 7 and Day 28 (by ITT)	~38%	~26%	---
BPRS PSS 50% at both Day 7 and Day 28 (in patients with baseline BPRS PSS ≥ 12)	60%	30%	p=.006 at Day 7 p=.004 at Day 28
Adverse events	Comparable		---
Decrease in antipsychotic use	Down more	Down	Nss

DOV PHARMACEUTICAL

➢ **Ocinaplon**. There was no new information on this anxio-selective agent for GAD.

➢ **DOV-216,303.** There was no news on this triple reuptake inhibitor (with effects on norepinephrine, dopamine, and serotonin), which is in Phase II trials.

FOREST LABORATORIES

➢ **Lexapro (escitalopram).** When Celexa (citalopram), an SSRI, goes off patent, the outlook for Lexapro depends on how the generic citalopram performs. When Merck's statin, Mevacor (lovastatin), and AstraZeneca's ACE inhibitor, Zestril (lisinopril) went off patent, the molecules (brand+ generic) gained market share, but when Lilly's Prozac (fluoxetine), the first SSRI, went off patent, the molecule lost market share. A source explained that the problem with generic fluoxetine was that doctors did not find it worked as well as the brand, but managed care often mandated the generic, so they simply cut their use of the brand and generic. A South Carolina doctor said, "Generic Prozac was not equivalent to the brand, and the insurance co-pays pushed the generic, but fluoxetine wasn't as good." A Rhode Island doctor said, "Generic citalopram will reduce Lexapro use."

➢ **Namenda (memantine).** The exact mechanism by which memantine works is unknown. The only known molecular targets are ionotropic receptors, but most experts believe there is some kind of glutamate action. At clinical levels (therapeutic concentrations), the only effect is to "plug" NMDA receptors, allowing calcium to go in when needed but preventing excessive calcium influx. There is no effect on nicotinic receptors.

Measurement	Alzheimer's Disease	Treatment with Memantine
Glutamate	++	--
GABA	++	--
Acetylcholine	--	++

➢ **Neramexane.** This follow-on to Forest's Namenda (memantine) for Alzheimer's Disease in Phase II trials. It is a "tweaked" version of memantine, based on the NMDA theory of action for memantine, but a Forest researcher commented, "Of course, we could learn in the future that the 5HT3 action is more important than we now think." There was no new data on neramexane at NCDEU. A Forest official said any data will come from either Lundbeck or Merz, that Forest is not releasing anything yet. A memantine researcher said, "There won't be any data on neramexane for six to 12 months, but two double-blind, placebo-controlled trials have started enrolling – one as monotherapy, and one in combination with an acetylcholinesterase inhibitor. The trials have the same design and endpoints, and each arm will have about 200 patients."

GLAXOSMITHKLINE'S Lamictal (lamotrigine)

There was a lot of interest in the use of lamotrigine for bipolar maintenance and depression. Lamotrigine already is approved for epilepsy, migraines, and bipolar maintenance, and a speaker called it the "800 pound gorilla" in unipolar depression.

Speakers made several interesting points about the use of Lamictal for bipolar disorder and depression, including:

- Prevents depression but not mania in bipolar patients, while lithium prevents mania but not depression.
- The effect size of lamotrigine appears to be dose-related. He advised, "Don't putz around with 50 mg lamotrigine; go up to 200 mg."
- Lamotrigine, lithium, and Zyprexa delay depressive episodes, but Zyprexa has never been studied long-term in the recently depressed.

- Lamotrigine may be effective as an antidepressant only in combination with another agent. A large trial of lamotrigine as augmentation therapy in treatment-resistant unipolar depression is ongoing, with enrollment expected to be completed in November 2004.

- Showed good efficacy in BP-2, but not BP-1, patients in a six-month study of 52 rapid cycling bipolar patients.

- Lamotrigine possesses moderately large acute anti-depressant effects. It also significantly reduces the core symptoms of depression, including suicidal thoughts.

- "Two double-blind trials plus an open label study and case reports indicate lamotrigine improves the positive symptoms and general psychopathology of schizophrenia …Added to Risperdal in very refractory patients, you can see very dramatic improvement with lamotrigine in terms of the PANSS score."

- "Lamotrigine has the capacity to activate manic or hypomanic cycles in patients…I've seen it a number of times with patients and some anecdotal reports." Another speaker said, "Manic induction is fairly infrequent, but I've seen it, too…It is hard to differentiate from activation due to the compound…This really is an activating anticonvulsant…(But) the switch rates with lamotrigine tend to be low…so my sense is there are sporadic patients out there, and if you see it in individual patients, pay attention, but the risk across the population is no worse than placebo."

- An agent with bimodal activity (e.g., lithium) should be tried before lamotrigine in bipolar disorder.

JOHNSON & JOHNSON

➢ **Risperdal Consta (risperidone depot).** Psychiatrists were very enthusiastic about this agent. The problems are cost and reimbursement. A New York doctor said, "Consta is a terrific medication. Reimbursement is the barrier, and it is a state-to-state issue." A Connecticut doctor said, "The U.S. experience with long-acting drugs is different than the European experience. Here long-acting medications have a reputation as a punishment, and that has to be overcome. The cost and lack of samples also have limited use."

➢ **Topamax (topiramate).** In epilepsy trials, topiramate showed significant weight loss, so it is being explored in eating disorders (e.g., binge eating, bulimia nervosa). A speaker said the weight loss effect peaks at 15-18 months in epilepsy patients, "I tell patients this is a great drug as long as it doesn't make them sleepy or stupid…There is a fairly high drop out rate…but when it works, it works extremely well…Patients who've used it successfully say they just quit thinking about food…They go from constant thoughts about food to something that is a distant part of their everyday existence…So, there is a subjective change in the internal state of the person and what they think about."

LILLY

➢ **MGluPro.** A trial of mGluPro failed, and the molecule is on clinical hold, but the company is not abandoning it. Lilly also has several other candidate mGlu agents in Phase I trials. An official said, "We are trying to find an indication."

Data was presented at NCDEU on LY-354740, a structural analog of glutamate with specificity for mGlu 2/3 receptors that was the basis of Lilly's mGlu platform. However, LY-354740 was discontinued due to adverse events. A researcher said, "The problem with LY-354740 is the bioavailability was only 2%-5%, so it is not being developed. But several other mGlu agents in the pipeline are going forward. The platform is going ahead full force…And there is no weight gain with mGlu."

➢ **Cymbalta (duloxetine).** A Lilly official insisted this new SNRI has already been filed with the FDA for neuropathic pain. It is not viewed as a major threat to the SSRIs, but it is expected to impact most heavily on Wyeth's Effexor (venlafaxine). A Rhode Island doctor warned, "We still need to see the patient experience with duloxetine."

➢ **Zyprexa (olanzapine).** The FDA required similar label changes relating to weight gain and diabetes to Zyprexa, Geodon, and Abilify. Some industry-watchers have argued that this label change will give Lilly a more even playing field since competitors had been trying to differentiate themselves by suggesting their products have less effect on weight and diabetes than Zyprexa does.

➢ **Depot Zyprexa (olanzapine).** Doctors are excited about a long-acting depot form of Zyprexa, which is expected to be administered once every four weeks. The depot is in Phase III trials, but the program reportedly is taking longer than might have been expected because of a need to show relapse prevention. A Lilly researcher commented, "The Phase II data was impressive, and we may have Phase II data by 2005. The key advantages over Risperdal Consta are no need for titration, faster onset, and cost." A New York psychiatrist said, "The time to steady-state is not what matters with this; it is the convenience of a four-week schedule instead of a two-week schedule that's important." A Connecticut psychiatrist said, "Depot Zyprexa should boost use of depots overall. I expect Lilly will make access good."

PFIZER

➢ **Asenapine (licensed from Akso-Nobel).** A source said this is "in a transition phase right now," and will go into the clinic soon, for psychosis (schizophrenia), not anxiety. A Pfizer source said Pfizer hasn't done any trials of its own yet with asenapine, but there is likely to be data at NCDEU 2005.

➢ **Geodon (ziprasidone).** Psychiatrists agreed that Pfizer remains committed to Geodon, and they predicted that sales of Geodon would pick up. A Minnesota doctors said, "Patients don't gain weight on Geodon…I think usage will grow slowly…The main reason the market didn't pick this up was competitive negative marketing." A New York psychiatrist said, "There has been no marketing let up on Geodon…Pfizer hasn't spent a zillion dollars on Geodon Phase IV studies…but I think use will increase. Clinically, Geodon and Abilify are very similar – in terms of weight, the cognitive profile, and non-sedating. I let patients choose between Abilify and Geodon. I think doctors will consider Geodon more as a subclass that includes Abilify, and that will drive prescriptions more to this subclass…There is a revival in enthusiasm at Pfizer. They are doing more trials and providing more support for investigators." A Connecticut doctor said, "I think Geodon will get new life at higher doses."

➢ **Pregabalin – weight gain as a side effect?** In 4Q03 Pfizer submitted one of the largest NDA filings ever to the FDA, seeking multiple indications for pregabalin right from the start – for the management of neuropathic pain associated with diabetic peripheral neuropathy and herpes zoster, as adjunctive therapy in the treatment of partial seizures, and for the treatment of generalized anxiety disorder in adults. The PDUFA date is August 30, 2004. Pfizer hopes pregabalin will replace its Neurontin (gabapentin), which is going off-patent, plus expand the market.

An expert startled some doctors in the audience the first day of the meeting, revealing that pregabalin, unlike Pfizer's Neurontin (gabapentin), is associated with weight gain. He looked at weight gain in three Pfizer studies: two Phase II studies in GAD, and a social phobia study. He concluded that patients gain 2.2 kg (almost five pounds) over four weeks.

Just how much weight patients gain on pregabalin and for how long is not yet clear, but a Pfizer official confirmed there is some degree of weight gain with this drug in all indications. The source said weight gain occurs in 5.6% of patients across the entire pregabalin database, measured at four to 12 weeks, averages 1.6 kg (±3.1 kg), and 7.7% of patients gain weight in long-term (six month) data. This source said the weight gain occurs in 3.7% of GAD patients, and weight gain occurs more often in epileptics. There is no long-term data beyond six months – and the six month data is not public yet – on weight gain with pregabalin, but the Pfizer source said, "Pregabalin is not similar to Zyprexa (in terms of weight gain). With pregabalin, there is no cardiovascular risk and no increase in HDL, lipids, glucose, or HbA1c. There are a minority of patients who have a change in weight, but we can't predict who those are…300 mg is the target dose, but individual patients will need more or less…Pregabalin seems to work best at the highest dose in social phobia, and there is more weight gain there."

Indications where pregabalin weight gain was discussed included:

➢ **Generalized anxiety disorder** (GAD). A Pfizer official said the company considers GAD an important area for pregabalin use. Pfizer's Zoloft (sertraline), GlaxoSmith-Kline's Paxil (paroxetine), and Lexapro are all approved for treating GAD and would be competitors, as well as alprazolam. Doctors said not a lot of gabapentin is used in GAD because of side effects, but they anticipate greater use of pregabalin – provided the weight issue resolves. A review of two published studies of pregabalin in GAD found that patients in those trials gained an average of 2.2 kg in four weeks compared to a 0.2 kg weight loss with lorazepam and a 0.2 kg weight gain with placebo. A speaker said, "I wonder if longer term that will be an issue with this compound."

Comparison of GAD Therapies

Anxiolytic	Advantages	Disadvantages
Alprazolam (Xanax)	Effective	Controlled substance; daytime sedation
SSRIs	Safer for primary care doctors	Takes 2 weeks to work; Less robust effect than Xanax
Pregabalin	Works in 1 week; Little effect on memory, psychomotor coordination, or reaction time; Not associated with abstinence syndrome	Weight gain

➢ **Social phobia.** A speaker said, "I'm excited about the possible use of pregabalin in this indication…There is a good effect only in the high dose group – 600 mg/day – and the side effect profile is similar to the lower dose (150 mg/day). But there is some tendency to weight gain."

➢ **Epilepsy.** A source said the most weight gain occurs in these patients.

Most doctors questioned about how important the weight gain issue would be agreed that it would chill usage. Even though stopping/switching an anxiolytic might appear far less problematic than stopping/switching an antipsychotic, doctors were surprisingly negative on using an anxiolytic that might require stopping/switching. They simply do not want to have to deal with switches.

Among the comments doctors made about this issue were:

- *New England*: "Five pounds of weight gain with pregabalin would be concerning, even if it is in less than 10% of patients. The fact that I could switch patients who gain weight to something else is not helpful – I don't like to switch patients."
- *New York*: "The outlook for pregabalin depends on whether the weight gain continues past one month."

- *Massachusetts*: "Weight gain is a big concern for younger women."
- *Texas*: "People are more sensitive to weight gain now. There is weight gain with the SSRIs, but it takes patients longer to get there. People will be nervous about a drug that causes weight gain so fast."
- *Ohio*: "In GAD, there are so many options that weight gain would chill use of pregabalin…Anything that causes weight gain will have a problem…The weight gain will be a issue. The question is how much of an issue."
- *South Carolina*: "Pregabalin works quickly, but it makes patients drowsy…The weight gain side effect is important. It may cause patients to want to switch (to something else)."
- "Weight change is less important than no sexual dysfunction, but it will be an issue. I would still use pregabalin first-line."
- "I'd never use pregabalin first-line in GAD until there is two-year data on weight gain."

On the other hand, sources agreed that pregabalin works. It is effective and well-tolerated, starts working within one week, and has little effect on memory, psychomotor coordination, or reaction time. It improves slow-wave sleep, has less daytime sedation than alprazolam, and is not associated with abstinence syndrome. It also appears to have fewer side effects (except perhaps the weight gain) than Pfizer's Neurontin (gabapentin), which reportedly has a fairly high drop out rate in GAD due to adverse events. A speaker said, "Gabapentin can be useful, but it does have tolerability problems in some patients." Another speaker said, "Six large, double-blind, placebo-controlled trials in GAD (generalized anxiety disorder) show efficacy (with pregabalin), including comparisons to 1.5 mg alprazolam, 6 mg lorazepam, and 75 mg venlafaxine. There is also one positive study in social phobia, with the onset of efficacy as early as one week."

Thus, the impact of the weight gain issue on use of pregabalin is likely to be affected by:

➢ **Early clinical experience** with the drug – how often patients gain weight, how much they gain, and how often doctors have to switch their patients to another drug after starting pregabalin. A source said, "The issue will be how much patients gain over six months, and we don't know that."

➢ **Whether the weight gain continues over time** as occurs with Zyprexa. And whether patients develop metabolic syndrome or diabetes.

➢ **Patient reaction** to the warning that they could gain weight on this drug. Most doctors questioned said they expect to advise patients about the potential for weight gain. They said this is a "hot button" with patients right now and were concerned that it could dampen patient enthusiasm for pregabalin.

➢ **Marketing.** Lilly marketed heavily against Pfizer's Geodon (ziprasidone), but there may not be any significant competitor counter-marketing against pregabalin.

PFIZER/NEUROCRINE BIOSCIENCE'S Indiplon (NBI-34060)

Pfizer researchers were excited about Indiplon, but one admitted that Takeda's TAK-375 will be a threat even though efficacy is less than Indiplon – because it is likely to be non-scheduled. He said, "Indiplon will have the advantage in efficacy, but Takeda's drug (TAK-375) will have a safety advantage…AmbienMR (Pfizer, zolpidem) will benefit from brand loyalty and a generic strategy."

SEPRACOR

➢ **R-sibutramine.** This triple reuptake inhibitor is an isomer of an active metabolite of Abbott's Meridia (sibutramine). It reportedly is on hold at the Phase II level.

➢ **Estorra (eszopiclone).** A Sepracor official said this has been re-filed with the FDA, and the company is waiting for the agency's decision whether it will be a Class 1 or Class 2. On labeling, all he would say is that the FDA is "taking the six-month trial into consideration, so we are hopeful."

SOMERSET'S EmSam (transdermal selegiline)

This MAO-inhibitor patch is in Phase III trials for severe depression. It is a joint venture between Mylan and Watson Pharmaceuticals, but they reportedly are looking for a partner to market it. There was no new data on EmSam at NCDEU.

TARGACEPT'S TC-1734

This is being developed (Phase II trials) as a preventive for age-associated memory impairment, but there currently is no FDA category for that, so the company will need to get the FDA to agree on the indication as well as prove the drug works. Targacept also has a deal with Aventis to take another, related agent into Alzheimer's Disease.

TEVA

➢ **Valrocemide (TV-1901).** This broad-spectrum anti-convulsant is active in a wide range of relevant animal epilepsy models. NIH chose it as a candidate drug with a high anti-epileptic potential. A 13-week Phase II study of valrocemide as add-on therapy was conducted in refractory epileptics in Europe. Valrocemide also is being explored in neuropathic pain, bipolar disease, migraine, and other indications. There was no new data on this at NCDEU.

➢ **Rasagiline.** This second-generation, irreversible monoamine oxidase type B (MAO-B) inhibitor for Parkinson's Disease differs from earlier propargylamine

MAO-B inhibitors in its chemical structure, its greater potency, and a lack of amphetamine metabolites. It is being developed in conjunction with Lundbeck and will be marketed in the U.S. jointly by Teva and Eisai.

Two Phase III clinical trials in patients with advanced PD were completed in 2003, comparing oral once-daily rasagiline plus levodopa to placebo plus levodopa. In both trials, statistically significant results for the primary endpoint were achieved – reduction in the duration of "off" time (when patients are unable to function normally).

A pivotal, double-blind, placebo-controlled, 404-patient, Phase III trial of rasagiline as monotherapy also showed positive results in early-stage PD in the U.S. and Canada. Teva also completed two successful double-blind Phase II studies in the U.S., Israel, and Hungary as well as several Phase I studies in healthy volunteers.

TITAN'S Probuphine (depot buprenorphine)

Currently, Reckitt Benckiser's Subutex (a sublingual buprenorphine) is approved to treat opiate addiction. Titan has a six-month depot version of this partial agonist in development, also for opioid addiction (in lieu of methadone). A key feature of Titan's depot is the copolymer ethylene vinyl acetate (EVA), which forms a matrix in combination with the drug. The combined EVA/buprenorphine matrix is then shaped into a small rod that can be placed under the skin. As body fluids absorb the drug, drug levels reportedly are maintained in the blood, as with IV administration, thereby avoiding the peaks and troughs of oral dosing.

The issues with this drug are:

- **Trial design.** Doctors suggested that a methadone arm rather than a placebo control would be appropriate in designing a trial for this depot. A source said, "There would be too high a drop out rate with placebo for that to be practical. A methadone comparator would be legitimate." Another source said, "Using methadone as a comparator would be good, but it would be okay to use an oral version of the same drug as a comparator, but a placebo control would not be ethical."
- **Scheduling.** A source explained, "What sets (sublingual and injectable) buprenorphine apart is that it is a Schedule 3 drug, making it the first opiate-withdrawal drug that can be prescribed in a doctor's private office. However, qualifying to use it isn't easy, and a group of doctors is limited to just 30 people on it at a time…We looked and we don't have anyone qualified to give it…The depot could be a big deal, but I'm not sure how good the market will be if it is still limited to specially-certified doctors…There are only around 1,200 methadone clinics and specially-certified doctors right now." Another source said, "Buprenorphine is a very good drug, but there is a huge problem with access…The depot would be an advantage for compliance, but they need to loosen access, especially for institutions if not for individual psychiatrists. For a (medical) group not to be able to treat more than 30 patients is absurd."
- **Formulation.** A pharmacologist said, "I'm dubious the company can do a depot because of the molecule."

UCB's Keppra (levetiracetam)

This is approved for epilepsy, but it is being used off-label for bipolar disorder. A doctor in the audience at one session asked about reports of Keppra inducing mania in patients, of being stimulatory. The speaker responded, "Case reports suggest there is a subpopulation where this happens, but I'm not making the case that this is a population-wide effect…Levetiracetam and gabapentin look like they are associated with more behavioral problems in kids…It could be those medications do have a signal in terms of creating some mania in some folks, and maybe they should be looked at in bipolar depression…Other data suggests Keppra has a good cognitive profile, which is different from topiramate."

WYETH/SOLVAY'S Bifeprunox (DU127090), SLV-310, SLV-313, and SLV-314

These atypical antipsychotics are being jointly developed by Wyeth and Solvay. It is in Phase III trials. It couples a partial agonist of the dopamine D2 receptors with a 5HT1A receptor partial agonist effect.

WYETH'S DVS-233

There was no new data on this metabolite of Effexor (which goes off patent in 2008). DVS-233 is in Phase III development, with a filing expected in 2006.

GENERAL TOPICS

Atypical Antipsychotics

Among the general comments offered about these agents were:

- "Most patients are only partial responders."
- "Anticonvulsants such as lamotrigine may be considered for partial responder patients with schizophrenia…The choice of anticonvulsant should be considered to match the target symptoms of the patient and tolerability issues."

Metabolic Syndrome

Treating psychosis still trumps concerns over weight gain with psychiatrists, but they have become much more sensitive to weight gain and the metabolic syndrome. As a result, sources predicted that Zyprexa use in schizophrenia would continue to decline, but slowly, while use of Geodon and Abilify are likely to increase – as well as higher dose Seroquel.

Data from the CATIE trial of 1,493 patients indicates metabolic syndrome occurs in 29.9% of schizophrenics, which compares to 24.1% of whites in the Framingham Study and 30.9% in Hispanics from the San Antonio Sample. Researchers have been looking for factors that can identify which patients will develop metabolic syndrome. One study of drug-naive schizophrenia patients found that cortisol but not age, BMI, or the waist:hip ratio is a factor. Another small study suggested that intra-abdominal fat is the issue, not age or BMI.

A small (16-patient) study of Lilly's Zyprexa and Johnson & Johnson's Risperdal (risperidone) found no difference between those drugs in terms of intra-abdominal fat, subcutaneous fat, or total body fat. A larger (46-patient) study comparing atypical antipsychotics [Risperdal and chlorpromazine (GlaxoSmithKline's Thorazine)] to placebo found the atypical antipsychotics statistically significantly worse on the basis of intra-abdominal fat, cholesterol, and triglycerides but not glucose. These findings led to the following opinions on the risk of weight gain, diabetes, and worsening lipid profile. A speaker said the recommendations in starting treatment are: To measure all components of the metabolic syndrome and take a family history, and then, as frequently as possible (monthly) track BMI, and if it increases by 5%, then consider switching to another antipsychotic.

Atypical Antipsychotics and Metabolic Syndrome Risk

Brand	Generic	Company	Weight gain	Diabetes risk	Worsening lipid profile
Abilify	Aripiprazole	Bristol-Myers Squibb	+/-	–	–
Clozaril	Clozapine	Novartis	+++	+	+
Geodon	Ziprasidone	Pfizer	+/-	–	–
Risperdal	Risperidone	Johnson & Johnson	++	+	+
Seroquel	Quetiapine	AstraZeneca	++	+	+
Zyprexa	Olanzapine	Lilly	+++	+	+

Dr. Alan Breier, Chief Medical Officer and Vice President of Eli Lilly, said his company has been working on trying to identify which patients will gain weight with atypical antipsychotics, "If we could identify who gained weight, it would be useful…We set out to do that…We found 41 genes that seemed candidates to Zyprexa weight gain…but none were definitive…So then we tried a whole genome scan…and we found 30,000 SNPs that separated them…Then we did individual genotyping of all patients and found a list of genes that would be surprising to most of you…This kind of work is laborious and full of pitfalls. We now need to go back and confirm the 20 genes, replicate the data, and move the work forward…When we started, we thought it was pretty simple, but we were humbled by the complexity of this."

Anticonvulsants for Bipolar Disorder

"After a drought of 15 years with only one me-too benzodiazepine, we have a mania of drug development in the last 10 years…You might be tempted to think they are mostly mood stabilizers…but what we have is a hodge-podge of different agents called anticonvulsants…As a class the newer anticonvulsants do ***not*** work in acute mania…(but) they all do seem to cause weight loss. We didn't think of anticonvulsants in the past as agents that allow weight loss, so that is a little of a paradigm buster."

He added that researchers are hoping to develop subtype schemas:

- Categorical – as "sedating" vs. "activating"
- Categorical-mechanistic – GABAergic vs. antiglutameter-gic
- Stabilizing from above vs. below baseline. Above base-line helps mania, hypomania, and mixed episodes. Stabilizing from below baseline helps major depressive episodes.

Types of Anticonvulsants

Sedating	Mixed	Activating
Characteristics		
Antimanic	---	Antidepressant
Anxiolytic	---	Anxiogenic
Sedative	---	Stimulant
Weight gain	---	Weight loss
Drugs		
Benzodiazepines	Topiramate	Felbamate
Carbamazepine	Zonisamide	Lamotrigine
Gabapentin		
Levetiracetam		
Oxcarbazepine		
Tiagabine		
Valproate		

Comments on various anticonvulsants included:

- "**Felbamate** – the first of a new generation of agents – is generally too dangerous for us to use…It has a informed consent form, problems with fatal hepatitis and aplastic anemia…It increases anxiety in epilepsy patients but not much in non-epilepsy patients."
- "**Gabapentin** (Pfizer's Neurontin) is not an anti-manic agent."
- "**Lamotrigine** has good clinical utility…The effect seems to come more from preventing depression than affecting mania."
- "We have looked at using **valproate** in acute depression, with about a one-third response rate…It causes weight gain, but it works in bipolar disorder."
- **Zonisamide** has some effect on obesity in bipolar patients. A speaker said, "It took two years to enroll 25 patients. 75% of patients dropped out – not for cognitive side effects, but for GI side effects. The average weight loss is about one pound a week."

REGULATORY ISSUES

The Physician Perspective

Getting drugs approved for bipolar maintenance may have gotten harder. A speaker said that the FDA has changed what it wants in bipolar maintenance drugs, that the agency now wants randomized data showing patients have been stabilized on the test medication for at least six months. He added, "That makes it a much harder hurdle for competitors."

The NIMH Perspective

According to a recent FDA report, U.S. pharma spending and the NIH budget for research and development have risen substantially, but the number of new molecular entities (NMEs) submitted to the FDA has decreased – so government and industry are spending more and getting less. Dr. Wayne Fenton, Deputy Director of the National Institute for Mental Health (NIMH), commented, "Our observation is that we funded a great deal of research on cognition over the last two decades…but the number of human clinical trials has barely budged (increased at all)."

Dr. Fenton cited several barriers to targeting cognition in schizophrenia, including:

- Lack of consensus on cognitive targets
- An unclear path to FDA approval and labeling
- Barriers to compound acquiring for testing
- No widely accepted clinical trial endpoints
- Ambiguity regarding optimal clinical trial design. Dr. Thomas Laughren, Team Leader for Psychiatric Drug Products at the FDA, said the FDA's current approach to trial designs for psychiatric drugs is:
  - Longer acute studies (up to 12 weeks)
  - More fixed dose studies
  - More 3-way studies (active, control, and placebo)
  - More long-term studies (randomized withdrawal)
  - Add-on studies
  - Fixed combination trials
  - Large, simple trials

Dr. Fenton said NIMH plans to survey the drug discovery literature to look for opportunities and talk to the biotech and pharma industry plus news services, "We are looking for the field to bring agents forward that look promising. Our priorities over the next several years will be:

- Develop new (non-DSM) clinical endpoints and efficient measurement tools.
- Human proof-of-concept trials for novel agents.
- Studies of the mechanisms of therapeutics with established efficacy.
- Development of biomarkers for disease and treatment response."

Dr. Thomas Insel, Director of NIMH, described the public health burden by condition, in declining order:

- Unipolar depression
- Alcohol use
- Drug use
- Bipolar disorder
- Schizophrenia. The cost of antipsychotics has been increasing 20%-35% per year for the past three years. In 2004, the cost of antipsychotic medications to the federal and state governments is expected to be about $5 billion.
- Hearing loss
- Migraine
- Iron deficient anemia

NIMH is hoping to reduce the public health burden of mental health conditions and increase the public trust in NIH by priming the product pipeline. Dr. Insel said NIMH plans to do this by helping to develop novel clinical targets (e.g., cognition in schizophrenia). He said, "We will be talking about new targets…I will be mostly thinking of new molecular targets, but there is also an opportunity for new clinical targets…Currently we have fewer than 120 molecular targets, and the top 100 selling drugs are based on 43 targets…Current psychiatric drugs target fewer than 20 targets out of a potential 300,000 targets. I suggest there are at least 5,000-10,000 interesting targets that could turn out to be far more important for drug development…The end game for us is personalized healthcare. What parents don't want to hear is that 30% of kids get 50% better when they take this medicine. What they want to know is if their kid will get better."

Key trials that are ongoing which will finish in the next year include:

- STEP-BD: treatment of 3,065 adults with bipolar disorder
- TADS: treatment of 432 adolescent patients with depression. This trial will be completed in 2004.
- CATIE: effectiveness of atypical antipsychotic drugs, with 1,450 patients enrolled
- STAR*D: treatment strategies in patients who fail to respond to a standard trial of an SSRI/SNRI (what strategies, what order or sequence, what combinations are acceptable to patients and effective).

The FDA Perspective

Rolling submissions are not yet being utilized in psychopharmacology.

The FDA's Dr. Laughren highlighted two issues in the psychopharmacologic drug approval process:

1. Collecting safety information pre-marketing – adverse events, lab data, vital signs (e.g., ECGs). He said, "We are seeing a lot of things where we think companies could have done a better job on safety. Our problem is that without adequate research support to back up our advice,

it is hard to give advice...Efficacy has had a lot of attention, and I think we need more attention on safety and to do a better job on that." He said Phase IV trials in psychopharmacology have been "pretty good." He cited three safety areas that are "hot points" with the agency right now:

- **Suicidality**. The agency hopes to have guidance soon on this for trials.
- **Liver toxicity**. The agency currently is looking at previous NDAs to see if there is a signal in the pre-market data that, if it had been seen, would have predicted hepatotoxicity. A guidance document is close to finalization. Dr. Laughren said, "A lot of psych drugs elevate ALT, but it may not cause hepatotoxicity post-marketing, so that finding alone is not a signal, but it is also rare for a drug to be hepatotoxic without ALT elevation…I don't think we know yet how to predict hepatotoxicity."
- **QT prolongation**.

2. Coding safety information. He said there is a movement in the direction of using MEDRA as a standard, "That is in use on the post-marketing side, and there is a movement to using it in pre-marketing…but presently the sponsor chooses the thesaurus (preferred terms) and then codes the adverse events, and what the FDA does is evaluate the coding. So, in essence, the sponsor creates the dictionaries as they code investigator terms, and selective review of these listings (dictionaries) is a critical part of the drug review…Terms like abnormal thinking are useless."

Among the things that go wrong with coding:

- Lumping dissimilar terms
- Splitting similar terms
- Coding to the wrong preferred terms

Dr. Laughren called coding the "weak link" in the Food and Drug law. He said this is the reason the FDA initially missed the sexual dysfunction side effect with SSRIs and SNRIs and the suicidality with psychiatric drugs in kids. He noted there is:

- No standard for what testing is needed for specific event.
- Very little research to support optimal approaches to testing.
- Generally an ad hoc approach to agency judgments.
- Wide variability across review divisions.
- A "penalty" for sensitive testing. A company that uses sensitive criteria disadvantages itself vs. companies that don't.
- Typically, little attention is paid to severity ratings, but looking at the functional effect of adverse events can be as important as the effect on function.

Among the data collection failures that sponsors make include:

- Failure to cover the spectrum from timing issues to insensitive methods.
- Not obtaining QT data at C_{max}.
- Not obtaining fasting glucose or orthostatic measures.
- Poor methods for assessing height and weight.

A new initiative began at the FDA this year – the Critical Path Initiative. It focuses on safety, medical utility, and manufacturing (industrialization). Dr. Laughren said, "This is a good idea and the right direction…I think it will be important for FDA to invest the resources to make this a success…so we will see where this goes." The FDA plans to develop a list of opportunities for research, such as:

- Pharmacogenomics in drug development
- Imaging technologies that may contribute as biomarkers in early drug development
- Application of quantitative disease models to drug development

The Industry Perspective

Lilly's Dr. Breier said the current cost per NME of $750 million to $1.0 billion is not sustainable, and he urged that industry and government begin to do things differently. He said, "Absolutely fundamental will be greater reliance on partnerships and alliances. Lilly is a mid-size company, and adding to our infrastructure year after year will not work for us …We can extract greater synergy and reduce redundancy in R&D spending by NIH, biotech, and pharma working together …I'm proposing a futuristic idea: Pulling Phase IV trials more tightly into the drug development cycle…We do an awful lot of work on Phase III…Would it be possible to bring Phase IV more tightly into the drug development process? …The idea is to redefine Phase IV as integral to the regulatory approval process…We would like to see more failures early, but very few failures late…We would like to move forward with Phase II molecules that have a greater chance of making it to launch…What is important in ascertaining early failures is having a better list of candidates…Larger use of biomarkers is fundamental to this happening."

Among the advantages Dr. Breier cited to this were:

1. Labeling would become more "iterative" across the drug's life cycle.
2. Staged/controlled launches for specific agents.
3. Assess potential safety signals in large, naturalistic settings.
4. Effectiveness, health outcomes, and risk/benefit data for labeling would be obtained under real world conditions.

Dr. Breier also commented on the large federal fines that have been levied against some big pharmas, "It has gotten our attention…and it can't continue." ♦