

Class Labeling for Psychiatric Drugs: FDA Perspective

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Topics to Cover

- What is class labeling?
- Evidence base for class labeling?
- Interpreting a box warning
- Modifying class labeling
- Comparative safety information in labeling

What is Class Labeling?

- No regulatory definition for class labeling
- Not recognized in CFR
- No guidance on class labeling
- Generally considered to be the use of standard language to convey a risk that is thought to be common for drugs in a defined “class”
- Handled differently by different review divisions

What is a “Drug Class”?

- No consistent definition for drug class either
- Common approaches to defining a “drug class”
 - Pharmacological effect
 - E.g., “SSRIs”
 - Therapeutic effect
 - E.g., “antidepressants”
 - Structural similarity
 - E.g., “benzodiazepines”

Examples of Class Labeling for Psychiatric Drugs: Antipsychotics

- Mortality in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Leukopenia, neutropenia, agranulocytosis
- Body temperature regulation
- Dysphagia

Examples of Class Labeling for Psychiatric Drugs: SSRI/SNRI Antidepressants

- MAOI contraindication
- Suicidality
- Serotonin syndrome or NMS-like reactions
- Hyponatremia
- Abnormal bleeding

Where in Labeling is Class Language Found?

- Anywhere where risk information is communicated
 - Box warning
 - Contraindications
 - Warnings/Precautions
 - Adverse reactions
 - Drug interactions
 - Special populations
 - Drug abuse and dependence
 - Overdosage

Evidence Base for Class Language

- Meta-Analysis of randomized controlled trials
 - E.g., suicidality warning/antidepressants
 - E.g., mortality warning/atypical antipsychotics
- Observational studies (case control, cohort)
 - E.g., extension of mortality warning to conventional antipsychotics
- AERS reports
 - E.g., MAOI contraindication for SSRIs

Understanding Box Warnings

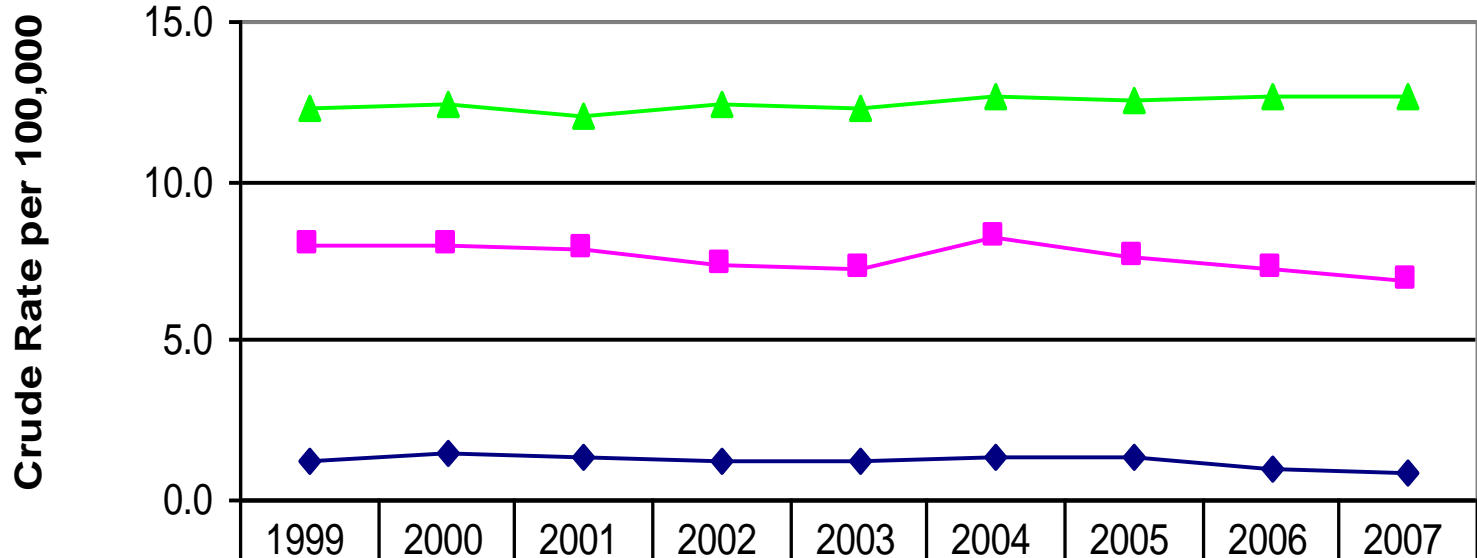
- Correct terminology is “boxed warning”, not “black box warning”
- When is a box used?
 - Alert prescribers to risk of sufficient importance relative to benefits of a drug that needs to be considered in prescriber’s risk/benefit assessment
 - Alert prescribers to risk that can be prevented or reduced in frequency or severity by appropriate use of drug
- Does not mean “don’t use”



Box Warning on Suicidality for Antidepressants

- Antidepressants increase the risk compared to placebo in children, adolescents and young adults
- If considering use, balance risk with clinical need
- Depression itself increases risk
- Appropriate monitoring for worsening is important

United States Suicide Rates 1999 - 2007



	1999	2000	2001	2002	2003	2004	2005	2006	2007
◆ Ages 10-14	1.2	1.5	1.3	1.2	1.2	1.3	1.3	1.0	0.9
■ Ages 15-19	8.0	8.0	7.9	7.4	7.3	8.2	7.6	7.2	6.9
▲ Ages 20-24	12.3	12.4	12.0	12.4	12.3	12.7	12.6	12.7	12.7

What Does it Take to Modify Class Labeling?

- Evidence of important differences among members of a class
- Example of evolution of class labeling:
Hyperglycemia with atypical antipsychotics
 - Began as class label
 - As differences among drugs became apparent, labeling language has evolved

Current Approach to Characterizing Metabolic Risks with Atypical Antipsychotics

- All pertinent information included in Warnings/Precautions
- Structure of Metabolic Section
 - Hyperglycemia
 - Weight Gain
 - Lipid Changes
- Individual data for drug included as well
- Provides prescriber differentiating information in predictable location in the label

Current Approach to Characterizing Metabolic Risks with Atypical Antipsychotics (Continued)

- Atypical antipsychotics fall along a continuum, with olanzapine and clozapine on one end, and aripiprazole and ziprasidone on the other
- Zyprexa language: acknowledges that olanzapine is worse than others

What about Including Comparative Information in Psychiatric Drug Labeling?

- Clinical value of comparative information
 - Focus on safety
- Designs for superiority and noninferiority trials
- Principles for “fair comparisons” on safety endpoints

Is There a Need for Comparative Information on Psychiatric Drug Treatments?

- Not from a regulatory standpoint (unless a comparative claim is being sought)
- From a clinical standpoint, valid comparative efficacy and safety information would be valuable
- Some argue that this type of information is the only useful information (e.g., Rothman and Michels)

Differences in Safety for Psychiatric Drugs Within Defined Classes

- Often acknowledged for members within various classes in clinical practice (but rarely in labeling)
- Common reason for selection of specific drug
- Examples:
 - TCAs: More toxic profile vs other antidepressants
 - SSRIs: More sexual dysfunction vs some other antidepressants
 - Newer antipsychotics: Less EPS vs older antipsychotics

Approaches to Comparative Safety Claims

- Designs
 - Superiority
 - Equivalence
 - Always noninferiority, i.e., “no worse than” a standard
- Key question for comparative safety trial
 - Is it a fair comparison?

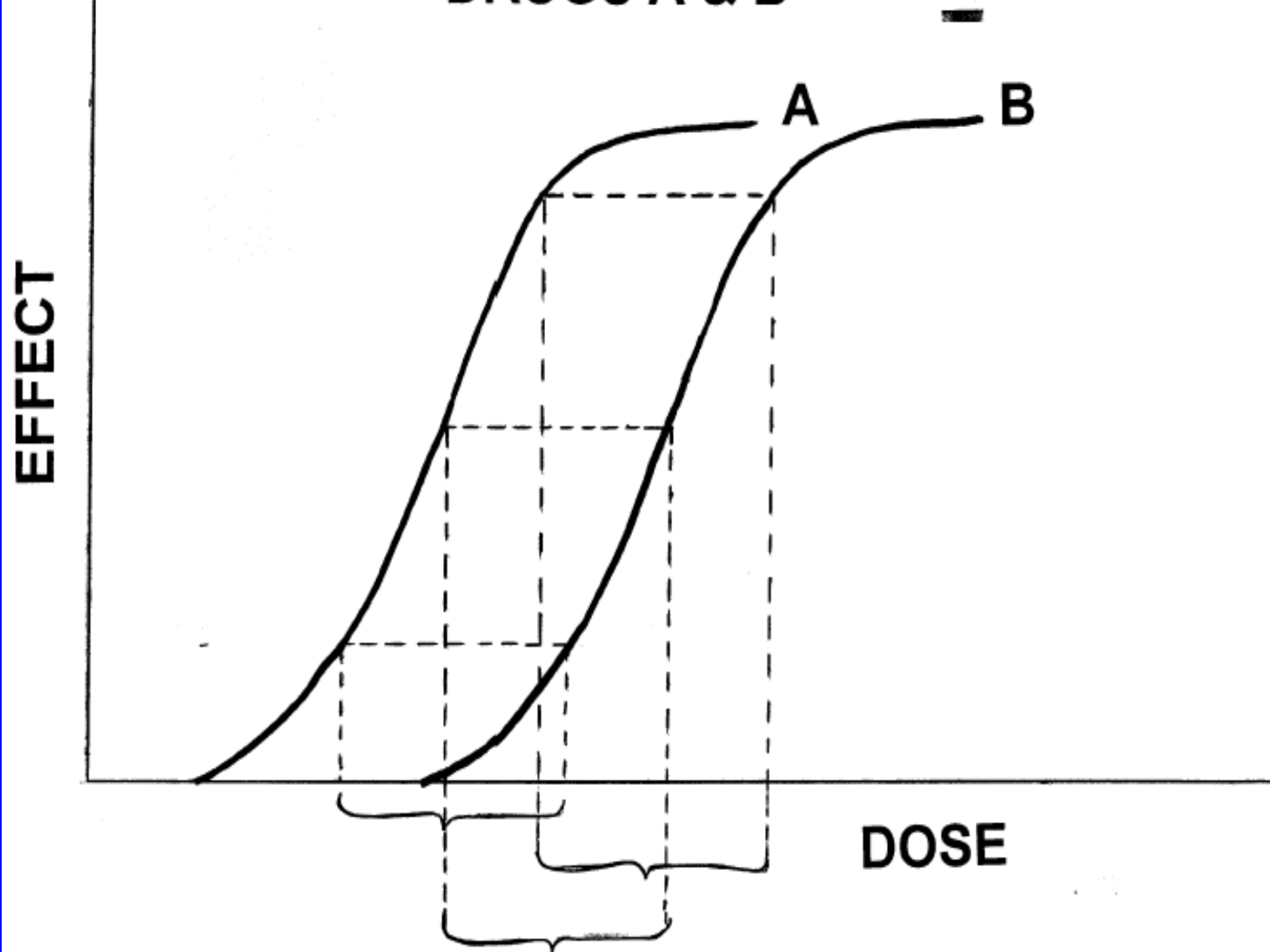
DPP Principles for Fair Comparison Regarding Safety Outcome

- Equi-effective doses
- Optimal use of comparator agent
 - Dose schedules
 - Titration schedules
 - Use of adjunctive medication if appropriate
- Appropriate comparator (s)
- Sensitive assessment methods
- Population studied
 - Unbiased
 - Broad sampling
- Comparisons on all important domains
- Comparisons at all relevant times
- Replication

Need for Equi-Effective Doses in Safety Comparison

- Problem Case: Low dose of new drug vs high dose of active standard
- Remedies:
 - Multi-arm Trial (compares dose/response curves of the two drugs)
 - Compare high dose of new drug with wide dose range of standard comparator

COMPARING SAFETY OF DRUGS A & B



Examples of Failure to Dose Comparator Agent in Optimal Manner

- Give comparator in am when optimally given in pm
- Use more rapid titration of comparator agent than is conventional
- Failure to permit use of anticholinergic agents for control of EPS when using haloperidol as comparator

Examples of Bias in Selection of Comparator Agent

- Using the most sedating antidepressant in class
- Using the typical antipsychotic with most prominent EPS
- Using the atypical antipsychotic with most prominent weight gain
- Remedy: Requiring comparisons with representative members of the class

Examples of Bias in Selection of Assessment Method

- Failure to use sensitive instrument for sexual dysfunction
- Failure to use orthostatic testing
- Failure to assess frequently and sensitively during discontinuation phase
- Failure to obtain ECGs at T_{max}
- Remedy: Require the most sensitive instrument and method for the safety finding of interest

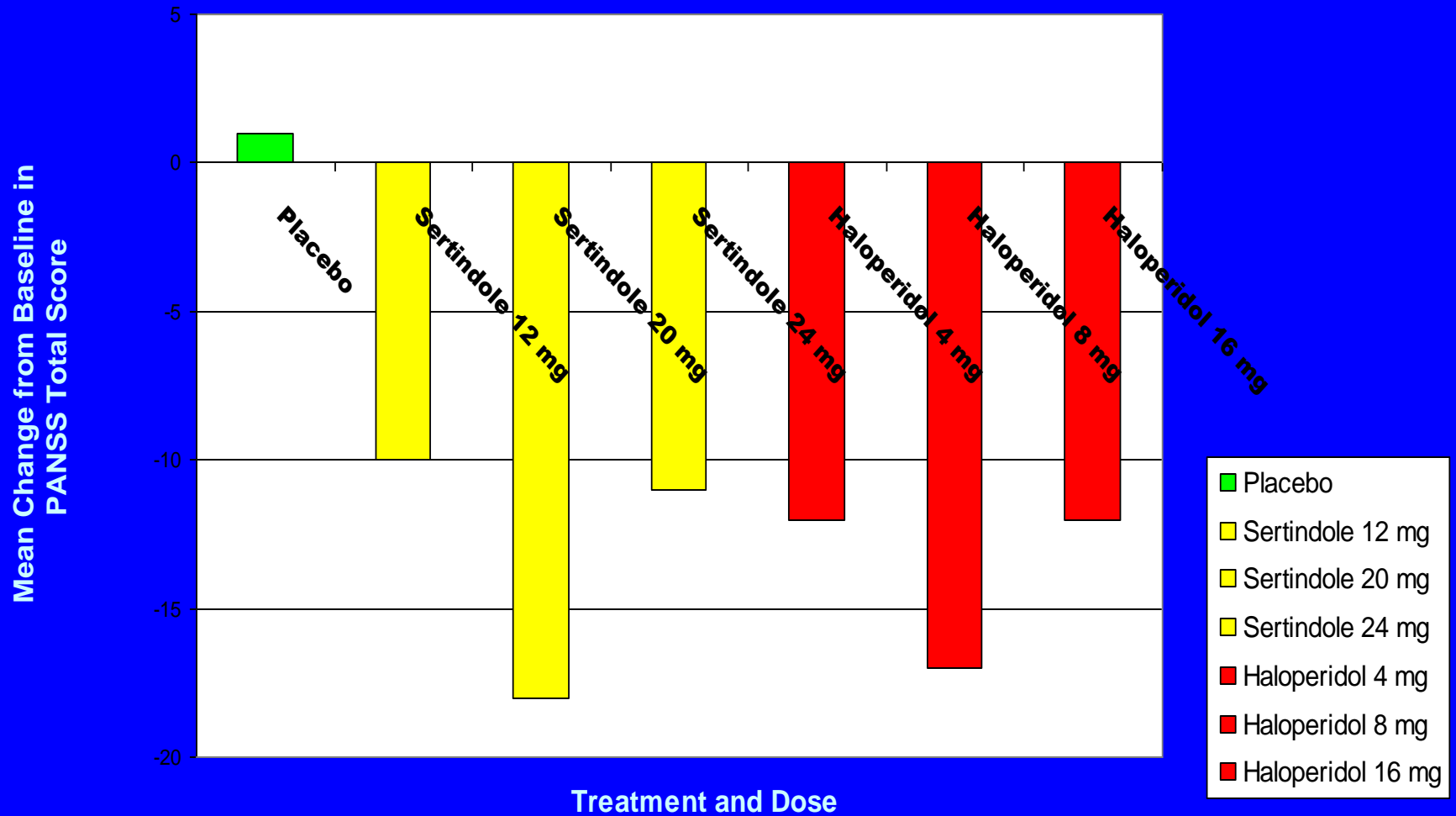
Examples of Population Bias

- Selecting patients who have history of intolerance to comparator
- Selecting patients who have history of tolerating the new drug
- Selecting patients who are not vulnerable to the event of interest
- Remedy: careful attention to population sampled

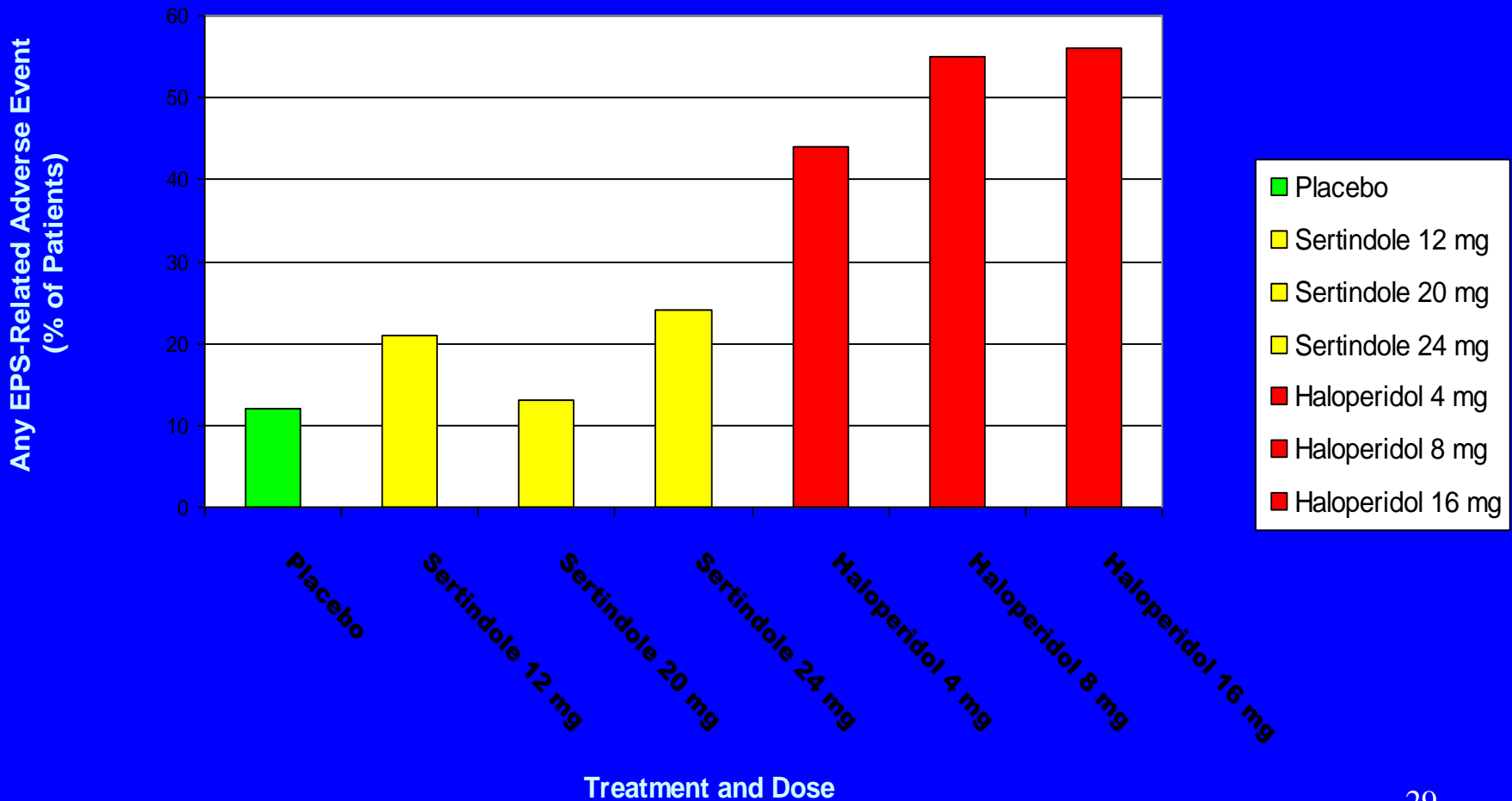
Importance of Assessing Drugs Across the Domains of Interest

- Narrow focus on one safety domain may obscure the “big picture”
- Cannot fairly assess 2 drugs unless they are compared on adequate range of safety and efficacy outcomes

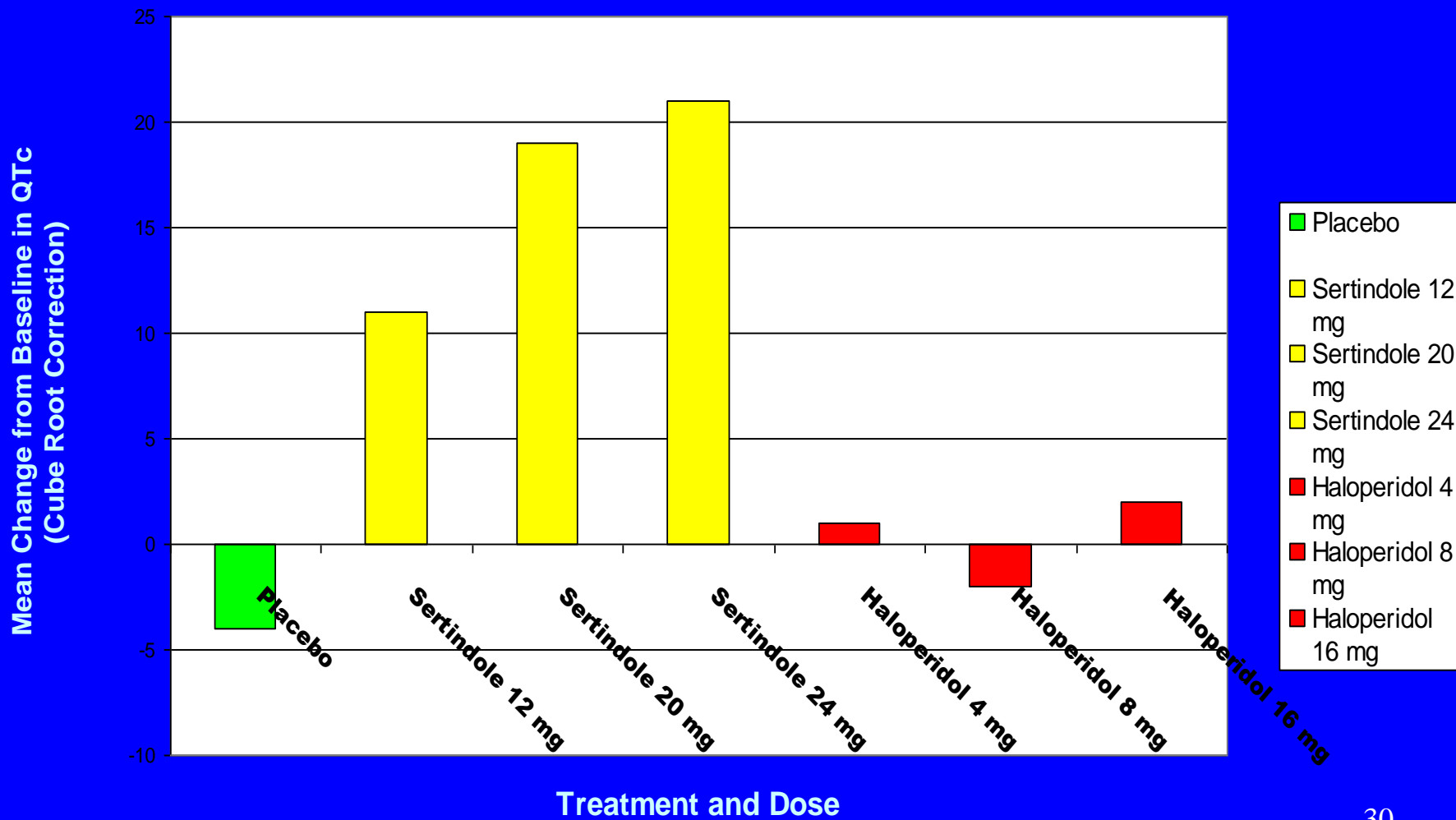
Comparative Efficacy of Sertindole and Haloperidol



Comparative Safety of Sertindole and Haloperidol (EPS Effects)



Comparative Safety of Sertindole and Haloperidol (QTc Effects)



Importance of Comparing Drugs at All Relevant Times

- Particularly important for drugs with different time-concentration profiles
 - Example: different methylphenidate formulations have very different pk profiles, and need to be evaluated across the entire time interval of interest, including evening and night
- Need to observe for both early and late-emerging adverse events
 - Example: new drug might have early advantage for certain safety outcomes (e.g., EPS), but disadvantage longer-term (e.g., weight gain, diabetes mellitus)

Summary Comments

- Class labeling has an important role
- Requires modification as evidence accumulates
- Appropriate interpretation of class labeling, in particular, a box warning, is critical
- Comparative safety claims can be considered, but need careful attention to design of trials, particularly regarding “fairness” of comparison