National Trends in Antiobesity Medication Use

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Background: The use of medications to treat obesity remains controversial. Our goal was to assess national trends in antiobesity medication use with a focus on patterns surrounding the 1997 removal of antiobesity drugs from the market.

Methods: Using a serial cross-sectional study design, we analyzed a nationally representative sample of US office-based physician visits from 1991 to 2002. Data come from the IMS HEALTH National Disease and Therapeutic Index. These data include a sample of 134,525 patient visits for which a diagnosis of clinical obesity was made, with annual visits ranging from 666 in 1994 to 1854 in 1996. The unit of analysis is the patient visit, while the primary outcome measures are the annual and quarterly number of antiobesity drug mentions for clinically obese patients.

Results: At its peak in the second quarter of 1997, 2.5 million Americans were taking antiobesity medications, a 4-fold increase over the prior 2 years. Although antiobesity medication use diminished following the market exit of fenfluramine hydrochloride and dexfenfluramine hydrochloride, current levels of use remain above those in the early 1990s. Phentermine has consistently been the most common antiobesity medication. In 2002, an annualized 1.2 million mentions of phentermine use were noted (31% of drug-treated obese patients). Newly released medications, orlistat (0.6 million) and sibutramine hydrochloride (0.4 million), were used less often. Most antiobesity medication use occurs in patients without other reported medical conditions.

Conclusions: Use of antiobesity medications increased rapidly with public and professional interest in fenfluramine-phentermine (fen-phen) combination therapy. Despite reports of adverse outcomes associated with fenfluramine agents (fen-phen and dexfenfluramine), the use of these medication therapies did not diminish until soon before their removal from the market in 1997.
The inhibitor, and orlistat (April 1999), a pancreatic lipase inhibitor (November 1997), a serotonin and noradrenaline reuptake inhibitor (May 1999), was approved, sibutramine hydrochloride monohydrate (May 1999), a 6/1996, 9/1997. Two new antiobesity drugs have since been approved during and after the events of 1997, including whether patterns of treatment are consistent with guideline recommendations. Using data from the National Disease and Therapeutic Index (NDTI) produced by IMS HEALTH, we have examined trends in the pharmacological treatment of obesity from 1991 to 2002. As a specific example of technology adoption, we focus special attention to the rise and fall of fen-phen and dexfenfluramine.

## Commonly Used Antiobesity Medications

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name(s)</th>
<th>OTC/Rx</th>
<th>Function</th>
<th>FDA Approval Date</th>
<th>Withdrawal Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>Rx</td>
<td>Lipase inhibitor that reduces fat absorption</td>
<td>4/1999</td>
<td></td>
</tr>
<tr>
<td>Sibutramine hydrochloride</td>
<td>Meridia</td>
<td>Rx</td>
<td>Serotonin and noradrenaline reuptake inhibitor</td>
<td>11/1997</td>
<td></td>
</tr>
<tr>
<td>Diethylpropion hydrochloride</td>
<td>Tenuate</td>
<td>Rx</td>
<td>Amphetamine-related and other sympathomimetic appetite suppressant</td>
<td>8/1959</td>
<td></td>
</tr>
<tr>
<td>Phendimetrazine tartrate</td>
<td>Bontril, Adipost, others</td>
<td>Rx</td>
<td></td>
<td>9/1982</td>
<td></td>
</tr>
<tr>
<td>Benztropine hydrochloride</td>
<td>Didrex</td>
<td>Rx</td>
<td></td>
<td>10/1986</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate hydrochloride</td>
<td>Sanorex, Mazaron</td>
<td>Rx</td>
<td></td>
<td>6/1973</td>
<td></td>
</tr>
<tr>
<td>Phenylpropanolamine hydrochloride</td>
<td>Acatrim, Dexatrim, others</td>
<td>OTC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine sulfate</td>
<td>Various</td>
<td>OTC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; OTC, over the counter; Rx, prescription only.
*Withdrawn in the European Union; remains available in the United States.
†OTC medications do not have formal FDA approval dates. Both phenylpropanolamine and ephedrine have been in use since the 1960s.

Data for this study were obtained from the 1991-2002 National Disease and Therapeutic Index (NDTI) (IMS HEALTH NDTI Diagnosis Reference File, 1991-2002. Plymouth Meeting, Pa: IMS HEALTH). The NDTI is a continuing survey of US office-based physicians conducted quarterly by IMS HEALTH that provides nationally representative diagnostic and treatment data.20-23 Office-based physicians are selected from the Masterfile lists of the American Medical Association and the American Osteopathic Association (both Chicago, Ill) through random stratified sampling by specialty and geographic region. Once selected, physicians are permitted to remain in the sample as long as they wish. New participants are selected by region and specialty to account for attrition. Each quarter, approximately 3000 physicians participate. The geographic and specialty distribution of the participants closely matches national patterns.

Each quarter, 2 randomly selected physician workdays are identified for data collection. On these 2 days, physicians complete encounter forms for each patient with whom they have clinical interactions. Patient contacts are largely comprised of office visits (86% in 2001), but also include hospital visits (10%), telephone calls (3%), and other contacts (1%). From each encounter, physicians report information on patient diagnoses, all prescribed and known over-the-counter medications, visit characteristics (eg, old vs new patient), and patient demographics. The physician is asked to record all newly prescribed or continued medications used by the patient. A unique record is created for each diagnosis; therefore, a single patient encounter may generate multiple diagnosis records, each of which may list multiple medications used specifically for that diagnosis. The NDTI reports comorbidities associated with each diagnosis. Diagnosis records list no medications if none were used to treat the condition. Drug mentions refer to the estimated national number of occurrences of medication use among office-based physicians.

We identified patients whom physicians reported to have obesity as a clinical problem. Between 1991 and first quarter 2002, a total of 13432 visits by patients with obesity were reported in the NDTI sample. Annual sample sizes ranged from 666 visits made by obese patients in 1994, to 1854 visits in 1996. We also examined quarterly data from 1995 through the third quarter of 1999, with sampled quarterly visits for obesity varying from 141 in the first quarter of 1995, to 626 in the second quarter of 1999.
Disease and Therapeutic Index. Data for 2002 are an estimate (E) based on antiobesity medications, and number of patients receiving medication to 2002 for clinical obesity in the United States. The national estimate of 55 million patient visits made from 1991 patients who are prescribed medications for this condition. 

In practice, it successfully captures those obese patients who are prescribed medications for this condition.

Our principal outcome measure was the estimated national number of drug mentions for antiobesity medications among the population identified to be clinically obese. We also examined the likelihood of physicians reporting patients to be obese, the likelihood of providing antiobesity medications to this population, and the mean number of antiobesity medications provided. These data are weighted to reflect national estimates of physician practice for each of these measures. Given the sample sizes available for obesity visits, the 95% confidence intervals around our national estimates of annual medication mentions are less than ±3% of the estimate in relative terms. For the quarterly information presented here, the 95% confidence intervals were generally less than ±6%.

We defined medication categories based on generic names, including phentermine, fenfluramine, dexfenfluramine, orlistat, and sibutramine. For fenfluramine and phentermine, we combined multiple generic and brand name listings of these drugs into single generic categories. An additional category consisted of other amphetamine-related and sympathomimetic compounds besides phentermine (mostly diethylpropion hydrochloride, but also including benzphetamine hydrochloride, phendimetrazine tartrate, phenylpropanolamine hydrochloride, and ephedrine sulfate). Although several other medications also were listed as therapies for obesity, such as herbal therapies and diuretics, none of these were reported more frequently than in 1% of obese patients.

Limited information also was available on the characteristics of visits by patients reported as obese, including patient age, patient sex, the presence of other medical conditions, and physician specialty. We examined trends in these characteristics among patients reported to have clinical obesity.

RESULTS

The NDTI sample of 13452 diagnosis visits represents a national estimate of 55 million patient visits made from 1991 to 2002 for clinical obesity in the United States. The number of patients physicians reported as obese decreased from 4.9 million in 1991 to 2.6 million in 1993 and then increased dramatically to 7.8 million in 1996 before leveling off near 4.2 million in the late 1990s. The patients reported to be obese in 2002 were predominantly female (79%) and between the ages of 20 and 59 years (87%)—characteristics that did not change over time. By physician specialty, primary care physicians provided most of the visits, with 32% of visits to family or general practitioners, 25% to general internists, 8% to osteopathic physicians, and 11% to obstetrician-gynecologists in 2002. This specialty distribution has changed little over time, with these primary care specialties always comprising the vast majority of visits from 1992 (84%) through 2002 (76%). Most patients (60%) were listed as having seen their physicians on multiple occasions, with 45% having last seen the physician within the last 3 months, suggesting that a substantial fraction of medication therapy may have been sustained, rather than short-term.

Medical comorbidities were not common among the reported obese patients. In 1991, 59% of obese patients were reported to have obesity as their only medical problem. In concert with the growing number of reported obese patients in the mid-1990s, an increasing number of patients were noted to have obesity alone (71% in 1996). Among specific comorbidities, hypertension was the most common, accounting for between 7% (1996) and 14% (1992) of obese patients.

Between 1995 and 1997, the use of medications to treat obesity increased dramatically (Figure 1). From 1991 to 1994, the number of annual drug mentions for antiobesity medications varied from 1.4 million to 2.4 million. In 1996 (10.6 million) and 1997 (9.4 million), there was substantially more antiobesity drug use. Following the removal of fenfluramine and dexfenfluramine from the market, a sharp reduction in medication treatment occurred. Nonetheless, drug mentions from 1998 (3.7 million) through 2002 (annualized, 2.8 million) remained above those noted in the early 1990s (2.7 million in 1991 through 1.8 million in 1994).

Because obesity is likely reported only for patients where treatment is contemplated, the likelihood of these patients receiving antiobesity medications is substantial. Nonetheless, the likelihood of drug treatment increased from 50% of patients in 1991 to 85% in 1996 before falling to 64% in 2002. The number of antiobesity medications used per patient also increased dramatically from 1995 to 1997, reflecting increased use of fen-phen. The mean number of medications among those treated increased from 1.13 in 1991 to 1.61 in 1996 before falling to 1.08 in 2002.

The rise in antiobesity medications in 1995-1996 largely reflected the increased use of phentermine and fenfluramine (Figure 2). Phentermine increased from 1.0 million to 1.5 million annual drug mentions in 1991 to 1994 to 2.3 million in 1995 and then 5.0 million in 1996. While fenfluramine had been used at low levels in 1993 and 1994 (0.1 million), its use increased dramatically in 1995 (0.8 million) and 1996 (3.8 million). The use of dexfenfluramine also contributed to increased antiobesity medication use, with 1.1 million mentions in 1996, the year of its release. After initial reports of adverse outcomes associated with fenfluramine and dexfenfluramine in 1996, use of these medications stabilized and
reached a yearlong plateau beginning in the third quarter of 1996 (Figure 3). In contrast, phentermine use continued to grow through the second quarter of 1997, peaking at 1.8 million mentions in that quarter. Decreased use of fenfluramine and dexfenfluramine did not occur until both of these drugs were removed from the market in September 1997. By the end of 1997, phentermine use had decreased to less than a third (0.5 million quarterly mentions) of its peak level of use. After 1997, phentermine use has continued to decline gradually, although in 2002 it remains the most common antiobesity medication (0.3 million quarterly mentions).

Newly released antiobesity medications have filled a portion of the void left by the declining use of phentermine and the exit of fenfluramine and dexfenfluramine. Released in November 1997, sibutramine quickly gained a sizable share of antiobesity medication use (0.7 annual million mentions in 1998), but has experienced generally declining use after the second quarter of 1999 (Figure 3). Released in April 1999, orlistat quickly exceeded the use of sibutramine by the third quarter of 1999 (0.26 vs 0.1 million quarterly mentions). Subsequently, orlistat use has remained relatively stable. The use of other amphetamine and sympathomimetic drugs has decreased gradually from 0.3 million annual mentions in 1991 to an annualized 0.15 million in 2002. In part, this trend reflected diminished use of phenylpropanolamine in the mid-1990s, well before its market withdrawal in 2000.

Based on national data on trends in antiobesity medication use over the past 12 years, use of these medications remains common even after the sharp rise in use from 1995 to 1997 and the drastic reduction in use occurring when the fenfluramine agents were removed from the market in 1997. Patterns leading up to this sudden decline suggest that despite warnings about potential adverse events, use of fenfluramine and dexfenfluramine did not decrease until their market withdrawal. This suggests a pattern of rapid and unbridled medication adoption that resulted in greater risk exposure.

While the rise and fall of combination therapy with fen-phen has been recounted in the general media and the medical literature, our study is the first to track patterns of antiobesity medication prescribing before, during, and after the events of 1997. As expected, our results show a dramatic rise in the use of phentermine and fenfluramine between 1995 and 1997, with an accompanying increase in patients identified as obese, the mean number of medications used per patient, medication treatment rates for obese patients, and treated patients lacking coexisting morbidities.

More surprising perhaps is that despite early reports of adverse outcomes associated with fenfluramine and dexfenfluramine, use of these medications did not fall until both medications were removed from the market. The leveling in use that did occur between mid-1996 and mid-1997 implies that without these adverse outcomes, the tremendous growth in the use of antiobesity medications may have continued. The rapid adoption of these medications, particularly fen-phen combination therapy, may reflect public and professional frustration with lifestyle modification as a weight loss strategy. At the same time, rapidly changing practices increased the number of patients exposed to a risk of adverse outcomes.

Patterns after 1997 indicate that antiobesity medications remain more widely used than in the early 1990s. Even with the dramatic loss of treatment options, physicians’ willingness to consider antiobesity medication therapy has increased. Newly released medications, sibutramine and orlistat, have only partially filled the niche once occupied by fen-phen. Given that obesity remains largely undertreated,11-13 our results are encouraging in suggesting that physician practices regarding obesity are not immutable.

What remains unknown is the extent to which patterns of antiobesity medication use are dependent on patients seeking treatment of their obesity. Most antiobesity medications were used in patients lacking obesity-related comorbidities. Consistent with past studies,11-13 this finding suggests that influences other than scientific evidence, including patient demand for treatment, may be important. Similarly, our results suggest that sustained treatment with antiobesity medications may be the norm. While short-term therapy has significant disadvantages,14-16 the
observed patterns of use may run counter to both recommended guidelines and the FDA-labeled uses of medications other than orlistat and sibutramine.

Several limitations of this study must be acknowledged. The reporting of obesity is likely closely linked to physician decisions regarding treatment and may be subjective. Given the national prevalence of obesity, only a small fraction of obese patients are so reported in NDTI. We were unable to determine the severity of obesity among those treated. The use of over-the-counter and herbal therapies may not have been reliably reported in NDTI. In addition, nonlabeled uses of other prescription medications (eg, metformin or selective serotonin reuptake inhibitors) also may have been underreported. Finally, NDTI may underestimate the prevalence of specific comorbidities in its sample of obese patients.

Our results are based on patient encounters with office-based physicians and may differ from estimates based on a community population sample. In particular, the experience of patients seeing physicians more often will be overrepresented in the NDTI sample. While NDTI has been designed to provide a representative sample of office-based physicians, NDTI participants may differ from nonparticipants. Despite these potential disadvantages, NDTI offers a short lag time to data availability and our estimates appear consistent with past reports based on different data sources.11,24,25

Our findings have several implications. The rapid adoption of fen-phen from 1995 to 1997 illustrates that mechanisms of technology adoption may not always serve public health goals. Rapid growth in antiobesity medications did not follow expert recommendations nor FDA labeling regarding patient selection, duration of therapy, and drug combinations. This suggests the need for strategies to more reliably and rapidly translate scientific evidence into clinical practice. It also indicates the importance of mechanisms to more closely monitor patterns of medication adoption. Optimizing the diffusion of new therapies into clinical practice is a broad issue that permeates discussion of the underuse and overuse of medications.

These results reinforce the widely held perception that antiobesity medications offer an alternative to weight loss strategies that rely on lifestyle changes. Despite the events of 1997, there remains substantial physician willingness to use antiobesity medications. There appears to be a niche willingness to be filled by new medications, particularly if these medications are well studied and relatively free from adverse effects. However, given the growing prevalence of obesity, the limits of currently available medications, and the widespread lack of attention physicians give to obesity, physicians should consider redirecting their energies elsewhere. While lifestyle modification strategies may have inherent frustrations, physicians may undervalue this approach and fail to use behavioral strategies and ancillary personnel that could make nondrug therapies more successful.26 Confronting the epidemic of obesity in the United States will require changes throughout the health care system. While antiobesity medications have a role to play, a broad range of other approaches by physicians, patients, and policymakers will be required.

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REFERENCES


