

- Essential PsychopharmaStahlogy -

# Prescribing Off-Label in Psychopharmacology

## Is it the exception or the rule?

**[The FDA and Pharma] do not dictate how practitioners can actually use drugs in the practice of medicine.**

Stephen M. Stahl

Adjunct Professor of Psychiatry, UCSD  
Editor-in-Chief

### Practice of medicine or sale of medicine?

The influence of Pharma and the FDA has become so dominant in psychopharmacology that we may forget the distinction between what they do—sell medicines or regulate the sale of medicine—and what prescribers do—practice medicine. Once a drug is approved for marketing, it enters the practice of medicine, where its use is regulated by the standards set by practitioners, not by Pharma nor by FDA regulators. The distinction between the on-label promotional practices of Pharma and the off-label educational activities of practitioners of psychopharmacology has been discussed previously in this column.<sup>1</sup> With Pharma becoming much more compliant about following the label, and with the FDA filling labels with increasingly restrictive warnings, it may be useful to remind ourselves that while input from Pharma and the FDA are important regulators of the sale of medicine, they do not dictate how practitioners can actually use drugs in the practice of medicine.

research and clinical observations evolve into the actual use of a drug in mainstream clinical practice.

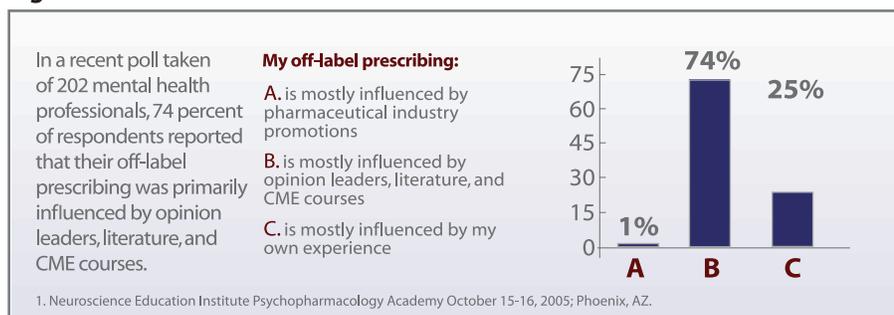
It is a good thing that the PDR is not a textbook because it would severely restrict the potential uses of drugs in clinical practice. A recent poll of top prescribers in psychopharmacology attending one of the Neuroscience Education Institute's Psychopharmacology Academies indicates that most of their clinical practice was off-label (see page 1). It actually makes a lot of sense that the majority of drug use is off-label in the field of psychopharmacology. Think about it. How many of your patients would meet the inclusion criteria for the clinical trials that generate the evidence for the label? Namely, patients 18 to 65, given a single drug, who have a single diagnosis, no comorbidity, no personality disorder, no substance abuse, no concomitant medical illness, no concomitant medications, no prior failure of treatments or treatment resistance—just like everybody in your practice? I don't think so.

patients even if they do not “work” to a regulator's satisfaction, and even if they have scary warnings? The standard of care states that yes we can, and the reality is that yes we do. Sorting out the risks versus the benefits of any given drug for any given patient is an important and increasingly time consuming part of medical practice, requiring increasingly more defensive legal documentation. Nevertheless, prescribers can and should make the judgment to prescribe a drug for an unapproved use despite warnings or even contraindications if it is in the best interest of the patient and is within the standard of care.

### How much does Pharma influence off-label uses?

Top prescribers of psychotropic drugs in a recent poll also felt that their off-label prescribing was influenced much more by evidence and by their own observations in clinical practice, and hardly at all by pharmaceutical promotions (Figure 1). Although there have been some notable abuses in the past by Pharma inappropriately promoting off-label (e.g., Neurontin/gabapentin), the off-label influence of Pharma is now declining since they are currently adhering much more closely to the label. In fact, information from Pharma sales reps, from exhibit booths at Congresses, and from lecturers at promotional dinners are so much on-label now that they may not be good sources of information about how the drug is actually used in clinical practice.

Figure 1



### Thank heavens the PDR is not a textbook

The labels for all marketed drugs in the United States are printed in the *Physician's Desk Reference*, or PDR.<sup>2</sup> This is the blueprint for drug approval and for regulating the sale of medicine. It is not, however, a textbook nor a compendium of the standard of care for the use of these drugs in clinical practice. Rather, it is merely the starting point from which

It is no wonder that when we take generalizations from clinical trials into clinical practice, the use of a drug changes and evolves to new dosing, new populations, new illnesses, and new drug combinations. This may not be good Pharma marketing policy nor good FDA regulating, but it is good medicine. For example, do we prescribe antidepressants to children with depression or atypical antipsychotics to agitated elderly dementia

On the other hand, Pharma has become increasingly sophisticated about expanding the use of psychotropics appropriately by adding them to the label over time. This is the way to go if Pharma wants to actively promote a new use, but there are certain commercial restraints to this approach, including patent life, and the size of the commercial opportunity compared to the costs of the studies necessary to win the label change. Last month, we discussed strategies

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**Table 1: New On-Label Uses Approved For Various Psychotropic Drugs**

DRUG	ORIGINAL INDICATION(S)	LATE NOVEL INDICATION(S)
Clozapine (Clozaril)	-schizophrenia (Europe)	-treatment-resistant schizophrenia -reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder
Clomipramine (Anafranil)	-major depression (Europe)	-obsessive-compulsive disorder
Fluvoxamine (Luvox)	-major depression (Europe)	-obsessive-compulsive disorder
Carbamazepine (Tegretol)	-seizures, pain associated with trigeminal neuralgia	-bipolar mania (extended-release)
d and l amphetamine salts (Adderall)	-weight loss/obesity	-attention deficit hyperactivity disorder in children and adults (extended-release)
Bupropion (Wellbutrin)	-major depression	-smoking cessation (twice daily extended-release)
Selegiline (EMSAM, Eldepryl)	-Parkinson's disease	-major depression (transdermal) (pending)
sodium oxybate (Xyrem)	-none	-narcolepsy/cataplexy (orphan drug)
Alprazolam (Xanax)	-generalized anxiety disorder	-panic disorder
SSRIs [selective serotonin reuptake inhibitors; fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), escitalopram (Lexapro)]	-major depression	-obsessive-compulsive disorder -panic disorder -social anxiety disorder -post-traumatic stress disorder -premenstrual dysphoric disorder -bulimia nervosa -bipolar depression (fluoxetine in combination with olanzapine) -pediatric depression (fluoxetine)
Venlafaxine (Effexor)	-major depression	-generalized anxiety disorder -social anxiety disorder
Duloxetine (Cymbalta)	-major depression	-neuropathic pain (diabetic peripheral neuropathy)
Divalproex (Depakote)	-seizures	-bipolar disorder; migraine
Lamotrigine (Lamictal)	-seizures	-bipolar maintenance
Modafinil (Provigil)	-narcolepsy	-obstructive sleep apnea -shift-work sleep disorder
Ropirinole (Requip)	-Parkinson's disease	-restless legs syndrome
atypical antipsychotics [risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify)]	-schizophrenia	-bipolar mania -bipolar depression (fluoxetine in combination with olanzapine)

**Table 2: Pending New Indications in Development for Approved Drugs**

DRUG	APPROVED FOR	POTENTIAL NEW INDICATIONS
Atypical antipsychotics [risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify)]	-schizophrenia -bipolar disorder	-cognitive symptoms of schizophrenia -negative symptoms of schizophrenia -major depression -treatment-resistant depression -borderline personality disorder -stimulant abuse
Guanfacine (Tenex)	-hypertension	-attention deficit disorder (extended-release)
Modafinil (Provigil)	-narcolepsy -sleep apnea -shift-work sleep disorder	-attention deficit disorder
Pregabalin (Lyrica)	-neuropathic pain	-anxiety disorders -fibromyalgia
Pramipaxole (Mirapex), dopamine agonists	-Parkinson's disease	-restless legs syndrome -bipolar depression
Eszopiclone (Lunesta)	-insomnia	-adjunctive treatment of major depression

to enhance innovations on-label with controlled-release technologies, active enantiomers, and active metabolites.<sup>3</sup> Listed in Table 1 are successful innovations that took the approach of winning new claims for new uses based upon further research, thus allowing full promotional efforts by Pharma and greater commercial rewards.<sup>4</sup> Table 2 lists similar innovations that are still in development and may lead to much expanded on-label uses for several recently approved drugs. Table 3 lists possible missed opportunities for Pharma to have developed some drugs for new indications. These agents are late in their patent lives or off patent, and can be used off-label on the basis of current rationale, data, and standards of medical practice, but it seems unlikely that Pharma will develop the necessary data for on-label use due to the lack of commercial incentives. Finally, Table 4 lists some older drugs that are off patent but that have come to be used off-label without formal label changes because of their obvious utility in clinical practice.

**The bottom line**—The well-informed practitioner of psychopharmacology should be aware of the FDA labels for drugs but should use drugs according to the standard of care, not according to the marketing of Pharma or the regulation of Pharma through the label. In fact, off-label uses of psychotropic drugs are perhaps the greater part of psychopharmacology practice, and appropriately so, when rational and based upon evidence or empiric clinical observations. ■

**Table 3: Missed Opportunities?**

DRUG	POTENTIAL CLAIM
Oxcarbazepine (Trileptal)	-bipolar disorder; neuropathic pain
Amantadine (Symadine)	-fatigue; Alzheimer's dementia
Riluzole (Rilutek)	-bipolar depression
Divalproex (Depakote)	-adjunctive treatment of schizophrenia
Modafinil (Provigil)	-attention deficit disorder (too late?)
Bupropion (Wellbutrin)	-attention deficit disorder
Lithium (Cibalith-S, Eskalith, Eskalith-CR, Lithane, Lithobid, Lithonate, Lithotabs)	-reduction of suicide -vascular/cluster headache
Mirtazapine (Remeron)	-anxiety disorders; insomnia
Zaleplon (Sonata)	-chronic insomnia treatment
Venlafaxine (Effexor)	-neuropathic pain -fibromyalgia
Lamotrigine (Lamictal)	-neuropathic pain
Clomipramine (Anafranil)	-cataplexy
Cholinesterase inhibitors donepezil (Aricept, Aricept ODT), rivistigmine (Exelon), galantamine (Razadyne, Razadyne ER)	-vascular dementia -mild cognitive impairment
atypical antipsychotics	-children -behavioral disturbances in dementia
Milnacipran (Ixel)	-major depression
Tiagabine (Gabitril)	-anxiety disorder -chronic pain
Topiramate (Topamax)	-eating disorders; alcoholism
Duloxetine (Cymbalta)	-stress urinary incontinence
Reboxetine (Edronax)	-major depression; attention deficit disorder; neuropathic pain
Citalopram (Celexa)	-anxiety disorders
Loxapine (Loxitane)	-at low doses, an atypical antipsychotic
Mazindol (Sanorex)	-stimulant abuse; geriatric depression
Amisulpride (Solian)	-schizophrenia, mania
Quetiapine (Seroquel)	-behavior disturbances in Lewy Body dementia and Parkinson's dementia; -psychosis in levodopa (Dopar, Larodopa) treatment of Parkinson's disease

**Table 4: Successful Off-Label Use Without Claims**

DRUG	POTENTIAL CLAIM
Clonazepam (Klonopin)	-panic
Trazodone (Desyrel)	-insomnia
Gabapentin (Neurontin)	-neuropathic pain -anxiety -bipolar disorder -miscellaneous psychiatric disorders
Zolpidem (Ambien)	-chronic insomnia treatment

**References**

1. Stahl SM. PsychEd Up 2005;3:6-7.
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**Contact Information**

5857 Owens Avenue, Suite 102  
Carlsbad, CA 92008  
Tel: (760) 931-8857  
Fax: (760) 931-8713  
E-mail: [psychedup@neiglobal.com](mailto:psychedup@neiglobal.com)  
URL: [www.neiglobal.com](http://www.neiglobal.com)

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