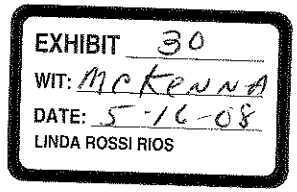
SEROQUEL and Metabolic Syndrome



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Metabolic Syndrome

- Characterized by excessive visceral fat distribution
  - Hallmarks=disturbed glucose + insulin metabolism, obesity, dyslipidemia, HTN
- Causes=Obesity, physical inactivity, + genetic factors
  - Life style, poor diet, + lack of exercise may contribute
- No uniformly accepted criteria for diagnosis

Worldwide Prevalence

- Prevalence range=10-33% (Ford et al 2002, Meigs et al 2003)
  - True prevalence unk d/t varying rates + definitions around world
- Estimate of prevalence determined by prevalence of components (Hausen 1999)
  - 1997: Approx 124 million persons worldwide w/ diabetes. Estimated by 2010 the # would=221 million.
  - Theorized that # of people w/ metabolic syndrome is 2-3x ↑ than # w/ diabetes

Metabolic Syndrome in Patients with Schizophrenia

- Prevalence of insulin resistance appears ↑ in schizophrenia compared to general population.
- Studies (all 4 limited by small sample size)
  - 1st episode, drug naïve Pts w/schizophrenia. 15% impaired FBS levels + more insulin resistant than healthy controls (Ryan et al 2003).
  - CT scans: healthy Pts w/ drug naïve + drug free schizophrenia (n=15). Schizophrenics had central obesity + ↑levels of cortisol compared to healthy controls. Schizophrenics also had ↑BMIs + >3x as much intra-abdominal fat (Thakore et al 2002).

Metabolic Syndrome in Patients with Schizophrenia (contd)

- Studies (contd)
  - Outpatients (US [n=98])/Inpatients (Taiwan [n=27]) w/ schizophrenia/schizoaffective disorder. Pts taking variety of psych meds. Prevalence of metabolic syndrome=51% + 22%, respectively (criteria for metabolic syndrome unspecified) (Litrell et al 2003)
  - Frequency of metabolic syndrome in schizophrenics=37% (receiving either clozapine, olanzapine, or conventional antipsychotics) (Heiskanen et al 2003).

Clinical Trials

Limitations

- Clinical trials w/ quetiapine have recorded BMI measurements; no waist circumferences
- Plasma glucose, triglycerides, + cholesterol values generally not fasting values

Criteria for Identifying Metabolic Syndrome

(Pt needs to fulfill 3 of 5 criteria)

NCEP ATP III Criteria for Metabolic Syndrome	
Risk Factor	**Defining Level**
Abdominal Obesity/ Waist Circumference Men Women	 ≥102 cm (≥40 in) ≥88 cm (≥35 in)
Triglycerides (fasting)	≥150 mg/dL
HDL cholesterol (fasting) Men Women	 <40 mg/dL <50 mg/dL
Blood pressure	≥130/≥85 mmHg
Glucose (fasting)	≥110 mg/dL

Modified Set of Criteria for a Metabolic-Syndrome Like Event	
Risk Factor	**Defining Level**
Body Mass Index	>30 kg/m^2
Non-fasting triglycerides	≥150 mg/dL
HDL cholesterol (non-fasting) Men Women	 <40 mg/dL <50 mg/dL
Blood pressure	>130 mmHg systolic or >85 mmHg diastolic*
Non-fasting glucose	≥140 mg/dL

*Individual (systolic + diastolic) BPs were used to meet ever this criterion

CDS Listed for Seroquel

- Seroquel Core Data Sheet:
  - As with other antipsychotics weight gain has been associated w/ Seroquel
  - Elevations in non-fasting serum triglycerides

Last value per Patient: Changes in Triglycerides Placebo-controlled Monotherapy Phase II/III/IV Trials

Treatment group	Mean baseline (mg/dL)	Mean change from baseline (mg/dL)
Quetiapine	161.92	26.13
Placebo	171.32	-5.95

Analysis

- Three criteria did not have to be met concurrently
- Pts who had ≥3 criteria at baseline excluded
- Used mean of 3 last supine systolic/diastolic BP values
  - Either systolic **OR** diastolic BP could be above threshold
- Only final post-baseline BMI value was used
- Labs: Worst values during last 2 wks used for analysis
- Relevant AEs during final 2 wks of treatment taken as evidence of fulfilling a criterion

Back-up analysis slide (w/ few more details if needed) 1st back up slide (#)

Placebo-Controlled
Monotherapy Trials

All Criteria Emerged During Treatment Phase of Study

Overall Metabolic Syndrome in Placebo-Controlled Monotherapy Phase II/III/IV Clinical Trials: 0+3[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	0	554	60.4	0.0
Placebo	0	299	33.3	0.0

Note that only Placebo-Controlled Monotherapy trials are included in this table. [a]All metabolic syndrome criteria emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt-years of exposure x 100

One Criterion Already Fulfilled Prior to Onset of the Clinical Trial and 2 Emerging During the Trial Period

Overall Metabolic Syndrome in Placebo-Controlled Monotherapy Phase II/III/IV Clinical Trials: 1+2[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	21	587	60.0	35.0
Placebo	1	289	31.7	3.2

Note that only Placebo-Controlled Monotherapy trials are included in this table. [a]One metabolic syndrome criterion was present prior to trial onset; two criteria emerged during the trial period. [b]Total number of Pts with one criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in PY-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total PY years of exposure x 100.

Two Criteria Already Fulfilled Prior to the Onset of the Clinical Trial and 1 Emerging During the Trial Period

Overall Metabolic Syndrome in Placebo-Controlled Monotherapy Phase II/III/IV Clinical Trials: 2+1[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	67	274	26.5	252.7
Placebo	11	130	14.0	78.7

Note that only Placebo-Controlled Monotherapy trials are included in this table. [a] Two metabolic syndrome criteria were present prior to trial onset; one criterion emerged during the trial period. [b] Total number of Pts with two criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c] Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d] Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100

Summary of Placebo-Controlled Trials

- Using modified criteria
  - No cases of a metabolic-like syndrome in Pts w/o pre-existing risk factors
  - Incidence density for metabolic syndrome-like conditions in quetiapine treated Pts w/ ≥1 criteria at baseline is generally ↑ than for placebo-treated Pts w/ similar baselines
    - Results may reflect ↑ wt, triglycerides + total cholesterol seen in some Pts w/quetiapine use + described in Seroquel Core Data Sheet

Risperidone-Controlled Trials

All Criteria Emerged During Treatment Phase of Study

Overall Metabolic Syndrome in Risperidone-Controlled Phase II/III/IV Clinical Trials: 0+3[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	0	822	182.5	0.0
Risperidone	0	426	81.5	0.0

Note that only Risperidone-Controlled trials are included in this table. [a]All metabolic syndrome criteria emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt-years of exposure x 100

One Criterion Already Fulfilled Prior to Onset of the Clinical Trial and 2 Emerging During the Trial Period

Overall Metabolic Syndrome in Risperidone-Controlled Phase II/III/IV Clinical Trials: 1+2[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	9	92	8.3	108.8
Risperidone	3	98	10.9	27.5

Note that only Risperidone-Controlled trials are included in this table. [a]One metabolic syndrome criterion was present prior to trial entry; two criteria emerged during the trial period. [b]Total number of Pts with one criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as Total number of Pts with event/total Pt years of exposure x 100

Two Criteria Already Fulfilled Prior to the Onset of the Clinical Trial and 1 Emerging During the Trial Period

Overall Metabolic Syndrome in Risperidone-Controlled Phase II/III/IV Clinical Trials: 2+1[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	21	82	9.2	229.4
Risperidone	26	92	9.1	284.8

Note that only Risperidone-Controlled trials are included in this table. [a]Two metabolic syndrome criteria were present prior to trial onset, one criterion emerged during the trial period. [b]Total number of Pts with two criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt-years of exposure x 100

Haloperidol-Controlled Trials

All Criteria Emerged During Treatment Phase of Study

Overall Metabolic Syndrome in Haloperidol-Controlled Phase II/III/IV Clinical Trials: 0+3[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	0	915	175.1	0.0
Haloperidol	0	684	122.1	0.0

Note that only Haloperidol-Controlled trials are included in this table. [a]All metabolic syndrome criteria emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt-years of exposure x 100

One Criterion Already Fulfilled Prior to Onset of the Clinical Trial and 2 Emerging During the Trial Period

Overall Metabolic Syndrome in Haloperidol-Controlled Phase II/III/IV Clinical Trials: 1+2[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	1	427	74.4	1.3
Haloperidol	1	284	46.7	2.1

Note that only Haloperidol-controlled trials are included in this table. [a]One metabolic syndrome criterion was present prior to trial onset; two criteria emerged during the trial period. [b]Total number of Pts with one criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100.

Two Criteria Already Fulfilled Prior to the Onset of the Clinical Trial and 1 Emerging During the Trial Period

Overall Metabolic Syndrome in Haloperidol-Controlled Phase II/III/IV Clinical Trials: 2+1[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	4	98	18.4	21.7
Haloperidol	1	49	9.2	10.8

Note that only Haloperidol Controlled trials are included in this table, [a]Two metabolic syndrome criteria were present prior to trial onset; one criterion emerged during the trial period, [b]Total number of Pts with two criteria fulfilled at baseline. Pts must have received at least one dose of trial medication, [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment, [d]Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100

Post-marketing Data

Search Strategy

- Clintrace searched for reports w/ following MedDRA PTs: Metabolic syndrome, Insulin resistance, Insulin resistance syndrome
- Additionally, individual searches for each of 5 components of metabolic syndrome
  - From output, SAS program identified Pts w/ ≥3 components
    - Each report read to identify Pts who met modified criteria for metabolic syndrome
    - Pts w/ ≥3 pre-existing components excluded

Search Results

- No reports w/ PTs of Metabolic syndrome, Insulin resistance, Insulin resistance syndrome
- 15 reports (10 serious/5 non-serious) described Pts w/ ≥3 components of modified metabolic syndrome criteria
  - At least 1 component had to develop during treatment w/ Seroquel

Global Spontaneous Reports
(through 18 May 2004)

Number of reports describing metabolic syndrome	15
Estimated population exposure	7,160,000
Reporting rate	0.0002% Very rare

Overview of All Metabolic Syndrome Reports (modified criteria)

Possible Confounders					
Meds	Risk factors (≥ 1)	Meds + risk factors	Scant clinical detail	Other	Total
1	0	7	2	5	15

Description of 5 Reports Classified as "Other"

- Developed all criteria while on Seroquel
  - 1: ↑TRIG (2.8 nmol/L [248 mg/dL]), ↓HDL (0.86 mmol/L [33.2 mg/dL]), ↑FBS (7.2 mmol/L [131 mg/dL]) by Day 777
    - 31 yr female Pt; no baseline lab data provided
    - Developed hypothyroidism 1 yr prior to events (while on Seroquel); may have contributed to metabolic instability
    - Seroquel contd, Pt not yet rec'd
  - 1: ↑TRIG (2920 mg/dL), ↓HDL (34 mg/dL), DM (FBS=269 mg/dL) by Day 838
    - 44 yr male Pt w/ baseline BG=91 (no other baseline lab data provided)
    - Reporter stated DM was d/t "Pt's predisposition". No med hx or risk factors reported
    - Seroquel d/c'd; Pt outcome unk

Description of 5 Reports Classified as "Other" (contd)

- Developed 2 criteria while on Seroquel
  - 1: ↑wt (50 lb) + DM (no lab data provided) (pre-existing HTN)
    - 47 yr female Pt; No baseline lab data provided
    - Seroquel d/c'd; Pt recovering from DM but not wt gain (no lab data provided)
    - Reporter stated "Seroquel caused wt gain which brought out DM in this Pt likely predisposed for this condition"
    - No info provided re: risk factors for DM

Description of 5 Reports Classified as "Other" (contd)

- Developed 1 criteria while on Seroquel
  - 1: ↑BG (203 mg/dL) (pre-existing obesity + hyperlipidemia)
    - 35 yr male Pt; No baseline lab data provided
    - One Seroquel 1200 mg + paroxetine 20 mg. Pt escaped from hospital. No meds x 12 days. Returned to hospital + given 1 dose Seroquel 1200 mg + paroxetine 20 mg. Pt became unresponsive. ↑BG. Unk what tx given @ time of event. ↑BG may have been r/t IV infusion.
    - Pt rec'd (no lab data provided); Seroquel contd
  - 1: ↑BG (pre-existing HTN, ↑lipids)
    - 60 yr male Pt; No baseline lab data provided; reporter stated baseline BG WNL
    - On Seroquel x 3 mos + developed ↑BG (500), ↑HbA1c=15%
    - Seroquel d/c'd + reporter stated BG "almost returned to normal (no lab data provided).

Summary of Post-marketing Data

- Limitations
  - Concomitant medications + other med conditions
  - Unclear temporal sequence of exposure + outcome
  - Limited info
  - No waist circumferences
  - Unclear if lab data was fasting in some reports
- No reports of Metabolic Syndrome per se
- Very rare reports of constellation of criteria
- Causal relationship not established

Literature

- 12-week, prospective, open-label study; antipsychotic naïve Pts (5-18 years) (Correll et al 2004)
  - Seroquel n=9, risperidone=37, olanzapine=25
  - FBS, insulin, + insulin resistance ↑significantly but 2nd generation antipsychotics didn't differ among themselves
  - Effect on relative HOMA-IR smallest for Seroquel (24.5%) compared to risperidone (49.5%) + olanzapine (62.7%)
  - Limitations
    - Available as abstract only w/ limited info
    - No placebo control group
    - No info re: baseline risk factors for insulin resistance
    - Small # of Pts in Seroquel group

Summary

- Definition of syndrome is evolving
  - Constellation of CDS listed symptoms
  - May not add to our current understanding
- Data difficult to interpret
  - Random, not fasted
  - No waist circumference
- Data collection in current and future studies
  - Fasted glucose, triglycerides, cholesterol
  - Waist circumference in long-term studies

Back Up Slides

Other Lipid Data Placebo Controlled Studies

Last value per Patient: Changes in Total Cholesterol in Placebo-controlled Monotherapy Phase II/III/IV Trials

Treatment group	Mean baseline (mg/dL)	Mean change from baseline (mg/dL)
Quetiapine	195.75	11.51
Placebo	197.61	0.47

Last value per Patient: Changes in LDL Cholesterol in Placebo-controlled Monotherapy Phase II/III/IV Trials

Treatment group	Mean baseline (mg/dL)	Mean change from baseline (mg/dL)
Quetiapine	116.48	4.33
Placebo	116.02	1.06

Last value per Patient: Changes in HDL Cholesterol in Placebo-controlled Monotherapy Phase II/III/IV Trials

Treatment group	Mean baseline (mg/dL)	Mean change from baseline (mg/dL)
Quetiapine	48.87	-0.30
Placebo	48.29	0.01

Last value per Patient: Changes in non-HDL Cholesterol in Placebo-controlled Monotherapy Phase II/III/IV Trials

Treatment group	Mean baseline (mg/dL)	Mean change from baseline (mg/dL)
Quetiapine	146.70	9.44
Placebo	148.85	0.94

Results

All Trials

All Criteria Emerged During Treatment Phase of Study

Overall Metabolic Syndrome in All Clinical Trials: 0+3[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	0	4694	1906.8	0.0
Placebo	0	379	38.2	0.0
Chlorpromazine	0	204	27.7	0.0
Haloperidol	0	684	122.1	0.0
Lithium	0	56	10.3	0.0
Mosapramine	0	74	8.6	0.0
Risperidone	0	426	81.5	0.0

[a]All metabolic syndrome criteria emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100

One Criterion Already Fulfilled Prior to Onset of the Clinical Trial and 2 Emerging During the Trial Period

Overall Metabolic Syndrome in All Clinical Trials: 1+2[a]				
Treatment	Pts w/ Event	Total Pts[b]	Exposure[c]	Incidence density[d]
Quetiapine	36	2391	855.7	4.2
Placebo	1	358	36.3	2.8
Chlorpromazine	0	113	15.6	0.0
Haloperidol	1	284	46.7	2.1
Lithium	0	36	6.3	0.0
Mosapramine	0	15	1.7	0.0
Risperidone	3	98	10.9	27.5

[a]One metabolic syndrome criterion was present prior to trial onset; 2 criteria emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100

Two Criteria Already Fulfilled Prior to the Onset of the Clinical Trial and 1 Emerging During the Trial Period

Overall Metabolic Syndrome in All Clinical Trials: 2+1[a]				
Treatment	**Pts w/ Event**	**Total Pts[b]**	**Exposure[c]**	**Incidence density[d]**
Quetiapine	105	802	240.4	43.7
Placebo	16	175	16.3	98.2
Chlorpromazine	1	29	4.0	25.2
Haloperidol	1	49	9.2	10.8
Lithium	0	6	1.1	0.0
Mosapramine	0	1	0.2	0.0
Risperidone	26	92	9.1	284.8

[a]2 metabolic syndrome criteria were present prior to trial onset; 1 criterion emerged during the trial period. [b]Total number of Pts with no criteria fulfilled at baseline. Pts must have received at least one dose of trial medication. [c]Exposure in Pt-years. Exposure is censored at first event. For Pts who had no event, exposure is the total duration of the treatment. [d]Incidence density calculated as total number of Pts with event/total Pt years of exposure x 100

Post-marketing Data

All Criteria Emerged During Treatment w/ Seroquel

- 3 patients developed all criteria on Seroquel
  - 1: Developed obesity, DM + hyperlipidemia by Day 490
    - Pt also on risperidone
  - 1: Developed ↑triglycerides, ↓HDL + DM by Day 838
    - Reporter stated "DM d/t Pt's pre-disposition"
  - 1: Developed ↑triglycerides, ↓HDL + ↑FBS by Day 777
    - Pt developed hypothyroidism 1 yr prior, Seroquel contd, Pt outcome ?

One Criterion Fulfilled Prior to Treatment w/ Seroquel and 2 Emerged During Treatment

- 6 patients w/ 1 pre-existing criterion + developed 2 on Seroquel
  - 3: w/ pre-existing obesity
    - 2: Developed HTN + ↑BG
    - 1: Developed ↑BG + ↑triglycerides
  - 3: w/ pre-existing HTN
    - 2: Developed DM/↑BG + obesity (50 lb wt gain)

Two Criteria Fulfilled Prior to Treatment w/ Seroquel and 1 Emerging During Treatment

- 6 patients w/ 2 pre-existing criteria + developed 1 on Seroquel
  - 3: w/ pre-existing obesity + hyperlipidemia
    - 1: Developed ↑BG
    - 1: Developed sugar in urine (3+)
    - 1: Developed HTN
  - 2: w/ pre-existing HTN + hyperlipidemia
    - 2: Developed ↑BG
  - 1: w/ pre-existing DM + HTN
    - 1: Developed hyperlipidemia