Endocrine Advisory Board - AREAS FOR OPPORTUNITIES

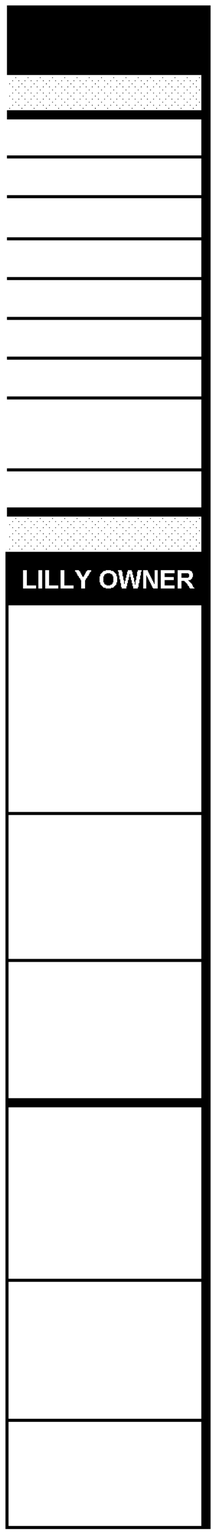
OVERALL

Expand scope to Metabolic Syndrome
Continue to have challenges on these issues - no safe harbor! Broader patient issue and competitors will continue to challenge positioning
Weight gain - "strawman on the table"...right message, tone and guidelines emerging. Need to provide something practical for physicians!
Admit that there are some patients that you have to give up, but, continue to provide solutions for patients that do stay on Zyprexa for the superior efficacy
Tip the scale back to efficacy; good MD confidence in superior efficacy despite liabilities
Patients ability to stay on drug and limit relapse can further strengthen efficacy message
Keep statements about issues focused on "patients" not on your relationship with physicians
Opportunity to engage physicians through mechanism differentiation, on both the efficacy front and that of issues, to help physicians better understand how to manage the patient benefits with liabilities
Very interested in ADA ruling; impressed and think we were right to take the lead in approaching them

SPECIFICS

TOPIC AREA	UNDERLYING KEY TAKE-AWAY	RECOMMENDATION
Diabetes	Debate continues on whether "Persistent Mental Illness" should be added as an independent risk factor; even more pronounced when exacerbated by ethnic diversity. CDA - Canadian Diabetic Association has approved the addition of "persistent mental illness" as an independent risk factor for diabetes. In process of changing screening and treatment guidelines as result	Partner with ADA to identify group as "high risk" and partner with group to institute standardized screening and treatment guidelines across all products. Fits with recent trends around tighter controls and screening in general population - more than just a glucose test! Also eradicate the unbalanced screening that going on - Zyprexa is being singled out and in some settings non-compliance with screening is leading to citings and infractions.
	Data and trend tend to support the notion that Zyprexa does not cause diabetes; however, the perception is still there that it causes long term consequences "It is just a matter of time - current studies we only see weight gain --> progress to dyslipidemia --> insulin changes and diabetes".	Need to disarm that perception. Difficult when differential weight gain is considered an independent risk factor.
	Mark between Insulin resistence and progression to diabetes is moving; greater recognition that we are under-screening, under-diagnosing and under-treating! A vast amount of our general popultion is overlooked, let alone our mentally ill population.	
	Likely see the more refractory patients lining up with more risk factors - since Zyprexa tends to get used in sicker population, may see unfair weighting in direction of incidence. Also seeing "misinformation being fed to MDs by competition" which may be "contributing to inappropriate discontinuation and sub-optimal clinical decision-making"	Arm physicians to be proactive with patients on weight gain issues and interventions in preventative manner - "MD's should not allow patients to gain 100 lbs". Lilly should openly acknowledge that there may be a subset of patients that need to be switched - "avoid temporary denial"
	Not clear what impact the differential weight gain will have in 5-10 years. Disconnect currently in message that "weight gain" doesn't count and yet by ADA and AHA standards it is an independent risk factor for cardiovascular and other (including diabetic) complications.	More exaccerbated concern when you start to treat with combination therapy, as per new indication
	Not just a clear cut case of mean weight change - type and distribution (interabdominal versus visceral) may be a more important predictor of risk. Cases where thin patients not escaping a high level of weight gain around the waist, coined	Interested to understand what type of fat you get and where is it going? Helpful to have tool to identify patient at greatest risk and identify them in earlier timeframe to optimize treatment/intervention.

Weight Gain	"central obesity" . Thakore's data suggested no significant difference in Zyprexa's location of fat distribution versus baseline and versus Risperdal	May be able to use some simple interventions like a waist tape or simple body shape classifications - "pear", "banana" and "apple" with the latter being the high risk group.
	Some findings suggested that the long term presence of mental illness may cause a whole host of changes that may predispose the patient to greater risk. Examples cited included: 1) Changes in intima thickness of carotid arteries, 2) Corticol levels affecting CRP and homeocysteine, 3) Changes to the platelet aggregation cascade and 4) Glucose level changes in response to stress fluctuations.	
	BMI of >30 represents 35% of the general population today; only accentuated by additional risk factors and the presence of persistent mental illness	
	Need to study this population more broadly to give full credance to complicated interface of factors - weight gain, lipids, diabetes and other comorbidities etc	Focus studies that look at "Metabolic Syndrome" as a comorbidity to mental illness
General Comments	Competitors are taking up the message of "mechanism" to differentiate themselves and underscore issues/problems with competing agents	Opportunties to discuss some mechanism advantages with Olanzapine to drive home differential efficacy benefits - includes sharing Intercept suicide data
	Unrealistic to keep going after Schizophrenia - 60-70% market share.	Opportunity for Lilly is with Bipolar; 1 year ahead of the Competition. Solidify position in Bipolar before they catch up.
Response to Letter and Statements	Expand facts/programs on diabetes to "metabolic syndrome" its relationsip to persistent mental illness. Lilly reps are not armed with this information and are not able to have informed dialogue with MD on Zyprexa differentiation	Require inclusion of CV survival rates. Add smoking into the mix.
		Create more linkages between Endocrinologists and Psychiatrists
	Use "assess, council and refer"	Want to be armed with the education and tools to "treat" not just "refer"; enhanced linkages between healthcare professionals will be important to bridge education/ treatment gaps and ensure Pyschiatrists have ability to manage "whole" patient
	Watch some of the confrontational language "armed with the facts" and "setting the record straight"	Suggest language like "address the issues" instead
	Use the word "drug"	Change to "medication"
	"Change" in weight to "potential" weight gain.	Want to keep the "sorry, we lied" message really clean
	"Manageable" seems to denote a black mark against physicians; saying "somehow we let the patient gain all this weight"	Adopt a long-term strategy; acknowledge and then deliniate how we can address the issues. Includes talking more about "appetite increase" and which foods to eat in response
	Have to individualize it for patients - only way you are going to get traction with the patient and physician to work through weight issues but understand that there is a subset of patients that may not be suited to Zyprexa.	Help physicians understand when to walk away from Zyprexa; when "tolerabilty outweighs efficacy" or "weight gain precludes benefits" --> discussion with the patients on appropriate next steps. By taking this less defensive stance, you will have opportunity to reposition Zyprexa's efficacy benefits first; MD can say to the patients"this drug has the best promise of efficacy but it comes with some challenges that we need to work on together"
		Opportunity to use Dr. Jackson's VENN diagram…
	Avoid "I" statements focused on the physician	Refocus on the patient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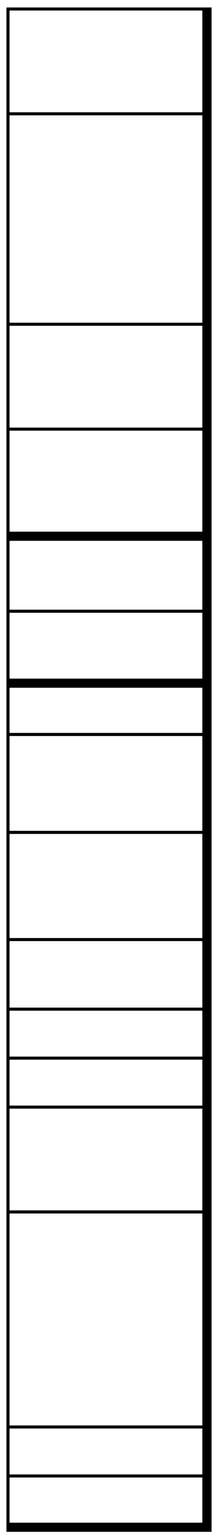

Author/Researcher	Poster Title	Strengths
Bellnier TJ, Patil K, Ortega T, Decatur A	The prevelence of metabolic disturbances in schizophrenic and bipolar I patinets prior to antipsychotic use	Historical perspective
		Large N; 1000 patients reviewed and 592 met criteria for Schizophrenia or Bipolar
		Utilized an appropriate comparator
Casey D, L'Italien G, Waldeck R, et al	Metabolic syndrome comparison between Olanzapine, Aripiprozole, and Placebo	
Kato M, Gonzalez-Blanco M, Sotelo J, et al.	Metabolic syndrome in schizophrenia: a pilot study	First investigation using "real criteria" in terms of biological
		Conclusions were modest and fit type of study
		Outpatient focus... applied population
Mausand	Effects on weight change of switching from Olanzapine to Quetiapine	Common practice addressed (e.g. market data)
		BMI 35
		Good screening
		Robust collection of tests

Smith RC, Lindenmayer J, Bark N, et al.	A prospective cross-sectional study of glucose and lipid metabolism with atypical and conventional antipsychotics	Length of treatment on average was about 6 months Good sample size

Poster Review	
Weaknesses	**Anti-Lilly**
Psychiatric diagnostic criteria not standardized at time of study (1940-50) and has changed dramatically in last 50 years	Patient at risk at all weights; additional weight gain with Zyprexa is just "adding fuel to fire" in this vulnerable population
Gender and ethnicity bias - homogeneous	If diabetes was so prevlent, why wasn't it recognized?
Diet differed between hospitalized and community patients	Results can't be extrapolated to current time because methodology flaws
Artifact with glucose urine	
Other risk factors such as smoking and family history not controlled for	
Counting of "worsening criteria" questionable - not clear on severity	Going to see a lot of "weight proxies" coming; painting picture of links to outcomes particularly death
Curve #2 flat; no fall out rates given... likely if flat, people left in study are ones who are not at risk	"Wonder how much fishing was going on when developed criteria" - worry about post-hoc cuts
Close to 60% didn't complete overall and of the 40% who did, 34% relapsed	
Pooled analysis in figure #3 questionable	
Control group - Hispanics have > risk factors for diabetes (re: National average 22% versus Hispanic 32%)	By using Zyprexa, you are putting "gas on an already raging fire"
Treatment demographics unknown - med profile	
Illness severity unknown	
Under target dose	"taste great, less filling"
4/16 dropped out and not covered in analysis	Solution to common problem with no loss of efficacy
Methodology for switch not done (re: random/blind switch)	"Metabolic stabilizer" also seen with Clozapine
Type of weight gain not shown. Not clear if weight changes are clinically significant relative to patient's size	Zyprexa has a long lasting effect; Quetiapine "can't undo the damage in 10 short weeks"; in fact, damage may be irreversible!
Duration not clear. Was it 10 or 12 weeks (re: includes switch time?)	
No comorbidities given and no BP reported	
Cross-section design	Increased TG and statin use

Lack of sufficient information elated to risk factor (e.g. diet, exercise)	Funded by Lilly; results seem to favor the funder
Pre-morbid history unknown (e.g. hospitalizations, treatment resistance, extent of othr meds, # of schizoaffective)	
Increased weight on other meds versus Zyprexa sample	

Pro-Lilly	Grade or Recommendations
DM was higher than average in patients with schizophrenia and bipolar well before the introduction of atypical; primary disease effect not a drug effect	Conclusion a "little far reaching to say it is protective"
First systematic review of diabetes in patients with persistent mental illness before the introduction of and widespread use of novel pharmacotherapy	Evidence is clear that this is not a new problem; issues with the disease! This study could help make the case to the ADA that persistenet mental illness should be an independent risk factor for diabetes.
At any given weight, patients with schizophrenia and bipolar have higher rates of DM	Large systematic review that favors OLZ; can be strong response to claims based on case reports
Treatment of mental illness may improve diabetes	
Patients were "spilling glucose" so severe	
Appears to have greater maintenance rates in trials	Going to see a lot of noise around soft criteria; important to redirect this with good, solid data
Probably a worse outcome because better survival	
It is a disease issue	All patients need to be screened - start with an Accu Check and a tape measure around the belly
Poor methodology	"a lot to do about nothing"
Is weight change relevent?	Use at Journal Club
Patient selection bias	
Where is data from controlled trials?	
TG's increased 11%, Cholesterol 4% and HDL worsened 1%. Variables are moving in the wrong direction	
Glucose dysregulation and high leptin levels with Risperdal	"raises more questions than answers"

Olanzapine associated with lower BMI's and lower leptin levels	Value increased if follow-up study conducted at 6 months
	Might be able to position it as a response to Newcomer and underscores that consistency of finding not there so hard to draw conclusions in either case - for or against one atypical over another

Group Participants
Daiello, Gupta, Maguire, Poole-Hoffmann (Lilly), and Schuartz
Conley, Dufresne, Hardy (Lilly), Kato, and Micca
Jackson, Jordan (Lilly), Perry, Steinberg and Thakore
Baker (Lilly), Ereshefsky, Ganda, and Kabinoff

Bielman (Lilly), Citrome,
Fawver, Mudalier, and Popkin

Endocrine Advisory Board - PROJECT OWNERSHIP

Topic area	Focus	Project Owner	Team Support	KOL's	Required Resources	Indicators of Success	Date Planned

Note: Project Update Meeting to be scheduled