Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Nicotinic acetylcholine receptor agonists are a promising new class of drugs to treat cognition in schizophrenia and/or Alzheimer's Disease, and there are a variety of them in development, but none have even shown proof-of-concept yet. ♦ Doctors were not very excited about the use of Cephalon's modafinil in ADHD. ♦ Both Pfizer's Geodon (ziprasidone) and AstraZeneca's Seroquel (quetiapine) look promising in bipolar disorder. ♦ Novartis's antipsychotic Clozaril (clozapine) was described as "vastly underutilized," and safety may be better than previously thought. ♦ The FDA is urging sponsors to submit better and more complete new drug applications, and to respond quicker to the Agency's safety questions.

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NEW CLINICAL DRUG EVALUATION UNIT (NCDEU)

Boca Raton, FL
June 6-9, 2005

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

The NCS-R Study results, released the day before NCDEU, found that the incidence of mental disorders is about what was expected. NCS-R, a five-year study of 9,000 English-speaking U.S. households, found:

- 6% of the population has a mental disorder causing serious disability.
- 50% report onset by age 14.
- Less than 1/3 received "minimally adequate" treatment.
- Most treatment is outside mental health care sector.

Dr. Thomas Insel, Director of NIMH, called for a very different vision for the next 20 years. Among the points he made were:

➢ **Better diagnostics.** Currently, diagnoses are made by symptoms, and treatment is episodic by trial and error. A better understanding of the pathophysiology of mental disorders is needed, with use of biodiagnostics and treatment of the core pathology. He said, "We have lots of effective treatments, but we don't know which works for which patient…At NIH we have really taken this on – the development of tools for discovery, molecular libraries, networks of assays that can run through millions of compounds in a few days to identify 'hits.' We are not so much going after drug development, though that could happen, but it is an attempt to develop the tools for annotating the genome."

➢ **Individualized care.** This is the ultimate goal. Dr. Insel said, "This requires understanding risk, who really needs intervention, and what the best intervention might be. With a focus on treatments, cures, and strategic prevention…Will genomics allow individualized psychiatric diagnosis and treatment? I think we are still in the early stages of this. I hope so…There is no hope that the paradigm we have developed for 40 years will pay off with drugs with new mechanisms of action. That paradigm is all about me-too agents, mainly reducing side effects, but it will not get us where we want. We need to target the core pathophysiology of these disorders, and that is where we should focus in the future."

➢ **Faster therapies.** He said, "We have very good treatments for depression… with perhaps a 70% overall response (at three months). If I were talking about severe headaches, and I said we have pretty good treatments and 70% of people won't be in pain at three months, you would think I was in dream land. Why don't

we have a focus on antidepressant therapies that work in three hours or three days, not three months? Why can't we intervene at the very earliest phase of a psychotic break, so patients don't go through the worst part of that? A lot of this will involve new technologies and new discoveries:

- Clinical genomics.
- Neuroimaging.
- Proteomics.
- Molecular diagnostics.
- Preventive interventions."

➢ **Vaccines.** Vaccines for schizophrenia are further away than vaccines for cocaine addiction or cancer.

Identification of Molecular Pathophysiology

Disease/Disorder	Genes	Cells	System	Organism
Alzheimer's Disease	Yes	Yes	Yes	Yes
Fragile X	Yes	Yes	No	Yes
Schizophrenia	Some	No	Yes	No
Depression	Some	No	Yes	Some
Bipolar	No	No	No	No
PTSD	No	No	Yes	Some

➢ **Genomics.** How do we get from understanding the genome to understanding mental disorders? Dr. Insel said the International HapMap Project (www.hapmap.org) was completed about 8-10 weeks before NCDEU. With HapMap, comparing SNPs was simplified from an ~$60 million/2-3 year project to an ~$2 million/2 week project. He also noted that a New Zealand study >1,000 people over 26 years found that neither life stress nor polymorphisms in the 5-HTT gene predicted a major depressive disorder (MDD), but the combination of 4+ life stress events and a "short" genotype doubled the risk of a major depressive disorder (33% vs. 17% with stress+long genotype).

➢ **Subgenual prefrontal cortex.** If there is a frontier area in the forebrain, this is it. Dr. Insel said there is 30%-40% decrease in volume in this area in people with MDD, which is quite striking. He added, "When patients get deep brain stimulation in this area, they improve quickly. Those people with short genotype – because of changes not just in one brain region but in the entire system for processing negative emotion – failed to process it the same way as people with long genotypes, which may explain why short genotypes are susceptible or why long genotypes have protection from MDD …Genetic variation also may cause altered development, which may lead to biased information processing, and that may result in a mood disorder."

ALZHEIMER'S DISEASE (AD)

FOREST'S Namenda (memantine)

Doctors at NCDEU said they are generally satisfied with the results they are getting with Namenda. One source noted, though, that three-quarters of prescriptions for Namenda are written by primary care doctors. A meta-analysis of 6-month Namenda trials in AD found the drug had a statistically significant benefit over placebo on cognition, function, and global status.

PACIFIC NW BIOTECHNOLOGY'S COG-83

This is still in preclinical development, and it is probably not the final agent that will go forward, but it is an interesting agent for AD and stroke.

NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

Nicotinic acetylcholine receptor agonists – particularly alpha-7 nicotinic agonists – are a promising new area of research in cognition, and numerous companies are working on these drugs to improve cognition in schizophrenia, Alzheimer's Disease, ADHD, etc. The following information is based on interviews with experts at NCDEU as well as the International Neurodegeneration in Alzheimer's Disease, Parkinson's Disease, and Related Disorders Conference in April 2005, and the American Psychiatric Association meeting in May 2005.

Proof-of-principle

Experts agreed that nicotinic agonists are an interesting and promising area of research, but they cautioned that there is still no proof-of-principle that any of them work. Until some Phase II efficacy data are available, they are reserving judgment on these agents. One expert said, "It is way too early to see if they will hit pay dirt, but they are at the top of the list of promising things to test, but it will be a tough road. It (cognition in schizophrenia) is an unmet need, but the basic discovery hasn't been done. We don't know the molecular targets or the pathophysiology yet…I think most nicotinic agonists are failing, and I think pharmas are doing Phase II studies in multiple indications – a shotgun approach – to see what might work." A speaker at NCDEU said, "Multiple (neuroprotective) compounds show efficacy in vitro, but there is no proof of concept in humans."

Different disease states

Cognition data from one disorder (e.g., schizophrenia) may not be able to be used to shorten the regulatory path for another disorder (e.g., Alzheimer's Disease). Experts differ on this point. One said, "If a drug works in cognition for schizophrenia, it would probably work for cognition in Alzheimer's Disease and ADHD." Another said, "There is no reason to think cognition in schizophrenia will translate to Alzheimer's Disease or other disorders."

Formulation issues

An NIH source said there have been problems with this group of compounds due to their short half-life and that dosing was required up to 10 times per day. A sustained release formulation of one of the alpha-7 agonists is being developed.

Regulatory issues

The regulatory hurdles are seen as high for nicotinic agonists, primarily because they are new agents and because FDA trial requirements are tough. Reportedly, the FDA has limited the number of new nicotinic agonist trials that can begin until results of the current trials have been presented. A Targacept official said, "No doubt there is a large regulatory hurdle."

At NCDEU, FDA officials outlined the requirements for cognition studies. Treatment of cognition in schizophrenia is considered by the FDA as a treatment of negative symptoms, and the FDA outlined the requirement for a trial of negative symptoms in psychopharmacology. An FDA official said, "FDA has accepted cognitive impairment in schizophrenia as a legitimate target. We are considering non-DSM entities to grant claims for many reasons." As a target for a treatment claim, he noted that negative symptoms:

- Are a serious unmet medical need and a core feature of schizophrenia.
- Are a distinct, separate feature of schizophrenia.
- Respond poorly to available treatments.
- Are associated with poor function and outcome.
- Have face validity as a disease manifestation.
- Represent a loss of normal functions.

The key take-aways about the design of a negative symptom/ cognition trial in schizophrenia were:

- A co-primary functional endpoint is not likely to be required in negative symptom trials.
- A defined population and outcome measures need to be prospectively defined upfront. These need to be hammered out with the FDA well in advance of starting the trial.
- The residual phase of the illness must be targeted, not the acute phase. An FDA official said, "We simply wouldn't entertain the idea of an acute negative symptom trial." There is no consensus yet on including patients who are in the prodromal phase of schizophrenia.
- The design must be adjunctive, add-on therapy.
- Six months is probably the minimum time frame.
- The FDA strongly discourages a broad spectrum agent (monotherapy, with active control) trial design. An official explained that this is more complex and interpretations might be difficult, making it difficult to make an efficacy claim in labeling.
- There is no accepted outcome scale right now for a negative symptom trial, and the FDA encourages companies to make proposals. However, any scale used must be validated.

Other interesting points made about cognition trials included:

- An NIMH official commented, "I agree with the FDA…As clinicians, I'm not sure we can identify changes in cognition and in a clinical interview note them. How would a practitioner know if a patient has responded? But on negative symptoms, we can readily discern change in negative symptoms."
- A speaker said, "We know cognition and negative symptoms are apparently correlated phenomena…Both tend to be stable over time and stable over changes in psychosis. Negative symptoms also are associated with social and occupational functioning and independent living."
- There is no correlation between negative symptoms and cognitive function – because the courses are different. Negative and cognitive symptoms are much more strongly correlated cross-sectionally than longitudinally. They respond differently to environmental changes, and they are differentially related to functional outcomes. It appears that negative symptoms and cognition are separate treatment targets in schizophrenia, and trials must use instrumentation and/or analysis that consider the overlap between these symptoms.
- An expert said, "If patients get medication for cognition but still have depressive symptoms, they probably won't have any change in functioning in the real world. We might not see a change in real world trials in six weeks if we don't treat the depression as well as cognition…You can't expect patients to improve functionally just because cognition improves…We have to help them acquire the skills they probably never acquired."

An NIH Consensus Development Conference met in January 2005, and its report is tentatively scheduled for publication in January 2006. The NIH Consensus Development Program does evidence-based assessments of medical practice and state-of-the-art science on behalf of the medical community and the public. Organized conferences are held that produce consensus statements and state-of-the-science statements on controversial issues in medicine important to healthcare providers, patients, and the general public.

A speaker summed up some of the conclusions of this Consensus Development Conference relating to psychiatry:

- The current treatment of negative symptoms is really not very satisfactory.
- Negative symptoms and cognition are separate.
- Negative symptoms have face validity as disease manifestations and represent a loss of normal function and/or decrease in the quality of life.
- A proof-of-concept trial can be brief (4-12 weeks), but a registration study will need to be substantially longer to document persistent efficacy.

- The paradigmatic design of clinical trials of persistent negative symptoms would:
  - Include stable patients where negative symptoms persist with adequate antipsychotic medication.
  - Be double-blind, placebo-controlled comparison of parallel groups.
  - Have the putative negative symptom treatment administered as co-medication with an antipsychotic.
- Primary negative symptoms may mark biologically meaningful subgroups, but this distinction is not essential for the purpose of testing therapeutics for negative symptoms. There is some evidence suggesting there are differences in pathophysiology for primary vs. secondary negative symptoms, indicating that a treatment shown to be effective for persistent negative symptoms may not be effective for primary negative symptoms. Most studies of treatment of negative symptoms will probably focus on patients with both primary and secondary negative symptoms, to maximize the number of patients.
- The domains of negative symptoms include: blunted affect, alogia (inability to speak), asociality, anhedonia (lack of pleasure or interest in activities that the patients once enjoyed), and avolition (lack of energy, spontaneity, and initiative).
- SANS is preferred to PANSS, but both are appropriate for application in current clinical trials.
- Development of a new instrument with five agreed-upon domains is a goal. A Work Group of nine members has been formed to work on development and testing of this instrument.
- A framework needs to be developed to promote the identification and testing of drugs for negative symptoms. It is expected that this process would be similar to the MATRICS process. This Work Group has not yet been formed.

National Institutes of Health (NIH)

NIH has been collaborating with the pharmaceutical industry on nicotinic agonists, and at least one specific NIH nicotinic agonist trial – with Targacept's TC-1734 – has been confirmed. A UCLA researcher explained that the TURNS (Treatment Units for Research on Neurocognition in Schizophrenia) review group chose two compounds for TURNS-conducted trials.

One of these is Organon's ORG-24448 (an AMPA-R receptor in the glutamate system), and the other is Targacept's TC-1734, a partial agonist of the alpha-4/beta-2 nicotinic acetylcholine receptor. The TURNS network is planning to study these compounds this year. The TURNS program is a NIMH-supported network that does clinical studies of pharmacological agents for enhancing neurocognition in schizophrenia patients.

Specific companies with nicotinic acetylcholine receptor agonists in development include:

Abbott Laboratories

- **ABT-089.** This is in Phase II development, and we believe there are multiple Phase IIa trials ongoing, including schizophrenia, Alzheimer's Disease, and perhaps ADHD. An expert said Abbott tested ABT-418 eight years ago as a transdermal medication, and it failed for lack of efficacy. A researcher said this agent shows "even greater potency after chronic treatment…with little propensity to induce adverse effects such as ataxia, hypothermia, seizures, cardiovascular, or GI side effects."
- **A-85380.** This is a radiolabeled alpha-4 agonist. The company reportedly is recruiting patients for a brain imaging study in Alzheimer's Disease, with cognitive tests as the endpoint.
- An unidentified alpha-7 is believed to be in preclinical development.
- **A-35380.** This is a neurone NACHR nicotinic ligand in early discovery stage. The hope is that it will work in Alzheimer's, pain, neurodegenerative disease, smoking cessation, anxiety disorder, and/or schizophrenia.
- **A-366833.** This is a nicotinic agonist in early discovery stage. The hope is that it also will work in Alzheimer's, pain, neurodegenerative disease, smoking cessation, anxiety disorder, and/or schizophrenia.

AstraZeneca

AZD-0328 reportedly failed in human trials in the U.K. because of liver toxicity, and no alpha-7 could be identified that is currently in human clinical trials.

En Vivo

This company has an un-named alpha-7 in preclinical development, for Parkinson's Disease and Alzheimer's Disease, with an IND expected in 2006.

Galapagos Genomics

This company is believed to have an alpha-7 in preclinical development.

Lilly

Lilly is working on a drug dubbed PSAB-OFP, but no information was available on this agent, and it may or may not be a nicotinic agonist.

MEMORY/ROCHE

- **MEM-3454.** This is a selective alpha-7 agonist. It reportedly started a Phase I trial for schizophrenia in February 2005.
- **MEM-63908.** This is an alpha-7 partial agonist in preclinical development for Alzheimer's Disease.

MERCK

Through its purchase of Sibia Neurosciences, Merck got an alpha-4 which has since been abandoned, and we believe there may be an early alpha-7. SIB-1553-A and SIB-1765-F are both Sibia nicotinic agonists They are thought to be still in discovery, but it is possible one has moved as far as Phase II. If there is an agent in human clinical trials, it most likely is being developed for Alzheimer's Disease or Parkinson's Disease.

MITSUBISHI

Several sources said they believe the company is working on a nicotinic agonist, but no one had any details.

NEUROSEARCH'S NS-2330

This triple uptake inhibitor was in Phase IIb, but it is thought to have been discontinued.

NOVARTIS

Several sources said Novartis is working on nicotinic agonists, but no one had any details.

OSPREY PHARMACEUTICALS

GTS-21 (also known as DXMB-A) is a mixed alpha-4/alpha-7 nicotinic agonist believed to have been developed at the University of Florida by Taiho. An expert described it as a "dirty" drug. It is licensed to Osprey Pharmaceuticals, which is currently recruiting for a Phase II trial to improve attention and other neuropsychological dysfunctions in schizophrenia. A source said, "Osprey had a non-selective nicotinic agonist. That compound went into clinical trials, had some effect for cognition, but was a lousy drug. Patients had to take it five times a day or something like that. Still, there were beneficial effects. Possibly it may have been reformulated to once a day."

A 12-patient, double-blind, crossover, Phase I trial was completed in January 2005 in non-smoking schizophrenics who were concurrently treated with neuroleptics during the study. Two doses were compared to placebo: high dose (150 mg initially and then 75 mg 2 hours later) or low dose (75 mg initially and then 37.5 mg 2 hours later). A significant effect was reported on neurocognition (measured by the Repeatable Battery for Assessment of Neuropsychological Status) and on sensory gating (measured by P50 auditory evoked potentials). No significant side effects were noted, though one patient had a transient drop in white blood cell count.

A 24-patient, randomized, double-blind, placebo-controlled, crossover, Phase II study started enrollment in January 2005. This trial is assessing the ability of GTS-21 to improve attention and other neuropsychological dysfunctions in schizophrenia, leading to improved psychosocial outcome. GTS-21 is being administered BID for four weeks. The primary endpoint is neurocognitive improvement on the MATRICS Battery, and the secondary endpoint is psycho-social function. The last follow-up is expected to be in December 2006, with results in early 2007. The FDA reportedly is requiring the drug show a clinical effect beyond changes in laboratory neuropsychological performance.

Two Phase III studies are planned when the Phase II trial is finished. Both of these are expected to include safety assessments on GTS-21 and related compounds.

PFIZER

- **Varenicline.** This is an alpha-4 partial agonist in Phase III development only for smoking cessation.
- **CP-601932,** a nicotinic partial agonist. Even our best Pfizer sources have no knowledge of this agent or Pfizer's nicotinic agonist program outside of the smoking cessation drug. They've heard rumblings that there is a program, but it is very quiet and access limited.

R.J. REYNOLDS

- **RJR-2429.** This nicotinic agonist is believed to still be in discovery stage.
- **RJR-1401.** The status of this nicotinic agonist is unknown but it is believed to be in either discovery or preclinical development.

SANOFI-AVENTIS

- **SSR-591813.** This partial alpha-4 agonist is in Phase IIb development for smoking cessation.
- **SSR-180711.** This alpha-7 agonist is in late preclinical development for neurocognition, probably in schizophrenia.

SCHERING-PLOUGH

This company is believed to have an un-named alpha-7 in preclinical development.

TARGACEPT

Targacept is working on several nicotinic agonists, which it got from R.J. Reynolds research when the company was

created. Targacept is not testing its agents in smoking cessation.

- **Ispronicline** (TC-1734), an alpha-4/beta-2 nicotinic agonist, is in Phase II development for cognitive impairment in both schizophrenia and Alzheimer's Disease.
  - ***Schizophrenia.*** This is being done by TURNS. Dr. Jeffrey Lieberman of Columbia University is working on this, along with five other sites in a 4-8 week trial of ispronicline as add-on therapy to an antipsychotic vs. placebo+antipsychotic. The primary endpoint is a MATRICS test battery.
  - ***Alzheimer's Disease.*** Targacept itself is doing a Phase IIb trial in Age-Associated Memory Impairment (AAMI), which is normal aging. Another trial will start in early 2006 in AAMI. A third trial of six-month monotherapy in mild-to-moderate AD will use a "fairly standard" trial design. This trial will be conducted in English-speaking countries outside the U.S. (Canada, New Zealand, U.K., and Australia).
- **TC-1827.** This is an alpha-4 selective agonist in preclinical development. It may be close to an IND.
- **TC-2559.** This nicotinic agonist is still in discovery for neurodegenerative diseases.
- **TC-1698.** Development of this alpha-7 has been discontinued.
- **TC-5619.** This alpha-7 agonist is in preclinical development for neurodegenerative diseases.

Miscellaneous

- University of Queensland, Australia, has some alpha-conotoxins, which are nicotinic antagonists (muscle relaxants) in discovery for neurological diseases.
- NIH has BTG-A derivatives, including a nicotinic modulator and a muscarinic modulator, in discovery stage.
- University of Nottingham, U.K., has some pilantho-toxins, including a nicotinic antagonist and an AMPA antagonist, in discovery for neurodegenerative disease and cognitive disorders.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

SHIRE'S Adderall XR (a mixed salt of a single amphetamine product)

In February 2005, Health Canada pulled Adderall XR from the Canadian market, citing several cases of sudden cardiac death (SCD). At the time, the FDA took that action seriously but did not duplicate it. At NCDEU, Dr. Joseph Biederman of Mass General/Harvard presented a meta-analysis of five pediatric and two adults trials of Adderall XR that looked at the cardiovascular risk. He said the analysis found:

- No dose response for Adderall XR 20 mg - 60 mg for any vital sign. There was no dose effects for CV parameters.
- No serious CV adverse events.
- Only one subject with ECG measurements that were considered clinically significant by the investigator.
- No serious CV adverse events in an outlier analysis. Six patients discontinued from the study due to CV adverse events – one for tachycardia and hypertension, and the other five for hypertension.
- Small increase in blood pressure and pulse that were not considered to be clinically significant and which were common to all medications used for ADHD.
- No effect on ECG intervals or findings.

Dr. Biederman added, "We just submitted a very large study of Strattera (Lilly, atomoxetine), and I did an exhaustive study analysis of the cardiovascular parameters and found the same...small but statistically significant changes in CV parameters, but no change on ECG…There was talk about stroke being one of the mechanisms of SCD – clot formation with embolus leading to stroke…All the stroke cases had confounders…With Adderall IR/XR, the overall incidence was 0.09-0.3 vs. a background rate of 2.3-600 per 100,000 patient years. The conclusion is that the incidence of stroke is not increased over the observed incidence in the pediatric population, and it is not increased over the adult population."

CEPHALON'S Provigil (modafinil)

A different formulation of Provigil was developed for pediatric ADHD – the tablets are film-coated – and it probably will be marketed under a different name. Modafinil was submitted to the FDA for ADHD on December 4, 2004, so a regulatory decision is likely soon.

Doctors at NCDEU were not very excited about Provigil in ADHD, but they also were not very worried about Stevens-Johnson syndrome or other side effects.

- *New York #1:* "I've inherited patients on it. It is not at the top of my list, but I would use it, though not first-line…More neurologists will prescribe it than psy-chiatrists…One of my patients on Provigil got psychotic, and then got better when taken off it."
- *New England:* "There is only one case in 600 of Stevens-Johnson, and the post-marketing surveillance (with Provigil for narcolepsy) has shown no signal of Stevens-Johnson, so if there is a risk, it is very tiny…But a second case of Stevens-Johnson would be concerning…The incidence of insomnia is numerically high (about 30%), but there is rapid accommodation – it's gone in three weeks – and usually tolerable. Patients don't spend the

night walking around…I use it off-label now in patients with tolerability problems with stimulants or in whom stimulants are not working as well as I want, or in patients who don't want the stimulant effect. If it gets approved for ADHD, I would use it upfront. It lasts at least through the extended school day (~12 hours). It is an alternative, and we need options to treat patients…It won't be a blockbuster, but it will be a player."

- *New York #2:* "It is useful to have options. Provigil has appeal to families who want to avoid stimulants, but it is not nearly as effective as stimulants. I'm not using Provigil off-label because I can make stimulants work, but when it is approved, I will use it. I can't get it reimbursed off-label. It will be second-line after stimulants, and I'd estimate 15%-20% of ADHD patients will get it, but being non-scheduled is ***very*** important."
- "This will be interesting in combination therapy – if we can lower the dose of a stimulant…Stevens-Johnson is not concerning, even if there are two cases…To avoid insomnia, just don't give it at night."
- "I use Provigil off-label in ADHD second-line. If it gets approved about 10%-15% of my patients are likely to get it – unless it can be used in combination with a stimulant. Then, usage could be higher. It will stay second-line unless I see compelling new data."

Cephalon also has a follow-on to Provigil in development – Nuvigil (armodafinil). Nuvigil has a longer half-life, but sources weren't sure if it had real advantages over Provigil.

BIPOLAR DISORDER

New data were presented on Pfizer's Geodon (ziprasidone) in bipolar kids. Based on this data, Pfizer intends to start Phase III studies at 20 mg/day and titrate upward to a target dose of 120-160 mg/day (60-80 mg BID) over a period of 7-14 days. An investigator said, "You need to get to a higher dose, but with slow titration (10 days is too fast). You really need 160 mg QD for efficacy. QT prolongation is not an issue, which is in contrast to what was recently published."

Seroquel in Bipolar II Disorder at 8 Weeks

Measurement	Seroquel 600 mg/day	Seroquel 300 mg/day	Placebo
Rapid cyclers	23.3% (Nss)	32.2% (Nss)	25.8%
Discontinuations	50%	39%	32%
Primary endpoint: Mean change from baseline in MADRS score	~ -15%	~ -15%	~ -14%
Secondary endpoints: **Mean change from baseline**			
MADRS score in rapid cyclers	~-22% (p<.01)	~ -16% (p<.05)	~ -10%
MADRS score in non-rapid cyclers	~ -15% (Nss)	~ -15% (Nss)	~ -15%
HAM-D	~ -15% (p<.05)	~ -13% (Nss)	~ -11%
CGI-S	~ -20% (p<.05)	~ -16% (Nss)	~ -14%

AstraZeneca also presented a study which found Seroquel (quetiapine) useful in bipolar II disorder, particularly in rapid cycling patients, though the trial missed its primary endpoint. The study examined 181 patients given either 300 mg daily or 600 mg daily vs. placebo for up to 8 weeks. Concomitant use of other psychoactive drugs was not allowed, except for low doses of zolpidem (Sanofi-Aventis's Ambien) and lorazepam (Wyeth's Ativan) during the first three weeks of treatment.

DEPRESSION

Among the comments sources had about various anti-depressants were:

- **LILLY'S Cymbalta (duloxetine).** A Virginia doctor said, "It's just another antidepressant, but it is helpful to have in our armamentarium. All the SSRIs and SNRIs are equally effective…The nausea side effects are less an issue for me because patients come to me already on an SSRI, so they are selected to be able to take an SSRI."
- **FOREST LABORATORIES' Lexapro (escitalopram).** A doctor said, "It is good for acute patients, but the side effects – sexual dysfunction, sleep changes, weight gain, cognition – are about the same as with other SSRIs. My use of Lexapro has been affected by generic citalopram, but I've been less affected than primary care doctors …There actually may be differences in SSRIs on premature ejaculation, but I don't see those patients."
- **Premature ejaculation.** A Florida doctor said, "Any SSRI works for premature ejaculation. They are all equally good."

INSOMNIA

Several new therapies for insomnia have recently been approved or are near approval. There was not a lot of data on these at NCDEU, but the following comments were interesting:

MERCK/LUNDBECK'S gaboxadol. A source said, "This looks promising."

NEUROCRINE BIOSCIENCES/PFIZER'S Indiplon. The outlook for this agent is likely to depend on the data, sources said. One commented, "Sepracor has set the bar on data (with Lunesta)."

PHASE 2 DISCOVERY'S LY-156735. A study is underway in moderate-to-severe primary insomnia. An investigator said, "This is much better than TAK-375 in subjective sleep latency. Sleep latency is increased with TAK-375, but I'm not sure it is clinically significant. Ours is clinically significant."

SANOFI-AVENTIS'S Ambien MR (zolpidem). A doctor predicted, "Ambien MR will cut into use of Lunesta."

SEPRACOR'S Lunesta (eszopiclone). A doctor said, "I've started a number of new patients on Lunesta. I'm comfortable with it, and the data are good. I'll probably start switching some existing benzodiazepine patients to it." Another source said, "Lunesta only works in 50%-60% of patients, so we need Indiplon and TAK-375. The number of insomniacs is increasing, and awareness is increasing, so the market is growing…I'll use Lunesta for new patients, and I'll switch some patients from other drugs. New patients will do better on it because of the withdrawal that happens when you switch patients. Use of Lunesta will increase."

TAKEDA'S Rozerem (ramelteon, TAK-375). The FDA approved Rozerem in July 2005. At NCDEU, doctors said they planned to use it. One commented, "I'm looking at using it in patients with shift work or jet lag…The advantage is sleep latency is increased, and it is good for that subset of patients. There are no problems with tolerance or rebound. And next day cognition and psychomotor effects are minimal, which is good for the elderly…In six months, about 25% of new patients will go on Lunesta and 25% on ramelteon. I'll tailor treatment to the underlying cause of the insomnia."

SCHIZOPHRENIA

The U.S. atypical antipsychotic market is large and expanding, but the results of a major trial that is expected to be published this month in the ***New England Journal of Medicine***, CATIE, may significantly alter usage patterns. CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) is an NIMH-sponsored research program to evaluate the efficacy of antipsychotic medications for schizophrenia and Alzheimer's Disease in "real world" settings. It is attempting to determine whether second generation antipsychotics (SGAs) – AstraZeneca's Seroquel (quetiapine), Bristol-Myers Squibb's Abilify (aripiprazole) Johnson & Johnson's Risperdal (risperidone), Lilly's Zyprexa (olanzapine), and Pfizer's Geodon (ziprasidone) – are more effective than first-generation antipsychotics, what the comparative effectiveness is of the various SGAs, and whether SGAs are cost effective. The primary endpoint is all cause treatment discontinuation.

Antipsychotics for dementia-induced psychosis

An FDA official noted that Lilly had informed the agency about a statistically significant increase in mortality with treatment of dementia-induced psychosis with Zyprexa, and an sNDA for Risperdal showed higher but not statistically significant mortality relative to placebo. He said, "We are not picking up all the deaths…They are not being reported…I suspect we have an ascertainment bias."

Several possibilities were suggested as the causes driving the increased mortality:

- Unrecognized cause which would be detectible with better observation and data collection.
- Union cause (novel mechanism).
- "Squeaky wheels" get better supportive care.
- "Will to live" in dementia patients – manifested as behavioral problems – that are suppressed by anti-psychotic drugs.

A review was presented of 17 randomized clinical trials of antipsychotics, including 3 of Abilify, 2 of haloperidol, 5 of Zyprexa, 2 of Seroquel, 7 of Risperdal, and 1 of Geodon. The analysis included 5,377 patients, and the studies ranged from 28-182 days.

Causes of Death in Dementia Patients on Antipsychotics

Measurement	Causes	Antipsychotics n=3,611	Placebo n=1,766
Cardiac	CHF, CAD, MI, SCD	47.5%	28.2%
CV	CHF, CAD, MI, SCD, atherosclerosis, CVA	59.9%	39.5%
Cardiopulmonary	CHF, CAD, MI, SCD, respiratory failure, PE, pneumonia	86.8%	52.7%
Infection	Pneumonia, cellulitis, sepsis, UTI	44.9%	20.7%

Safety of Antipsychotics in Dementia-induced Psychosis

Measurement	Advantages	Disadvantages	Poisson regression	p-value
Death within 4 days of last dose	Reduces noise, simple and reliable	Significant bias if drug tolerability is related to the mortality risk	All antipsychotics 1.93	.017
Death within intended treatment period	---	---	All antipsychotics 1.68 Atypical antipsychotics 1.60	.011 .023
Death within 30 days of intended treatment period	More information, minimal bias	More noise, more uncertainty about follow-up	All antipsychotics 1.72 Atypical antipsychotics 1.66	.002 .006
Open label extensions	More information, less noise, no contamination	Potential biases in follow-up	All antipsychotics 1.66 Atypical antipsychotics 1.65	.010 .013

Weight gain

A researcher from Ireland suggested that pre-diabetic changes occur in schizophrenics, are an inherent part of the illness, and may have a hereditary basis. Dr. Alan Schatzberg of Stanford (who has equity in Corcept, Elan, Merck, Pfizer, and Cypress Biosciences) reported on a study he led, sponsored by Lilly, in which all of the Zyprexa trial data was analyzed both by Lilly and by an outside group. According to him, the common beliefs in the psychiatric community are that Zyprexa is associated with weight gain, new onset diabetes, and hyper-lipidemia, but the literature is not clear on this.

He said, "There is a kind of sense that the weight gain is the responsible agent for the increased risk of hyperglycemia and should be the key monitoring focus, but there are questions about whether this is the wisest approach. The Lilly data do not support weight gain as the culprit in hyperglycemia… People need to understand the metabolic model is based on five factors, only one of which is fasting blood sugar. Triglyceride (TGL) and HDL levels would be more predictive of long term cardiovascular diseases…and Clozaril and Zyprexa data indicate they cause insulin resistance which is not caused by other atypicals…People on the borderline of diabetes and cardiovascular risk problems will be pushed into that by the drug. I would like to see 26-28 week data looking at TGL/HDL levels, and that will inform people about true risk more than short-term change in one measure – fasting blood sugar – which is a weak predictor…I think the diabetes is a red herring, largely. I think, in fact, it misleads the field…We've shown that TGL change is your big effect…What you need to report is TGL and HDL levels…We showed Zyprexa increased TGL significantly greater than ziprasidone."

NOVARTIS'S Clozaril (clozapine)

A speaker noted that Clozaril is "vastly underutilized," with close to 90% of prescriptions for newer antipsychotics (second generation antipsychotics or SGAs) under the assumption that they are better. He cited a survey of U.S. psychiatrists about the management of treatment-resistant symptoms in schizo-phrenia. These doctors all had 4+ schizophrenic patients who had a medication change in the past year.

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An FDA official provided an update on the white blood cell monitoring program for Clozaril. Clozaril was first approved outside the U.S. in 1970, but in 1975 it was withdrawn from the worldwide market following 16 cases of agranulocytosis, eight of which were fatal. Clozaril sales resumed in a limited fashion outside the U.S. shortly after that, and usage grew over time with the introduction of strict patient monitoring systems.

Identification of Molecular Pathophysiology

Most commonly prescribed antipsychotic	Antipsychotic considered most effective	How treatment-resistance was handled
49% Risperdal	79% Clozaril	78% switched to another agent
33% Zyprexa	46% Zyprexa	49% started another medication
	39% Risperdal	Added another antipsychotic

The FDA approved Clozaril in 1989, specifying it could only be sold with a patient monitoring system in place to prevent fatalities due to agranulocytosis. For many years, providers who dispensed clozapine had to ensure that a patient's white blood cell count was monitored weekly. The use of clozapine also was restricted to three sub-populations: (1) treatment-resistant schizophrenics, (2) patients who cannot tolerate the extrapyramidal symptoms of conventional antipsychotics, and (3) patients with evident tardive dyskinesia that was not suppressed. Clozapine therapy also had to be initiated in an inpatient setting, where the dose could be titrated to reduce the risk of agranulocytosis.

Currently, weekly monitoring is only required for the first six months of Clozaril use. After that, white count monitoring can be reduced to once every two weeks for the next six months, with the added requirements of rANC monitoring. Patients who are re-challenged with Clozaril must undergo weekly monitoring for 12 months. Clozaril is only available through a distribution system that ensures the patient's white blood cell count is in an acceptable range. An FDA official said, "We were very concerned – and it was not a tremendous surprise – that patients with less severe blood dyscrasia have an increased risk of going on to agranulocytosis. There is a big jump in the rate of agranulocytosis in patients who have a second episode of moderate leukopenia. The increased risk persists for about one year following recovery from the original episode. It doesn't look like the risk of a third or four episode is more likely after the first."

BRISTOL-MYERS SQUIBB'S Abilify (aripiprazole)

A pivotal Phase III study in acute schizophrenia found intramuscular (IM) Abilify 10 mg rapidly improved the symptoms of agitation, and the improvement over placebo was similar to that achieved with haloperidol 6.5 mg IM but with fewer EPS-related adverse events.

REGULATORY ISSUES

The FDA's Division of Neuropharmacologic Drug Products is being divided into the Division of Neurology Products and the Division of Psychiatry Products. Dr. Thomas Laughren will be Director of the new Psychiatry Products Division. Dr. Russell Katz, who will head the Neurology Products Division, offered some personal observations based on his 6.5 years as head of the Division of Neuropharmacology. Among the points he made were:

- **Resources.** "There is a vast asymmetry between the FDA's resources and those of industry. This is a fundamental fact underlying our relationship and this disparity cannot be over-stated…I suspect the depth you can delve into something is far

greater than it is possible for agency reviewers to reach in the timeframes available. And it is these disparities that are the primary reason stated for splitting the division, so additional reviewers can be hired to ease the burden on individual agency reviewers. I hope this turns out to be true, but I don't think the burden will be substantially reduced in the near term given the difficulty in finding qualified applicants and training them."

- **Missing or incomplete data.** He said this is stressing and frustrating the FDA staff, causing them to fall further behind. "It is our responsibility to get past the spin, to expose the weakness in the data, if any, and then make a decision. We expect you to present data in the best possible light…But the less complete the data, the longer it will take…You are disease experts; we are not…When we read documents prepared by experts that offer unsubstantiated data or skirt critical questions, the process becomes tainted…and it can be difficult for us to see the right way forward, and cynicisms can develop …We rely on your objectivity…Public suspicion of the agency is running rather high at the moment."

- **Problems in assessing safety signals –** and the time it takes industry to respond to FDA questions about a safety signal. "We are aware you will put the best face on the data. But I have to say that I suspect those efforts prolong the time for you to respond to us and leads to prolonged review time… My greatest fears involve some significant safety issue that is lurking in our queue, either not analyzed or partially analyzed …and it is not easy to prioritize reviews when the issues we send up can have significant public health implications."

- **Pediatric conduct disorder.** "This may be a bonafide clinical illness…and drug development is proceeding in this area…but we are not so far from the time when homosexuality was considered a psychiatric illness…so I think we need to tread lightly."

Other FDA officials offered advice to companies and researchers conducting trials of new drugs. Among the points they made were:

➢ **SPAs.** With a special protocol assessment, the final statistical plan must be an amendment to the protocol submitted to the IND prior to breaking the blind. An official stressed that this is new and was being stressed, adding, "We have run into too many situations that, when we get the analysis plan, it is different from the one specified in the protocol, and that makes our statisticians wild. We want to make sure HARK (hypothesis after results are known) doesn't occur."

➢ **Complete submissions.** The FDA is still experiencing problems with the requirement for a complete submission, which must include all data necessary for approval, be readable, be organized with an accurate table of contents, and preferably be in electronic format. An official also called for "better" submissions.

➢ **Rolling reviews.** This is still a pilot program, and all material should be available in the submission. Sometimes, an official explained, a company submits data such as open label extension trials, after the submission, which is problematic.

➢ **Clinical reviews of safety.** These must include deaths, serious adverse events, dropouts due to adverse events, but it is also affected by patients "lost to follow-up." An official commented, "Those patients are un-interpretable and lead to questions about data integrity. Reports that are now standard requirements include: treatment-emergent suicide (completed, attempted, or ideation) and thorough QT studies.

➢ **Late data.** An official said, "We strongly discourage new (data) analyses after the FDA has sent its analyses to the Psychopharmacologic Drugs Advisory Committee."

➢ **Coding and narratives.** An official urged companies to submit data with better coding and better narratives.

On the topic of using atypical antipsychotics in demented patients, an FDA official said, "We are not contraindicating it. It is not approved, and we know that people are likely to continue to use it (an antipsychotic), but at least people will be informed (with the new labeling). That is sometimes the easiest answer – labeling."

On the balance between risk and benefit, Dr. Katz said, "People talk about the risk/benefit ratio or equation. I'd ban that talk. Risk/benefit is like comparing apples and typewriters. They are different scales. There is no rule for it... We tolerate a tremendous amount of serious toxicity…We make an assumption these are bad diseases, people need to be informed, and we put it in the label. In rare occasions, we turn something down for side effects. When we do that, we decided the indication is maybe not so serious and there are other things out there, so it is not worth it. Or the adverse event is serious, life-threatening, and not easy to monitor. You try to cap or quantify the risk. We err in serious diseases on trying to keep the drug out there."

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