Trends-in-Medicine

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Quick Pulse

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AMERICAN PSYCHIATRIC ASSOCIATION (APA)

May 21-23, 2005
Atlanta

The APA meeting conflicted with another medical conference this year, so this is not a comprehensive report but, rather, a look at a few specific topics from APA.

ALCOHOLISM

ALKERMES' Vivitrex (naltrexone by injection)

The open-label, 12-month, post-Phase III safety trial of Vivitrex long-acting injections is fully enrolled, with more than 400 alcohol dependent, opiate dependent, and mixed substance dependent patients. The study will compare once-monthly 380 mg intramuscular (IM) injections of Vivitrex to daily oral naltrexone 50 mg. An interim analysis is expected near the end of 2005. All patients are also receiving psychosocial support during the trial. Safety will be evaluated based on adverse events, injection site assessments, serum chemistry, hematology, urinalysis, and physical examination.

APA sources were not very upbeat about Vivitrex. A California doctor said, "I'm dubious about it. Naltrexone has been around a long time. I tried it, without good results. Subxone (Reckitt Benckiser, combination buprenorphine HCl and naloxone HCl dihydrate sublingual tablet) has done better marketing, and it works better."

SCHIZOPHRENIA

CATIE

There were no results presented at APA from this trial, which is sponsored by the National Institute of Mental Health (NIMH). CATIE is an 18-month trial comparing the effectiveness and tolerability of several atypical and typical anti-psychotics in 1,600 schizophrenics. The brand drugs being tested are: AstraZeneca's Seroquel (quetiapine), Bristol-Myers Squibb's Abilify (aripiprazole), Johnson & Johnson's Risperdal (risperidone), Lilly's Zyprexa (olanzapine), and Pfizer's Geodon (ziprasidone). The generic agents are: Clozaril (clozapine), Prolixin Decanoate (fluphenazine decanoate), and Trilafon (perphenazine).

In Phase I, patients were assigned to a treatment regimen for 18 months. In Phase II, patients who were unable to continue on their Phase I regimen were randomly assigned to another antipsychotic for either the remainder of the 18 months or another six months, whichever was longer. In Phase III patients who failed Phase II were allowed to get any of these drugs or a combination of two drugs.

Relapse prevention

With multiple, effective antipsychotic medications available today, psychiatrists now are focusing more on preventing relapses.

Sources agreed that **Johnson & Johnson's Risperdal Consta** (long-acting risperidone) is catching on and usage is growing. A major barrier appears to be insurance reimbursement. An expert said, "The injections would save money, but it is not an easy message to get across to payors."

Among the interesting points speakers made at a J&J-sponsored symposium on relapse prevention in schizophrenia were:

- Brain abnormalities are evident at the time of first episode. They don't increase in magnitude with each relapse. The magnitude of brain abnormalities does not correlate with the duration of untreated psychosis.
- Acute psychosis is associated with elevated levels of dopamine and increased dopamine release with amphetamine, but stable, remitted patients do not show these features.
- Patients who have evidence of ongoing dopamine system hyper-responsiveness are more likely to relapse. Other factors that increase the risk for psychosis relapse may be acting through dopamine-mediated mechanisms (e.g., cannabis, stress).
- Antipsychotic medications are highly effective in preventing relapse, particularly in remitted patients, but all patients can be expected to relapse once medication is discontinued.
- Continuous blockade of dopamine receptors does not seem to be required to prevent relapse. How many receptors need to be occupied, for what amount of time, and at what intervals is not yet known. One speaker suggested that patients can take atypical antipsychotics every other day or every third day with no negative repercussions, but another speaker insisted intermittent therapy is not viable.
- Antipsychotics appear to exert a lasting effect on behavior even in the absence of the drug.
- Relapse into psychosis has important neurochemical features. There is very little evidence to suggest that ongoing psychosis or relapse is, in itself, toxic to the brain.

Risk of Psychotic Relapse

Year	Relapse rate (n=104)
1	16.2%
2	53.7%
3	63.1%
4	74.7%
5	81.9%

- Non-compliance is a big problem. A one-year naturalistic study of prescription refills found the mean number of days patients went with no prescription available was 110 days for atypical antipsychotics and 125 days for conventional antipsychotics ($p<.05$).

The consequences of relapse are enormous. With each relapse:

- Recovery can be slower and less complete.
- More frequent admission to the hospital is likely.
- Illness can become more resistant to treatment.
- The risk of self-harm and homelessness increases.
- Regaining the previous level of functioning is harder.
- Patient has a loss of self-esteem and experiences social and vocational disruption.
- The use of healthcare resources increases.
- The burden on families and caregivers increases.

There is little difference in remission rates among antipsychotics – atypical and typical – during the first 50 days of treatment, but there are differences between the two classes of drugs and among the various atypicals after that. Long-acting injectables have several advantages including:

- Reduce relapses by 20%-50%.
- Avoid first-pass metabolism, so the lowest effective dose can be used.
- Reduce hospital time. The mean number of episodes and the mean duration of inpatient care decrease per patient-year.
- Some patients prefer them.

JOHNSON & JOHNSON'S paliperidone

There was no discussion of this long-acting, atypical antipsychotic, which is in Phase II development, even at a J&J-sponsored session on schizophrenia remission/relapse, and no data were presented at APA. J&J sources and speakers declined to talk about paliperidone at all, saying it was too early. They wouldn't talk about the Phase I or Phase II trials.

Paliperidone is an active metabolite of – and a follow-on to – J&J's Risperdal (risperidone). Two formulations are being developed: (1) oral, using the OROS drug-delivery technology J&J got through the acquisition of Alza, and (2) IM using Elan's NanoCrystal technology, which increases the bioavailability of drugs by transforming them into nanometer-sized particles that can be used in tablets, capsules, liquids, and powders.

Second generation antipsychotics (SGAs)

Speakers addressed several questions/issues relating to SGAs, including:

- ***Are all second generation (atypical) antipsychotics (SGAs) similar in efficacy?*** He said, "Seroquel and Geodon are regarded as weak and not as potent (as other SGAs), but it may be that they are under-dosed, and Seroquel needs to be dosed to 1000 mg/day. Geodon may have been under-dosed because of QTc concerns."
- ***Are there major differences in the safety or tolerability profiles of SGAs?*** He said, "They do differ in the propensity to cause EPS, prolactin elevation, weight gain, sedation, hypotension, QTc prolongation, and other adverse effects."
- ***Antipsychotic drug-induced weight gain.*** A speaker said that, as a class, the atypical antipsychotics cause a substantial increase in appetite, adiposity, and weight gain, though the amounts vary from drug to drug. They may also alter glucose metabolism, independent of any changes in adiposity. He estimated that weight typically increases at a rate of 0.5-1 kg (1.1-2.2 pounds) per week. His personal opinion is that the weight gain is related to the histamine receptor, and the variation in weight gain by drug is related to the drug's affinity for the histamine receptor.

Atypical Antipsychotics and the Histamine (H1) Receptor

Drug	Affiliation for H1 receptor
Clozaril (clozapine)	1.2
Lilly's Zyprexa (olanzapine)	2.0
AstraZeneca's Seroquel (quetiapine)	11.0
Johnson & Johnson's Risperdal (risperidone)	15.0
Bristol-Myers Squibb's Abilify (aripiprazole)	9.7
Pfizer's Geodon (ziprasidone)	43.0
Haldol (haloperidol)	180.0

Brain Stimulation for Major Depression

Sources insisted that there is no stigma holding back doctors from reporting psychosis of major depression (PMD). As one expert explained, "It is not a stigma-related issue, but it is difficult to make the diagnosis. The PMD subtype in DSM-IV is broad and kind of loose, so what one physician may call psychotic would not be called that by another physician." Another expert said, "Five years ago, the stigma (with PMD) mattered a great deal, but there is so much more information today. Stigma still exists, but it is not necessarily the stigma it was with celebrities talking about their depression, drug company advertising, etc – so the stigma is less, and recognition is better."

The number of patients with treatment-resistant depression is high. One expert estimated that 20% of patients with depression are not where they should be after two therapy trials, "Whether you should jump to something invasive is not clear."

Electroconvulsive Therapy (ECT)

ECT, a treatment for severe mental illness in which a brief application of electric stimulus is used to produce a generalized seizure, has been in use for more than 60 years. During ECT, a patient receives electrical currents to the brain until a seizure is induced. General anesthesia and muscle relaxants are used to minimize discomfort and to avoid spinal fractures during a seizure. Although its over-use and mis-use in the early days have given ECT a bad reputation, it has been improved in recent years, and it can be useful, particularly for severe or life-threatening depression, especially in patients for whom antidepressant medications are ineffective.

About 100,000 patients start ECT each year, but the number varies significantly by geography and income, with more use in people with higher income. ECT is typically prescribed when patients are hospitalized because they are not getting better or are even getting worse on medications, and often they are suicidal. The typical patient gets three treatments a week for 3-4 weeks, for an average of 10-12 doses. However, another expert suggested the average number of doses actually may be slightly lower (6-9 doses).

ECT has a number of limitations, including:

- Headache and jaw aches.
- Cognitive side effects – short-term memory loss, some antegrade memory loss, and, in some cases, continuing memory problems.
- Access to a facility that offers it.
- Stigma. Many patients associate some stigma with ECT, and this discourages patients from accepting the therapy. An expert said, "Many patients avoid ECT because of the stigma. They think it is too primitive…or they've seen the movie, ***One Flew Over the Cuckoo's Nest***."
- Anesthesia risks.
- Cost.

ECT is currently in the process of being redesigned. The founding principle that guided the field for 50 years is now known to be wrong – that efficacy and cognitive side effects are determined by the anatomic distribution of current density (where and how much is given). Among the points made about ECT were:

- There is no reliable marker that maximally effective treatment was given.
- Traditional brief pulse stimulation is highly inefficient, producing unnecessary cognitive side effects.

- Ultrabrief stimulation is more efficient than regular ECT. Ultrabrief stimulation also leads to a marked reduction in side effects and preserves efficacy. Asked if ultrabrief ECT should be the standard now, a speaker said, "Ultrabrief is available with all the (ECT) devices now. There is no proscription on use. We use it for 90% of patients at (our hospital)."
- Bilateral ECT does not work with ultrabrief stimulation, but ultrabrief stimulation was reported to be associated with:
  - Marked savings in a variety of cognitive measures.
  - No difference from normals in terms of memory loss for autobiographical information, which is highly sensitive to ECT technique.
  - An effect that persists at six months.
  - An extension of the range of devices.
- Adverse cognitive effects are persistent and, at times, profound.
- Bilateral ECT has an inferior benefit/risk ratio in treating depression and leads to persistent cognitive deficits.
- Future ECT treatment may ***not*** require convulsions.
- Antidepressants can increase the remission rate obtained with ECT, affect the intensity, or decrease cognitive side effects.
- Subjective memory complaints and greater objective retrograde amnesia are associated with bilateral ECT treatments.

A review of seven hospitals found widely differing ECT practices in the community setting:

- Hospitals differed in magnitude of short- and long-term cognitive effects.
- No differences in efficacy were seen among the hospitals.
- Cognitive differences were due to technique.
- Two hospitals still use sine wave stimulation. Those patients started with 450 ms reaction time and ended with 900 ms reaction time, and they were still slow at six months.

Transcranial Magnetic Stimulation (TMS)

TMS doesn't require general anesthesia, and no seizure is involved. It is an "electrode-less" electrical stimulation. A current is run through a coil of wire, generating a magnetic field, which passes through the skull and into the brain.

There are two kinds of TMS:

1. Single-pulse or paired TMS, non-rhythmic.
2. Repetitive TMS (rTMS) – repeated pulses at regular intervals, often but not always >1 Hz.

With TMS:

- No neurological deficits are seen.
- Side effects include:
  - Local discomfort, muscle tension, and headache (<10%).
  - Temporary increase in auditory threshold without earplugs.
  - Heating of metallic objects within the head or on the scalp.
  - Malfunction of very close electronic/magnetic devices.
- Procedures should be performed in a medical setting with appropriate emergency facilities to manage seizures and their consequences.
- Patients can be positioned based on:
  - Individual structural anatomy.
  - Individual functional anatomy.
  - Probabilistic group maps.
- There have been marked technical improvements in the last 10 years.

NEURONETICS' CRS Repetitive TMS (rTMS)

rTMS uses a new coil design that makes it easier to target small areas of the brain. The coil is placed on the head of an awake patient, a magnetic field passes through the skull, and an electrical current in the cortex depolarizes neurons. rTMS is approved in Canada and Israel, and the devices are used off-label in the U.S. rTMS works by stimulating parts of the prefrontal cortex, resulting in dopamine release in the caudate region. It has a limited range in the brain, but appears to have deeper activity. rTMS is an outpatient procedure and is associated with headaches and seizures.

A speaker at APA described rTMS as safe, with minimal side effects. He said relapse rates appear to be the same as ECT, but an Australian study found that most people re-respond to re-treatment.

Neuronetics is currently conducting a 286-patient, randomized, parallel-group, sham-controlled, multicenter Phase III trial in the U.S. of rTMS for major depressive disorder (MDD). The trial started in January 2004, and is expected to be completed in February 2006. The primary endpoint is the antidepressant effect of a course of rTMS. Secondary endpoints include safety and tolerability of rTMS, change in depressive symptomatology, and short-term durability of the effect.

An NIMH-sponsored trial is currently underway in 240 patients with treatment-resistant unipolar depression and who are medication free. This trial is nearing completion, and an interim DSMB report permitted the trial to continue. The

focus is on remission. MRI studies are being conducted to try to determine the best places to stimulate. The trial is investigating the safety and efficacy of repeated daily left prefrontal 5 Hz rTMS at 120% of motor threshold (MT). In subjects showing an antidepressant response after three weeks, rTMS will be administered for up to six weeks to achieve remission of clinical symptoms of depression. Patients who do not remit with the initial fixed dose will be administered 1 Hz rTMS in an open trial over the right prefrontal cortex.

Magnetic Seizure Therapy (MST)

MST is more efficient than ECT, though MST can be approached/surpassed with FEAST (focal electrically-administered seizure therapy). FEAST is uni-directional stimulation with a special electrode array with an anode and cathode differing markedly in surface area, allowing for sharper focusing of current density. In a small study in animals, FEAST resulted in seizure activity without convulsions. A speaker, asked why ECT use should continue if MST is safer than ECT, said, "It is not enough to be safer. It also has to work. We don't have enough data on efficacy or safety…Only 50 patients have gotten MST. You really want larger numbers before you say the treatment is ready for prime time."

Comparison of MST and TMS

Measurement	MST	TMS
Seizure induced	Yes	No
Frequency	50-100 Hz	0.3-20 Hz
Anesthesia	Yes	No
EEG monitoring required	Yes	No
Dosing	3 times a week for 3-4 weeks	5 times a week for 6 weeks
Target population	Severe depression, including psychotic subtype	Moderate depression, non-psychotic

CYBERONICS' VNS (Vagus Nerve Stimulation)

With VNS, a pulse generator is implanted in the left chest wall area and connected to leads attached to the left vagus nerve. A telemetric wand is attached to a computer. The on/off cycle is programmable, with the typical cycle on for 30 seconds, and off for five minutes.

VNS is currently approved for the treatment of epilepsy, and the company is hoping for FDA approval in treatment-refractory depression soon. However, that approval has become controversial. In June 2004, an FDA advisory committee recommended approval, but the FDA issued a not-approvable letter. Then, on February 2, 2005, the FDA reversed itself and issued an approvable letter (with four conditions) over staff objections, and it looked as if the company might gain approval by June 2005. Then, in June 2005, the ***Wall Street Journal*** reported that the Senate Finance Committee is looking into the FDA's handling of this product.

Public Citizen is urging the FDA ***not*** to approve VNS for depression. Dr. Sid Wolfe and his colleagues blasted Cyberonics' data in a lengthy letter to the FDA. The letter concluded, "We strongly oppose this approval because there are no randomized, controlled data demonstrating efficacy for the primary endpoint. The non-randomized efficacy analysis is riddled with the potential for bias and confounding. The FDA statistical review repeatedly called Cyberonics' analysis 'questionable,' and concluded that it was not clear that efficacy had been established…The FDA has raised questions about increased suicides, worsening depression, and sudden death, all of which deserve further investigation. The FDA would never approve a drug under these conditions. With so many uncertainties and red flags, it is a serious mistake for the FDA to be prepared to approve this device for use in millions more people for whom it has not been proved to work. Do not let justified empathy for this patient population lead to the unjustified approval of a device that does not come close to meeting FDA's approval standards, and may well do more harm than good."

A speaker at an industry-sponsored APA dinner said she is "very confident" about the safety of VNS, "The depression trial experience indicates there is no safety difference from epilepsy, and I'm not convinced it worsens depression. The study data on efficacy are compelling and statistically significant. Given the design limitations (of the trial), I can't say the data don't suggest efficacy." She pointed out that many VNS patients have already failed ECT, and she argued that a randomized trial is not really possible with VNS. However, an expert at another session disagreed, saying that a randomized, double-blind trial with VNS is possible.

Speakers were rather aggressive in estimating the number of patients who might be eligible for VNS therapy if the device is approved by the FDA. One speaker said, "If you start with 100 patients with depression, at least 20 are not where they should be after two (medication) trials." Another said, "I think the number is much higher. I think we've oversold the pharmacologic treatments…I would think maybe half of our patients after two or three treatments are eligible."

VNS is not indicated for patients with personality disorders or a lot of psychosocial disorders, experts agreed. And reserving it for the most treatment-resistant patients was discouraged by speakers. One said, "I'd recommend it for patients with mid-level treatment resistance, who failed some but not all things in the armamentarium…I am most impressed with people who still have some ability to have responses to treatment but quickly become tolerant to medications – patients who are adherent, come to appointments, and are non-psychotic."

Speakers at a Cyberonics-sponsored breakfast were asked if they felt the data on VNS in depression are sufficient for approval.

- The moderator wouldn't talk to the press at all.
- The VNS speaker simply responded, "No comment," and then took off with no further discussion.
- Another expert on the panel offered this comment: "As a clinician, I've seen lots of people whose lives were improved with VNS. As a scientist, I want a randomized clinical trial and proof of efficacy – and that can be done." Asked what type of brain stimulation he would choose – VNS, ECT, rTMS, MST, DBS – if all were approved today, he answered, "I would probably base it on the patient's condition. If the patient were suicidal/psychotic, I'd try ECT, MST, or TMS. If the patient had a long-term, lifetime course of depression with relapses, I'd probably try VNS or DBS. There are not enough data on MST or TMS for maintenance therapy. I'd use the least invasive first, and then longer term in patients who fail acute treatments…But I think the selegiline patch (Sommerset Pharmaceuticals) and other products in development may cut the number of patients likely to get devices by a third."

According to FDA sources, there is an internal debate going on within the agency over what was described as the "poor science" in the Cyberonics clinical trials, with a strong segment of experts calling for another randomized clinical trial. This internal FDA debate started weeks before the Senate Finance Committee investigation was revealed. It might be politically difficult for the FDA to reverse itself again. More likely, the FDA will approve VNS, but not necessarily quickly, and possibly with a very restrictive label. The devil could be in the four conditions cited in the approvable letter, and those really aren't known. The FDA does not reveal conditions in an approvable letter, and Cyberonics has not clearly laid them out. The FDA may stall for a while on this.

The data in the following charts were presented at APA on VNS in depression.

Pivotal VNS Results

Time period	IDS-SR	$HAMD_{24}$	MADRS
Response			
3 months (n=203-205)	14%	15%	17%
6 months (n=192-197)	18%	17%	20%
9 months (n=184-186)	20%	23%	27%
12 months (n=180-181)	22%	30%	32%
24 months (n=157)	27%	33%	N/A
Remission			
3 months (n=203-205)	6%	7%	10%
6 months (n=192-197)	8%	7%	12%
9 months (n=184-186)	10%	11%	N/A
12 months (n=180-181)	15%	17%	17%
24 months (n=157)	13%	17%	23%

Pilot VNS Study of Response and Remission Rates

Time period	Response	Remission
10 weeks of therapy	31%	15%
1 year VNS (by LOCF)	44%	27%
2 years VNS (by LOCF)	44%	22%

Questions about VNS include:

➢ ***Which patients are most appropriate for VNS?*** A speaker suggested the device is ***not*** only for end-stage patients but could and should be used much earlier. A speaker said, "People who respond (to VNS) tend to hold it (maintain a response)…So, I think we want to look for someone who showed clinical benefit to other therapy but didn't hold the benefit. The big question with this treatment is that in trials so far it seemed critical to get them out to one year and then hold to Year 2. What if we use something else to get the benefit to one year, and then use VNS to keep that benefit?"

➢ ***What are the distal effects of VNS?*** A speaker said, "Surprisingly little, both from the epilepsy data and from these (depression) trials. There are essentially no cardiac effects and no effects on blood pressure."

➢ ***What is the optimal VNS stimulation?*** A speaker said, "We are basing treatment on epilepsy treatment. We have tried to refine the algorithms, but I can't say we have any conclusions. I hope there will be further research on design parameters in the future."

➢ ***If there is no response after 6-12 months, do you remove the device?*** A speaker said, "There will be some patients who will get a response after a year, and some who get fluctuating responses…So, if a patient is tolerating it well, we won't necessarily recommend taking it out. After a couple of years, we have had one patient take it out. We first try turning it off and leaving it in to see if there is deterioration."

MEDTRONIC'S Kinetra for Deep Brain Stimulation (DBS)

DBS is an accepted treatment for movement disorders but not, at least yet, for psychiatric conditions. In March 2005, Medtronic announced that Kinetra had been implanted in six patients with treatment-resistant depression, and four of the patients had a strong and sustained reduction in their depression. Based on this small study, Medtronic plans further investigation of DBS in depression.

A speaker said no patients have been explanted for lack of efficacy or for persistent adverse events. He said the first three patients experienced stimulator battery depletion during chronic stimulation, accompanied by symptom worsening. In all cases, symptoms improved when DBS resumed. He said, "We had more a sense of mood elevation coupled with a reduction of anxiety compared to calm and peacefulness."

Asked about the death rate in DBS surgeries, an expert said, "It is low, and most of these are older patients with Parkinson's Disease…So, it doesn't necessarily apply to a younger group…But it is probably ≤1%. The rate of hemorrhage with neurological sequelae can be 1%-2% per procedure, which could cause permanent motor effects. That rate looks like it is going down as the imaging technology improves…DBS may play a role in facilitating the effects of other treatments."

Specific Companies and Drugs

Cephalon

➢ **Gabatril (tiagabine).** According to investigators, a recent FDA warning about seizures with Gabatril has not affected enrollment in the generalized anxiety disorder (GAD) trials. The warning does not appear to be causing any patients to drop out of those trials, and it also is not causing problems with the open label extension trial. Researchers do not believe the warning will negatively affect approval for GAD unless seizures are noticed in the GAD trials. A researcher said, "I'm convinced that it works…The worry (about seizures) was that the blood levels might be higher in non-epileptics taking it, but we haven't seen a seizure, and no one I know has seen a seizure…I've seen one seizure with a tricyclic antidepressant in all my years of practice, and if the rate is in the range of SSRIs or tricyclics (~1%), then it would be okay for primary care physicians to prescribe safely, but I need to see the (side effect) numbers…It would be just one more tool in our toolbox…I would be comfortable with approval, but we need to be cautious and do careful monitoring." Gabatril takes "some weeks" to be effective, but if it doesn't have the dependence issues that other GAD agents have, the slow efficacy is not expected to be an issue.

➢ **Provigil (modafinil) in cognition.** A Cephalon-sponsored dinner was aimed at introducing psychiatrists to the idea that modafinil has utility in improving cognition in schizophrenia and perhaps in geriatric depression, even though a recent randomized, double-blind trial in overall depression was not positive. Neither indication is currently approved.

➢ **Modafinil in attention deficit hyperactivity disorder (ADHD).** Cephalon is creating a new formulation of modafinil for use in ADHD. These are film-coated tablets (FCTs). Three trials in ADHD have been undertaken of modafinil FCTs, and Dr. Christopher Kratochvil of the University of Nebraska Medical Center presented the results of one of these – Study 311 – which found the drug improved ADHD symptoms.

ADHD, a neurological disorder with ill-defined patho-psychology, is generally treated empirically. Traditional stimulant therapy is unsuccessful in ≤40% of patients due to side effects or to inadequate response. He said, "It makes sense that modafinil might work in ADHD. It increases alertness and task performance…It activates the prefrontal cortex without widespread CNS (central nervous system) stimulation. There are still questions about the mechanism of action of this drug."

Study 311 was a randomized trial with flexible dosing (170-425 mg QD) in patients age 6-17 who were attending school full time. Modafinil was given only in the morning. Patients were titrated according to clinical response at 85 mg increments at Days 1, 3, 8, 15, and 22. The double-blind treatment duration was nine weeks. The primary endpoint was the ADHD rating scale, done through phone calls with teachers. Data were also collected from parents.

Results of Study 311 of Modafinil in ADHD

Measurement	Modafinil n=164	Placebo n=82
Moderate/markedly ill	84%	85%
Severely ill	16%	15%
Completers	59%	40%
Discontinuations		
Total	41%	61%
Due to adverse events	3%	4 %
Due to lack of efficacy	21%	44% *
Consent withdrawn	3%	5%
Lost to follow-up	4%	1%
Non-compliance	1%	1%
Other	10%	6%
Stable Dose		
≤255 mg/day	19%	17%
340 mg/day	22%	12%
425 mg/day	59%	71%
Results		
Primary endpoint: School ADHD rating scale total	-15.0	-7.3
Inattention	-8.8	-5.0
Hyperactivity	-6.3	-2.3
Parent rating total	-14.3	-7.0
Physicians improvement in Clinical Global Improvement (CGI) by LOCF	48%	17%
Clinical Global Improvement ***(percentage of patients improved or very much improved)***		
Week 1	13%	10%
Week 2	29%	17%
Week 3	39%	22%
Week 5	52%	31%
Week 7	63%	24%
Week 9	65%	33%
Most common adverse events		
Insomnia	29%	4%
Headache	20%	15%
Appetite decrease	1%	4%
Pharyngitis	9%	6%
Rash	6%	4%
Fever	5%	2%
Pain	5%	1%

*** enrollment into one-year open label extension allowed after 4 weeks**

By Week 1-2, there was a separation from placebo in the primary endpoint, but it wasn't clear how much of this was due to dose escalation. Dr. Kratochvil said, "After a couple of weeks, you see a benefit, but it gets better over time. You can't determine the onset of action from Study 311…With Strattera (Lilly, atomoxetine), you see a clinical response in a couple of weeks, and a robust response in four weeks. With the amphetamines, you see a response in a couple of days."

A fixed dose trial is needed to tell efficacy, Dr. Kratochvil said, adding, "I assume the company will pool data from the three trials (Studies 309, 310, and 311)…The effect size (in Study 311) was similar to what is seen in some Strattera trials. We really need a head-to-head trial of Strattera and modafinil to compare them, but they are in the same ballpark." He said the effect size with Strattera is about 0.68, and the amphetamine agents are about 0.7-0.9.

With respect to side effects, Dr. Kratochvil said there is a difference between adults and children, and he speculated that this could be due to differences in metabolism by kids.

- There was no leukopenia reported. At the investigator's meeting, the investigators looked at it and decided it was a non-issue. However, the company wanted to document it, so it was looked at very closely. Blood tests were taken from every patient at every visit.
- No cases of psychosis were seen.
- No cases of Stevens-Johnson syndrome were seen in Study 311. Dr. Kratochvil said, "We are taking this seriously, and watching for it. I expect we'll see more cases as use increases."
- Asked if there is a difference in response in treatment-naïve vs. pre-treated patients, Dr. Kratochvil said that data had not yet been analyzed.
- Asked about the outlook for use of modafinil in ADHD, Dr. Kratochvil said, "(Lack of) scheduling and non-stimulant status will spur use, but the proof will be in the pudding as clinicians try it in refractory kids."

CORCEPT'S Corlux (mifepristine)

Mifepristine is in Phase III development as an alternative to electroconvulsive therapy (ECT) in psychosis of major depression (PMD). There are no treatments currently approved by the FDA to treat PMD, which is more prevalent than either schizophrenic or manic depressive illness. PMD has been associated with a 70-fold increase in the likelihood of suicide. Given this unmet medical need, Corlux has been given fast track status by the FDA.

Experts estimated that about 1 in 20 adults in the general population are depressed at any given moment, and one in five will have an episode of major depression. Of people who get major depression, half respond to talk therapy or an SSRI, 25% respond to a second SSRI, and 25% are considered treatment resistant (about 4 million Americans).

Corlux is thought to work by selectively blocking the binding of cortisol to one of its two GR-II receptors, thus decreasing cortisol levels, which are known to be high in psychotics. In early trials, patients responded to Corlux, but side effects were an issue. A new dosing regimen – with patients getting Corlux for only seven days – may have resolved much of this. After treatment with Corlux, patients are then put on another drug. Whether or how often this Corlux "shock therapy" can be used has not been determined. The major side effects are rash (4%-10%) and some nausea, but there is no correlation between rash and response.

Experts at APA who were asked about the outlook for this agent were uniformly dubious. An expert said, "It is promising because it is a new molecular target, and we are desperate for new agents, but it faces a huge hurdle. It is incredibly promising biologically but difficult practically." Another commented, "It's an abortifacient, but it might be efficacious in some treatment-resistant patients."

Sources cited three problems with Corlux:

1. The politics of the religious right.
2. The street value of the drug.
3. It could potentially cause abortions. The dose being used for PMD is seven times the dose needed as an abortifacient.

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

Wyeth's atypical antidepressant Effexor (venlafaxine) goes off patent in 2008, and sustained-release desvenlafaxine has to be meaningfully better if Wyeth is going to convert patients from Effexor/Effexor-ER (extended-release venlafaxine) to sustained-release desvenlafaxine before the patent expiration. Desvenlafaxine-SR also has to differentiate itself from Lilly's Cymbalta (duloxetine). An expert at APA who is participating in the desvenlafaxine trials was asked how desvenlafaxine differs from venlafaxine, and his answer was: "They don't. There is nothing to distinguish desvenlafaxine."

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