

Therapeutic drug substitution: The proof of the pudding is in the eating.

## Abstract

In many countries reimbursement rules regulate whether, and how, drugs are reimbursed after market authorization. The Netherlands' reimbursement system is based on a reference price model which maximizes reimbursement to fixed prices per cluster of drugs. By lowering the reference price, a co-payment may be required for more expensive drugs. The government now plans to lower the reference prices in the reimbursement clusters to include at least one drug which is out of patent and therefore available as a generic. However, resetting the reference price to the price of the cheapest generic means that a co-payment is then needed for other, mainly patented, higher-priced drugs in the same cluster.

The government's plans affect more than 150 reimbursement clusters, representing approximately 50% of all drug clusters and including thousands of different drugs. The expected savings are estimated to range between € 150 and € 250 million per year. Our study reveals that 60% of these savings consist of co-payments from 100.000 heavy drug users, representing severely ill patients, suffering from cardiovascular and psychiatric problems. The premise of the new policy is that the financial consequences for individual patients can be offset by switching to cheaper drugs which are equally effective and safe. Here it is assumed that drugs grouped into the same reimbursement cluster are interchangeable and hence that the financial problems can be dealt with through therapeutic drug substitution.

There is, however, a misunderstanding among decision makers that drugs that are classified within the same reimbursement groups are pharmaco-therapeutically interchangeable on the level of each individual patient. However, direct comparative studies between drug A and B are mostly lacking. In most, if not in all cases, drugs are already classified before they are ever used in daily practice. Based on pharmacological arguments, and without direct comparative testing, it is expected, but not scientifically proven that two drugs are interchangeable from a medical perspective. Moreover, clustering can not be the result of scientific studies because studies addressing the relative effectiveness of drug are lacking. Therefore, the financial drive may conflict with medical needs and ethics, if drugs within drug reimbursement clusters are less interchangeable than expected.

In this report we studied the scientific base of therapeutic drug substitution, i.e., substituting one drug with another made up of a different chemical composition, but both grouped into the same reimbursement group. In general the results of several analyses indicated that switching between reimbursement groups could cause medical chaos and that the expected savings in the pharmaceutical budget are very uncertain. This is because of flaws in the reimbursement system and the massive number of drugs affected by the

new policies. The pending policy can also be expected to result in an increase in both the pharmaceutical and medical budgets.

On the other hand, limited experiments in the US with single drug groups suggest that savings are possible without substantial medical problems. However, a major problem of many of these studies is that the financial effects are studied while the medical effects are merely suggested or implied. In general there is no scientific evidence of the medical consequences of therapeutic drug substitution in daily practice.

In some drug groups affected by the new policy (e.g. anti-cancer drugs, antibiotics), therapeutic substitution is beyond medical reasoning and contrasts with prescription guidelines endorsing good clinical practice.

In conclusion, results of this study can be summarized in six potential problems:

1. The consequences of drug substitution should not be evaluated from a pharmacological point of view or a population-based perspective. Pharmacological studies (RCT) may predict similarity but cannot exclude the possibility that drugs may have different therapeutic effects if used in daily practice.
2. Studies on relative effectiveness, comparing drug A and B in daily practice, are rare and, from a methodological perspective, impossible. Therefore there is no scientific basis for therapeutic drug substitution. Moreover, substitution based on pure financial reasons may have unexpected medical consequences and may therefore be considered unethical.
3. The negative, medical consequences, of therapeutic drug substitution depend on the pharmacological heterogeneity of the individual reimbursement clusters. This heterogeneity may range from dangerous substitution of anti-cancer drugs or the unknown effects of substituting antidepressants, to the reasonably safe substituting of proton pump inhibitors. Even in the latter categories, there is evidence that substitution may have adverse effects.
4. The current reimbursement system is based on the ATC classification system, a system that is not devised for that purpose. Although the ATC system is adapted for the objective of reimbursement, it includes several flaws and inconsistencies resulting in changing prescribing behaviour that costs rather than saves money.
5. The pending policy results in co-payment for an estimated 6 million out of 16 million Dutch patients. However, 60% of the savings are generated by approximately 100.000 severely ill cardiovascular and psychiatric patients. Co-payment among these patients may add up to € 1000 a year.

6. The administrative costs of implementing and maintaining the pending drug policy are considerable and may be as large as at least 50% of the projected savings.