Slide 1	**CLASS EFFECTS** **Rational Basis for Strength of Prediction** Nick Holford Department of Pharmacology, University of Auckland Auckland, New Zealand	Acknowledgement: The ideas expressed here were developed in collaboration with Dr David Woolner. His broad knowledge of clinical pharmacology, drug development and medicines regulation were essential to cover the scope of this topic.
Slide 2	## Drug Classes and Class Effects "almost all of the …drugs currently available can be arranged in about 70 groups" "many drugs within each group are very similar…" Katzung 2014 Drug groups also referred to as *drug classes* **Extrapolation** of knowledge from one class member to another has become increasingly common, a concept of so called *class effects* Katzung BG. Introduction. In: Katzung BG, editor. Basic and Clinical Pharmacology. 13 ed. San Francisco: McGraw-Hill Professional Publishing; 2014. p. 12 	
Slide 3	## Class Effects Definition? • FDA Class Labeling (cited by Furberg) "all products within a class are assumed to be closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions" • Furberg "Since the concept of "class effect" is a term of convenience … untested drugs of a "class" should be considered to be **unproven** drugs " Furberg CD. Class Effects and Evidence Based Medicine. Clinical Cardiology 2000;23(Supplement IV):15-19 	

Slide 4	**Drug Sub-Classes** **A Science Based Hierarchy** • Chemical – According to shared chemical structure; for example, sulphonylureas or phenothiazines • Mechanism – According to a shared mechanism of action; for example, beta adrenoceptor blockers or ACE inhibitors • Genotype – According to a shared genotype; for example, HLAB association with severe skin reactions (*1501 carbamazepine, *1502 phenytoin, *5801 allopurinol) • Biomarker – According to a shared action on a common biomarker; for example, hypolipidaemics, or hypoglycaemic agents. • Outcome – According to the production of a shared clinical outcome; for example, reduction of mortality from ischaemic heart disease 	Drug classes used to compare outcome effectiveness based on chemical sub-class. Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen R, Pratt N, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. The Lancet. 2019;394(10211):1816-26.
Slide 5	**Class Effects and Sub-Classes** • Class Effects are observed '*within a sub-class*' and used for **prediction** of '*out of sub-class*' effects • '*Out of sub-class*' effects are an expression of an **expectation** rather than a statement of what is known • '*Out of sub-class*' **extrapolations** are the cause of class effect controversy 	
Slide 6	**Learners and Confirmers** • Learners don't know the answers but want to find them out (clinical pharmacology) – Class effects are useful • Confirmers want proof and dismiss partial answers (evidence based medicine) – Class effects are not useful Sheiner LB. Learning versus confirming in clinical drug development. Clinical Pharmacology & Therapeutics 1997;61(3):275-91 	

Slide 7

Class Effect Perspective I

- Basic Drug Discovery
  - Chemical sub-classes support a basic tenet of medicinal chemistry that shared action is based on some measure of shared structure
- Pharmacological
  - Pharmacologists tend to be more concerned with mechanism sub-classes, for example HMG-CoA-reductase inhibition, as this focuses on explanation and quantification of activity and helps lead towards treatment models and rational approaches to therapeutic decision making
- Regulatory
  - Regulatory agencies utilize the concepts of biomarker and outcome sub-classes. Drugs are registered whenever possible based upon proven clinical outcomes - that is, membership of a particular outcome sub-class. If such outcome data is unavailable drugs may be registered on the basis of biomarkers used as "surrogate endpoints".
- Medical
  - Doctors and patients may be more attracted to classification into outcome sub-classes, for example medicines that help reduce cardiovascular events in diabetes, as these focus on different treatment options and are clearly of more relevance to the end user than mechanism or biomarker considerations

Slide 8

Class Effect Perspective II

- Drug Funder
  - Drug funding organisations use *ad hoc* concepts of class effects, along with various other arguments, financial and political, depending on the particular approach used for benchmarking or controlling prices e.g. reference pricing and drug interchangeability
- Pharmaceutical Company
  - Companies that have outcome data will claim that drugs belonging to the same mechanism sub-class, or the same biomarker sub-class do not have the same clinical outcome.
  - But if they have other drugs without outcome data that share a common mechanism of action and/or a common biomarker they will promote outcomes.
- Educational
  - In some regards the student of pharmacology has the least contentious perspective on class effect concepts. They may be utilised fully in so far as they aid learning, but may be discarded at will if they cease to be useful.
  - *From this perspective there is no underlying bureaucratic or belief dimension to the class effect concept.*

Slide 9

Class Effect Strength I
More Sub-Classes the Better

- Class Effect strength increases with more shared sub-classes
  - e.g. thiazide is a diuretic and lowers blood pressure would share 3 sub-classes (chemical, mechanism, biomarker)
- Outcome Sub-Class alone makes no useful predictions
  - e.g. propranolol and aspirin reduce IHD morbidity (outcome sub-class effect) but do not share outcome benefit in CHF

Slide 10

Class Effect Strength II
Exposure-Response Relationship

- Within classes, only those drugs that exhibit comparable efficacy (Emax) and comparable time course of action can reasonably be expected to share similar class effects.
  - A statin that produces a maximal fall in cholesterol of, say, 20%, should not be expected to share a similar outcome class effect with a statin that produces a fall of 50%, without direct proof to the outcome effect [fluvastatin vs simvastatin]
  - A benzodiazepine with a rapid onset of effect should not be expected to have a similar outcome as one with slower onset of action [diazepam vs midazolam]

FDA. Guidance for Industry. Exposure-response relationships — Study design, data analysis, and regulatory applications http://www.fda.gov/cder/guidance/5341fnl.htm. 2003.

Slide 11

Class Effect Strength
Drug Development Challenges

- The drug development program for a drug should be able to identify the potency and maximum effect of a drug and the time course of response.
  - Cerivastatin was withdrawn soon after it appeared on the market because of several cases of rhabdmyolysis. Cerivastatin was more potent and produced lower cholesterol but with higher risk of muscle damage.
  - In cases where toxicity precludes estimation of Emax then presumptive evidence of similar efficacy would rely on showing that the highest tested dose of each drug in a biomarker class produces similar biomarker effects.
  - *Absence of data on potency, Emax and time course of response is a sign of an inadequate drug development program*

Slide 12

Adverse Effects

- Amongst drugs that share a common exposure-response relationship only effects that are clearly related to the shared action of the drugs can be considered as potential class effects
  - The cough produced by ACE inhibitors, presumed to result from the build up of bradykinin in the bronchi, could be a class effect within the mechanism class of ACE inhibitors
- Most adverse events are non specific and sporadic in nature and are not mechanism or biomarker based (at least in the light of current knowledge)
  - Skin rash, which is not based upon the shared mechanism of action, could not, even though most ACE inhibitors have been associated with rashes of various kinds
  - Note that some skin adverse reactions may be a genotype class effect
- Thus most adverse events should not be considered class effects.

Slide 13

The "Mediator" Scandal

- The appetite suppressant fenfluramine was withdrawn from the market in the late 1990s because of heart valve damage and other serious adverse effects.
- Servier (which marketed fenfluramine) brought out a structurally similar appetite suppressant (benfluorex – trade name "Mediator") which was used to help lower glucose in Type 2 diabetes. Shares a common cardiotoxic metabolite with fenfluramine.
- It is alleged that Servier promoted benfluorex to aid weight loss in patients without diabetes. Several hundreds (or even thousands) of patients are said to have died from use of benfluorex.
- This class effect appears to have been ignored by both Servier and the French medicines safety agency who approved the use of benfluorex to treat diabetes.
- http://en.wikipedia.org/wiki/Benfluorex

Slide 14

The "Mediator" Scandal

On March 29, 2021, a French court fined Servier €2.7m (£2.3m) after finding it guilty of deception and manslaughter, with Mediator linked to the deaths of up to 2,000 people. The former executive Jean-Philippe Seta was sentenced to a suspended jail sentence of four years. The French medicines agency, accused of failing to act quickly enough on warnings about the drug, was fined €303,000.

https://en.wikipedia.org/wiki/Benfluorex

Slide 15

The Usefulness Of Class Effects

- There exists a spectrum of possible statements concerning the comparability of drugs
  - "identical drugs produce identical effects" is plainly true, but of very limited use.
  - "completely different drugs produce identical effects " is plainly very useful, but is almost certain to be untrue
- Predictions of class effects are useful in bridging these extremes when direct evidence is lacking or controversial