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BRAINSTORMS—Clinical Neuroscience Update

Off-label prescribing: best practice or malpractice?

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ISSUE:

Standards for the *practice* of medicine are increasingly being confused with standards for the *sale* and *reimbursement* of medicines. Authority for prescribing of psychotropic drugs, whether on-label or off-label, is determined by the standard of medical care set by practitioners, not by regulators of the pharmaceutical industry.

Take-Home Points

- Most of psychiatric practice is "off-label," because randomized controlled trials leading to "labels" do not include most patients seen in clinical practice settings.
- The trends to save costs and to comply with evidence-based guidelines threaten to constrict psychiatric practice by ignoring the fact that the standard of medical care is set independently by practitioners.
- Prescribers need to know how to justify their off-label practices in order to continue best practice standards for their patients in real clinical practice settings.

"Labels" for medicines are also known as the "package inserts" that list the details of the approval granted by regulatory authorities such as the FDA (U.S. Food and Drug Administration) for the sale of medicines by the pharmaceutical industry. "Off-label" means utilizing an approved medicine in a manner not contained in the approved "label." Although it is illegal for employees of the pharmaceutical industry to promote "off label" use of their medicine, it is not illegal for licensed practitioners to prescribe off-label. In fact, the majority of the practice of psychiatry,[1–3] neurology,[4] pain medicine,[5] oncology, and of many other specialties[6] whose clinicians practice in the real world (rather than in clinical trial settings) is off-label, and in one of five categories listed in Table 1. It has been said that more than 80% of psychiatric diagnoses have no FDA-approved medical treatments,[2] a number that is likely to be even greater now with the recent launch of the new DSM 5 (*Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association*, 5th edition). Thus, it is more important than ever for prescribers to know the rules,[7–10] the risks (Table 2), and the benefits (Table 3) of off-label prescribing.

Regulating the Sale of Medicine Versus the Practice of Medicine

Recent law suits, scandalous publicity, and eye-popping fines for off-label promotion by the pharmaceutical industry in recent years have led to tightening of the standards for the sale of medicine as well as confusion and even fear about whether the long-standing practice of off-label prescribing of drugs in clinical practice can continue. This situation has also led to pressure on prescribers by various stakeholders to adhere to the same standards imposed on pharmaceutical sales personnel: by payers who wish to exploit labels in order to restrict the use of expensive medications to save them costs, and by government agencies and academics—most of whom are not in current clinical practice in the real world—who wish to exploit labels to promote elite guidelines only at the top of the pyramid of "evidence-based medicine" (see Figure 1). Although it is laudable to save costs

Table 1. *Common forms of off-label prescribing: using an approved medication but in an unapproved manner*

- For an unapproved (unlabeled) indication
- At an unapproved/unlabeled dose
- For an unapproved/unlabeled duration
- In an unapproved/unlabeled age group
- In combination with another drug not studied nor approved in the label

Table 2. *Off-label prescribing: what are the risks?*

- Lack of reimbursement
- Conflict of interest in fact or in appearance
- Accusation of doing research without ethical/institutional review board approval
- Need to better document informed consent
- Need to be able to document the literature on which it is based
- Invites more scrutiny

whenever possible and to practice according to the best available evidence, what is a practitioner to do when there is no evidence from the top of the pyramid for a given patient, but there is evidence other than that derived from meta-analyses of large, randomized, controlled clinical trials, which mostly come from labels? This situation of "off-label patients" is common in clinical practice, since it includes patients who have two or more illnesses or who take multiple drugs or who are resistant to prior standard treatments but who were likely excluded from almost all large randomized controlled trials at the top of Figure 1 (see also Table 1).

General Guidelines

According to professional societies, including the American Psychiatric Association,[7–10] prescribers can use drugs off-label if the use of the drug is safe and effective in the professional judgment of the prescriber and if it is properly documented. Psychiatrists are notorious for keeping poor records; however, off-label prescribing requires maintaining scrupulous records, including mention of informed consent. Obviously, prescribing off-label should not be done because of incentives provided by a drug company, but only for the benefit of the patient (Table 2). It is imperative that off-label use be supported by sound scientific evidence

Table 3. *Off-label prescribing: what are the benefits?*

- Using evidence rather than regulations to guide practice
- Using best practices rather than cost savings to guide practice
- Using best practices rather than pharmaceutical marketing to guide practice
- Ability to use higher/lower doses
- Ability to use agents for additional populations (e.g., children, pregnant women, elderly)
- Ability to use agents in comorbid, complex, or treatment-resistant patients not studied in controlled trials
- Ability to practice personalized medicine

and sound medical opinion, such as peer reviewed literature,[7–10] even if not from the tip top of the hierarchy of evidence (Figure. 1). Some state licensing authorities, such as California's,[7] suggest that off-label prescribing be supported by two articles from major peer-reviewed medical journals. Other acceptable sources of evidence include the *AMA Drug Evaluations*, the *United States Pharmacopeia*, the American Hospital Formulary Service (AHFS) Drug Information database, and well established textbooks and prescribers guides.[7–10] If the evidence for off-label use is weak or potentially risky, it may cross the boundary between clinical practice and research, and thus require ethical review board approval and written informed consent, especially for prescribers working in institutional settings.[7–10] Some states such as California[7] indicate that off-label prescribing is for life threatening conditions or for chronic and seriously debilitating conditions. It is also best to check with malpractice liability carriers to be sure that investigational or risky off-label prescribing is covered.

Off-Label Treatment Is Personalized Medicine

Evidence-based medicine is population-based medicine, whereas the practice of medicine is practiced one patient at a time, sometimes called personalized medicine.[11] What is right for the median patient is not always right for the individual patient, who may be an outlier and require customized treatment based on past treatment successes and failures, family history, and, increasingly, biomarkers (Table 1).[11] On the one hand, evidence-based treatment guidelines derived from the label define where to start for the

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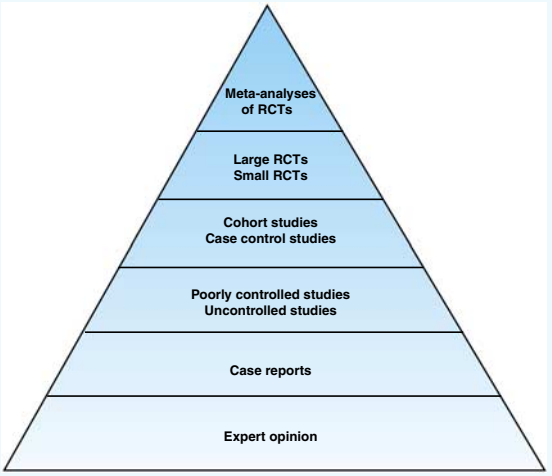
Figure 1. Hierarchy of evidence based medicine.



- RCT=randomized controlled trials.

typical patient included in the trials for that medication.[1–10] On the other hand, treating everyone as a median patient in a population of patients that actually excludes many individuals that a typical practitioner must treat (Table 1) can force a practitioner to treat everyone the same and in lock-step with guidelines that do not apply to many patients who themselves are off-label. Treating all patients only according to labels and only according to the results of large randomized clinical trials in simplified patient populations is a situation sometimes called the "tyranny of the majority."[11] Unless a more customized approach is available from off-label prescribing to such off-label patients, many real-world patients will not have effective treatments for their off-label condition (Table 1). In addition, the results of empirical trial-and-error treatment of such off-label individuals and from consulting the literature, as well as practice standards for how a reasonable practitioner in a given field of medicine and in a given geographic area manages the specific patients who are in the off-label situations shown in Table 1, are good tips for how to proceed.

Don't Be Fool

There are dangers of going too far and relying only on case-based/narrative-based evidence or opinion alone (Table 4).[12,13] It may be particularly important to remember the following when going "off label":

- Radiance of gray hair is not proportional to an understanding of the facts

Table 4. *Seven alternatives to evidence-based medicine to be avoided*[12]

- Eminence-based medicine
- Eloquence or elegance-based medicine
- Vehemence-based medicine
- Providence-based medicine
- Diffidence-based medicine
- Nervousness-based medicine
- Confidence-based medicine

- Eloquence, smoothness of the tongue, and sartorial elegance cannot change reality
- Qualifications and past accomplishments do not signify a privileged access to the truth
- Experts almost always have conflicts of interest
- Clinical acumen is not measured in frequent flier miles[13]

Now more than ever, there is the need for prudent, well-reasoned off-label prescribing in order to help many if not the majority of patients. As the pace of new drugs entering clinical practice slows down considerably, an increasing majority of all drugs will become generic—none of which will have any incentive or mechanism to update their labels. For the majority of drugs, therefore, the labels we have now are going to be the labels we have forever, despite any future advances in medical therapeutics for these agents. Furthermore, as we enter the era of genetic markers, new research findings will increasingly identify individuals who need specific drugs, at specific doses, and perhaps in specific combinations. However, these guidelines will find themselves into labels only for new drugs and not for any generic agents. Thus, mindful clinicians who follow the literature and who learn from individual patients will want to keep off-label prescribing as a properly honed and potentially powerful tool within their armamentarium of best practices.

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