

National Council of State  
Boards of Nursing (NCSBN®)

[www.ncsbn.org](http://www.ncsbn.org)

*Advancing  
Regulatory  
Excellence  
Worldwide*



**NCSBN Practice Knowledge Network Call:  
Off-Label Drug Use  
1/10/2013**

**Margaret Leonard, MS, RN-BC, FNP**

*Sr. Vice President, Clinical Services*

*Hudson Health Plan*

**Anand Patel, RPh**

*Director, Pharmacy*

*Hudson Health Plan*

**Cathy Miller, MPH, BSN**

*Commander, U.S. Public Health Service*

*U. S. Food and Drug Administration*



*National Council of State Boards of Nursing*

# Objectives

- Background on US FDA
- What constitutes Approved Indications
- Off-Label Drug use
  1. Describe what off label use is and isn't
  2. Review how and when drugs are used off label
  3. Discuss the role of the nurse when administering drugs off label
  4. Case example: off-label use of modafinil in patients diagnosed with Steinert myotonic dystrophy syndrome
  5. Recommendations for practice



# US Food and Drug Administration

- The FDA is tasked with approving new drugs, medical devices, vaccines, and biologics
- New drugs are approved for use for specific indications and FDA approval of new indications for existing drugs requires a supplemental NDA (New Drug Application)
- FDA regulates approval, labeling, and marketing of drugs. It has no bearing on how and for what uses, physicians prescribe a drug.



# What is an Approved Indication?

- To understand off-label use, it is important to understand what an approved indication is.
- Approved Indication: The FDA defines Indication for use as a general description of the disease or condition the drug, device, or biologic will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.
- Example - Metformin: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin immediate-release tablets and solution are indicated in patients 10 years of age and older. Metformin extended-release (ER) tablets are indicated in adults.



# Off-Label Drug Use

- Definition: The use of a medication in a manner different from that approved by the FDA
- Prescribing and using medications for off-label is a legal practice and not under the scrutiny or jurisdiction of the FDA.
- However, FDA does not allow pharma to market drugs for unapproved indications. There is plenty of controversy surrounding this, and there are numerous lawsuits alleging that the FDA is infringing on a salesperson's right to free speech under the First Amendment.



# Types of off-label use

The two major types of off-label use are:

- a) Use of drugs for unapproved clinical indications (ex. Avastin use for age related macular degeneration or various macular edema).
- b) It can also constitute use in unapproved patient populations(ex. Quetiapine use in children under 10).



# When are medications used Off-Label?

The following are situations that call for off-label use:

- a) Disease state that affects a very small population for which there are limited treatment options.
- b) Off-label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions (the use of the antiasthmatic montelukast [Singulair] for chronic obstructive pulmonary disease).<sup>1</sup>
- c) Expansion to distinct conditions sharing a physiological link (the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome), or extension to conditions whose symptoms overlap with those of an approved indication.<sup>1</sup>
- d) Selection of similar pharmacologic agents for unapproved use when it is more cost-effective (use of Avastin instead of Lucentis for AMD or macular edema - \$50 vs. \$2000 per dose).



# At what point in Tx to consider Off-Label use?

1. Guideline-recommended practice (aspirin in diabetes for prophylaxis against cardiovascular disease) as adjunct therapy<sup>1</sup>
2. Last-resort therapy (tacrolimus [Prograf] for autoimmune diseases, in addition to transplantation) <sup>1</sup>
3. First-line therapy (gabapentin [Neurontin] for painful diabetic neuropathy, in addition to its use in herpes zoster) <sup>1</sup>





# Prevalence of Off-Label use

- A 2003 report showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.<sup>1</sup>
- The highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%).<sup>1</sup>



# Is Off-Label drug use safe?

It depends on who you ask:

1. Providers will suggest that there are no studies suggesting that said drug is not safe when being used for unapproved indications.
2. The FDA would refer you to the drug approval process and urge that the said drug has only been proven safe and effective for the approved indication.



# Safety considerations

Caveats to consider for off-label use:

- Off-label uses have not been formally evaluated, and evidence provided for one clinical situation may not apply to others.<sup>1</sup>
- Regardless of the use, contraindications, warnings/black box, dosing modifications for renal impairment or liver disease, and drug interactions still apply and should be considered before use.
- Side effects/Adverse events should be reported via Medwatch.

<http://www.fda.gov/Safety/MedWatch/default.htm>



# Off-Label Use References

- Treatment guidelines published by various medical organizations
- Well designed high quality published clinical trials
- US Drug Compendia references that recognize clinically accepted off-label uses:

1) Pharmacology Online

<http://www.clinicalpharmacology.com/>

2) Micromedex 2.0 (Iphone/Ipad and Android apps are free)

<http://www.thomsonhc.com>

3) NCCN Drugs and Biologics Compendium

[http://www.nccn.org/professionals/drug\\_compendium](http://www.nccn.org/professionals/drug_compendium)



# Modafinil: An example of off label use

- Modafinil is an analeptic drug FDA approved for treatment of narcolepsy, obstructive sleep apnea, and shift-work disorder.
- Off-Label uses include treatment of ADHD, medication related somnolence, sleep deprivation, and Steinert myotonic dystrophy syndrome.
- Patients diagnosed with ADHD have several FDA approved safe and effective treatment options and use of modafinil would not provide any other safety or efficacy benefit over FDA approved Tx options.
- There is an opportunity for dosage adjustment, dosing time adjustment, or medication selection opportunities to alleviate medication related somnolence.

# Modafanil: An example of off label use

- Sleep deprivation needs to be managed and treated as opposed to using modafinil to treat residual effects associated with sleep deprivation.
- Steinert myotonic dystrophy syndrome (MMD1) is a form of muscular dystrophy that affects muscles and many other organs in the body. The most common type of myotonic muscular dystrophy, MMD1 is characterized by muscle weakness and myotonia, an inability to relax the muscles at will.<sup>2</sup>
- Daytime drowsiness is often associated with the subset of MMD1 diagnosed patients experiencing weakness with muscles integral to breathing and swallowing.



# Modafinil: An example of off label use

- As yet, there's no specific treatment that "gets at the root" of myotonic muscular dystrophy (MMD). Treatment is aimed at managing symptoms and minimizing disability.<sup>2</sup> Treating daytime drowsiness or fatigue with modafinil would be an acceptable off-label use for MMD diagnosed patients.
- Serious side effects to consider would be hypertension, hypersensitivity reactions, and mania.
- Other warnings include angioedema, increased risk of cardiac events, mitral valve prolapse with CNS stimulant use, and psychiatric adverse effects



# Practice Consideration

- Availability of drug references to identify clinically accepted off-label use
- Electronic Prescription Order Entry Systems: Many systems capture diagnoses specific to medications being ordered, and if configured, this can be used to identify off-label use.
- Electronic Health Records: Depending on the configuration, an EHR system may or may not capture off-label use.
- Any consideration for implementing systems to capture off-label drug use must consider an integrated approach where E-Rx and EHR systems both capture off-label drug use with a bilateral flow of off-label use data





# Practice Consideration

- Manual workarounds in lieu of systems capabilities include:
  - Prescription orders, dosing charts, medication labels, and other dosage administration documents include 'off-label use'. Example:

Off-Label Use:    Yes    No

Medication Related Dx: \_\_\_\_\_

- Maintain an electronic list of all medications and the specific off-label use commonly ordered at the practice setting. Example:

Drug Name	Off-Label use	Compendium Supported
Metformin	Polycystic ovary syndrome	Micromedex 2.0



## References:

1. Regulating Off-Label Drug Use – Rethinking the Role of the FDA,  
RS Stafford, NEJM 2008;358: 1427-1429
2. <http://mda.org/disease/myotonic-muscular-dystrophy/medical-management>



# Drug Information Resources

- **Drugs@FDA Database**: provides information on FDA approved drug products including proprietary name, active ingredient, approval date, manufacturer name, drug label (PI), Medication Guide (if applicable), and other information on the history of the drug such as labeling changes that have occurred over the life cycle of the drug. The website link is: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
- **FDA MedWatch (Home Page)**: This is the main homepage which provides links to recent Safety alerts for drugs, devices and other related products, information on subscribing to receive regular FDA MedWatch safety alert information, information on safety labeling changes for approved products and links to reporting adverse events. The MedWatch Home Page link is: <http://www.fda.gov/Safety/MedWatch/default.htm>
- **FDA MedWatch Reporting Website link (Reporting Serious Problems to the FDA)**: Provides a link for consumers, patients and healthcare professionals, to complete a MedWatch Report and submit the report to the FDA. The link is: <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>

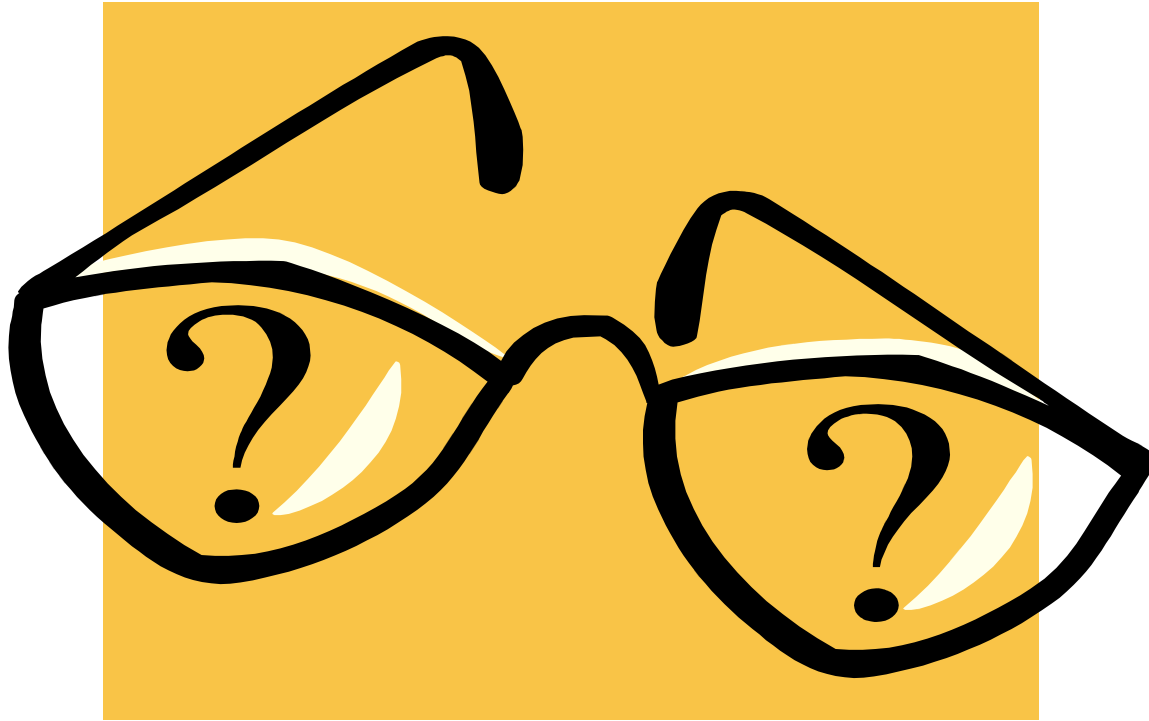
# Drug Information Resources

- **FDA MedWatch Safety Alerts (By Year):** Provides a listing of all published MedWatch safety alerts by year for drug products, devices and nutritional and cosmetic products, and undeclared ingredient safety information. The link is: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm>
- **FDA Drug Safety Labeling Changes (By Month):** Provides a listing and summary of all FDA approved products that have had safety labeling changes to the Boxed Warning, Adverse Reactions, Contraindications, Warnings and Precautions and Medication Guides section of the product label (monthly). The link is: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm>
- **FDA Safety Alerts – Subscribe to receive alerts:** When you subscribe to received MedWatch Safety Alerts, you will receive an email when a MedWatch Alert is published on a product. These alerts include new safety information, recalls, or other safety related information on FDA regulated products. The link to subscribe to MedWatch Alerts is: <http://www.fda.gov/Safety/MedWatch/ucm228488.htm>

# Drug Information Resources

- **Patient Network News newsletter:** Subscribe to receive twice monthly newsletters containing FDA-related information on a variety of topics, including new product approvals, significant labeling changes, safety warnings and more. Subscribe at:  
[https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic\\_id=USFDA\\_203](https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_203)
- **Health Professionals Updates newsletter:** Subscribe to receive the twice monthly newsletter on recent announcements, medical product approvals, opportunities to comment on proposed rules, upcoming public meetings/advisory committee meetings and other information of interest to health professionals. Subscribe at:  
[https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic\\_id=USFDA\\_59](https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_59)
- **FDA Office of Special Health Issues ‘For Health Professionals’ webpage:** Information of interest to healthcare professionals including new approvals, safety information, expert commentaries and FDA-Medscape collaborations on FDA-related issues. The link to the ‘For Health Professionals’ page is: <http://www.fda.gov/ForHealthProfessionals/default.htm>

# Questions?



# Contact Information

- Peggy Leonard  
mleonard@hudsonhealthplan.org
- Anand Patel  
apatel@hudsonhealthplan.org
- Cathy Miller  
cathy.miller1@fda.hhs.gov