Impact of Internet Pharmacy Regulation on Opioid Analgesic Availability*

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ABSTRACT. Objective: Access to prescription opioid analgesics has made Internet pharmacies the object of increased regulatory scrutiny, but the effectiveness of regulatory changes in curtailing availability of opioid analgesics from online sources has been not assessed. As part of an ongoing investigation into the relationship between the Internet and substance abuse, we examined the availability of prescription opioid analgesics from online pharmacies. **Method:** From a pharmacy watch Web site, we constructed a data set of postings entered every 3 months beginning November 1, 2005, that were related to the purchase of prescription opioid analgesics. Trained examiners assessed whether the final post described accessibility of pain medications that was increasing or decreasing. **Results:** We identified 45 threads related to the availability of opioid analgesics from Internet pharmacies. Of the 41 (91%) threads

describing the declining availability of opioid analgesic agents from Internet pharmacies, 34 (82%) received posts on November 1, 2007. Despite the subjective nature of the research question, there was high interobserver agreement between coders ($\kappa = .845$) that availability of opioid analgesics from online pharmacies had decreased. This finding was supported by a dramatic rise in the number of pageviews (an accepted measure of Web site visitor interest in a page's content) of Web pages describing decreased availability of opioid analgesics. **Conclusions:** These data suggest striking decreases in the availability of prescription opioid analgesic pharmaceuticals. This self-reported change in drug availability may be related to increased regulation of and law enforcement operations directed against Internet pharmacies. (*J. Stud. Alcohol Drugs* 69: 703-708, 2008)

INTERNET PHARMACIES, which are theorized to increase the risk of opioid misuse, abuse, dependence, and fatal overdose, are reputed to sell drugs to anyone who can afford to pay (Boyer, 2006; Compton and Volkow, 2006; Ryan's Cause, 2004). As early as 2002, researchers using simple Internet search strategies identified 300 unique Web sites offering opioid analgesics without a prescription (Forman, 2003). In 2004, a U.S. Government Accounting Office (GAO) investigation reported 9 of 11 online pharmacies delivered opioid analgesics that were purchased without a prescription (Forman et al., 2006; General Accounting Office, 2004a). These findings, along with increased rates of abuse of prescription opioids, prompted law enforcement operations against Internet pharmacies (Boyer et al., 2007). In 2005, the U.S. Drug Enforcement Agency (DEA) "Operation CYBERx" closed 22 "no-prescription" online pharmacies—represented online by more than 4,600 Web sites—that sold opioid analgesics such as hydrocodone/acetaminophen (Vicodin, among others), oxycodone (OxyContin), combina-

tion medications containing codeine, and tramadol (Ultram) (DEA, 2005). Despite the apparent success of this action, follow-up studies reported that Web sites offering opioids remained widely available to consumers and that law enforcement operations had failed to have a measurable impact on Internet pharmacy availability (Drug Strategies, 2007; Forman, 2006; Forman et al., 2006).

Unfortunately, the availability of Web sites that offer to sell opioids is less important than the actual ability to obtain the drugs themselves. The CYBERRx operation was the first in a series of actions targeting online pharmacies (Boyer, 2006; Boyer et al., 2007; Office of Diversion Control, 2007b). The disruption of opioid sales resulting from these efforts has compelled some consumers to consult "pharmacy watch" Web sites, sources that provide current information on online pharmacy business practices, medication pricing, and availability (Boyer, 2006; Boyer et al., 2007). A leading pharmacy watch Web site is Drugbuyers.com, a cyber-community of more than 110,000 individuals, many of whom self-treat chronic pain with prescription medications purchased from Internet pharmacies (Boyer et al., 2007). Because of its appreciation of online pharmacy operations, Drugbuyers is a useful location to identify sentinel events related to the use of opioid analgesics purchased online (Boyer, 2006; Boyer et al., 2007). We explored the potential impact on opioid availability of ongoing law enforcement, regulatory, and legal challenges against Internet pharmacies by examining posts entered into the discussion forums of Drugbuyers.com. The specific aim of this research was to

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assess the self-reported availability of prescription opioid analgesics from Internet pharmacies described by a population that purchases these medications online.

Method

Study design and sample

Using an existing Internet research methodology, we constructed a data set of postings related to the purchase of prescription opioid analgesic agents (e.g., hydrocodone, oxycodone, codeine, and tramadol) generated by the members of Drugbuyers.com (Boyer et al., 2007). People join Drugbuyers because these individuals procure pharmaceuticals from online pharmacies. Because members purchase medications to treat chronic conditions, membership on Drugbuyers is thought to be stable (Boyer et al., 2007). Up to 900 individuals visit Drugbuyers at any one time, with maximum visitation occurring in June 2005 (Boyer, 2006; Boyer et al., 2007). Among Drugbuyers' members with chronic pain, 90% self-treat the condition without physician oversight (Boyer et al., 2007). Members' average age is 38 (range: 18-67); 59% are female (Boyer, 2006). Members post an average of 0.5-1.0 messages per minute on the Web site (Boyer, 2006). Topics are assigned to specific forums, and Web site moderators move or reassign posts if the topic is inappropriate for the initial forum location. Definitions of terms pertinent to this investigation are presented in Table 1.

Assessments and outcome

We used the Drugbuyers.com archives to identify mentions—a series of messages posted as replies to one another on a specific forum—that contained content describing the availability of opioid analgesic medications from online pharmacies. We reviewed the final content of threads logged on the first day of the month, every 3 months. For example, data for threads whose last post was entered on November 1, 2005; February 1, 2006; May 1, 2006; August 1, 2006; November 1, 2006; February 1, 2007; May 1, 2007; and Au-

gust 1, 2007, were abstracted during September and October, 2007. Data for November 1, 2007, were abstracted during the first week of November 2007. We reviewed the "US Doctors, Pharmacies, and Referral Services" and "International Online Pharmacy" forums because members may start threads and introduce into these areas content related to the purchase of opioid analgesics. We determined the number of threads related to opioid availability and abstracted the final post on each thread. To minimize bias in thread content introduced by disgruntled consumers more likely to complain, for each thread we calculated pageviews, an accepted measure of the interest of those visiting a Web site in the content of that page (Burby and Atchison, 2007). We removed all identifiers such as Drugbuyer's boardname and placed all posts in random order before review. Because postings on Drugbuyer's forums are made anonymously and with no expectation of privacy, the institutional review board at the University of Massachusetts Medical School concluded that this study was excluded from review.

Statistical analyses

The data set used in this study was empiric and intended to provide preliminary information on the availability of opioid analgesics to Drugbuyer's members from online pharmacies. We analyzed the study variables using descriptive and kappa statistics. We used an abstraction form to collect information about pharmaceutical availability. By means of simple, dichotomous responses ("agree/disagree"), examiners assessed whether the final post described decreased accessibility of pain medications. Masked versions were coded independently by two examiners trained in the use of the form, working according to an instruction manual and blind to results until all data collection was complete. Discrepancies were resolved by consensus between coders. We determined, using the kappa statistic, the degree of interobserver agreement between coders. Then, we compared the number of visits to Web pages ("pageviews") describing decreased opioid availability with publicized DEA actions against Internet pharmacies.

Results

We identified 45 threads in the target forums that were related to procurement of opioid analgesics from Internet pharmacies. Of the 41 threads (91%) describing declining availability of opioid analgesics from Internet pharmacies, 34 (83%) received posts on November 1, 2007. In these posts, members overwhelmingly described the failure of online pharmacies to deliver purchased drugs, sought to learn if specific online pharmacies were operating, or indicated changes in business practice that limited availability of opioid analgesics. Despite the subjective nature of the research question, there was substantial agreement between coders

TABLE 1. Definition of terms associated with the Internet

Forum—a Web application for holding discussions and posting user-generated content on a distinct topic. A sense of virtual community often develops around forums that have regular users.
Mention—a thread (e.g., on Drugbuyers.com) that is a series of replies on a distinct topic, such as purchase of medications from online pharmacies
Pageview—a numeric value generated by Web page visitation. Each time a person visits a Web page on a Web site, it counts as one page view.
Post—a message sent to a computer system where it can be retrieved electronically on demand
Thread—a series of replies to one another on a distinct topic
Web page—an individual page of information loaded onto the World Wide Web
Web site—a series of interconnected Web pages located on the same server

TABLE 2. Selected themes related to decreased ability to purchase prescription opioid analgesics from Internet pharmacies

Themes	Postings related to opioid analgesic availability ^a
Effect of federal agencies activity against Internet pharmacies	<ul style="list-style-type: none"> • Just received an email from them. What a bunch of B.S. I lost over \$200 from them just a few months ago. First they said their doctor retired and I had to reconsult for my remaining refills. Right after they did this, they lost their Pharmacy so once again i was left high AND dry without my money and meds ordered. • Hey, I know I've killed the posting board tonight bu I need to find someone reliable to use. You see I moving to ohio next week and was wanting to have order placed as soon as I get their, So thats the reason with all the different post about different OCS. • What ROP [a class of online pharmacies that requires only that medical records and no prescription] has been operating for at least a year? Do we know of any? In my mind, ther all were closed down or shut down this winter [2006]...
Effect of customs' activity against international online pharmacies' shipments	<ul style="list-style-type: none"> • Got a LL [a US Customs notification that illegally imported medications have been confiscated known as a "love letter"] from that missing envelope today. That makes 100% confiscation!!! Habeeb [the operator of RxPuraViad.com, located in Costa Rica] needs to do something, don't know what, but this is ridiculous. • I believe people stopped using them because pretty much everything they sent ws getting seized.... [C]ustoms started catching ALL their packages, so I decided not to throw money away.
Effect of regulation by individual states	<ul style="list-style-type: none"> • OK... I have been from NWW [Norco World Wide, a popular OCS that was closed] to ... BDRX and now they no longer ship to T[ennessee] either???? Does anyone have a good ROP that will ship to TN?? I would prefer one that will ship 120# 10 [hydrocodone] / 325 [acetaminophen]. Anyone... Please hit me up as this is getting Old ... and sitting here in pain while it is raining outside ... really sucks• Everytime the weather changes ... I can tell!!! Ugghghhh.
Effect of prescribing practices by physicians employed by Internet pharmacies	<ul style="list-style-type: none"> • One thing to note: if you're a pill head with scant evidence of a real condition, or if your records aren't so good you won't get a script. Don't even bother. Their doctor was EXTREMELY thorough. He's going to ask a lot of questions ... no more of the 1 minute phone call deals. He spent at least 10-15 minutes asking me dozens of questions.
General outlook on prospect for obtaining opioid analgesics	<ul style="list-style-type: none"> • The prices are rising ... delays are the norm now ... I realize that I either have to live with pain (as the Dr. states, just buck-up and take it) or live with pain. It is almost out of my price range now...so the DEA won...the [Internet pharmacies] are happy with the "zero refill policy." ... and I am tired of waiting with my bundle of excuses and lost money paid for a refill that i ... • Can you tell me if Apain is shipping at all. I had a consult Tuesday and they say they shipped today but no tracking number has appeared.... I am done with them controlling my life it has been over a month without, I went thru the pain of no shipments, ripoffs and ultimately withdrawals so i can take it or leave it now. Thank goodness for Sub[oxone].

^aAll posts are presented here verbatim. All errors (spelling, grammar, punctuation, etc.) were in the original.

($\kappa = .845$, percent agreement 97%). Selected themes related to opioid analgesic availability from Internet pharmacies are presented in Table 2.

To better understand the timing of this change in self-reported opioid availability, we examined the number of pageviews of threads describing declining opioid availability. We identified an initial upsurge in pageviews in February

2007 that was followed by a striking increase in traffic to these Web pages (Figure 1).

Discussion

These data suggest decreases in the self-reported availability of opioid analgesic pharmaceuticals from Internet

FIGURE 1. Number of visits to Web pages ("pageviews") on Drugbuyers.com describing decreased opioid availability. The use of pageviews is an accepted measure of Web site visitor interest in a page's content.

pharmacies. Several factors may have contributed to this apparent decrease. First, the DEA has restricted the ability of domestic Internet pharmacies to obtain prescription opioid analgesic agents for retail sale. For example, in December 2006, the DEA suspended the Certificate of Registration of Southwood Pharmaceuticals, a leading wholesale pharmacy that supplied 44 million hydrocodone dosage units to an estimated 80% to 90% of online pharmacies (DEA, 2006; Office of Diversion Control, 2007a; RxList, 2006). In July 2007, Southwood's Certificate of Registration was revoked (Office of Diversion Control, 2007a). Although causality cannot be established, bursts of Drugbuyers activity in February 2007 and August 2007 may correlate with the timing of these legal actions (Figure 1).

Second, increased regulatory scrutiny has been applied to the practices of domestic online pharmacies. The CYBERRx operation was directed against "no-records online pharmacies" (NROP) but left untouched a major class of online

pharmacies known as Online Consultation Services (OCSs). These companies typically require an individual pay a fee for a "consult" with a clinician employed by the online pharmacy (Boyer, 2006). Because OCSs practice "telemedicine," the clinician neither meets the patient in person nor conducts a physical examination before submitting a prescription for opioid analgesic agents to be dispensed by the OCS. Federal agencies such as the DEA and the Food and Drug Administration, by asserting that legitimate doctor-patient relationships are unlikely to be established via Internet correspondence, have minimized the ability of OCSs to obtain legitimate prescriptions and, therefore, legally dispense opioid analgesics (Office of Diversion Control, 2001). These actions have been supported by professional organizations such as the National Association of Boards of Pharmacy, who have clarified regulations to ensure the legitimacy of a submitted prescription (DEA, 2007; North Carolina Board of Pharmacy, 2007).

Third, the U.S. Bureau of Customs and Border Protection and the Food and Drug Administration have aggressively interdicted medications entering the country from international online pharmacies, also known as IOPs. These businesses, often located in Asia, India, or Central/South America, frequently sell opioid analgesics at lower prices than domestic online pharmacies and are therefore popular among purchasers. Beginning in September 2004, however, the Bureau of Customs implemented a national policy for processing controlled substances imported through mail and carrier facilities (Committee on Energy and Commerce, 2005). Under this new policy, packages are treated as abandoned or unclaimed property, a procedural change that allows more rapid processing of packages. In the first year following implementation of this policy, more than 72,000 interdictions occurred, with almost all of these parcels abandoned and disposed; only 120 individuals elected to pursue a formal seizure proceeding (Committee on Energy and Commerce, 2005). Although not included in our analysis, numerous posts attest that this policy has interrupted the flow of opioid analgesics from international online pharmacies (Table 2). These qualitative data also suggest that the reported willingness of international pharmacies to reship seized medications appears to be waning (Boyer, 2006; Drug Strategies, 2007).

Our results, which have identified declining opioid availability from Internet pharmacies, diverge from those of previous investigations. Several reasons account for this difference. First, the 2004 GAO study purchased opioids from NROPs that were closed as a result of Operation CYBERx in late September 2005 (General Accounting Office, 2004b). Studies of Web site availability conducted in follow-up to CYBERRx were performed in October 2005. Coming so soon after the DEA operation, these follow-up studies may have identified pharmacies that stopped selling medications—but whose Web sites were not yet removed from the Web—because of the legal action against their operators (Boyer, 2006; Drug Strategies, 2007). Alternatively, previous studies have failed to account for variations in Internet pharmacy practice. As mentioned, Operation CYBERRx closed NROPs (which delivered medications to customers who completed brief online questionnaires) but left untouched the major class of online pharmacies known as OCSs (Boyer, 2006). After September 2005, legal and regulatory agencies focused their attention on these businesses, and the resulting closure of OCSs or modification of their business practices correlates with the decline in opioid availability reported by our study population. Finally, ongoing reports of the unabated online sales of opioid analgesics lack supporting data (Drug Strategies, 2007). Since the 2004 GAO report, no studies have, to our knowledge, assessed the availability of *opioids* from Internet pharmacies either by direct purchase or the use of surrogate measures such as self-reported availability.

We feel that our approach has several advantages over

existing methods for determining opioid availability. This research method steps beyond Web site cataloging in that it focuses on reports of opioid availability made by opioid users themselves. We feel that self-reported information improves our data quality because the identity of Drugbuyers' members is unknown; information is submitted on a computer in a secure environment; and all Web-based interactions are anonymous. Each of these destigmatizing procedures, common in behavioral science studies, improves the precision of results by decreasing participants' incentive to lie (Turner et al., 1998). Finally, the use of a single data source represents another advantage because of the prominent role that the study Web site plays in the exchange of information related to online pharmacy sales. In this study, we used the number of pageviews as a measure of topic popularity. Drugbuyers' Web pages are minimally interactive (e.g., they can only be read), and the reading or "viewing" of a Web page is the condition for which pageview measures were developed.

This exploratory study provides preliminary information on the impact of regulatory operations on the availability of opioid analgesic agents from Internet pharmacies. It also highlights the potential of the Web as a tool for identifying emerging drug-use practices among hidden populations. Because submissions to Web sites such as Drugbuyers.com are automatically entered and undergo no screening, these messages offer a glimpse at the drug-taking behaviors of the community populating the forum at the time the post was entered. This is, to our knowledge, the first investigation of availability of opioid analgesics to users in natural environments (Forman, 2003, 2006; Forman et al., 2006; National Center on Addiction and Substance Abuse, 2006). We recognize that our data are preliminary and our study population is selective. Nonetheless, these findings raise important questions regarding the impact of regulatory functions on opioid analgesic using behaviors of distinct populations. Whether limiting access to medications from Internet pharmacies can avert misuse of opioid analgesics by a vulnerable population remains a tantalizing hypothesis waiting to be tested.

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