

Details

Pharmacy Report



San Francisco
Health Network



BHS Medication-Use Resources and Initiatives

New Sedative-Hypnotic Guidelines Approved by MUIC

The Behavioral Health Services Medication Use Improvement Committee has updated the Safer Prescribing of Sedative-Hypnotics Guideline (available at the link below). This guideline acknowledges the significant risks for misuse, abuse, diversion and adverse effects of these agents. Organizationally, we have made significant efforts to reduce prescribing of these agents whenever possible.

The previous sedative-hypnotic guideline was developed and distributed in 2014. At that time, approximately 15% of the BHS population over 18 was prescribed a sedative-hypnotic. High risk populations of patients also prescribed methadone maintenance and older adults were also evaluated. Over a two year period, prescribing of sedative-hypnotics declined in all populations.

MUIC continues to monitor sedative-hypnotic use in BHS, and prescribing of benzodiazepines has remained fairly steady over the last two years, particularly in the older adult population. MUIC identified older adults as a population in need of further deprescribing due to the higher prescribing rate and greater risk for harm in this population.

Percent of Population with Chronic Prescription for Sedative-Hypnotic

Population	Oct 2013	Mar 2015
>18 years old	15.89%	12.21%
Older Adults (> 60 years old)	15.83%	13.27%
On methadone maintenance	26.37%	16.49%

Medication updates to the guideline include:

- Updated risk assessment for new and ongoing sedative-hypnotic prescriptions
- Considerations in special populations such as older adults, pediatrics, pregnancy and lactation
- Dose adjustments in renal/hepatic impairment
- Information about Suvorexant
- Alternative/Herbal treatments for insomnia and anxiety disorders

In addition to medication information about sedative-hypnotics, the guideline contains links to support materials for reducing or avoiding sedative-hypnotics for insomnia. Tools include:

- Sleep diaries and educational handouts
- Information on CBT for Insomnia
- Information on sleep clinic referral

1. Safer Prescribing of Sedative-Hypnotics Guide
<https://www.sfdph.org/dph/files/CBHSdocs/Sedative-Hypnotic-Guideline.pdf>

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New Drugs and Dose Forms

New Modified-PK Dose Form for Long-Acting Aripiprazole

Aripiprazole Lauroxil ER (Aristada Initio®) was approved by the FDA on 6/29/18. This dose form is a modified-PK-profile form of aripiprazole lauroxil ER (Aristada) that enters the systemic circulation much more quickly. It is intended to be given as a bridge to aripiprazole lauroxil ER from oral aripiprazole therapy or to be used to return to long-acting aripiprazole lauroxil after missed doses.

Aripiprazole Lauroxil ER is not to be used in aripiprazole-naïve patients due to concerns regarding tolerability. This new dose form prevents the need for oral bridging to ongoing aripiprazole lauroxil long-acting injections. Tolerability of aripiprazole should be established with oral dosing for at least two weeks before using the long-acting injectable formulation. A single injection of Aristada Initio 675 mg should then be given along with a single oral dose of aripiprazole 30 mg. This first dose of ongoing Aripiprazole lauroxil monthly injections may be given on the same day as the Aristada Initio dose or up to 10 days later. Giving these three different dose forms together resulted in aripiprazole concentrations equivalent to Aripiprazole lauroxil ER given with 21 days of oral aripiprazole overlap. Concentrations reach relevant levels within 4 days of this combined dosing.

Aristada Initio may also be used to supplement after missed doses of Aristada if too much time has elapsed since the last dose. For details of when to administer Aristada Initio in this situation, refer to LexiComp or the manufacturer's labeling.

Aristada Initio is **not** interchangeable with Aristada and should not be used for repeat dosing. Unfortunately, with such similar names (the generic names are exactly the same), the risk for mixing these products up is high.

1. Aristada Initio PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209830lbl.pdf accessed 8/7/18.

Non-Opioid Treatment for Management of Opioid Withdrawal Symptoms

On May 16, 2018, the FDA approved **Lofexidine** (brand name **Lucemyra®**) for mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids in adults. Lofexidine is an oral, selective alpha-2 receptor agonist that reduces the release of norepinephrine. It was shown safe and effective in reducing withdrawal symptoms in two large trials, measured using an objective patient-reporting scoring instrument.

Lofexidine is dosed 0.54 mg tablet four times a day during peak withdrawal symptoms; it may be increased to 0.72 mg per dose (up to 2.88 mg per day) and continued up to 14 days. It should be tapered down as withdrawal symptoms wane. Dose reduction is indicated for mild to severe renal or hepatic impairment. Common adverse effects include orthostatic hypotension, bradycardia, hypotension, insomnia, dizziness, sedation and dry mouth. There is a risk of rebound hypertension if the drug is stopped abruptly.

This drug was given fast-track status for approval by the FDA. "As part of our commitment to support patients struggling with addiction, we're dedicated to encouraging innovative approaches to help mitigate the physiological challenges presented when patients discontinue opioids," said FDA Commissioner Scott Gottlieb, M.D.

Although this new approval does add to our armamentarium of treatments for opioid withdrawal symptoms, it does not really offer a novel approach. Clonidine, an agent with similar pharmacology and adverse effects, has been used for years to treat symptoms associated with opioid withdrawal. It remains to be seen how this new agent will offer any true advantages over current treatments.

1. Lucemyra PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209229s000lbl.pdf accessed 7/26/18.
2. FDA approved the first non-opioid treatment for management of opioid withdrawal symptoms in adults. FDA press release. May 16, 2018. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm> accessed 7/26/18.

Cannabis Product to Treat Rare Forms of Epilepsy

Cannabidiol (brand name **Epidiolex**[®]) oral solution was approved by the FDA on 6/25/2018 for treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older. Cannabidiol, a pure cannabinoid derived from the *Cannabis sativa L* plant (aka marijuana), does not appear to have the psychoactive effects seen from tetrahydrocannabinol (THC), the other cannabinoid in marijuana. Other commercial products such as Dronabinol and Nabilone contain synthetic versions of THC. The precise mechanism of action of Cannabidiol in its anticonvulsant effects remains unknown, but it does not appear to produce this effect through interaction with cannabinoid receptors.

Cannabidiol dosing starts at 2.5 mg/kg/day and can be titrated up to a maximum dose of 20 mg/kg/day. Somnolence and sedation were reported commonly in clinical trials (approximately 3X more commonly with active treatment than placebo); these effects were dose-related. Cannabidiol is metabolized by and an inhibitor of CYP450 enzymes 3A4 and 2C19, and as such, can interact with many other medications.

Cannabidiol is currently classified by the DEA as a Schedule I controlled substance, but this classification is under review. This product will not be available commercially until its scheduling is changed.

1. Epidiolex PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf accessed 8/4/18.

Substance Use Disorders and Treatment

CDC Warns About Risk in Overdose Deaths Linked to Fentanyl Analogs

Fentanyl and fentanyl analogs are increasingly involved in opioid overdose deaths, and new analogs continue to be identified. Carfentanil, the most potent analog found in the U.S., is intended for sedation of large animals, and is estimated to have 10,000 times the potency of morphine.

From July 2016-June 2017, according to data analyzed from the CDC's tracking system, fentanyl analogs were detected in approximately 20% of opioid overdose deaths, with over 11% testing positive for carfentanil. The proportion of deaths with fentanyl analogs present nearly doubled during the time period analyzed.

The CDC recommends raising public awareness of the highly variable content of fentanyl present in illicit opioids and the potential lethality of this drug. They also recommend expanding the availability of naloxone and facilitating access to Medication-Assisted Treatment for opioid use disorder. Overdoses with these highly potent fentanyl analogs may require multiple doses and prolonged administration of naloxone to reverse the effects.

1. Morbidity and Mortality Weekly Report, July 13, 2018. <https://www.cdc.gov/mmwr/volumes/67/wr/mm6727a4.htm>
2. CDC Health Alert Network, July 11, 2018. <https://emergency.cdc.gov/han/han00413.asp>

Medication Assisted Therapy After Nonfatal Opioid Overdose Reduces Mortality

The good news is that people who survive an opioid overdose and receive medication treatment for their opioid use disorder (MOUD) are less likely to die in the following year. According to a study published in the Annals of Internal Medicine in June, in a cohort of over 17,000 people who had a nonfatal opioid overdose between 2012 and 2014 in Massachusetts, all-cause mortality at 12 months was 4.7 deaths per 100 person-years. Less than a third of participants received MOUD in the 12 months following a non-fatal overdose, but for those who received treatment with buprenorphine/naloxone or methadone, all-cause and opioid-related mortality were lower than for those who did not receive treatment.

1. Laroche MR, Bernson D, et al. Medication for Opioid Use Disorder after Nonfatal Opioid Overdose and Association with Mortality. *Ann Int Med* 2018; 169: 137-145.

Psychiatric Medications

New Treatments for Tardive Dyskinesia Not Cost Effective

Tardive Dyskinesia (TD) has been a challenge since the introduction of antipsychotics in the 1950s. Rates of TD are 5% per year for conventional antipsychotics and 3% per year with atypicals. Discontinuing antipsychotics may not reverse, and may temporarily exacerbate TD symptoms. After decades with little guidance or effective treatment, the first two agents with FDA-approval to treat TD, **valbenazine (Ingrezza®)** and **deutetrabenazine (Austedo®)** were introduced in 2017.

The Institute for Clinical and Economic Review (ICER) recently published an analysis of the clinical effectiveness, cost effectiveness and potential budget impact for these agents, known as Vesicular Monoamine Transporter 2 (VAMT2) Inhibitors. Both agents have been shown to produce significantly greater improvement in AIMS scores relative to placebo. Approximately a third of patients receiving either agent in these studies achieved a $\geq 50\%$ reduction in AIMS scores (defined as “responders”).

Despite demonstrated clinical effectiveness in short-term trials, with average wholesale prices ranging from \$4,150/mo-\$12,500/mo (\$50,000-\$150,000/yr) and the potential need for lifetime treatment, the analysis suggests that the cost of these agents far outweighs their benefits. Incremental cost effectiveness ratios over a lifetime horizon were \sim \$752,000 and \$1.101 million per Quality-Adjusted Life Year (QALY) for valbenazine and deutetrabenazine respectively. This far exceeds the generally accepted ratio of \$150,000 per QALY. Moreover, ICER estimates a potential 5-year budget impact of over \$22 billion for these agents.

Adverse effects of these agents include drowsiness, fatigue, headache and akathisia. Both agents are only available through limited distribution networks, requiring registration with the distribution program. The introduction of treatments for TD raised hopes for addressing a long-standing challenge in psychiatry. However, with limited availability, high cost and modest benefits, it is unlikely we will see these two agents in widespread use any time soon.

1. Atlas SJ, Agboola F, Curfman G. Effectiveness and value to 2 novel treatments for tardive dyskinesia. *JAMA Int Med* 2018; 178: 1110-1112.



Crossroads between Psychiatry and Medicine

Antidepressant Treatment Improves Cardiac Outcomes in ACS

Depression has been associated with poorer outcomes after acute coronary syndromes (ACS). In a recently published clinical trial, 300 patients with ACS and depression (screened by Beck Depression Inventory and diagnosed based on psychiatric interview) were randomized to receive escitalopram in flexible doses or matched placebo for 24 weeks. Over 8 years of follow up, 40% of patients who received escitalopram and 54% of patients receiving placebo experienced major adverse cardiac events (MACE, a composite of all-cause mortality, MI and percutaneous coronary intervention), resulting in a Hazard Ratio of 0.69 ($p=0.03$). These results are somewhat in contrast to other studies of the impact of antidepressants on MACE (SADHART,² MIND-IT³), which found no difference between groups receiving antidepressant vs. placebo. Further research is needed to assess the generalizability of the findings of this new study.

1. Kim J-M, Stewart R, et al. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in patients with Acute Coronary Syndrome. *JAMA* 2018; 320: 350-357.
2. Van Melle JP, de Jonge P, Honig A, et al; MIND-IT Investigators. Effects of antidepressant treatment following MI. *Br J Psychiatry* 2007; 190: 460-466.
3. Glassman AH, Bigger JT Jr, Gaffney M. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow up of SADHART participants. *Arch Gen Psychiatry* 2009; 66: 1022-1029.

Cumulative Incidence of Hypertension Much Higher in Blacks than Whites

A longitudinal study assessing the incident risk for hypertension in blacks and whites from ages 18-55 was published in the Journal of the American Heart Association. Nearly 4000 participants aged 18-30 without hypertension at baseline were followed to the age of 55 and assessed for hypertension (defined according to the 2017 American College of Cardiology/American Heart Association blood pressure definition of SBP≥130, DBP≥80 or self-reported use of antihypertensive medication). By age 55, cumulative incidence of hypertension was approximately 75% in black men and women, significantly higher than the 54% seen in white men and 40% seen in white women.

After full multivariate adjustment, blacks had a 1.5 to 2 times higher risk for hypertension compared with whites in any baseline BP category. Further, blacks were more likely to develop hypertension at a younger age, with 20% of black women and 30% of black men developing hypertension by the age of 35.

In this study, a higher DASH diet adherence score and lower BMI were associated with lower risk for developing hypertension in both blacks and whites. In a previous study (the Jackson Heart Study³), authors found a strong effect of concordance with the American Heart Association's Life's Simple 7 (LS7: nutrition, physical activity, cigarette smoking, body mass index, BP, cholesterol and glucose) and incident hypertension in blacks. Authors and editorialists recommend focusing on these modifiable risk factors to reduce the risk for hypertension in Black/African-Americans.

In light of added risks for metabolic complications of atypical antipsychotics in the behavioral health client population, focused efforts to ensure we support our Black/African-American clients in healthy lifestyle choices are essential. See references below for information about the AHA LS7 and the DASH diet.

1. Thomas SJ, Booth III JN, Dai C, et al. Cumulative incidence of hypertension by 55 years of age in blacks and whites: the CARDIA study. J Am Heart Assoc 2018; 7. doi: 10.1161/JAHA.117.007988.
2. Egan B. Defining hypertension by blood pressure 130/80 mm Hg leads to an impressive burden of hypertension in young and middle-aged black adults: follow-up in the CARDIA study. J Am Heart Assoc 2018; 7: e009971. doi: 10.1161/JAHA.118.009971.
3. Diaz KM, Booth JN III, Seals SR, et al. Physical activity and incident hypertension in African Americans: The Jackson Heart Study. Hypertension 2018; 68: 421-427.
4. Your Guide To Lowering Blood Pressure. National Institutes of Health. National Heart, Lung, and Blood Institute (includes info on DASH diet) https://www.nhlbi.nih.gov/files/docs/public/heart/hbp_low.pdf accessed 8/8/18.
5. My Life Check—Life's Simple 7. American Heart Association. <http://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7> accessed 8/8/18.

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Details is produced by the Behavioral Health Drug Information Service. It summarizes internal medication use information and initiatives as well as behavioral health medication news updates, recent literature and responses to pertinent drug information questions. Please feel free to submit questions or ideas for topics to Jeanette.Cavano@sfdph.org.

The Drug Information Consultation Service responds to drug information requests regarding behavioral health drug therapy. This service is available Monday through Friday 9:00am to 4:30pm and is free of charge to all BHS clinicians. Questions and requests for consultation may be submitted by calling 415-255-3705 or emailing Jeanette.cavano@sfdph.org.