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REVIEW ARTICLE

Removal of Opioid/Acetaminophen Combination Prescription Pain Medications: Assessing the Evidence for Hepatotoxicity and Consequences of Removal of These Medications

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Abstract

Opioid/acetaminophen combination products are widely prescribed for the management of moderate to moderately severe pain. Acetaminophen, when improperly used, can lead to liver damage and even acute liver failure. In June 2009, an FDA advisory committee recommended elimination of prescription acetaminophen combination products because of the risk of hepatotoxicity associated with use of these medications. The FDA advisory committee reviewed numerous observational studies and adverse event reporting data. The aims of this article are to: 1) provide a summary and epidemiologic critique of the studies and evidence the FDA advisory committee reviewed; 2) examine the potential consequences, such as poorly managed pain or a shift to treatment with other medications with greater potential toxicity and/or restricted availability, if the FDA follows the advisory committee vote; and 3) outline alternate strategies the FDA should consider for reducing hepatotoxicity associated with opioid/acetaminophen combination products.

Key Words. Safety; Hydrocodone; Oxycodone; Pain Management; Opioids

Introduction

On June 29–30, 2009, the Food and Drug Administration (FDA) convened an advisory committee to discuss the safety of acetaminophen-containing over-the-counter (OTC) and prescription medications. Following presentation and review of information on acetaminophen hepatotoxicity, the advisory committee voted 20–17 to recommend elimination of prescription acetaminophen combination products [1]. This was one of 10 votes held during the course of the 2-day meeting. Ironically, the committee voted 24–13 against eliminating nonprescription acetaminophen combination products.

Data presented to the committee suggested that acetaminophen was the leading cause of acute liver failure (ALF) in the United States, with 63% of unintentional overdoses associated with opioid/acetaminophen use. The proportion of ALF cases associated with acetaminophen increased from 28% in 1998 to 51% in 2003. While these studies may give valid counts of events and highlight that improper use of acetaminophen-containing medications can lead to severe and life-threatening liver damage, the number of acetaminophen users, a denominator necessary to calculate risk and thereby provide an appropriate response by the FDA, is conspicuously absent as well as difficult to define. As all of these studies were retrospective and observational and had inherent design limitations, the evidence from them must be carefully evaluated.

This is especially important, as the impact of removal of these medications from the market would be far-reaching and have a substantial effect on the practice of pain management. Pain is the most common reason that persons seek medical attention. Twenty-six percent of people 20 years old and older who participated in the 1999–2002 National Health and Nutrition Examination Survey reported a problem with pain lasting more than 24 hours in the month prior to being interviewed [2]. There is compelling evidence that unrelieved pain has significant adverse physiological and psychological effects [3–5]. Pain has significant economic consequences as well, costing $61.2 billion per year in lost productive time and resulting in over 50 million lost workdays annually [6,7].

Opioid/acetaminophen combination products are very commonly prescribed for the management of pain. In fact, hydrocodone/acetaminophen combination products are the most prescribed drugs in the United States, accounting for more than 89 million prescriptions dispensed in 2003 [8]. The elimination of opioid/acetaminophen combination products would come at a significant sacrifice to those whose pain is well controlled with these drugs. Patients may experience loss of pain control with decreased quality of life. They may be treated with less effective therapies or with medications with potentially more serious adverse effects. Patients' timely access to treatment could be compromised due to a reduction in the availability of conveniently prescribed, effective pain medications. Changes could require more frequent and/or more numerous provider visits, resulting in an increase in health care utilization and costs.

The primary objective of this work was to review the strengths and weaknesses of the data and primary studies considered by the FDA advisory committee that voted to recommend removal of opioid/acetaminophen combination products from the market. A second objective was to consider whether the evidence presented warrants the removal of these medications especially in light of their benefits and the unintended consequences/potential risks associated with their removal from the market.

Evidence for Acetaminophen-Associated Hepatotoxicity from the Use of Acetaminophen-Containing Prescription Pain Medications

The evidence for acetaminophen-associated hepatotoxicity presented to the FDA advisory committee came from numerous sources and published studies that assessed acetaminophen-associated adverse events (ALF and acetaminophen-associated deaths), the incidence of acetaminophen overdose, and health care utilization associated with acetaminophen-associated hepatotoxicity. No efficacy and safety data were required at the time most of the opioid/acetaminophen combination products were approved by the FDA [9]. The lack of randomized, controlled safety studies leaves only results from observational studies to estimate the risks associated with opioid/acetaminophen combination products. A thorough review of each of these sources indicates that while acetaminophen containing medications may be implicated in some events, *the absolute risk and rate associated with these medications and the incremental contribution from these medications cannot be estimated from current data*.

Epidemiologic Studies Assessing Acetaminophen-Associated Hepatotoxicity

Evidence presented to the advisory committee included a study by Larson et al. [10], which assessed risk factors for ALF and outcomes among patients with acetaminophen-associated ALF at tertiary care facilities in the United States. Patients with ALF who presented to participating centers of the Acute Liver Failure Study Group from 1998 through 2003 were identified. Broad diagnostic criteria were used to define acetaminophen-associated ALF: probable use of a toxic dose of acetaminophen within the week prior to admission, detection of any amount of acetaminophen in the patient's serum, or an elevated serum alanine aminotransferase level with a report of acetaminophen ingestion. Acetaminophen use was classified as either intentional or unintentional ingestion. Unintentional ingestion and overdose may occur when acetaminophen is taken inconsistently with its prescribed use. This may occur if a person takes more doses of a medication with acetaminophen than is indicated, or this may occur when a person takes multiple medications containing acetaminophen and the total amount of acetaminophen from the various medications exceeds a safe amount.

During the 6-year period, 662 ALF cases were identified and 275 (42%) were identified with acetaminophen-related hepatotoxicity; among these acetaminophen-associated cases, 131 (48%) were unintentional overdose. The proportion of ALF cases attributed to acetaminophen rose from 28% in 1998 to 51% in 2003 and the absolute number of ALF cases increased from 85 to 128. Forty-four percent of the acetaminophen-associated ALF subjects reported ingestion of opioid/acetaminophen combination products.

There are several facts that should be noted while reviewing the evidence from this study. First, it is based solely on the number of ALF cases identified over a 6-year period. No estimate of total medication users in the catchment area of the Acute Liver Failure Study Group sites was provided. This makes the quantification of risk impossible. Without a denominator-based risk estimate, the magnitude of impact on public health cannot be assessed. Moreover, while the number of ALF cases and the percent of acetaminophen-associated ALF cases rose over time, it is very likely that the number of users of OTC acetaminophen and opioid/acetaminophen combination products also increased. For example, between 2001 and 2005, prescriptions for acetaminophen combination medications increased 38.1% [11]. It is possible that the incidence or risk of ALF associated with these products remained stable or even decreased over time. *Without denominator-based information, it is impossible to determine in which direction risk is changing*.

Second, the overall rise in acetaminophen-associated ALF cases over time could be explained by various external factors separate and distinct from an increase in use of acetaminophen containing medications. Changes in patient demographics, such as an increase in the age of the population, could have effects. Patients over 40 years of age who overdose on acetaminophen have a higher risk of ALF, liver transplant, and death [12]. The proportion of ALF cases related to acetaminophen may also increase over time if the proportion of ALF cases due to other causes decreases. For example, the proportion of ALF cases due to hepatitis B, the most common cause of ALF in the 1980s, is likely to have decreased due to vaccination campaigns in the 1990s.

An important limitation of this study is the lack of information on the medical history of these patients. It is possible that some who took opioid/acetaminophen combination products also had pre-disposing medical conditions (e.g., neoplasms, IV drug use, arthritis, heart failure, blood transfusions). Other drug use may have pre-disposed some of these patients to ALF resulting in acetaminophen being incorrectly identified as the cause. Toxicology screens were available for 77 subjects and positive for 58 subjects: 10 tested positive for marijuana, 11 for cocaine, 5 for amphetamines, and the remaining were positive for substances which were probably prescribed medications. Cocaine is known to have toxic effects on human hepatocytes [13]. Without identifying and adjusting for these confounding factors, one may not attribute the elevated number of ALF cases in this group entirely or directly to the use of acetaminophen. The fact that about one-quarter of the opioid/acetaminophen users were elderly and had multiple co-morbidities could have led to overestimation of the number of acetaminophen-associated cases. In addition to these limitations cited previously, an ALF case could be classified as acetaminophen-associated if the person recalled ingesting a toxic dose in the prior week; recall bias could misclassify the person's true acetaminophen exposure, particularly if someone's mental status was altered due to ALF. Similarly, a case was labeled acetaminophen-associated if *any* serum level of the drug was detected. This means that even therapeutic use of the drug could have been incorrectly included in the case definition.

The investigators reported that 19 persons (7%) reported taking 4 g of acetaminophen per day, which is the maximum recommended daily dose. These persons were older and more likely to use or abuse alcohol than were those who took greater than this amount. Thus, the apparent risk associated with therapeutic doses of acetaminophen is confounded by alcohol or other unmeasured factors. This gives pause to arguments that the current recommended maximum daily dose, when used properly, results in hepatotoxicity.

Using the data from this study the authors estimated that at least 250 cases of acetaminophen-associated ALF present to transplant centers in the United States each year. However, the authors also noted that national survey data indicate that 36% of Americans take an acetaminophen-containing product at least once per month, indicating that the incidence of acetaminophen-associated ALF is probably low given the widespread use of these medications. While 250 cases of acetaminophen-related ALF may occur each year in the United States, more than 112 million people use acetaminophen each month, which translates to a yearly risk of less than two per 10 million. The yearly odds of being struck by lightning, considered a rare event, are one in 700,000 [14].

Realizing that most studies on ALF were conducted in tertiary care facilities and that these patient populations may differ from the general population, Bower et al. [15] conducted a population-based surveillance study of ALF. Each week an intensive care unit medical staff member at participating hospitals in the metropolitan Atlanta area determined whether there were patients who met the ALF case definition. Patients or family members provided information on medication usage. ALF etiology was determined by patient or family member reports and laboratory findings. Diagnosis of acetaminophen toxicity required a toxic serum acetaminophen level based on an acetaminophen toxicity nomogram or a history of ingesting an acetaminophen level in excess of the therapeutic dose. Non-acetaminophen-related hepatotoxicity was based on reported exposure to a suspected drug and exclusion of other causes, including viral infections, autoimmune hepatitis, alcohol use/abuse, and ischemia.

Ninety-four patients were classified as ALF cases; acetaminophen-associated ALF was the most common etiology. Acetaminophen toxicity was identified in 46% of adult ALF cases; 45% were due to intentional overdose and 55% to unintentional overdose. Among the adult ALF cases where acetaminophen was implicated, alcohol was believed to be a contributing factor in six cases (27%). Acetaminophen was the second leading etiology for pediatric ALF cases and was implicated in 25% of cases. Using the number of ALF cases and the estimated catchment population for the participating hospitals, the investigators estimated there are approximately 1,600 cases of ALF per year in the United States.

There are significant limitations to population-based surveillance studies as stated earlier. In addition, the surveillance area contained only 94 ALF cases; the small sample size renders the extrapolation to the entire United States population unreliable. A total of 1,600 ALF cases per year in the United States translates to about 5 per million people. If as the authors conclude, 46% of these cases are related to acetaminophen, the ALF acetaminophen-related risk is 2.3 per million.

As with any study where participants are asked to report past exposures, recall bias may have affected reports of past drug exposures. The diagnoses of exclusion for assigned acetaminophen- associated ALF were based on a limited set of etiologies. The authors did not consider alcohol or biliary pathologies as rule-out diagnoses. This may lead to an over-estimation of acetaminophen-associated hepatotoxicity.

Analyses of Adverse Event Reporting and Acetaminophen-Related Hepatotoxicity

Analyses of adverse event reporting systems, namely the FDA Adverse Events Reporting System (AERS) and Toxic Exposure Surveillance System (TESS), have also been conducted to examine acetaminophen-related hepatotoxicity. AERS is a database of adverse event reports voluntarily sent from consumers and health care providers; when manufacturers learn of an adverse event associated with their product from a consumer or health care provider, they are required to report the event to AERS [16].

TESS is a surveillance database that includes exposures reported to select poison control centers throughout the country [17].

Analyses of AERS data showed that the crude count of all adverse events related to either OTC acetaminophen or opioid/acetaminophen combination products was 2,458 in 2005. This included both serious and non-serious events. That figure is higher than that for ibuprofen, ketoprofen, naproxen, and aspirin. The AERS data from 2002–2006 show that acetaminophen was the number one drug associated with hepatotoxicity. In an analysis of AERS data using the Multi-Item Gamma Poisson Shrinker algorithm, which generates scores that indicate the relative reporting rate of an adverse event for one drug relative to other drugs and events in the database, there were high association scores between acetaminophen and hepatic events [18].

Using AERS data to determine the association between an adverse event and a drug is problematic for numerous reasons [19]. First, it is impossible to use AERS alone to quantify a risk or rate because the total number of users is unknown. The data only reflect adverse event reporting rates, which are subject to numerous biases. Media coverage of a particular drug may increase reporting for that drug. Webber effects, where reporting rates peak during the early years of a product's introduction, can affect relative reporting rates of drugs. In addition, as reporting adverse events is voluntary, there may be differential reporting of pharmaceutical products and underreporting in general. Reports are generally not investigated; in the United States, they do not have to be medically confirmed, and the quality of the reports is widely variable. In addition, the crude counts presented are not adjusted for patient characteristics. As stated previously, concomitant medication and/or alcohol use and underlying disease may vary across users of analgesics and therefore confound the observed association. The analysis did not stratify the adverse events by degree of severity. Non-serious events may not be clinically meaningful, and it is unknown how many of these cases are non-serious. Obviously, analyses of AERS data should not be considered hypothesis-confirming.

A subsequent investigation of deaths reported among acetaminophen users detected by AERS data revealed inadequacies that can threaten the validity of measures obtained from this system. In a follow-up study, 100 cases were randomly chosen in 2005. Four were found to be duplicates. Of the remaining 96, 24 were excluded from subsequent analyses because further review of the reports revealed no mention of an acetaminophen containing medication; death was mostly likely due to a co-morbid condition or a co-suspect drug or substance. Review of the remaining 72 deaths indicated that an opioid/acetaminophen combination pain medication was associated with 43 deaths (59%). Of the 72 deaths, 4 (6%) were associated with unintentional overdose; 11 (15%) were associated with intentional misuse; 9 (13%) with unknown intent, and the remaining 67% with suicide. The vast majority (82%) of the deaths associated with opioid/acetaminophen combination products were due to misuse (including suicide); overdose of unknown intent was indicated in an additional 13% of deaths. These deaths therefore do not implicate opioid/acetaminophen combination products when properly used. Many medications, including OTC ones such as aspirin, can be deadly when intentionally overdosed. These factors make it impossible to draw conclusions from the use of this database.

In another analysis of AERS data [19], 282 adult cases with liver injury possibly associated with acetaminophen exposure were identified. One hundred and twenty-two patients reported exposure to an opioid/acetaminophen combination medication. Among 70 patients who reported exposure to more than one acetaminophen containing medication, 50 (71%) reported taking an opioid/acetaminophen combination medication. This study suffers from the same limitations as those stated for the previously described AERS study: there is no denominator to enable estimation of a risk and there is no reference group with which to compare this risk. In addition, nearly half of the persons in this study were unable to specify the acetaminophen-containing medication they ingested, casting into doubt actual exposure to significant amounts of acetaminophen.

Analysis of the TESS database examined reported poison exposure cases and deaths among opioid/acetaminophen combination prescription medication users [18]. Cases of poison exposure were included when acetaminophen was mentioned as the primary exposure. Of the 41,999 cases in 2005, 1,470 (3%) resulted in a major effect, defined as life-threatening or one that resulted in a disability or disfigurement.

As is the case with the AERS data, there is no known denominator for these counts so it is not possible to present risks or rates based on these numbers. The information is limited because there are no data on a reference group. Without a comparison group, the incremental risk for a given outcome due to an exposure cannot be determined. However, the data come from poison control centers serving nearly 296 million people. Therefore, the estimated annual risk of a major adverse effect from a prescription acetaminophen combination medication is less than five per million.

Nourjah et al. [20] used five national databases to estimate acetaminophen-associated overdoses and AERS data to identify reasons for the overdoses. Data sources included: the National Hospital Ambulatory Care Survey (NHAMCS), an annual survey of ambulatory services and hospital emergency departments characterizing cause of injury; the National Electronic Injury Surveillance System (NEISS), an annual survey that collects information on consumer product-related injuries treated at emergency departments at 66 hospitals; the National Hospital Discharge Survey (NHDS), conducted annually by the Centers for Disease Control and Prevention to describe inpatients

discharged from non-federal hospitals in the United States; the National Multiple Cause of Death File; and lastly, the TESS.

According to NHAMCS data there were 56,000 emergency department visits annually for acetaminophen overdoses during 1993–1999; 56% cases involved intentional overdose. Data from NHDS indicated there was an average of 26,256 hospitalizations annually due to acetaminophen overdose during 1990–1999; 74% involved intentional overdose. There were 1,375 deaths between 1996 and 1998 where acetaminophen was either the primary or a contributing cause of death; in 73% of these deaths, suicide or intentional overdose was mentioned. The number of acetaminophen overdoses estimated from TESS data in 2001 was 112,809.

AERS data were searched to identify cases of hepatic injury in the United States, where an acetaminophen-containing medication was the suspected cause. Among the 478 cases of serious hepatotoxicity reported in AERS data, 198 (41%) were related to unintentional overdoses. Of the 103 cases that contained dosing information, 70% indicated the patient had exceeded the maximum recommended daily dose of 4 g. Of the 170 cases of unintentional overdose who had used acetaminophen for therapeutic reasons, and among the 89 patients for whom dose information was available, 44 (49%) reported alcohol use and 29 (33%) reported a history of liver disease. The mean total daily dose for these subgroups was 6.1 g and 6.3 g, respectively.

The estimates obtained in this study suffer from the same limitations stated for previously cited studies. The estimates for annual emergency department visits and hospitalizations from NHAMCS and NHDS are extrapolations of reported data. As the investigators emphasized, the case definition and identification of cases may have varied and it was not possible to confirm diagnoses of cases by a review of medical records. Estimates from TESS data in particular may be high, as these data are based on calls to poison control centers and are not confirmed by healthcare providers.

Estimates from AERS data are limited by various factors stated earlier, such as that the data reflect adverse reporting rates which are subject to numerous biases. Of note, among those who used acetaminophen for a therapeutic indication and reported dose information, nearly half reported alcohol use and nearly one third reported prior liver disease. These data again highlight that confounders such as alcohol use and concomitant disease may be responsible for many of the reported acetaminophen-related cases of ALF and deaths.

Summary of the Evidence

A review of the limited studies on opioid/acetaminophen combination products and hepatotoxicity reveals that there is no reliable information from which we can draw conclusions about the absolute or relative risk of these medications. The epidemiologic studies that have been cited and the analyses of AERS and TESS data were not denominator-based and, therefore, cannot be used to provide a valid estimate of risk.

Furthermore, as ALF is a rare event, the epidemiologic studies involved relatively small numbers of observations. This fact, coupled with how data were collected, did not allow investigators to adjust for potential confounders like concomitant medical conditions, age, and other medications that may have affected the observed association between ALF and acetaminophen exposure. In addition, the small number of observations does not allow investigators to explore how variations within opioid/acetaminophen combination exposure categories relate to the outcome. Currently, opioid/acetaminophen combination products vary in the dose of opioid and acetaminophen, which ranges from 300 mg to 750 mg acetaminophen per tablet with many doses in between (e.g., 325, 400, 500, 650, and 660 mg).

In order to know the incremental risk of ALF associated with use of opioid/acetaminophen combination products, an epidemiologic study needs to be conducted where there is a reference group. If a reference group of individuals not using opioid/acetaminophen combination products were included, and adjustment were made for identified confounders, the incremental risk of ALF due to opioid/acetaminophen medications could be evaluated. Hepatotoxicity among opioid/acetaminophen users and patients using other analgesics such as opioid/NSAID combination or opioids alone could be compared.

Consequences of Following Advisory Committee's Recommendation

Eliminating opioid/acetaminophen combination products will have a very significant impact on pain management. In one analysis of claims data for hydrocodone or short-acting oxycodone pain medications, one in six claimants received an opioid/acetaminophen combination medication at some time over an 8-year period [21]. The actual consequences on patient care of removing the most commonly prescribed pain medications for patients with moderate to moderately-severe pain are unknown. There are multiple potential adverse consequences that should be considered. Removing opioid/acetaminophen combination products from the market will have widespread effects on pain management, healthcare utilization, and the ability to meet the needs of patients in pain. These unintended consequences must be balanced against the risk of hepatotoxicity from opioid/acetaminophen combination products.

At the advisory committee meeting, Dr. Jane Filie presented an overview on pain management [22]. Currently, there are more than 50 million people in the United States who are disabled due to pain, and this number is expected to increase as the population ages. The undertreatment of pain continues to be a significant public health problem. For some patients, management of pain

begins with non-opioid analgesics for mild to moderate pain; an opioid/non-opioid combination medication might be used if pain intensity increases; more severe pain would require treatment with a pure opioid agonist. The removal of opioid/acetaminophen combination products could therefore jeopardize an important step in pain management for patients suffering from moderate to moderately-severe pain. Given the deleterious impact of pain of this intensity on patients' ability to work, sleep, and engage in normal activities of daily living, the unintended consequences of removing these products from the market need to be carefully evaluated.

Potential for Increased Adverse Events Due to Increase in NSAID Use

If opioid/acetaminophen combination prescription pain medications are removed from the market, patients who are well-managed with these medications will need to be treated with alternate therapies. The remaining opioid combination analgesics that are Schedule III would include opioid/NSAID combination prescription pain medications. For patients who are unable to tolerate NSAIDs this is particularly concerning, as acetaminophen products are an important alternative. A shift in treatment to opioid/NSAID combination prescription pain medications may also induce more frequent and devastating adverse events given the substantial evidence for complications resulting from NSAID use in general and the known adverse events that occur. It should be noted that these events commonly occur within the therapeutic range and in those who are felt to be able to tolerate NSAIDs or aspirin. Adverse events include gastrointestinal ulcers, bleeding, perforation [23] and acute renal failure [24].

Numerous studies have shown that hospitalizations and deaths due to NSAIDs used alone impose a large burden on the healthcare system. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) Post-Marketing Surveillance Program prospectively followed more than 11,000 arthritis patients identified through eight institutions in the United States and Canada. In a subset of patients, the annual rate of hospitalization for a gastrointestinal event was 1.5% for rheumatoid arthritis patients taking NSAIDs and 0.7% for osteoarthritis patients taking NSAIDs. After applying these rates to the estimated number of arthritis patients using NSAIDs and deaths resulting from gastrointestinal events requiring hospitalization, the authors estimated there were 30,000 NSAID-associated gastrointestinal hospitalizations per year resulting in 4,400 deaths among rheumatoid arthritis patients, and an estimated 56,000 NSAID-associated gastrointestinal hospitalizations per year resulting in 8,800 deaths among osteoarthritis patients [25]. The extrapolation of the risk of hospitalization and death in the cohort to the estimated number of arthritis patients using NSAIDs is a limitation, as the later number is not well defined. However, in comparison, there were an estimated 56,000 emergency department visits, 26,000 hospitalizations and possibly over 450 deaths in the US each year [20] related to acetaminophen use across all diseases. Using NSAIDs instead of acetaminophen would increase not decrease morbidity and mortality. One study estimated that if 10% of acetaminophen users shifted to NSAIDs there would be 35 less acetaminophen poisoning associated deaths but an additional 166 deaths from gastrointestinal bleeds and 144 from acute renal failure [26].

Impact of Switch to Treatment with Single Entity Opioids

While oxycodone/acetaminophen combination drugs are in Schedule II, the other opioid/acetaminophen combination products are in Schedule III (hydrocodone and codeine), Schedule IV (propoxyphene) or not scheduled (tramadol). Prescription orders for Schedule III and IV drugs can be called in, and a maximum of five refills is allowed within 6 months from the date of issue. In contrast, a physician must write a prescription for Schedule II drugs except in emergencies, and no refills are allowed. Therefore, if patients are prescribed opioids in Schedule II, rather than the Schedule III or IV or unscheduled opioid/acetaminophen combination drugs, prescribers may be more burdened. A decrease in Schedule III medications may make it difficult for providers to issue prescriptions and thus impact access to medication. Patients may be burdened as well because insurance providers may only pay for a 30-day supply of the medication. This would result in more frequent clinic visits. Given the cost of an outpatient visit from the Centers for Medicare and Medicaid Services, this could result in more than $700 per patient per year just to prescribe this type of medication.

While there is concern that patients taking opioid/acetaminophen combination pain medications could develop addiction and tolerance, and thus escalate their intake and put themselves at risk of acetaminophen toxicity, there is also concern that there may be an increase in harmful use of single entity opioids if patients are switched to these drugs. There are limited published data to assess harmful use of opioid/acetaminophen in the treatment of chronic pain [9]. In one study, patients with chronic non-cancer pain taking NSAIDs, tramadol or hydrocodone were interviewed up to nine times over a 12-month period and assessed for abuse/dependence. For NSAIDs, tramadol and hydrocodone, the percent of patients who had a positive abuse score at least once during follow-up was 2.5%, 2.7%, and 4.9%, respectively; the percent of patients who had a positive abuse score more than once, indicating persistence of abuse, was 0.5%, 0.7%, and 1.2%, respectively [27]. However, while abuse scores may be higher among patients taking hydrocodone it must be remembered that NSAIDs and tramadol, which has weak opioid activity, may provide inadequate analgesia for more severe pain and be insufficient for pain relief.

Several studies have estimated prevalence or incidence of harmful use of single entity opioids [28–31]. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System combines data on cases of drug abuse from four signal detection systems with data from other sources on the number of unique recipients of

a dispensed drug in a given geographic area to approximate national rates of abuse for various opioid analgesics [31]. This study is limited by the fact that the rate estimates are based on combining data from various sources and that not all people who are dispensed a drug (in the denominator of the rate calculation) would be detected by the surveillance system (and thus counted in the numerator of the rate calculation), and that some persons who abuse a drug and are detected by the surveillance system (and thus counted in the numerator) may not be prescribed the drug (and therefore not counted in the denominator). Nonetheless, the rates of prescription opioid abuse of hydrocodone medications (always combinations with acetaminophen or aspirin or ibuprofen) were among the lowest compared with those for eight other prescription opioids. The other eight prescription opioids included tramadol, and opioids which are sometimes or always administered as single entity products (the seven included short-acting oxycodone, extended release oxycodone, fentanyl, morphine, methadone, hydromorphone, and buprenorphine). The abuse rate of the hydrocodone products group was lower compared to the rates of each of these seven other opioids. The hydrocodone products group was comprised of opioid combination product users only; the other seven opioids included either single opioid product users or both single and opioid combination product users. This suggests that opioid combination medications may have a lower abuse potential than single entity opioids. In analyses of all four signal detection systems, hydrocodone had the lowest or second lowest rate of abuse after tramadol.

Rather than having single entity opioids as the only treatment option, limiting and not removing acetaminophen from opioid/acetaminophen products has been suggested as one approach to reduce hepatotoxicity associated with these medications. As no efficacy data were submitted during the approval process for nearly all opioid/acetaminophen combination products there are little data on the efficacy of opioid/acetaminophen combination products vs opioids alone. However, there is biologic plausibility that the combination of medications is advantageous. The combination may present additive and synergistic analgesic effects while decreasing adverse events, as individual components can be administered at lower doses [9]. Therefore, reducing rather than eliminating acetaminophen from these products may be advantageous. Currently, opioid/acetaminophen combination products contain amounts of acetaminophen ranging from 300 mg up to 750 mg. Results from some studies show that the number needed to treat for at least 50% pain relief for treatment with 15 mg oxycodone vs 5 mg oxycodone/325 mg acetaminophen vs 10 mg oxycodone/650 mg acetaminophen was similar which suggests that the dose of oxycodone may be lowered if acetaminophen is given [32]. Moderate acetaminophen doses in combination with oxycodone may be as effective or more effective than high doses of acetaminophen. Hepatotoxicity risk that may be associated with opioid/acetaminophen combination products could potentially be reduced by eliminating products that contain higher amounts of acetaminophen while retaining products with moderate acetaminophen doses. Limiting the variability of the acetaminophen dose could also reduce hepatotoxicity. Variability in the acetaminophen dose of prescription pain medications may contribute to confusion for both providers and patients about the actual amount of acetaminophen in a product, and thus lead to unintentional overdose.

Increased Pill Burden for Patients

Removing opioid/acetaminophen combination products from the market and requiring patients to take separate opioid and acetaminophen medications will mandate that providers educate their patients on new dosing schedules. Taking multiple pills may increase misuse, decrease patient adherence to medical management plans, and present an undue burden on patients experiencing pain who may already have a high pill burden. Decreased adherence may lead to worsening pain control and a subsequent negative impact on quality of life and productivity

Limited Alternatives Available to Patients

Hydrocodone/acetaminophen is the most commonly prescribed medication [8]; there is no single entity hydrocodone product on the market. If opioid/acetaminophen combination prescription pain medications were eliminated, patients using hydrocodone/acetaminophen may need to take one of the single entity opioids. Tramadol is one commonly prescribed single entity opioid, but it is classified as a weak opioid [33] and therefore may be insufficient to meet the needs of all patients in pain. An analysis of prescriptions in 2007 for hydrocodone and oxycodone products showed that the total number of prescriptions for oxycodone products was approximately 40 million, considerably less than the nearly 120 million prescriptions dispensed for hydrocodone products [22]. It is questionable whether manufacturers would be able to respond to the needs of patients given the low production of alternate medications relative to current hydrocodone utilization. It could take a substantial amount of time for production of the medications to be adjusted to meet the needs of the market if other medications were not available. This could result in patients lacking adequate treatment until production ability catches up with patient needs.

Alternate Interventions

In lieu of removing opioid/acetaminophen combination prescription pain medications, there are several measures the FDA could recommend to increase the safe use of acetaminophen and lower risk of hepatotoxicity without jeopardizing patient access to appropriate pain treatments. Eliminating patient access to this large segment of pain medications will affect pain control for a large number of the more than 100 million Americans who suffer acute or chronic pain each year. Previous working groups have described various initiatives that the FDA could embrace to address this issue. In 2008, a working group voted against elimination of opioid/acetaminophen combination products, citing the potential risks mentioned earlier that

may be associated with removal of these medications [34]. As stated in the report from that meeting, the potential for improper acetaminophen use to cause hepatotoxicity should not be a reason to discourage its proper use. Among the recommended interventions the working groups did support were enhancing education, improving labeling, and limiting dose strength. In addition, limiting the variability of the dose of acetaminophen in opioid/acetaminophen combination products could minimize patient/clinician confusion, and reduce the risk of inadvertent overdose.

Many consumers are unaware that overuse of acetaminophen can result in hepatotoxicity, and are also unaware of the numerous OTC and prescription medications that contain acetaminophen, so a logical intervention would be for the FDA to increase its efforts to educate both consumers and healthcare providers. To reach healthcare providers, free on-line continuing education initiatives could be provided and reinforced through content in peer-reviewed journals and professional society websites/publications. Articles on acetaminophen-associated hepatotoxicity could be published in the FDA *Consumer* and the consumer webpage. The FDA could also support studies on consumer awareness of acetaminophen and liver toxicity [34].

Enhanced product labeling could also reduce the risk of acetaminophen-associated hepatotoxicity. The ingredient acetaminophen could be bolded to alert the consumer, and prominent "shelf-talkers" could be affixed to the OTC sections of the pharmacy. A parallel approach would be to develop a universal symbol to designate the presence of acetaminophen in a product. Just like the universal poison symbol warns of the presence of a dangerous toxic substance, a new symbol on the packages of acetaminophen-containing medications could accomplish the same effect. A warning about severe liver injury associated with overuse could appear on the packaging along with warnings about taking any alcohol with the product. A boxed warning could indicate that overuse of these drugs, as a class, cause hepatotoxicity.

The acetaminophen dose in opioid/acetaminophen combination products could be narrowed or made more uniform; this could have the dual effect of reducing the risk of hepatotoxicity caused by unintentional overdose, and would also simplify the clinician's task of educating patients about maximal dosages. Currently, combination medications may contain as much as 750 mg or as little as 300 mg of acetaminophen per dose. Medications on the market could include only those containing 500 mg acetaminophen or less; there would still be an analgesic effect from the acetaminophen, but the likelihood of acetaminophen-associated hepatotoxicity would be less if they were used improperly.

Conclusions

If the FDA follows the advisory committee's recent vote to eliminate opioid/acetaminophen combination products from the market there will be many repercussions and it is unclear whether the objective of decreasing ALF will be met. While acetaminophen can cause hepatotoxicity when used improperly, the evidence that opioid/acetaminophen combination products present a substantial risk to the public is not compelling enough to warrant their removal from the market. No denominator-based studies utilizing appropriate statistical techniques such as adjusting for confounding factors exist to inform a decision about the true risk of opioid/acetaminophen combination products in contributing to serious hepatotoxicity. Furthermore the many patients who are well-managed with opioid/acetaminophen prescription pain medications would have to be shifted to medications with greater toxicity and/or limited availability. In light of these reasons, the FDA should act very cautiously before eliminating these products.

There are numerous approaches the FDA working in collaboration with pharmaceutical companies, professional organizations and advocacy groups could implement to address opioid/acetaminophen combination products and hepatotoxicity. Enhancing patient education so consumers are aware of the acetaminophen content in all products that contain acetaminophen is one approach. Improved labeling on OTC and prescription packaging should prominently indicate the presence of acetaminophen in a product and the risk of hepatotoxicity when taken in excess. Medication guides and better practitioner training for communicating risk could also be implemented. Reducing the amount of acetaminophen and the variability in the amount in opioid/acetaminophen combination products is another potential intervention. These alternate approaches should be seriously considered instead of eliminating opioid/acetaminophen combination products which have been of great benefit to pain patients.

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