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Empirical Evidence on the Value of Pharmaceuticals

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I. Introduction

The last several decades have seen dramatic increases in overall medical spending as a share of GDP. While debate continues about the exact source of this increased spending, evidence suggests that it is being driven at least in part by the development and implementation of new technologies. Newhouse (1992) and Smith et al. (2009) found that technological advancements were a primary driver of increased medical spending.

An important component of these advances in medical technology is the introduction of new pharmaceutical treatments. This can be seen by both the absolute and relative growth of spending on prescription medications over the last two decades. For example, from 1980 to 2005, spending on pharmaceuticals increased from $12 billion to $200.7 billion—and as a result its share of total health care spending more than doubled. According to the Kaiser Family Foundation, "[a]lthough prescription drug spending has been a relatively small proportion of national health care spending (10% in 2006, compared to 31% for hospitals and 21% for physician services), it has been one of the fastest growing components, until recently growing at double-digit rates compared to single-digit rates for hospital and physician services" (Lundy, 2008). A large portion of this increase appears to be generated by changes in utilization. In the ten year period from 1997 to 2007, there was a 72 percent increase in the number of prescriptions purchased. Over the same time period, the U.S. population only grew by 11 percent (Lundy, 2008).

Examining prescription drug spending by specific condition shows even larger increases in utilization. For example, from 1987 to 2001, Americans' spending in inflation adjusted dollars on drugs for hypertension increased by 181%, on diabetes drugs increased by 533%, on mental health pharmaceutical treatments by 1,000%, and on statins by 3,900% (Stagnitti and Pancholi, 2004). In recent years, the majority of this increased spending came from higher usage of new drugs as opposed to simply increased prices on existing drugs (Smith, 2004). This spending pattern is not expected to change. According to the U.S. Department of Health and Human Services, expenditures on pharmaceuticals are

expected to increase by approximately 120% from 2008 to 2017 (Center for Medicaid and Medicare Services, 2007).

The increased utilization of pharmaceuticals is driven, at least in part, by a perception among patients that these medications are providing meaningful health improvements. According to survey data from the Kaiser Family Foundation, "[o]n the whole, a majority of Americans agree that prescription drugs developed in the past 20 years have improved the lives of people in the US in general (73%) as well as their own and their family members' lives (63%)" (Kaiser Family Foundation, 2008). For a variety of reasons, determining empirically if this perception reflects reality is a difficult task. First, the sheer number of treatments often makes it difficult to estimate the effect of pharmaceuticals on overall health. The number of conditions for which there are now treatments, and the ways in which these conditions are inter-related, generates a large number of confounding factors that can hamper attempts to estimate the causal effects of these drugs on overall health. Overcoming this difficulty often requires researchers to focus on the effect of only one medication, or one class of medications. This limits efforts to generate a single number for the value of these medications. The focus on a narrow range of conditions is particularly true in the case of clinical trials, which often are only concerned with the effect of one medication compared to a placebo. While this is useful for demonstrating the absolute value of a medication, it makes it difficult to understand the relative value of pharmaceuticals—particularly new drugs. These new medications are important because they are often introduced to the market at higher costs than existing alternatives (many of which no longer enjoy patent protection) and as a result they must provide significant benefits in order to be considered cost-effective.

In the initial section of this paper we summarize the existing evidence concerning the effect of pharmaceuticals on overall health. As discussed above, it will quickly become clear that establishing the health benefits of prescription medications at this macro level is difficult. Therefore, we examine evidence of the health benefits of pharmaceuticals for the most commonly used treatments for widespread chronic and life threatening conditions. In selecting the conditions we focused on both the most

widespread conditions and those for which the utilization of prescription medication has changed the most dramatically over the last two decades. In evaluating the health benefits of pharmaceuticals at the condition level, we primarily utilized information from clinical trials which most often evaluate the effectiveness of a medication compared to a placebo.

A broader question about the total *value* of pharmaceuticals involves the net benefit of these medications. There is a growing debate in the literature specifically about whether new drugs are worth more than their costs. The largest debate in the literature focuses on whether spending on these new drugs lead to even larger decreases in non-prescription drug spending , whether they are cost effective (i.e., they provide enough health benefits to outweigh their costs relative to an alternative treatment method), or neither. We focus this section on existing evidence concerning the net benefits of these medications in terms of cost savings from nondrug health spending. This focus results from the fact that it is currently the most compelling area of debate between researchers regarding the value of pharmaceuticals.

Finally, we will discuss the growing body of literature focusing on the non-health benefits of pharmaceuticals. Traditionally, evaluations of medications focus on solely health benefits of prescription drugs. Increasingly, medications are intended to treat chronic conditions and therefore can generate a variety of non-health benefits. For example, the development of effective treatments for mental health conditions can result in lower crime rates and the distribution of anti-retroviral medications for HIV/AIDS patients in Africa has been shown to increase productivity and labor force participation. The studies discussed in this section provide clear evidence about the growing value of pharmaceutical medication in everyday life.

II. Effect of Pharmaceuticals on Overall Health

The primary means of measuring the empirical benefit of pharmaceuticals is to examine their impact on health. Several studies have attempted to examine the impact of pharmaceuticals on society.

Miller and Frech (2000) examined the effect of pharmaceutical spending on life expectancy. Using OECD data, the authors estimated the effect of a variety of factors, including prescription medications, on life expectancy at birth, 40 years of age, and 60 years of age. The authors found that higher levels of pharmaceutical expenditures at the country level were related to increases in life expectancy. This relationship was stronger at older ages. Similar results were found in Frech and Miller (2004). Expanding on this work, Shaw, Horace, and Vogel (2005) estimated a similar model, but included each country's age distribution as an additional explanatory variable. The authors argued that failing to include this variable generates a downward bias in the estimated effect of pharmaceuticals on health. Including this control, the authors find large effects for prescription drug consumption on increased life expectancy over several age ranges.

Similar to these cross national studies, authors have also used country-specific data to more completely analyze the effect of pharmaceutical spending on health. Concentrating on specific countries increases the depth of data available on health outcomes beyond simply life expectancy. For example, Cremieux et al. (2005) estimated the effect of pharmaceutical spending on health outcomes in Canada. The authors found that higher rates of prescription drug consumption were associated with decreased infant mortality as well as increased overall life expectancy. Similarly, Cremeiux et al. (2001) used state level data from the United States and found that higher levels of prescription drug spending were associated with decreased infant mortality.

In related work, Lichtenberg (2004) used national-level data for the U.S. to estimate the effect of new drug releases on life expectancy. He focused on new drug releases, as opposed to all medical innovations, because pharmaceuticals are a component of innovation for which there is high quality data (from the U.S. Food and Drug Administration) about the date of adoption. Lichtenberg found that increases in medical innovation, in the form of new prescription medications, were positively associated with changes in life expectancy. Similarly, using data from 52 OECD counties, Lichtenberg (2005) found that new drug launches were associated with increases in life expectancy.

III. Effect of Pharmaceuticals on Specific Health Conditions

Examining the causal effect of pharmaceuticals on overall health is complicated by the variety of confounding factors that could bias the estimates. Often, these studies are only able to identify broad correlations in the data. This is particularly true for studies using national level observations data to compare effects across countries. A more accurate, but also narrower, measure of the health benefits of pharmaceuticals can be obtained from clinical trial evidence concerning the efficacy of new medications. These trials have the benefit of providing explicit experimental evidence regarding the effect of medications on health. Unfortunately, many trials concentrate only on the effect of medications against a placebo. Few attempts are made to estimate the efficacy of medications relative to existing treatments and as a result little is known about the relative efficacy of new medications.[1] We will provide a brief summary of the evidence in the medical literature documenting the health benefits of the commonly used pharmaceutical treatments for four widespread conditions: heart conditions, diabetes, HIV/AIDS, and mental health disorders.

Heart Conditions

Heart conditions are a widespread chronic and life-threatening condition. According to the United States Centers for Disease Control, heart disease was the leading cause of death in the United States—accounting for over 600,000 deaths in 2006 alone. This section will address the existing clinical evidence regarding the pharmaceutical treatment of hypertension, high cholesterol, and the secondary treatment of acute myocardial infarction—three of the most common heart conditions.

Hypertension, or high blood pressure, is a deadly chronic condition. Turnbull et al. (2003) reports that approximately half of the incidence of ischemic heart disease and two-thirds of the cerebrovascular disease burden is attributable to elevated blood pressure. The last several decades have seen a dramatic increase in the number of available treatments for this condition. Cutler et al. (2007)

[1] This is likely a result of current Food and Drug Administration requirements that new medications need only be proven to be safe and efficacious compared to a placebo.

stated, "[l]imited drug therapy was in use in the 1950s and early 1960s; the only drug therapies for hypertension approved by the Food and Drug Administration (FDA) by 1955 were vasodilators (approved in 1946) and peripherally acting agents (1953). Now we have a wide variety of medications." Currently, there are five main classes of pharmaceuticals that are indicated for the treatment of hypertension: diuretics, β-blockers, ACE inhibitors, calcium channel blockers, and Angiotensin II receptor blockers (ARBs).

Moser and Herbert (1996) and Herbert et al. (1993) reported that a meta-analysis of 17 trials covering 45,000 patients from 1966 to 1991 found that the use of diuretics and β-blockers to treat hypertension reduced cardiovascular mortality, stroke, and heart failure. These benefits ranged from a 21 percent relative risk reduction in cardiovascular mortality to a 52 percent relative risk reduction in heart failure. In subsequent work, Psaty et al. (1997) found that the use of diuretics, either in low or high doses, provided superior health benefits to β-blockers.

While all five treatments for hypertension are recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines, differing efficacy and cost has created some doubt concerning the most appropriate order of prescribing these medications. Thiazide diuretics are generally seen as the most effective first line therapy for patients with hypertension. Wright and Mussini (2009) conducted a meta-analysis of studies evaluating drugs in at least one of these categories. The authors found evidence indicating that low dose thiazides were effective at reducing all morbidity and mortality outcomes. While the authors also found evidence for ACE inhibitors, these results were less robust and the authors point out the ACE inhibitors are far more costly than diuretics. The authors also found that the use of β-blockers as a first line therapy was inferior to low dose diuretics. Similarly, Cushman (2003) found that most hypertension patients should first be treated with a diuretic alone or a combination of a diuretic and another medication. The use of either diuretics in isolation or in combination with other medications has contributed to an decrease in hypertension and an increase in cardiovascular health. Cutler (2007) estimated that without effective anti-

hypertensive treatment, the average blood pressure for individuals over age 40 in the 1999-2000 time period would have been 10 to 13 percent higher. This would have led to an additional 86,000 premature deaths from cardiovascular disease in 2001.

In addition to hypertension, high cholesterol represents a widespread chronic cardiovascular condition that is associated with a wide variety of negative health outcomes. Until 1987, there were few pharmaceutical treatments available for individuals afflicted with high cholesterol (Tobert, 2003). In this year, the first statin—Lovastatin—was approved for sale in the United States. Since that time, these drugs have become among the top selling pharmaceutical treatments in the country. According to the industry trade publication MedAd News, in 2007 the highest grossing drug in the United States was the statin Lipitor. Two other statins were also among the 50th highest selling medications: Zocor (25th) and Crestor (42nd).[2]

One reason for the commercial success of these medications is the clinical trial evidence and meta-analyses that have clearly demonstrated that they are effective in lowering cholesterol and reducing mortality. For example, initial clinical trials of Lovastatin found that it reduced mean cholesterol by 40 percent (Havel et al., 1987). Since the original introduction of Lovastatin there have been a number of additional statins approved for sale in the United States. A meta-analysis by Wilt et al. (2004) found that "use of statins, in moderate doses, lowered LDL-C levels 20% to 40% and reduced CHD mortality or nonfatal MI by 25%, all-cause mortality by 16%, and CHD mortality by 23%. Several other clinical trials and meta-analyses have also demonstrated the effect of statins on lowering cholesterol, cardiovascular events, and all-cause mortality (Gould et al., 1998).

While statins are now the recommended treatment for individuals afflicted by high cholesterol, there is a debate regarding which patients are appropriate for these drugs. For example, Brugts et al. (2009) found that the use of statin therapy even in patients without cardiovascular disease (but who had risk factor for cardiovascular disease) was associated with higher survival rates and a reduction of adverse

[2] In 2005, prior to many statins losing patent protection, drugs to treat cholesterol were the 1st, 2nd, 17th, and 31st high grossing medications.

cardiovascular events. Similarly, Thavendiranathan et al. (2006), in a meta-analysis of seven clinical trials covering over 40,000 patients without coronary vascular disease, found that that use of statins was associated with a decreased incidence of major coronary events, cerebrovascular events, and revascularizations. Unlike Brugts et al. (2009) this study did not find any statistically significant effect on coronary heart disease mortality (though the point estimate suggested a statistically insignificant 22.6 percent relative risk reduction) on overall mortality.

A third category of cardiovascular conditions that has seen dramatic progress from pharmaceuticals is the secondary treatment of acute myocardial infarctions. In the 1950's, treatment for individuals suffering from a heart attack amounted to little more than bed rest. Since that time period, there have been a wide variety of interventions developed to address the negative health effects of a heart attack. While a number of these innovations are non-pharmaceutical interventions, a variety of medications have been introduced to improve health following a heart attack. Three of the most commonly used and recommended treatments are aspirin, β-blockers, and statins.

From 1975 to 1995, the use of aspirin following a heart attack increased dramatically. In 1975, only 5 percent of patients suffering an AMI received aspirin. By 1995, this number had increased to 75 percent (Heidenreich and McClellan, 2001). The increased use of aspirin is likely driven by the large number of clinical trials that have demonstrated improved mortality for individuals taking aspirin soon after suffering an AMI. The ISIS-2 clinical trial found that for every 1,000 patients treated with a month-long course of medium dose aspirin, there were approximately 25 fewer deaths, and 10-15 fewer non-fatal re-infarctions or strokes (ISIS-2 Collaborative Group, 1988). Similarly, the Antiplatelet Trialists' Collaboration found that medium dose aspirin was effective at decreasing re-infarctions, stroke, and mortality. The study also found that no other anti-platelet therapy was superior to aspirin (Antiplatelet Trialists' Collaboration, 1994). A subsequent study examining the 10-year health outcomes of ISIS-2 participations found that the long term health benefits for individuals treated with aspirin were better—but

much of this benefit was gained during the period immediately following the original infarction (Baigent et al., 1998).

Recent decades have also seen a marked increase in the use of β-blockers following an AMI. This is likely a result of several studies demonstrating the efficacy of these medications (Norwegian Multicenter Study Group, 1981; Hjalmarson et al., 1981; Beta-blocker Heart Attack Trial Research Group, 1982). From 1975 to 1995, the percentage of heart attack patients being treated with these medications more than doubled (from 21 percent to 50 percent). The β-blockers Heart Attack Trial found decreased mortality for individuals taking these medications and recommended their use for three years following a heart attack (Beta-blocker Heart Attack Trial Research Group, 1982). Similarly, Gottlieb et al. (1998) examined the medical records of over 200,000 patients and found mortality benefits from the use of β-blockers following myocardial infarction. Despite the medical evidence of efficacy over several decades, these medications are still underutilized—particularly for patients who are female and/or elderly (Krumholz et al., 1998; Soumerai et al., 1997; McClaughlin et al., 1996; Newby et al., 2006). Philips et al. (2000) reported results from a simulation which showed that increasing the utilization rate of these medications would dramatically improve health (as measured by prevented future myocardial infractions, mortality, and life years gained) among patients—even those patients with conditions previously thought to contraindicate the use of these medications.

In more recent years, researchers have investigated the benefits of post-heart attack usage of statins—even among patients who did not previously have high cholesterol. The usage of statins is based on the belief that, "[b]y influencing the determinants of myocardial injury, statins may product direct cardioprotective effect in the ischemic myocardium and prevent further damaging recurrent events" (Scalia, 2005). Clinical trials have shown that the use of statins immediately following a myocardial infarction improves health (Liberopopolous et al. 2005; Schwartz et al., 2001; Spencer et al., 2004). Schwartz et al. (2001) found that in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) clinical trial, individuals who were treated with atorvastatin soon after a myocardial

infarction had reduced rates of death and recurrent ischemic events. These positive health benefits were even found for individuals who previously were not diagnosed with high cholesterol and had never taken any statins. Spencer et al. (2004) found that among patients who previously had not been prescribed statins, the initiation of stating therapy during hospitalization for an AMI reduced the probability of dying in the hospital or experience the primary composite endpoint of death, in-hospital myocardial infarction, or stroke. It is clear that the health benefits of statins exist beyond simply lowering cholesterol. These medications also have demonstrated health benefits in the secondary treatment of AMI.

Diabetes

Diabetes is a metabolic disorder where the body does not produce enough or does not respond to the hormone insulin. It is one of the most prevalent chronic conditions afflicting Americans. The most effective means of controlling the harmful side effects of the disorder is appropriate control of mean A1C (glucose) levels. The Diabetes Control and Complications Trials (DCCT) found a lower level of microvascular complications among individuals who lowered their mean A1C levels. These benefits were found up to seven years after the completion of the trial (DCCT, 1993), Hoerger et al. (2008) found that across society, A1C levels have been decreasing over time. Specifically, mean A1C levels dropped from 7.82 in 1999-2000 to 7.18 in 2003-2004. The difference between these levels was statistically significant. Furthermore, the percentage of individuals with A1C levels below the recommend level of 7.0 rose from 36.9 percent in the 1999-2000 to 56.8 percent in 2003-2004. Again this difference was statistically significant. Similar improvements in glycemic control were found by other authors (Cheung et al., 2009).

While there were many recommended lifestyle changes among diabetes patients over this time period, "[a]t the same time, new drugs became available in the U.S., including metformin (available by brand name since 1995 and as a generic drug since 2002) and the thiazolidinediones (available in current brands since 1999)" (Hoerger et al., 2008). It is clear that these pharmaceutical innovations have played a

key role in controlling A1C levels and improving the health and quality of life of diabetics. Clinical trial evidence has found that the use of pharmaceuticals to manage glucose levels is superior to lifestyle changes and dietary restrictions alone. For example, Turner et al. (1998a) found that the pharmaceutical management of glucose levels was associated with a decrease of microvascular complications. In a subset of obese patients in the United Kingdom Prospective Study Group treated specifically with metformin, pharmaceutical treatments were associated with a decrease in diabetes related endpoints including diabetes related death and all-cause mortality (United Kingdom Prospective Diabetes Study Group, 1998a; 1998b).

Currently, there are five distinct classes of medications for treating diabetes: Sulfonylureas, α-Glucosidase Inhibitors, Thizolidinediones, non-SU Secretagogues, and metformin. Izneuchi (2002) reviewed the clinical trial evidence and finds that these five classes of medications are equally efficacious at controlling glucose levels. According to Krentz and Bailey (2005), "[m]etformin does not promote weight gain and has beneficial effects on several cardiovascular risk factors. Accordingly, metformin is widely regarded as the drug of choice for most patients with Type 2 diabetes."

HIV/AIDS

Acquired Immune Deficiency Syndrome (AIDS) is a chronic condition that damages, and ultimately destroys an individual's immune system. AIDS is caused by the human immunodeficiency virus (HIV), a member of the retrovirus family that attacks vital components of an individual's immune system. Specifically, the disease invades and ultimately destroys a body's CD4 cells—a type of white blood cell that is primarily responsible with assisting the body in fighting off opportunistic infections. When this virus first appeared, the available treatment was primarily limited to fighting the opportunistic illnesses afflicting individuals with the disease. This treatment pattern changed dramatically with the introduction to the market of Retrovir (AZT) in 1987. This drug was the first medication approved in the therapeutic class known as nucleoside reverse transcriptase inhibitors (NRTIs). Despite the development

and introduction of three new NRTIs from 1991 to 1994, the utilization of this class of medications among patients with AIDS actually declined from 1992 to 1995 (Duggan and Evans, 2008). These declines in use were reversed when Epivir and three additional drugs in the protease inhibitors (PI) class were approved for sale in 1995 and early 1996. Subsequently, the first NNRTI (non-nucleoside reverse transcriptase inhibitor) was introduced to the market in June of 1996. These new medications were following by twelve additional drugs that were approved for sale between 1997 and 2003.

The introduction of Epivir/PI reversed the declining trend in drug utilization in part due to its use as a component of highly active antiretroviral therapy (HAART)—often referred to as the "AIDS cocktail." This therapy involves the simultaneous use of two or more anti-retroviral medications (ARVs) to treat HIV. Quickly following its introduction, Epivir/PI as a component in HAART became the medically accepted treatment for individuals with HIV. Furthermore, the swift increase in the use of these drugs occurred simultaneously with substantial declines in mortality among AIDS patients (Duggan and Evans, 2008). According to data from the U.S. Centers for Disease Control, the mortality rate for individuals with AIDS fell by 70 percent between 1995 and 1998.

There is plentiful evidence regarding the efficacy of these new ARVs. These studies include both large trials utilizing randomized designs (Hammer et al., 1997; Delta Coordinating Committee, 2001; Floridia et al., 2002) and observational studies containing highly detailed clinical information (Palella et al., 1998; Detels et al., 1998; CASCADE Collaboration, 2003; Duggan and Evans, 2008). In general, all of these studies have found statistically significant reductions in mortality from the use of ARVs. Among the randomized trials for example, Hammer et al. (1997) found that 48-week mortality rates among individuals taking a protease inhibitor was 55 percent lower than comparable individuals. Duggan and Evans (2008) used administrative data from the state of California's Medicaid system and found a 68 percent reduction in mortality—a number in line with the consensus estimate of randomized clinical trials. The authors also found a short term reduction in medical spending among ARV recipients.

Together, these drugs cost an estimated $19,000 per life year saved —far below most cost-effectiveness thresholds.

In aggregate, the utilization of these medications appears to have significantly increased the length of life for individuals suffering from HIV/AIDS. Walensky et al. (2006) estimated that over 3 million life years in the United States have been saved over the first 10 years of using ARVs.

Mental Health Conditions

Mental health is an area that has seen dramatic increases in the availability of effective pharmaceutical treatments. These treatments have been shown to be either more effective at relieving the symptoms of the underlying condition, have fewer side effects, or both. In this chapter we will consider the evidence concerning the health effects of pharmaceuticals to treat depression, psychosis, and attention deficit hyperactivity disorder (ADHD).

Chronic depression is one of the most widespread mental disorders. According to the CDC, nearly 16 percent of respondents to the Behavioral Risk Factor Surveillance System (BRFSS) in 2006 reported being told by a health care provider that they had depression at some point in their lifetime (Strine et al., 2008). There are currently four main types of anti-depressant medications available for sale in the United States: selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and newer generation antidepressants (NGAs). SSRIs, marketed under brand names such as Prozac and Zoloft, are the most popular of these medications. Introduced in the late 1980s, these medications quickly rose in sales until they were the highest selling class of drugs in the United States in the year 2000.

Clinical trials and observational studies have generally found that anti-depressants (often in combination with nondrug treatments) effectively reduce the symptoms of major depression. Summarizing the evidence, Lawrenson et al. (2000) reported that in records from 151 computerized practices in the United Kingdom covering 1.8 million patients, 70 to 80 percent of patients with moderate

to severe depression experienced an improvement in symptoms compared to 30 percent of those taking a placebo. Williams et al. (2000) found that in a meta-analysis of 315 eligible trials, new and old anti-depressants were both shown to be effective. The similar efficacy between different generations of anti-depressants has also been reported in other studies. Song et al. (1993) found that SSRIs and TCAs were similarly efficacious. The authors concluded that the first line use of SSRIs could substantially increase treatment costs while providing limited benefits.

While efficacy may be similar between different types of medications, side effects have been found to vary dramatically. One side effect of anti-depressants in general, and SSRIs in particular, that has received a great deal of attention is a potential increase in suicides. This line of research dates back to a 1990 case study of six individuals who committed suicide after taking Prozac (Teicher et al., 1990). Little clinical trial evidence exists evaluating the effect of anti-depressants on actual suicides. This is due to the fact that suicide is such a rare outcome and therefore the sample size of the trial necessary to detect an effect is prohibitively large. Instead, researchers tend to focus on behaviors such as non-lethal suicidality. For example, the FDA review of studies examining the effect of SSRIs on suicidal behavior among teenagers found that the use of SSRIs doubled the risk of suicidal behavior (Food and Drug Administration, 2003). There were no actual suicides among these trials. Bridge et al. (2007) found an increased risk of suicide ideation among pediatric patients with major depressive disorder. Fergusson et al. (2005) found an increase in suicidal behavior among adult patients treated with SSRIs compared to those treated with a placebo. All of these studies, however, are hampered by the fact that their primary endpoints are suicidal thoughts and not actual suicide attempts or completed acts.

To analyze the effect of anti-depressants on suicidal behavior it is necessary to use observational data. Only in these instances can researchers acquire the sample sizes necessary to detect an effect on actual suicides. A clear difficulty in using observational data in these cases is potential endogeneity in the decision to start taking the medication. One attempt to overcome this problem is the use of longitudinal data and panel estimation methods. For example, Gibbons et al. (2005, 2006) estimated the effect of

SSRIs on suicide by exploiting variation in use over time across and within counties in the United States. He found that the use of SSRIs is associated with lower suicide rates for all age groups. Similarly, Ludwig and Marcotte (2005) used cross-national data from 27 countries over 20 years to estimate the effect of SSRI use on suicides. They also found a reduction in suicides resulting from these medications.

Panel data methods, while superior to designs relying on interrupted time series, are still susceptible to time varying conditions that affect both SSRI use and suicidal activities. Ludwig, Marcotte, and Norberg (2009) used exogenous variation in the utilization of SSRIs created by institutional differences in regulation, distribution, and pricing of these medications to estimate the effect of SSRIs on suicidal behavior. This quasi-experimental variation is superior to previous efforts utilizing panel data methods. They find that an increase in sales of SSRIs of one pill per capita, which equals approximately 12 percent of SSRI sales in 2000, results in a 5 percent reduction in suicides. Cuellar and Markowitz (2007) used state-level variation in Medicaid expansions to estimate the effect of anti-depressants on suicides (among other outcomes). The authors find that spending on older anti-depressants is associated with a reduction in adult suicides. No effect is found for spending on newer anti-depressants. Among teenagers and children, however, the authors found that spending on newer anti-depressants increased the number of suicides. Spending on older anti-depressants is associated with a statistically insignificant reduction in suicides among these younger patients.[3] Overall, there is no consensus in the literature about the net effect of anti-depressants on suicidal behavior.

Anti-psychotic medications are intended for the treatment of individuals suffering from schizophrenia, bipolar disorder, or dementia. They are most frequently prescribed for the treatment of schizophrenia—a chronic mental illness that afflicts approximately 2 million people in the United States. This disease is characterized by a wide range of symptoms that include, but are not limited to, delusions, hallucinations, cognitive impairments, and social withdrawal. Prior to 1990, individuals suffering these

[3] The authors caution, however, that they do not have age specific spending data and therefore if the patterns of spending are different between older and younger Medicaid patients these results may not accurately reflect the effect on suicide from these medications

symptoms were prescribed either haloperidol or another "first-generation" antipsychotic for the treatment of schizophrenia. Clinical trial evidence found that while these early medications were effective at eliminating the effects of the mental disorder, they also had a fairly extensive side effect profile. Specifically, individuals consuming these drugs were found to experience a higher rate of extrapyramidal symptoms (EPS) such as Parkinsonism (tremors and rigidity), tardive dyskinesia (involuntary movements), acute dystonia (muscle contractions), akathisia (restlessness), and neuroleptic malignant syndrome (changes in heart rate or breathing).

The relatively large side effects profile of these medications resulted in the development and introduction of second generation anti-psychotic medications. This began with the FDA's approval of Clozaril in 1990. The medication has been found to reduce the incidence of EPS (Lamberg, 1998; Keefe et al, 1999; Meltzer et al, 1999). Clozaril's side effects, however, resulted in its use being limited to patients who could not tolerate existing medications. The shift towards the utilization of second generation anti-psychotics accelerated with the subsequent release of Risperadal, Zyprexa, and Seroquel in the mid-1990s (Duggan, 2005).

An even larger body of research has examined the effect of second-generation antipsychotics on the prevalence of adverse side effects, including extrapyramidal symptoms, diabetes, abnormal weight gain, and hyperlipidemia (Gianfrancesco et al, 2002; Kerwin, 1994; Koro et al, 2002; Leucht et al, 2002; Lund et al, 2001; Meyer, 2001; Sernyak et al, 2002). Taken together, these studies suggest that second-generation drugs have fewer adverse extrapyramidal side effects than the earlier drugs but that they may increase the prevalence of diabetes and related illnesses. Both sets of results are controversial, however, with some finding no impact of second-generation antipsychotics on EPS (Rosenheck et al, 2003) and others no effect on diabetes (Kabinoff et al, 2003).

Attention Deficit Hyperactivity Disorder (ADHD) is a mental health disorder that primarily presents itself in the early years of childhood. Visser, Lesene, and Perou (2007) reported that the incidence of ADHD among individuals aged 4 to 17 years of age was 7.8 percent. This differed greatly

by gender—with boys being diagnosed at a rate 2.5 times greater than girls. The recommended treatment of ADHD involves a combination of behavioral management and medical treatment. Of the 7.8 percent of youths reporting an ADHD diagnosis in the National Survey of Children's Health data, more than half were currently taking medication for their disorder (Visser, Lesene, and Peroi, 2007).

The MTA Cooperative Group study involved a clinical trial evaluating the relatively long term (14 months) effects of stimulants on ADHD symptoms. The authors found that the use of stimulants was superior to behavior therapy (MTA Cooperative Group, 1999). Similarly, Brown et al. (2005) reported that a review of the empirical literature suggests that nonpharmacologial interventions alone were inferior to the use of stimulant medication. The authors do report that the combined use of medication and other therapies is effective and may result in smaller doses of stimulants. Barbaresi et al. (2006) reported results from a long term observational study. These authors found that the results regarding the efficacy of stimulant medications found in clinical trials with relatively short follow-up periods were similar to the results over their longer observational period. The empirical literature has found that the use of stimulant medication has been effective at managing the core behavioral symptoms of ADHD. These included indicators of behaviors such as impulsivity and distractibility. Far less evidence was found that these medications increased academic performance (Brown et al., 2005).

While few studies directly compared the efficacy of different stimulants, Faraone and Buitelaar (2009) reported results from a meta-analysis that showed the amphetamine based products are superior to methylphenidate across a variety of outcomes. These differences in efficacy were found to be modest. Given potential differences in side effects and potential heterogeneity in treatment benefits, there is no consistent empirical evidence suggesting the use of one type of stimulant medication for the treatment of ADHD.

Over the last decade there has been a dramatic increase in the prescription of medications for ADHD. Zuvekas, Vitiello and Norquist (2006) found that in the Medical Expenditure Panel Survey (MEPS) there was a fivefold increase in the reported use of stimulants from 1987-2002. Castle et al.

(2007) found that among a sample of privately insured children, there was a 12 percent increase in stimulant use from 2000 to 2005. Due to the lack of a specific test for ADHD, and the wide variability in the use of medications across socio-demographic lines, there is some concern that these medications are being overprescribed. Evans, Morrill, and Parente (2009) used variation in eligibility for kindergarten at the state level to estimate whether relative age to others in your class influences the probability of a child being prescribed a stimulant. They find that children who are born just after the cutoff date, and are therefore relatively old for their grade, have a significantly lower probability of being diagnosed and treated for ADHD. Due to the fact that there are no identifiable medical factors that should be driving the incidence of this disease across birth dates, this study provides evidence that non-medical factors may be playing a role in the prescription patterns of these medications.

IV. Net Benefits of Pharmaceuticals

While the discussion above clearly demonstrates the health benefits of many different pharmaceutical treatments, it provides little evidence about the relative value of these mediations. In particular, the effect of these drugs on health says little about their net benefits. This relative value is of increased importance for new drugs because these medications are often significantly more expensive than existing treatments—especially when the original medication no longer enjoys patent protection. Due to these higher costs, new medications often have to clear a high bar in order to be cost effective. One strategy for identifying the net benefits of pharmaceuticals has been to examine the effect of drug spending on expenditures of other medical services. The rationale is that effective pharmaceuticals should lower spending on more expensive and invasive treatments. Authors have examined this effect across all drug categories (Lichtenberg, 1996 and 2001; Zhang and Soumerai, 2007) and for specific therapeutic categories such as anti-psycotics, (Duggan, 2005) and cardiovascular medications (Miller, Moeller, and Stafford, 2005). Authors have also attempted to estimate the net benefits of pharmaceuticals

using quasi-experimental variation in insurance coverage or copayments (Soumerai, 1991; Zhang et al., 2009).

A series of studies have attempted to address the question of the effect of pharmaceutical expenditures on total health spending. Lichtenberg (1996) estimated the effect of increased utilization of drugs, and the consumption of more effective medications, on the number of hospital days experience by patients. Utilizing data from the National Ambulatory Medical Care Survey (NAMCS), National Hospital Discharge Survey (NHDS), and the Vital Statistics-Mortality Detail file, Lichtenberg estimated the effect of changes in the utilization patterns of pharmaceuticals on the consumption of other medical services such as hospital stays. The estimates imply that a $1 increase in pharmaceutical spending is associated with a $3.65 decrease in hospital expenditures. For this to be the true causal estimate one must assume that factors affecting the usage of hospital services (e.g., changing health of people with a particular condition) that were unrelated to pharmaceutical innovation did not vary across health conditions over this time period. Given the number of changes in the health care and health insurance sector over this time period, this may not be a reasonable assumption.

A second paper, Lichtenberg (2001), used data from the Medical Expenditure Panel Survey (MEPS) to examine if increased expenditures on new medications were associated with lower spending on other medical services. Overall, Lichtenberg found that patients consuming newer medications (as measured by drug vintage) were less likely to die and missed fewer work days over the sample period. Furthermore, these individuals experienced a reduction in nondrug health spending. While this work did exploit the panel nature of the MEPS to control for individual-specific fixed effects, it is possible that there are time varying factors influencing both the vintage of drugs consumed and other factors such as mortality and nondrug health spending. In subsequent work, Zhang and Soumerai (2007) re-estimated the model in Lichtenberg (2001). The authors reported that while they were able to replicate the original results, they found that the original results were very sensitive to particular modeling decisions. Under a

number of alternate specifications, there is no detectable effect on health spending resulting from the vintage of drugs.

In contrast to these primarily longitudinal analyses, several authors have attempted to use quasi-experimental variation in the utilization of pharmaceuticals generated by changes in insurance coverage or coinsurance rates to estimate the effect of drug spending on the consumption of other medical services. (Chapter 12 also reviews some of the literature on the effect of drug spending on non-drug spending). In one of the earliest such studies, Soumerai (1991) used a reduction in the number of reimbursable medications under Medicaid as a source of exogenous variation in pharmaceutical consumption. Examining three years of data from the Medicaid systems in New Hampshire (which had a cap on the number of covered prescriptions for 11 of the 36 months) and New Jersey (which did not), Soumerai estimated the effect of the pharmaceutical cap on the utilization of nursing home and hospital services. While no evidence was found for an increased risk of hospitalization, elderly patients in New Hampshire faced a greater risk of admission to a nursing home during the months when the cap was in place. After removal of the cap, this risk returned to baseline levels. These results suggest that there are effects on nondrug spending from reduced utilization of pharmaceuticals, but Soumerai could not definitively say these increases were greater than the cost savings of the policy.

In more recent work, Hsu et al. (2006) estimated the effect of caps on pharmaceutical spending for individuals participating in the Medicare+ Choice program compared to individuals with no caps as part of their employer provided plan. The authors found that patients whose prescription medications were capped at $1,000 had lower rates of adherence to drug protocols. In addition, and perhaps as result of this lower adherence, these individuals also suffered less favorable clinical outcomes such as increased spending on hospitalizations and emergency department visits.

In similar work that utilized an arguably more exogenous change in prescription coverage, Zhang et al. (2009) exploited the increase in prescription drug coverage generated by the implementation of Medicare Part D to estimate the effect of the increased utilization of pharmaceuticals on nondrug health

spending of American seniors. The authors compared the expenditure patterns of Part D eligible individuals who had either no prescription coverage or limited coverage (as defined by a quarterly cap on expenditures of either $150 or $350) prior to the implementation of the program to the spending of individuals who originally had prescription coverage through Medicare Advantage or an employer provided plan—and thus are assumed to be unaffected by Part D. The authors found that spending increased for all groups with expanded coverage, and those with no coverage prior to Part D experienced the largest increase. The largest spending increases were seen for lipid lowering drugs and anti-diabetic agents. The results regarding decreased nondrug medical spending were mixed. For individuals with no coverage or a $150 quarterly cap in the pre-Part D period, nondrug medical spending decreased. In contrast, individuals with a $350 quarterly cap before Part D experienced increased nondrug health spending. Due to these heterogeneous results, the authors are unable to say what the net effect on nondrug health spending was as a result of Medicare Part D.

While not specifically examining health care spending, Tamblyn et al. (2001) estimated the effect of increased prescription coinsurance and copayments on the rate of adverse events among a large sample of Canadians. The authors found that this increase in financial costs decreased the utilization of prescription medication. Furthermore, there was a statistically significant increase in the rate of adverse events and emergency room visits. Without data on the drug expenditures and adverse event rates of another Canadian province, the authors are unable to say that the observed post-cost sharing trends are not the result of other unrelated factors. In addition, without data on changes in costs it is not clear what the net effect of the policy change was on overall health spending.

Gaynor, Li, and Vogt (2007) estimated the effect of differing copayment levels for Medicare Advantage beneficiaries on the utilization of prescription drugs and outpatient medical services. They found that consumers do decrease their expenditures on pharmaceuticals in response to higher copayment levels. They also found, however, that approximately 35 percent of these savings are eaten away by the increased utilization of outpatient medical services. Similarly, Chandra, Gruber, and McKnight (2010)

examined an increase in cost sharing for public employee retirees in California. These authors found reductions in the utilizations of prescription medications in response to the policy change. Furthermore, they found an increase in hospital utilization among these employees. Perhaps unsurprisingly, this increase was concentrated among patients with chronic conditions.

In addition to using quasi-experimental variation in insurance coverage for all drugs, some authors have attempted to estimate the net benefits of pharmaceuticals by examining a specific subset of conditions. For example, Miller, Moeller, and Stafford (2005) estimated the effect of increasing spending on new drugs for the treatment of cardiovascular conditions. The authors used data from the MEPS to estimate the effect of the average age of drugs used on overall medical expenditures. This is based on the hypothesis that if new drugs are actually cost saving, then individuals using relatively newer drugs should have lower overall expenditures. The authors use data on the total number of drugs reported as an attempt to control for time-varying changes in condition severity. Overall, they find no association between decreased health expenditures and the average age of drugs consumed by patients. The authors argue that these results contradict earlier research, particularly Lichtenberg (2001), which found a reduction in total health expenditures from an increased utilization of new medications.

Duggan (2005) examined the effect of increased spending on second generation anti-psychotic medication among Medicaid patients on overall health spending. Duggan used several identification strategies including exploiting regional variation in the diffusion of these medications to the market and individual level variation in the probability of particular physicians prescribing a second generation medication. Across three separate identification strategies, Duggan was unable to find evidence that the 610% increase in Medicaid spending on these medications from 1993 to 2001 was associated with any reductions in nondrug medical spending. Furthermore, he found suggestive evidence that these drugs were associated with an increase in the prevalence of diabetes and a reduction in extrapyramidal symptoms among the mentally ill. Taken together, the results suggest that these new drugs did not justify their increased costs with savings from other areas.

In addition to considering the effect of pharmaceuticals on expenditures for other medical services, the pharmacoeconomics literature often discusses the cost-effectiveness of medications using metrics such as quality adjusted life years (QALYs). Chapter 13 of this volume summarizes the evidence involving these measures. Another way to analyze the net benefits of medications is with hedonic pricing methods. While a great deal of attention has been paid to the increasing spending on pharmaceuticals over the last two decades, it is not immediately clear that the associated increased benefits exceed the incremental costs. This is especially true when studies show that a majority of the increased spending in recent years has been the result of new drugs and increased utilization and not simply price increases. Economists have implemented hedonic pricing methods, more commonly used in other consumer settings such as the market for personal computers or automobiles, to estimate quality adjusted price indices for medical spending. Chapter 14 provides a detailed summary of the methods and existing papers in this area.

V. Non-Health Benefits of Pharmaceuticals

The benefits and value of pharmaceuticals are primarily evaluated on their ability to improve physical and mental health. Comparatively little attention is paid to the non-health benefits of these medications. This is despite the fact that a growing portion of pharmaceutical spending is focused on conditions that potentially improve an individual's quality of life along dimensions that are not covered solely by standard health outcomes. In addition, the effective use of medication can also generate societal benefits along non-health dimensions.

Mental Health Medication and Lower Crime

One example of potential non-health related societal benefits from pharmaceuticals comes from the effect on crime from the increased utilization of more effective anti-psychotic medications. A variety of studies have found potential causal relationships between mental health disorders and crime. For

example, survey evidence shows that inmates in federal, state, and local prison are twice as likely as the general population to have been diagnosed with a major mental illness in the year prior to their arrest (Marcotte and Markowitz, 2009). It is therefore logical to hypothesize that more effective management of these conditions could lead to non-trivial reductions in crime. As discussed above, over the last several decades there have been dramatic increases in the efficacy of pharmaceuticals in this area. Cuellar and Markowitz (2006) examined the increased utilization of both stimulants (for the treatment of ADHD) and anti-depressants among Medicaid patients. The authors found that the increased utilization of stimulants was associated with a negative and statistically significant change in violent crime. The authors also find suggestive evidence of decreases in property crimes resulting from the utilization of these drugs. Similar results for violent crimes were found for spending on older anti-depressant medications. No effect was found for the newer classes of anti-depressants. A placebo test using spending on cholesterol medications found no effect, suggesting the estimates for anti-depressants represent a causal effect.

Implementing a similar identification strategy, Marcotte and Markowitz (2009) found that increased spending on mental health medications was associated with lower crime rates. In contrast to Cuellar and Markowitz (2005), this study found that spending on newer generation anti-depressants was associated with a reduction in crime. The authors also found evidence supporting crime reductions from stimulant use. Specifically, the authors found that "a one percent increase in the total prescription rate is associated with a 0.051 percent decrease in violent crimes. To put this in perspective, doubling the prescription rate would reduce violent crimes by 5 percent, or by about 27 crimes per 100,000, at the average rate of 518 crimes per 100,000 population." Weaker support was found for a connection between lower crime rates and the use of anti-psychotic medications. The authors also provide evidence that even the relatively small magnitude responses they find for crime reduction from mental health medication would pass most cost benefit thresholds.

Effect of Anti-Retroviral Medications on Economic Outcomes

For a variety of valid reasons, the primary focus of the analyses of anti-retroviral medications (ARVs) and HAART (the "AIDS Cocktail") has been the mortality-improving benefits of these medications. Given the high death rates from HIV/AIDS, it is not surprising that this has been the primary focus of both clinical trials and observational studies. These medications can also confer sizeable economic benefits. The relatively swift decline in health, combined with the fact that a large portion of affected patients are in their prime years of labor force participation, means that there could be large economic benefits gained by the effective treatment of HIV/AIDS. This is especially important when discussing the case of African nations. The United States Agency for International Development, estimates that one in 12 workers in sub-Saharan Africa is infected with HIV. In some countries this ratio is as high as one in three (USAID, 2002). Therefore, improving the length of life and labor supply among these individuals can generate dramatic changes in country-wide economic conditions.

Researchers have primarily addressed the question of the economic effects of HIV/AIDS and effective ARV treatment in the context of these developing countries—particularly sub-Saharan Africa. Fox et al. (2004) examined the work histories of workers on a Kenyan tea estate. The authors find significant declines in productivity among HIV-infected employees. The authors do not, however, attempt to estimate the potential effects on these productivity declines from the treatment of HIV.

Thirumurthy et al. (2008) examined the labor supply effects of effective ARV treatment for HIV positive workers in Kenya. The authors link one year of longitudinal socioeconomic data collected throughout rural Kenya to detailed medical data. These data provide key information on health status and ARV treatment regimes and are used to estimate the effect of treatment on both the patient and on the patient's family. The authors' identification strategy relies on the fact that the implementation of ARV treatment is dictated in large part by biological factors that are not easily manipulated by patients with late stage HIV/AIDS. Furthermore, the authors collect data from a large number of non-patient households to account for seasonality and other secular factors that may influence economic outcomes. Overall, they find that the utilization of ARV treatments results in large and statistically significant increases in labor

supply. Furthermore, these benefits accrue very quickly. Within six months of initiating ARV treatments, the authors found a 20 percent increase in the probability of participating in the labor force. In addition, there was a 35 percent increase in hours worked in a past week—an increase of 7.9 hours. The authors argue that due to the fact that untreated AIDS patients will see continuing declines in health over these six months, at times even resulting in death, these estimated labor supply effects should be viewed as a lower-bound estimate of the true benefit of ARV treatment on labor supply. They also find that the utilization of ARV treatment results in a reduction in labor supply for young boys in the patient's household. This could result in significant societal economic benefits, particularly if this decrease in labor supply is matched by an increase in primary schooling—which has especially large returns in developing countries (Thirumurthy et al., 2008).

While Thirumurthy et al. (2008) demonstrates short-term labor supply benefits from the initiation of ARV treatment, the medium and long term benefits of these medications are not detectable in the authors' data. Habyarimana et al. (2009) used data from 1998-2006 to estimate these medium and long term effects. Their data come from the Debswana Diamond Company—the first company to provide free ARV treatment to its employees. The authors are able to link information from this treatment program to employee records of both doctor sanctioned and non-medical episodes of absenteeism occurring at two of the firm's mines. The authors find that in the 15 months to 5 years before enrollment in the treatment program there is no difference in the rate of absenteeism between workers. In the year prior to the initiation of treatment, enrolled workers are absence about 20 days from work. The introduction of ARV treatment is associated with immediate reductions in absenteeism. Similar to the results in Thirumurthy et al. (2008), these declines in absenteeism are seen in the 6-12 month period following the initiation of ARV treatment. The authors find that over the next 1-4 years, these rates of absenteeism remain similar to that of non-enrolled workers. This suggests that the economic benefits of ARV treatment exist in the short, medium, and long term.

Mental Health Medication and Labor Supply

Individuals who suffer from a variety of mental health disorders have seen decreased labor market performance. Perhaps as a result of this fact, this is a set of conditions for which the non-health benefits of pharmaceuticals have been carefully considered. This should not be surprising given that these non-health benefits make up a larger portion of the explicit benefits profile of many medications in this area. As a result, economic outcomes such as labor supply and productivity have even been utilized as documented endpoints in clinical trial settings.

Overall, the evidence suggests that across a large number of medications aimed to treat depression and other mental health disorders there are significant benefits in economic outcomes. Timbie et al. (2006) conducted a meta-analysis of clinical trials from 1980-2004 that included either labor force participation or workplace productivity as a measured endpoint. These authors found evidence of a small effect on labor force outcomes for the treatment of major depressive disorder. Berndt et al. (1998) also examined the role of anti-depressant medication on workplace productivity. Using data from a clinical trial involving individuals with a long spell of diagnosed depression, the authors examined the change in short term productivity (12 weeks) from the initiation of anti-depressant treatment. The authors found that a reduction in the severity of mental health symptoms was associated with an increase in the patients work performance. The largest effects were for individuals with low baseline work performance and with the least severe forms of depression. This study uses a self-reported composite measure of workplace performance. In contrast, Berndt et al. (2000) used data from over 2,000 claims processors at a large multi-site insurance claims processing company. The authors are able to use an objective measure of workplace productivity—the number of claims processed per day per employee. The authors found that the at-work productivity of individuals with diagnosed and treated mental health disorders was no different from the performance of other employees. Given the large number of studies demonstrating lower productivity for individuals with mental health disorders, this is suggestive of a benefit from effective treatments for these conditions.

Anti-Arthritic Medications and Labor Supply

Arthritis is a widespread condition that greatly affects individuals from around the world. According to the Center for Disease Control, an estimated 46 million people in United States have some form of arthritis. In total, 5 percent of the population and 30 percent of the arthritis population report work limitations resulting from the disease (Lorig, 2007). Yelin (1995) reported that disability rates for individuals with musculoskeletal conditions range from 38 to 72 percent.

Arthritis is also a condition that has seen dramatic improvements in pharmaceutical treatments. Until recently, individuals affected by this painful condition were limited to drugs such as non-selective non-steroidal anti-inflammatories (NSAIDs). These medications, which include ibuprofen and naproxen, provide pain relief and reduced inflammation, but require continual use involving pills taken several times throughout the day. Unfortunately, for a large number of arthritis sufferers the continual use of these medications greatly increases the risk of gastro-intestinal bleeding. Each year, an estimated 16,500 individuals die from non-selective NSAID-related gastrointestinal complications. This amounts to 1 death for every 1,200 patients taking these drugs for two months or longer (Schmidt et al., 2004). Therefore, individuals who were susceptible to this bleeding were unable to use this class of medication and often found themselves without effective pain medication.

In 1997, COX-2 inhibitors (a new class of NSAID medication) were approved for sale in the United States. These medications were believed to offer the same or even a higher level of pain relief as non-selective NSAIDs without the gastrointestinal side effects. Primarily marketed under the brand names Vioxx and Celebrex, these medications quickly rose to be among the top selling medications in the world.

Clinical trial evidence in the years following Vioxx's release to the market found that the benefits in terms of gastro-intestinal safety were apparently gained at the expense of an increased incidence of negative cardiovascular events for patients taking the medication. This resulted in Vioxx being

voluntarily removed from the global market in 2004. This represented the largest voluntary recall of a medication in United States history—with an estimated 1.3 million Americans taking the medication at the time of the removal. Garthwaite (2009) estimated the effect of Vioxx on the labor supply of older Americans. The author utilized the removal of Vioxx from the market as a plausibly exogenous source of variation in the utilization of the medication and found that Vioxx is associated with an economically and statistically significant increase in the probability of working for older men. No effect was found for an increase in hours. His findings suggest that the recent increase in labor supply among men in their sixties is at least partly attributable to the increasing use of these treatments during the past decade.

VI. Conclusions

A review of the medical literature provides clear evidence of the health benefits of pharmaceuticals. While the purpose of this article was not to summarize the benefits of all drugs across all conditions, it does provide clear documentation that for many of the most prevalent conditions the utilization of effective pharmaceutical medication has been shown to improve health, often dramatically. This exists for both physical and mental health conditions.

The evidence concerning the cost offsetting effects of pharmaceuticals is less clear. While a series of highly cited studies have shown dramatic cost savings from the increased utilization of new medications, subsequent studies have cast doubt on the validity of these earlier results. This should perhaps not be surprising. Due to the large number of confounding factors, it is very difficult to econometrically identify the benefits of these medications. This is particularly true when utilizing aggregate observational data. Furthermore, due to the large amount of heterogeneity in the efficacy of different treatments, it is unlikely that one study could generate a single number summarizing the overall net benefits of pharmaceuticals. Instead, it is clear that more research is needed in this area before anything definitive can be said about the cost saving nature of spending on pharmaceuticals. The most

fruitful avenues of this research will likely need to focus on a narrow range of conditions, employ an exogenous change in utilization, or both.

When judging the cost effectiveness of medications, particularly those that are aimed at chronic physical conditions, it has become increasingly clear that factors other than simply the health benefits of these medications must be considered. New medications offer a broad profile of quality of life benefits such as an increased ability to participate in the labor force. In addition, these new medications can provide broad societal benefits that extend far beyond those measured in terms of spending on public health programs—a common measure of their success. This is most clearly seen in the connections between more effective mental health treatments and lower crime rates. Failing to consider this wider profile of benefits can underestimate the value of pharmaceutical medications.

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