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Review

Generic versus branded pharmacotherapy in Parkinson's disease: Does it matter? A review☆

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ABSTRACT

There is an ongoing debate about generic drug use for a multitude of conditions including epilepsy, psychosis, hypertension, post-organ transplantation, and several infectious diseases. Most of the concerns involve drugs with narrow therapeutic indices. There is a heightened attention to health care costs and macroeconomic policy as well as microeconomic business decisions that may impact the use of generic drugs. The issues surrounding generic substitution for chronic degenerative conditions such as in Parkinson's disease (PD) continue to be controversial subjects for physicians, pharmacists, patients, Medicare/governmental insurance programs, and for private insurance companies. The United States Food and Drug Administration (FDA) requires that generic drugs meet a standard for bioequivalence prior to market approval, but this may not translate to therapeutic efficacy or to overall patient tolerance. In this review we will address issues related to the use of generics versus branded drugs in PD, and the potential impact substitution of generics may have on patients and on clinicians. Having proper documentation may help in deciding the appropriate usage of these drugs in PD. Medicare, governmental run health care systems, and third party insurance companies should in a complex disease such as PD, allow physicians and patients the chance to properly document the superiority of brand versus generic approaches. Currently, in the U.S, and in many countries around the world, there is no obligation for payers to respect these types of patient specific bedside trials, and there has been no standardization of the process.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting both dopaminergic and non-dopaminergic neuronal systems. The typical motor manifestations include tremor, bradykinesia, and rigidity. Gait, postural instability, cognitive dysfunction, and other axial motor disturbances may occur with advancing disease. There is usually a good to excellent response to dopamine replacement therapy (i.e. levodopa or a dopamine agonist), particularly early in the disease course. Presently, there is still no cure, nor is there a proven disease modifying therapy. Since its discovery approximately 40 years ago [1], levodopa has been the standard medical therapy for PD. However, with disease progression, the response to medication may become increasingly inconsistent. Inevitably, patients usually later in the course of PD will require higher dosages, more frequent dosing, and the use of complex drug combinations to treat symptoms and to try to maintain as much quality of life as possible. Long term levodopa therapy is associated with motor fluctuations and dyskinesia, and these two issues may pose a challenge for both specialist and non-specialist physicians. Additionally, emergence of non-motor manifestations and comorbidities requiring use of a multitude of other non-dopaminergic drugs (e.g. SSRIs, antipsychotics, anticholinergics) have a largely unknown impact on levodopa absorption and transport in a PD patient.

PD incidence is known to increase with age [2], and as the population continues to age, the prevalence of PD will therefore increase. The progression of PD and its psychosocial consequences usually have a demonstrable impact on patients' health related quality of life [3,4]. The increase in the aged population, will stress health care utilization and also increase prescription drug use. Private and public insurers, as well as policy makers have been recently examining different strategies to lower health care costs.

Reducing health care related expenses is a compelling force for the use of generics as substitutes for branded products. The cost of medications creates both an economic burden for payers, and for patients, as the direct patient payment is typically a function of the total cost of the medication. Various reports have extensively examined the effects of generic substitution among patients with epilepsy [5–7], psychosis [8–10] organ transplant [11] and cardiac disorders [12], but no report has looked in depth into PD. This review article will examine the relevant issues pertaining to the use of generic drugs in the treatment of PD.

2. Economic impact of Parkinson's disease

PD is a chronic disease that often requires long term treatment with medications. In a study performed by Noyes et al. in 2006 [13], health related expenditures in PD patients were two times higher than the average American without PD (>65 years old). Medicare beneficiaries with PD tended to use more health care related services than beneficiaries without PD [14].

Medicare plays a major role in the U.S. health care system accounting for 23% of the total national health care spending [14] and its spending is influenced by prices of health care services, increasing volumes of patients, and the use of new services and new technologies. Drug prices for brand name products may increase as a result of economic inflation, and Medicare may have a difficult time compensating and adjusting for this change. Medicare may attempt to lower its spending by decreasing the amount paid to physicians, or alternatively by strategies such as increasing the requirements to use generic medications. The hope is that by the increased use of generic formulations, Medicare spending will be reduced in 2011 [15].

The number of PD cases in the US has been estimated at 340,000 in 2005, and is predicted to double by 2030. Estimating the number of undiagnosed and misdiagnosed patients, some estimates put the total number as high as 1 million [16]. According to a study done by O'Brien et al. [17], the annual economic cost of PD in the United States is approximately $10.8 billion, and 58% of this is direct medical costs. Skilled nursing costs are the single largest line item at $4.4 billion (41%) [17] and prescription drugs are second at $1.5–$2.4 billion (14%–22%). A study by Winter et al. [18] revealed that patients may use up to 43% of their income to shoulder drug costs. With the new U.S. health insurance law this may change with less out of pocket expenses. Additionally, in Italian [19] and German cohorts [20], it was found that the highest co-payments made by PD patients were for their antiparkinsonian drugs, and for medical equipment. These financial burdens have pushed insurance companies and the government health care systems toward generic formulations.

3. Generic drugs and bioequivalence

In an effort to reduce health related expenditures, many insurance companies have turned to generic substitution. Generic drugs are typically available at a fraction of the cost of branded forms. Currently, there are multiple pharmaceutical companies that manufacture a generic formulation of carbidopa/levodopa (i.e. Actavis US, Sandoz and Teva Pharmaceuticals among others). Dopamine agonists, monoamine oxidase inhibitors and anticholinergics are also available through various generic brands.

The manufacturers of a generic formulation must show that there is an "essential similarity" between the generic formulation and the commercially available branded originator. The US Food and Drug Administration (FDA) must approve whether a generic drug formulation is bioequivalent with its branded counterpart [21] before it can be marketed in the US. The basic assumption in bioequivalence is that the two (generics and brand) products are pharmaceutically equivalent, and that their bioavailabilities (rate and extent of availability) after being administered in the same molar dose are similar such that their efficacy and safety, can be expected to be the same. Pharmaceutical equivalents [22] mean that the two drugs have the same active ingredients, are of the same dosage form, route of administration and are identical in strength or concentration. The regulatory limits applied in bioequivalence studies require that the areas under the drug concentration versus time curves (AUC ratio of generics versus brand) be within 90% confidence intervals and the maximum plasma concentrations (C_{max} ratio between generics versus brand) fall within 80–125% [8,21]. These integral measures by definition do not consider that different rates of drug delivery may impact efficacy.

The development of a brand name formulation requires the demonstration of pharmacokinetics, efficacy, safety and tolerability. This must be performed in healthy subjects, and also in the target patient population. The development of a generic equivalent however, requires only the demonstration of bioequivalence with brand name counterparts and testing is done only in healthy subjects [23]. The fact that the generics are not tested on PD patients has the potential to result in a "relative therapeutic inequivalence," because of the uniqueness of the PD population. For example, PD patients often experience slow absorption of their first orally-administered dose of medication in the morning due to low gastric motility [24]. PD patients often use multiple drugs (i.e. dopamine agonists, anticholinergics, psychotropics) which may amplify differences between generic and branded formulations. Issues regarding drug–drug interactions with the different formulations of carbidopa/levodopa (extended release, immediate