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Date:	10/28/2003 01:24:55 PM
From:	CN=Mark Enerson/OU=AM/O=LLY
Subject:	Re: Annual Psychopharmacology Update - Cincinnati, Oct 18th

Hi Karen, thanks for providing the summary. I am copying the global marketing team so they are aware of the some of the comments made by the speakers. Thanks, Mark

> Henry Nasrallah's presentation - extremely disappointing. It sounds very much like the presentation he did for AstraZeneca at APA, but with a focus on Abilify.
> The presenters focused on comparable efficacy between antipsychotics. Not comparable tolerability.
> The presenters focused on Abilify for agitation. Comments like "Aripiprazole is good for agitation and depression but not for psychosis."

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10/25/2003 01:03 AM

To:	US_Neuro_ML@Lilly
cc:	Mark Enerson/AM/LLY@Lilly, Kevin W Piezer/AM/LLY, Ellen Schoenberger, Patrick Toalson
Subject:	Re: Annual Psychopharmacology Update - Cincinnati, Oct 18th

Report form Annual Psychopharmacology Update: Combination Therapies.
Saturday, Oct. 18th, 2003, Cincinnati OH

Sponsored by University of Cincinnati College of Medicine and Dept of Psychiatry, Ohio Psychiatric Association
Education Grants provided by Bristol-Myers Squibb and Otsuka America Pharmaceutical, Inc.

Faculty:

Henry Nasrallah (U of Cincinnati): Schizophrenia
Stephen Strakowski (U of Cincinnati): Bipolar Disorders
Sheldon Preskorn (U of Kansas): Rational Pharmacy
Jacobo Mintzer (Medical University of S Carolina): Dementia/Psychosis
Michelle Riba (U of Michigan): Combining Psychotherapy with Psychopharmacology
Susan McElroy (U of Cincinnati): Major Depression
Peter Buckley (Medical College of GA): Broadening Use of Atypicals

Nasrallah: **Very biased against olanzapine. Pro aripiprazole.**

All atypicals have same efficacy. "I really believe that." Showed several slides (Tandon, Daniel, Lieberman, Conley, Data on file Pfizer, BMS, Cornblatt- No Lilly data) supporting premise that at equivalent doses, the efficacy of atypical antipsychotics is almost identical to placebo-controlled clinical trials and head-to-head comparisons.

Focus on Abilify's unique binding properties as partial agonist to maintain dopamine activity between 30-40% (not too low, not too high).

Data from Abilify's TR study (pts. who hadn't responded to olanzapine or risperidone randomized to aripiprazole or perphenazine with 27% responders). Focus on improvement of QOL for aripiprazole, improvements in verbal memory that predict ability to return to work, New studies will be presented that show combo of psychotherapy and pharmacotherapy (ABILIFY) enhance QOL through cognitive improvements, implications for neurogenesis. Abilify not only has comparable efficacy but is a cleaner drug. No EPS. No prolactin elevations (as compared to risperidone and olanzapine).

Discussed Intercept Study. Comparison of olanzapine and clozapine that showed that clozapine is better than olanzapine.

Discussed CONSTA. "useful addition for enforced compliance". Need to supplement with oral for at least 3 weeks. Consta has lower prolactin, EPS. Doses of 25 and 50 better than 75. Pts. on CONSTA 4 year follow-up are stable, working, attending school. Good drug.

Not all atypicals have same safety profile: **Movement disorders** - EPS seen with risperidone, olanzapine, ziprasidone (higher doses). aripiprazole no PD, no akathesia, no TD (improvement in akathesia compared to haldol 1st 3-4 weeks; akathesia transient and probably related to Dx schizophrenia. Cited data showing 1st episode drug naive pts. have EPS). **Prolactin** - risperidone, olanzapine at higher doses, ziprasidone. Quetiapine and clozapine okay. aripiprazole decreases prolactin levels. **Metabolic Syndrome** - #1 Killer. Five factors (3 or more means slow and sure death). 1. abd obesity(> 40 males, > 35 females), 2. triglycerides > 150, 3. HDL- C (< 40 males, < 50 females), 4. B/P > or equal to 130/85, 5. fasting glucose (soon to be > or equal to 100). Avoid medication that will worsen. **OLANZAPINE.** Weight a concern, not only in terms of metabolic syndrome, but other comorbid medical illnesses including increased risk of CAs, higher association with hormone related CAs (women - breast, ovarian, cervical, endometrial; men - prostate, testicular). Ziprasidone wt neutral. **"Zyprexa is worst antipsychotic."** To Lilly's credit they released weight data that showed just how bad weight gain is. Showed Beasley's 1 yr. follow-up, published in J Clin Psych. "Zyprexa is worst. Rest of antipsychotics are reasonable." Multiple risk factors in schizophrenic pts., including smoking.

Focus then turned to Diabetes. Incidence has increased 330% last 20 years. **STOP GAINING WEIGHT!. Don't prescribe olanzapine or clozapine.** Koro data, Pfizer study, Henderson data discussed. 1/3 of pts. developed DM. Zyprexa causes 4/5 cases of DM. 1/5 cases other atypicals. Data continues to grow. Many pts. on olanzapine get DM without weight gain. This is a direct effect. This is drug induced diabetes due to olanzapine. DO NOT PRESCRIBE OLANZAPINE TO PATIENTS WITH ANY OF THE RISK FACTORS: overweight, elevated blood sugar, family hx of DM, metabolic syndrome, ethnicity (DO NOT PRESCRIBE TO AFRICAN AMERICANS). Reviewed rest of atypicals to show low or minimal risk. Brought up label change and said, **"Lilly is very happy. They sent a press release saying, 'See we**

said it's a class effect'. It's not a class effect." Olanzapine compared to risperidone - much higher risk for olanzapine, ziprasidone versus olanzapine - much higher risk for olanzapine. Abilify lowers LDL, increases HDL, lowers triglycerides. "It's good for you." Talked about his own clinical practice and said he never prescribes zyprexa. Since he's moved to Cincinnati, he has to prescribe it occasionally when teaching residents. However, he will only prescribe after reviewing all risk factors. If none, then it is okay to prescribe but this pt. needs to be monitored closely.
Briefly mentioned QTC and said that Pfizer had bad press. "This was fear mongering". However, aripiprazole shortens QTC and is very safe.
Questions and Answers: Are you saying this is a drug effect? " Yes. Insulin goes up when you give olanzapine. Whenever pts. gain wt., pts. will develop insulin resistance and insulin levels will go up. This causes diabetes."
Close: "Lilly reps are going around telling all my residents to use topirimate. I strongly am against this." "They're even saying start pts. on glucophage. (Cited R Petty's talk.) This is the most outrageous thing I've ever heard! Only 20-25% of pts will get diabetes. Why give glucophage to the other 75%?" Interesting reaction by audience. Lots of pushback. Zyprexa has market share. People are familiar with work of Keck and McElroy (use of topirimate and zonisamide).

Strakowski: Update on Pharmacotherapy of Bipolar Disorders. Great speaker. Fair balanced.
Atypical antipsychotics in mania. Atypicals are the same. Olanzapine has the indication but they are all going for the indication and will get it in the next few years. Increased speed of response. "No evidence that there is a difference in efficacy but there is a side effect difference". "I truly believe that there is no difference in efficacy. You might think differently".
Reviewed olanzapine, risperidone acute mania slides. Presented aripiprazole acute mania data presented at APA 2003, data in press Am J Psych. Reviewed add-on studies: olanzapine, risperidone, quetiapine. Switched to bipolar depression. Discussed usefulness of lithium (his personal preference) need to dose to therapeutic levels and monitor blood levels. Presented lamotrigine data. Redacted Redacted No switch to mania. Safe combination. Predicted that "all atypicals will be shown to be effective in maintenance of BPD. Olanzapine is not unique in this respect. It's trial and error".
Switch to tolerability. "It doesn't matter how good the drug is, it depends upon tolerability". Weight gain important. Sedation is important. EPS is important. Risk of rash with lamotrigine is same as for carbamazapine. Very low risk.
Discussed importance of mood charting to assess pts. closely.
Audience Q & A: Metabolic syndrome. "Increased weight, increases the risk of metabolic syndrome. However, there is no evidence of a direct metabolic effect." "This is where Henry and Peter and I disagree". Henry and Peter both stated there belief that olanzapine causes diabetes. Studies are going on now at U of Cincinnati that will be able to put this issue to rest once and for all.

Preskorn: Can polypharmacy be rational?
First speaker due to need to catch flight. Presentation was interesting but less useful due to need to fit 1 1/2 hr. presentation into 45 min. presentation.
Refer to his website: www.preskorn,com for complete presentation.

Mintzer: Update in the Pharmacotherapy of Cognitive and Behavioral Symptoms of Dementia. Highly entertaining speaker. Fair balanced. Had the audience laughing throughout his presentation.
Emerging treatments reviewed: ginkgo biloba, NSAIDS, NMDA receptor antagonists, atypical antipsychotics, SSRIs.

Nice overview of memantine.
Fair balanced review of risperidone, olanzapine, aripiprazole (too credit for study design that did not hit primary efficacy but did show good efficacy in control of agitation).
Mood stabilizers good for agitation but no efficacy for psychotic symptoms. SSRIs may treat depression and/or agitation.
Aripiprazole is good for agitation and depression but not for psychosis. It has a mild antidepressant effect.
Citalopram if better for agitation and emotional lability than placebo.
Rule of thumb: For depression - treat NE deficit. For agitation - target 5HT. For psychosis - target DA.

Riba: Split Treatment : Problems and Opportunities. President of APA. Focus of talk was on split treatment versus integrated treatment and effect on patients treatment and outcomes.

McElroy: Update on Pharmacotherapy of Major Depression. Excellent presentation. Excellent speaker.
Nice review of major depression. Epidemiologic data.
Subtypes of depression: atypical versus melancholic (diminished versus elevated HPA activity, or fat versus thin).
TRD. Comorbidities. Stressed the importance of treating comorbidities.
Switching vs. Augmentation strategies.
Augmentation vs. combination strategies.
Nice overview of existing data. Redacted
Lots of audience interest.
Experimental strategies: VNS, Transcranial magnetic stimulation, NK-1 antagonists (toxicity issues), CRH antagonists (toxicity issues), mefipristone, (hastens onset of response), omega-3 fatty acids, high protein/low carb diets.
Very interactive Q & A. It was obvious that Susan is well respected and highly sought out. She was followed out into hallway following her presentation and had a line of people seeking her advice while program was going on.

Buckley: Broadening Use of Antipsychotic Medication Great presenter.
Provided broad overview of current uses as well as off -label usage (particularly in children). Comparable efficacy between antipsychotics. Not comparable tolerability.
Focus of topic was on treatment of aggression and desirable characteristics of an anti-aggressive drug (selective, broad spectrum), rapid onset of action, sustained effect, availability in multiple forms, low toxicity, low potential for drug-drug interactions.
Setting up aripiprazole as market lead for treatment of aggression. Excellent efficacy and tolerability.