Olanzapine Core Medical Efficacy and Safety Beliefs

File
Zyprexa

Weight Gain

1) We currently do not know all of the mechanisms that cause weight gain in patients taking Olanzapine.
2) There are currently no weight gain interventions or preventatives that are completely and consistently effective for all patients (i.e. patient response varies among the interventions)
3) The rate of weight gain in patients taking Olanzapine decreases over time and may, based on group analysis, eventually reach a plateau.
4) Weight Gain with Olanzapine varies by patient – some patients will not gain any weight while some patients may gain a significant amount of weight.
5) Early rapid weight gain is an important predictor of significant total weight gain.
6) Low Baseline BMI may be a good predictor of the patients who may gain weight while taking Olanzapine. However, weight gain has been reported as greater in Olanzapine-treated patients with low, medium and high BMI compared to placebo.
7) Patients taking Olanzapine are more likely to gain weight than those taking any antipsychotic or mood stabilizer other then Clozapine (definitely), Depakote (probably), or Quetiapine (possibly). However, there are no weight neutral antipsychotics.
8) Weight Gain with Olanzapine is not dose dependent (including starting dose) between 5-20 mg.
9) Treatment with Olanzapine is associated with an increase in appetite, but it is not clear whether or not this increase fully explains the weight gain.
10) Patients who are naïve to psychotropic drugs may be at an increased risk for weight gain
11) There are similar patterns of Weight Gain with Olanzapine in Schizophrenic and Bipolar patients treated in monotheraphy.

Diabetes

1) In an analysis of our clinical trial databases, the strongest predictor for treatment-emergent diabetes was the patient's baseline risk factors for diabetes.
2) Patients with schizophrenia-spectrum disorders, bipolar disorder, and major depressive disorder are at greater risk of diabetes than the general public.
3) Being overweight (and hence weight gain) is associated with an increased risk for diabetes. Over time, our hypothesis is that this same association holds for patients who become overweight while taking Olanzapine. However, many factors other than being overweight also influence diabetes risk (including genetic predisposition, diet, exercise, and comorbid conditions). Diabetes frequently affects individuals who are not overweight and most people who are overweight do not develop diabetes. In a retrospective analysis of our clinical trial data (including double-blind treatment of 6-52 weeks), we did not identify a significant association between treatment-emergent weight gain and diabetes for patients taking Olanzapine. A potential reason for this is that most of our studies were not designed (especially given the relatively short duration of these studies) to study a link between Olanzapine therapy and Diabetes. This issue requires additional research. Based on our data and our review of the published data on this subject, we believe that:

a. Currently available study results do not consistently support differences in the risk of diabetes in patients treated with Olanzapine compared with other atypical agents.
b. A causal link between Olanzapine therapy and Diabetes has not been established.

Lipids

1) In general, Weight Gain is associated with rises in Triglyceride and Total Cholesterol levels. In our data, we have seen this same association in patients taking Olanzapine.
2) Lipid changes primarily associated with Olanzapine are a moderate mean increase in Triglycerides and a small mean decrease in HDL. There were no consistent changes in LDL.
3) Severe hypertriglyceridemia (TG>1000) has been reported (in spontaneous databases) in patients taking Olanzapine. Reports of these cases are very rare and causality has not been established.
4) Statistically significant differences in the rate of clinical dyslipidemia (based on NCP criteria) were infrequent in our clinical trials.

Cardiovascular Disease (CVD) (i.e. Ischemic Heart Disease)

1) The development of Cardiovascular Disease is determined by a multitude of factors that include genetic vulnerability and acquired risk factors (such as: diabetes, hypertension, physical inactivity, smoking, weight gain, age, and dyslipidemia). Being overweight (and hence weight gain) is associated with an increased risk for Cardiovascular Disease. Over time, our hypothesis is that this same association holds for patients who become overweight while taking Olanzapine. Based on one cross-sectional study, which included patients who had been on Olanzapine for a minimum of 12 months, we have not been able to identify an association between Olanzapine treatment and an increased risk for CVD. However, because the incidence of CVD during Olanzapine therapy has not been studied prospectively, the risk of CVD during long-term treatment with Olanzapine has not been evaluated.

QTC

1) In a Pfizer clinical study, which compared patients treated with Olanzapine, risperidone, quetiapine, haloperidol, ziprasidone, and low dose thioridazine, the Olanzapine treatment group had the smallest mean change increase in QTC. However, some of the other treatment groups (specifically, risperidone) were very close to Olanzapine.

EPS (i.e. Dystonia and Parkinsonism)

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1) Olanzapine-treated patients have a low risk of EPS.
2) There is not a differential risk for EPS in Schizophrenic and Bipolar patients taking Olanzapine.
3) Olanzapine can be dosed to efficacy without an increased risk for EPS, at least as determined by rating scales.

4) Olanzapine has a lower liability for EPS than typicals and a lower liability than Risperidone (for doses > 4mg).
5) Olanzapine has a low liability for acute dystonia.

TD

1) Olanzapine-treated patients have a low risk for TD. The data are inconclusive whether Olanzapine has an advantage over other atypicals. Olanzapine does have an advantage in long-term use vs. typicals. Patients with TD, when switched to Olanzapine from typicals or Risperidone may experience a reduction in TD.

Prolactin

1) Olanzapine-treated patients have a low risk for prolactin.
2) Drug-induced hyperprolactinemia is associated with significant sexual, reproductive, and medical morbidities.
3) Olanzapine-treated patients may have a lower risk for male sexual dysfunction than those treated with Risperidone.

Efficacy – Schizophrenia

1) Olanzapine sometimes wins, but is never beaten in Acute Efficacy.
2) There are no consistent differential advantages for Olanzapine vs. Risperidone in Acute Efficacy.
3) Olanzapine is associated with longer durations of treatment vs. typicals, Risperidone, Quetiapine, and Ziprasidone.
4) Olanzapine may reduce depressive symptoms vs. typicals and has unknown advantages (but positive trends) vs. other atypicals.
5) The likelihood of maintenance of response is greater with Olanzapine than with typicals, Ziprasidone, Quetiapine, and possibly with Risperidone.
6) Olanzapine has greater efficacy in negative symptoms vs. Haloperidol and possibly greater efficacy in cognition.
7) In patients who have an inadequate response to typical antipsychotic treatment (Treatment Resistant), treatment with Olanzapine may provide a further response – particularly in the areas of negative symptoms, cognition, and general psychopathology. Olanzapine may provide more advantages than Risperidone in this patient population.

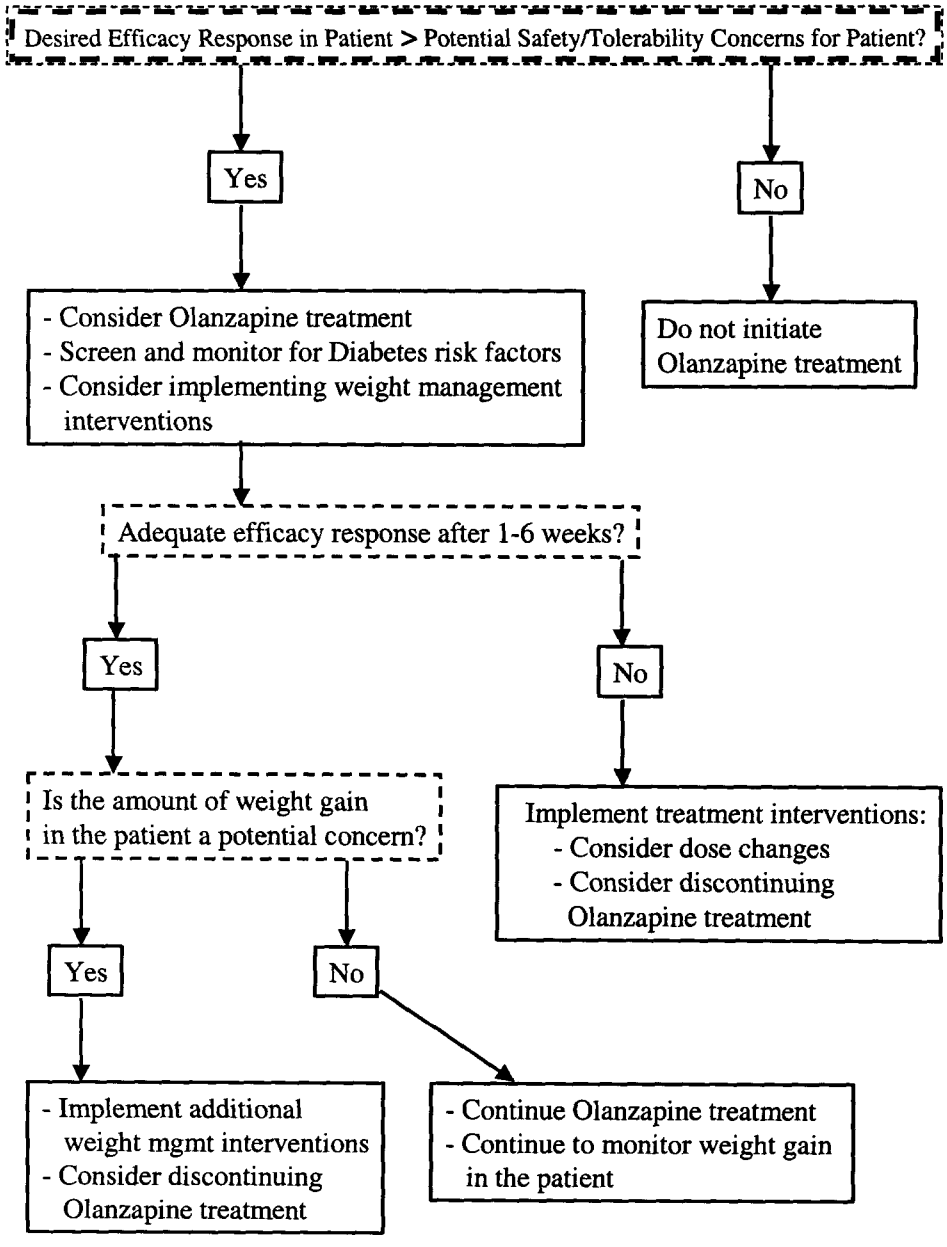
Efficacy – Bipolar

1) Olanzapine is a highly effective treatment for Acute Bipolar Mania. Olanzapine appears to be a more effective and rapid-acting treatment than Depakote. Olanzapine appears to be equivalent to Haloperidol and Risperidone in Acute Mania.
2) Olanzapine is an antimanic as well as an antipsychotic.
3) Olanzapine may be effective in treating rapid-cycling and nonrapid-cycling and in delaying rapid-cycling.

4) Olanzapine is effective in mixed bipolar episodes – including improvements in depressive symptoms and appears to have efficacy advantages in these areas vs. Haloperidol.
5) Olanzapine is effective in treating manic and mixed episodes in combination with other mood stabilizers (Depakote or Lithium).
6) More Bipolar patients remain on Olanzapine treatment at one year than those who are on Lithium.
7) Olanzapine is a more effective treatment at preventing manic episodes than Lithium and is as effective in preventing depressive episodes.
8) Olanzapine is effective in preventing depressive and manic relapse.

Redacted

Draft Treatment Algorithm



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Vital Sign Comments — R.D. Gamva

1) Wgt significantly increased ($p<.001$) baseline to endpoint for Olz compared to Hal

2) Categorical analysis of Wgt - % Patients ≥ 7% wgt gain Significantly increased ($p<.001$) for Olz ALSO % Patients ≥ 7% wgt loss significantly decreased ($p=.025$)

3) Usually don't mention Baseline to Max within text BOT Temp had a significant increase on rank analysis ($p=.044$), The large difference between raw and rank analysis partially due to outliers Patient 1199 had recorded Temp = 82.2 °C!

4) ~~Use~~ Phrases like 'No ~~significa~~ statistically significant differences ~~were observed~~ between Olz and Hal were observed.'

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These are the changes made to an early HGAP table. Just in case you copied it into your report. Also note, we have decided to use dl not dL. Susan.

Table HGAP.7.1.24. Conversion Table for Conventional Units to SI Units
F1D-MC-HGAP Acute Phase

Analyte	Conventional Unit	Conversion Factor (x)	SI Unit
Total bilirubin	mg/dl	17.1	µmol/L
Alkaline phosphatase	IU/L	1.0	U/L
GGT	IU/L	1.0	U/L
ALT/SGPT	IU/L	1.0	U/L
AST/SGOT	IU/L	1.0	U/L
Urea nitrogen	mg/dl	0.357	mmol/L
Creatinine	mg/dl	88.4	µmol/L
Uric acid (urate)	mg/dl	59.48	µmol/L
Inorganic phosphorus	mg/dl	0.3229	mmol/L
Calcium	mg/dl	0.2495	mmol/L
Glucose, nonfasting	mg/dl	0.0555	mmol/L
Total protein	g/dl	10	g/L
Albumin	g/dl	10	g/L
CPK	IU/L	1.0	U/L
Sodium	mEq/L	1.0	mmol/L
Potassium	mEq/L	1.0	mmol/L
Bicarbonate	mEq/L	1.0	mmol/L
Chloride	mEq/L	1.0	mmol/L
Cholesterol	mg/dl	0.02586	mmol/L
Hemoglobin (Fe)	g/dl	0.6206	mmol/L (Fe)
RBC	mill/mm^3	1.0	TI/L
MCV	µM^3	1.0	fL
MCH (Fe)	pg	0.06206	fmol (Fe)
MCHC (Fe)	g/dl	0.6206	mmol/L (Fe)
WBC	thou/mm^3	1.0	GI/L
Platelets	thou/mm^3	1.0	GI/L
Hematocrit	%	0.01	1
Neutrophils	thou/mm^3	1.0	GI/L
Bands	thou/mm^3	1.0	GI/L
Monocytes	thou/mm^3	1.0	GI/L
Eosinophils	thou/mm^3	1.0	GI/L
Basophils	thou/mm^3	1.0	GI/L
Lymphocytes	thou/mm^3	1.0	GI/L

Abbreviations: SI = Systeme International; GGT = Gamma-glutamyl transferase; ALT/SGPT = alanine transaminase; AST/SGOT = aspartate transaminase; CPK = creatine phosphokinase; Fe = iron; RBC = red blood cell (erythrocytes); MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; WBC = white blood cell (leukocytes).

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CONVERSION OF LABORATORY UNITS

The trend is to report lab results in the universally-accepted S.I. units. This chart is presented as an aid for comparision of results in conventional and S.I. units. The Lilly Reference Range (III) values for a caucasian male, <50 yrs. are used here as an example.

********CONVENTIONAL********				********S.I.**********		
TEST	RANGE	UNITS	FACTOR →	RANGE	UNITS	← FACTOR
T. BILIRUBIN	0.2-1.8	mg/dl	17.1	3-31	µmol/L	0.0585
ALK.PHOS.	30-153	IU/L	1.0	30-153	U/L	1.0
GGT	5-194	IU/L	1.0	5-194	U/L	1.0
ALT (SGPT)	7-125	IU/L	1.0	7-125	U/L	1.0
AST (SGOT)	11-79	IU/L	1.0	11-79	U/L	1.0
UREA	7-25	mg/dl	0.357	2.5-8.9	mmol/L	2.8
CREATININE	0.7-1.6	mg/dl	88.4	62-141	µmol/L	0.0113
URATE	2.8-9.2	mg/dl	59.48	167-547	µmol/L	0.0168
In.PHOS.	2.2-5.0	mg/dl	0.3229	0.71-1.61	mmol/L	3.1
CALCIUM	8.3-10.6	mg/dl	0.2495	2.07-2.64	mmol/L	4.0
GLUCOSE	67-194	mg/dl	0.0555	3.7-10.8	mmol/L	18.0
TOTAL PROTEIN	6.3-8.3	g/dl	10	63-83	g/L	0.1
ALBUMIN	3.6-5.2	g/dl	10	36-52	g/L	0.1
CK	17-640	IU/L	1.0	17-640	U/L	1.0
SODIUM	135-147	mEq/L	1.0	135-147	mmol/L	1.0
POTASSIUM	3.5-5.5	mEq/L	1.0	3.5-5.5	mmol/L	1.0
BICARBONATE	21-35	mEq/L	1.0	21-35	mmol/L	1.0
CHLORIDE	96-113	mEq/L	1.0	96-113	mmol/L	1.0
CHOLESTEROL	110-331	mg/dl	0.02586	2.84-8.56	mmol/L	38.7
TRIGLYCERIDES	44-844	mg/dl	0.01129	0.50-9.53	mmol/L	88.6
HDL	17-78	mg/dl	0.02586	0.44-2.02	mmol/L	38.7
LDL	58-237	mg/dl	0.02586	1.50-6.13	mmol/L	38.7
HBG	12.7-18.2	g/dl	10	127-182	g/L	0.1
RBC	4.2-6.2	mill/mm^3	1.0	4.2-6.2	TI/L	1.0
HMT	38-55	%	0.01	0.38-0.55	1	100
MCV	78-105	µ M^3	1.0	78-105	fL	1.0
MCH	26-35	pg	1.0	26-35	pg	1.0
MCHC	31-37	g/dl	10	310-370	g/L	0.1
WBC	3.6-13.8	thou/mm^3	1.0	3.6-13.8	GI/L	1.0
PLATELETS	136-425	thou/mm^3	1.0	136-425	GI/L	1.0

LILLY RESEARCH LABORATORIES

P.J. SIMPSON - Updated September 10, 1993

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