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

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Neil S. Kaye, MD, DFAPA
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**

CATIE – Strengths & Limitations

Clinical

Antipsychotic

Trials

Intervention

Effectiveness

Lieberman et al, N Engl J Med 2005; 353:12:1209-1223

CATIE - Methodology

1493 patients (18-65)

Diagnosed schizophrenia

57 sites

Mixed settings

18 months

Double blind

“….significant differences in ..effectiveness”

DRUGS

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

Notes

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

Results-Discontinuation

- One sites data (n=33) was discarded due to data integrity issues
- 74% (1061/1432) discontinued in <18 months
- The time to 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 d/c for lack of efficacy was longer in the Olz group but not significantly longer than for the Zip group
- The time to d/c for side effects was not different among the groups
- The time to d/c for patient's decision was not different among the groups

Results 2

- 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

Results 4

- 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

CATIE Trial

- Patients in the olanzapine group gained more weight that 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

CATIE 2: Tolerability
AM J Psych 2006; 163:611-622

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

CATIE 2: Efficacy
AM J Psych 2006; 163:600-610

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=Olz)>, Que or Ris

CGI-Clz >Olz, Que, Ris

Mean Modal Dosing-CATIE 2E

Clz-332.1

Olz-23.4

Que-642.9

Ris-4.8

CATIE 1 & 2 Conclusions

- 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

Formulary Issues (1)

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

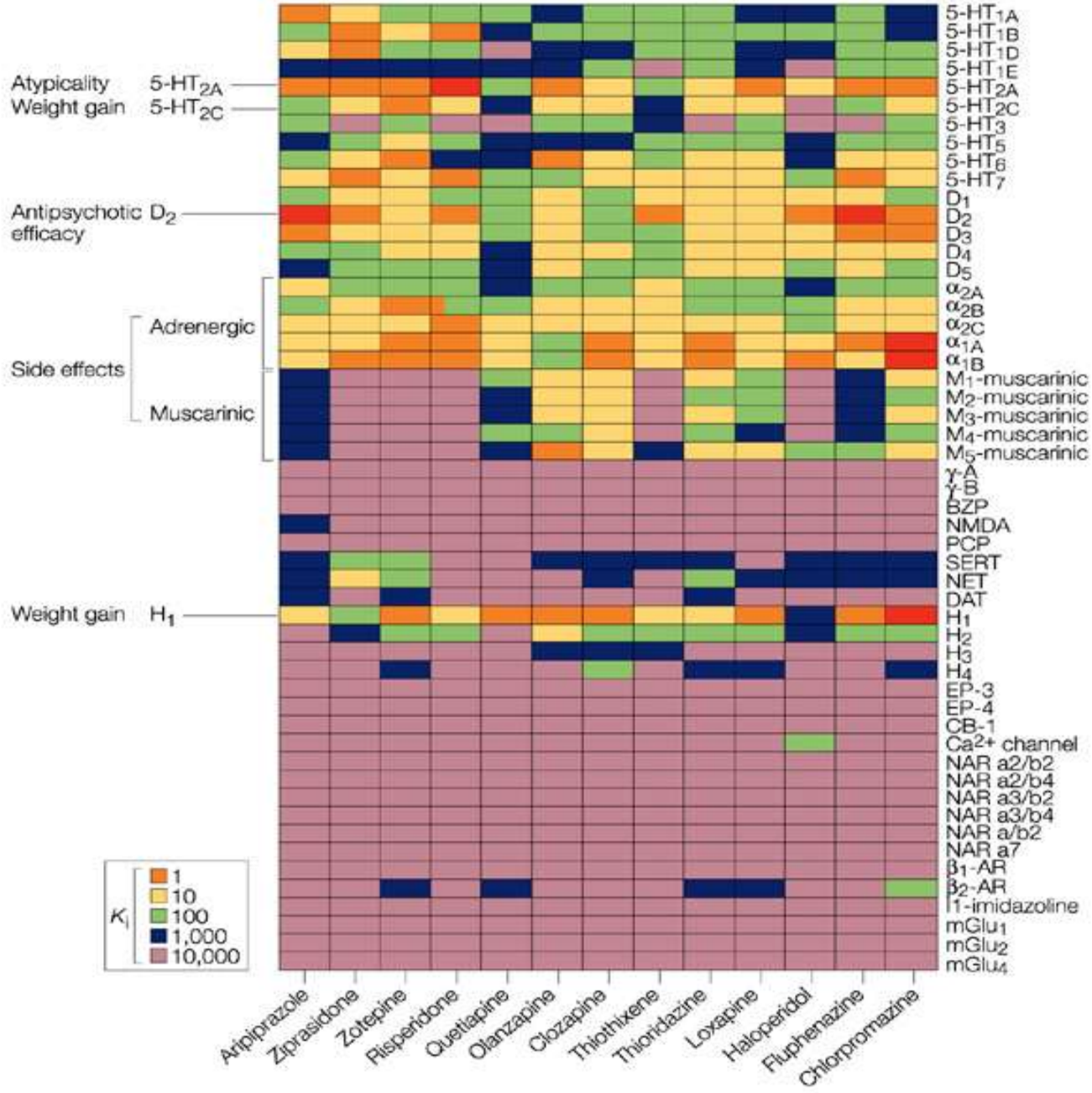
Formulary Issues (2)

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 se 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 out comes, 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 health care 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.



53 receptors

***Roth BL, Sheffler DJ and Kroeze WK. Nat Rev Drug Discov. 2004 Apr;3(4):353-9**

Nature Reviews | Drug Discovery

Receptor binding affinities of atypical antipsychotics

K_i (nM)

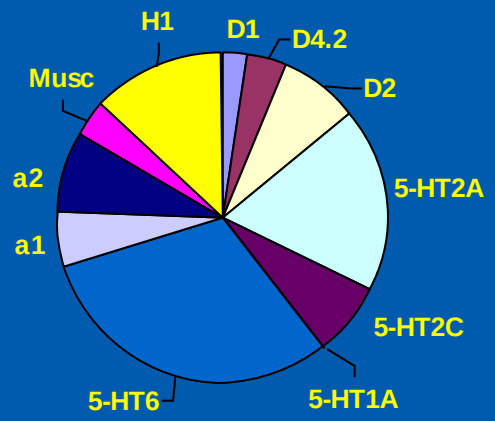
	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine
D_2	3.1	2.2	20	180	130
5-HT_{2A}	0.39	0.29	3.3	220	8.9
5-HT_{2C}	0.72	10	10	1400	17
5-HT_{1A}	2.5	210	2100	230	140
5-HT_{1D*}	2.0	170	530	>5100	1700
α_1-adrenergic	13	1.4	54	15	4.0
M_1-muscarinic	5100	2800	4.7	100	1.8
H_1-histaminergic	47	19	2.8	8.7	1.8

K_i <1 nM — very high affinity; K_i = 1-10 nM — high; K_i = 11-100 nM — moderate;
K_i =101-1000 nM — low; K_i >1000 nM — negligible.
*Bovine binding affinity; †rat synaptosomes; all other affinities human.

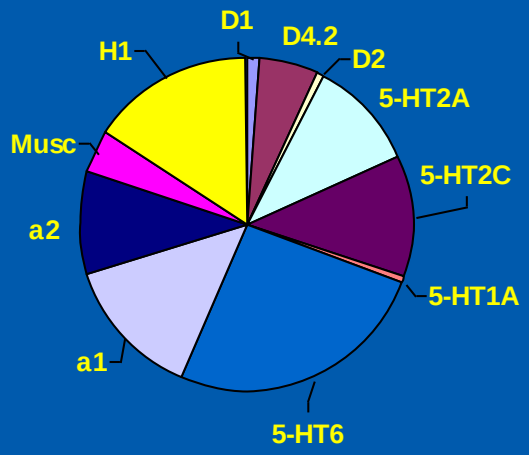
Zorn SH et al. *Interactive Monoaminergic Brain Disorders*. 1999;377-393.
Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.

Different Antipsychotic Drugs Act Differently on Brain Receptors

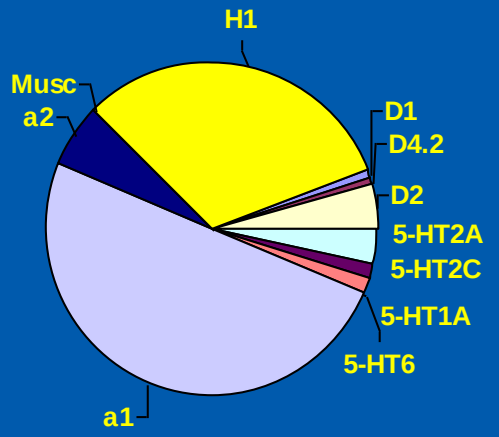
Olanzapine



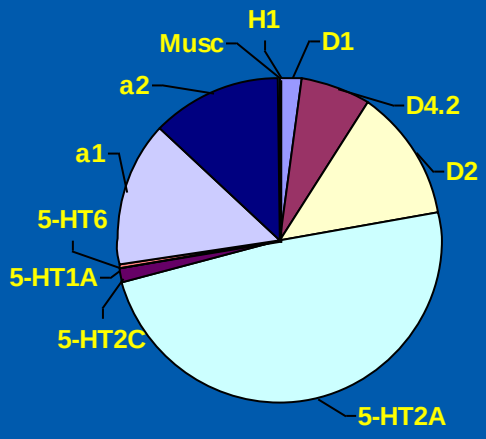
Clozapine



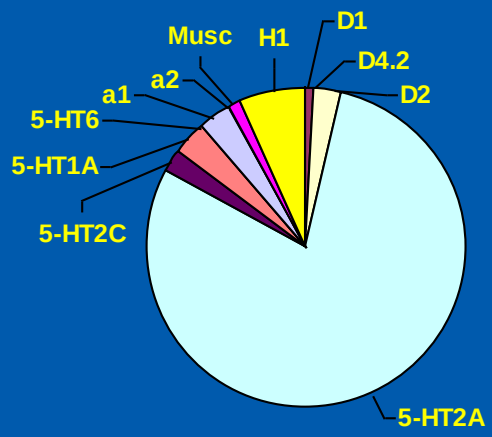
Quetiapine



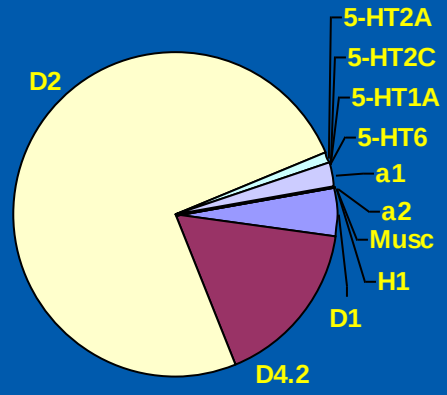
Risperidone



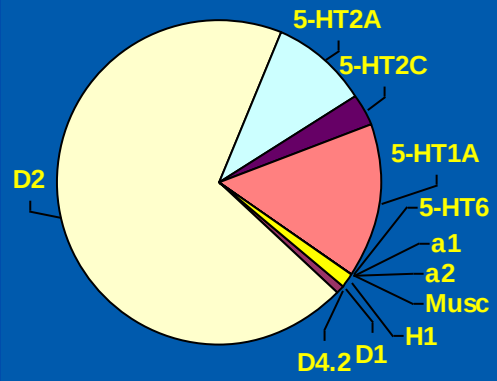
Ziprasidone



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

FDA-PDR 60th Edition

"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."

Atypical Dosing

“The dose range approved by the FDA for quetiapine and ziprasidone may be below their optimal therapeutic doses…”

Lieberman, J. et al: NEJM 2005; 353:1209-1223

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?

CATIE 1 & 2 Editorial

“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.

Taminga, C.: AM J Psych 2006; 163:563-565

CATIE: Legal & Ethical Implications

Philip Candilis, MD
UMass Medical School

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 sxs
- 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)