Executive Summary

Pharmacotherapeutic decisions in psychiatric care should be made with a careful assessment of numerous factors, including comorbidity and polypharmacy. Although the use of multiple medications to treat multiple disease states is not independently problematic, polypharmacy has been shown to result in unnecessary and/or inappropriate medication prescribing, increasing the risk for medication interactions and adverse reactions. Another factor that must be considered when making pharmacotherapeutic decisions is whether the U.S. Food and Drug Administration (FDA) has approved a medication for a specific indication. Although off-label drug use is legal and can be beneficial for some patients, most off-label uses have little or no scientific support. Insurance companies and the government now scrutinize off-label uses much more closely, and do not cover most off-label prescriptions unless the uses meet specific plan language for standard of care or evidence-based medicine.

An independent review organization (IRO) can provide ready access to specialists, which healthcare plans may lack internally, allowing for timely determination of whether the requested medications fall under medical necessity guidelines. Independent medical reviews provide unbiased evaluation of medical need for psychiatric medications, thereby facilitating the individualization and optimization of patient care.

Introduction

Polypharmacy and off-label prescribing of medication are fairly common in psychiatric practice. Unfortunately, these prescribing practices often lack solid scientific evidence on efficacy and safety, and they can increase risk for poor patient outcomes. While evidence for the added benefit of polypharmacy with psychiatric medications remains limited, there is growing evidence that some medication combinations are unnecessary and produce increased adverse events. In addition, off-label prescribing may produce more pronounced side effects or adverse events. Although all medications carry some risk of side effects or adverse events, off-label prescribing increases the risk for unforeseen consequences.

Since limited data exist to support the efficacy of some of the most common medication combinations and off-label medication uses, further research is needed to properly assess the efficacy and safety of these uses. Obtaining an accurate medication and medical history and linking each prescribed medication to a disease state are critical components to reduce inappropriate or unnecessary prescribing. Medications that are treating side effects should also be identified, as discontinuing one drug that is causing a side effect can lead to the discontinuation of several drugs.

Provigil (Modafinil)

FDA-Approved Indications

Modafinil is a wake-promoting quasi-stimulant that is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder. In patients with obstruc-
Modafinil has a low likelihood for abuse in individuals who do not abuse drugs. However, there is debate surrounding its potential for abuse—modafinil has been shown to increase dopamine levels in the brain, which is associated with the potential for abuse. Modafinil has also been shown to produce psychoactive and euphoric effects that are typically associated with central nervous system (CNS) stimulant drugs such as Ritalin (methylphenidate), which is a commonly abused medication.

**Polypharmacy and Contraindications**
Modafinil may be combined with antidepressants (clomipramine, protriptyline) for patients suffering from narcolepsy with cataplexy. Patients who have a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia, or other clinically significant manifestations of mitral valve prolapse associated with the use of CNS stimulants should not take modafinil. In addition, modafinil should not be used in patients with a history of severe mental illness.

**Buprenorphine Formulations: Buprenex or Subutex (Buprenorphine HCL) and Suboxone (Buprenorphine HCL and Naloxone HCL)**

**FDA-Approved Indications**
Buprenex is an injectable formulation of buprenorphine, which is a partial opioid agonist, indicated for the relief of moderate to severe pain. Subutex and Suboxone are medications approved for the treatment of opiate dependence. Both medications contain the active ingredient, buprenorphine hydrochloride (HCl). Subutex contains only buprenorphine HCl, while Suboxone also contains naloxone, which was added to discourage the intravenous misuse of buprenorphine. Subutex is intended for detoxification and is given during the first few days of treatment, and Suboxone is used during the maintenance phase of treatment.

Buprenorphine is a controlled substance that can easily be abused. In 2002, the U.S. Drug Enforcement Administration (DEA) classified buprenorphine and any products containing buprenorphine as Schedule III drugs, which are illegal to sell without a license and illegal to possess without a valid license or prescription.

**Off-Label Uses and Potential for Abuse**
Before Suboxone and Subutex were approved for the treatment of opioid addiction in 2002, clinicians may have prescribed Buprenex off-label for opioid dependence. The FDA now recommends that Buprenex not be used to treat opioid addiction and that the drug not be administered to those living with or recovering from addiction. Buprenex is more likely to be diverted and abused because it is administered by injection, rather than taken sublingually (Suboxone and Subutex). Use of Buprenex by an individual addicted to narcotics can result in withdrawal symptoms.
Suboxone and Subutex are sometimes used off-label for the treatment of depression or pain. Currently, study data do not support the use of these buprenorphine formulations for either condition. The FDA does not recommend the use of Suboxone or Subutex for pain, especially for opioid-naïve patients.

All buprenorphine formulations have the potential for abuse and produce dependence of the opioid type. They are, however, associated with lower risk for overdose compared with short-acting opioids such as hydrocodone.

**Polypharmacy and Contraindications**

Many patients with addiction disorders also have some type of mental health disorder, which require polypharmacy. Buprenorphine formulations should not be combined with CNS antidepressants, benzodiazepines, and other opioids. The synergistic effects of these combinations could lead to overdose.

**Vivitrol (Naltrexone XR Inj) (Monthly Injection)**

**FDA-Approved Indications**

Vivitrol, which is an opioid-receptor antagonist administered by intramuscular injection once per month, is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol (patients should not be actively drinking at the time of initial Vivitrol administration). Vivitrol is also indicated for the prevention of relapse to opioid dependence, following opioid detoxification. Vivitrol should be part of a comprehensive program that includes psychosocial support.

**Off-Label Uses and Potential for Abuse**

Low dose naltrexone (LDN) has been studied for the treatment of pain in a wide range of diseases, including HIV/AIDS, multiple sclerosis, Parkinson’s disease, and certain cancers. However, the trials have largely been pilot studies, which are useful in directing future research but do not provide scientific evidence to justify clinical use. Larger, more rigorous studies are needed to thoroughly assess the effects and safety of LDN for treating pain.

Unlike other anti-addiction medications such as methadone and buprenorphine, Vivitrol is not an opioid and does not have addictive properties.

**Polypharmacy and Contraindications**

Although concurrent opioid and alcohol dependence is common, **Vivitrol should not be taken in combination with buprenorphine.** In addition, Vivitrol should not be used for patients receiving opioid analgesics, patients with current physiologic opioid dependence, and patients in acute opioid withdrawal.

**The Role of Independent Medical Review in Addressing Increasing Issues of Polypharmacy and Off-Label Drug Use in Psychiatric Care**

An independent medical review, which is normally used by healthcare payers, looks at whether or not a specific therapy or procedure was medically necessary. Effective psychiatric care requires an in-depth understanding of developments in psychopharmacology so that disease management can be individualized for each patient. The specialty match that an IRO provides is especially important in psychiatric care due to the high rates of polypharmacy and off-label medication use, which often result from comorbid mental and substance use disorders and physical health problems. The board-certified physician specialists who work with IROs keep up-to-date with the latest medical research literature and...
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with the latest standard of care, staying on top of continually evolving therapies as they are studied more extensively and potentially accepted into clinical guidelines.

Conclusions

Polypharmacy often has a negative connotation, with the implication of inappropriate or irrational use of multiple medications. The use of multiple medications increases the risk for medication-related adverse events, and it often creates the need for additional medication. The use of multiple medications, however, can sometimes be an effective clinical intervention, depending on the medications used and the characteristics of the individual patient. Similarly, off-label uses of medications, although legal and beneficial for some patients, often have little or no scientific support.

By providing unbiased evaluation of medical need for medications in psychiatric care, external independent medical review facilitates effective psychiatric care, which is often complicated by comorbid conditions and polypharmacy. Independent medical review also provides ready access to specialists, which healthcare plans may lack internally, allowing for timely determination of whether the requested treatment falls under medical necessity guidelines and the latest standard of care.

Sources


