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Subject: Zyprexa questions from the field

Area Zyprexa Champions:
Below is a response from Zyprexa medical to recent questions from the field. Please disseminate to your respective areas. Also, for future questions, please send them to Art Snow in training and development. I have enjoyed working with all of you and will miss our interactions in my new assignment. Thanks!
Darren

Question:

- We know that Zyprexa has a low potential for drug-drug interactions, but we need to feel a little more confident about a "cocktail" question that has come up for several of the reps: Can doctors use Zyprexa with Aricept or Excelon? It is thought that Aricept/Excelon works on the Alzheimer's and Zyprexa can pick up the unmet need of agitation that goes with it. Is it common to add Zyprexa; what doses of Zyprexa are added; anything to warn the doc about? Also, if Zyprexa is going after the Alzheimers indication, wouldn't it make sense to forget the Aricept/Excelon (we know that we can't discuss future indications, but is there good data/ medical letter to support Alzheimers efficacy).

Answer:

- Zyprexa has multiple metabolic pathways and though it has not been studied with Aricept or Excelon, we would not expect any significant interaction between Zyprexa and these medications. During other interaction studies, it was found that other medications metabolized through similar pathways as Zyprexa (1A2 and 2D6) may influence the plasma levels of Zyprexa (the other drug's plasma levels are not effected). With Zyprexa's broad range of dosing and blood levels, changes in the blood levels for Zyprexa does not create a concern unless there are more factors involved (i.e. elderly, smoking). Additionally, the notion that Zyprexa has significant anticholinergic effects (thus negating the increase in acetylcholine by Aricept and Exelon) has not been a factor during our studies in the elderly. In fact, we have seen a trend toward cognitive improvement with Zyprexa. Secondly, at the current time, we are not pursuing an indication for treatment of Alzheimers. We had submitted for an indication for the behavioral disturbances associated with Alzheimers; however, it was withdrawn due to vagueness on the FDA's part regarding a definition of efficacy that they would utilize to determine a medications approval for this use.

Question:

- Since the diagnosis of our 3 patients in the Zyprexa core message piece are: Martha - dementia, David - bipolar, Christine - schizo; can you enlighten us a little more about dementia. We know that we are to describe the symptoms and stay away from diagnoses, but for our own background, can you elaborate on dementia and how it is different from other things like Alzheimers, etc. We are getting a little grief from some of our docs about promoting Zyprexa for dementia, but according to the slides in the audioconference set, there is no FDA approved drug for dementia.

Answer:

- Dementia is a broad classification that basically indicates a disease which produces a decline in cognitive functioning. As we know, there are many other symptoms associated with this as well

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(behavioral disturbances, psychosis). Alzheimers disease is the most prevalent form of dementia, estimated at over 80% of dementia cases. Other forms may include vascular dementia, leweybody dementia, dementia NOS.

Question:

- Dosing of 2.5 mg vs 5 mg - we are finding that 2.5 mg is the dose most often used in nursing homes. We want to stay consistent with our 5 mg message for ambulatory outpatients. For our own benefit, what are the real differences between 2.5 and 5 mg in efficacy and safety for the "Martha" type patient. If the patient is on multiple meds, when and how are patients started on Zyprexa in both settings - the nurse home and outpatients.

Answer:

- Regarding 2.5mg efficacy, we currently do not have any firm evidence of the efficacy at this dose. While some of the patients in our Alzheimer studies were taking a 2.5mg dose, the dose most efficacious was 5mg and 10mg. Support for the 2.5mg dosing at this point is anecdotal in nature. The only evidence we have to date of efficacy at 2.5mg is that 20% of patients in an open label, flexible dosing dementia study by Kinon et. al. were on a mean dose of >0 -2.5mg (mean dose of the study was 5mg). As you know, our package insert states efficacy at 5 to 20mg, not 2.5 to 20mg. More studies are needed with regard to dosing in elderly populations to clearly identify if 2.5mg is both safe and efficacious.

Thanks to Marlis Morrison for forwarding these questions.

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Board 46: DIVALPROEX SODIUM VS. OLANZAPINE FOR THE TREATMENT OF MANIA IN BIPOLAR DISORDER

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Divalproex sodium (DVPX, Depakote®) is a mood stabilizer approved in the United States for the treatment of acute mania associated with bipolar disorder. Olanzapine (OLZ, Zyprexa®) is an atypical antipsychotic agent, recently approved for the treatment of mania. This study compared the efficacy and safety of DVPX and OLZ in the treatment of acute mania in bipolar disorder. Pharmacoeconomic and quality-of-life data were also collected.

This randomized, double-blind, parallel-group, multicenter study included a screening period (1-3 days) and a double-blind treatment period (12 weeks). Subjects received DVPX (n=63) or OLZ (n=57) at initial dosages of 20 mg/kg/d and 10 mg/d, respectively (maximum allowed dosage: 20 mg/kg/d + 1000 mg DVPX and 20 mg/d OLZ). Subjects who met improvement criteria at or before day 21 were discharged from the hospital; those not meeting discharge criteria at day 21 were discontinued from the study. The efficacy analysis compared changes from baseline (to day 21) in mean Mania Rating Scale (MRS), Clinical Global Impression (CGI) scale, Brief Psychiatric Rating Scale (BPRS), and Hamilton Depression Scale (HAM-D) scores for the two groups. Safety evaluations included weight change, adverse events, laboratory parameters, and vital signs data collected during the 12 weeks of the study. Pharmacoeconomic data, including medication, outpatient, and inpatient costs, were collected at weeks 6 and 12. Quality of life was assessed after hospital discharge and at weeks 6 and 12 using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

The mean maximum daily dosages were 2115 mg (range: 750-3250 mg) for the DVPX group and 14.7 mg (range: 5-25 mg) for the OLZ group. No statistically significant difference was seen between the DVPX group (-14.8) and the OLZ group (-17.2) in mean change to day 21 in MRS score (P=0.210). Changes from baseline to day 21 for the CGI, BPRS, and HAM-D were also similar between groups. Mean changes in body weight from baseline to the final evaluation were significantly greater in the OLZ group (+8.8 lb), than the DVPX group (+5.5 lb, P=0.049). Adverse events occurring in a statistically significantly greater proportion of OLZ-treated subjects than DVPX-treated subjects included somnolence (29% DVPX vs. 47% OLZ), weight gain (10% DVPX vs. 25% OLZ), rhinitis (3% DVPX vs. 14% OLZ), edema (0% DVPX vs. 14% OLZ), and speech disorder (0% DVPX vs. 7% OLZ). No adverse events occurred with statistically significantly greater incidence in the DVPX group. One death occurred during the study (diabetic ketoacidosis in an OLZ-treated subject with a baseline glucose level of 86 mg/dL). No statistically significant differences between groups existed in change from baseline in Q-LES-Q scores, but a numerical trend toward improvement of DVPX-treated subjects (vs. OLZ-treated subjects) existed for the physical portion of the Q-LES-Q (P=0.09). Total 12-week outpatient costs of the DVPX group ($554) were statistically significantly lower (P=0.0028) than the OLZ group ($1109).

These results suggest DVPX and OLZ are equally efficacious in treating mania and have similar effects on subject quality of life. However, DVPX appears to exhibit a superior adverse event profile and is associated with significantly less weight gain and lower outpatient costs than OLZ.

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