

# CLASS EFFECTS AND THE RATIONAL COMPARISON OF DRUGS

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## INTRODUCTION

No two molecules are exactly the same. Even minor differences in molecular structure can sometimes result in important differences in pharmacological activity. Paracetamol, phenacetin and acetanilide for example, differ by only single chemical groupings, but exhibit markedly different toxicity profiles [1].

Despite this, drugs have long been placed in groups. According to Katzung [2], it is unnecessary “To learn each pertinent fact about each of the many hundreds of drugs” as “almost all of the ...drugs currently available can be arranged in about 70 groups”, and “many drugs within each group are very similar...”. Typically, groupings are built around some original or prototypical drug about which much is known, and other group members are then studied in terms of similarities and/or differences between these drugs and the original. Such groupings have formed the basis for teaching, studying and presenting pharmacology, and appear as chapter headings in most textbooks of the subject. As such, they are mainly an aid to understanding and learning rather than a means of predicting characteristics of drugs, and are largely uncontroversial.

More recently, the pace of pharmaceutical development has increased. The number of drugs available, including so called “me too” drugs has risen dramatically. There has been increasing promotion of drugs by the pharmaceutical industry, and there has been increasing pressure from various groups to control drug usage and prices. Against this backdrop, drug groupings of various kinds have become increasingly important tools, not least for pharmaceutical companies, advocates of treatment guidelines, and pharmaceutical funding agencies [3].

Such groupings are nowadays typically referred to as *drug classes*. An approach of (more or less) controlled extrapolation of knowledge from one class member to another has become increasingly common, a concept of so called *class effects*.

Despite widespread usage, definitions of the terms “drug class” and “class effect” are not easy to find. Most pharmacological texts are silent on the matter, despite using the terms more or less widely. There is no established regulatory definition of these terms. The FDA utilizes class labeling when “all products within a class are assumed to be closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions”, although the term *class* and the grounds for such assumption are undefined. Furberg has pointed out this lack of clarity and has referred to *class effects* as a term of convenience [4].

In this paper we examine the question “Convenient to whom, and for what purpose?”, and attempt to develop some definitions and rational approaches surrounding the use of the concept of *class effects*

## DRUG CLASSES

Drugs can be classified according to the following attributes.

### **1. Chemical Class**

According to shared chemical structure; for example, sulphonylureas or phenothiazines.

### **2. Mechanism Class**

According to a shared mechanism of action; for example, beta adrenoceptor blockers or ACE inhibitors.

### **3. Biomarker Class**

According to a shared action on a common biomarker; for example, hypolipidaemics, or hypoglycaemic agents. .

### **4. Outcome Class**

According to the production of a shared clinical outcome; for example, reduction of mortality from ischaemic heart disease .

Drugs may be placed into one or more of these classes.

## DRUG CLASS PERSPECTIVES

It is important to remember that the concept of drug classes is an heuristic device, or a model for thought, rather than a necessary description of reality. If everything was known about every single drug then no extrapolation of knowledge would be required, and the concept of drug classes and class effects would become essentially redundant, apart perhaps from its use as a teaching aid. Any use of the concept of drug classes needs to be considered against the backdrop of who is proposing the class, and for what purpose. In this regard, the study of drug classes resembles that of pharmacoeconomics in that analysis is conducted from a particular viewpoint, and that viewpoint needs to be understood and acknowledged. Our current analysis is proceeding from a pharmacological perspective.

The basis chosen for grouping may vary according to individual perspective and the purpose such grouping will serve. Consequently, drugs may be grouped differently at any one time by different people, or grouped differently on different occasions by the same person.

### ***Basic Drug Development Perspective***

Chemists and basic drug developers make use of the concept of chemical class. That shared action is based on some measure of shared structure is a basic tenet of

medicinal chemistry. The discovery of a new lead compound, for example, commonly triggers the systematic examination of a range of molecules with similar structure, in the search for alternative or improved compounds [5]. Chemical groupings however, may have limited application for others as chemical similarity may not necessarily be reflected in other characteristics [1].

### ***Pharmacological Perspective***

Pharmacologists tend to be more concerned with mechanism 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 Perspective***

Regulatory agencies utilize the concepts of biomarker and outcome classes. Drugs are registered whenever possible based upon proven clinical outcomes—that is, membership of a particular outcome class. This is the ideal. Frequently, however, such outcome data is unavailable and some drugs may then be registered on the basis of so called “surrogate endpoints”. Surrogate endpoints are not the basis for a separate class. Rather they are a subset of biomarkers that, for various reasons, are accepted by regulatory agencies as being indicative of some kind of clinical outcome. There appear to be no systematic rules for bestowing surrogate status upon a particular biomarker, each instance being decided by agencies in a piecemeal fashion. Most antihypertensives for example have been approved and used on the basis of their blood pressure lowering effect, rather than any proven effect on cardiovascular outcomes. Drugs are not registered by agencies solely on the basis of membership of a mechanism or chemical class.

### ***Medical Perspective***

Doctors and patients may be more attracted to outcome 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.

### ***Drug Funder Perspective***

Drug funding organizations may use concepts of drug class effects, along with various other arguments, financial and political, depending on the particular approach used for benchmarking or controlling prices.

### **Reference Pricing**

Reference pricing is a system used in a variety of forms around the world. It was introduced in 1989 in Germany, and has subsequently been taken up in various forms by Denmark, Holland, Sweden, Australia and New Zealand amongst others (3). Reference pricing schemes have 2 broad steps. Firstly, drugs are grouped in some way. Secondly, some kind of price setting exercise is undertaken. This may

involve judgment of the value of the group versus other groups and a mechanism for setting the price of a particular group.

#### Interchangeability and Reference Pricing

Reference pricing has been defined by Zammit-Lucia and Dasgupta [6] as “a system by which the reimbursement level of a drug is determined by reference to a comparable or interchangeable alternative or group of alternatives”. Clearly the meanings of the words “comparable” and “interchangeable” are of crucial importance, and have much to do with concepts of drug class effects.

Zammit-Lucia and Dasgupta [6] also noted that the concept of interchangeability between drugs cannot always be objectively defined, and as a result it varies from country to country, and can be considered a bureaucratic concept, not a medical one.

Three broad levels of interchangeability and/or comparability have been described in reference pricing schemes, termed “chemical”, “pharmacological” and “therapeutic”. [6-8]. It is important to remember that these levels are descriptions of what exists (for whatever reason) in various market places, not necessarily a prospectively designed, logical framework. Level 1 (chemical) involves grouping all available versions of the same molecule, whether generic or patent expired original and setting the price of all to the average price of the group or to the price of the cheapest version. This has been the practice in Denmark and Norway. It is based upon a subset of a chemical class in that these are all an identical molecule, albeit from different sources. Generally bioequivalence is required to register the drugs and judge them to be interchangeable, bioequivalence being a surrogate end point for effectiveness and safety (outcome classes) comparable to the original product.

Other schemes such as those in Holland, Germany and New Zealand, may involve groupings at levels 2 and 3. Level 2 groupings involve grouping drugs according to “pharmacological” equivalence. Such groups typically share route of administration, mechanism of action and effect on common biomarkers. They may not however necessarily share registered indications.

Level 3 involves “therapeutic equivalence”. Such groupings are based upon the production of the same or similar effects in treating the same or similar conditions. These groups are slanted more towards clinical outcomes and contain drugs that may share mechanism of action and/or effects on biomarkers.

Level 2 and 3 groupings seem mainly to be based around various combinations of mechanism, biomarker and outcome class concepts (Table 1).

**Table 1 Comparison of Drug Classes and Reference Price Levels**

<b>Drug Class</b>	<b>Reference Pricing Level</b>
Chemical	Level 1 (single molecule)
Mechanism	Level 2
Biomarker	
Outcome	Level 3

It is important to remember that reference pricing is primarily an exercise in pricing, not in pharmacological taxonomy. Pricing arguments have many strands and the focus of drug funders is on the end result -- the price. Drug class arguments, whilst widespread and frequently cogent, are not the only consideration in debates over drug prices, and are essentially a means to an end. Drug class comparative arguments may be presented in support of funding decisions that have in fact been based in large part on financial or cost utility grounds.

A simple classification of various current reference pricing schemes is shown in Table 2.

The schemes are grouped according to the level of equivalence utilized to group drugs, and whether groupings include patented and/or off patent molecules. Schemes that group off patent, identical molecules are concerned with managing generic prices, and are the least contentious, as interchangeability of the group members is widely accepted as reasonable. Schemes that group patented with off patent drugs are more controversial, as they run into arguments over the value of intellectual property. Schemes such as those in British Columbia, Holland, Australia and New Zealand attract most comment as they have the potential to group unlike molecules that may or may not be under patent. They therefore run into arguments over interchangeability and intellectual property.

**Table 2 A simple classification of existing reference pricing schemes according to product coverage. (Lopez-Casasnovas and Puig-Junoy [3])**

<u>Interchangeability level</u>	<u>Off patent drugs</u>	<u>On and Off Patent</u>
Chemical	Sweden	
	Denmark	
	Norway	
Chemical and Pharmacological		British Columbia Australia
Chemical, Pharmacological And Therapeutic	Germany	New Zealand The Netherlands

The issues of the perceived lack of equivalence or interchangeability between drugs included in the same group probably constitute the most controversial issue in the literature on reference pricing [3]. Controversy has occurred when, for example, statins were referenced priced in New Zealand, based on their apparent shared mechanism of action and shared effect on biomarkers, (cholesterol lowering) despite differing availability of outcomes data, and differing cholesterol lowering efficacy of various members of the class [9].

### ***Pharmaceutical Company Perspective***

Pharmaceutical companies use various approaches to drug classes depending on their position in the market place. It is usually in the interests of companies that have

clinical outcome data to highlight an outcome based class and claim that drugs belonging to the same mechanism class, or the same biomarker class may not necessarily have the same clinical outcome. On the other hand, companies that have biomarker or surrogate endpoint data, are better served by the argument that drugs that share a common mechanism of action and/or a common effect on an established biomarker are logically expected to share outcomes.

### ***Educational Perspective***

Despite any controversy surrounding the use of class effect concepts, the usefulness of the approach for the teaching and learning of pharmacology and therapeutics should not be forgotten. In an increasingly information rich world, mechanisms for ordering thought and simplifying understanding have a vital role to play. In some regards the student of pharmacology has the least contentious perspective on class effect concepts. They may be utilized fully in so far as they aid learning, but may be discarded at will if they cease to be useful. In this context there is no underlying bureaucratic or belief dimension to the class effect concept.

## **THE VARIABILITY OF CLASS ASSIGNMENT**

The choice of grouping, and even the extent to which consistency and rigor are brought to bear surrounding grouping are largely uncontroversial unless some form of extrapolation or prediction is intended from one member of the class to another. Then, different conclusions can potentially be drawn depending on how grouping is handled, and medicine, science and bureaucracy become deeply entangled.

For example all the currently available statins belong to the same mechanism class in that they all inhibit HMG CoA reductase. The statins also belong to the same biomarker class in that they have all been shown to reduce blood cholesterol levels. They have not yet, however, all been shown to belong to the same outcome classes. They are commonly *assumed* to belong to the same clinical outcome class, however, because cholesterol reduction is taken to be a surrogate endpoint for reduction in cardiovascular morbidity and mortality. Morbidity and mortality data are available for some statins and not others. Moreover, the reported lower incidence of muscle related adverse events in heart transplant patients receiving pravastatin versus some others, and the recent withdrawal of cerivastatin based on an unacceptably high incidence of muscle damage in some patients may indicate, their outcomes in terms of adverse event profile may differ [10, 11].

Antihypertensive agents belong to a number of different chemical and mechanism classes, but all belong to the same biomarker class in that they reduce blood pressure. Lowering blood pressure has been regarded as a surrogate end point for reducing risk of cardiovascular morbidity and mortality. Antihypertensives have therefore been regarded by many as belonging to the same outcome class, despite outcome data being available until fairly recently only for beta adrenergic blockers and thiazide diuretics [12]. More recent data and analyses have shown that ACE inhibitors and calcium channel blockers appear to produce similar outcomes to those of beta adrenergic blockers and thiazides, adding support to the view that lowering blood pressure is a surrogate endpoint [13].

However, more recently, a large comparative trial of an angiotensin II receptor antagonist with a beta adrenergic receptor blocker has reported a 25% difference in stroke prevention between the two treatments, despite similar reductions in blood pressure [14]. This must at least raise the possibility that stroke reduction is not simply related to reduction of blood pressure alone. Drugs that share a biomarker, but not a mechanism class, may differ, at least quantitatively, with respect to outcome.

A new ACE inhibitor might be perceived as an exciting new member of a well established mechanism class by the developer, as just another member of the antihypertensive biomarker class by a weary prescriber, or as a me too entry into an outcome class whose price could set a new level for the whole group, by a drug funding agency.. Each viewpoint may carry some validity and serves a different function.

As prescribing, pricing, access or reimbursement decisions commonly hinge on the comparability of drugs it is essential that a clear and rational approach be applied to the use of drug classes and the concept of class effects to ensure that the chances of extrapolation and prediction being borne out in practice are maximised.

## **CLASS EFFECTS**

The term *class effect* is frequently applied when drugs are included in one type of class--most commonly an outcome class--based on membership of another class--most commonly a mechanism and/or biomarker class-- even though there may be no direct data in support of this. The outcome class in question may be concerned with the therapeutic effectiveness of the drug, or may relate to certain types of adverse effects. All statins are expected to reduce cardiovascular morbidity and mortality, for example, and all ACE inhibitors are expected occasionally to produce a cough. So far, available data seem to support these assumptions but, until all available class members have been directly shown to have these outcomes, it is the expression of an expectation rather than a statement of fact.

It is clear that great care is necessary to define which grounds for grouping drugs might support the notion of a class effect, and which effects within that group could reasonably be expected to be shared.

### ***An Approach To Defining Class Effects***

#### Class Definition

We propose that only drugs grouped as follows be considered as having the potential for reliably sharing class effects.

1. Drugs in the same mechanism class. They may or may not share a chemical class.
2. Drugs in the same biomarker class. They may or may not share the same mechanism class.
3. Drugs in the same outcome class which also share a common mechanism and biomarker class, or a common biomarker class.

Drugs grouped according to outcome alone (eg drugs reducing risk of cardiovascular morbidity such as aspirin and beta-blockers) are likely to have too diverse a pedigree to support a class effect approach.

### Exposure Time Relationship

Further, within such classes, only those drugs that exhibit comparable efficacy ( $E_{max}$ ) and comparable time course of action can reasonably be expected to share class effects. A statin, therefore, that produces a maximal fall in cholesterol of, say, 20%, should not be expected to share an outcome class effect with a statin that produces a fall of 50%, without direct proof to that effect.

This consideration requires that the drug development program for a drug is able to identify the maximum effect of a drug. In cases where toxicity precludes identification of  $E_{max}$  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.

### Shared Effects

Amongst drugs that share a common  $E_{max}$  and time course of action, only effects that are clearly related to the shared action of the drugs can be considered as potential class effects. For drugs in the mechanism only class, only mechanism related effects could be class effects. In the biomarker only class, only biomarker related effects could be class effects. In the shared classes (mechanism/biomarker, outcome mechanism biomarker etc.) mechanism or biomarker effects could be class effects. The cough produced by ACE inhibitors could, based on a mechanism produced build up in bradykinins, be a class effect within the mechanism class of ACE inhibitors. 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 [15]. 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). Thus most adverse events should not to be considered class effects.

As much of the usefulness of the notion of class effects resides in assigning drugs to outcome classes it is important to realise that differing degrees of effect upon a common outcome may place drugs in different outcome classes. For example, a drug that has a small effect on mortality should not automatically be grouped with one that has a marked effect. In such circumstances one would commonly expect to see along with differing degrees of outcome, differing degrees of effect on relevant biomarkers, in which case class effects would be ruled out based on non-comparability of efficacy ( $E_{max}$ ) and time course of response.

### ***The Usefulness Of Class Effects***

There clearly exists a spectrum of possible statements concerning the comparability of drugs. At one end a statement such as “identical drugs produce identical effects” is plainly true, but of very limited use. At the opposite end a statement such as “completely different drugs produce identical effects “ is plainly very useful, but is



almost certain to be untrue. The art and science of comparing drugs is concerned with finding a methodology that can reliably yield outcomes that are accepted as useful, probably true, and not subject to manipulation according to the outcome desired. That this methodology is somewhat elusive is well evidenced by the ongoing debates by agencies, companies and funders over fair comparison of different drugs. The approach that we have set out is towards the conservative end of the comparability spectrum. It is largely derived from the viewpoint of clinical pharmacology and is based on science and potentially reproducible and objective concepts.

### ***Limitations Of The Class Effect Concept***

There are a number of limitations of the class effect concept. When drugs share one or more class effects it does not mean that they are identical.

#### Adverse Events

Idiosyncratic adverse events are still likely despite identical mechanisms of action, and/or identical effects on biomarkers.

#### Multiple Mechanisms of Action

The mechanism of action that places a drug within a particular class may not be the sole mechanism of action of that drug. If these other actions are not related to the clinical outcomes of interest, then this may be innocent enough. Difficulty arises, however, if more than one mechanism of action (known or unknown) contributes to the outcome that is being ascribed to the drug as a class effect. The finding that statins may exert a number of different effects (such as actions on inflammation and vascular endothelium) quite apart from their action on HMG CoA reductase, raises the question of the extent to which these other actions contribute to clinical outcomes [16]. Suspicion that the clinical effect may be produced by a number of means perhaps unrelated to HMG CoA reductase inhibition or cholesterol lowering might throw the statin mechanism/biomarker class into doubt along with the notion that any statin will share clinical outcomes [4].

#### Refinements of Mechanism of Action

It is useful to appreciate that class effects are not static. A mechanism of action that has been used to assign class effects may undergo subsequent refinement (the identification of receptor subtypes for example) that renders class members less comparable than previously thought. Non steroidal antiinflammatory agents have long been regarded as an established mechanism class based upon their shared mechanism of action on the enzyme cyclooxygenase. Any blocker of cyclooxygenase would be expected to reduce levels of a number of prostaglandins, exhibit antiinflammatory action, and cause gastrointestinal bleeding. That is, they would, along with a common mechanism class, share biomarker and outcome classes. The discovery of the isoforms of cyclooxygenase and the development of the COX 2 specific inhibitors has necessitated a major redefinition of this view. COX 2 specific inhibitors are members of a different (albeit related) mechanism class from mixed inhibitors, share effects on some biomarkers but not others (the specific

markers of COX 1 and COX 2 activity for example), and belong to the same outcome class with respect to pain relief, but to a different outcome class with respect to gastrointestinal adverse events.

## CONCLUSION

The concept of class effects can be defined in a systematic way that is transparent and reproducible. In this context the concept can serve a useful purpose as a model for thought about the comparability of drugs. It is not a guarantee of truth. The concept can serve different purposes for different people at different times, and this important but often unrecognized aspect of class effects needs to be understood and acknowledged.

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