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Switching and Selecting Atypical Antipsychotic Drugs: Quetiapine

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Switching and selecting atypical antipsychotic drugs: Quetiapine

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Disclosure
Research, education & travel grant. Speakers group & advisory panels

- Janssen Cilag
- Janssen Ortho
- AstraZeneca Canada & UK
- Pfizer
- Roche Pharmaceuticals
- Nicolus Pharmaceuticals
- SUN Pharma
- Prempharma
Atypical antipsychotics: Clinical experience:

1. Factors warranting switch
2. My experience with XR
3. Are there differences amongst atypical
4. How to maximize clinical advantage
Despite lack of clarity in selection, 90% times each clinician gets it right.
Quetiapine Optimization: Case report

- Mrs B, 48 Years, Married
- Chronic schizophrenia with Chronic unremitting alcoholism, and chronic suicidality,
- H/O 4 major attempt,
- F/U regular, > 20 Admissions,
- on Quetiapine 525 IR + Olanzapine 20 mg.
- Readmitted, APE,
- Day 1 – QUT.IR, 100 mg QHS, syncope attack, two episodes,
- Ref. General hospital, Cause-Unknown,
- Re-evaluated: opinion ‘she has this problem since the age of 20,
- no diagnosis was made,
- Reassessed for diagnosis and care plan
Schizophrenia with alcoholism & Suicidality Case Report..Conti.

- Target: psychosis, suicide, alcoholism, Involuntary admission
- Discontinued passes, Family Meeting.
- Discontinued olanzapine,
- Plan: Increase quetiapine to 800 mg/day gradually & monitor
- Once escalation was complete, we switch to XR 800 mg Q Super
- Increased 5 mg a day, i.e. 25 mg every 5th day,
- Vitals monitored, psychosocial therapy continued.
- 800 mg in 10 weeks, No further syncope
- Mental state: Remarkable change, ‘Never felt like this’, No suicidality.
- Discharged under care of her outpatient psychiatrist
Why do we need to switch?

- Lack of efficacy
- Acute relapse
- Side effects
  - Intolerability
  - Burden
- Failed
  - optimization
  - adjunct treatment
  - ‘Patients-Choice’
Fundamental Process in switching APD

1. Establish a causal attribution
2. Understand course of side effect
3. Understand potential risk of individual patient
4. Be aware of the SE profile of other possible antipsychotics
5. Calculate SE risk of switch
6. Calculate efficacy risk of switching
Symptoms warranting a switch

- Persistent Positive symptoms
- Persistent Negative symptoms
- Persistent Cognitive symptoms
- Persistent affective symptoms
- Persistent poor Social Functioning

Weiden PJ, 2006, Psychopharm
Switching strategies for antipsychotic medication

Figure 4. Antipsychotic Switching Strategies

- **Abrupt Switch**
  - Immediate Discontinuation of Previous Antipsychotic
  - Immediate Start of New Antipsychotic

- **Taper Switch**
  - Immediate Start of New Antipsychotic
  - Gradual Discontinuation of Current Antipsychotic

- **Cross-Taper Switch**
  - Taper Current Antipsychotic
  - Gradually Start New Antipsychotic

- **Plateau Cross-Taper Switch**
  - At Plateau, Treat With Both Current and New Antipsychotic
  - Gradual Start of New Antipsychotic
  - Taper Current Antipsychotic

Clinical Consequences of switching

- **NOT so Good experience**
  - Withdrawal symptoms
  - Secondary symptoms (anxiety-insomnia)
  - Persisting side effects of prior APD
  - New psychiatric symptoms
  - Side effects of newer APD
  - Break-through Psychosis
  - Fall, giddiness, fainting

- **Emergency situation**
  - (Seizure, low blood count, Cardiac event, Steven-Johnston)

- **Good experience**
Figure 1. Time Course of Side Effects: Withdrawal, Early, and Persistent

- "Withdrawal" Side Effects
- "Early" Side Effects
- "Persistent" Side Effects

Previous Antipsychotic

New Antipsychotic

Time: Days, Weeks, Months
Pharmacology of Atypical Antipsychotics

*In vitro* findings may not correlate with clinical results.
The mechanism of action of second-generation neuroleptics (risperidone)
How long to wait for response

- An average of 3 weeks
- Sometimes as long as 3 months (clozapine)
- Variability in medical decisions.
- Early responders
- Late responders
- >50% reduction in PANSS over 12 weeks
- Drug trials 2, 4, 12 weeks
- Sustained response Vs lost response in long-term
• Considerable divergence of expert opinion
  • One survey of experts indicated that a period of 2.6 to 5.5 weeks was required.
  • Lack of minimal response after 1 or 2 weeks is a powerful Predictor of subsequent poor response

Reviews and Overviews

Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus

Nancy C. Andreasen, M.D., Ph.D.

New advances in the understanding of schizophrenia etiology, course, and treatment have increased interest on the need for group reviewed available definitions and assessment instruments to provide a conceptual framework for psychiatric fung...
Criteria's for Response

Poor Social functioning also a criteria for non-response \(^1\)

Predicting response: early response (2 wks) correlates to long-term efficacy.

Partial Adherence in Schizophrenia Begins Early and Prevalence Increases Over Time

Medication Gaps Increase Risk of Hospitalization in “Adherent” Cohorts

Dosing Frequency & Compliance

Adapted from Kastrissios & Blaschke. *Ann Review Pharmacology & Toxicology, 1997*
Switch & persistent symptoms

- Positive symptoms
  - HALD, QUET, OLANZ
- Negative symptoms
  - RISP, QUET, CLOZ, ARIP, PALP
- Cognitive
  - RISP, ZPS, CLOZ, ARIP
- Suicide
  - Clozapine
- Violence
  - Clozapine
- Substance abuse
  - Clozapine
- Poor social functioning
  - Clozapine
Switch to Quetiapine

From Olanzapine
- Reduced
  - Akathesia
  - Dyslipidemia
  - EPS
  - Prolactin
  - Weight

From Ziprasidone
- Reduced
  - Akathesia
  - EPS
  - insomnia
Experience with Quetiapine XR
Clinical details

- N = 40
- Minimum Duration: 6 Weeks
- Maximum duration: 12 months
- Continued Treatment: 30
- Currently under follow up: 25
- Discontinuation: 10
  - Side effect: 3
  - Loss of effect: 3
  - Intolerability: 4

- Efficacy: excellent
- Good outcome: 18/25 (72%)
- Inadequate response: 2/25 (12%)
- Good Tolerability: 32/40 (82%)
- Significant side effects: 5/40 (12.5%)
  - Increased sedation
  - Dryness of mouth
  - Rebound Insomnia
  - Somnolence
# Dosing (N=33)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>04</td>
</tr>
<tr>
<td>200</td>
<td>02</td>
</tr>
<tr>
<td>300</td>
<td>07</td>
</tr>
<tr>
<td>500</td>
<td>05</td>
</tr>
<tr>
<td>600</td>
<td>03</td>
</tr>
<tr>
<td>800</td>
<td>06</td>
</tr>
<tr>
<td>1000</td>
<td>01</td>
</tr>
<tr>
<td>1200</td>
<td>03</td>
</tr>
</tbody>
</table>

**Diagnostic category**

- Acute psychosis
- Schizophrenia (paranoid, Undifferentiated)
- Bipolar Affective Disorder (Manic episode)
- Bipolar depression
- Bipolar spectrum disorder
- Schizoaffective disorder
- Anxiety-insomnia
Symptom-syndrome response

Good: Behavior, Mood & affect, Sleep, Positive symptoms, Disorganization, Negative symptoms, Affective symptom, Depressed mood, Manic and hypo manic, Irritability, Insomnia, Suicidality, Concentration

- Limited efficacy: Thought disorders, Delusions, First rank symptoms, Cognitive function, Residual feature, motivation

Merits
- Rapid titration
- Once a day dosing
- Easy administration
- Increased compliance
- Day time alertness
- Rapid response for behavior and mood symptoms
- Effect of suicidality
Why XR?

- Historically:
  - From Rapid Neuroleptization-to- Rapid Tranquilization in a range of indications
  - Chlorpromazine IM/PO
  - High dose fast escalation of Haloperidol IM/IV
  - Rapid escalation of Lithium PO
  - Rapid and fast valproic acid IM/PO
  - Rapid Benzodiazepine IM/IV/PO
  - Bolus Opiates IM

- No clinical benefit
- High risk of side effect
- CNS depression
- Acute cardiac event
- Delirium
- Movement disorder
- NMS
Comprehensive therapy
XR Quetiapine
1. Only oral
2. Less life-threatening side effects
3. No seizure or cardiac event
4. 800 mg day 2
Is switch clinically effective?
Switch studies

1. Switch to XR: 68% **achieved clinical** benefit

2. Rosenheck RA et al, 2009, switch from Olanzapine to quetiapine: Vs. Continued on Olanzapine: **No added benefit** but High weight gain in Olanzapine

3. Debert W, et al 2008, Olanzapine Vs Switch to Quetiapine: **No difference in Relapse Rate** at 200 days

4. CATIE Switcher’s Vs Stayer’s: **No difference in outcome** at 18 Months within 5 groups, High weight gain for Olanzapine, 2009

5. Switch to Quetiapine Vs Paliperidone: **No difference in Long-term, extension phase**, 2009
Are there differences amongst atypical

1. No differences amongst SGA except Clozapine

2. Non-significant differences on axis & domains of schizophrenia

3. Choice within SGA remains mainly guided by side effect profile
The new ‘statistics’
Meta analysis

Are there differences which are not seen?
OR
Are the differences not there, & we are trying to ‘fish’?

All Atypicalss are SDA
Differences are expected on efficacy & side effect

- Positive
- Negative
- Affective
- Cognitive
- Social functioning New skills
- QOL
- ADL

Domains

Outcome

Degree of improvement

Symptoms & Function

Various domains

Skills

Time line, earliest
Differences are expected on efficacy & side effect.
Parameters of monitoring

- Absence of side effects
- Symptom Remission
- Social Recovery
CATIE – Phase 3, Symptom response
No difference across all groups, However individual variations

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ARIP</th>
<th>CLOZ</th>
<th>COMB</th>
<th>FLU-D</th>
<th>OLAN</th>
<th>PERP</th>
<th>QUET</th>
<th>RISP</th>
<th>ZIPR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS – 3 months</td>
<td>0.506</td>
<td>0.002</td>
<td>0.002</td>
<td>0.005</td>
<td>0.002</td>
<td>0.084</td>
<td>0.013</td>
<td>0.044</td>
<td>0.045</td>
<td>0.832 ✗</td>
</tr>
<tr>
<td>PANSS -6</td>
<td>&lt;0.00 1 ✔✔</td>
<td>0.006 1 ✔</td>
<td>&lt;0.00 1 ✔</td>
<td>0.43</td>
<td>0.003</td>
<td>0.018</td>
<td>0.100</td>
<td>0.009</td>
<td>0.371</td>
<td>0.515 ✗</td>
</tr>
</tbody>
</table>

- **Outcome of switch is dependent upon**
  - Medication switched to, Medication switched from.

Stroup T et al, Schizophrenia Research 107 (2009) 1-12
Cognition, atypical antipsyhotics & Schizophrenia

- Commonest manifestation
- Deficit leads to functional & social decline
- Improvement mediates social recovery
- Number of Studies attempted, CATIE, CAFÉ, biases?
- General impression – SGA – beneficial
- Benefit is small in effect size
- Better than FGA
- No difference across different molecules
“our hope from atypical antipsychotics for cognitive enhancement is lost… we may have to look somewhere else for this effect..”

M. Green, Editorial in AJP, 2007
There is a moderate procognitive effect for early psychosis, poorly correlated with symptoms & all SGA have similar results, at 2, 6, 18 months

– June 2009, AJP
FGA & SGA: Broad spectrum Case report. AB 52 years, Clozapine

- Blood count improved in 2 weeks. Antipsychotics- free state for 3 weeks

- **Re-challenging clozapine??**

- Started Pimozide 4 mg, increased to 12 mg per day,

- Discharged after 4 weeks, Regular follow up for 18 months,

- Good remission, ADL, good QOL, No major concerns,
Are there differences in side effect profile

EPS across AAPD at 6 month outcome

Stroup T et al, Schizophrenia Research 107 (2009) 1-12
TD: High in Geriatric Population with SGA

Akathesia
- High dose
- High potency SGA
- Combination of SGA
- SGA with other psychotropics
- Bipolar depression
- Palliative care setting
- Comorbid SUD

<table>
<thead>
<tr>
<th>EPSE, Akathesia Prevalence SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>Quetiapine V Placebo</td>
</tr>
<tr>
<td>Aripiprazole</td>
</tr>
</tbody>
</table>
## Antipsychotic Drugs and Obesity and Diabetes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole* (Abilify)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone* (Geodon)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = increase effect; - = no effect; D = discrepant, results. *Newer drugs with limited long-term data, 1.

ADA/APA Consensus Conference
Early Weight gain persists
Short (N=1717, 4-12 wks) & Long-term (N=1649, 52 wks),

Bruce, P et al, Weight effects associated with antipsychotics: A comparative database analysis, Schizophrenia research 110 (2009) 103-110
Diabetes and Antipsychotics

- **Schizophrenia & Diabetes Mellitus:**
  - Many studies shown ↑ risk in schizophrenia:
    - IGT, Insulin resistance
    - Type 2 Diabetes mellitus
      - 10% Schizophrenia > 6–8% general population
  - Studies over several decades, predating both typical & atypical neuroleptics

- **RCT Data – Summary:**
  - Results:
    - 9% of all patients Rx with antipsychotics developed new DM
    - clozapine, olanzapine, haloperidol ↑ FBS
    - clozapine, olanzapine ↑ Fasting Cholesterol
    - No correlation between weight gain and FBS in this study
Do Atypical antipsychotics cause DM?

- **Basic Science**
  - Normal insulin secretion, ↓ insulin sensitivity with ↑ weight
- 1 flawed RCT, Cohort Studies, Case Reports/Studies
  - 9% of patients Rx with any antipsyhotic developed new DM
  - clozapine, olanzapine, haloperidol ↑ FBS
  - clozapine, olanzapine ↑ Fasting Cholesterol
  - Less DM risk with Risperidone?

- **Can DM be predicted or prevented?**
  - Risk factors for T2DM
    - Obese, older, ethnic groups, FHx DM, etc.
  - Risk factors for DKA
    - Thin, younger, female?
Metabolic profiles of SGA in early psychosis: Findings from the CAFE study. 2009

## Cardio-metabolic Disease Risk Factor

<table>
<thead>
<tr>
<th>Modifiable risk factor</th>
<th>Estimated Prevalence of risk factor (%)</th>
<th>Relative Risk</th>
<th>Estimated Prevalence of risk factor (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>45-55</td>
<td>1.5-2 x</td>
<td>26</td>
</tr>
<tr>
<td>Smoking</td>
<td>50-80</td>
<td>2-3 x</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10-14</td>
<td>2 x</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;18</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Up to 5 x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bipolar Disorder</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
Public Health measures for metabolic side effects

- CVD leading cause of death in SMI: US public sector data.
- 8.3X (5x Female) increase in death 1991-1995, CVD mortality in ‘first hospitalization’.
- Varying effect on FGA & SGA
- Adiposity dependent effect
- Insulin resistance.
- Risk of dyslipidemia, obesity, weight gain, raised blood sugar

Under detected metabolic Side effects: UK sample

- Diabetes: 1 known, 1 missed
- Hypertension: 4 known, 1 missed
- Dyslipidemia: 7 known, 1 missed
Sedation – related Discontinuation

- It is every day -affair

Weiden PJ. J. Clin Psychiatry 2007;68 [suppl 1]:12-19
Prolactin and antipsychotics

Stroup T et al, Schizophrenia Research 107 (2009) 1-12
Factors compromising outcome and efficacy in treatment of schizophrenia

- **Axis I** – Psychiatric co morbidity (>20%),
  - SUD (>50%)
- **Axis II** – Learning disability, (5%)
  - Personality Disorder (10-15%)
- **Axis III** – Physical comorbidity (30-40%),
  - Treatment emergent symptoms (>50%)
- **Axis IV** – Rarely absent
- **Axis V** - Functioning – consider as outcome criteria
Sketch model of barriers in Care in Schizophrenia

- Patient & their Personalities
- Mental illness & illness-related disability-stress
- Treatment – related factors
- Family related factors
- Organizational & mental health system barriers
Need for Change in Strategy

Maximizing Outcome: Strategies

- Care plan
- Continuity
- Rapport
- Multi-factorial
- Goals
- Achievable objectives
- Assessment
- Follow up

1. Treatment of side effects
2. Use of
   1. ADJUNCT
   2. COMBINATION APD
   3. Potentiation of APD
   4. For added efficacy
3. Treatment of psychiatric comorbidities
   1. Anxiety – phobia, dysthymia, OCD
Clinical options: need for innovation
Varying level of evidence

- Typical antipsychotics
- Atypical antipsychotics
- SGA + BZ & ADD + & Mood stabilizers
- Combination of FGA + SGA
- Combination of 2 SGA
- Clozapine
- Clozapine + SGA
- Clozapine + FGA + SGA
- ECT
- Clozapine + ECT
- TMS
Psychosocial therapies are part of comprehensive management

- Various Psychosocial therapies
- Family therapy
- CBT in Psychosis
- Cognitive remediation
Experiments

Add-on Risperidone & Clozapine to haloperidol non-responders. Randomized Open level. N=90

Schizophrenia has substantially high risk of comorbidity (Vs. population): OR: 4.6

Nonadherence in schizophrenia and comorbid substance abuse. ¹ High rates of psychiatric and other medical conditions. More than 75% ²

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¹Hunt GE et al, Schizphr.Res, 2002; 64: 253-264,
Cannabis

Explanation for close relationship between Psychosis & cannabis is still unclear.
High suicide in recently discharged patients

N=238, Death by suicide within 3 month of discharge

- History of self-harm
- Symptoms at last contact
- Initiated own discharge
- Missed last appointment
- Detained for compulsory treatment: low risk

Died within one month: 43%
Died before first follow-up: 47%
Final message

- It should be opted only if clinical conditions are compelling.
- Whenever switch, due consideration should be given to all denominators of its outcome.
- Not to compromise efficacy.
- Not to persist with side effects.