

Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations

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ABSTRACT

Objectives: Suboptimal compliance and failure to persist with drug treatments are important determinants of therapeutic nonresponse and are of potential economic significance. The present article aims to describe the methodologies that may be appropriate for integrating noncompliance and nonpersistence in economic evaluations.

Methods: MEDLINE and NHS-EED were searched for economic evaluations published in the period between 1997 and 2005. Articles were included if they explored the dependence of cost-effectiveness results on varying levels of some form of compliance-related measure. The different methodologies used were reviewed and articles were appraised critically. Alternative methodological approaches are proposed, illustrated by an example of the impact of different persistence rates on a treatment's cost-effectiveness.

Results: Ten articles were selected for inclusion. These were generally scant on detail relating to how compliance/

persistence was assessed and what the impact was on health outcomes. The methods used included Markov models and decision analyses. Markov models allow for persistence to be included directly in the analysis, as patients transit during each cycle. Net-benefit regression models are well suited for analyzing prospective and retrospective studies where patient-level data are available, whereas discrete event simulations have the potential to offer more flexibility.

Conclusions: Compliance and/or persistence are not included routinely in pharmacoeconomic analyses, despite their potential impact. Where compliance and/or persistence are included, a lack of methodological rigor and consistency in definitions often limits the usefulness of the analyses. The analytical techniques discussed in this article should serve as a basis for developing guidelines on appropriate methodology.

Keywords: adherence, compliance, cost-effectiveness, economic evaluation, persistence.

Introduction

Pharmacoeconomic evaluations assess whether incremental improvements in outcome associated with a given drug justify the cost. The specific nature of this assessment can take various forms, but essentially requires a comparison of alternative treatments' costs and benefits. Many factors impact on these costs and benefits, one of which is how "well" the medicines are taken. Suboptimal compliance and/or failure to persist with therapy for the prescribed duration reduce the therapeutic potential of drug treatment, and account for many of the observed differences between efficacy and clinical effectiveness [1]. The purposes of this article are to highlight the importance of integrating compliance and persistence in pharmacoeconomic analyses, to identify and appraise recent evaluations that have integrated compliance and/or persistence, and to develop recommendations on how pharmacoeconomic evaluations should integrate medication

noncompliance and nonpersistence, in line with standard economic evaluation methodological guidelines.

Definitions

There is great disparity in how compliance and persistence are defined, particularly in the health economic literature [2]. Recently, the International Society of Pharmacoeconomics & Outcomes Research (ISPOR) special interest group on medication compliance and persistence set out to standardize definitions and these are summarized below.

Medication compliance (synonym: adherence), as defined by ISPOR, is "the extent to which a patient acts in accordance with the prescribed interval, dose, and dosing regimen. It is typically expressed as a percentage of total number of doses taken (if prospectively measured) or therapy-days available (if retrospectively measured), in relation to the time period of observation during which compliance is measured" [3].

Medication persistence is "the length of time from initiation to discontinuation of therapy and is measured in units of time" [3].

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Although not considered in these definitions or in the present review, compliance has also to do with patients' quality of medicine taking, e.g., whether medicines are taken with or after food, swallowed whole and not chewed, and so forth. These are less easily measured or quantified but for some medicines, are of equal importance.

Impact of Compliance and Persistence on Clinical Effectiveness

Since pharmacoeconomic evaluations assess the cost-benefit balance, the impact of poor compliance and persistence on effectiveness is as important as the impact on costs. Highly efficacious medicine may have poor clinical effectiveness unless taken, and taken properly. The exact extent to which poor compliance and persistence will affect clinical effectiveness is a complicated issue, but a question that must be addressed in any quantitative pharmacoeconomic evaluation that wishes to take account of compliance and persistence.

Any relationship between compliance, persistence, and a medicine's effectiveness relies on the fundamental premise that the medicine can work (i.e., is efficacious). It is important to recognize that in some instances, noncompliance may not always result in clinically meaningful differences between efficacy and effectiveness. An example may include a drug that has a long duration of action in relation to its dosing interval, so that missing one or two doses may not be so critical (e.g., atorvastatin, aspirin). This is referred to as forgiveness, and is a measure of the ability of a drug to maintain therapeutic activity despite the presence of noncompliance [4].

Impact of Compliance and Persistence on Health-Care Resource Utilization and Costs

The impact of noncompliance and nonpersistence on health-care resource utilization (HCRU) and, therefore, costs are likely to work in two ways:

1. The immediate and direct impact of poor compliance/persistence on medicine acquisition costs; and
2. The less immediate and indirect impact of poor compliance/persistence on subsequent overall HCRU associated with the condition being treated, as a result of affecting clinical effectiveness, and thus health outcomes as discussed above. The contribution of adverse drug reactions to noncompliance and nonpersistence, and their impact on HCRU are also likely to feature.

Logically, poor compliance/persistence is likely to reduce medicine acquisition costs, but increase subse-

quent overall HCRU. These two cost-drivers may well thus be operating in opposite directions.

The impact on medicine acquisition costs is determined most obviously by the extent of poor compliance/persistence, i.e., a complete lack of compliance and persistence will not cost much. Nevertheless, a more complex issue is how medicine acquisition costs are generated in relation to medicine-taking behaviors. For example, if poor persistence is manifested by patients continuing to obtain prescriptions but stockpiling their medicines, then poor persistence will cost as much as perfect persistence. Further, the overuse of medicines, itself a form of noncompliance, may increase treatment costs.

The impact on subsequent overall HCRU will be determined primarily by the level of impact on clinical effectiveness, and on the relationship between effectiveness and HCRU. For example, if a medicine is highly "unforgiving" in relation to compliance, and the HCRU associated with suboptimal management of the condition is high, then the impact of poor compliance on HCRU will be large.

Sokol et al. [5] conducted a retrospective cohort study to evaluate the impact of medication noncompliance on HCRU and costs for hypercholesterolemia, diabetes, hypertension, and congestive heart failure in 137,277 patients in the United States. Compliance was defined as the number of days' supply of maintenance medications (expressed as a 1-year percentage), obtained from administration claims data, for each condition. For hypercholesterolemia and diabetes, high levels of compliance (80–100%) were associated with lower disease-related medical costs. Higher medication costs were more than offset by medical cost reductions, producing an overall reduction in health-care costs. For hypertension, there was a trend toward lower medical costs at 80% to 100% compliance, but this was not statistically significant. No differences in costs between compliance levels were evident for congestive heart failure.

Controlling for demographic and socioeconomic characteristics, increases in 12-month risk of hospitalization were evident in all four conditions as compliance declined [5]. For diabetes, patients in the 80–100% compliance group had a 13% risk of diabetes-related hospitalization, compared with 20% in the 60–79% compliance group, and 24% in the 40–59% compliance group. Similarly, for hypertensive patients, high levels of compliance (80–100%) were associated with a reduced risk of hypertension-related hospitalization (19%) compared with lower levels of compliance (40–59% compliance, 24% risk). When considering all-cause hospitalization, a more pronounced difference was apparent, possibly an indication that noncompliance with one medication is associated with noncompliance with other medications for a comorbid condition.

Compliance, Persistence, and Pharmacoeconomics from the Perspectives of the Pharmaceutical Industry and the Health-Care Provider/Payer

From the perspective of the pharmaceutical industry, compliance is becoming increasingly important for product differentiation. By this we mean whether manufacturers of product X can claim superiority over competitor product Y on the basis of improved compliance (as opposed to the traditional factors such as efficacy, safety, cost, and cost-effectiveness). This is often accomplished by developing products that require less frequent dosing which makes them more patient-friendly, or that are administered by different methods (e.g., injectable depot preparations compared with oral) which can help to ensure compliance. These include, among others, once-weekly and once-monthly bisphosphonates for the treatment of postmenopausal osteoporosis; long-acting transdermal, implantable, and injectable hormonal contraceptives; and fortnightly injectable risperidone for the management of schizophrenia. Moreover, combination preparations or products that replace the need for taking an additional medication to provide protection against the adverse effects of a drug (e.g., gastroprotective agents coprescribed with nonsteroidal antiinflammatory drugs) may also help increase compliance.

Manufacturers of such preparations often seek to demonstrate whether simplification of the dosing regimens result in better health outcomes [6] and how this alters the cost-effectiveness of the product. This in turn may allow positive reimbursement decisions and increased market access, thus improving the commercial success of these products. Nevertheless, factors besides compliance are likely to affect the relationship between dosing regimens, health outcomes and costs, and these may not always favor the product [7].

Providers and payers of health care are increasingly concerned about value for money. Nevertheless, the extent to which patient compliance and persistence is considered by decision-making authorities is unclear. The National Institute for Health and Clinical Excellence in the UK, for instance, considered compliance and persistence as a determinant of cost-effectiveness in their recent evaluation of long-acting reversible contraception [8], but not in the evaluation of newer drugs for epilepsy in adults [9] or in the guidance on glitazones for patients with type 2 diabetes [10]. The selective incorporation of compliance and persistence in some economic evaluations probably reflects a lack of standardization in the guidance on health technology appraisals for their consideration [11]. Data availability is also an issue, particularly as information relating to patients who discontinue treatment is almost never reported or even collected. This makes it difficult to incorporate compliances into economic analyses, and

often requires broad assumptions be made. More complete patient follow-up (e.g., comprehensive cohort trial design), drug utilization data (such as administrative claims databases in the United States), and compliance measurements (such as electronic monitoring devices) are necessary to facilitate data availability.

Empirical Evidence of the Impact of Compliance and Persistence on Cost-Effectiveness

The combined impact of noncompliance/nonpersistence on both health outcomes and costs requires the use of economic evaluations. Hughes et al. [12] and Cleemput et al. [13] reviewed the literature for pharmacoeconomic evaluations that considered noncompliance and identified a need for better methods for integrating noncompliance/persistence in economic evaluations. Here, we describe an update of the reviews to gain an insight as to whether approaches of incorporating noncompliance into pharmacoeconomic evaluations have improved since the original publications. The present work, however, is not intended to be a systematic review with full methodological rigor.

Methods

Pharmacoeconomic evaluations published between 1997 and June 2005 and which included (non)compliance or (non)persistence as inputs in the evaluation process were identified through searches of MEDLINE and NHS-EED. Appropriate Boolean operators were specified for pharmacological treatments to identify articles that were common to the following two groups of search terms:

1. references to a cost-effectiveness evaluation in the title: cost-effective\$, cost-utility; and
2. compliance, non-compliance, noncompliance, adherence, non-adherence, nonadherence, persistence, non-persistence, nonpersistence, discontinuation, concordance.

No language restrictions were specified.

The search identified 84 articles, of which 21 were retrieved after screening the abstracts. Of these, 10 reported how cost-effectiveness results changed according to varying levels of some form of compliance measure, and were included in the review.

Findings

All included evaluations considered pharmacological treatments for chronic use, ranging from antipsychotic medications to antituberculous drugs. A summary of the reviewed evaluations, details of the type of noncompliance considered, and the impact of noncompliance on the costs, effects, and cost-effectiveness results is presented in Table 1.

Table 1 Summary of the methods, assumptions, and results of the economic analyses identified in the literature review

Reference/ disease/ interventions examined	Model design and how compliance/ persistence is captured	Measure of compliance/ persistence	Values of compliance/ persistence	Assumption of effectiveness and costs with noncompliance	Effects/costs	ICER	Sensitivity analysis with regards to rates of compliance
Edwards [14] Schizophrenia risperidone long- acting injection (LA); oral risperidone; oral olanzapine; haloperidol decanoate LAI	Decision analysis model Decision tree with branches representing different rates of compliance	Compliance: mean number of medication bottle openings not exceeding the number of doses prescribed for the day divided by the prescribed daily doses	Compliant (>50%): risperidone LAI; oral risperidone; oral olanzapine; haloperidol decanoate LAI, respectively: 59.2%, 20%, 20%, 13.4%. Partially compliant (stopped taking medication for <1 week), respectively: 36.2%, 70.9%, 70.9%, 73%; Noncompliant (stopped medication for >1 week)	Relapse rates are a function of patient compliance and drug efficacy	Effects risperidone LAI more effective for each outcome measure Costs risperidone LAI associated with USD 397, USD 1742, USD 8000 savings vs. oral risperidone, oral olanzapine and haloperidol decanoate LAI, respectively	Risperidone LAI dominates all comparators	No sensitivity analysis applied to compliance
Hughes [15] Urge urinary incontinence associated with overactive bladder oxybutinin extended release (Oxy-XL); tolterodine extended release Tol-ER; tolterodine immediate release (Tol-IR); oxybutinin immediate release (Oxy-IR)	Empirical models of efficacy and persistence to extrapolate drug effect to 1 year	Persistence: proportion of patients who remained on their initially prescribed drug	Biexponential model with lagged time that fitted observed data best	In base-case scenario, treatment fails in patients who discontinue as a result of adverse effects. These are assumed to adopt baseline disease characteristics. Those who discontinue as a consequence of experiencing some health benefits are assumed to adopt placebo characteristics	Effects For Oxy-IR, Oxy-XL, Tol-IR, Tol-ER, annual number of incontinent free weeks: 7.5, 11.1, 9.6, 10.9, respectively, Costs Total annual cost: £39.61, £78.77, £74.21, £63.91, respectively, for Oxy-IR, Oxy-XL, Tol-IR, Tol-ER	Cost per incontinent free week £5.26 for Oxy-IR (vs. placebo); £7.14 for Tol-ER (ICER vs. Oxy-IR); and £84.82 for Oxy-XL (ICER vs. Tol-ER); Tol-IR was dominated	Alternative scenarios: All patients who discontinued adopted baseline- disease characteristics; All patients who discontinued adopted placebo characteristics; All patients continued with therapy Oxy-IR remains cost-effective and Tol-IR dominated in all scenarios

Table 1 continued

Reference/ disease/ interventions examined	Model design and how compliance/ persistence is captured	Measure of compliance/ persistence	Values of compliance/ persistence	Assumption of effectiveness and costs with noncompliance	Effects/costs	ICER	Sensitivity analysis with regards to rates of compliance
O'Brien [16] Urge incontinence related with overactive bladder Generic oxybutinin with switch to tolterodine for patients who discontinue; generic oxybutinin with no further treatment for patients who discontinue	Markov model with dropout as one of the health states; transition probability is determined by discontinuation rate	Discontinuation rate from RCT adjusted by observational data	Adjusted discontinuation rate for oxybutinin, and tolterodine, respectively: 47.8% and 14.96%	Not stated for effects Cost of physician visit for change of therapy incurred when drug is discontinued	Effects For those discontinuing oxybutinin, the use of tolterodine is associated with 6 months per year in a normal/ mild disease state compared with 3 months for those who do not receive further therapy Costs Tolterodine results in an annual additional cost of Can\$163 per patient	Incremental cost per QALY was Can\$9982	Discontinuation rates were not varied in sensitivity analysis
Chisholm [17] Idiopathic epilepsy and syndromes phenobarbitone (PB); phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA)	State-transition population model Movement between states determined by a set of epidemiological transition probabilities. Compliance is one element in deriving transition rates	Adherence: not stated	70% in base-case; 60% and 80% in sensitivity analysis	Disability and remission improvements (efficacy) were adjusted by treatment coverage level, treatment response and compliance rate	Effects No difference was found between different drugs with respect to efficacy or effectiveness Costs Order reflecting drug acquisition costs	Average cost- effectiveness ratios: PB or PHT (\$800–2000 International dollars) per DALY averted; CBZ or VPA 1\$1100–3000	Compliance was varied in multiway extreme case analyses. In best- case scenario, total costs were 15–30% lower and effects 43% greater; in worst-case scenario costs were up 20–35% and effects lower 36%
Hemels [18] Severe depression, escitalopram, citalopram	Decision analysis model Treatment discontinuation at 8 weeks and compliance at later stage form branches of decision tree; probabilities determined by rates of compliance	Discontinuation of treatment at 8 weeks; switch to new treatment; premature discontinuation (before 6 months)	Discontinuation rate at 8 weeks: 0.117 and 0.137 for escitalopram and citalopram, respectively. Compliance with both regimens: 0.634. Compliance with switched treatment: 0.697 in both cases	Spontaneous remission rate of 20% for those who discontinued or switched at 8 weeks; for premature discontinuation, remission rate was 52%. Costs associated with treatment discontinuation included adverse events, use of other antidepressants, additional GP and psychiatrist visits, hospitalization	Effects Clinical remission rate 53.7% and 48.7%, for escitalopram and citalopram, respectively. Costs Total cost of treatments per successfully treated severely depressed patient was Euro 5610 and Euro 6979, for escitalopram and citalopram, respectively	Escitalopram dominates citalopram	Escitalopram remained the dominant strategy by varying the discontinuation rate at 8 weeks between 0.057 and 0.197

<p>Haby [19] Major depressive disorder in children and adolescents Cognitive behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs) compared with "current practice"</p>	<p>Decision analysis model Compliance with intervention forms branches of decision tree</p>	<p>Compliance: completion rates from RCTs</p>	<p>68% for CBT (50-85% in sensitivity analysis); 63% for SSRIs (50-76% in sensitivity analysis)</p>	<p>For cases not compliant with treatment there was no improvement is disability but costs of treatment were still incurred</p>	<p>Effects 360 and 230 DALYs averted vs. current practice for CBT and SSRIs, respectively Costs AUS\$5.8 million for CBT; AUS\$7.8 million for SSRIs vs. current practice</p>	<p>AUS\$9000 per DALY averted for CBT; AUS\$23,000 per DALY averted for SSRIs</p>	<p>Probabilistic sensitivity analysis, but effect of varying compliance rate is not presented. Nevertheless, compliance is acknowledged to contribute to uncertainty</p>
<p>Donnelly [20] Childhood attention deficit hyperactivity disorder dexamphetamine (DEX), methylphenidate (MPH) compared with "current practice"</p>	<p>Decision analysis model Compliance with intervention forms branches of decision tree</p>	<p>Percentage of patients complying with intervention. Adherence: taking the medication for 5 or more days per week throughout the follow-up period, with the exception of "drug holidays" totalling no more than 14 weeks</p>	<p>Minimum 56% Maximum 81%</p>	<p>Noncompliant patients incur costs (equal to those receiving current practice) and no health benefits</p>	<p>Effects 435 DALYs for DEX, 480 DALYs for MPH Costs Total costs: AUS\$1.7 million for CBT, AUS\$7 million for MPH</p>	<p>AUS\$4100 per DALY averted for DEX, AUS\$15000 per DALY averted for MPH</p>	<p>Probabilistic sensitivity analysis, but effect of varying compliance rate is not presented</p>
<p>Suarez [21] Patients with chronic tuberculosis kanamycin, (first 3 months); ciprofloxacin; ethionamide; pyrazinamide; ethambutol; second-line drug therapy vs. isoniazid</p>	<p>Prospective follow-up</p>	<p>Default with treatment regimen: Patients who did not attend to take their drugs for one or more months after registration</p>	<p>7% default rate assumed for all regimens except for patients treated with individualized regimen after nonresponse to the standardized second-line drug regimen, where 12% default rate was assumed</p>	<p>No cure for defaulters; costs were incurred in defaulters</p>	<p>Not reported</p>	<p>Cost per DALY gained US\$270, 493 and 672, respectively, for the 3 programs</p>	<p>Results are only presented for those who completed the treatment</p>

Table 1 continued

Reference/ disease/ interventions examined	Model design and how compliance/ persistence is captured	Measure of compliance/ persistence	Values of compliance/ persistence	Assumption of effectiveness and costs with noncompliance	Effects/costs	ICER	Sensitivity analysis with regards to rates of compliance
Jasmer [22] Patients with radiographic evidence of previous TB and positive tuberculin test who had no prior treatment	Markov model with 1000 hypothetical patients aged 52–99 years	Completion of therapy: complete if patients returned for all clinic visits and were deemed to have been compliant with therapy. Standard protocol was used to question patients regarding medication ingestion	Isoniazid: completion of 12 months 79.8%; 6–11 months 3.4%; <6 months 16.7% Isoniazid and rifampin: Completion of 4 months treatment 83.6%; 2–3 months treatment 7.1%; <2 months 9.2%	Isoniazid: 12 months reduced the annual risk of TB by 89%; 6–11 months by 67%; <6 months no benefits; Isoniazid and rifampin: 4 months, 89% reduction; 2–3 months of treatment 67%; <2 months, no benefits	Effects Both regimens increased life expectancy by 1.4–1.5 years Costs \$539 and \$405 per patient for isoniazid and isoniazid plus rifampin, respectively	Isoniazid and rifampin produced net incremental savings of \$135 per patient treated over the isoniazid strategy	Completion rates were not varied
Cobos [23] Simulated cohort of 10,000 hypercholesterole- mic patients fluvastatin; lovastatin; pravastatin; simvastatin	Stochastic simulation model Probability of treatment discontinuation was taken into account	A Bernoulli random variable indicating probability of discontinuation was added to the model to simulate the effect of therapy	Probability of discontinuation was 60% in first year of treatment, distributed as 25% in first month, 50% within first 3 months and 25% to the end of the year	Lack of compliance was classified as therapeutic failure, LDL-C values were set back to baseline levels	Effects Highest success rate with simvastatin, followed by pravastatin, fluvastatin, and lovastatin. LDL-C reduced by between 36% and 40% Costs Fluvastatin was least expensive	Fluvastatin most cost-effective	Compared with the more efficacious alternative, differences in efficacy, never exceeded 4% for dropout rate scenarios 40% and 60%, or 6% with full persistence. Fluvastatin was most cost-effective strategy in 30 scenarios; lovastatin was most cost-effective in 2 (with 0% dropout rate)

DALY, disability-adjusted life-year; ICER, incremental cost-effectiveness ratio.

An explicit definition of compliance or persistence was not given in all studies. Nevertheless, the measure of compliance (or persistence) was provided in most cases; therefore, it was possible to obtain an implicit definition. The data sources for compliance or persistence rates were based on relevant studies, randomized controlled studies, or observational data. Edwards et al. [14] based their analyses on electronic measurement of medication bottle openings. In some cases, patients were considered compliant above, and non-compliant below, an arbitrary cutoff point. This ranged from 50% to 93% without evidence justifying the clinical relevance of the chosen value among the articles reviewed [14,21].

The most important assumptions underlying these studies are those relating noncompliance (or nonpersistence) to the effects and the costs of treatment. A few studies had some supporting evidence for the link between noncompliance and effects [14,18,22], but others relied on simple assumptions, e.g., noncompliant patients incurred no health benefits [19,20,21,23]. The impact of noncompliance on costs, if accounted for at all, was derived indirectly from the assumed changes in effects [16,18,20,21].

Modeling in the Reviewed Evaluations

A variety of decision-analytic, Markov, and other modeling techniques were used in the evaluations (Table 1).

In the cases of decision-analysis models, the branches of the decision trees represented different levels of compliance, and probabilities were assigned accordingly [14,18,19,20]. In the cost-effectiveness analysis of various antipsychotic drugs, Edwards et al. [14] specified three branches in the decision tree: compliant, partially compliant, and noncompliant. Patients had different levels of compliance with the evaluated drugs, based on evidence from the literature. Relapse rates in schizophrenia were specified as a function of patient compliance and drug efficacy, based on two studies; one of which utilized the medication event monitoring system, which is considered to be an objective method of assessing compliance.

In Markov models, dropping out was one of the possible health states, and the transition probabilities were determined by the discontinuation rates based on a combination of randomized controlled trial (RCT) and observed data [16,22]. Jasmer et al. [22] applied different rates of completion to different durations of isoniazid or isoniazid plus rifampin therapies in patients with radiographic evidence of previous tuberculosis, and positive tuberculin test that had no prior treatment. The reduction in the annual risk of tuberculosis varied according to how long patients continued with their respective therapies. The efficacy of varying durations of preventive strategy for tuberculo-

sis was based on a 5-year follow-up strategy (isoniazid) and on assumptions (for the combination of isoniazid plus rifampin).

In the pharmacoeconomic evaluation of drugs for the management of urge incontinence associated with overactive bladder, Hughes and Dubois [15] built an empiric model that combined observational data on the proportion of patients who remained on their initially prescribed therapy with trial data on drug efficacy. In the base-case analysis, patients who discontinued because of adverse effect were assumed to adopt baseline disease characteristics and those who discontinued as a result of experiencing some early health benefit were assumed to adopt placebo characteristics.

Some of the studies that were identified explored the impact of varying compliance in sensitivity analyses [17,18,23], and it is likely that there are other unidentified pharmacoeconomic evaluations that did so as well. Nevertheless, in general, there was a great deal of inconsistency in the definitions adopted and methods used, and no overall improvement is apparent since the reviews of Hughes et al. [12] and Cleemput et al. [13]. These limitations make it difficult to draw valid conclusions on the impact of noncompliance on the cost-effectiveness of treatments, and to compare this across different therapeutic areas.

Integrating Compliance and/or Persistence in Pharmacoeconomic Evaluations

Since earlier studies have shown that definitions to be inconsistent, and output inconclusive, the section that follows describes different techniques that are suitable for incorporating noncompliance and/or persistence in pharmacoeconomic evaluations. Emphasis is placed on approaches to modeling to improve methodological rigor, with the choice of model being dependent on:

1. the condition being treated (e.g., acute vs. chronic);
2. data availability (individual vs. aggregated data); and
3. type of compliance (compliance vs. persistence).

Net-Benefit Regression

When patient-level data are available on costs, health outcomes, compliance and/or persistence, the most comprehensive approach is to include a measure of compliance as a covariate in a model of net monetary benefit—an extension to the framework suggested by Hoch et al. [24]. This is one approach for analyzing the results of an economic evaluation that has been conducted alongside a prospective clinical trial.

The net-benefit regression approach exploits the linear nature of the net-benefit statistic, which circumvents the disadvantages related to behavior of incremental cost-effectiveness ratios when differences in

benefits approach zero. For the individual, the net monetary benefit (NMB) is calculated as follows:

$$NMB_i = \lambda E_i - C_i$$

where λ is used to denote the maximum willingness to pay for an additional unit improvement in health outcome, E_i and C_i are the observed effect and cost for subject i . Within a regression framework, the contribution of compliance and other explanatory variables to the NMB may be calculated. Thus, for instance, the NMB of a drug in patient i may be specified as follows:

$$NMB_i = \alpha + \beta_1 Age_i + \beta_2 DRUG_i Compliance_i + \beta_3 DRUG_i Persistence_i + \dots + \delta DRUG_i + \varepsilon_i$$

Where α is an intercept term, β s are the coefficients of the regression relating to each covariate, and ε is a stochastic error term. DRUG represents a treatment dummy, taking the value of 0 for the standard treatment, and 1 for the test treatment. Interaction terms that may include a time dimension, or both compliance and persistence (for instance), may also be included in the model. The regression coefficients can be used to estimate the incremental net benefit of the drug at varying levels of persistence and compliance; at 100% compliance and persistence it would be $\delta + \beta_2 + \beta_3$. Within such a framework, compliance would need to be measured using a standardized metric that is the strongest independent predictor of outcome and/or cost.

The advantage of this approach is that the impact of compliance on cost-effectiveness may be assessed at an individual patient level, thereby providing a robust estimate of population cost-effectiveness together with fully characterized uncertainty. There are, however, certain disadvantages to the net-benefit regression model, and these include the fact that both costs and outcomes are analyzed concurrently. Greater power may be afforded by explaining costs and effectiveness separately. With regards to persistence, and in common with other methods of survival analysis, attention must be given to the phenomenon of censoring: some patients may discontinue treatment prematurely after the time horizon of analysis.

Decision-Analytic Model

When a model is to be developed from existing published sources of evidence, a decision-analytic model, as described in some of the articles identified in the literature review [14,18–20], is appropriate, particularly for acute conditions. Branches of the decision trees may be used to represent different levels of compliance, which may be available from published sources. This requires that an understanding is made of the relationship between compliance and outcomes: categorizing compliance into greater or equal to 80% and less than 80%, is often not appropriate. Neverthe-

less, in most instances, differentiating patients to the broad categories of compliers and noncompliers, or a number of clusters with different levels of compliance, based on tablet counts or electronic monitoring data, is probably a reasonable approximation to make.

Discrete Event Simulation

Discrete event simulations (DES) are a form of modeling that observe the time-based (or dynamic) behavior of a system, and are therefore potentially well suited to analyzing the pharmacoeconomic impact of noncompliance and nonpersistence [25]. DES specified with patients as entities and treatment discontinuation as events, allow the analyst to assign patient attributes, which may alter depending on the occurrence of discontinuation. Modeling at the level of the individual allows for continuous measures of compliance, and greatly facilitates interactions between compliance and time, as well as individual characteristics (e.g., compliance with drugs for asthma may be highly correlated with the severity of symptoms). No examples of the use of DES to assess compliance or persistence have been identified.

Markov Model

Hughes et al. [2] advocated a method for integrating persistence in health economic evaluations by use of a Markov model. Examples of the use of Markov models were also identified in the literature review, and are appropriate for chronic diseases where nonpersistence is an issue. For each cycle in a model, a proportion of patients who discontinue therapy experience a higher risk of disease progression than those continuing treatment.

This is illustrated with a simple hypothetical example (Fig. 1) of a relatively inexpensive drug treatment for a chronic condition that may be represented by two health states “progressive” and “remissive.” Progression from the remissive state to progressive state is dependent on an annual transition probability, Pt_1 . For those patients who discontinue treatment, Pt_1 is assumed to increase—in other words, disease progression is accelerated in comparison with treated patients. The probability of death from progressive and remissive health states is represented by transitional probabilities Pt_2 and Pt_3 , respectively. These are assumed to be independent of whether or not patients continue treatment. The parameter estimates used in the model are listed in Table 2.

Age-standardized life-table probabilities were assumed for death in the remissive state [26]. The results of the model show that over a lifetime, a cohort of 100 hypothetical patients (which includes patients who persist and those who discontinue), would accumulate 58 less years of life, 94 less quality-adjusted life-years (QALYs), but at £19,224 less cost (all undiscounted) than a corresponding cohort of patients with

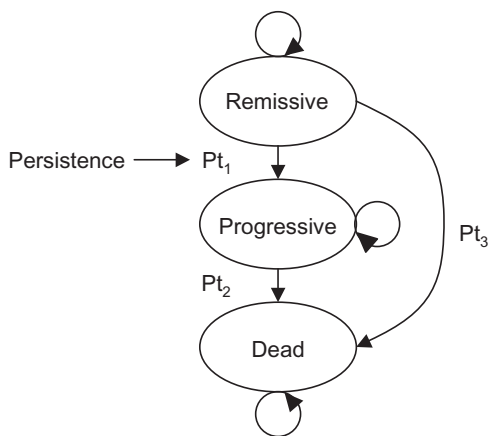


Figure 1 Schematic representation of a Markov model representing a disease with two health states, remissive and progressive, and death. Transition among health states is determined by transition probabilities Pt_1 (which is increased in patients who do not persist with treatment), Pt_2 and Pt_3 .

100% persistence. The reduction in cost is owing to fewer drugs being used as a consequence of nonpersistence. Figure 2 illustrates the relationship between persistence (%) at 5 years, and the changes in total health-care costs, and disaggregated (drug and nondrug) costs. Figure 3 presents changes in outcomes (life-years gained and QALYs) that would be expected in a hypothetical cohort of 100 patients with different persistence rates.

The cost-effectiveness plane, obtained through plotting differences in total cost against differences in outcomes (QALYs), for different persistence rates, is depicted in Figure 4. The origin in Figure 4 represents 100% persistence. For a hypothetical base-case scenario of £1000 per annum in the progressive health state, incremental changes in costs and outcomes, resulting from reduced persistence, render the drug less effective, and less costly at 5-year persistence rates greater than 35%. At lower persistence rates, savings in drug costs are outweighed by increases in nondrug costs, resulting in a shift to the northwest quadrant of the cost-effectiveness plane. It is evident from Figure 4

Table 2 Parameter estimates for the Markov model of the impact of persistence on cost-effectiveness

Parameter	Estimate
Age of entry to the model	45 years
Pt_1 (patients on therapy)	10%
Pt_1 (patients off therapy)	20%
Relative risk of death (progressive vs. remissive), Pt_2/Pt_3	2
Persistence (percentage of patients continuing at 5 years)	60%
Utility in "progressive" health state	0.7
Utility in "remissive" health state	0.9
Annual cost in "progressive" health state	£1000
Annual cost in "remissive" health state	£200
Annual drug cost	£100

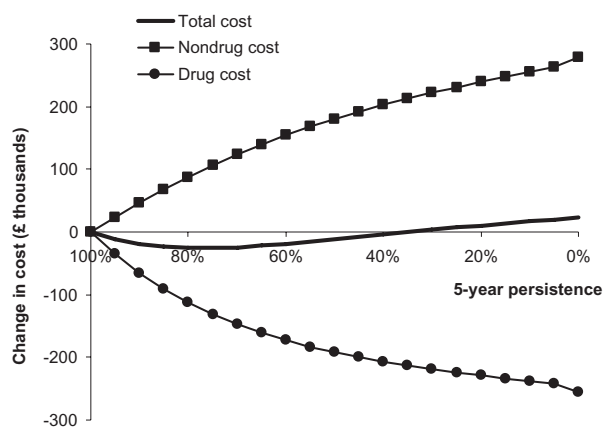


Figure 2 Impact of persistence on drug costs, health-care costs and total costs.

that the impact of nonpersistence on the cost-effectiveness is sensitive to the costs of health care associated with the progressive health state.

When developing a model that incorporates a measure of persistence, data are required on health outcomes and costs in patients who discontinue. If costs are dependent on time in a health state and duration of drug therapy, as in the illustrative example, a model will require estimates of transition probabilities that would be affected by drug discontinuation. In the example, the transitional probability of advancing from a remissive to a progressive health state, Pt_1 , in patients "off therapy" may be regarded as being equivalent to disease progression observed in the placebo group of a RCT [15,27]. It is important, however, to assess this in the light of any specific reason why patients may not persist with treatment and any trial inclusion/exclusion criteria that may not be representative of the wider population [28].

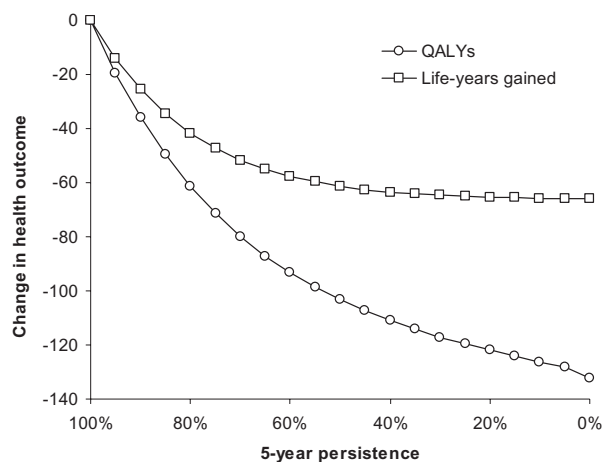


Figure 3 Impact of persistence on quality-adjusted life-years (QALYs) and life-years gained.

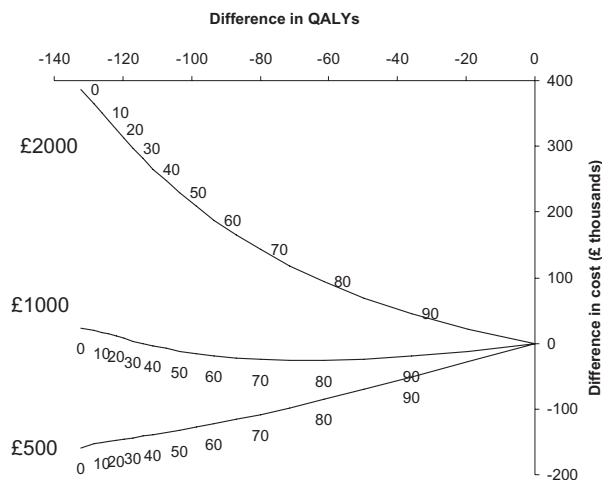


Figure 4 Cost-effectiveness plane, illustrating the impact of decreasing the 5-year persistence from 100% (at the origin) to 0%. The analysis is repeated, by use of sensitivity analysis, for annual costs in the “progressive” health state of £500, £1000 (base case), and £2000. QALY, quality-adjusted life-year.

Statistical bias may therefore be introduced when evidence on compliance and/or persistence is omitted from pharmacoeconomic evaluations. Bias is also introduced if compliance and/or persistence is incorrectly integrated, resulting from either problems of definitions (e.g., not being specific whether percentage compliance relates to percentage of patients who persist, or percentage of prescriptions filled), or methodological problems, for instance, if incorrect assumptions are made regarding the impact of noncompliance (persistence) on health outcomes and costs.

The example illustrates that the lack of persistence with effective therapies results in not only worsening of health outcome, but also a change in cost-effectiveness. A drug that is cost-effective when economic calculations are based on efficacy studies is less likely to be cost-effective when consideration is made of real-world (effectiveness) utilization data on persistence. Thus, a different decision on resource allocation may be arrived when considering persistence in an economic evaluation.

Conclusions and Recommendations

Compliance and persistence with drug therapies are important determinants for successful management of chronic conditions. They also impact on the economics of disease management, in terms of both drug acquisition costs and HCRU that may be associated with drug side effects and the sequelae of the untreated condition. Therefore, consideration of the effects of noncompliance and nonpersistence should be an integral part of pharmacoeconomic evaluations and in the health-care decision-making these evaluations inform.

Nevertheless, to date, the work in this is sparse, and the limited evidence available has methodological limitations. Further, the terms “compliance” and “persistence” themselves have been variously and unclearly specified, and a lack of consensus on their quantitative measurement poses a challenge for analysts. Research on the effects of compliance and persistence on real-life clinical effectiveness and cost is inherently problematic, and often seems to be the “poor cousin” of traditional randomized trials of efficacy and safety. Lastly, the development of economic modeling techniques to investigate relative compliance and persistence is consequently challenging; this is reflected in the results of the literature search reported in this article, and the lack of consensus guidelines from Health Technology Assessment (HTA) bodies in this area.

Nevertheless, as reviewed in this article, a range of approaches can, and have been applied to assessing the pharmacoeconomic effects of compliance and persistence. These include:

1. the possibility of designing prospective trials with both compliance and persistence variables, in addition to clinical and economic end points;
2. regression analyses of retrospective studies providing these same data;
3. modeling the extrapolated clinical and cost impact of compliance and persistence; and
4. the subsequent decision-analytic model which could synthesize information from any of these methods.

The results of these analyses are of interest to a wide range of stakeholders, from prescribers and patients, to health-care policymakers, and the manufacturers of these drugs. It is our recommendation that further research in this field is required, with one objective being the development of formal HTA guidance on appropriate methodology and standards. The approaches described herein might serve as a basis for developing such guidance.

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