CATIE 1 & 2: the Dilemma of Effectiveness in the Treatment of People with Schizophrenia

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Philip Candilis, MD
Henry Levine, MD

For the AAPL Committee on Psychopharmacology and the Law
Introduction

Graham Glancy, MB
ISSUES

Clinical
- objective
- subjective

Formulary Changes
Standard of Care
Off-label Prescribing
Informed and Reinformed Consent
CATIE – Strengths & Limitations

Introduction (Graham Glancy)
A Critical View of the Results (Henry Levine)
Implications
  - Standard of Care
  - Formulary (Neil Kaye)
Ethical Issues
  - Informed Consent/Reinformed Consent (Philip Candilis)
Questions & Answers
  - Participants

AAPL Psychopharmacology Committee
CATIE – Strengths & Limitations

Clinical Antipsychotic Trials Intervention Effectiveness

CATIE - Methodology

1493 patients (18-65)
Diagnosed schizophrenia
57 sites
Mixed settings
18 months
Double blind

“….significant differences in ..effectiveness”
Olanzapine [7.5 mg – 30 mg per day]
Risperidone [1.5 mg – 6.0 mg per day]
Quetiapine [200 mg – 800 mg per day]
Ziprasidone [40 mg – 160 mg per day]
Perphenazine [8 mg – 32 mg per day]
GOALS

Efficacy: Symptom reduction
Tolerability: Side-effects
Safety
Acceptability
Effectiveness
231 patients with TD were not randomized to perphenazine
Ziprasidone was added after 40% of enrollment was completed
Outcome Measure

Primary: Discontinuation of treatment for any cause - 18 month study

Secondary: Reason for stopping: inefficacy, intolerability (side effects), PANSS, CGI

Tertiary: SAE’s, neurologic SE’s, weight change, ECG changes, labs
Results

Henry Levine, MD
One site's data (n=33) was discarded due to data integrity issues.

74% (1061/1432) discontinued in <18 months.

The time to discontinuation (d/c) for any reason was longer in the Olz group but not significantly longer than for the Zip or Per groups.

The time to discontinuation for lack of efficacy was longer in the Olz group but not significantly longer than for the Zip group.

The time to discontinuation for side effects was not different among the groups.

The time to discontinuation for patient’s decision was not different among the groups.
PANNS and CGI scores showed no significant differences among groups.

Specific statistically significant differences in SE’s causing discontinuation were seen:

- Ris had the lowest dropout for SE’s (10%)
- Olz had the highest dropout for SE’s (18%)
- More pts. d/c Olz due to weight gain or metabolic side effects (9% vs. 1-4%)
- More pts. d/c Per due to EPS (8% vs. 2-4%)
Results 3

Olz and Que caused the least insomnia
Zip caused the most insomnia
Que had the highest rate of anticholinergic side effects
No differences in EPS, akathesia or movement disorders as reflected in rating scale measures
Olz caused more weight gain (~ 2 pounds/month)
30% Olz group gained 7% or more of their baseline weight vs. 7-16% in other groups
Olz & Que have effects consistent with the development of metabolic syndrome: increased HgA1c, cholesterol, TGA’s
Only Zip patients showed improvement in every metabolic parameter: HgA1c, cholesterol, TGA’s

Only Ris patients showed a substantial increase in prolactin levels

No differences in QTc changes (Que longest)

No differences in incidence of new cataracts
CATIE 1: Mean Modal Dosing

Olz 20.1 mg
Per 20.8 mg
Que 543.4 mg
Ris 3.9 mg
Zip 112.8 mg
Patients in the olanzapine group gained more weight than any other group.

More patients in the olanzapine group gained 7% or more of their baseline weight (30% vs. 7-16%).

Olanzapine patients had more metabolic changes than the other groups.

Ziprasidone showed no QTc issues.
444 who stopped Phase 1 due to tolerability (42%)
Double-blind, randomized to Olz, Que, Ris v. Zip
Measured effectiveness as in CATIE 1
74% did not complete Phase 2
Effectiveness: Ris & Olz were more effective than Que or Zip as measured by d/c for any reason
Efficacy: Total PANSS: (Olz=Ris)>Zip & Que
PANSS-Positive Symptoms: OLZ>Zip, Que & Ris; Ris>Zip
PANSS-Negative Symptoms: No differences
CGI-No differences
CATIE 2T

Mean modal dosing—essentially same as CATIE 1
Side effect issues—essentially same as CATIE 1
Sedation: Olz, Que
Sexual side effects: Ris (29%)
Gynecomastia/gallactorrhea: Ris (5%)-raised prolactin
Orthostasis: Que (13%)
EPS—no differences on rating scales
Weight gain: Olz (1.3 pounds/month)
Weight loss: Zip (1.7 pounds/month)—42% who gained over 7% in Phase 1 lost over 7%; improved lipids as in Phase 1
99 who stopped Phase 1 due to inefficacy (9% of original N)

Sicker patients overall, male, more episodes, higher PANSS

Clz (open label n=49) or Olz, Que, Ris (blind-n=50)

Measured effectiveness as in CATIE 1

69% did not complete Phase 2 (5 month study)

Patients got sicker during this phase (PANSS increased 7)

Effectiveness: Clz was more effective than Que or Ris as measured by d/c for any reason

Efficacy: Total PANSS: Clz >Olz, Que, Ris

PANSS-Positive Symptoms: (Clz=O lz)> Que or Ris

CGI-Clz >O lz, Que, Ris
Mean Modal Dosing-CATIE 2E

Clz-332.1
Olz-23.4
Que-642.9
Ris-4.8
AA’s: first attempt-similar in efficacy, different SE’s
Olz on second attempt is more effective; dosing is still an issue in Phase 2 of CATIE
Clz is the clear winner for effectiveness & efficacy and is underused
Que is the most anticholinergic
Ris raises prolactin
Zip is the cleanest metabolically and lowers weight
Standard of Care

Neil S. Kaye, MD, DFAPA
1. Schizophrenia and Bipolar Disorder are two of the most difficult, complex, and expensive chronic diseases faced by physicians and society.

2. While drug costs are an issue, they are a very small part of a much larger pie.

3. Physicians need, and patients deserve every chance to get well. Limiting options under these circumstances is foolish, unethical and prevents doctors from practicing to the standard of care, risking malpractice and further reducing access to treatment by those who need it most, but often have the weakest voices.

4. Claiming that all antipsychotics are the same and thus interchangeable is not supported by the relevant scientific evidence. To make this claim would be as silly as saying all antibiotics are the same and thus only PCN should be used/covered.

Kaye, N.: Testimony to Delaware Medicaid Preferred Drug List Committee Hearing, 8/10/06
5. Looking at the pie charts I have prepared for you (now published in Advanced Studies in Medicine, a JHH peer reviewed journal with CME credits available in hard copy or on-line), you will see the stark differences in key receptor binding for these drugs. I have tried to make this simple. In fact, we have identified and cloned 52 brain receptors and identified where and to what extent each of these drugs binds. Needless to say, they are very different from one another.

6. Psychiatry is not a black box, the way it may be portrayed in Hollywood. Biological psychiatrists use these key binding differences to try to best tailor treatment to any given patient. Doctors need to know about these specificities in order to get better outcomes, and to more safely and effectively combine medications, whether that be 2 psychiatric medications or when adding a psychiatric medication to a non-psychiatric medication. Failure to take this into account jeopardizes patients and contributes to higher overall healthcare costs.

7. Similarly, these drugs have different half-lives, protein binding properties and means of excretion/elimination from the body. It is imperative for doctors to always treat the individual patient, but taking into account what the evidence based medicine says.

8. The evidence based medicine says these are not interchangeable medications for many patients. Physicians and patients need access to all of them.

Kaye, N.: Testimony to Delaware Medicaid Preferred Drug List Committee Hearing, 8/10/06
53 receptors
## Receptor binding affinities of atypical antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Ziprasidone</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Clozapine</th>
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<tbody>
<tr>
<td>$D_2$</td>
<td>3.1</td>
<td>2.2</td>
<td>20</td>
<td>180</td>
<td>130</td>
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<tr>
<td>5-HT$_{2A}$</td>
<td>0.39</td>
<td>0.29</td>
<td>3.3</td>
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<td>5-HT$_{2C}$</td>
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<td>5-HT$_{1A}$</td>
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<td>2100</td>
<td>230</td>
<td>140</td>
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<tr>
<td>5-HT$_{1D}$*</td>
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<td>170</td>
<td>530</td>
<td>&gt;5100</td>
<td>1700</td>
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<tr>
<td>$\alpha_1$-adrenergic</td>
<td>13</td>
<td>1.4</td>
<td>54</td>
<td>15</td>
<td>4.0</td>
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<td>M$_1$-muscarinic</td>
<td>5100</td>
<td>2800</td>
<td>4.7</td>
<td>100</td>
<td>1.8</td>
</tr>
<tr>
<td>H$_1$-histaminergic</td>
<td>47</td>
<td>19</td>
<td>2.8</td>
<td>8.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

$K_i < 1 \text{ nM} — \text{very high affinity;}$  
$1-10 \text{ nM} — \text{high;}$  
$11-100 \text{ nM} — \text{moderate;}$  
$101-1000 \text{ nM} — \text{low;}$  
$>1000 \text{ nM} — \text{negligible.}$

* Bovine binding affinity; † rat synaptosomes; all other affinities human.

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Different Antipsychotic Drugs Act Differently on Brain Receptors

- **Olanzapine**
- **Clozapine**
- **Quetiapine**
- **Risperidone**
- **Ziprasidone**
- **Haloperidol**
- **Aripiprazole**
Standard of Care

Neil S. Kaye, MD, DFAPA
Standard of Care

One of the 4 D’s of Malpractice
Similarly trained physician
Similar circumstances
National vs. local standards
How do we determine the Standard?
Treatment guidelines-APA and others
Algorhythms-TIMA/TMAP and others
Consensus Statements-ADA/APA and others
Physician surveys
Issues in Prescribing

Age
Diagnosis
Dose
Duration
Monitoring
FDA/PDR vs Standard of Care
High Dose (Off Label) of Quetiapine

About 30% over 750 mg/d

About 9.5% over 900 mg/d

About 3% over 1200 mg/d

Citrome, L. et. al.: NYS OMH Data, 2006
“The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product is approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved drug labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling.”
“The dose range approved by the FDA for quetiapine and ziprasidone may be below their optimal therapeutic doses…”

CATIE 1 & 2 Raises Questions/Issues

Should Clz be second step in algorithm?

Safety-how many months of additional treatment justify the risk of metabolic syndrome or diabetes?

Risk management-for doctor and patient

Informed Consent and documentation

Combination therapy?

Affective disorders?
“The possibility of a dose disparity across the administered drugs, often cited (even in these two articles themselves) as probably accounting for outcome differences, highlights the crudeness of our dosing measures.”

“Treatment discontinuation for any reason might be more a measure of physician hopefulness for a next medication than an estimate of failure of the current treatment.”

“There is no clear “winner” among the 2nd generation of antipsychotics, weighing effectiveness and efficacy against side effects, nor a clear “loser.” Only Clz is superior.

Legal: Standard of care

Pattern of practice
Reasonable, prudent physician/similarly situated/similar specialist
Professional organizations, academia
Journals, texts
Panels, task forces
Expert testimony
Statutory, common law standards
Standard of care (cont.)

Not best practices
But reasonable/average/prudent practices must be adequate to clinical need
Often provided by generalists
Expert testimony distinguishes optimum treatment standard from SOC
Acknowledge bias, uncertainty

Simon 2002, 2005
Informed Consent

Process, not event

Disclosure of information
  Nature of procedure/Rx
  Significant, material r/b (+probability)
  Alternatives (incl. No Rx)
  Nature/purposes/limits of consent

Understanding

Voluntariness

Time for reflection, questions, 2d opinion
Consent for Innovative/New Practices

Part of APA ethics annotations revision

Possible elements:
- Sound theoretical reasoning
- Best available research
- Mainstream clinical experience

Shared decision-making
- How Rx is being chosen
- Uncertainties of Rx

Innovation is not research
Ethics: Uncertainty

**Technical uncertainty**
- Incomplete knowledge

**Conceptual uncertainty**
- Untested hypotheses

**Personal uncertainty**
- Patient wishes
- Vagaries of morality

Beresford, 1991
Technical Uncertainty

Is the condition itself clearly defined?

Are indications for use of an intervention clearly defined?

Is there adequate data to predict the effects of treatment?
Conceptual Uncertainty

The problem of incommensurability

Applying abstract criteria to specific cases
Personal Uncertainty

In the pt-physician relationship
How are risks and benefits weighed?
What pt/MD values affect the decision?

In the weighing of ethical principles
Autonomy v. Beneficence
Capacity assessment: how much capacity is necessary?
CATIE: More Implications

Violence Risk (Swanson et al, 2006)
  PANSS Pos scale, response to AH/VH
  Suspiciousness, persecutory delusions
  Grandiosity, excitatory sx's
  Youth, conduct d/o, arrests

Research Decision-making (Stroup et al, 2006)
  PANSS Neg scale
  Working memory (encoding, manipulation)

Surrogate decision-makers (Stroup & Appelbaum, 2006)