Supportive Neurology: QoL for Patients with Neurological and Neuro-Psychiatric Disorders

Ginger S. Johnson, PhD., Vice President
Defined Health

Defined Health’s Insight Series
London, United Kingdom
Basel, Switzerland
Basking Ridge, New Jersey

Therapeutic Insight 2008
New York, April 2008
REGISTER NOW! APRIL 28 - 30, 2008
THE WESTIN NEW YORK AT TIMES SQUARE

THERAPEUTIC INSIGHT 2008

THE GLOBAL THERAPEUTIC GROWTH STRATEGIES CONFERENCE
“...anything but another conference.”
Our Disclaimer

The information in this presentation has been obtained from what are believed to be reliable sources and has been verified whenever possible. Nevertheless, we cannot guarantee the information contained herein as to accuracy or completeness.

All expressions of opinion are the responsibility of Defined Health and, though current as of the date of this report, are subject to change.
Neurology Supportive Care: The Size & Magnitude of the Need

• What is “supportive neurology”?
• Is there a real unmet need (and how big is it)?
• Is this a viable commercial opportunity?
Neurology Supportive Care: The Size & Magnitude of the Need

• Patients with neurological disorders have a host of symptoms beyond those directly related to their neurological condition. These “associated” symptoms significantly impact quality of life (QoL) for millions of patients. Just in the US, there are:

— ~350,000 multiple sclerosis patients,
— ~1 M Parkinson’s disease patients,
— ~1.5 M traumatic brain injury patients,
— ~2.5 M people with epilepsy,
— ~4 M Alzheimer’s patients, and
— ~4.5 M people living with complications of stroke.
Neurology Supportive Care: The Size & Magnitude of the Need

• The concept of Neurology Supportive Care is the recognition, diagnosis and treatment of conditions beyond those of the central neurological disorder including:
  — Somatic/neurological symptoms – e.g. fatigue, spasticity, tremor, and pain
  — Medical complications – e.g. sexual dysfunction, incontinence, dysphagia
  — Psychiatric disturbances:
    • Affective disorders (e.g., depression, anxiety)
    • Cognitive impairments (e.g., dementia, milder cognitive syndromes)
    • Disturbances of perception/psychosis (e.g., hallucinations, delusions)

At the Annual Meeting of the American Academy of Neurology (AAN) in May 2007, Carlo Colosimo, MD, assistant professor of neurology at La Sapienza University in Rome presented unpublished data from the ongoing, 2-year, longitudinal, observational Parkinson and Non-motor Symptoms (PRIAMO) study showing that mood and sleep disorders are at the top of a list of common non-motor symptoms seen among patients with PD.

- Mood disorders—primarily depression and anxiety—were diagnosed in a full 67% of the study cohort (1072 patients).
- Sleep disorders were diagnosed in 64%.
- Both pain and GI problems were diagnosed in 61%, followed by fatigue in 58%, and urinary tract disorders in 57%.
- Apathy, attention and memory deficits, respiratory disorders, postural instability, and psychotic disorders also were in the mix.
Neurology Supportive Care: The Size & Magnitude of the Need

- Multiple Sclerosis (MS) symptoms that are hard to see include fatigue, pain, cognitive problems like memory loss or trouble solving problems, weakness, blurred vision, numbness, prickly or tingling sensations, heat sensitivity, dizziness, and bladder or bowel problems.

National Multiple Sclerosis Society Brochure.
Neurology Supportive Care: The Size & Magnitude of the Need

• While dementia is the most prominent psychiatric disturbance associated with Alzheimer’s disease (AD), other neuropsychiatric symptoms occur in almost all AD patients over the lifetime of their condition.

• Most common are affective symptoms such as depression, apathy, and anxiety, although 40% to 50% of patients also develop delusions or hallucinations.

William Utermohlen’s self-portraits reveal his descent into dementia over the span of nearly four decades.


© Defined Health, 2008
Supportive Neurology Insight Briefing
Neurology Supportive Care: The Size & Magnitude of the Need

• “Neurologists are frustrated, along with their patients and caregivers, and would love to have something to effectively treat depression, cognitive impairments, aggression and fatigue.”

• “The most common cause of disability for the multiple sclerosis (MS) patient is cognition, not motor symptoms.”

• “We can have the best immunomodulator in the world (for the treatment of MS), but patient quality of life will still suffer.”

• “Psychosis is the major reason why patients with Parkinson’s disease (PD) and Alzheimer’s disease are admitted to nursing homes.”

• “Even at the early-stages, PD patients have significant issues with memory and problem solving.”
How Does This Affect the Patient?

- Tired
- Depressed
- Can’t Think
- Just Don’t Care
- Seeing & Hearing Things
- Poor Quality of Life
- Anxious
- Can’t Sleep
- Forgetful

© Defined Health, 2008
Supportive Neurology Insight Briefing
Why Should the Biopharmaceutical Industry Pay Attention? CNS is Risky.

- Increasing generic competition and inherent risk in novel mechanisms of action, particularly in CNS, suggest that companies will need to be creative in order to grow or even preserve CNS franchises.
Why Should the Biopharmaceutical Industry Pay Attention? **CNS is Risky.**

CNS Has Historically Been One of the Therapeutic Areas Showing A Low Success Rate in the Clinic

![Graph showing success rates from first-in-man to registration](image)

**Figure 1 | Success rates from first-in-man to registration.** The overall clinical success rate is 11%. However, if the analysis is carried out by therapeutic areas, big differences emerge. The data are from the ten biggest drug companies during 1991–2000. (The companies are AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-LaRoche, GlaxoWellcome, Johnson & Johnson, Novartis, Pfizer, Pharmacia, Schering-Plough and SmithKline Beecham; data were obtained by Datamonitor in the Pharmaceutical Benchmarking Study). CNS, central nervous system.

Why Should the Biopharmaceutical Industry Pay Attention? CNS is Risky.

With a Particularly Poor Showing in Neurodegenerative Diseases


% Failed before Phase III % Failed in Phase III Total

Cancer

Inflammation

Alzheimer's disease

Huntington's disease

Multiple sclerosis

Parkinson's disease

Pipeline failures

© Defined Health, 2008
Supportive Neurology Insight Briefing
Why Should the Biopharmaceutical Industry Pay Attention? *Disease Delay.*

**QoL is a Growing Market ...**

- With the availability and new introduction of disease modifying therapies for diseases like multiple sclerosis, Alzheimer’s disease and Parkinson’s disease, quality of life issues will become even more important in the future.

- Early stage imaging, spectroscopic, histopathologic, transmitter and molecular genetic observations indicate that patients with neurological disease also have distinctive neurobiological and related neurotransmitter alterations that could represent therapeutic targets for the treatment of associated psychiatric symptoms.
**Why Should the Biopharmaceutical Industry Pay Attention?** *Distinct Therapeutic Targets.*

- Psychiatric symptoms associated with neurological disease reflect the affected population of vulnerable cells characteristic of each disorder.

<table>
<thead>
<tr>
<th>Neurodegenerative disorder</th>
<th>Associated neuropsychiatric symptoms (common)</th>
<th>Associated neuropsychiatric symptoms (less common)</th>
<th>Vulnerable cell populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Apathy, agitation, depression, anxiety and wandering</td>
<td>Delusions, hallucinations and abnormal sexual behaviour</td>
<td>Hippocampus, posterior parietal association cortex and nucleus basalis</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations, delusions, depression and rapid eye movement sleep behaviour disorder</td>
<td>Hallucinations in other modalities</td>
<td>Substantia nigra and brain stem pigmented nuclei, parieto-occipital cortex and nucleus basalis</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Depression, anxiety, delusions, hallucinations and rapid eye movement sleep behaviour disorder</td>
<td>Obsessive–compulsive symptoms and abnormal sexual behaviour</td>
<td>Substantia nigra and brain stem pigmented nuclei, and nucleus basalis</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Apathy, disinhibition and dietary alterations</td>
<td>Euphoria, compulsions and emergence of unusual artistic talent</td>
<td>Dorsolateral prefrontal association cortex</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Apathy</td>
<td>Disinhibition</td>
<td>Globus pallidus and thalamus</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Depression</td>
<td>Apathy</td>
<td>Striatal nuclei and frontoparietal cortex</td>
</tr>
</tbody>
</table>

*Cummings, J.L. and Zhong, Kate Jan 2006 Vol 5 Nature Reviews.*

© Defined Health, 2008
Supportive Neurology Insight Briefing
Supportive oncology represents a diverse set of conditions related to the administration of treatment (e.g. chemotherapy, radiation) as well as to the disease itself. In the US Supportive Oncology is a $10+B market.

Sixth International Symposium on Supportive Care in Oncology: Cancer Management in the Era of Targeted Agents

New York Marriott Marquis Times Square
New York, NY
February 22-23, 2008
Why Should the Biopharmaceutical Industry Pay Attention? *Proof of Commercial Concept*

December 10, 2007

- Japan's Eisai to Acquire MGI Pharma for $3.9B.
- Through the acquisition, part of its "Dramatic Leap" business plan, Eisai will gain five oncology products — including MGI's lead drug, *Aloxi* — that are expected to generate annual sales nearing $375 million.
- Eisai's leading product, the Alzheimer's disease treatment *Aricept*, will lose U.S. patent protection in 2010. Almost two-thirds of *Aricept*'s $2.3 billion in fiscal 2007 sales were in the U.S.

The Role of Biotech, Specialty Pharma & Big Pharma in Supportive Neurology??

Life Cycle Management

Product Differentiation

Repurposing

Market Expansion Strategy
First, Let’s Define the Opportunities?

• Where are the unmet needs?
  
  3, *for example*

  - Cognitive Impairment
  - Psychosis / Behavior
  - Fatigue
PD & Cognitive Impairment

- Most patients with PD experience some cognitive impairment, with 25% to 40% developing dementia over the course of their illness.

- Pathologic studies have shown mixed results, with some studies suggesting that the primary pathology relates to dopaminergic loss and associated cortical connection loss, whereas other studies report that at least a subgroup of patients with PD also have Alzheimer’s pathology, while others have disseminated Lewy bodies in the cortex (“dementia with Lewy bodies”).

- The pathologic substrate of dementia in PD patients remains uncertain and likely represents several etiologies.

PD & Cognitive Impairment

• Acetylcholinesterase inhibitors are the standard of care for PD-associated cognitive impairment but do not typically produce marked improvements.

PD & Cognitive Impairment

• Despite its minimal efficacy and side effect issues, an acetylcholinesterase patch, *Exelon* (Novartis) was approved in 2007.

Approved by the US FDA for treatment of mild-to-moderate Parkinson’s disease dementia

• Approval of the Parkinson's disease indication was based on 24-week data from the large-scale, international EXelon in PaRkinson's disEaSe dementia Study (EXPRESS; n = 541), which showed that rivastigmine oral therapy yielded significant improvements compared with placebo in terms of cognitive function and overall functioning, as evaluated using the ADAS-cog (+2.1 vs.-0.7; \( P < .001 \)) and ADCS-CGIC (3.8 vs. 4.3; \( P = .007 \)).

• These data were judged to be applicable to the patch formulation as well.

• In Parkinson's disease dementia, parkinsonian symptoms, particularly tremor, occurred or worsened in some people taking EXELON® (rivastigmine tartrate) capsules.

MS & Cognitive Impairment

• Approximately 50% of people with MS will develop some degree of cognitive dysfunction, affecting the ability to think, reason, concentrate or remember.

• There is no relationship between level of physical disability and degree of cognitive impairment.

• The cognitive function most likely to be affected appears to be memory. Other cognitive functions frequently affected in MS include speed of information processing, executive functions (planning and prioritizing), visuospatial functions (impairment in visual perception and constructional abilities), abstract reasoning and problem-solving, and attention and concentration.

• Cognitive symptoms and fatigue are two primary reasons for early departure from the workforce.

National Multiple Sclerosis Society Brochure.
MS & Cognitive Impairment

• Some uncontrolled studies, and a few small controlled studies, suggest that the cholinesterase inhibitors, such as donepezil (*Aricept*), provide some improvement.

• Brain imaging data indicate that cognitive impairment is correlated both with lesion load and cerebral atrophy.

• Although the disease modifying therapies (e.g., interferons) do not appear to appreciably improve cognitive functioning, they do seem to slow the rate at which it worsens.
PD & Psychosis

- The development of psychotic phenomena in PD has been linked to dopaminergic therapy but it may predate the use of these agents.
- The association between the dose of therapy and occurrence of symptoms is weak, and many patients have such symptoms either before they begin to take L-dopa, or after it has been stopped.
- Disease factors other than dopaminergic therapy are likely involved in the development.

PD & Psychosis

• Standard of care is off-label use of atypical antipsychotic agents.

Treatment: Antipsychotics

• Balancing benefits (antipsychotic effects) and risks (worsening parkinsonism)
• Atypical antipsychotics
  – Concerns about worsening parkinsonism
  – Quetiapine medication of choice (range 25-200 mg/day)
    • However, only randomized clinical trial with quetiapine was negative
• Clozapine
  – Efficacious in three randomized studies
  – Low doses (mean of 25-36 mg/day)

Other Treatments

• Cholinesterase inhibitors
  – In large-scale DLB study, rivastigmine demonstrated improvement on psychosis subscale
  – In recent PD dementia study, rivastigmine group less likely to report psychosis as an adverse event

AD & Psychosis/Behavior

- Behavioral symptoms such as agitation, wandering, delusions, hallucinations, severe psychomotor agitation, and combativeness become common as Alzheimer’s disease progresses.

- These behavioral symptoms are especially challenging to the primary caregiver.

American Family Physician, Volume 65, Number 12 / June 15, 2002
Alzheimer’s Patients Unresponsive to Antipsychotics

Thursday, November 15, 2007 - NEW YORK (Reuters Health)

• Second-generation antipsychotic drugs are no better than placebo — from a cost-benefit viewpoint — for treating the psychosis and aggression that can develop in Alzheimer disease patients, according to a report in the Archives of General Psychiatry.

• “These drugs do not generate enough benefit to justify their cost in this off-label situation,” Dr. Robert A. Rosenheck from the VA Connecticut Health Care System, West Haven, Connecticut told Reuters Health.

• He notes, however, it’s not clear how these findings will influence treatment policy for these patients. About half of second-generation antipsychotic use is off-label.”

Antipsychotics, Nursing Homes & Increased Risks  
November 19th, 2007

• Psychosis and behavioral problems associated with dementia are the No. 1 reason people end up in nursing homes.

• Despite an undeniable and growing need for safer meds to control dementia, drug makers have little incentive to develop such drugs when their existing products are still bringing in billions.

• Even though, in 2005, the FDA ordered manufacturers of atypical antipsychotic medications to add a warning to already existing black-box warnings noting that the drugs are associated with an increased risk of death related to psychosis and behavioral problems in elderly patients with dementia.

• “There’s very high risk for trying to study new drugs in older patients because it’s always more complicated,” says Bruce Pollock, with the Rotman Research Institute at Baycrest in Toronto. “But what good does it do if drug trials are only conducted in healthy, middle-aged people with only one condition? It’s a disservice to the biggest consumers of pharmacy that we don’t have adequate data.”
MS & Fatigue

• Fatigue is one of the most common symptoms of MS, occurring in about 80% of people.

• Characteristics of “MS Fatigue” that make it different include:
  — Occurs on a daily basis
  — Occurs even after a restful night’s sleep
  — Worsens as the day progresses
  — Comes on more easily and suddenly
  — Generally more severe than other fatigue
  — More likely to interfere with daily responsibilities
  — Aggravated by heat and humidity
  — Does not appear to be directly correlated with either depression or degree of physical impairment

• Fatigue with MS is a most important cause of early departure from the workforce.

“It can be frustrating when you tell someone you’re tired and they say they know the feeling, they had a big night last night, too.” (MS Patient)
MS & Fatigue

• Amantadine hydrochloride and modafinil (Provigil, Cephalon) are the most commonly prescribed medications for the treatment of fatigue in MS patients.

• While neither is approved specifically by the FDA for the treatment of MS-related fatigue, each has demonstrated some benefit in clinical trials.

• The most recent trial of modafinil, however, reported no difference between modafinil and placebo in relieving fatigue.

National Multiple Sclerosis Society Brochure.
MS & Fatigue

Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study

Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L, et al.; Neurology 2005; 64 (7); 1139-1143

Comment by Dr Morten Blinkenberg, 20 May 2005

“The study showed no improvement of fatigue in MS patients treated with modafinil compared with placebo, which is problematic since the drug is widely used and the cost of treatment is considerable.”
Modafinil for daytime somnolence in Parkinson's disease: double-blind, placebo-controlled parallel trial.

- **BACKGROUND:** Excessive daytime somnolence (EDS) commonly complicates Parkinson's disease (PD). The etiology of EDS is probably multifactorial but is probably exacerbated by dopaminergic medications...

- **METHOD:** A double blind, placebo controlled parallel design trial was conducted to assess the efficacy of modafinil (200-400 mg/day) for the treatment of EDS in PD. The primary efficacy measure was the Epworth Sleepiness (ES) scale score.

- **RESULTS:** Of a total of 40 subjects (29 men, mean (SD) age 64.8 (11.3) years), randomized to modafinil or placebo, 37 completed the study. Modafinil failed to significantly improve ES scores compared with placebo (2.7 v 1.5 points improvement, respectively, p = 0.28).

- **CONCLUSION:** Modafinil failed to significantly improve EDS in PD compared with placebo. The drug did not alter motor symptoms in PD and was well tolerated.

Cephalon Gets a Warning

WARNING LETTER (posted 3/1/07)

Dear Dr. Baldino:

The Division of Drug Marketing; Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a promotional piece distributed on behalf of your company to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee (Committee) on August 17, 2006. This piece recommends or suggests uses for Provigil (modafinil) Tablets [C-IV] (Provigil) that have not been approved by FDA, and thus creates new "intended uses" for Provigil for which the product lacks adequate directions, broadens the indication for Provigil, and fails to communicate any risks associated with its use. …

… This promotional piece is false or misleading because it states or suggests that Provigil is safe and effective for use in the treatment of various disorders associated with fatigue, sleepiness, or inattentiveness, when in fact, Provigil is not indicated for fatigue at all and is indicated only for specific groups of patients with excessive sleepiness, as stated above.

Multiple Sclerosis Related Fatigue
Parkinson's Disease Related Fatigue
Chronic Fatigue Syndrome Fibromyalgia, & chronic pain conditions
Attention Deficit Disorder
Double blind placebo controlled studies have shown significant improvements in multiple cognitive measures in this population without the risks attendant to the traditional stimulants used to treat this condition [referring to attention-deficit hyperactivity disorder].
Depression
In a retrospective case series, modafinil was found to augment actions of antidepressants, especially in patients with residual tiredness or fatigue. . . .
C YA Strategy

Wakefulness Franchise

Strategy:
Switch to second generation product with expanded indications

NUVIGIL™: Extending the Wakefulness Franchise

Fatigue
Cancer
Multiple Sclerosis

Excessive Sleepiness
Major Depressive Disorder
Jet Lag Disorder
Restless Leg Syndrome

Cognitive Deficits
Schizophrenia
Cancer

Bipolar Depression

Potential New Indications
What About Depression?

• Depression is one of the single most important psychiatric symptoms impacting QoL for patients with neurological disorders.
• Are the agents we have at hand good enough?
• Maybe?

**Example: Depression & Parkinson’s**

**Treatment**
- Only 3 randomized antidepressant studies
  - Nortriptyline positive
  - Two small SSRI studies negative
- Even open-label studies with limited response rates
  - Mean decreases of ≈ 30-40% on depression rating scales
- Recent meta-analysis found no difference between active and placebo treatments
  - Antidepressant effects may be less than in non-PD patients

**Antidepressant Tolerability and Safety**
- SSRIs
  - Case reports of motor worsening
  - Case literature in psychiatry of SSRI’s causing parkinsonism (primarily tremor)
  - Review and meta-analysis found that ≈ 85% of PD subjects completed SSRI treatment
- Combination with selective MAO-B inhibitors is controversial
  - Selegiline or rasagiline can cause serotonin syndrome
  - Anecdotal experience is that this occurs very rarely


© Defined Health, 2008
Supportive Neurology Insight Briefing
What About Depression?

- Is there a role for a “supportive neurology” antidepressant that targets psychiatric (or even somatic) symptoms beyond depression?
  - Via multiple mechanisms?
  - As a combination agent?

Of Course, It’s Not That Simple

- Psychiatric symptoms associated with neurological disorders are interconnected making definition, diagnosis and clinical development complicated.

(i.e., If we address the fatigue, do we improve cognition?)
Supportive Neurology: Pathways for Drug Approval

- The FDA has recently defined two pathways to drug development for behavioral symptoms associated with neurological disorders:

1) Definition of a **specific behavioral syndrome** in a neurological disorder and validation of its response to therapy in two well-conducted, randomized, double-blind, placebo-controlled trials

2) Definition of a **behavioral syndrome present in multiple neurological conditions** and validation of its response to treatment in pivotal double-blind, placebo-controlled trials in several disorders.

Supportive Neurology: Pathways for Drug Approval

- Each FDA pathway requires that the syndrome be defined first and measured with rating scales at baseline and trial completion.

- Approval of an agent for a behavioral indication requires that the agent presented has both a specific behavioral benefit and a global benefit.

Supportive Neurology: Definition & Diagnosis

- Progress has been slow in developing operational definitions of behavioral syndromes in patients with neurological disorders.

- There are consensus definitions for psychosis and depression in AD, but there are no consensus definitions for most other important symptoms such as agitation and anxiety.

Supportive Neurology: Clinical Trial Endpoints

- The NPI is the behavioral measure most widely used in clinical trials to assess behavioral outcomes of anti-dementia agents and has been applied in trials of psychotropic medications.

- The NPI assesses the frequency and severity of 12 neuropsychiatric symptoms: aberrant motor behavior, agitation, anxiety, apathy, delusions, depression, disinhibition, eating disturbances, euphoria, hallucinations, irritability, and sleep disturbances.

A First Mover: Cognitive Impairment Associated with Schizophrenia (CIAS)

Characteristics of CIAS
- Highly prevalent
- 1-2 SDs below normal
- Distinct from negative symptoms
- Precedes first clinical episode
- Persistent
- Long-term disability
- Non-progressive

Cognitive outcomes
- MATRICS Consensus Cognitive Battery (MCCB)
- Optimized for CIAS
- Ideal cognitive tests
- Targets critical domains
- High reliability, validity
- Easy to administer
- Sets the standard

Functional outcomes
- Consensus is early stage


© Defined Health, 2008
Supportive Neurology Insight Briefing
A First Mover: Cognitive Impairment Associated with Schizophrenia (CIAS)

- Although CAIS is lower in terms of number of patients with cognitive impairment, it is the area with the most activity in the pipeline.

*Decision Resources webinar, Feb 2008, Obstacles and Opportunities in Cognitive Dysfunction: A Look at Cognitive Impairment Associated with Schizophrenia (CIAS).*
## A First Mover: Cognitive Impairment Associated with Schizophrenia (CIAS)

**Pipeline Activity: Select Ongoing Trials in CIAS**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Mechanism</th>
<th>Length</th>
<th># patients</th>
<th># doses</th>
<th>Formulation</th>
<th>Primary outcome</th>
<th>Functional outcome</th>
<th>TURNs</th>
<th>Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD-3480</td>
<td>α4β2 nAChR agonist</td>
<td>12</td>
<td>400</td>
<td>2</td>
<td>Oral</td>
<td>IntegNeuro battery</td>
<td>√</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>MEM-3454</td>
<td>α7 nAChR partial agonist</td>
<td>8</td>
<td>160</td>
<td>3</td>
<td>Oral</td>
<td>MCCB</td>
<td>√</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>AL-108</td>
<td>Neuroprotective peptide</td>
<td>12</td>
<td>60</td>
<td>2</td>
<td>Intranasal</td>
<td>MCCB</td>
<td>√</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>MK-0777</td>
<td>GABA agonist</td>
<td>--</td>
<td>90</td>
<td>2</td>
<td>Oral</td>
<td>MCCB</td>
<td>√</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>AVE-1625</td>
<td>Selective CB1 antagonist</td>
<td>24</td>
<td>700</td>
<td>3</td>
<td>Oral</td>
<td>MCCB</td>
<td>√</td>
<td>2007-2008</td>
<td></td>
</tr>
<tr>
<td>Armodafinil</td>
<td>α2a adrenergic receptor agonist</td>
<td>4</td>
<td>44</td>
<td>1</td>
<td>Oral</td>
<td>MCCB</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORG-24448</td>
<td>AMPA kinase</td>
<td>8</td>
<td>135</td>
<td>2</td>
<td>Oral</td>
<td>MCCB</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL-108</td>
<td>Selective CB1 antagonist</td>
<td>MK-0777</td>
<td>Selective CB1 antagonist</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>α2a adrenergic receptor agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM-3454</td>
<td>Neuroprotective peptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORG-24448</td>
<td>AMPA kinase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes
- **Primary outcome**
  - IntegNeuro battery
  - MCCB
- **Functional outcome**
  - √
- **TURNs**
  - √
- **Expected completion**
  - 2008
  - 2009
  - 2008
  - 2007-2008
  - Terminated

---

*Decision Resources webinar, Feb 2008, Obstacles and Opportunities in Cognitive Dysfunction: A Look at Cognitive Impairment Associated with Schizophrenia (CIAS).*

© Defined Health, 2008
Supportive Neurology Insight Briefing
A First Mover: Cognitive Impairment Associated with Schizophrenia (CIAS)

- CIAS affects multiple cognitive domains, suggesting agents that show efficacy in this disorder may also have efficacy in other cognitive disorders some of which represent HUGE patient populations.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Most-Frequently Cited Domains</th>
<th>Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>M</td>
</tr>
<tr>
<td>MCI</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CIAS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TBI</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

“If I had to design a trial—I would get the most homogeneous population that I could identify to start the study. So, it would be amnestic multidomain mild cognitive impairment—that would be executive functioning and judgment and visual-spatial.”

— Neurologist, United States

“The majority of, if not all, cognitive domains are affected. There is a gradient of impairment, though. Processing speed is most impaired, probably followed by episodic and working memory. Attentional abnormalities are clearly present—and executive functioning. Clearly, it’s a multidomain profile of impairment.”

— Psychiatrist, United States

“It’s a problem of recall speed, visual-spatial recognition, and attention span. These are the basic domains of cognitive dysfunction.”

— Neurologist, Europe

“The main cognitive problems in TBI are memory problems and problems related to executive functions, both cognitive and behavioral aspects of executive functions.”

— Neurologist, Europe

A = Attention; CIAS = Cognitive impairment associated with schizophrenia; EF = Executive function; L = Language; M = Memory; MCI = Mild cognitive impairment; MS = Multiple sclerosis; PS = Processing speed; TBI = Traumatic brain injury; VS = Visuospatial.
AZD3480 (TC-1734) is an α4β2 NNR partial agonist being developed as a treatment for Alzheimer’s disease, cognitive deficits (Phase II) in schizophrenia and potentially other conditions marked by cognitive impairment such as attention deficit hyperactivity disorder (ADHD), age associated memory impairment (AAMI), and mild cognitive impairment (MCI).

In December 2005, Targacept entered into a collaborative research and license agreement with AstraZeneca for the development and worldwide commercialization of AZD3480.

<table>
<thead>
<tr>
<th>NNR Subtype</th>
<th>Localization</th>
<th>Physiological Functionality</th>
<th>Potential Therapeutic Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>α4β2</td>
<td>Hippocampus, cortex</td>
<td>Working memory</td>
<td>• Alzheimer’s disease</td>
</tr>
<tr>
<td></td>
<td>Amygdala, brainstem, thalamo-cortical</td>
<td>Learning</td>
<td>• Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>pathway</td>
<td></td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>Hippocampus, Cortex</td>
<td>Neurodegeneration</td>
<td>• Huntington’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Other neurological disorders characterized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>by cognitive impairment</td>
</tr>
</tbody>
</table>
Sidebar
AAMI: The Next Big Market?

• AAMI is a recognized syndrome relating to memory changes associated with normal aging.

• In the United States, it is estimated that approximately 40% of people aged 65 and above, or 16 million, have AAMI.

• It is characterized by gradual memory impairment (subjective memory decline and objective memory loss) with the absence of dementia.

http://www.fda.gov/OHRMS/DOCKETS/AC/01/slides/3724s1_3_ferris.PPT#2.
Sidebar
AAMI: The Next Big Market?

• Individuals with AAMI have been shown to have a three-fold greater risk for development of dementia than individuals who do not meet AAMI criteria.

• MCI is often a very early stage of dementia (with most patients eventually progressing to dementia, 10 - 15% per year, 80% over 10 years).

http://www.fda.gov/OHRMS/DOCKETS/AC/01/slides/3724s1_3_ferris.PPT#2.
Supportive Neurology

• To expand into larger markets, safety will be key. Does the recent safety warning for Chantix (Pfizer), also an α4β2 NNR partial agonist (like AZD-3480), spell trouble for the mechanism/class?

New Safety Warnings for Chantix

• FDA issued a Public Health Advisory on Feb. 1, 2008, to alert health care providers, patients, and caregivers to new safety warnings concerning Chantix (varenicline). Chantix is a prescription medication used to help people stop smoking.

• Chantix was approved by FDA in May 2006. In November 2007, FDA issued an Early Communication to tell the public and health care providers that the agency was evaluating adverse event reports on Chantix related to changes in behavior, agitation, depressed mood, suicidal thoughts, and attempted and completed suicide.

• As FDA continues its review of the adverse event reports, it appears increasingly likely that there may be an association between Chantix and serious mood and behavior symptoms.

• MEM 3454 is a partial agonist of the nicotinic alpha-7 receptor being developed as a potential therapy for Alzheimer’s disease and cognitive impairment associated with schizophrenia (CIAS).

• In November 2007, Memory announced positive Phase 2a data for MEM 3454 in AD. MEM 3454 demonstrated a statistically significant effect on cognition at the 5 mg and 15 mg doses on both the primary and key secondary endpoints for that trial.

• Roche has the option to obtain a license to MEM 3454 following completion of the first Phase 2a clinical trial for this candidate.

Memory Pharmaceuticals website.
Summary of new data

• Data were presented from a phase 2a study evaluating the efficacy of MEM 3454 in Alzheimer’s disease patients.

• The primary efficacy endpoint, an improvement in episodic memory, was met.

• Once daily dosing no longer appears to be sufficient as efficacy was lost after 8hrs.

• Potential hurdles include a loss of effect at higher doses and the frequency of constipation.

• Further studies are expected at lower doses.

*LeadDiscovery Nicotinics Monthly Jan 2008.*
Pimavanserin for Treatment of Parkinson's Disease Psychosis

Pimavanserin (ACP-103) is a potent and selective 5-HT2A inverse agonist in development for:

- Levodopa-induced psychosis in Parkinson’s disease (Phase II)
- Levodopa-induced dyskinesias in Parkinson’s disease (Phase II)
- Adjunctive therapy for schizophrenia (Phase II)

Acadia Pharmaceuticals website.
Supportive Neurology | Market Expansion Strategy

Partner or go it alone?

### Pipeline Review

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Development Status</th>
<th>Partnership Status</th>
<th>Target</th>
<th>Next Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP-103 Pimavanserin</td>
<td>Parkinson's Disease; Treatment-Induced Dysfunctions</td>
<td>Phase 3</td>
<td>Unpartnered</td>
<td>5HT-2a Inverse Agonist</td>
<td>Results (2009)/Initiate 2nd Phase 3 trial (1Q08)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia: Adjunctive Therapy</td>
<td>Phase 2b</td>
<td>Unpartnered</td>
<td></td>
<td>Seek Partner (ongoing)</td>
</tr>
<tr>
<td>ACP-104 Schizophrenia</td>
<td></td>
<td>Phase 2b</td>
<td>Unpartnered (Funding from Stanley MRI)</td>
<td>5HT-2a Inverse Agonist D2/D3 Partial Agonist M1 muscarinic agonist</td>
<td>Phase 2b Results (2Q08)</td>
</tr>
<tr>
<td>TBA Neuropathic Pain</td>
<td></td>
<td>Phase 2</td>
<td>Allergan</td>
<td>Selective Alpha Adrenergic Agonists</td>
<td></td>
</tr>
<tr>
<td>AC-262271 Glaucoma</td>
<td></td>
<td>Preclinical</td>
<td>Allergan</td>
<td>Non-steroidal Androgen Receptor Agonist</td>
<td></td>
</tr>
<tr>
<td>ACP-105 Endocrinology</td>
<td></td>
<td>Preclinical</td>
<td>Unpartnered</td>
<td>5HT-2a Inverse Agonist</td>
<td></td>
</tr>
<tr>
<td>ACP-106 CNS</td>
<td></td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic Program</td>
<td>Various</td>
<td>Preclinical</td>
<td>Sepracor</td>
<td>Muscarinic Receptors</td>
<td></td>
</tr>
<tr>
<td>Cannabinoid Program</td>
<td>Obesity and Substance Abuse</td>
<td>Preclinical</td>
<td>Unpartnered</td>
<td>CB1</td>
<td></td>
</tr>
</tbody>
</table>

Source: Company reports

Acadia Pharmaceuticals website.
Core to ACADIA's strategy is to pursue strategic collaborations. In CNS areas that involve more extensive development or require a large sales force, we intend to complete late-stage clinical development and commercialization in collaboration with partners. In CNS areas where our products can be commercialized by a specialty sales force, we plan to retain selected commercialization rights.

ACADIA reported in March 2007 that the company intends to conduct a Phase II trial of pimavanserin in patients with sleep maintenance insomnia. This study did not appear to have been initiated as of January 2008.

Acadia Pharmaceuticals website: Adis R&D Insight.
Promising Data on cognitive effects of safinamide in early Parkinson’s disease

- **June 8, 2007** – Newron Pharmaceuticals and its partner Merck Serono announced data which suggest that safinamide, a new agent in Phase III development for the treatment of Parkinson’s disease, has an effect on cognitive performance in study patients with early PD.

- The data, from a 6-month (24 weeks), randomized, double blind, placebo-controlled, international Phase III trial, demonstrated that the addition of safinamide to a stable dose of a single dopamine agonist in study patients with early stage Parkinson’s disease resulted in an **improvement in cognitive domains often impaired in these patients**, in particular executive function (the ability for planning, organizing, strategizing and paying attention to and remembering details) and working memory.
Supportive Neurology

Product Differentiation

Market Expansion Strategy

- Safinamide is an oral alpha-aminoamide derivative with multiple mechanisms: selective and reversible inhibitor of MAO-B, sodium and calcium channel antagonist, dopamine uptake inhibitor and a glutamate release antagonist.

- Merck Serono has exclusive worldwide rights to develop, manufacture and commercialize safinamide in Parkinson’s disease, Alzheimer’s disease, other cognitive disorders and restless leg syndrome.

Company website.
• BCG20-1259 is a unique, multi-functional compound that has demonstrated both AChE and SERT (serotonin transporter) inhibitor activities in vivo and neuroprotective effects in vitro.

• As such, BGC20-1259 should alleviate cognitive impairment, depression and apathy in Alzheimer's patients, while also having the potential to slow down the progression of the disease process.

• As Dr. Russell Hagan Senior Vice-President, Head of R&D of BTG explained, "All of the focus right now is on slowing disease. But we have to recognize that until a preventative medication is available, symptomatic treatments will be critical in the overall care of Alzheimer's patients. Our approach with BCG20-1259 has been to develop a multifunctional drug, which does both. That is, improve the treatment of core symptoms – cognition, mood and sleep disturbances – whilst also protecting against neurodegeneration."
Acorda is currently developing fampridine, an oral potassium channel blocker (also used as a bird poison) for treatment of spasticity in MS. The agent is in Phase III development to improve walking speed in patients with MS spasticity. There is no established clinical development path for this indication and Acorda has developed a unique scale for functional improvement.

**Acorda Therapeutics Begins Second Phase 3 Clinical Trial of Fampridine-SR in Multiple Sclerosis**

- HAWTHORNE, N.Y.--(BUSINESS WIRE)--June 6, 2007--Acorda Therapeutics (Nasdaq: ACOR) announced today that it has begun a second Phase 3 clinical study of Fampridine-SR in multiple sclerosis (MS).
- The MS-F204 study, which is conducted under a Special Protocol Assessment (SPA) issued by the FDA, will evaluate the safety and efficacy of Fampridine-SR in improving walking ability in people with MS. Pending clinical results from MS-F204, FDA has agreed that this study together with the previous Phase 3 study would be adequate to support a New Drug Application (NDA) for Fampridine-SR.
- The primary outcome measure for the study will be a walking response criterion, defined as a consistent improvement in walking speed as measured by the Timed 25-Foot Walk. The secondary outcome measure for this study is the Lower Extremity Manual Muscle Test (LEMMT).
Acorda Therapeutics Announces Positive Results of Phase 3 Study of Fampridine-SR on Walking in People with Multiple Sclerosis

Supportive Neurology Insight Briefing

Market Cap $583 M (3/1/08)
Supportive Neurology: What’s Next?

- Molecular genetic investigations have begun to provide insight into the neurobiology of behavioral changes in patients with neurodegenerative disease; leading to new targets?? Biomarkers??

Gene Polymorphisms and Neuropsychiatric Symptoms

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Associated neuropsychiatric symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>T102C polymorphism of the gene encoding the 5-HT_{2A} receptor</td>
<td>Visual and auditory hallucinations, psychosis and agitation</td>
</tr>
<tr>
<td>C23S polymorphism of the gene encoding the 5-HT_{2C} receptor</td>
<td>Visual hallucinations and hyperphagia</td>
</tr>
<tr>
<td>Insertion of 44 base pairs in the L-form of the 5-HTT promoter region</td>
<td>Psychosis and aggression</td>
</tr>
<tr>
<td>5-HT, 5-hydroxytryptamine; 5-HTT, 5-hydroxytryptamine transporter.</td>
<td></td>
</tr>
</tbody>
</table>

The Role of Biotech, Specialty Pharma & Big Pharma in Supportive Neurology?

- **Life Cycle Management**
- **Product Differentiation**
- **Repurposing**
- **Market Expansion Strategy**

**Big Pharma**

- Still chasing blockbusters, one indication at a time.

**Biotech**
- Specialty Pharma

Carving out a piece for themselves.
REGISTER NOW! APRIL 28 - 30, 2008
THE WESTIN NEW YORK AT TIMES SQUARE

THERAPEUTIC INSIGHT 2008

THE GLOBAL THERAPEUTIC GROWTH STRATEGIES CONFERENCE
“...anything but another conference.”