



An analysis of the high psychotropic off-label use in psychiatric disorders The majority of psychiatric diagnoses have no approved drug

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ABSTRACT

Objective: The authors' goals were to determine the extent of unapproved indications in the DSM-IV-TR, to highlight common off-label uses of psychotropic medications and offer insights into the rationale of the widespread off-label prescribing in psychiatry.

Method: Indications for approved psychotropic agents, obtained from the Physicians Desk Reference and the Drug Information Handbook, Clinical Handbook of Psychotropic Drugs, 15th edition, and the Drugs@FDA online database were analyzed in the context of the DSM-IV-TR to determine the percent of DSM-IV-TR disorders that are indications for psychotropic agents. A literature search was performed to determine common off-label uses of major classes of psychotropic medications.

Results: 88.5% of all DSM-IV-TR categorized disorders lack an approved medication for their treatment. Atypical Antipsychotics had the most extensive off-label use for DSM-IV-TR categorized disorder, whereas Mood Stabilizers showed the greatest off-label use with regards to disorders and symptoms that are not DSM-IV classified. For each class of medications, more off-label uses exist than FDA-approved uses.

Conclusions: The vast majority of DSM-IV-TR categorized disorders lack approved medications for their treatment. The large unmet need for approved psychiatric indications may explain the widespread off-label use of psychotropic medications in clinical practice.

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1. Introduction

The role of prescribing medications off-label has become a widespread practice amongst physicians in the United States. Depending on the clinical setting, up to 60% of prescriptions may be written for purposes extending beyond the FDA approved label (Kramer and McCall, 2006). When considering the major pharmaceutical classes of medications, however, psychotropic medications are among the most widely prescribed for off-label purposes. A survey of office-based physicians shows that 31% of all antidepressants, anticonvulsants and antipsychotic medications prescribed were done so off-label (Radley et al., 2006).

While general practitioners report a high prevalence of off-label prescriptions for psychotropic medications, such practice has been especially prevalent amongst psychiatrists as well. A survey of 200 psychiatrists shows that 65% claimed to have prescribed psychotropic medications off-label in the previous month (Kramer and

McCall, 2006). Furthermore, a study of prescriptions in an inpatient psychiatric setting reports that 46.4% of all patients were receiving off-label prescriptions (Haw and Stubbs, 2005). Overall, recent studies show that 40–80% of recipients of commonly prescribed psychotropic medications including second generation antidepressants, anticonvulsants, and antipsychotic are receiving these medications for off-label purposes (Chen et al., 2006). While highly prevalent, the practice of prescribing medications off-label has become a controversial issue with implications extending into the economic, legal and ethical realms.

Prescribing medications off-label has a significant economic impact. For example, it has been noted that the off-label use of Central Nervous System (CNS) drugs can range from 25% to more than 80% of a drug's annual sales (Blazinski, 2002). Specifically, antidepressants, anticonvulsants, and antipsychotics, the three most commonly prescribed CNS drug categories, increased 40% in annual sales in the U.S. market from 2000 to 2002 (Chawla et al., 2004) with off-label indications for these three drug categories expanding each year.

While such an economic impact is felt within the pharmaceutical industry, insurance companies and ultimately patients are also affected. In the United States, drug costs are increasing

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annually at a rate of 13%, with a 20% annual increase in psychotropic medications contributing to the overall effect (Chen et al., 2006). As a means to control rising costs of prescription medication, insurance companies may deny coverage to certain individuals with off-label prescriptions. Some states, however, require insurers to cover all off-label prescriptions of FDA approved medications.

Although the off-label prescription of medications is not illegal, it is not without consequences. It is within the FDA's stance to regulate drug approval and safety; however, it claims no authority over physician prescribing practices. Although this is the case, malpractice and liability issues may arise when prescribing medications for indications not formally approved.

Ethical guidelines also play a role in prescribing off-label. Professional ethics require physicians to always consider the most-effective and safest treatments. However, the efficacy and safety of off-label treatments are only established for the approved indications, and not for the unapproved ones. As such, questions regarding the ethics of such treatments may be raised.

Although it is common knowledge in the psychiatric community that the use of medications off-label is highly prevalent, to the authors' knowledge, this practice pattern has yet to be portrayed in relation to the DSM-IV-TR. The goal of this study is to highlight psychiatric disorders with FDA approved medications in the context of the DSM-IV and review common off-label uses of the major classes of psychotropic medications. Our analysis is intended to provide psychiatric researchers and clinicians an overview of the current state of psychiatric pharmacotherapy and to provide further insight into the rationale and drivers behind off-label prescription patterns in psychiatry at this time.

2. Method

Using Psychotropic Drug Information Handbook, Clinical Handbook of Psychotropic Drugs 15th edition (Fuller and Sajatovic, 2005), and the Psychotropic Dosing and Monitoring Guidelines (Schatzberg and DeBattista, 2004), the generic names of all psychotropic drugs currently available in the United States were obtained. FDA approved labels with drug indications were obtained using the FDA drug database, Drugs@FDA.gov (www.fda.gov) along with the Physicians Desk Reference Online (www.pdr.net). All psychotropic medications were categorized to fit in the context of a specific DSM-IV category. While most

current psychotropic medications (DSM-IV era) are already indicated according to a DSM-IV disorder, many older drugs are lacking a specific DSM-IV categorized indication. The drugs lacking specific indications were categorized as deemed suitable by a practicing psychiatrist. Appropriate numerical statistics were conducted using Microsoft Excel.

In order to determine common off-label uses of general classes of psychotropic medications various MEDLINE searches were conducted. Key words and phrases included the class of interest followed by each of the following in separate attempts: "off-label, new indication, potential use, therapeutic use, novel-use, population, new-population." Both original reports including controlled studies and case reports along with review papers were analyzed for mentions of off-label use.

3. Results

Of 313 specific disorders in the DSM-IV TR, only 36 (11.8%) have FDA approved psychotropic medications specifically indicated for those disorders. The ten categories of disorders that have at least one indicated medication include the following: Disorders Diagnosed in Infancy, Childhood and Adolescence; Delirium, Dementia and Amnestic and Cognitive Disorders; Schizophrenia and Psychotic Disorders; Mood Disorders; Substance-Related Disorders; Eating Disorders; Sleep Disorders; Anxiety Disorders; Sexual and Gender Identity Disorders; and Other Conditions That May Be a Focus of Clinical Attention. The remaining seven categories lacking any FDA approved psychotropic medications for their respective disorders include: Somatoform Disorders, Factitious Disorders, Personality Disorders, Dissociative Disorders, Adjustment Disorders, Impulse Control Disorders, and Mental Disorders Due to a Medical Condition Not Elsewhere Classified. Anxiety Disorders have the highest percentage of disorders with FDA approved medications at 41.7% (see Table 1 for further numerical analysis).

Our research into common off-label uses of Atypical Anti-psychotics, Antidepressants/Anxiolytics, Mood Stabilizers, Benzodiazepine and Stimulants revealed a broad utility amongst these five classes of medications for uses outside of their approved indications. Atypical Antipsychotics have been used off-label to treat various other DSM-IV categorized disorders more so than the other four classes of medications studied. Mood Stabilizers, on the other hand, have the greatest use amongst the five classes with

Table 1
An analysis of DSM-IV-TR diagnostic categories with and without approved medications.

| Disorder type | No. of subcategories | No. subcategories with approved medications | % with approved indication |
|---|----------------------|---|----------------------------|
| Disorders diagnosed in childhood, infancy or adolescence | 39 | 4 | 10.3 |
| Delirium, dementia and amnestic and cognitive disorders | 12 | 2 | 16.7 |
| Mental disorders due to general medication condition not elsewhere classified | 3 | 0 | 0 |
| Substance related disorders | 112 | 10 | 8.9 |
| Schizophrenia and other psychotic disorders | 9 | 1 | 11.1 |
| Mood disorders | 10 | 3 | 30.0 |
| Anxiety disorders | 12 | 5 | 41.7 |
| Somatoform disorders | 7 | 0 | 0 |
| Factitious disorders | 2 | 0 | 0 |
| Dissociative disorders | 5 | 0 | 0 |
| Sexual and gender identity disorders | 30 | 1 | 3.3 |
| Eating disorders | 3 | 1 | 33.3 |
| Sleep disorders | 14 | 3 | 21.4 |
| Adjustment disorders | 1 | 0 | 0 |
| Personality disorders | 11 | 0 | 0 |
| Impulse control disorders | 6 | 0 | 0 |
| Other conditions that may be a focus of clinical attention | 37 | 7 | 0 |
| Total | 313 | 37 | 11.8 |

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