The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies

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Objective. To determine the role of clinicians in the discovery of off-label use of prescription drugs approved by the United States Food and Drug Administration (FDA).

Data Sources. Micromedex Healthcare Series was used to identify new uses of new molecular entities approved by the FDA in 1998, literature from January 1999–December 2003 was accessed through MEDLINE, and relevant patents were identified through the U.S. Patent and Trademark Office.

Data Synthesis and Main Finding. A survey of new therapeutic uses for new molecular entity drugs approved in 1998 was conducted for the subsequent 5 years of commercial availability. During that period, 143 new applications were identified in a computerized search of the literature for the 29 new drugs considered and approved in 1998. Literature and patent searches were conducted to identify the first report of each new application. Authors of the seminal articles were contacted through an electronic survey to determine whether they were in fact the originators of the new applications. If they were, examination of article content and author surveys were used to explore if each new application was discovered through clinical practice that was independent of pharmaceutical company or university research (field discovery) or if the discovery was made by or with the involvement of pharmaceutical company or university researchers (central discovery). Eighty-two (57%) of the 143 drug therapy innovations in our sample were discovered by practicing clinicians through field discovery.

Conclusion. To our knowledge, the major role of clinicians in the discovery of new, off-label drug therapies has not been previously documented or explored. We propose that this finding has important regulatory and health policy implications.

Key Words: off-label drug use, prescription drugs, new molecular entities, lead users.

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Clinician use of drugs approved by the United States Food and Drug Administration (FDA) in off-label applications is a very important part of medical practice. Data suggest that in some practice areas, such as chemotherapy and prescriptions for children, off-label use of drugs accounts for as much as 85% of total prescriptions.[1] Indeed, for some diseases, such as non–small cell lung cancer and cystic fibrosis, off-label uses of existing drugs are either the only drug therapies available or are the therapies of choice.[2]

Research on innovation processes in other fields has documented that both product users

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(medical clinicians in this study) and product manufacturers (pharmaceutical manufacturers in this study) play important and distinct roles in the development of new products and new product applications. Innovation process scholars have assumed that product manufacturers would be the developers of all or most new products. However, empiric research during the past 2 decades has shown that product users rather than manufacturers are the actual developers of many of the commercially important new products and new product applications in fields studied to date. User innovation has been demonstrated to exist in both industrial and consumer products, as exemplified in Table 1.[3–11]

Table 1. Proportion of Respondents Who Reported Developing and Building or Modifying Products for Their Own Use in Eight Product Areas[3–11]

Product Type	User Innovators (%)
Industrial Products	
Printer circuit software	24
Paper hanger hardware	36
Library information systems	26
Apache OS server software security features	19
Medical surgery equipment	22
Consumer products	
Outdoor consumer products	10
Extreme sporting equipment	38
Mountain biking equipment	19

Research has also shown that user-developed products tend to differ from manufacturer-developed products in an important way: they tend to be "functionally novel." That is, users identify new applications of existing products not originally envisioned by the product manufacturer. In the field of scientific instruments, users tend to develop innovations that enabled the instruments to do qualitatively new types of things for the first time.[3] In contrast, manufacturers tend to develop innovations along dimensions of merit that enabled users to do the same things they had been doing, but to do them more conveniently or reliably (Table 2).[12] For example, users were the first to modify electron microscopes to enable them to image and analyze magnetic domains at submicroscopic dimensions. In contrast, manufacturers were the first to computerize electron microscope adjustments to improve ease of operation. Improvements in sensitivity, resolution, and accuracy fall somewhere in the middle. These types of improvements can be driven by users seeking to do specific new tasks or by manufacturers applying their technical expertise to improve the products along known general dimensions of merit, such as accuracy, ease of use, size, or efficiency.

A source of the difference between user and manufacturer innovation has been traced to information asymmetry. Users, in general, tend to know more about their heterogeneous needs and about the context of use and therefore have the information required to develop new uses for existing products or new products. Because the information is held at the user level, it is not easily available to the manufacturer. This local knowledge may be thought of as "sticky" information. The concept of stickiness of information has been previously described and shown to alter the sources of innovation.[12, 13] We believe the same holds true for clinicians. We hypothesized that their heterogeneous patient mix and patients' diversity of concomitant diseases produce diverse clinical needs among clinicians. These needs may not have been envisioned by the manufacturer of a particular product and are not easily transmitted from clinicians in the field to the producer of FDA-approved drugs; hence, the information is sticky.

Not all users innovate, however. Studies of users who innovate (both individuals and firms) show them to have the characteristics of lead users. Lead users are defined as users distinguished by two characteristics: first, they are ahead of most users in their populations with respect to an important market trend, and second, they expect to gain relatively high benefits from a solution to the needs they have encountered at that leading edge. This group of users falls outside the traditional technology adoption life-cycle classification: innovators, early adopters, pragmatists, and laggards. Lead users may be thought of as preadopters in advance of a product or market recognition of a new use for an existing product.[13]

Thus, studies in other types of innovation and in a range of fields support the probability that clinicians in regular medical practice will be the source of many and diverse innovations, such as innovations in the off-label use of drugs. The sheer number of clinicians prescribing an approved drug relative to the much smaller number of researchers who studied it in formal clinical trials is likely to increase the probability that clinician users will be the discoverers of new off-label drug therapies. Our reasoning echoes

Table 2. Source of Innovations by Nature of Improvement Effected[12]

Type of Improvement	No. (%) of Innovations Developed by User	No. (%) of Innovations Developed by Manufacturer	Percentage of Total Innovations[a] (n=64)
New functional capability (n=17)	14 (82)	3 (18)	27
Sensitivity, resolution, or accuracy (n=23)	11 (48)	12 (52)	36
Convenience or reliability (n=24)	3 (13)	21 (88)	38

[a]Total is greater than 100% due to rounding.

that offered by another author regarding Linus's Law in software debugging.[14] In software, the writing of new code and repair of subtle code errors or "bugs" can be a very costly matter.[15] However, the same task can be greatly reduced in cost and also made faster and more effective when it is opened up to a large community of software users.[14]

Although this concept refers to innovation in software development and debugging,[14] we believe that the general principles also apply to the discovery of new off-label therapies. Open source software provides both source code transparency and source code access to user communities. This allows users to freely innovate in a number of functional domains, including adaptation, refinement, and correction. The phenomenon of user innovation has been shown to be pervasive and robust in terms of problem resolution and software adaptation when source code transparency and availability are present. This open access allows users to not only correct problems but also adapt existing software to new uses. The user community freely shares these adaptations to software, allowing others open and unrestricted access to their altered source code. Through the process of iteration, this source code is improved by users. The improvements may be related to correction of programming errors, extensions of functionality, or new uses. If the improvement is deemed worthy (e.g., widespread in its applicability), the new software is incorporated into the new releases of the product.

We propose that there are parallels between open source software development and innovation in drug therapy. In the case of formal manufacturer-funded clinical trials, the total volume of experiments going on in humans per new molecular entity probably only numbers in the hundreds or thousands of subject exposures for each new indication or use. Each defined use is subject to intense scrutiny by the manufacturers and from the FDA during the submission and approval process. In the case of clinical practice, the total volume of "experiments" going on is equivalent to the number of prescrip-tions generated for the product. The volume of patients treated in clinical practice will exceed the number of subjects enrolled in clinical trials sponsored by the manufacturer. These "experiments" may be formally conducted under the auspices of an institutional review board with the informed consent of patients or, as is perhaps often the case, may be conducted without benefit of formal oversight being considered as clinical practice. Users in the field are likely to collectively have a more broad-based understanding of the value of a particular drug than does the manufacturer based on volume as well as diversity of need.

We sought to explore how new and off-label applications of previously approved new drugs are discovered. We proposed that there are two distinct and simultaneous processes of innovation in pharmacotherapy. Some new applications for FDA-approved drugs will be identified in a centralized process by pharmaceutical firms in laboratory settings and in clinical trials (central discovery), whereas others will be discovered by the noncentralized observations and experimentation of clinicians in the field (field discovery).

Examples of Field Discovery

If field discovery is a significant factor in the process of defining new drug indications, examples should be readily apparent. In our preliminary investigations, we did find this to be the case. Two examples of field discovery are provided.

Botulinum Toxin Type A

Botulinum toxin type A (Botox; Allergan, Inc., Irvine, CA) was originally approved in 1989 as an orphan drug for the treatment of strabismus, hemifacial spasms, and blepharospasm. The indications for use increased so that by 2002

botulinum toxin type A was approved for the treatment of cervical dystonia in adults to reduce the abnormal head position and neck pain associated with cervical dystonia and for the treatment of strabismus and blepharospasm associated with dystonia. In April 2002, the FDA approved Botox Cosmetic for the temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients aged 65 years or younger.[16] The financial impact of this change in FDA approval was substantial. According to the Allergan annual report, domestic and international sales of Botox rose from $239.5 million in 2001 to $439.7 million in 2003. This 84% increase in sales volume for Botox Cosmetic was well in excess of the 20.9% increase in sales for the company's eye care products and 31.2% increase in sales of skin care products.[17]

The first reported use of botulinum toxin type A for cosmetic purposes was published by two ophthalmologists in 1992.[18] We contacted the first author and confirmed that their use of botulinum toxin type A for cosmetic purposes was the result of observations made in using the drug for its FDA-approved indications. According to this author, the manufacturer did not play any role in the development of the clinical trial.

Propofol as an Antipruritic

Propofol (Diprivan; Zeneca Pharmaceuticals, Wilmington, DE) was approved by the FDA for use as an anesthetic in 1989.[19] It is used as a sedative-hypnotic drug in the induction of anesthesia. Although it is now a mainstay in the early phases of anesthesia, having replaced thiopenthal, the mechanism by which propofol works is not understood.

The practice of anesthesia has evolved over the years with greater attention to postoperative management, a key concern before surgery. To that end, many anesthesiologists will routinely provide for pain control by using an epidural drug administration technique. Narcotic drugs such as morphine or local anesthetics such as lidocaine can be injected into the epidural space or given by continuous infusion into the space. Many patients experience intense itching initially when morphine or another narcotic is administered in this manner. This intense itching can be very troublesome and is difficult to treat with the usual drugs.

In 1992, anesthesiologists published the results of the first use of propofol for the relief of itching due to epidurally administered narcotics.[20] The first author was contacted to determine the events leading up to the use of propofol in this rather novel fashion. On questioning, he noted that the initial observation was serendipitous. A patient's complaint of intense itching, nausea, and vomiting related to epidural morphine was inadvertently but successfully treated with the coincident administration of subtherapeutic doses of propofol. This use of propofol, although not approved by the FDA, is common in hospitals across the United States today.

Note that neither of these two discoveries emanated from a centralized or planned investigation. Both were made in the field by observant clinicians who then chose to report their findings. In each case, a clinician identified a previously unknown use of a drug, conducted initial observations, and then reported the observations to their peers through publication. In the first example (botulinum toxin type A), the new use led to a significant economic gain for the manufacturer, which chose to pursue formal approval for the new indication.

Methods

We used both available published information and apparent innovator surveys in a stepwise research strategy. The schema for the search is displayed in Table 3. Newly approved drugs were identified by using the FDA's Web site (http://www.fda.gov). The approvals are categorized in numerous ways including a segregation of new molecular entities. The sample chosen consisted of only new molecular entity new drug applications (NDAs) that had been approved in 1998. We then analyzed the introduction of new clinical uses for these newly approved drugs during a 5-year period from January 1999–December 2003. This period was chosen to allow sufficient product maturity for widespread clinical use, as well as time for reporting of findings in the literature. The FDA approved 30 new molecular entity drugs in 1998. However, one newly approved drug, technetium-99m apcitide injection, was excluded from the sample because of its sole application as a diagnostic agent.

Because the definition of a new and effective use may be considered arbitrary, we chose to use a presumably objective abstracting subscription (Micromedex; Thompson Scientific and

Table 3. Search Methodology

Task	Methods	Uniform Resource Locator
Identify initial data set	Food and Drug Administration New molecular entities approved in 1998	http://www.fda.gov/cder/rdmt/nmecy98.htm
Identify new uses for new molecular entities approved in 1998	Micromedex Healthcare Series: Main keyword search Drugdex System Drug evaluation Clinical applications Therapeutic uses References	http://www.thomsonhc.com/hcs/librarian
Identify seminal citations from January 1999–December 2003 with daily updates	OVID MEDLINE search	Accessed through secure institutional Intranet
Contact author(s)	Google search of e-mail accounts	http://www.google.com
Identify relevant patents	U.S. Patent and Trademark Office: Patent search Quick search	http://www.uspto.gov

Healthcare, Inc., Greenwood Village, CO) to initially identify new published uses for the 29 new molecular entity drugs in our sample. The choice to use Micromedex, a commercial drug information service, was not made arbitrarily. Other drug information services may not provide the same information for the sample chosen. Additional information resources such as *Facts and Comparisons Off-Label Drug Facts*, MEDLINE, and others were considered. A recent survey of 81 institutional drug information centers in the United States and Puerto Rico noted the preferred use of Micromedex Healthcare Series as a source of drug information.[21] Survey respondents were asked to provide the five most useful references for answering drug information queries. Micromedex was noted in 14 of the 15 categories polled. As a result, Micromedex was chosen as the primary reference source.

Only uses defined within the Micromedex Drugdex System Drug Evaluations (therapeutic uses) as effective or possibly effective were considered. Each defined use listed in either category was counted toward the total. Several drugs (e.g., sildenafil) noted multiple new uses that may be construed as sufficiently similar to list collectively (i.e., erectile dysfunction with diverse causes). Because of the inherent bias associated with rolling multiple associated diagnoses under a single definition, we chose to list the new uses as explicitly described within Drugdex Drug Evaluations. Individual therapeutic uses as described in the Clinical Applications suite were considered and evaluated. A total of 143 new and possibly effective or effective uses for these new drugs were identified. New potential but ineffective uses were not included in the data set.

Citations for each of the 143 new uses identified in Drugdex Drug Evaluations were explored sequentially to the earliest identifiable literature reports. Based on these earliest publications, a detailed literature search was conducted. Seminal published articles were identified by using a computerized database (OVID MEDLINE; Ovid Technologies, New York, NY). Citations were sought electronically for the period from January 1999–December 2003. This identification was accomplished by using cited references and working backward in time, as well as through a computerized search of the literature using dates of publication. Once seminal articles were identified, contact information for first authors was obtained.

Drug manufacturers may envision a new and important use before clinical application. In many instances, these parallel and tangential uses are identified in the original patent application for the compound. We therefore searched for all patents by using the U.S. Patent Office Web site (http://www.uspto.gov) for those citations in which the name of the disease and the name of the drug were present in the same patent. To do so, we searched the database for any notation of the drug in question and the disease or disorder of interest. The decision to conduct a broad-based search rather than searching only in the explicit claim was in recognition of the

heterogeneous nature of patent language and specificity. For example, some patents identified included only very specific disorders within the claim, whereas others included generalized terms such as inflammatory disorders. Foreign patents were not searched. Under the Patent Cooperation Treaty, applicants filing a U.S. patent have a temporary right to file specified foreign patents. This right to file expires 1 year after U.S. filing. Given the size of the market for pharmaceuticals in the United States compared with the total worldwide market, we assumed that the U.S. patent would be filed in advance of any other patent application.

Dates of patents were compared with those of the seminal published article. After checking on both patent and journal publication databases, we coded the discoverer of each NDA based on priority of discovery as follows:

- If there was no patent filed by a central developer before publication by a field author, then it was coded field discovery.
- If there was a patent and a journal publication and the article was published after the patent filing date but before patent publication, then it was coded parallel discovery by the authors of these two forms of publication. (If both authors were clinicians, then it was coded as a field discovery. To be conservative in our findings, we coded all cases involving publications with mixed authorship in the central discovery in our tallies.)
- If the article was published after publication of the patent, the patent filer was assumed to have priority of discovery.

To confirm and deepen our findings regarding field discovery of new applications for existing drugs, first authors of seminal publications were contacted through electronic mail and offered a standardized questionnaire pertaining specifically to the seminal article. If the discovery was made in the field, data were collected on the circumstances of its discovery along with key characteristics of the clinician(s) making the discovery.

A total of 102 e-mail addresses were obtained, and the authors were contacted with a standardized survey instrument (the survey instrument may be accessed at http://userinnovation.mit.edu/survey/login.cgi?n=4&p=785NUQJ). Of the 102 authors, 70 (69%) were assumed to have made field discoveries and 32 (31%) were assumed to have been involved in a central discovery. The overall response rate was 32% (33/102).

A total of 33 complete and partial responses were obtained. Twenty-nine of the authors responding to our survey of clinicians were initially assumed to have been participants in a field discovery. All confirmed this original coding. Data were also collected on the specific circumstances of each filed discovery along with the key characteristics of the clinician(s) making the discovery. Although 32 authors of research that we coded to be of central origin were contacted, only four responded. Three of these respondents confirmed our coding was correct, and the other author reported that his off-label application discovery for candesartan was in fact due to field discovery rather than central discovery.

Findings

Recall that we define central discovery of new off-label drug applications to be those made in the course of an organized research discovery process involving a pharmaceutical manufacturer or other laboratory. We define field discovery of new off-label drug applications to be those identified by clinicians in the care of patients. Of the 143 new uses that were identified for the 1998 new drug approvals, 85 (59%) were initially categorized as field discovery based on simple inspection of the authorship and content of the seminal articles. We tested and refined this initial categorization in the survey questionnaire. We explored the possibility that the drug's manufacturer played a behind-the-scenes role in the apparent field discovery process. None of the respondents noted the manufacturer as a source of the idea. However, one discovery was recategorized from central to field discovery based on comments from the author. With this correction made, we found that 86 (60%) of the 143 new off-label drug applications in our sample were the result of field discovery, and 57 (40%) were originally encoded as the result of central discovery. This categorization was considered as a preliminary conclusion pending exploration of patent applications.

A total of 34 patents were identified for the new uses defined as field discoveries. Twenty of the patents were filed after the publication of the apparent seminal article. The remaining 14 patents identified were general in nature relating to either a family of compounds or a general category of disease. Of the 14 general claims, 10 did not note the therapeutic use explicitly. Four

of the general claims patents that included the therapeutic use in question were filed and published before publication of the seminal article. Three new and effective uses of citalopram and one for lepirudin were noted in patent applications filed and/or published before the journal article. None of the identified patent filing and publication dates met our criteria for parallel discovery. Based on a review of the publications and patent applications, at total of 82 (57%) of 143 drug therapy innovations were categorized as field discovery. This finding was not altered by the previously noted responses from the responding authors, as none were associated with the patents in question.

Table 4 lists the relevant clinical and regulatory history for each of the identified new molecular entity drugs. The number of FDA-approved indications, post-NDA clinical uses identified, and number of new uses sourced from field discovery are reported. Of note, the editors of Drugdex have previously chosen to list FDA-approved uses somewhat inconsistently. For example, the index for FDA-approved uses for montelukast notes a total of six FDA-approved uses; however, only four uses are noted in the body of the drug monograph. In each case, however, we listed the information as described in the drug monograph.

Table 4. United States Food and Drug Administration New Molecular Entity Approvals, 1998

Drug	FDA-Approved Indications	Post-NDA Indications	Apparent Field Discovery
Tolcapone	1	1	1
Naratriptan	1	2	1
Montelukast	4	9	8
Lepirudin	1	8	2
Loteprednol	2	1	0
Tolterodine	1	0	0
Risedronate	3	3	0
Sildenafil	1	21	6
Brinzolamide	1	0	0
Sacrosidase	1	1	1
Paricalcitrol	0	0	
Capecitabine	2	5	1
Tirofiban	1	3	1
Eptifibatide	2	2	0
Candesartan	2	7	2
Rifapentine	1	1	0
Rizatriptan	1	2	0
Thalidomide	1	36	32
Citalopram	1	18	11
Fomivirsen	1	0	0
Leflunomide	1	4	3
Efavirenz	1	1	0
Valrubicin	1	0	0
Sevelamer	1	0	0
Telmisartan	1	3	0
rH Thyrotropin	1	1	0
Abacavir	1	0	0
Modifanil	3	8	7
Celecoxib	4	6	6

FDA = U.S. Food and Drug Administration; NDA = new drug application.

Discussion

The finding that 57% of new drug uses arise from field discovery is, we believe, of significant interest. Apparently, based on this single sampling, innovation in the field of drug therapy follows patterns identified in other domains. The role of lead users and functional novelty appears to be consistent with that of previous research.

There is considerable heterogeneity in the source of discovery of new uses, with thalidomide having the highest number of uses identified in the field (89% [32/36]) and sildenafil having the highest number of new uses identified in company-initiated research (71% [15/21]).

Further research can refine this finding considerably. For example, why do only a few of the drugs among the 29 in our sample—notably thalidomide—experience most of the discovery of new off-label applications? Based on anecdotal evidence, we speculate that this may be related to the pharmacology of the drug in question. The extent to which clinicians have an understanding of the pharmacology of a new drug (transparency) and the widespread availability of the agent (accessibility) are similar to the scenario seen with open source software. Although field discovery may well represent advantages to some stakeholders, it may not to others. Clinical "learning by doing" in the field is likely to identify many unexpected effects—both positive and negative.

As we noted previously, user-developed innovations tend to be developed by lead users.[14] Recall that lead users display two characteristics. First, they face needs that will be general in the marketplace, but face them months or years before the bulk of that market encounters them. Second, they are positioned to benefit significantly by obtaining a solution to their leading-edge needs. We found, in agreement with studies of the sources of innovation in other fields, that our field discoverers were lead users. That is, they had a high need for the new indication to better serve the needs of their personal caseload.

Table 5. Examples of the Potential Implications of Off-Label Drug Use

Consideration	Implication
Economic	Economic gains for manufacturer from off-label use Costs and savings of off-label use to consumers and private and governmental insurers Regulatory oversight to diffuse model of innovation as compared with manufacturer centric model
Regulatory	Oversight of off-label prescribing by governmental agencies including FDA, OHRP, and others Different definitions of safe and effective for off-label as compared with FDA-approved indications
Medicolegal	Change in definition of the standard of practice of medicine Medical liability for not applying well-described off-label drug use
Ethical	Informed consent of patient for off- label drug use Oversight by institutional review boards and peer review
Clinical	Safety and efficacy of off-label use

FDA = U.S. Food and Drug Administration; OHRP = Office for Human Research Protections.

Seventy-two percent of the 13 authors who responded to the question noted a high level of importance of the discovery to the care of their patients. The needs of these clinicians also foreshadowed general demand, as measured by the number of follow-on studies that developed their discovery further. Fifty-nine percent of the 29 field discoverers reported that they had made their discovery by applying their understanding of the pharmacology of the drug to the clinical problem. Serendipity, information from others, and other factors appeared to have played a lesser role. The high proportion of discoveries made through a deep understanding of the method of action of a drug and of specific disease processes again fits with our expectations for innovation by lead users. A recent study suggests that clinician dissatisfaction with available therapies may be a strong motivator for off-label drug use.[22]

The indications developed by field discoverers were judged to be clinically important by our survey respondents. The discoveries were rated as the first drug that can be used to treat the indicated condition and/or as a significantly better way to treat this condition in 100% of cases. Further research is needed to establish the relative economic importance of field- versus manufacturer-discovered new drug indications. From simple inspection, it is clear that the indications developed by field discoverers were not in economic "blockbuster" categories at the time they were discovered. However, the categories, as one would expect in the case of innovations by lead users, have expanded since the time of discovery (as was the case, for example, with the field discovery of cosmetic uses for botulinum toxin type A).

Although beyond the scope of this article, we believe the health policy, regulatory, ethical, medicolegal, and economic implications of off-label prescribing deserve additional discussion in the literature. We describe some of the implications in Table 5. An understanding that users are an important source of new innovations has enabled other industries to reduce product cycle times and improve product performance.[4] If much innovation and related improvement in patient care is derived from field discovery, the same advantages may be obtained by proper "reengineering" of the field discovery of new applications for existing drugs. One approach may be to provide for additional journal space for case reports and small series with pre- and/or postpublication peer review. This model is similar to an information collection and dissemination process modeled on open source software projects.

We should make it clear that we are not advocating unfettered experimentation on the part of clinicians. Misapplication of drug therapy has as great a potential to harm as it does to help. There is an obvious and appropriate concern with the widespread dissemination of incorrect information in drug therapy. Other disciplines have developed robust mechanisms that enable them to rapidly self-monitor and self-correct. For example, experiments in which incorrect information has been purposely inserted into open information compilations like the free online encyclopedia Wikipedia (http://www.wikipedia.org) have shown very rapid discovery and removal of the faulty information by other users.

This approach would appear at first glance to be in direct contradiction to the current ethos of evidence-based medicine.[23] Evidence-based medicine has been defined as "…the conscientious, explicit and judicious use of current best

evidence in making decisions about the care of individual patients."[23] Although some have argued for a rather restrictive definition including only randomized clinical trials, others have not. Indeed, as noted by the same authors,[23] "However, some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there."

It may be argued that open discourse or narratives concerning novel uses for FDA-approved drugs may serve to enhance formalized research into the safety and effectiveness of approved drugs in new settings. We would argue that these initial reports of off-label usage of approved drugs provide a valuable source of possible new indications. Further, far from providing evidence of safety and efficacy, we propose they provide reasonable hypotheses to be tested with use of scientific methods.[24] This perspective echoes that of some in the pharmacovigilance community who have advocated for journals to provide guidelines for reporting of cases and small series of adverse events.[25] These initial reports may be construed as a medical narrative. Narratives, including anecdotes, case reports, clinical conferences, and the like, have been central to medicine and its progress.[26] It has been suggested that narratives provide for the emergence of the unexpected. Quantitative methods, it has been argued, can only measure those attributes that are predefined.[27] If this is indeed the case, more qualitative research and widespread availability of narratives may increase the rate of innovation in drug therapy.

There are obvious limitations to this study and the conclusions. The present sample of newly discovered off-label applications is quite limited in both size and scope. We examined 143 new applications for drugs newly approved in only 1 year, 1998. However, our findings are quite similar to those found in a range of other industries by other investigators. The impact of field discovery may be different for different years or drugs approved. The response rates from clinicians were relatively low but within the expected response rate from physicians to surveys in general.[28] There may have been a bias in the responses that skewed the data toward field discovery. Drug manufacturers possibly may have played a behind-the-scenes role in the apparent field discoveries. The physician survey attempted to address this by posing a specific question related to the source of the idea. None of the respondents noted a drug company representative as the source of the idea.

Conclusion

These data suggest that field discovery is an important contributor to the identification of new applications for existing FDA-approved prescription drugs. Regardless of the impact, it is clear that field discovery of new uses for drugs is widespread and cuts across many pharmacologic classes of drugs. We suggest that this method of discovery is not well described or well understood, despite a previous call for a reallocation of research monies to off-label drug use research.[29] Additional research should be conducted to determine the attributes of clinicians involved in field discovery and the health policy and regulatory implications of this observation.

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