Trends-in-Medicine

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Quick Pulse

Trends-in-Medicine
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American College of Neuropsychopharmacology

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The American College of Neuropsychopharmacology (ACNP) meeting offered an interesting look at a variety of drugs in development for addiction, anxiety, bipolar disorder, depression, migraine, obsessive compulsive disorder, and schizophrenia. The meeting also offered an overview of several new classes of agents, including endocannabinoids, histone deacetylase (HDAC) inhibitors, neurosteroids, metabotropic glutamate receptors (mGLuRs), and glycine T inhibitors.

Drugs and Devices by Disease State

Addiction

A University of Washington study in rats found that 5-HT_{1B} receptor modulation may be a promising therapeutic treatment for drug addicts.

Bristol-Myers Squibb's Abilify (aripiprazole)

There were a number of Abilify posters at ACNP, including:

- A study conducted at the New York Psychiatric Institute, in which aripiprazole increased cocaine self-administration and increased stimulant abuse when given to cocaine addicts. The suggestion was that this might not be a good drug to give to cocaine addicts. Experts who saw the poster also suggested it might not be a good drug to give to a patient with any drug addiction.
- A mouse study by Medical University of South Carolina researchers who concluded:
  - Abilify decreased alcohol consumption in dependent mice in a dose-related manner but did not alter alcohol intake in non-dependent mice.
  - When Abilify was terminated (during a washout period), elevated drinking behavior returned to vehicle-treated levels in the dependent animals.
  - Abilify may be effective in reducing excessive alcohol consumption associated with dependence.

Johnson & Johnson's Risperdal (risperidone)

A pilot, 34-patient, open-label, 8-week study by Puget Sound Healthcare System and University of Washington researchers suggested that Risperdal may decrease methamphetamine use. The effect was noted immediately and may occur with either oral or injected Risperdal. While this was an open-label trial, it suggested further investigation is warranted.

BIPOLAR DISORDER

ASTRAZENECA'S Seroquel XR (quetiapine extended release)

Seroquel XR is approved for use in schizophrenia, and the company plans to seek approvals in major depressive disorder (MDD), generalized anxiety disorder (GAD), and bipolar disorder. A poster at ACNP presented the results of one of two worldwide studies of maintenance treatment in bipolar with Seroquel XR concomitantly with lithium or divalproex (Abbott's Depakote). AstraZeneca researchers reported that the combination therapy significantly prevented the recurrence of mania or depression mood events. The efficacy of the combination therapy was independent of the polarity of the index episode or rapid-cycling disease course. Long-term treatment with the combination was generally well tolerated. The researchers noted that this is one of the first studies to demonstrate sustained effectiveness of an atypical anti-psychotic as maintenance treatment in a large cohort of bipolar patients.

BRISTOL-MYERS SQUIBB'S Abilify (aripiprazole)

A poster at ACNP presented the results of 296 pediatric bipolar patients (age 10-17) randomized to either Abilify or placebo for 30 weeks. Researchers reported that both the 10 mg and 30 mg Abilify doses were superior to placebo, and both doses were generally well tolerated. The three most common adverse events were somnolence, extrapyramidal side effects (EPS), and fatigue. There was no clinically significant weight gain observed.

FOREST LABORATORIES' Namenda (memantine)

Preliminary results of a study by Indiana University researchers suggested that memantine may augment the anti-depressant effects of lamotrigine in bipolar disorder. Patients on 100 mg lamotrigine were started on 5 mg memantine, with the memantine dose increased weekly to 20 mg and then treated for 8 weeks. There was no statistically significant change in HDRS score, YMRS, or cognitive testing vs. placebo. Researchers concluded that the combination showed "some efficacy" in alleviating depression as well as some benefits on cognitive performance.

DEPRESSION AND ANXIETY

Major depressive disorder (MDD) affects 14 million Americans and 340 million people worldwide. Even more people have depression. The STAR*D trial found that even with four medications ~33% of MDD patients remained refractory to treatment.

Devices

➢ **CYBERONICS' VNS for treatment-resistant depression (TRD).** The company convinced the FDA to approve VNS, but CMS isn't convinced of the efficacy and isn't reimbursing for it for this indication. Three- and six-month data from a TRD post-market registry of VNS was presented at ACNP. At six months, there was a trend to improvement, but not in the key measure of MADRS. A researcher said, "My take-home message is: This is TRD, and when you wait too long for VNS, it may be too little too late. There was very minimal effect." At six months, 22% of VNS patients vs. 12% of non-VNS patients showed an improvement in QIDS-SR – the only statistically significant measure that favored VNS. However, VNS devices are still being put in patients – occasionally and in carefully selected refractory patients – at the presenter's hospital, but reportedly at a much lower rate than in the past.

➢ **NORTHSTAR NEUROSCIENCE'S implantable cortical stimulation for MDD.** Northstar sponsored a feasibility study in 12 patients of an epidural cortical stimulation system targeting the left dorsolateral prefrontal cortex (DLPFC). Preliminary results suggested that the treatment effect exceeded sham and increased over time. Researchers suggested that the effect may be optimized by refining the location of the stimulation electrode on the DLPFC. To date, they said: 1 patient is in remission, 2 patients met the criteria for classical response, and 3 patients had "clinical benefit."

Drugs

ASTRAZENECA'S Seroquel XR (quetiapine extended release)

➢ **MDD.** A poster at ACNP presented the results of a 6-week, randomized, double-blind, parallel-group, placebo-controlled, double-dummy, international study of 493 MDD patients with an inadequate response to antidepressant therapy. The study found adjunctive Seroquel XR was effective in reducing depressive symptoms and in reducing anxiety symptoms in MDD patients. The onset of action was seen as early as Week 1.

Seroquel XR in MDD at Week 6

Measurement	Placebo n=160	Seroquel XR 150 mg/day n=166	Seroquel XR 300 mg/day n=161
Primary endpoint: MADRS (change from baseline)	- 12.21	- 15.26 (p<0.01)	- 14.94 (p<0.01)
MADRS response (>50% reduction from baseline)	46.3%	55.4% (Nss, p=0.107)	57.8% (p<0.05)
MADRS remission (score <8)	23.8%	36.1% (p<0.05)	31.1% (Nss, p=0.126)
HAMD change	- 11.3	- 13.81 (p<0.001)	- 13.56 (p<0.01)
CGI-S change	- 1.25	- 1.72 (p<0.01)	- 1.64 (p<0.01)

➢ **GAD.** The results of a double-blind, placebo-controlled, 10-week, parallel group, Phase III study of Seroquel XR in 673 GAD patients was presented in poster form at ACNP. The study found that both 50 mg/day and 150 mg/day were effective in improving symptoms of anxiety in GAD patients. The onset of action was seen as early as Day 4. The higher

dose (150 mg/day) was superior to placebo in improving the health-related quality of life in GAD patients without major depression.

Seroquel XR in GAD at Week 8

Measurement	Seroquel XR 50 mg/day n=219	Seroquel XR 150 mg/day n=216	Paroxetine 20 mg/day n=214	Placebo n=160
Primary endpoint: HAMA (change from baseline)	- 13.95 (p<0.05)	- 15.96 (p<0.001)	- 15.45 (p<0.01)	- 12.30
HAMA responders	62.6% (p<0.05)	70.8% (p<0.001)	65.9% (p<0.001)	52.1%
HAMA remitters	32.4% (Nss, p=0.28)	42.6% (p<0.01)	38.8% (p<0.05)	27.2%
CGI-S change	- 1.9 (Nss, p=0.082)	- 2.10 (p<0.001)	- 1.95 (p<0.05)	- 1.53

BRISTOL-MYERS SQUIBB'S Abilify (aripiprazole) in MDD

A poster at ACNP presented a pooled analysis of suicidality in two double-blind, placebo-controlled adjunctive therapy trials in MDD patients with an inadequate response to an antidepressant alone. Researchers found that treatment-emergent suicidality was low, and treatment-emergent suicidal ideation was numerically (but not significantly) lower with Abilify vs. placebo. They concluded that adjunctive Abilify therapy did not increase the risk of suicidality in patients with MDD without psychosis.

Another study looked at the metabolic effects of Abilify adjunctive therapy in MDD subgroups. Researchers found that change in body weight did not appear to be dose-related and did not correlate with changes in triglyceride levels. They concluded that this is "reassuring for short-term use of adjunctive aripiprazole given the potential metabolic impact of either antidepressants or antipsychotics alone," but they noted that "the results also reinforce the need for metabolic monitoring according to consensus guidelines in patients treated with antipsychotics either alone or as adjunctive therapy to antidepressants."

EPIX PHARMACEUTICALS' PRX-00023

There were no data at ACNP on this 5-HT_{1A} receptor agonist which is being developed for MDD patients with high levels of anxiety. However, a company researcher discussed it. He said it is a potential competitor to Fabre-Kramer's gepirone, but it reportedly has less headache and BID dosing. It can be force-titrated to maximum tolerated dose (MTD) in one week and has shown a 12-point shift in MADRS, which he said suggests "something is happening." The only measure in the current trials is MADRS, but the researcher believes the FDA will accept that. A non-Epix researcher was less optimistic, saying it failed in anxiety, so now it is being tested in depression and pointing out that the efficacy is being overestimated and the side effects underestimated.

FABRE-KRAMER PHARMACEUTICALS/ GLAXOSMITHKLINE'S gepirone ER

The FDA rejected this highly selective 5-HT_{1A} receptor agonist, but the company apparently is not giving up and hopes to overcome the non-approvable letter. A researcher said the FDA wants more dose data and more definitive positive data. He wasn't sure if this means the company will need another trial. Currently the company is analyzing the data it has, based on patients who got the dose they think is most effective (60-80 mg).

A meta-analysis of 7 studies of gepirone in MDD favored gepirone (p=0.002). This included two positive studies, four positive but not statistically significant studies, and one negative study. However, it is likely that the company will have to do at least one more fairly significant trial to get approval, not a small trial, and there is still a significant risk that this trial will not be statistically significant.

Side effects are a big issue; they are extremely common though reportedly mostly mild. However, there are no sexual side effects, and there was only 2.5% discontinuation rate in all the trials for side effects. If this ever gets approved, it is likely to be as an add-on to an SSRI – not first-line treatment because the effect just isn't large enough for that.

In addition, GSK researchers presented a poster at ACNP on an 8-week, multicenter, double-blind, parallel group, placebo-controlled, flexible dosing study (FKGBE007) of gepirone ER in adult MDD outpatients. They reported that HAMD responders became significant (vs. placebo) at Week 4, and remitters became significant at Week 3.

Gepirone ER Trial Results

Measurement	Placebo	Gepirone ER 20 mg/day titrated to 60-80 mg/day	p-value
Primary endpoint: HAMD17 total score (change from baseline)	- 8.0	- 10.2	0.032
Secondary endpoints (change from baseline)			
MADRS	- 9.9	- 13.7	0.008
HAMD28	- 11.8	- 15.0	0.032
HAMD depressed mood	- 1.0	- 1.2	Nss, 0.101
Bach-6	- 4.2	- 5.6	0.016
CGI-S	- 0.9	- 1.3	0.015
Adverse events			
Dizziness	9.7%	45.2%	---
Nausea	12.9%	36.3%	---
Headache	1.1%	24.2%	---
Somnolence	4.8%	10.5%	---
Urinary tract infection	8.9%	9.7%	---
Dry mouth	5.6%	7.3%	---
Diarrhea	4.8%	6.5%	---
Insomnia	2.4%	5.6%	---
Palpitations	0.8%	5.6%	---

JOHNSON & JOHNSON'S Risperdal (risperidone)

Researchers from the University of Alabama at Birmingham studied the efficacy of Risperdal in 23 patients with MDD, and they found that Risperdal was beneficial in augmenting treatment in MDD patients with suicidal risk during a depressive episode:

- Symptom severity was significantly reduced.
- A dose of 0.25 - 2.0 mg/day was effective in reducing suicidality in patients with MDD.
- Risperdal was superior to placebo in reducing core symptoms of depression.
- There was less irritability with Risperdal than with placebo.
- More Risperdal patients completed the study.

Drugs in Development for Depression and Anxiety

Company	Drug	Type	FDA status
Amarin	Miraxion, LAX-101	"Purified" Omega-3	Phase II
AstraZeneca	AZD-6765, AZD-2327	Unknown	Phase I/II
Bristol-Myers Squibb	Pexacerfont (BMS-562086)	CRF01 antagonist	Phase III
Clinical Data Online	Vilazodone	5-HT_{1A} partial agonist, SSRI	Phase III
Epix	PRX-00023	5-HT_{1A} agonist	Phase II
Fabre-Kramer	Gepirone ER	5-HT_{1A} partial agonist	Not approvable
	TGWOOAD/AA	5-HT_{1A} agonist, 5-HT_2 antagonist	Phase II
	TGBA01AD	SSRI, 5-HT_{1A} agonist, 5-HT_2 antagonist, 5-HT_{1D} antagonist	Phase II
GlaxoSmithKline	Caspitant, vestipitant, and orvepitant	All NK-1 antagonists	Phase I/II
GSK/Neurocrine Biosciences	GW-372475 (NS-2359)	Dopamine, serotonin, and norepinephrine reuptake inhibitor	Phase II
	G-876008	CRF-1 antagonist	Phase II
Johnson & Johnson/ SK Pharmaceuticals	YKP-10A, R228060	Phenylalanine derivative with unknown mechanism	Phase II
Johnson & Johnson/Taisho	JNJ-19567470 or TS-041	CRF-1 antagonist	Phase I
Lilly	LY-2216684	Norepinephrine reuptake inhibitor	Phase II
Lundbeck	LuAA-21004 and LuAA-24530 and LuAA-34893	bis-aryl-sulphanyl modulator and other targets	Phase II Phase III (21004)
	LuAA-44608	Neuropeptide Y receptor antagonists	Phase I
Merck/Dov Phamaceutical	DOV-21,947	Dopamine, SNRI	Phase II
Novartis	AFQ-056	mGluR5 receptor antagonist	Phase I
Novartis/Servier	Valdoxan (agomelatine, AGO-178)	5-HT_{2C} antagonist, 5-HT_{2B} antagonist, melatonin M1/M2 receptor agonist	Phase III
NPS	Delucemine (NPS-1506)	NMDA antagonist	Phase I
Ono Pharmaceuticals	ONO-2333Ms	CRF-1 antagonist	Phase II
Pfizer	PD 332-334	Alpha2delta calcium channel blocker	Phase II
	Elzasonan, CP-448,187	5-HT_{1B} and 5-HT_{1D} receptor antagonist	Phase II
Pfizer/Organon	ORG 34517/34850	GR antagonist	Phase II
	URB-597	FAAH (fatty acid amide hydrolase) inhibitor	Phase II
Pharmos	R-tofisopam	R-isomer of racemic tofisopam (a benzodiazepine)	Phase I
Prescient	PRE-703	mGluR agonist	Phase I
Roche	R-1647 and R-1661	Unknown	Preclinical/Phase I
Sanofi-Aventis	Saredutant (SR-48968)	NK-2 antagonist	Phase III
	SSR-149415	V1B antagonist	Phase II
	SSR-125543	CRF-1 antagonist	Phase I
	SSR-126374	CRF-1 antagonist	Preclinical
	SSR-411298	FAAH (fatty acid amide hydrolase) inhibitor	Preclinical
	SAR-102279	NK-2 receptor antagonist	Preclinical
Sepracor	SEP-225289	Da/Ne/5-HT reuptake inhibitor	Phase I
SK Pharmaceuticals	YKP-3089	Unknown	Phase I
	YKP-581	Unknown	Preclinical
Targacept	TC-2216	Nicotinic acetylcholine receptor (nAChR) antagonist	Phase I
	TC-5214	Non-selective (nAChR) antagonist	Phase I
Tetragenex	Nemifitide (INN-00835)	IV pentapeptide analog of melano-cyte-inhibiting factor (MIF-1)	Phase II
Tikvah Pharmaceuticals	TIK-101	NMDA antagonist	Phase II
Wyeth	Pristiq (desvenlafaxine, DVS-233 SR)	Metabolite of Effexor (venlafaxine)	Approvable but additional trials needed

LILLY

➢ **Strattera (atomoxetine) in SAD.** A randomized, double-blind, placebo-controlled study by Lilly researchers in adults with ADHD and co-morbid SAD found Strattera was safe and effective vs. placebo in treating the core symptoms of ADHD and SAD.

Strattera in ADHD+SAD at 14 Weeks

Measurement	Strattera n=127	Placebo n=137	p-value
Primary endpoint: CAARS total ADHS symptom score (change)	Down ~ 11	Down ~ 5	<0.001
Secondary endpoint: LSAS total score (change)	Down ~ 27	Down ~ 16	<0.001
Treatment-emergent adverse events			
Headache	20.3%	14.2%	Nss, 0.122
Insomnia	17.0%	9.0%	0.020
Nausea	16.0%	7.6%	0.010
Dry mouth	15.6%	4.3%	<0.001
Dizziness	7.5%	2.4%	0.023

➢ **Cymbalta (duloxetine).** An open-label study of fluoxetine in MDD found female gender, younger age, baseline HAMD3 core, treatment-emergent worsening of depression, and treatment-emergent major psychomotor activation to be significant risk factors for the emergence of suicidal ideation. Lilly researchers did a database analysis of 15 studies with 1,564 Cymbalta and 1,004 placebo-treated patients and found baseline suicidal ideation, history of suicide attempts, insomnia, and treatment-emergent worsening of depression were statistically significant risk factors for both placebo and Cymbalta groups. Treatment-emergent major psychomotor activation was a risk factor for emergent suicidality for both treatment groups, but it was only statistically significant for placebo. There were no potential risk factors tested which were risk factors for the Cymbalta group but not for placebo. The researchers concluded, "This finding, that major psychomotor activation is a clear risk factor with placebo (and perhaps a stronger risk factor than with active treatment), fails to support the finding in the fluoxetine database that such activation is a risk factor with active treatment and possibly protective within placebo treatment."

PGX's vilazidone

This 5-HT_{1A} receptor agonist was first tested by GSK, which reportedly could separate it from placebo, but PGX may have found a way to turn it into a winner (*NOTE:* The company was formerly Genaissance, which then became Clinical Data, and is now PGX.) There were no data at ACNP on this, but a researcher said PGX ran one positive efficacy study and is now planning a second trial. He said the company collected DNA for marker analysis in the first trial to look for response markers, and predicted that if vilazidone gets approved, it is likely to be marketed either as a marker or as a drug with a laboratory test.

WYETH

➢ **Effexor ER (venlafaxine ER).** There appeared to be no benefit with Effexor over Lilly's Prozac (fluoxetine). Dr. Alan Gelenberg of the University of Arizona presented the PREVENT study results, which he said showed that "no matter how you look at it, there is no significant difference between fluoxetine, an SSRI, and venlafaxine ER, an SNRI, as much as Wyeth had wanted there to be."

➢ **Pristiq (desvenlafaxine).** The data from two identical Phase III trials of this SNRI in outpatients with MDD were presented in one poster at ACNP, and the data did not appear to really distinguish it. Furthermore, the efficacy was not very good, especially in the U.S. trial. Both trials were 8-week, randomized, double-blind, multicenter, placebo-controlled trials comparing 50 mg and 100 mg desvenlafaxine to placebo.

- **International study in 485 patients.** Both doses met the primary and all secondary endpoints.

Phase III Pristiq Trial Results at 8 Weeks

Measurement	Pristiq 50 mg	Pristiq 100 mg	Placebo
U.S. Trial (*by LOCF*)			
Primary endpoint: Mean change in HAMD17	- 11.5 (p=0.018)	- 11.0 (Nss, p=0.065)	- 9.5
Secondary endpoint #1: MADRS change	- 15.0 (p=0.022)	- 14.3 (Nss, p=0.095)	- 12.3
Secondary endpoint #2: CGI-score change	- 1.5 (Nss, p=0.074)	- 1.4 (Nss, p=0.208)	- 1.2
Secondary endpoint #3: COVI total change	- 1.5 (Nss, p=0.080)	- 1.4 (Nss, p=0.346)	- 1.2
International trial (*by LOCF*)			
Primary endpoint: Mean change in HAMD17	- 13.2 (p=0.002)	- 13.7 (p<0.001)	- 10.7
Secondary endpoint #1: MADRS change	- 16.4 (p=0.004)	- 17.5 (p<0.001)	- 13.3
Secondary endpoint #2: CGI-score change	- 2.1 (p=0.003)	- 2.2 (p<0.001)	- 1.6
Secondary endpoint #3: COVI total change	- 1.6 (p=0.001)	- 1.7 (p=0.004)	- 1.1
Treatment-emergent adverse events in U.S. study			
Any adverse event	84%	76%	70%
Dizziness	17%	7%	4%
Insomnia	14%	12%	4%
Sweating	7%	10%	3%
Dry mouth	11%	16%	4%
Constipation	9%	11%	3%
Drug-related serious adverse events	1 patient (migraine)	2 patients (1 hypotension, 1 liver elevation)	---
Treatment-emergent adverse events in U.S. study			
Any adverse event	78%	77%	62%
Dizziness	10%	7%	4%
Insomnia	10%	10%	5%
Nausea	27%	30%	11%
Asthenia	9%	10%	5%
Srious adverse events	0	0	0

- **U.S. study in 474 patients.** Both doses performed very poorly. The 100 mg dose was not statistically significant on any measure vs. placebo, and the 50 mg dose met the primary endpoint and one secondary endpoint but failed to meet the other two secondary endpoints.

What are the advantages of Pristiq over Effexor ER? A researcher said that with Pristiq:

- The 50 mg dose may not need titration.
- There is no CYP450 interaction, so it might be less interactive with other medications. "Venlafaxine isn't bad, but this is better."
- Nausea actually was more with Pristiq than with Effexor in European studies, but the nausea was less in U.S. studies.
- On efficacy, it is too early to tell if there is any differentiator.

Ketamine

One of the problems with the current antidepressants is that they take a while to work, so there is interest in development of a rapid-acting antidepressant, and that was the topic of a session at ACNP. However, much of this session focused on the use of ketamine – a dissociative anesthetic used for human and veterinary medicine.

Dr. Dennis Charney of Mt. Sinai School of Medicine said that 4-5 studies have found that a subanesthetic dose (0.5 mg/kg) given IV over 40 minutes produced a rapid antidepressant effect in 60%-70% of patients, and the effect lasted longer than the half-life of ketamine or its metabolite. He concluded, "We found IV ketamine (0.5 mg/kg) has acute-onset antidepressant properties in a highly treatment-resistant sample. The durability and persistence of response in outpatients were similar to those reported in previous inpatient samples. Overall, tolerability was acceptable, and by 24 hours virtually all adverse events had resolved." He noted that the optimal dose isn't known, and a lower dose may be just as effective.

Dr. Charney said he is initiating a new study to test strategies for maintaining the acute ketamine response. Patients who respond to a single IV ketamine dose will be maintained with continuation of IV ketamine (5 additional doses every other day for 2 weeks) and followed to see how long they maintain their response. He said, "So far, we've done 3 patients – very seriously depressed, highly refractory patients. As we gave the 6 doses, the initial response is, in general, maintained as long as they are getting the ketamine. But in two patients, when the ketamine was stopped at 2 weeks, the return of symptoms occurred very quickly. I don't know about the other patient. And we don't know if 6 doses is the right amount… We did find in these patients that, if anything, repeated dosing of ketamine is better tolerated than an initial single dose."

Dr. Husseini Manji of the National Institute of Mental Health (NIMH) suggested that an agent that increases AMPA such as Sanofi-Aventis's Rilutek (riluzole), a selective NR2B antagonist, may sustain the initial effects of ketamine, "Preliminary evidence suggests that combining a glutametergic modulator (riluzole) with ketamine prolongs ketamine's early response."

Migraine

Merck's MK-0974

The results of a randomized Phase II trial of MK-0974 – the first oral CGRP (calcitonin gene-related peptide) receptor antagonist – in acute migraine was presented at ACNP. In a 330-patient Phase I study MK-0974 was shown to have a T_{max} of ~1.5 hours, $T_{½}$ ~6 hours, good tolerability, no significant safety issues, and no significant effect by age, gender, or gastric status. The Phase II trial was a two-stage adaptive design testing 2 doses of MK-0974. The primary endpoint was 2-hour pain relief, and there was a statistically significant (p=0.015) overall treatment effect vs. placebo. The 300-600 mg doses were effective, but doses from 25-200 mg were dropped after an interim analysis for lack of efficacy. Researchers concluded that the results suggested:

- Superiority vs. triptans, especially in 2-24 hour pain freedom.

MK-0974 Phase II Results in Acute Migraine

Measurement	MK-0974 300 mg n=39	MK-0974 400 mg n=45	MK-0974 600 mg n=40	Rizatripan 10 mg n=34	Placebo n=115
Primary endpoint: 2-hour pain relief	68.1%	48.2%	67.5%	69.5%	46.3%
2-hour pain freedom	45.2%	24.3%	32.1%	33.4%	14.3%
2 - 24 hour sustained pain relief	52.6% *	37.8% *	52.5% *	35.3%	23.5%
2 - 24 hour sustained pain freedom	39.6%*	22%*	32%*	18.4%	11%
Other endpoints at 2 hours					
Photophobia	46.0%	57.6%	36.1% **	47.0%	61.3%
Phonophobia	30.l% **	51.5%	39.6%	46.5%	56.9%
Nausea	22.0%	38.1%	7.8%	17.2% ***	34.9%
Functional disability: normal	55.3% *	35.6%	47.5% ***	41.2%	26.1%
Optimal second dose	25.5% *	35.4% **	31.8% **	43.4%	59.5%
Adverse events					
Any adverse event	35.3%	36.5%	40.8%	42.0%	36.2%
Drug-related adverse events	25.5%	26.9%	24.5%	28.0%	23.4%
Dry mouth	3.9%	3.8%	2%	2%	2.1%
Nausea	5.9%	7.7%	10.2%	2%	12.8%
Dizziness	5.9%	1.9%	8.2%	2%	4.3%
Parasthesia	0	0	2%	4%	0

* p≤0.001 ** p≤0.01 *** p≤0.05

- Efficacy at the top 3 doses (300 mg, 400 mg, and 600 mg).
- Reduction in the symptoms of photophobia and phonophobia, with a positive trend in reducing nausea.
- Well tolerated without the typical triptan side effects (chest pressure, parathesia, dysaesthesia, or hyperaesthesia).

OBSESSIVE COMPULSIVE DISORDER (OCD)

JOHNSON & JOHNSON'S Topamax (topiramate)

Dr. Heather Berlin of Mt. Sinai School of Medicine and colleagues at other institutions conducted a 36-patient, double-blind, placebo-controlled trial of Topamax vs. placebo in OCD. They found Topamax significantly decreased compulsions over 12 weeks but did not change obsession scores.

Efficacy of Topamax in OCD

Measurement	Topamax	Placebo	p-value
Compulsion	Down 4.01 points	Down 0.34 points	---
Effect on Y-BOCS compulsions	N/A	N/A	0.013
Effect on Y-BOCS obsessions	N/A	N/A	Nss, 0.763
Effect on Total Y-BOCS score	N/A	N/A	Nss, 0.115

OREXIGEN

Researchers from the company and Virginia Commonwealth University reported on a rat study which found that 8 mg/day of fluoxetine combined with naltrexone 10 mg/day is synergistic in OCD. The combination reduced SIP (schedule-induced polydipsia) – a model for OCD – by 67%. They concluded the combination "merits a human proof-of-concept trial in OCD."

SCHIZOPHRENIA

Schizophrenia, a chronic, disabling brain disorder characterized by hallucinations, delusions, and disordered thinking, affects ~24 million people worldwide, including >2 million in the U.S. and >4 million in Europe.

ABBOTT/MERZ'S MK-801, an NMDA receptor antagonist

A rat study suggested that drugs impairing cognition in informal subjects may have therapeutic potential in reversing certain "hypercognitive" phenomena associated with schizophrenia, such as proactive interference (which is possibly one of the contributors to the cognitive deficits associated with schizophrenia).

ACADIA PHARMACEUTICALS' pimavanserin (ACP-103)

The data looked very good for this as a potentiator of Risperdal. A poster indicated that when you add pimavanserin to 2 mg of Risperdal, you get the same efficacy as 6 mg of Risperdal but with fewer side effects and a faster onset of action. A researcher said, "I think you could start with the combination and then get rid of the Risperdal after six weeks."

Pimavanserin boosted all PANSS (Positive and Negative Syndrome Scale) scores – a measure of positive symptoms (e.g., hallucinations and delusions) ***and*** negative symptoms (such as lack of emotion expression). It also increased CGI and was associated with less weight gain than Risperdal. A researcher said pimavanserin also was cognitive-enhancing.

This was a multicenter, randomized, double-blind, placebo-controlled, 6-week study of 423 recently hospitalized schizophrenics. There were five arms:

- Risperdal low dose 2 mg (RisLD).
- Risperdal high dose 6 mg (RisHD).
- Pimavanserin 20 mg + RisLD (Pim/RisLD).
- Pimavanserin 20 mg + low dose haloperidol 2 mg (Pim/Hal).
- Haloperidol 2 mg (Hal).

Pimavanserin Trial Results

Measurement	RisLD	Pim/RisLD	RisHD	Hal	Pim/Hal
Reduction in total PANSS score at Day 43	- 23.0 (p=0.007 vs. placebo)	- 23.2	- 16.3		
PANSS ≥20% change from baseline (responders) at Day 15	37.7%	62.3% (p=0.013 vs. RisHD, p=0.002 vs. RisLD)	42.1%	~ 45%	~ 48%
PANSS ≥20% change from baseline (responders) at Day 43	37.7%	~ 70% (p=0.001 vs. RisLD, Nss vs. RisHD)	~ 60%	~ 60%	~ 60%
PANSS positive change at Days 15-43	---	p<0.05 vs. RisLD, Nss vs. RisHD	---	---	---
PANSS negative change at Days 15-43	---	p<0.05 vs. RisLD, Nss vs. RisHD	---	---	---
PANSS general change at Days 15-43	---	p<0.05 vs. RisLD, Nss vs. RisHD	---	---	---
PANSS cognitive change at Day 22	---	Nss vs. both RisLD and RisHD	---	---	---
PANSS cognitive change at Day 36	---	p<0.05 vs. RisLD, Nss vs. RisHD	---	---	---
CGI-Severity change on Days 15-43	---	p<0.05 vs. RisLD, Nss vs. RisHD	---	---	---
Weight gain >7% at end of study	~ 16%	~ 7% (p=0.08 vs. RisLD, p=0.031 vs. RisHD	~ 19%	~ 3%	~ 5%

Researchers concluded:

- Pimavanserin potentiated the efficacy of RisLD on psychopathology while reducing side effects.
- Pimavanserin did not potentiate haloperidol.
- RisLD was significantly less effective than the other treatments.
- Pimavanserin enhanced the efficacy of RisLD at all time points from Week 2 on with regard to PANSS total, positive, negative, general, and CGI.
- Pim/RisLD was more effective than RisHD or RisLD at Day 15 in terms of PANSS responders.
- Pim/RisLD was ***as effective*** as RisHD, haloperidol, and Pim/Hal at all time points.
- There were fewer patients with ≥7% weight gain with Pim/RisLD than RisHD or RisLD.
- Serum prolactin levels were lower with Pim/RisLD than RisHD and lower with haloperidol than Risperdal.
- There was a trend to less akathisia in the pimavanserin groups.
- Pimavanserin may be more effective in enhancing the efficacy of atypical antipsychotics with a lower D2 receptor occupancy.

Can pimavanserin be used to potentiate all antipsychotics? Probably not. Haloperidol is not potentiated by pimavanserin.

Currently, pimavanserin is in Phase II in schizophrenia and in Phase III for L-dopa psychosis (as monotherapy). However, a GSK researcher and other sources were dubious about the outlook for this drug. They warned that it is difficult to use an adjunctive therapy with an atypical antipsychotic in the first 6-12 weeks because that's when the patient's dose is being either titrated or adjusted, so using pimavanserin would just confuse the dosing of the atypical antipsychotic until the patient was stabilized. There was also some concern about the placebo effect in some groups studied.

JOHNSON & JOHNSON

➢ **Invega (paliperidone ER).** Studies showed no significant benefit over J&J's Risperdal. A J&J researcher said Invega is not selling well in the U.S. because it simply hasn't been able to be differentiated but that it is doing well in Europe. Another researcher with extensive paliperidone experience said, "J&J really doesn't know yet if paliperidone is better than Risperdal – but they need it to be…It is a little smoother than Risperdal, but I'm not sure there is much difference."

Dr. Ira Glick of Stanford presented a study with paliperidone ER that caused him to conclude that schizophrenia trials in general should be longer, "Eight weeks is too short. We need at least 12 weeks. Clinicians keep changing drugs, but they need to stay with each drug longer – to hang in there – and not keep switching."

A study by University of Maryland researchers found that haloperidol does not increase social behavior or cognitive function in a rat model of schizophrenia, but paloperidone (for 7 days) caused a dose-related increase in social interaction behavior. The data suggested that "paliperidone may increase sociality by increasing PVN OT mRNA production, reversing a deficit in the oxytocinergic system."

➢ **Razadyne (galantamine, formerly Reminyl).** A study by Yale and University of Toronto researchers suggested that Razadyne, which helps with cognition in Alzheimer's patients, may not be useful in reducing neurocognitive dysfunction in schizophrenics. Researchers found no evidence that Razadyne altered neurocognitive outcomes as a function of drug dose, smoking status, or the interaction of smoking and drug dose.

LILLY'S Strattera (atomoxetine)

Preliminary results from a study by Yale and University of Toronto researchers suggested that 80 mg/day of Strattera ***selectively*** reduces deficits in VSWM (visuospatial working memory) and phonemic verbal fluency in schizophrenics who were heavy smokers (≥15 cigarettes/day). However, smoking consumption and craving were not affected. Strattera was well tolerated, with no change in positive or negative symptoms. Researchers concluded that the results suggest that Strattera may decrease certain prefrontal cortical and executive function deficits in schizophrenics.

Another study by University of Maryland researchers studied 32 patients and found Strattera was ***not effective*** in increasing cognitive function in schizophrenics, and there was a trend to an increase in EPS. They concluded, "Atomoxetine was well tolerated…suggesting it can be used safely in patients with schizophrenia controlled on second-generation antipsychotics. (However) atomoxetine has at best small-to-moderate effects on cognition in schizophrenia." Cognition was not better than placebo on any measure.

Strattera in Heavy Smoking Schizophrenics

Measurement	Placebo	Strattera 40 mg/day	Strattera 80 mg/day
Number of cigarettes per day	Nss	Nss	Nss
VSWM 30-sec. delay	Nss	Nss	Improved 64%
VSWM 60-sec. delay	N/A	N/A	Improved 48.5%
COWAT	N/A	N/A	Improved 61.8%

PFIZER'S Geodon (ziprasidone)

The ZODIAC study was presented at ACNP, comparing mortality with Geodon to Lilly's Zyprexa (olanzapine) in real-world use. This was an open-label, prospective, randomized, post-marketing study of 18,154 schizophrenics in 18 countries

(53.3% in the U.S.). There were no p-values; only relative risk was reported. The only statistically significant difference between the two agents was all-cause hospitalization, which was more common with Geodon. However, researchers said that "exploratory analyses indicate that this difference is largely due to the incidence of hospitalization for psychotic reasons (11.9% with Geodon vs. 7.5% with Zyprexa)."

The researchers concluded: "The modest QTc prolongation observed with ziprasidone does not translate into an increased risk of clinically-meaningful outcomes.

Another Geodon poster provided a pooled analysis of 4 short-term (4- or 6-week), fixed-dose, placebo-controlled trials to see if agitation is inversely associated with Geodon dose or if somnolence is directly related to Geodon dose. The study found numeric trends but no statistically significant results, which the researchers speculated could be do to the infrequent occurrence of either agitation and somnolence in the trial database.

A third poster reported the long-term results of Geodon on negative symptoms of schizophrenia. Evidence has been conflicting on whether second-generation antipsychotics improve negative symptoms, thereby enhancing clinical and quality of life outcomes. In this analysis, Geodon (80-160 mg/day BID) was significantly more effective on negative symptom remission than haloperidol and was associated with a direct treatment effect on primary negative symptoms. A logistic regression analysis showed that early improvement in the PANSS total score (>20% from baseline to Week 40) was predictive of negative symptom remission during the subsequent 3-year period.

ZODIAC Post-Marketing Study Results at 1 Year

Measurement	Geodon n=9,077	Zyprexa n=9,077	Relative risk
Primary endpoint: Non-suicide mortality	0.91%	0.90%	1.01
Secondary endpoint: All-cause mortality	1.13%	1.13%	1.00
Cardiovascular mortality	0.03%	0.09%	0.38
Suicide	0.21%	0.18%	1.19
Sudden death	0.02%	0.03%	0.67
All-cause hospitalization	15.09%	10.08%	1.39
Hospitalization for arrhythmia	0.08%	0.04%	1.75
Hospitalization for MI	0.14%	0.12%	1.18

Asenapine in Acute Schizophrenia

Measurement	Asenapine 5 mg BID n=111	Asenapine 10 mg BID n=105	Haloperidol 4 mg BID n=115	Placebo n=123
Completers	68%	70%	58%	57%
Primary endpoint: Change in PANSS from baseline at Day 42	- 21.3 (p=0.004 vs. placebo)	- 19.4 (p=0.038 vs. placebo)	- 20.0	-14.6
Secondary endpoints				
Change in PANSS positive subscale	- 7.5 (p≤0.05 vs. placebo)	- 6.9 (p≤0.05 vs. placebo)	- 7.3 (p≤0.05 vs. placebo)	-5.0
Change in PANSS negative subscale	- 4.5 (p≤0.05 vs. placebo)	- 4.3 (Nss vs. placebo)	- 4.2 (Nss vs. placebo)	-3.0
Change in PANSS general psycho-pathology score	- 9.6 (p≤0.05 vs. placebo)	- 8.5 (Nss vs. placebo)	- 8.6 (Nss vs. placebo)	-6.8
Reduction in PANSS ≥30% (PANSS responders)	55% (p=0.0005 vs. placebo)	49% (p=0.015 vs. placebo)	43% (Nss vs. placebo)	33%
Change in CGI	- 1.2 (p≤0.05 vs. placebo)	- 1.1 (p≤0.05 vs. placebo)	- 1.2 (p≤0.05 vs. placebo)	-0.8
CGI responders	48% (p≤0.05 vs. placebo)	44% (Nss vs. placebo)	44% (Nss vs. placebo)	N/A
Adverse events				
Any adverse event	65%	76%	76%	72%
Treatment-related	44%	52%	57%	41%
Serious	6%	9%	7%	7%
Discontinuations related	3%	4%	4%	5%
Insomnia	20%	18%	14%	15%
Oral hypoesthesia (reduced sense of touch)	11%	9%	0	2%
Somnolence	9%	8%	2%	1%
Akathisia (restlessness)	5%	12%	15%	3%
Weight change	+ 0.7 kg	+ 0.6 kg	+ 0.3 kg	- 0.4 kg
Clinically significant weight gain	5%	4%	4%	2%
EPS	15%	18%	34%	10%
Parkinsonism	8%	7%	5%	14%
Initiation of anti-Parkinsonian drugs	17%	19%	43%	12%

SCHERING-PLOUGH/ORGANON'S asenapine

This 5-HT_{2A}- and D2-receptor antagonist is being developed, at least initially, for acute schizophrenia – e.g., patient first presents with psychotic symptoms or experiences a relapse. In addition to experiencing delusions and hallucinations, these patients can prove uncooperative, display aggressive and hostile behavior, and may represent an immediate danger to

themselves and others. Asenapine is a fast-dissolving, sub-lingual tablet. It is being tested at two doses: 5 mg BID and 10 mg BID.

There were five asenapine posters presented at ACNP.

1. **Swedish researchers** found it worked well in schizophrenia on negative symptoms and on cognitive symptoms.
2. **A rat study** which found: "The improvements in behavior are not likely to be mediated by the action of asenapine within the mPFC because this region was lesions. Rather, improvements are likely to be mediated by structures (e.g., striatum) over which the mPFC exerts modulatory influence."
3. **A Canadian rat study** which found that asenapine acts as a partial agonist at postsynaptic hippocampal and raphe nucleus 5-HT_{1A} receptors and is a potent antagonist at α-$_{2A}$-adrenergic and 5-HT_{2A} receptors. They concluded that the effects at 5-HT_{1A}, α-$_{2A}$-adrenergic, 5-HT_{2A}, and D_2 receptors may contribute to its efficacy and tolerability in patients with schizophrenia and bipolar disorder.
4. **Two randomized, placebo- and Zyprexa- (olanzapine)-controlled trials** in the treatment of mania of bipolar I disorder. These were both 3-week studies of flexible-dosing asenapine (10 mg BID which could be titrated to 5 mg BID) vs. Zyprexa 15 mg QD that could be titrated to 5 mg, 10 mg, or 20 mg QD vs. placebo. In both these studies, asenapine produced rapid control of symptoms, with good tolerance and a low incidence of EPS and weight gain. In a 9-week extension study, it was shown to be non-inferior to Zyprexa.
5. **A randomized, double-blind, international trial.** Organon researchers reported both doses of asenapine were significantly more efficacious than placebo in improving PANSS scores, in patients with acute exacerba-tion of schizophrenia, with more insomnia and oral hypothesia and somnolence than either placebo or haloperidol but weight loss rather than gain.

   According to the results of this 6-week, 448-patient study, asenapine 5 mg twice daily and 10 mg twice daily were both significantly more effective than either placebo or the active comparator (haloperidol 4 mg BID) at improving the PANSS score from baseline at Day 42.

VANDA'S iloperidone

This atypical antipsychotic is currently under review as a treatment for schizophrenia by the FDA, with a PDUFA date in July 2008. There were two posters at ACNP on it:

1. **Comparing it to Risperdal (risperidone).** Three randomized, double-blind, placebo- and active-controlled trials (Study 3000, 3004, and 3005) were presented in one poster. Efficacy and weight gain looked comparable to Risperdal, with less EPS but more dizziness. A company official said this trial had been run by Novartis, from whom Vanda licensed iloperidone:
   - Takes longer to titrate than Risperdal, so there were more dropouts in the first week or two.
   - Because of the dropouts, on LOCF it was not equivalent to Risperdal in efficacy.
   - If patients who got to target dose and were kept on the dose, then iloperidone would be equivalent to Risperdal.

Iloperidone vs. Ziprasidone at 4 Weeks

Measurement	Iloperidone 12 mg BID n=300	Ziprasidone 80 mg BID n=150	Placebo n=147
PANSS-T score change	- 12.01 (p=0.006)	- 12.27 (p=0.012)	- 7.08
PANSS-P score change	- 4.2 (p<0.001)	- 4.2 (p=0.003)	- 2.2
PANSS-N score change	- 3.0 (p=0.027)	- 3.1 (p=0.036)	- 1.9
BPRS change	- 7.4 (p=0.013)	- 7.2 (p=0.042)	- 4.6
CGI-S change	- 0.7 (p=0.01)	- 0.7 (p=0.05)	- 0.4

QT Prolongation with Iloperidone vs. Ziprasidone at 4 Weeks

Measurement	Iloperidone 12 mg BID	Ziprasidone 80 mg BID	Placebo
QT prolongation at 14 days	11.4 ms (<0.001)	11.3 ms	---
QT prolongation at 28 days	7.2 ms	6.1 ms	<0.001
>15% increase in QTc	2	1	0
QTc >500 ms	0	0	0

Other Treatment-Emergent Adverse Events with Iloperidone vs. Ziprasidone at 4 Weeks

Measurement	Iloperidone 12 mg BID	Ziprasidone 80 mg BID	Placebo
At least one adverse event	85%	87%	74%
Dizziness	17%	13%	8%
Sedation	13%	27%	8%
Weight increased	11%	5%	2%
Dry mouth	9%	7%	0.7%
Heart rate increased	8%	6%	0.7%
Tachycardia	9%	2%	0.7%
Agitation	3%	7%	3%
Orthostatic hypotension	7%	0	2%
Orthostatic response (drop of ≥30 mmHg)	13%	2%	6%
EPS	3%	9%	2%
Anxiety	3%	5%	0.7%
Akathisia	1%	7%	0
Serious adverse events	0	0	0
Discontinuation due to adverse events	5%	8%	8%
Mean weight gain	2.8 kg	1.1 kg	0.05 kg

Iloperidone vs. Risperdal at 4 Weeks

Measurement	ILO 4-8 mg/day n=316	ILO 10-16 mg/day n=417	ILO 12 mg/day n=114-149	ILO 20-24 mg/day n=118	Risperdal 4-8 mg/day n=265	Haloperidol 15 mg/day n=87	Placebo n=350
BPRS change in Study 3000	- 6.4 (p=0.070)	- 6.2 (Nss, p=0.095)	- 6.8 (p=0.042)	- 6.8 (p=0.042)	---	- 9.0 (p<0.001)	- 3.6
BPRS change in Study 3004	- 6.2 (p=0.012)	- 7.2 (p=0.001)	---	---	- 10.3 (p<0.001)	---	- 2.5
BPRS change in Study 3005	---	- 7.1 (Nss, p=0.090)	---	- 8.6 (p=0.010)	- 11.5 (p<0.001)	---	- 5.0
Combined analysis of BPRS scores	- 7.9 (p<0.05)	- 9.2 (p<0.05)	---	- 10.0 (p<0.05)	- 11.9 (p<0.05)	- 11.4 (p<0.05)	- 5.4
Adverse events							
Any adverse event	81.0%	78.9%	---	76.0%	78.4%	94.9%	75.7%
EPS	5.4%	4.8%	---	4.0%	9.5%	20.3%	5.8%
Dizziness	12.1%	10.3%	---	23.2%	7.2%	5.1%	6.8%
Dry mouth	5.2%	7.9%	---	10.4%	2.9%	2.5%	1.4%
Somnolence	5.0%	5.7%	---	8.0%	5.9%	6.8%	2.7%
QTc prolongation >500 ms	0	0	0	0	0	0	0
Weight gain	1.5 kg	2.1 kg	---	1.7 kg	1.5 kg	0	0

2. **Comparing it to Geodon (ziprasidone)**. In that 4-week, prospective, randomized, double-blind study (run by Vanda) in the U.S. and India, similar titration schedules were used, and at Week 1 there were similar adverse events, which a company official said lowered the drop-out rate. Efficacy appeared comparable, and iloperidone had less sedation, EPS, akathisia, and agitation than ziprasidone, but iloperidone also had more weight gain, and it didn't have a better QT profile.

What are the advantages of iloperidone? The company official said there are fewer extrapyramidal side effects and akathisia, but added, "We are currently figuring out what the correct message should be…We have used a very conservative titration schedule, and we still showed efficacy. We are looking at the possibility of altering the titration schedule."

Supposedly, there are some "interesting" PK data on iloperidone that will be presented at future meetings.

WYETH'S vabicaserin, a 5-HT_{2C} receptor antagonist

A mouse study by Wyeth researchers found that vabicaserin enhances the potency of both antipsychotics and antidepressants. The company is planning a Phase II study in schizophrenia. The researchers concluded:

- In schizophrenia with vabicaserin:
  - There was a significant decrease in positive symptoms that was greater than with either haloperidol or clozapine alone.
  - Vabicaserin potentiated the effect of haloperidol or clozapine. This suggests the dose of haloperidol or clozapine could be reduced with the addition of vabicaserin, without any loss of efficacy but with a reduction in side effects.
  - There was no catalepsy.
  - Vabicaserin was not effective when given alone – only in combination with another agent – but in combination it increased the treatment effect of the other agent and improved the side effect profile.
  - There were hints that vabicaserin improved cognition but that has not been fully explored yet.
- In depression with vabicaserin:
  - There was a small enhancement of the treatment effect of a sub-therapeutic dose of paroxetine (but not much).

NEW DRUG CLASSES

ENDOCANNABINOIDS

A University of Chicago study provided the first functional neuroimaging evidence that cannabinoid modulation – acute administration of THC – may decrease threat-induced amygdala reactivity.

Dr. Xavier Pi-Sunyer, director of obesity research at St. Luke/Roosevelt Hospital Center in New York and an Acomplia researcher, discussed Sanofi-Aventis's Acomplia (rimonabant), an endocannabinoid that is approved in Europe and Latin America but which was rejected by the FDA because of psychiatric side effects. Asked why the FDA did not approve Acomplia, Dr. Pi-Sunyer said, "They were worried by depression, mood changes, and (patient selection). No (patients) were supposedly in the trials who had a history of depression or had been on an antidepressant. I think the feeling of the FDA was that since 17% in different surveys of obese patients in the U.S. have depression, that they would be

vulnerable to possible problems that might occur by blocking this so-called pleasure receptor. And they didn't want to take the chance. There was a lot of talk about suicide vs. suicide ideation. There were three suicides in 6,000 patients, one with placebo, one in 5 mg (rimonabant), and one at 20 mg."

Dr. Pi-Sunyer reviewed the RIO trials of Acomplia. He called the safety profile "controversial" and emphasized that:

- The overall dropout rate was high in all arms of the trials (45%-49%).
- Discontinuations due to adverse events were 9.4%-12.8%.
- Depressed mood disorders were "low but definitely higher with rimonabant" than with placebo.
- There appear to be some weight-independent effects.
- Efficacy (weight loss) at one year is maintained in the second year, but patients who stopped taking Acomplia regained the weight they lost in the first year.

Asked what this means for future endocannabinoids, Dr. Pi-Sunyer said, "I guess the drug companies feel there is a future for this class because other Phase II and Phase III trials are ongoing. I think some of the things that will determine how this goes is post-marketing surveillance in Europe. They are doing very strict post-marketing surveillance in Europe...and it (rimonabant) has now been out for a year…and I think we will get a pretty good idea if people are getting trouble there, and I think that will have a big impact on the future of this class…I think it would be instructive to do a small trial in patients on an antidepressant or in people with a history of depression. FDA did not want the drug company to do that…They wanted a history of psychiatric disorders eliminated, so that study was not done…I hope companies in Phase III will do that."

Asked what cognitive and mental health findings were shown in the SF-36 quality of life questionnaire, which was used in all the Acomplia RIO trials, Dr. Pi-Sunyer said, "A shortened SF-36 was used, and it (the finding) was never published."

Another expert commented, "I think the fact that (Acomplia) ran into the side effects that prevented approval in the U.S. is not surprising…On a philosophic plane, it is hard to imagine that blocking (CB-1) will only produce useful effects…We have a manuscript submitted where if you knock out CB-1 in the liver, animals become fat but remain resistant to diet-induced metabolic and lipid changes…I'm sure many companies are thinking about it…and a few are already doing something to develop periodically-restricted CB-1 drugs…We may come back to rimonabant if long-range Phase IV studies justify it. The reason I think there is reason for hope: animal studies show the appetite reducing effects are rapid but weight reduction is maintained, which suggests that under chronic conditions, the peripheral effects are dominant, and there is little effect on appetite…I'm also struck that at two years the incidence of psychiatric effects tended to go down…So, perhaps only people who tolerated (rimonabant) stayed in (the trial)…but another explanation is that if people can weather the initial unpleasant mood disorder and stay on the drug, they may get back to a level where the psychiatric side effects disappeared."

PFIZER/ORGANON also has a cannabinoid receptor antagonist in development, URB-597, a FAAH inhibitor. An expert said that when this is given alone it has no effect on catalepsy in an animal model of Parkinson's disease, but when it is given with quinpirole (a D2 agonist), the catalepsy disappears – "they basically wake up." He suggested that this could become a treatment for Parkinson's disease catalepsy, adding, "Several biotechs are actually pursing that."

HISTONE DEACETYLASE (HDAC) INHIBITORS

Dr. Eric Nestler of the University of Texas Southwestern Medical Center in Dallas discussed epigenetics (broadly defined as chromatin remodeling). He noted that over the last five years, a growing body of literature suggests that the epigenetic mechanisms – chromatin remodeling – are involved in a variety of psychiatric disorders including developmental disorders (e.g, Fragile X, Rett Syndrome, etc.), depressions, addiction, schizophrenia, and normal learning and memory.

A study of chromatin remodeling, he said, "can provide unique insight into the molecular changes induced in the brain in animal models of depression and addiction. Complex gene sets can be mined to identify biochemical pathways that mediate (a) depression pathology and its reversal by anti-depressants and (b) addictive behavior. And eventually it can be used to develop fundamental, novel treatment approaches." Dr. Nestler cited three advantages to studying chromatin remodeling:

1. It provides information about transactional regulation in the brain *in vivo*.
2. It provides a new avenue for therapeutics, but this is very, very early.
3. It provides long-lived changes.

One possible chromatin remodeling therapeutic approach is to treat depression with HDAC inhibitors, which are currently under investigation in oncology. He explained, "Systemic administration of an HDAC inhibitor is antidepressant-like... The bar for cancer is lower than for depression…We might develop a rather rapid trial of HDAC in depression." However, Dr. Nestler said he believes that selective HDAC inhibitors may be needed for psychiatric uses, "The current drive in the field is to look for more selective HDAC inhibitors."

Do cancer patients taking HDAC inhibitors have less depression? Dr. Nestler said that hasn't been studied yet, but the effect on depression should be measured first in cancer patients.

Merck's Zolinza (vorinostat, SAHA) is just one of the HDACs, which all differ somewhat. Dr. Nestler said, "There are ~10 HDACs, and they differ somewhat, but they are all broadly expressed. MS-275 (Bayer/Schering AG) is selective to Class 1 HDACs. It is being used in the clinic, where it has shown some toxicity. So, I'm not sure a Class 1 is a good idea. Class 2 HDACs may be better…A number of biotechs and big pharma have taken that approach. We won't know how effective and safe this is until we get a prototype and try it."

There also may be a role for HDAC inhibitors in addiction, particularly cocaine addiction. Dr. Nestler explained, "Chronic cocaine use induces HDAC5 phosphorylation, which shuttles HDAC5 out of the nucleus. This may contribute to cocaine induction of histone acetylation and hence to gene activation …Overexpression of HDAC5 – but not HDAC9 – in the NAc reduces sensitivity to the rewarding effects of cocaine…We are starting to look at gene expression arrays and chromatin arrays to look at cocaine action in HDAC5 knockout mice."

Asked if valproic acid has been tested, Dr. Nestler said, "No, one of the problems with that from our point of view…is it is such a dirty drug…When you give it to an animal, you never know which of the pharmacologic actions are causing the effect…So, we purposely avoided that and targeted more specific agents."

METABOTROPIC GLUTAMATE RECEPTORS (MGLURS) AND GLYCINE $T_{1/2}$ INHIBITORS

An expert said clinical researchers are more interested in mGLuRs, and basic scientists are more interested in glycine T_1 ($GlyT_{1)}$ inhibitors.

mGLuR agents

Mark Bear PhD of Massachusetts Institute of Technology discussed the therapeutic implications of the mGLuR theory of mental retardation and autism. He said, "Perhaps in Fragile X all the protein synthesis-dependent consequences are exaggerated…and this may be responsible for many of the phenotypes in the disorder…The psychiatric and neurological aspects of Fragile X are a consequence of exaggerated response to $mGLuR_{1/5}$ activation, so aspects of Fragile X should be rescued by reducing signaling through Gp1 mGluRs."

mGLuRs also may have therapeutic potential in autism. Dr. Bear said, "The hypothesis is that a substantial number of autism cases could be due to excess protein synthesis, which would help to explain the different manifestations in different people."

Asked if anyone has ever reversed any of the lack of social interaction in autism, Dr. Bear said, "It is frustrating…Efforts are underway, but so far there hasn't been a good phenotype in the Fragile X mouse to study…There is a great deal of excitement among us working with neurodisabilities…This is a wonderful advance…but the dilemma is that these genetic syndromes are not models of classic autism."

Reportedly, Lilly has seen "very good results" with a recent Phase II trial of an mGLuR.

ROCHE'S R-1315. This oral, selective, non-competitive, $mGLuR_{2/3}$ receptor antagonist was tested in a rodent and marmoset study. Roche researchers found it was protective of short-term memory and spatial acquisition, suggesting it may provide a new therapeutic approach in Alzheimer's disease.

Glycine T_1 ($GlyT_1$) agents

A $GlyT_1$ researcher warned that the side effect to be wary of with these agents is seizures. He also agreed that non-sarcozine agents are likely to be more effective in treating schizophrenia than sarcozine agents. Roche may have the lead here with its non-sarcozine $GlyT_1$, since most of the $GlyT_1$s in Phase I and II development are sarcozines, but other non-sarcozines are in development.

Note: Glycine T_2 reportedly is more common in the spinal cord and less effective in schizophrenia.

ROCHE'S L-687,414. This oral $GlyT_1$ looks very promising. It is a non-sarcozine glycine T_1 ($GlyT_1$) inhibitor.

SANOFI-AVENTIS'S SSR-103800. This selective, reversible $GlyT_1$ inhibitor has shown potential therapeutic activity in animal models representative of positive, cognitive, or depressive symptoms observed in schizophrenics. Researchers reported that SSR-103800:

- Is active in animal models of depression.
- Is active in animal models of schizophrenia-related symptoms, including agitation, memory impairment, and attention deficits.
- May represent a promising drug candidate to treat not only positive, negative, and attention/cognitive symptoms of schizophrenia but also co-morbid depressive states.

NEUROSTEROIDS

Neurosteroids are steroids found in the brain, are able to be synthesized *de novo* in the brain from cholesterol, and are active on many different receptor systems (e.g., GABA, NMDA, glycine, sigma, nicotinic, etc.), and the actions are immediate and do not need translational proteins.

There was some excitement about these agents at the meeting, but big pharma does not appear very interested. A Novartis researcher said his company tried a neurosteroid that worked on pregnenolone indirectly, and it failed in both generalized anxiety disorder (GAD) and depression. The side effect to watch out for with any agent in this class would be seizures, sources agreed.

Duke researchers are trying to generate interest in someone to license generic pregnenolone. While it is generic, a researcher suggested there is use patent potential.

Schizophrenia

Dr. Adam Savitz of Cornell is working on pregnenolone in schizophrenia under an FDA IND (investigational new drug) application. He said a semi-synthetic pregnenolone needs to be developed, "We need to get industry interested. Industry looked at this in the past, but those were low-potency (studies)." He explained that pregnenolone:

- Binds to the receptor in a dose-dependent saturable manner.
- Leads to the receptor being open longer.
- Is an indirect agonist, not binding at glutamate or glycine sites and does not lead to receptor functioning on its own.
- NMDA receptor antagonists prevent the memory-enhancing effects of pregnenolone.

In animals (rats and mice), lower levels of pregnenolone are found in older rodents, and the level of pregnenolone correlates with the animal's ability to run a maze. An increase in pregnenolone (or pregnenolone sulfate) increases performance, counters the memory and motor-impairing effect of alcohol, and counters the amnesic effects of scopolamine. Pregnenolone enhances learning and memory in rodent models, enhances neurotic outgrowth, stabilizes microtubules, and increases myelination.

There are several possible mechanisms of pregnenolone action:

- Indirect agonist of the NMDA receptor.
- Inverse agonist of the $GABA_A$ receptor.
- Indirect agonist of the sigma receptor.
- Increase acetylcholine.
- Increase the formation of microtubules leading to axonal and dendritic outgrowth.
- Increase neurogenesis in the hippocampus.

Pregnenolone is generally considered a safe drug that is absorbed orally in humans. It is regulated by the FDA as a dietary supplement and has been available for more than 50 years without reports of significant adverse events in humans. It is sold at health food stores and even at Wal-Mart. Pregnenolone is used in doses up to 1000 mg/day to treat rheumatoid arthritis (RA) with minimal side effects. As a steroid, it is effective but not as potent as the glucocorticoids.

The potential risks with pregnenolone include:

- It is not known how much is converted to other steroids.
- There is a theoretical risk of increasing the likelihood of seizure.
- There is a theoretical risk of increasing the damage from a stroke.
- It is not known how it interacts with other medications.

Dr. Savitz conducted an 8-week (plus 2-week lead-in), proof-of-concept, double-blind, placebo-controlled study in schizophrenia with four arms: (a) placebo, (b) low dose (100 mg) pregnenolone, (c) slow titration of pregnenolone from 100 mg to 500 mg, and (d) rapid titration from 100 mg to 500 mg. Dr. Savitz described this as more of a "typical, real-world population." In the study, pregnenolone was well tolerated out to two years, improving negative symptoms and possibly attention and verbal memory – and the patients had an improved sense of well-being. Pregnenolone is markedly increased after administration of clozapine, which may explain some of the therapeutic action of clozapine.

Dr. Savitz said the side effects were similar in all arms, with only one patient on drug dropping out because of side effects, though there were some patients who had mild and transient insomnia and others who complained of dyspepsia. He said there were:

- No patients who had more side effects than placebo.
- No change in lab values.
- No change in levels of clozapine or valproic acid in patients taking either of those drugs.
- No change in vital signs or weight.
- No change in steroid (estradiol, DHEA, cortisol) levels – only pregnenolone went up.

At Week 2, there was an improvement in total PANSS in the rapid titration group, and an improvement in negative symptoms by both PANSS and SANS with both high dose groups. There was no change in positive symptoms. He added, "Some people responded to the lower 100 mg dose, and some didn't." Among completers, there was significant improvement in verbal memory and attention, but no improvement in working memory or visual perception. However, it was in the sustained attention test that Dr. Savitz said he saw the most benefit.

Efficacy with Pregnenolone

Measurement	% correct at Week 0	% correct at Week 10
Placebo	89.3%	89.8%
Low dose	100%	100%
High dose, slow titration	70.3%	80%
High dose, fast titration	87.8%	96%

Interestingly, the major benefit was described as something Dr. Bear couldn't quantify – patients simply felt better, had an improved sense of well-being. He explained, "They tended to attend groups and/or work more regularly, felt they had better concentration and energy, and preferentially asked to remain

on study…We had few patients on the 500 mg dose who couldn't figure out if they were on the medication."

In an open continuation study, patients had the option of continuing or starting pregnenolone (if they had been on placebo). Among those patients:

- Total PANSS score continued to improve out to 8 months and then stabilized. This was just 5 patients, but Dr. Bear described the data as "interesting."
- Total SANS score showed a continuous improvement out to 24 months.
- Two patients went from part-time to full-time employment. One person went from minimal structured activity to working part-time, one person completed college courses for the first time, and one person (a hoarder) was able to start cleaning his apartment with some help.

A Phase II trial in schizophrenia is planned, and Dr. Savitz is considering studying pregnenolone in other illnesses, such as depression and dementia. *Will generic pregnenolone ever get FDA approval?* Perhaps not, but Dr. Savitz said he hopes that semi-synthetic compounds with improved efficacy will be developed and gain FDA approval.

Dr. Christine Marx of Duke University also conducted a proof-of-concept trial of pregnenolone (given on top of atypical antipsychotics) in schizophrenia. She said pregnenolone appeared to significantly decrease negative symptoms (on SANS) and significantly improve cognitive symptoms (on BACS, MATRICS) and was well-tolerated. She said, "The results need to be replicated, but there are potentially promising…PANSS did not change very much, perhaps because dosing was low for the first three weeks...I'm not convinced 500 mg is the best dose; we may need to go higher …You might have expected to see a reduction in symptoms quickly, which we did not see. It really took 8 weeks, but we had a low dose at the beginning." QT prolongation tests were conducted (EKGs), and no interval changes were observed.

4-Week Efficacy with Pregnenolone

Measurement	Placebo n=9	Pregnenolone n=9
Mean age	49.4	52.7
SANS decrease	~ 4	~ 13
Z-score change on BACS	~ 0.2	~ 0.6 (Nss)
Adverse events (all mild)		
Disorientation	2 patients	2 patients
Decreased interest in sex	2 patients	1 patient
Restlessness	0	2 patients
Muscle pain/stiffness	0	1 patient
Cold in extremities	0	1 patient
Dry mouth	1 patient	1 patient
Hypertensions	1 patient	1 patient
Impaired sexual performance	2 patients	0

Other disorders

Pregnenolone may have utility in a variety of other disorders, including:

- **Post-traumatic stress disorder (PTSD).** A pilot study in 90 American male war veterans found that pregnenolone levels were lower in patients with increased local severity of symptoms and increased paranoid ideation. Thus, pregnenolone also is being explored as a treatment for PTSD.
- **Alzheimer's disease.**
- **Pain** (moderate/severe lower back pain or moderate chest pain).
- **Mild traumatic brain injury (TBI).** There are more cases of TBI annually in the U.S. (1.5 million) than breast cancer (176,300) or new HIV/AIDS (43,681), spinal cord injury (11,000), or multiple sclerosis (10,400). Dr. Donald Stein of Emory University pointed out that numerous treatments for TBI have been tried over the last 40 years, but none worked in the acute stage, and, in fact, some – like magnesium sulfate – actually worsened mortality. Among the therapies still being investigated are: EPO, sertraline (Pfizer's Zoloft), and hyperbaric oxygen.

However, Dr. Stein is more excited about the potential for a neurosteroid – progesterone. He said progesterone doesn't just treat the brain injury but also other inflammatory processes in the body that are triggered by the brain injury. The ProTECT trial – a small (100-patient), randomized study – found no statistically significant benefit in moderately-injured patients vs. placebo, but in severe patients there was a significant benefit. These findings were sufficiently intriguing that the 1,030-patient, multicenter ProTECT-3 trial is now planned to start in July 2008.

MARINUS PHARMACEUTICALS' ganaxolone

Dr. Michael Rogawski of the University of California, Davis, and a consultant to Marinus discussed the potential for ganaxolone in adults with partial seizure disorder. Ganaxolone is an oral, synthetic steroid that is almost identical to allopregnenolone. He claimed the advantages of ganaxolone are that it has no hormonal activity, no back conversion to intermediate with hormonal activity, and no evidence of anticonvulsant tolerance, (based on tolerance studies in rats). Animal studies did show tolerance to benzodiazepams with increased administration of ganaxolone.

Dr. Rogawski said an oral suspension of ganaxolone had:

- Predictable and proportional plasma concentrations over a dose range of 50-500 mg/day.
- T_{max} of 1.2-2.5 hours (5.5 hours when administered with a high fat or high carbohydrate meal).
- Terminal elimination of 15.8-43.1 hours.
- High protein binding.
- 80% excretion in feces, 20% in urine.

- A very large food effect. He said, "When administered on an empty stomach, it produced much lower blood levels than with a high carb meal, and with a high fat meal blood levels were up to 12-fold higher."
- A relatively low therapeutic window.

However, a new solid-dosage formulation has been developed which solved the food effect program, improved PK, reduced C_{max} – which reduced the side effects – and may enhance compliance and lower cost. With this formulation, submicron particles are milled to 300 nanometers (measured by laser light scattering), which Dr. Rogawski said increases the absorption rate by increasing the surface area and the kinetic dissolution rate.

Dr. Rogawski said that 14 Phase I and 11 Phase II studies with the older oral suspension formulation were encouraging, with no unexpected safety events. Side effects in Phase I included: fatigue/somnolence 42%-90%, feeling "drunk" 25%, gait disturbance 20%-56%, and dizziness 17%-63%, with all of these reversible upon discontinuation. In a Phase II trial in acute migraine, the main adverse events were dizziness and somnolence, but Dr. Rogawski said those dizziness and CNS side effects were not seen in a Phase II trial in adult chronic epilepsy.

On efficacy, Dr. Rogawski said there have been 4 studies to date, and 2 are ongoing:

1. 52 U.S. adult presurgical patients – with a trend toward seizure reduction.
2. 15 U.S. pediatric patients with infantile spasms (Phase II study) – with 10 showing a reduction in spasm frequency. Dr. Rogawski said, "Five had >50% reduction in seizures, and 5 had <50% reduction but still a reduction."
3. 15 French highly refractory pediatric epilepsy patients (open label study) – with 7 showing a reduction in seizure frequency.
4. 45 French pediatric patients with infantile spasms (open-label outpatient study) – with the results not yet published.
5. 60 adults (multicenter, single-blind, placebo-controlled, crossover study) with uncontrolled or complex partial seizures – ongoing.
6. 54 children with infantile spasms (multicenter, double-blind, placebo-controlled, crossover study) – ongoing.

Asked if there is a potential scheduling issue with ganaxolone, Dr. Rogawski said, "That is a very interesting question. We have, at the moment, not carried out careful studies to look at the abuse potential of the compound. It is possible that the FDA may ask us to do those studies. We are still in Phase II, so we have plenty of time to do those studies…Further down the road it might be necessary to discuss that with the Agency."

MISCELLANEOUS TOPICS

Biomarkers

Indiana University researchers have identified a series of high probability candidate biomarker genes for identifying mood states. They said the biomarkers are not for diagnosis but for response to treatment and drug development. Indiana University has filed patents so a commercial test can be developed.

Mood State Biomarkers

Best high mood biomarkers	Best low mood biomarkers
MBP	RPLPO
EDG2	FGFR1
FZD3	MAG
EDNRB	PMP22
CCNC	ERBB3

Predictive Ability of Identified Biomarkers in Bipolar Disorder

Predictive ability	High mood biomarkers	Low mood biomarkers
Specificity	68.8%	81.3%
Sensitivity	84.6%	76.9%

GLAXOSMITHKLINE'S GR-205171. In a gerbil study, 5 mg/kg GR-205171 significantly decreased contextual fear-potentiated startle (a model of anxiety). Lower doses (0.3 mg/kg and 1.0 mg/kg) were not significantly effective vs. placebo. All three doses tested increased the percent of open-arm entries, and there was a significant linear relationship between drug dose and percent of time in open arms.

LILLY'S LY-686017. This second-generation substance P (NK-1 receptor antagonist) failed to show any benefit in a Phase II proof-of-concept study in social anxiety disorder (SAD), and a researcher said Lilly hasn't decided what to do with it now. A PET study showed adequate CNS penetration with the 50 mg QD dose, but there was no clinical efficacy in SAD on either the primary endpoint (Liebowitz social anxiety scale) or any secondary endpoint. A researcher said the data don't "add to confidence in the molecule or mechanism."

Another study of LY-686017 in irritable bowel syndrome (IBS-C and IBS-D), conducted by Lilly researchers in 29 patients, found no improvement in the primary endpoint of mean rectal discomfort threshold (p=0.84) or on any secondary endpoint. Researchers commented, "More studies are needed to fully understand the reason for LY-686017's inability to offset enhanced perception of adverse visceral stimuli in humans with IBS (since preclinical models showed modulation of pain perception)."

However, LY-686017 has shown utility in reducing alcoholism, and Lilly may be taking the drug forward as adjunctive therapy in alcoholism.

In an NIAAA study, LY-686017 reduced craving and stress in anxious alcoholics. The NIAAA study looked at 50 patients who smelled either water or their preferred alcoholic drink for 3 minutes. The conclusions were that LY-686017 caused:

- A significant increase in global patient impact and reduced cravings for alcohol.
- A significant decrease in the craving and cortisol response associated with the stress and alcohol-cue exposure.
- A significant decrease in brain activation in response to negative sensory input while increasing activation of positive stimuli.
- There was significant positive effect in anxious alcoholics, warranting further study.

In another study – this time on alcoholics in an inpatient treatment unit – LY-686017 reduced anxiety and alcohol craving. Researchers said it is not a cure, but a good adjunctive therapy. At Week 6:

- Craving was down (p=0.039).
- Global severity was down (p=0.001).
- Cue-reactivity craving was blocked (p=0.002).

NEUROCRINE BIOSCIENCE/GLAXOSMITHKLINE'S NBI-34041. There was a poster on this CRF-1 receptor antagonist, but the data had already been published, and the poster was just selected data from that publication. A Neurocrine researcher said NBI-34041 has been discontinued, but two other back-up compounds are at the end of Phase I trials. *What's the future of Neurocrine's CRG-1 program?* The researcher said, "Now, it depends on what GSK does. Will they go to Phase II?" He really didn't know yet.

Sarentis Therapeutics' NT-69L, an NT receptor agonist. A rat study suggested this drug may potentiate the effect of morphine, so a lower morphine dose could be used, reducing side effects and the potential for developing tolerance. Mayo Clinic researchers suggested, "Anti-nociceptive activity supports the hypothesis that synergistic combination would improve the pharmacological treatment of pain while minimizing the specific adverse effects of each drug at a higher dose."

University of California, San Diego's PD-149163, a neurotensin agonist. A rat study by UCSD researchers found this neuropeptide – which they said does not cross the blood brain barriers, so it has little abuse potential – has an anxiolytic effect. In their study, there was a significant decrease in startle magnitude at all three doses (0.01 mg/kg, 0.1 mg/kg, and 1.0 mg/kg), but only the highest dose blocked fear-potentiated startle. The effects were described as "robust" at 1.0 mg/kg.

University of Chicago's intranasal corticotropin releasing hormone (IN-CRH). A double-blind, crossover study suggested that anti-CRH might work in neurotics. Researchers noted, "There is some evidence that high central CRH levels are seen in paranoid personality disorder, which may be conceptualized as a trauma-related disorder. Dysregulated CRH drive is also an important risk factor for depression disorder." They found the IN-CRH lowers heart rate but IV CRH did not, and IN-CRH did not change blood pressure.

♦