NBER WORKING PAPER SERIES

HEDONIC ANALYSIS OF ARTHRITIS DRUGS

Iain M. Cockburn
Aslam H. Anis

Working Paper 6574
http://www.nber.org/papers/w6574

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
May 1998

We thank Ernst Berndt, Zvi Griliches, John Esdaile, and participants in NBER seminars for helpful comments, and Jennifer Anderson and David Felson for access to their databases on safety/efficacy profiles. We are grateful to BC Pharmacare for access to claims data, BEA, NBER and Eli Lilly for financial support, and Merck for access to library records. Sophia Wang provided invaluable and very competent research assistance. The authors take full responsibility for any remaining errors. Any opinions expressed are those of the authors and not those of the National Bureau of Economic Research.

Hedonic Analysis of Arthritis Drugs
Iain M. Cockburn and Aslam H. Anis
NBER Working Paper No. 6574
May 1998
JEL Nos. I11, L51

ABSTRACT

We examine the relationship between "quality"" and market outcomes for a group of drugs used to treat rheumatoid arthritis. Though this is a widespread and debilitating disease with very substantial impacts on the health of patients and on the economy, currently available drugs have limited efficacy and serious side effects. Clinical research conducted since these products were approved has resulted in substantial revisions to the body of scientific information available to physicians. The relative "quality" of these drugs (as captured by efficacy and toxicity measurements reported in peer-reviewed clinical trials) has changed markedly over the past 15 years. Yet in our analysis of US wholesale prices we find that relative prices appear to be only weakly related to quality. We do however find a relationship between changes in reported efficacy and toxicity and the evolution of quantity shares in this market.

Iain M. Cockburn
Faculty of Commerce
University of British Columbia
2053 Main Mall
Vancouver, BC V6T 1Z2
CANADA
and NBER
iain.cockburn@ubc.ca

Aslam H. Anis
Health Research Centre
St. Paul's Hospital
1801 Burrard Street
Vancouver, BC V6Z 1Y6
CANADA
anis@hivnet.ubc.ca

1 Introduction

This paper examines the market for a group of drugs used to treat rheumatoid arthritis (RA). Rheumatoid arthritis is a painful, debilitating, and progressive disease which affects millions of people worldwide, with very substantial effects upon health and the economy. Regrettably, in contrast to some other major health problems such as heart disease, depression, ulcers, and bacterial infections, this is an area where therapeutic innovations have thus far had comparatively little impact on physicians' ability to reverse the disease. RA currently has no "cure" and the effectiveness of available treatments is limited. Compared to other drug classes, the rate of new product introductions has been slow, and there have been no significant breakthroughs such as the discovery and development of SSRI's for treatment of depression, H2 antagonists for ulcers, or ACE inhibitors for hypertension.

Nonetheless, the market for RA drugs is far from static. There have been significant changes over the past 15 years in the market shares of competing products. Interestingly, relative prices have changed relatively little, and these market dynamics appear to be driven primarily other factors. In this paper we focus on the role played by publication of clinical research findings. In contrast to traditional hedonic analysis where product characteristics are fixed but new products incorporating different quality levels appear over time, here the set of products is fixed while their measured quality changes over time. New information about the relative efficacy and toxicity of existing drugs accumulates through the publication of clinical trial results, and this information appears to have had a significant impact on the pattern of drug use.

A number of clinical aspects of rheumatoid arthritis are important structural features of the market for drugs used to treat the disease. The paper therefore begins with a brief review of the nature of RA and its treatment. We then discuss issues related to the measurement of the relative efficacy and toxicity of drug treatments for RA. Next, we present economic data on the market for a specific set of drugs used in the treatment of severe RA, and consider

them in the context of models of demand for differentiated products. We then report the results of estimating price and market share equations. In the concluding section, we outline alternative approaches that may provide some additional insight, in particular the role of advertising and promotional expenditures.

2 Rheumatoid Arthritis

RA is one of the most prevalent diseases affecting joints and connective tissue. RA is an autoimmune disease: for reasons that are still poorly understood, the body's immune system begins to malfunction, attacking healthy tissue. Like related conditions such as lupus erythematosus, psoriatic arthritis, and scleroderma, the disease is *systemic* and *chronic*. Tissues are affected throughout the body, and although some patients experience prolonged periods of remission, most are affected for a lifetime.[1]

RA is characterized by inflammation of the synovium (a membrane which lines the joints) resulting in stiffness, pain, warmth, and swelling, of joints. As the disease progresses, inflamed cells release an enzyme which erodes surrounding bone and cartilage, resulting in increased pain, loss of movement, and eventually destruction of the joint[2]. As the disease progresses, patients experience greater and greater pain and loss of mobility. Fatigue often accompanies the "classical" joint symptoms. In late stages of the disease, skin and vascular problems (such as leg ulcers) may develop, along with damage to eyes, nerves, and inflammation of lymph nodes, heart and lungs.

Research into the fundamental causes of the disease has inconclusively investigated many factors ranging from endocrine disorders to nutrition, geography, psychological conditions, and occupational hazards. Current thinking suggests that some infectious agent may trigger the damaging autoimmune response in persons who have a genetic predisposition. However,

[1] Brewerton[9] gives a comprehensive and readable overview of arthritis and its treatment. See also[10] [25] and [22].

[2] Establishing a conclusive diagnosis of RA can be difficult, especially in its early stages since it shares many symptoms with other autoimmune diseases. Note that RA should not be confused with osteoarthritis, an even more prevalent disease, with a distinct clinical profile and disease process.

while a specific genetic marker (HLA-DR4) has been found to be present in large fraction of RA patients, not all patients have the marker, and only a small fraction of people who have the marker go on to develop RA. Neither has the proposed infectious agent (possibly an unknown virus) been identified, though various other arthritic and rheumatic conditions have been associated with infection by a number of organisms such as *borellia* (the Lyme Disease spirochete) and some streptococcal bacteria. RA affects between 1 and 2 percent of the population of OECD countries. Women are 2 to 3 times more likely than men to develop disease. In adults the onset of the disease is typically at age 40-60, though significant numbers of people experience severe symptoms in their 30's and 40's, and the disease can occur at any age. In some patients deterioration is rapid, while in others the disease progresses very slowly. Once affected, the outlook for most patients is poor. In many cases patients experience temporary relief of symptoms, but only very few have a complete remission of the disease. Even with aggressive drug therapy, 7% of RA patients are significantly disabled within 5 years, and 50% are too disabled to work 10 years after the onset of the disease.[17] The combination of severe health impact, widespread incidence, and relatively early onset mean that very substantial economic losses are attributable to RA. The Arthritis Foundation reports that musculoskeletal conditions such as RA cost the US economy approximately $65 billion per year in direct expenses and lost output. Chronic severe pain and restricted mobility have a very significant impact on the quality of life of RA patients[3].

[3]In Canada, RA occurs in approximately 1% of the population i.e., about 270,000 people. It has been estimated that the average Canadian has significant pain and/or disability from arthritis resulting on average of 2.5 quality adjusted life years[19] (QALY's) lost[21]. Since RA tends to be more frequently disabling than osteoarthritis, a conservative estimate of the total disability among Canadians from RA would hence be 675,000 QALY's lost. In addition to the morbidity effects of RA, Pincus et al.[20] estimate that life expectancy is also reduced among patients with RA by at least 10 years. Thus the overall burden and suffering from RA as reported by these studies are of considerable magnitude.

2.1 Treatment options for RA

Over the course of the disease, RA patients are treated with physical intervention and drug therapy.[4] Physical intervention takes the form of physical therapy directed towards preservation of joint function and surgical procedures to address severe pathologies of specific joints (e.g. hip replacement). Drug treatment, the focus of this paper, is given to almost all patients who consult a physician: of the approximately 5.1 million patient visits per year in the US where RA is a primary diagnosis, over 92% involved one or more drugs being prescribed. Two principal classes of drugs are used to treat RA: non-steroidal anti-inflammatory drugs (NSAID's) and disease-modifying antirheumatic drugs (DMARD's). These two classes account for over 65% of all prescriptions to RA patients, with corticosteroids accounting for a further 19%. (See Table 4.) It is important to note that drug therapy for RA normally follows a treatment hierarchy: treatment begins with NSAID's and moves on to DMARD's as the disease progresses.

NSAID's are the most frequently prescribed drugs for RA. Large numbers of drugs fall into the NSAID class, among the most commonly used are aspirin, ibuprofen (Motrin), naproxen (Naprosyn), diclofenac (Voltaren), and piroxicam (Feldene). NSAID's reduce inflammation and have an analgesic effect but do not affect progression of the disease. NSAID's act quickly and are well tolerated by many patients but can cause a number of dangerous side effects particularly when used in the high dosages indicated for RA. Gastrointestinal bleeding is the most frequently encountered severe side effect. While NSAID's are the "first line" of defence, they offer only palliative treatment of symptoms, and as the disease progresses patients will typically be given one of the DMARD's. Note that this does not usually imply discontinuation of NSAID therapy. In fact up to 80% to 90% of patients are prescribed drugs from both classes. DMARD's can suppress symptoms and slow the progress of the disease, though they cannot halt it. DMARD's are slow acting, taking weeks or months before any

[4]Counselling or other psychotherapeutic intervention may also play an important role in helping patients cope with the impact of the disease. Many patients also turn to "alternative" medicine.

significant improvement is noticed by the patient, and are often poorly tolerated. Different drugs are used with varying degrees of success in different patients. Furthermore many patients are forced to discontinue the drug because of serious side effects. Minor, though uncomfortable, side effects such as dermatitis, nausea, and mouth ulcers are quite frequently experienced. The incidence of serious side effects such as retinal damage, renal failure, liver damage and reduction in blood cell counts, while uncommon, nonetheless requires close medical supervision and frequent diagnostic testing.

The DMARD's are listed in Table 1. One point to note from this table is that many of these drugs are quite old, having been first introduced to the market many years ago. Auranofin (Ridaura) is the only strictly new molecule approved for RA in the last 15 years. Other products such as methotrexate are new to the market in the sense of gaining regulatory approval for treatment of RA, but have been used informally or in research settings for many years. (Lederle introduced Rheumatrex, a formulation of methotrexate specifically targeted at the RA market, in 1986). Sulfasalazine, methotrexate and the antimalarials are off-patent, but generic production is significant only for methotrexate. It is also important to note that the original or primary indication of most of the drugs was *not* RA. With the exception of the gold compounds, the activity of the DMARD's against RA was discovered subsequent to their first introduction to the market. Methotrexate was an early treatment for cancer, while hydroxychloroquine was developed as an antimalarial. The precise mechanism of action of most of these drugs is not well understood, though most have their therapeutic effect through suppressing the immune response. The anti-inflammatory activity of gold compounds appears to be specific to arthritic conditions, while the immunosuppressant activity of azathioprine and methotrexate is much more general.

In addition to DMARD's, physicians may also prescribe corticosteroids. (This occurs in about 20% of patient visits in the US.) While these drugs can often produce dramatic short term improvement in symptoms, their long term use is limited by serious side ef-

fects, principally osteoporosis and increased susceptibility to infections. As a last resort, patients may also be prescribed highly toxic "third line" immunosuppressant drugs such as cyclophosphamide, cyclosporine, or chlorambucil. Absent a new therapy which induces a lasting remission, physicians therefore face difficult decisions and tradeoffs in drug therapy for RA.[5] The timing of moving a patient from well tolerated NSAID's to the more toxic DMARD's is controversial, with some physicians arguing for early and aggressive "second-line" therapy to preempt irreversible joint damage, despite serious side effects. Even within the DMARD class it is far from clear which drug to prescribe. Only a fraction of patients obtain significant benefit from any one agent and even then the effect is often short-lived, typically lasting for only a few months or years. Over the 20 to 30 year course of the disease a patient will typically cycle through a series of therapeutic alternatives as their physician attempts to arrest, or often merely to minimize, the cumulative destruction wrought by the disease. Furthermore, professional opinion has changed over time regarding which drugs to use, and when. The information base on the relative efficacy and toxicity of these agents continues to evolve as new scientific evidence from clinical trials is published and physicians individually and collectively accumulate more experience. The efficacy/toxicity tradeoff lies at the heart of the prescribing decision, and changing perceptions of where drugs are located in this space drives our analysis of demand for these drugs.

3 Measuring the "Quality" of Drug Treatments for RA

We attempt to measure the characteristics of different DMARD drugs in two general dimensions: efficacy and toxicity. Unlike some previous work on hedonics of pharmaceutical products we pay little attention to differences in the dosage regimen. Though characteristics such as the number of times a day the patient must take the drug appear to be an

[5] A number of experimental drugs, largely from the biotech sector from the industry, hold some promise for significant progress in treating arthritis and other autoimmune inflammatory disorders, but are still in the very early stages of testing. See *Wall Street Journal*, July 17, 1997, pB1.

important determinant of the relative value of different ulcer drugs and antidepressants (see Suslow[23][24], and Berndt et al.[5]), we believe them to be much less important here. The very close involvement of the physician and the severe nature of the disease suggest to us that the impact of dosing regimen on patient compliance is unlikely to be an important factor.[6]

Our primary measures of efficacy and toxicity are computed from the reported results of published clinical trials. We assume that the best available information about the relative efficacy and toxicity of substitute drugs comes from published reports of clinical trials that appear in peer-reviewed scientific journals. These reports constitute a longitudinal dataset which tracks the evolution of information on each drug over time.

Based on Felson[12], we begin with the "universe" of 216 published trials published between 1966 and 1995 listed in the Medline database. Protocols and methodology vary widely across trials, and to establish a basis for comparison of results across trials (and to maintain a minimal level of methodological quality) papers were excluded if they did not meet the following criteria:

- Patient profile: adults 18+, meeting ARA diagnostic criteria for RA.
- Random assignment to treatment groups.
- Blinded trial.[7]
- Minimum dosage levels.
- At least 8 weeks duration.

[6]As a practical matter, dosage regimens for these drugs vary widely, are difficult to compare directly, and often involve complicated "ramp up" schedules paced over many weeks. For example, the maintenance dose of methotrexate is 7.5 mg spread over a week, while sulfasalazine must be taken in relatively large amounts several times per day, and most of the gold compounds are injectable. Quantifying dosage regimen with variables measuring route of administration, dosage frequency etc. is tantamount econometrically to simply using drug dummies.

[7]The precise protocols vary from one trial to another, at a minimum the trials were required to be single-blinded.

Imposing these criteria resulted in all but 66 of the original set of published trials being excluded.

3.1 Efficacy Measures

Efficacy of drugs in these trials is established by compiling measurements of a number of standard physiologic markers and outcome measures for patients in the different treatment groups at the beginning and end of each trial. These were:

- *Erythrocyte Sedimentation Rate* (ESR), which is a physiologic marker of the level of overall systemic inflammation, derived from testing blood samples drawn from trial participants at predefined intervals during the trial.

- *Tender Joint Count* (TJC), which is a measure of the extent and severity of the disease in terms of the number of affected joints, compiled according to a standard protocol by a physician or nurse who assesses the patient. This is measured as difference (or percentage difference) over baseline.

- *Grip Strength* (GS), which is another measure of the extent and severity of the disease, performed by measuring the pressure the patient is able to exert on a standard mechanical device. This is captured as either mean percentage improvement over baseline or the mean improvement standardized by baseline standard deviation.

Apart from these measurements, efficacy can also be measured by the reported rate at which patients dropped out of each trial due to "lack of efficacy".

3.2 Toxicity Measures

Toxicity is much harder to measure consistently. We have not been able to assemble consistent data on the actual incidence of side effects in each trial. Following previous work we have experimented with variables constructed by counting the number of side effects listed

under categories such as "severe" or "frequent" in standard reference sources, or constructing dummy variables reflecting the locus of specific side effects (kidney damage, CNS, retina etc.) but these perform poorly in experimental regressions.[8] Our preferred measure of toxicity is the reported rate at which patients dropped out of clinical trials due to "toxicity".

3.3 Changes in Quality over time

Since new trials are conducted periodically, information accumulates steadily over time, and variables constructed from reported trial results form a longitudinal data set. We combine data from different trials in a variety of ways intended to capture the evolution over time of the scientific information available to prescribing physicians.

One possibility is to simply assign a value to each variable in each year based on the most recently published study. Thus we "ratchet" the level of each variable up or down in each year that a new trial came out, and carry forward the previous value otherwise. (In tables below we refer to these measures as "latest".)

A second approach is to do a "rolling" cumulative meta-analysis which pools treatment groups over time and across drugs. As new trials are published results for each group of patients are added to the previous total, resulting in a continuously expanding sample. Mean treatment effects are the weighted sum of treatment effects in all trials to date.

Thirdly, we modify the cumulative meta-analysis by imposing various schemes of declining weights over time to capture "depreciation" of knowledge. We expect the results of trials conducted many years in the past to weigh less heavily upon current prescribing practice than more recent evidence. The simplest such weighting scheme is a 3 or 5 year moving average. Alternatives such as a perpetual inventory depreciation scheme, or fixed declining weights do not yield materially different results.

[8]Clinicians may be most strongly influenced by the relative incidence of severe adverse reactions. We have not yet compiled data on these effects. But note that since these events are very rare their probability of occurrence is difficult to measure precisely.

4 Model

The theoretical literature provides little guidance on the appropriate functional form for estimating quality adjusted prices. Following many previous hedonic pricing studies, such as Suslow's analysis of ulcer drugs [23] [24] or Berndt et al.'s work on antidepressants [5], we use a semi-log reduced form as below:

$$\ln(p_{jt}) = x_{jt}\beta + Z_t\gamma + \nu_{jt} \tag{1}$$

Where x_{jt} represents the measured quality (safety and efficacy) characteristics of drug $j; j = 1, ..., J$ at time t. Z_t is a set of time dummies, while p_{jt} denotes the time series of prices for drug j.

For the market share equation, we follow Berry[8] and Berry, Levinsohn and Pakes[7] in specifying a logit type discrete choice model of demand for differentiated products[2] to analyze the DMARD market. See King[16] for a successful application of this approach to the anti-ulcer market. Berry postulates the utility of consumer i for product j as a function: $U(x_j, \xi_j, p_j, \theta_d, v_i)$, where x_j, ξ_j, p_j, and θ_d are observed product characteristics, unobserved product characteristics, and price and demand parameters, respectively. The term v_i is unobserved by the econometrician and represents a consumer specific term. To implement the model, one has to make specific parametric assumptions about the consumer specific variables, analogous to the choice of functional form for a homogenous good demand equation. Assuming that utility derived by consumer i for product j can be written as:

$$u_{ij} = x_{ij}\tilde{\beta}_i - \alpha p_j + \xi_{ij} + \epsilon_{ij} \tag{2}$$

Averaging over consumers (and assuming that the physicians who exercise control over the drug consumption decision act as perfect agents for their patients) and introducing time subscripts to reflect the fact that the perceived safety and efficacy characteristics of drugs

change over time, we obtain a mean consumer utility level from choosing drug j at time t as:

$$\delta_{jt} = x_{jt}\beta - \alpha p_{jt} + \xi_{jt} \tag{3}$$

where ξ_{jt} may be interpreted as the mean of the consumer/physicians' valuation of an unobserved product characteristic that is not captured by x_{jt} and $E[\epsilon_{ij} = 0]$[9].

In addition to the competing DMARD's, $j = 1, ..., J$, we also assume the existence of an outside good $j = 0$ with price p_0. In this context, consumption of the outside good can be thought of as the quantities of NSAID's and all other non-DMARD's consumed by RA patients. (Empirically, almost all RA patients' visits to doctors result in them being prescribed either an NSAID or a DMARD or both. Only a tiny number of patients receive no drug therapy.)

Letting q_j and q_0 denote the quantities of DMARD j and the outside good, respectively, market shares can further be defined as $s_{jt} = \frac{q_{jt}}{q_{jt}+q_{-jt}+q_{0t}}$ and $s_{0t} = \frac{q_{0t}}{q_{jt}+q_{-j}t+q_{0t}}$.

In this model it is assumed that all aspects of market demand are completely determined by the mean utility level δ_{jt} and, without going into the specifics of supply side dynamics and alternative characterizations of market equilibrium, we adopt the special case of the logit model to solve for mean utility levels as a function of observed market shares[10]. Given the utility function in (2) and assuming $\tilde{\beta}_i = \beta$, ϵ_{ij} is an *iid* variable with the extreme value distribution function $\exp(-\exp(-\epsilon))$, the market share of DMARD j is given by the logit formula:

$$s_{jt}(\delta_{jt}) = \frac{\exp \delta_{jt}}{\sum_0^J \exp \delta_{jt}} \tag{4}$$

[9]See[8] for more on possible ways of decomposing $\tilde{\beta_{ij}}$ and on the assumptions that yield invariant α and β across individuals.

[10]We refer the reader to Berry et al.[7] for a complete discussion of the model and functional form assumptions.

By substitution and by normalizing the mean utility of the outside good to equal 0, we get the following linear model:

$$ln(\frac{s_{jt}}{s_{0t}}) = \delta_{jt} \equiv x_{jt}\beta - \alpha p_{jt} + \xi_{jt} \tag{5}$$

where s_{jt} is the quantity share and p_{jt} and price respectively of the jth DMARD at time t. ξ_{jt}, the unobserved characteristics of the jth drug at time t, becomes the error term.

In our implementation of this basic estimating equation we deflate prices p_{jt} by the BLS producer price index for pharmaceuticals to remove the general trend of inflation. (This is equivalent to a slightly different specification of (2) and normalization of the utility level of the outside good which leaves the price of the outside good in the estimating equation.) As argued below, we believe prices to be largely exogenous to this market and are therefore unconcerned about endogeneity of this variable. Given the panel structure of the data, we can address the issue of potential correlation between ξ_{jt} and the other explanatory variables by including a fixed drug effect, so that $\xi_{jt} = \mu_j + \eta_{jt}$ with η_{jt} assumed to have the usual desirable properties.

5 Price and Quantity Data

Econometric analysis of the market for DMARD's requires basic data on prices and quantities of these drugs sold, and careful attention to the definition of the RA market.

Our primary data on prices and quantities for the DMARD's are drawn from reports of wholesale transactions in the US published by IMS America Inc., a market research company. IMS collects information on revenues and quantities of individual drug products by wholesale distributors at a very fine level of detail, for example 100mg tablets, 100 count bottle. (We have also collected data on retail transactions in British Columbia which were reimbursed under the province's Pharmacare program. The Pharmacare program is universal and covers all residents with varying levels of coverage depending on socio-demographic status.)

A major difficulty with these kinds of data, however, is that they are collected by drug product, not by disease indication. As pointed out above, many of the DMARD's have multiple uses, and in fact their primary use may be for quite different medical problems. Analyzing demand for these drugs for treatment of RA requires that we distinguish between these uses. This may not be important for measuring prices: absent some means to discriminate among consumers through packaging or reformulation it is not unreasonable to assume that one price holds for all sales of a particular formulation of a drug regardless of the intended use. This is likely to be particularly true for the wholesale market. By contrast, in measuring quantities it is vitally important to distinguish between markets in the sense of different medical conditions. Large (and varying) amounts of these drugs are used for treatment of other diseases.

Figure 1 presents series on US wholesale prices for DMARD's for the period 1980-1992. Prices are measured in dollars per daily dose unit.[11] Perhaps the most striking feature of Figure 1 is that prices are so similar across the major products, and move so closely together. Over time prices rise steadily with general inflation, with few significant changes relative to one another. The major exception is sulfasalazine, whose roughly constant nominal price corresponds to a sustained decline in real terms a steady fall. Methotrexate's price rises relatively steeply during the mid 1980's, driven largely by the introduction of Lederle's branded Rheumatrex product, while the rate of increase in the price of the injectable gold products moderates somewhat towards the end of the period.

To address the market definition problem, we need information on the fraction of each drug's consumption specifically for the treatment of RA. For this we turn to another IMS publication, the *National Drug and Therapeutic Index* (NDTI). The NDTI reports results

[11] Daily doses are the "typical maintenance dose" taken from a number of standard reference publications such as the *Physician's Desk Reference*. It should be noted that the dosage given to any particular patient may vary substantially from the amounts we use here: treatment of most patients may involve considerable experimentation with dosages. Some of the drugs also have a fairly complicated "ramp-up" dosage regime lasting many weeks before the maintenance dose is treated. Relative prices based on the cost of initiating drug therapy and maintaining it for a total of three months are very similar to the daily dose prices presented here.

from surveying a sample of physicians. Each physician is asked to report information about patient visits, for our purposes the most useful is the primary diagnosis and which drugs (if any) were prescribed. In these reports a "drug mention" is equivalent to one prescription. IMS imputes figures for the total US population from the survey sample, and provides tabulations by drug and by diagnosis. Thus for each drug we can compute a breakdown of prescriptions by diagnosis, and for the diagnosis of RA, a breakdown of prescriptions by drug. These data provide valuable insight into market dynamics.

Table 3 summarizes information on consumption of DMARD's by diagnosis, reporting the percentage of prescriptions of each drug for which RA was the primary diagnosis. This fraction is high and stable for some drugs such as injectable gold salts and auranofin, indicating that their principle market is indeed RA. For other DMARD's, such as sulfasalazine and azathioprine, the "outside" uses are very substantial, averaging more than 75% of prescriptions. Furthermore, there are significant changes in these fractions over time. The fraction of d-penicillamine used for RA falls from 91% in 1980 to 72% in 1992, while the same statistic for azathioprine rises from zero in 1980 to a high of over 50% in the mid 80's before declining to 12% by 1992.

Table 4 summarizes prescriptions for each drug for the primary diagnosis of RA. The total number of "mentions" is greater than the number of visits since patients may be given more than one drug (this occurs in approximately 80% of visits). Since these data are compiled from simple counts of "mentions" and thus do not reflect differences in the size of prescriptions, these are approximations at best. The share of gold salts, for example, may well be overstated since patients make weekly visits to their physician for an injection. On the other hand, methotrexate may be prescribed in a more traditional manner with the patient visiting the physician (and obtaining a new or refill prescription) much less frequently. Nonetheless these fractions are our best estimate of each drug's share of the RA market[12].

[12]As an alternative to using NDTI data we have explored a small data set constructed from the BC Pharmacare database where we only include prescriptions written by rheumatologists. The shares of different DMARD's in these data are very similar to those in the NDTI, but the data covers a somewhat shorter time

Figure 2 summarizes quantity shares within the DMARD market graphically. The total size of the DMARD market (as measured by the number of mentions of these drugs in the NDTI) grew somewhat over time from about 1.9 million mentions per year in the early 1980's to around 2.4 million in the early 1990s. Much of this growth was driven however by increases in the numbers of patients diagnosed with RA, which reflect changes in the demographics of the US population. DMARD's as a class were a somewhat larger share of the total RA market at the end of our sample period (around 28% in 1992 compared to 21% in 1980) which may reflect some market-expanding effect of improved quality and new product introductions, but these changes are dominated by movements within the DMARD market. The very striking feature of Figure 2 is the substantial fall in the share of injectable gold and the rise in the share of methotrexate. D-penicillamine's share falls steadily over time while the other drugs are relatively small and stable. These patterns reflect the general impression to be gained from reading the clinical literature: an increasing tendency to use methotrexate at the expense of gold, with mixed opinions about the therapeutic value of the other agents. Auranofin, the only new chemical entity to enter this market was launched in the mid-1980s as an orally administered alternative to the injectable gold compounds, but achieved only a modest 10% share.

To examine the relationship of prices and quantities to measured quality more carefully, we turn next to our estimation results.

6 Results

6.1 Price equation

Table 5 reports results from estimating the reduced form hedonic price equation (1) using data on US wholesale prices. To the extent that we expect relative prices to respond to changes in measured characteristics, the results are disappointing. In Models 1 and 2 we

period.

regress the log of daily dose price on to characteristics variables alone. The estimated parameters are contrary to our prior beliefs: efficacy (whether measured by the fraction of patients who do not drop out of trials because of lack of efficacy, or by changes in the physiological measurements GRIP, TJC, and ESR) has a negative effect on price, while toxicity is positively associated. These results do not change when we add a set of year dummies to the list of explanatory variables, though the fit of the equation improves markedly. Coefficients on the time dummies imply a steady upward movement in prices, which is very similar whether or not we attempt to control for quality change.

Why the characteristics variables should perform so poorly is puzzling. Considerable experimentation with alternative ways of computing these quality measures from the clinical trials data did not "improve" these results. Regardless of whether efficacy and toxicity are measured relative to placebo or as unadjusted changes, or which of the alternative weighting and updating schemes discussed above is used, we still obtain the "wrong" signs on the estimated coefficients. One reason may be that measurement error is biasing the coefficient estimates.[13] This possibility should be taken seriously as the clinical trials literature is not unambiguous, and prescribing physicians may be unaware or skeptical of the results reported in the studies we use here.

We prefer to interpret these findings as evidence of an alternative hypothesis about the nature of this market. Given the serious medical situation of most patients who are given DMARD's, and their lack of alternatives, it seems likely that demand is fairly inelastic. With many of these drugs having their primary use elsewhere, it is plausible that their prices are largely exogenous to the RA market. Casual inspection of the raw data suggests that the level of prices for these drugs bears little relationship to measured characteristics, with the some of most toxic and least efficacious drugs having the highest prices. Furthermore, looking at changes over time we see that prices for most of the drugs move steadily upwards with

[13]Recall that with more than one variable potentially mismeasured, the resulting bias on estimated coefficients is hard to predict and need not always be towards zero.

general inflation, with little change in relative prices. Where movements in prices conform to our priors, any correlation with changes in measured quality appears to be swamped by the rest of the data. Seen in this light, the results obtained in the price equation may simply be spurious, with the coefficients on the characteristics variables reflecting confounding with other factors determining prices.

Experience with other pharmaceutical price data as well as informal evidence gathered in discussion with industry executives and other experts suggests also that relative prices for these products are very "sticky". There is some evidence for sensitivity of pharmaceutical prices to exogenous shocks such as regulatory changes, see Anis[1] and Scott Morton[18]. On the other hand, other studies have found prices of branded products to be remarkably insensitive to patent expiration and large-scale entry by generics[13]. It may not therefore be a gross miss-characterization of historical industry pricing practice to summarize it as setting prices once (in real terms) at the time of product launch, with subsequent revisions limited largely to adjustments for general inflation applied across a producers' entire product line. Any price premium related to improved quality will therefore be difficult to see except in markets with substantial numbers of new products entering over time, which is not the case here. In this light, it is worth pointing out that poor results were also reported in Berndt and Finkelstein's[4] study of hedonic pricing of anti-hypertensives, another drug class with a low rate of new chemical entities reaching the market.

With prices set exogenously to this market, and given that relative prices are likely far down the list of patients' and physicians' concerns when choosing which drug to use, it is likely that the impact of changes in quality manifest themselves in the market largely in changes in quantities, which is where we turn next.

6.2 Market share equations

Table 6 presents estimates of the parameters of equation (5), with and without fixed drug effects. In Models 6 and 8 the toxicity and efficacy variables are based only on the most

recently published trial in each year, while in Models 7 and 9 they are computed as a three-year moving average of published trial results. In both cases the drug effect is calculated relative to placebo, but very similar results are obtained using just the change relative to the baseline values.

Results in Models 6 and 7 are encouraging. The signs of the coefficients on the characteristics variables conform to our priors, with increased toxicity negatively associated with market share, and increased efficacy positively associated. characteristics are fairly large, of Though the coefficient on price is insignificant, and corresponds to a very low elasticity, it is at least negative in Model 6. A very small price effect is consistent with our interpretation of results from estimating the price equation.

Models 8 and 9 include fixed drug effects in the estimation to control for drug-specific problems in measuring market share or characteristics. Several of these dummies are highly significant, and they markedly improve the fit of the model, suggesting that we do indeed have systematic problems in measuring market shares. Furthermore the estimated coefficients on the other variables change substantially when we include fixed drug effects, indicating that the equations omit significant variables driving quantities consumed, either quality characteristics of drugs or other drug-specific factors which determine demand.

7 Conclusion

Economic considerations appear to play a relatively minor role in the market for DMARD's. Information from published clinical trials relating to key quality characteristics of these drugs (efficacy and toxicity) is statistically associated with changes in their quantity shares in this market, but has no consistent impact on relative prices. Given the nature of RA, these results may not be too surprising. They do however point to some interesting economic issues which we have not attempted to address in this paper.

Firstly, there is the question of using prices to measure the impact of technical change

upon consumer welfare in markets such as this one. Most prior work on innovation, quality change, and pricing has examined the prices of new goods which embody technological change in the form of improvements to tangible aspects of quality. Here the technical change takes a rather unusual form: R&D generates revisions to the intangible information set possessed by physicians and patients, affecting perceived quality rather than physical characteristics such as speed, durability, weight etc. R&D surely improves welfare in this context, but the fact that relative prices in this market change very little (and are most likely determined exogenously) and that demand appears to be quite price inelastic means that its impact is very difficult to see to see in price space. Rather, the most visible direct effect of changes in quality is seen on quantities, which has significant implications for how we should interpret movements in, for example, a fixed-weight price index.

Secondly, these results hint at an interesting variety of non-price competition. Rents to producers in this market are determined initially by the level of prices (which to a rough approximation they set once in real terms, and are often based upon conditions prevailing in unrelated markets) and then by the evolution of quantities as consumers and/or their agents respond to exogenous changes in perceived quality. In such circumstances the role played by marketing and promotional activity may well be very important. Our analysis here is based on the generation of new information about product quality in the form of publication of research results in peer reviewed journals by (hopefully) impartial authors. The question of how this information reaches practising physicians and their patients has not been examined here. In future work we hope to extend our analysis of this market to include marketing and promotional activity by producers of these drugs, which may shed light on the interesting question of the relative importance of objective versus persuasive information in drug choices.[11]

References

[1] Anis AH, Wen Q "Price regulation of pharmaceuticals in Canada", *Journal of Health Economics.* Forthcoming.

[2] Anderson SA, de Palma A, Thisse J-F, *Discrete choice theory of product differentiation.* Cambridge MA: MIT Press; 1992.

[3] Berndt ER, Bui L, Reiley DH, Urban GL "The roles of marketing, product quality and price competition in the growth and composition of the U.S. anti-ulcer drug industry". NBER Working Paper # 4904; 1995.

[4] Berndt ER, Finkelstein SN "Price Indexes for Anti-Hypertensive Drugs that Incorporate Quality Change: A Progress Report on a Feasibility Study" MIT Program on the Pharmaceutical Industry, Working Paper #6-92; 1992.

[5] Berndt ER, Cockburn IM, Griliches Z "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressant Drugs", *Brookings Papers on Economic Activity: Microeconomics* 1997; 133-188.

[6] Berndt ER, Griliches Z, and Rosett JG, "Auditing the Producer Price Index: Micro Evidence From Prescription Pharmaceutical Preparations", *Journal of Business and Economic Statistics*, 1993; 11(3):251-264

[7] Berry SB, Levinsohn J, and Pakes A, "Automobile prices in market equilibrium", *Econometrica* 1995; 63:841-890

[8] Berry SB, "Estimating discrete-choice models of product differentiation". *Rand Journal of Economics* 1994; 25:242-262.

[9] Brewerton D *All About Arthritis*, Cambridge MA: Harvard University Press, 1994.

[10] Cash JM and Klippel JH "Second-Line Drug Therapy for Rheumatoid Arthritis." *New England Journal of Medicine* 1994; 330:1368-1375.

[11] Hurwitz MA and Caves RE, "Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals," *Journal of Law and Economics* 1989; 31: 299-320

[12] Felson DT, Anderson JJ, and Meenan RF, "The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses". *Arthritis and Rheumatism* 1990; 33:1449-1459.

[13] Griliches Z, Cockburn IM, "Generics and New Goods in Pharmaceutical Price Indexes." *American Economic Review*, 1995; 84:1213-1232

[14] IMS America Inc. *National Drug and Therapeutic Index – Drugs*, Plymouth Meeting, PA; 1980-1994.

[15] IMS America Inc. *National Drug and Therapeutic Index – Diagnosis*, Plymouth Meeting, PA; 1980-1994.

[16] King C, "Marketing, product differentiation, and competition in pharmaceutical industry." MIT Program on the Pharmaceutical Industry, Working Paper #39-96; 1996.

[17] "Focus on Rheumatoid Arthritis" *Medical Sciences Bulletin*, Levittown PA: Pharmaceutical Information Associates, December 1994.

[18] Scott Morton F "The strategic response by pharmaceutical firms to the Medicaid most-favored-customer rules" *Rand Journal of Economics* 1997; 28:269-290.

[19] Torrance GW, Feeny D, "Utilities and quality-adjusted life years". *International Journal of Technology Assessment in Health Care* 1989; 5:559-575.

[20] Pincus T, Callahan LF, "The 'side-effects' of rheumatoid arthritis: joint destruction, disability and early mortality." *British Journal of Rheumatology*, 1993; 32 (suppl 1):28-37.

[21] Reynolds DL et al., "Modelling the population health impact of musculoskeletal diseases". *Journal of Rheumatology*, 1993; 20(6):1037-1047.

[22] Steinman L, "Autoimmune Disease". *Scientific American* 1993; 269[3]:106-114.

[23] Suslow V, "Are there better ways to spell relief? An hedonic pricing analysis of ulcer drugs". School of Business Administration, University of Michigan Working Paper. 1992; # 696.

[24] Suslow V, "Measuring Quality Change in the Market for Anti-Ulcer Drugs." in Helms R (ed) *Competitive Strategies in the Pharmaceutical Industry*, Washington DC: American Enterprise Institute, 1996.

[25] Wolfe F, "50 Years of Antirheumatic Therapy: the Prognosis of RA", *Journal of Rheumatology*, 1990; Supplement 22:24-32.

Table 1: DMARD Drugs

Drug	Brand Name(s)	US Mkt. Intro	Other Indications	Manu-facturer
auranofin	Ridaura	1985		SKB
azathioprine	Imuran	1968	Immune suppression for transplants	Glaxo Wellcome
gold sodium thiomalate	Myochrysine	<1980		Merck
aurothioglucose	Solganal	1989?		Schering
hydroxychloroquine methotrexate	Plaquenil Rheumatrex	1956 1955	Malaria Leukemia, psoriasis	Winthrop Lederle, generics
d-penicillamine	Cuprimine	1963	Chelation	Merck, Wallace
sulfasalazine	Azulfidine	1952	Ulcerative Colitis, Crohn's Disease	Kabi, generics

Table 2: Summary Statistics and Characterics of DMARD's

Drug		Sample Means				
Name	Daily Dosage	Efficacy			Toxicity	Price †
		TJC	GS	ESR	Dropout	
auranofin	6mg	8.44	26.98	10.79	0.16	$1.91
azathioprine	100mg	9.78	33.11	13.73	0.27	$1.67
gold salts	7mg	9.15	38.20	10.79	0.40	$1.07
antimalarials	400mg	9.21	39.89	11.41	0.04	$1.42
methotrexate	12.5mg	13.23	33.11	13.49	0.16	$1.31
d-penicillamine	600mg	8.78	37.26	22.65	0.33	$1.70
sulfasalazine	2.5g	12.28	28.53	20.64	0.37	$0.84
placebo	N/A	4.80	9.74	1.26	0.07	N/A

†1992 US dollars per daily maintenance dose

Table 3: NDTI Drug Mentions by Diagnosis: fraction of RA by drug

Drug	1980	Mean (1980-92)	1992	Major other use (Mean 1980-92)
auranofin †	92%	87%	84%	
azathioprine	0%	26%	12%	transplant, 56%
gold salts	92%	91%	91%	
antimalarials	79%	64%	56%	circulatory disorders, 9%
methotrexate, injectable	3%	21%	22%	cancer, 59%
methotrexate, oral	0%	65%	69%	skin disease, 17%
d-penicillamine	91%	81%	72%	
sulfasalazine	0%	8%	11%	digestive disorders, 83%

†introduced in 1985

Table 4: Share of NDTI Drug Mentions for RA (mean 1980-94)

Drug Category		Share of Mentions
Cortisone		19.8%
other		14.6%
NSAID's		36.2%
DMARD's		29.4%
... of which:	auranofin	4.7%
	azathioprine	4.5%
	gold salts	37.3%
	antimalarials	17.4%
	methotrexate	23.7%
	d-penicillamine	9.4%
	sulfasalazine	2.6%

Table 5: OLS Results: US Wholesale Prices 1980-1992

	Model 1	Model 2	Model 3	Model 4	Model 5
Constant	4.84 (0.94)	-0.14 (0.14)	-1.10 (0.14)	-0.12 (0.79)	-0.77 (0.17)
Efficacy†	-5.68 (1.03)			-1.11 (0.81)	
Toxicity††	1.15 (0.38)	0.82 (0.41)		0.55 (0.26)	0.83 (0.22)
Improvement in GS		-0.44 (0.42)			-1.37 (0.22)
Improvement in TJC		-1.22 (0.40)			0.22 (0.29)
Improvement in ESR		0.39 (0.38)			-0.36 (0.23)
Dummy 1981			0.11	0.10	0.04
Dummy 1982			0.30	0.26	0.09
Dummy 1983			0.51	0.44	0.23
Dummy 1984			0.66	0.59	0.41
Dummy 1985			0.83	0.77	0.72
Dummy 1986			0.95	0.88	0.82
Dummy 1987			1.03	0.96	0.89
Dummy 1988			1.17	1.10	0.78
Dummy 1989			1.23	1.14	1.12
Dummy 1990			1.34	1.22	1.24
Dummy 1991			1.44	1.32	1.34
Dummy 1992			1.48	1.36	1.38
R-squared	0.29	0.24	0.72	0.74	0.84

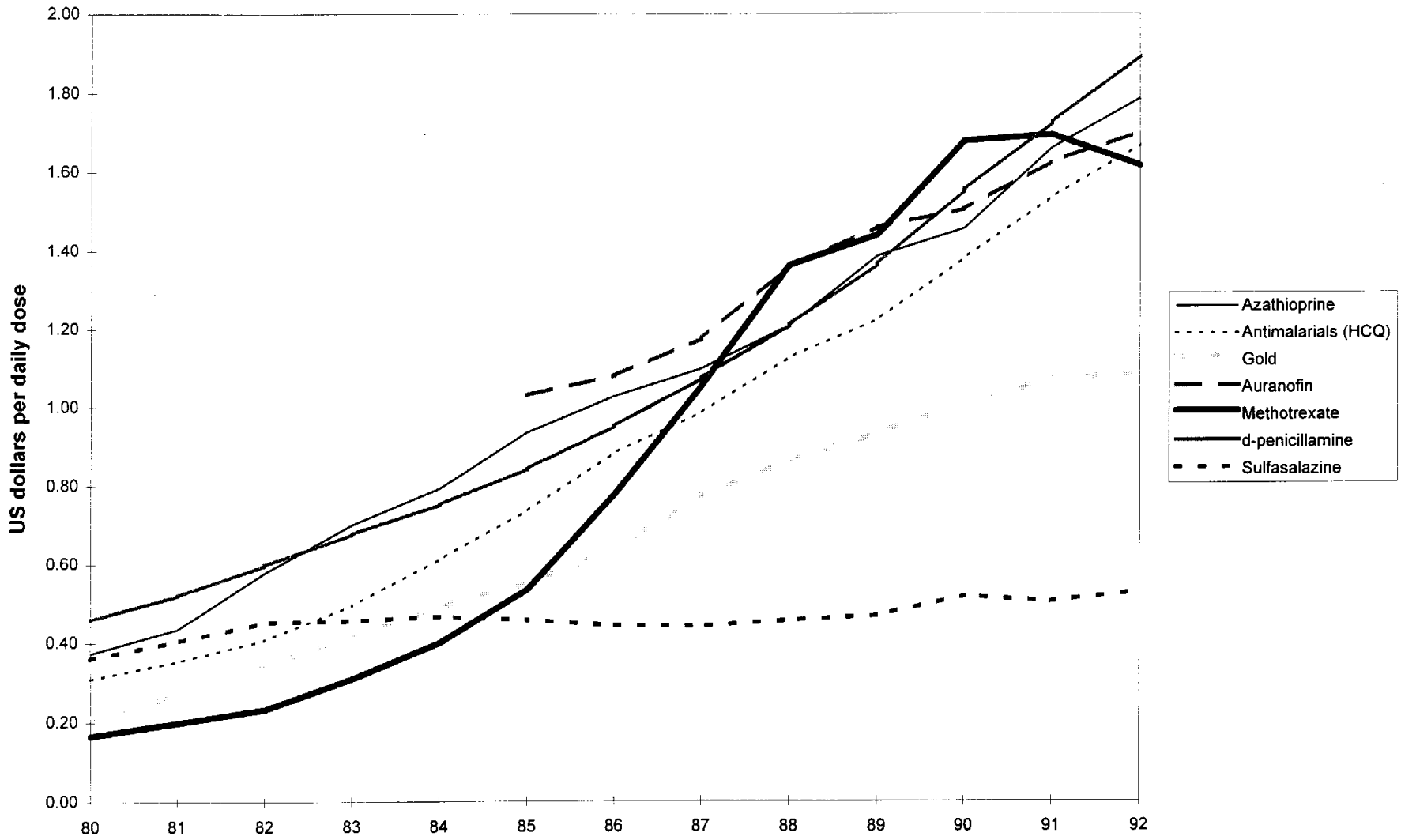
†Efficacy = (1 - dropout rate for lack of efficacy)
††Toxicity= dropout rate for toxicity
Dependent variable: current US dollars per daily dose
N=78
Standard errors in parentheses

Table 6: OLS Results: Quantity share regression 1980-1992

	Model 6 ("latest")	Model 7 (MA)	Model 8 ("latest")	Model 9 (MA)
Constant	-18.81 (3.47)	-15.73 (3.58)	-8.63 (2.15)	-8.50 (2.13)
Efficacy†	8.94 (3.73)	4.87 (4.04)	-0.94 (2.12)	-1.70 (2.27)
Toxicity††	-0.15 (0.91)	-0.53 (0.92)	-4.48 (1.59)	-4.11 (1.55)
Improvement in GS	1.59 (0.85)	2.48 (1.25)	0.38 (0.47)	0.00 (0.67)
Improvement in ESR	0.92 (0.72)	2.53 (0.99)	-0.41 (0.49)	1.23 (0.94)
Price	-0.43 (0.61)	0.09 (0.68)	0.30 (0.48)	0.36 (0.48)
Dummy auranofin			-0.48 (0.46)	-0.33 (0.46)
Dummy azathioprine			-0.52 (0.33)	-0.15 (0.39)
Dummy gold salts			2.36 (0.28)	2.34 (0.27)
Dummy antimalarials			-0.09 (0.51)	0.14 (0.50)
Dummy methotrexate			1.41 (0.31)	1.63 (0.34)
Dummy d-penicillamine			0.71 (0.31)	0.58 (0.30)
R-squared	0.26	0.29	0.79	0.80

†Efficacy = (1 - dropout rate for lack of efficacy)
††Toxicity= dropout rate for toxicity
Dependent variable: current US dollars per daily dose
N=78
Standard errors in parentheses

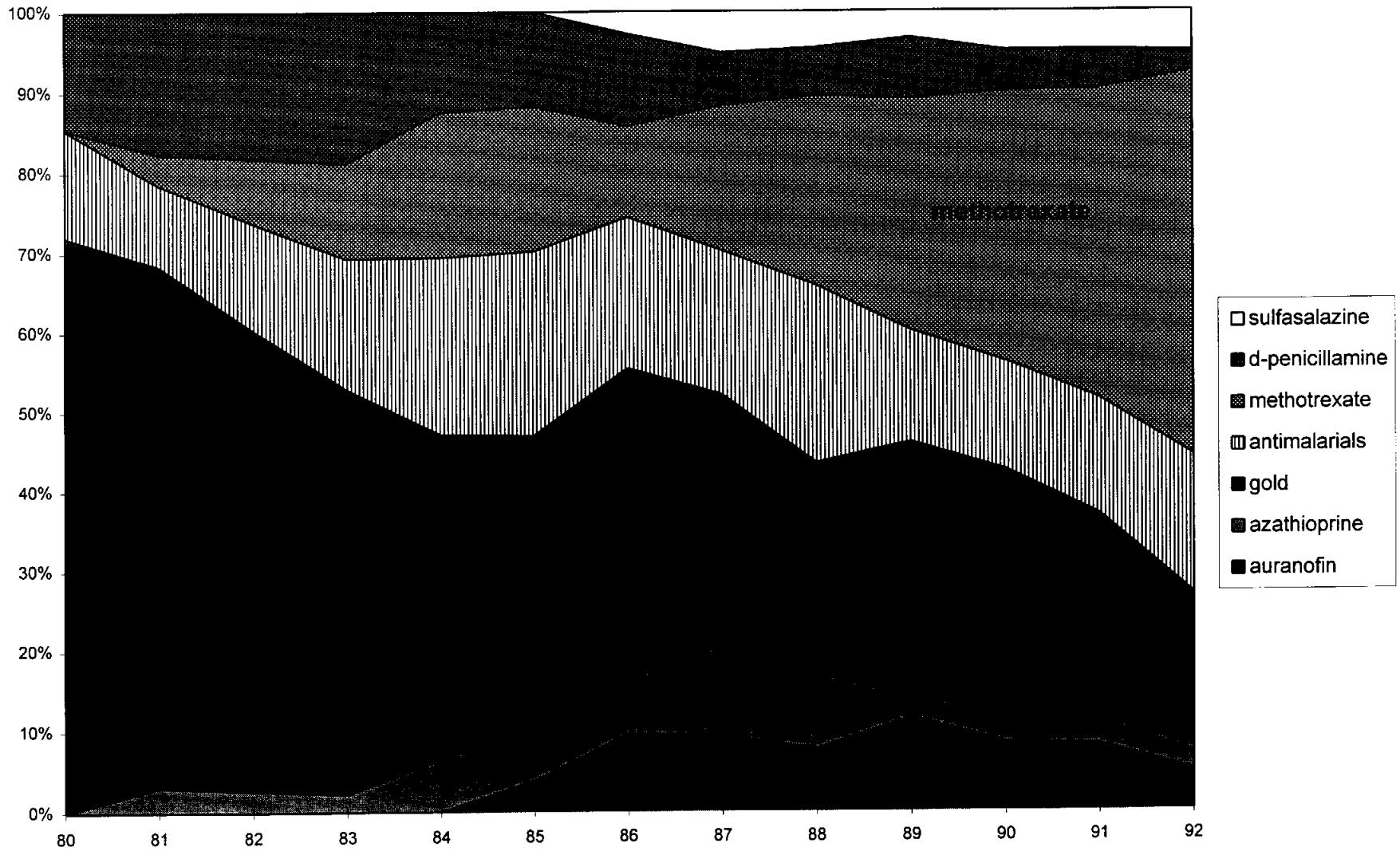
Figure 1
DMARD's: US Wholesale Prices



Source: IMS America

Cockburn/Anis "Hedonic Analysis of Arthritis Drugs"

Figure 2
DMARD's: Share Within Class of NDTI Mentions for RA



Source: IMS *NDTI*

Cockburn/Anis "Hedonic Analysis of Arthritis Drugs"