Assessment of Racial/Ethnic and Income Disparities in Opioid and Other Controlled Medication Prescriptions in California

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Background: Nonwhite communities in the United States have been disproportionately affected by most drug epidemics; however, the ongoing opioid epidemic predominantly affects low-income white communities. Potential rationales for why this particular community is most affected have not been explored.

Objective: This study evaluated exposure to prescribed opioids as related to race/ethnicity and income in order to determine if these factors could explain the disproportionate effect on low-income white communities. The study also compared trends in prescriptions for opioids compared with stimulants and benzodiazepines.

Study Design: A population-based study design was used. California’s prescription drug monitoring program was used to evaluate 29.7 million unique records of patients who received a controlled substance prescription from 2011-2015. The mean age of included patients was 46.5 years and patients were 57% female. Specifically, included data was characterized by zip code tabulation areas (ZCTAs) and the racial/ethnic composition and per capita income of the ZCTA. The 29.7 million records corresponded with 1760 ZCTAs in California. The main measure of the study was evaluating what percentage of individuals received at least one prescription each year of an opioid, benzodiazepine, or stimulant (prescription prevalence rate). Medications used to treat opioid dependence such as methadone or buprenorphine were not included in opioid counts.

Results: This study found a nearly 300% difference in prescription prevalence across race/ethnicity and income gradients. In the lowest-income and highest proportion-white population, 44% of adults received at least one opioid prescription each year, compared to only 16% of adults with the highest-income and lowest proportion-white population. Of all individuals aged 15 years or older, 24% received at least one opioid prescription each year. Stimulant prescriptions were most highly concentrated in mostly white high-income areas. Benzodiazepine prescription prevalence was not associated with an income gradient, but was concentrated in mostly white areas (16% of adults with the highest proportion-white population versus 7% of adults in the lowest proportion-white populations).

Conclusions: The study found that controlled medications were much more likely to be prescribed to those living in majority-white areas. The race/ethnicity and income pattern of opioid overdoses closely matches the prescription rates in these communities, which could imply that these
prescription rates have helped lead to majority-white areas being disproportionately affected by the opioid epidemic. Lower quantities of opioid prescriptions in nonwhite communities may have helped protect these communities from the opioid epidemic; however, this lower quantity of prescriptions likely also demonstrates healthcare disparities and a lack of access to care for nonwhite populations. The main limitation of the study is that only prescriptions from California were analyzed. As California has a low rate of controlled substance prescriptions compared to other states, this could limit generalizability. However, California has a highly diverse population and due to its immensity, likely represents a significant share of total prescribing in the United States.

Key Point: Patients in majority-white communities may be disproportionately affected by the opioid epidemic; in contrast, there is likely insufficiently medicated pain in nonwhite communities, based on implicit bias and inequity. Pharmacists can play a critical role in ensuring treatment of pain regardless of race/ethnicity or socioeconomic status.

Forming More Insight on Metformin

Haley Pals, Pharm.D.
GuidePoint Pharmacy

Background: The Diabetes Prevention Program (DPP) study aimed to provide more insight on metformin’s role as preventative therapy for type 2 diabetes mellitus (T2DM). Prophylactic use of metformin is currently off-label, however it has been used as a relatively low-risk option in conjunction with lifestyle modification for those at high risk of developing T2DM. 15-year follow-up results from DPP’s initial cohort were recently analyzed in the Diabetes Prevention Program Outcome Study (DPPOS) to build upon existing evidence for prophylactic metformin use.

Purpose: To examine the effects of metformin in diabetes prevention, and to determine which subgroups benefit the most from prophylactic metformin use.

Design: DPP was a randomized placebo-controlled cohort study following participants who were at high risk of developing T2DM. High risk was defined as impaired glucose tolerance, elevated fasting blood glucose, and BMI ≥ 24 kg/m². Onset of T2DM in those who received metformin 850mg twice daily was compared to those who received placebo. After DPP’s initial follow-up period of 2.8 years, those randomized to metformin continued to receive metformin unblinded. Additional stratification for other risk factors was analyzed to see which groups of participants benefited the most from this preventative therapy. Fifteen years later, researchers reassessed these participants to determine if the positive effects of metformin remained.

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Results: DPP and DPPOS both found positive correlation between metformin therapy and prevention of T2DM onset when compared to placebo. The effects were significant in those with higher baseline fasting blood glucose and women with a history of gestational diabetes. In those with a baseline fasting blood glucose of ≥110 mg/dL, there was a significantly lower rate of diabetes development (HR 0.75 [95% CI 0.62-0.90], P=0.0004) compared to those with a lower fasting blood glucose of 95-109 mg/dL (HR 0.83 [95% CI 0.71-0.98], P=0.0004). Metformin’s protective effects were also greater in women with a history of gestational diabetes (HR 0.59 [95% CI 0.42-0.84], P=0.03) than those without (HR 0.94 [95% CI 0.78-1.13], P=0.03). The incidence of T2DM overall was 17% lower in the metformin group (HR 0.83 [95% CI 0.73-0.93]).

Conclusion: In the short-term and long-term, metformin therapy was effective at reducing the risk of developing T2DM.

Key Point: These findings further strengthen the American Diabetes Association’s recommendations to prescribe metformin to lower the risk of developing T2DM in patients with elevated fasting blood glucose or prior gestational diabetes.

Tobacco Cessation: E-cigarettes versus Nicotine Replacement Therapy

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Background: Conflicting evidence is available when comparing e-cigarettes to nicotine replacement therapy (NRT) during a tobacco cessation attempt. Limited data indicates that switching from cigarette smoking to e-cigarette use is expected to reduce health risks. Another area of debate surrounds the risks and benefits of e-cigarette use in general.

Objective: To determine if use of e-cigarettes in tobacco cessation attempt facilitates success when compared to NRT.

Study Design: This study is a two-group, pragmatic, multi-centered, randomized, controlled trial, which occurred across three National Health Service sites from May 2015 to February 2018. Exclusion criteria included the following: pregnant/breastfeeding, strong preference for or against NRT or e-cigarettes, and current use of NRT or e-cigarettes. Non-pregnant, non-breastfeeding patients aged 18 years and older who were currently
smoking and had a desire to quit were randomized to NRT or e-cigarettes. In the NRT group, use of combination products (patch, gum, lozenge, nasal spray, inhaler, mouth spray, mouth strip, and microtabs) were encouraged and supplied for up to three months. In the e-cigarette group, a refillable starter pack and one refill of nicotine e-liquid was provided. Participants were encouraged to try e-liquids of different strengths and flavors as well as purchase refills online or from local vape shops. Behavioral support was provided for all participants which included weekly one-on-one sessions with local clinicians and carbon monoxide monitoring for at least four weeks following the quit date. The primary outcome was sustained abstinence for one year and secondary outcomes included abstinence between weeks 4 and 52 and respiratory symptoms.

Results: Out of a total of 886 patients included in the study, the one-year abstinence rate in the e-cigarette group was 18%, compared to a 9.9% abstinence rate in the NRT group (RR 1.8 [95% CI 1.30 - 2.58]). Of the participants abstinent for one year, participants in the e-cigarette group were more likely to continue use of the assigned product at 52 weeks (80%) when compared to the NRT group (9%). Throat or mouth irritation were more frequent for the e-cigarette group (65.3%) when compared to the NRT group (51.2%). Nausea occurred more often in the NRT group (37.9%) when compared to the e-cigarette group (31.3%). Reduction in cough and phlegm production from baseline to 52 weeks was reduced to a greater degree in the e-cigarette group. No significant differences were found between groups for symptoms of wheezing or shortness of breath.

Conclusions: E-cigarette use along with behavioral support was found to be more effective for a successful tobacco cessation attempt when compared to NRT with behavioral support. A limitation of the study includes the potential barrier in generalizability to a population with less strict follow-up. Overall, e-cigarettes may allow for individualizing the desired nicotine dose. However, health risks of long-term e-cigarette use have not been fully identified.

Key Point: Education on risks and benefits of e-cigarettes vs. NRT for tobacco cessation is necessary, especially with limited evidence-based data for e-cigarette use.

Therapeutic Thoughts

Therapeutic Thought
A Closer Look at the Increasing Cost of Insulin
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Background: The increasing cost of insulin has been a heavily debated topic in recent news. For patients with Type 1 Diabetes, insulin is a necessary medication for survival. First-hand stories of patients putting their lives in danger by rationing their insulin supply to cut down on costs or paying hundreds of dollars a month for their insulin to stay alive have riddled social media outlets. Many organizations have taken the initiative to research this issue and brainstorm ways to make insulin more affordable.

Evidence: Earlier this year, the Health Care Cost Institute (HCCI) published a brief entitled “Spending on Individuals with Type 1 Diabetes and the Role of Rapidly Increasing Insulin Prices”. They collected data on patients with Type 1 Diabetes by using health care claims between 2012 and 2016 and investigated trends in total health care spending. HCCI found that gross spending on insulin for these individuals doubled from 2012 to 2016. They were able to rule out increase in cost due to increase in insulin usage by calculating only a three percent increase in average daily insulin use by these individuals. While they did attribute a slight increase in spending to the transition to newer, more expensive alternatives (e.g. pre-filled insulin pens versus vial and syringe and using newer brands such as Tresiba and Toujeo), they credited the majority of the increase in spending to the rapidly increasing insulin prices. Because use of manufacturer coupons and rebates is not available to the public, HCCI was not able to evaluate their potential effect on gross insulin spending during this investigation.

Another perspective comes from Douglas Holtz-Eakin, President of the American Action Forum, who released a testimony earlier this year regarding his opinion on drug pricing in America. In his testimony to the United States Senate Committee on Finance, Mr. Holtz-Eakin stated that overall out-of-pocket (OOP) costs for prescription medications has declined since 2013. While the majority of prescription medications had an OOP cost of less than $50 in 2017, 0.1% of prescription medications had an OOP cost of more than $500, with an average OOP cost of $1,502 per prescription. These increased prescription medication costs likely belonged to specialty medications, including insulin. Mr. Holtz-Eakin did not discount the fact that specialty medications cost more to manufacture, and encouraged people to remember that the goal of specialty medications is not low cost, but instead high value. Mr. Holtz-Eakin related the increase in drug prices to increased government regulations and
Background: Black patients have a higher prevalence of hypertension, treatment resistant hypertension, and poorer blood pressure control. It is known that certain antihypertensive agents work better and have different adverse drug event frequencies in black patient populations, which guides monotherapy. However, various guidelines provide different direction on which two-drug combination is best to treat hypertension in black patients.

Evidence:
Current Guidelines
The American College of Cardiology and American Heart Association 2017 hypertension guidelines suggest initial therapy of a calcium channel blocker (CCB) or thiazide diuretic for black patients. Further, it states that two drugs are often needed for treatment of hypertension in black patients. When guiding two-drug combination selection comorbid conditions are considered, however the guideline ultimately endorses any combination including a CCB or thiazide diuretic with each other, an angiotensin converting enzyme inhibitor (ACE-I), or angiotensin-receptor blocker (ARB).

Joint National Committee 8 recommends initial therapies of a thiazide diuretic or CCB in black patients, but does not provide specific guidance on the best second agent to choose. In general, it recommends adding a CCB, thiazide diuretic, ACE-I, or ARB as a second drug if a patient is not responding to monotherapy.

The American Society of Hypertension and the International Society of Hypertension recommends a CCB or thiazide diuretic (CCB preferred, but thiazide diuretic if cost is a concern) as initial drugs of choice for black patients. If additional treatment is indicated, they suggest adding an ACE-I or ARB. If ACE-Is and ARBs are not available, a CCB or thiazide diuretic, whichever the patient is not already taking, may be added as a second agent.

The European Society of Cardiology and European Society of Hypertension suggest that black patients be initiated on two drugs to start. The guideline states that black patients respond better to thiazide diuretics or CCBs, and the combination or addition of an ACE-I or ARB can be used.

CREOLE Study 2019
The CREOLE study is a randomized, single-blind, multicenter, three-group trial that compared the safety and efficacy of three different two-drug combinations for the treatment of hypertension. Throughout six countries in sub-Saharan Africa, 621 black participants were randomized to the following groups in a 1:1:1 ratio: amlodipine 5 mg and hydrochlorothiazide 12.5 mg, amlodipine 5 mg and perindopril 4 mg (approximately equivalent to lisinopril 10 mg), or perindopril 4 mg and hydrochlorothiazide 12.5 mg. At two months, doses were doubled if the patient was tolerating the medication. The primary outcome was ambulatory systolic blood pressure at baseline and 6 months. Of participants, 63% were female, the mean age was 51 years old, and 4% of participants had diabetes. The combinations including amlodipine were shown to be more effective than the combination without amlodipine (Table 1).

### Table 1. CREOLE comparison of two-drug combinations

<table>
<thead>
<tr>
<th>Two-drug combinations</th>
<th>Mean difference (95% confidence interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine 5 mg and hydrochlorothiazide 12.5 mg vs. perindopril 4 mg and hydrochlorothiazide 12.5 mg</td>
<td>-3.14 mm Hg (-5.90 to -0.38)</td>
<td>0.03</td>
</tr>
<tr>
<td>amlodipine 5 mg and perindopril 4 mg vs. perindopril 4 mg and hydrochlorothiazide 12.5 mg</td>
<td>-3.00 mm Hg (-5.8 to -0.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>amlodipine 5 mg and hydrochlorothiazide 12.5 mg vs. amlodipine 5 mg and perindopril 4 mg</td>
<td>-0.14 mm Hg (-2.90 to 2.61)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Discussion: CREOLE shows two-drug combinations including amlodipine are superior to non-CCB combinations. Most guidelines thus far have advised the use of a CCB or thiazide diuretic first and to add on the opposite, an ACE-I, or an ARB for combination therapy. The CREOLE study provides evidence to support the addition of a thiazide or an ACE-I to a CCB. Of note, ARBs were not included in this study.

The CREOLE study is limited because it only looked at sub-Saharan African patients and was single blinded. In spite of these limitations, the recommendations provided from this study not only represent current standards of care, but specifically outline the best dual therapy for black patients for the treatment of hypertension.

Clinical Impact: When adding a second antihypertensive agent or initiating a two-drug combination for a black African patient, CREOLE demonstrates there are superior combinations to decrease systolic blood pressure over six months. Aside from other comorbidities that may influence drug selection, it may be beneficial to select combination therapy that includes a CCB.

A novel naloxone training compared with current recommended training in an overdose simulation

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Fairview Pharmacy Services

Background: With the growing concern of deaths caused by opioid overdose, naloxone education has emerged as a topic of interest. Currently, there is no standardized naloxone training or mandate for pharmacists on a federal level and can vary on a state level; Minnesota does not require naloxone training for pharmacists. Naloxone is available as three delivery systems with distinct administration techniques - nasal atomizer, nasal spray, and autoinjector. The American Society of Addiction Medicine (ASAM) recommends all clinicians who provide care to people with substance use disorders have naloxone readily available and be trained on appropriate response to an overdose. The Pennsylvania Act 139 (2014) states all first responders, including family and friends, are allowed to administer naloxone if an opioid overdose is suspected. The Act strongly advises that the person administering the agent complete a state approved training program. Currently, the state has approved an online training program for the general public, but it does not include education on the naloxone atomizer and stress management during an emergency situation.

Objective: The purpose of the study was to determine if a novel naloxone training program that addresses stress management has better results compared to current training in a simulated overdose response.

Study Design: This was a randomized prospective trial including pharmacy students in their third professional year during a substance use disorder series of the clinical laboratory course. Each student was randomized to either the state online training program or a novel training program created by the Wilkes University Nesbitt School of Pharmacy. The state training program is computer based with online voice-over modules covering signs and symptoms of overdose, use of naloxone intranasal spray, and use of the autoinjector. The novel training program is a voice-over Powerpoint that covers the same topics in addition to an overview of the opioid crisis, use of naloxone atomizer, laws of naloxone administration, tools to reduce misuse, and stress management during emergencies. After the training, students completed a simulated overdose response scenario with a panicked bystander. The simulation was timed and evaluated with a checklist. Results from the checklist were compared between groups. Students were aware their score would not impact their course grade. The study was approved by the Wilkes University Institutional Review Board and completed over two academic years.

Results: Of the 139 eligible students, 135 students completed the simulation. The median time to complete the simulation in the state training program was two minutes and ten seconds compared to two minutes for the novel training program (P=0.31). The following tasks from the checklist demonstrated a significant difference between the simulations of the state training and novel training groups, respectively: pulse was checked in 25% vs 90% of simulations; breathing was checked in 34% vs 68% of simulations; head was appropriately titled for exposure of nasal passage in 11% vs 90% of simulations; and naloxone was properly administered in 47% vs 97% (P<0.0001 for all). Average scores from the checklist for the state training and novel training groups were 64% and 89% (P=<0.0001), respectively.

Conclusions: The novel naloxone training program provided better training to pharmacy students for a live overdose simulation. The results of the simulation checklist were similar in many areas; however, there were significant differences in checking pulse and breathing, and properly administering naloxone. Missing pulse and breathing can be detrimental in a real-life emergency situation.
Key Point: Pharmacy students who completed the novel naloxone training program were able to respond to a live simulated opioid overdose more appropriately compared to the online state training program. Institutions should consider a more robust training program for naloxone and overdose response that includes assessing for pulse and breathing as well as stress management tactics.

Non-dihydropyridine Calcium Channel Blockers for the Treatment of Proteinuria

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Background: Proteinuria is a commonly assessed marker for progression of renal disease. The renoprotective benefits from the use of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) for proteinuria is well-documented and supported by many large, well-designed studies. The question still remains for preferred second line therapy, either for patients with a contraindication to ACE-Is/ARBs or for those who are on maximally tolerated ACE-Is/ARBs and have more room for improvement in proteinuria. There is evidence to support a role for nondihydropyridine calcium channel blockers (non-DHP CCBs) in such situations, although the data is far less robust than for ACE-Is or ARBs.

The mechanism of renoprotection for ACE-Is and ARBs is likely related to lower glomerular capillary bed pressure and protein filtration, however the mechanism for non-DHP CCBs is not well characterized. It is theorized that these medications act through mechanisms not related to known hemodynamic effects, such as reduction in glomerular permeability and prevention of mesangial matrix expansion and glomerulosclerosis. A recent review by Steuber et al. combed the literature to assess the role in therapy for non-DHP CCBs for proteinuria in patients with existing kidney disease.

Evidence: The review article included 13 trials evaluating the use of non-DHP CCBs; nine evaluated the use of verapamil, three evaluated diltiazem, and one included both medications. The trials used a variety of measures to assess progression of kidney disease including urinary evaluation of albumin secretion, albumin-to-creatinine ratio, protein-to-creatinine ratio, serum creatinine, creatinine clearance, and glomerular filtration rate. All of the studies suggested non-DHP CCBs have some beneficial effects on progression of kidney disease, but many had small sample sizes, making it difficult to show significant differences between treatment groups. Only three of 13 studies included more than 100 patients. Ten of the trials looked at non-DHP CCBs in addition to ACE-Is and three investigated non-DHP CCBs as monotherapy. Whether used as an add-on or monotherapy, the non-DHP CCB groups showed trends toward reduction in proteinuria.

The studies included had many limitations. Many measured surrogate markers rather than clinical outcomes, doses and trial design varied significantly, the majority of the trials were more than 10 years old, none of the trials measured adherence, and there were significant drop out rates in multiple studies. There is a clear need for larger studies that incorporate more patient-oriented renal and cardiovascular outcomes with non-DHP CCBs.

Clinical Impact: The data supports controlling hypertension and diabetes, and using ACE-Is or ARBs as first line treatment for proteinuria. The literature does suggest non-DHP CCBs can also be effective and are a reasonable option for patients who cannot tolerate or have a contraindication to ACE-Is or ARBs. These treatment options would also likely benefit patients on maximally tolerated ACE-Is or ARBs, but continue to have progression of proteinuria. Non-DHP CCBs should be initiated at the lowest dose and titrated up slowly based on tolerability.

Clinical Practice Guidelines: Sources We Can Trust

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St. Cloud VA

Keeping up with the latest research can be challenging, thus clinicians often turn to clinical practice guidelines (CPGs) for evidence-based decision-making. A recent review published in the Journal of the American Medical Association notes that the quality of CPGs is variable and objective measures to rate CPG quality are lacking. Molino et al. sought to systematically evaluate 421 primary care-focused CPGs by utilizing a validated tool, the Appraisal of Guidelines for Research and Evaluation Instrument, version II (AGREE-II). High quality CPGs were associated with inclusion of over 20 authors, development at governmental institutions, report of funding, use of a formal consensus process for
recommendations, and definition of a time at which an update should be written. Included CPGs were published in English, Spanish, or Portuguese between January 2011 and August 2017 and involved guidance for pharmacologic management of non-communicable diseases.

Researchers concluded that only 23.5% of CPGs reviewed were high quality. Common limitations were applicability and rigor of development. Interestingly, there was no association between geographic region and quality. Of note, approximately half of the recommendations were based on expert opinion, increasing risk of bias. Involvement of an interdisciplinary team in guideline development may aid in reducing risk of bias and diminishing groupthink.

Molino et al.’s findings indicate the need for higher quality CPGs in primary care. Before making a clinical decision based on a CPG, it is important to take a deeper look at the guideline development process, including presence of the factors associated with high quality, as noted above. Critical evaluation of CPGs and a focus on creation of high quality guidelines moving forward are essential to excellent patient care.

**FDA Approves First Generic Advair Diskus**

Anjoli Punjabi, Pharm.D., MPH
Federally Qualified Urban Health Network

The U.S. Food and Drug Administration (FDA) has approved the first generic Advair Diskus inhaler. “[The] approval of the first generic drug product for one of the most commonly prescribed asthma and COPD inhalers in the U.S. is part of our longstanding commitment to advance access to lower cost, high quality generic alternatives,” said Janet Woodcock, MD, director of the FDA’s Center for Drug Evaluation and Research. The generic inhaler has been approved in patients 4 years of age and older and is available in three strengths: fluticasone propionate 100 mcg/ salmeterol 50 mcg, fluticasone propionate 250 mcg/ salmeterol 50 mcg and fluticasone propionate 500 mcg/ salmeterol 50 mcg.

The approval of generic inhalers can often be more difficult than the approval of other generic agents, such as a solid oral dosage form. This is because inhalers are considered “combination products” given they contain both a drug and device. The FDA recognizes the challenges that exist for companies to gain approval for combination products and has a support mechanism in place to address this. For example, individual companies can meet with the FDA as part of their Pre-Abbreviated New Drug Application (Pre-ANDA) program to support the development of combination products. In 2013, the FDA published guidance documents to support the Pre-ANDA approval process including formulation and device considerations.

Patients living with asthma and COPD have a critical need for inhalers to manage their disease state. The introduction of the generic Advair Diskus inhaler is step towards increased market competition and increased access to inhaler therapy.

**Digital ProAir Inhaler Available**

Anjoli Punjabi, Pharm.D., MPH
Federally Qualified Urban Health Network

The first digital inhaler, ProAir digital, has now been approved by the U.S. Food and Drug Administration. Much like the non-digital version of this inhaler, the device is a dry powder breath activated inhaler. The inhaler has a dose counter and delivers 108 mcg albuterol sulfate and 90 mcg albuterol base per actuation. The inhaler “may help patients have a more informed dialogue with their health care provider about their asthma or COPD management,” stated Teva in a news release.

The inhaler has a built in sensor that sends information on inspiratory volume to a cell phone application via BlueTooth. Patients can review data trends over time and share this information with their provider, should they wish. The numbers on the counter display turn red when 20 doses are left and the dose counter display turns solid red when zero doses are remaining. This feature lets patients know when to contact their pharmacy or provider for a medication refill. The inhaler will be available in limited quantities through “Early Experience” programs in 2019 and will become more widely available in 2020.
**Esketamine (SPRAVATO™) – Janssen**

*Kristen Schroeder, Pharm.D.*

_St. Cloud VA*

**Indication:** Esketamine is indicated for treatment-resistant major depressive disorder in adults.

**Mechanism of Action:** As suggested by its name, esketamine is the (S)-enantiomer of ketamine. It is a non-competitive NMDA receptor; however, the mechanism for its antidepressant effects remain unclear.

**Dosage and Administration:** Esketamine is administered intranasally. Each nasal spray device contains 28 mg esketamine. There are also 56 mg and 84 mg kits available. The dose is dependent on phase of therapy. During the induction phase (weeks 1-4), esketamine is given twice weekly. The first dose should be 56 mg, while all subsequent doses may be either 56 mg or 84 mg. During the maintenance phase (weeks 5-8), it is administered once weekly, and thereafter it may be given once or twice weekly based on response. The dose must be administered in a clinician’s office to allow for at least 2 hours of post-dose monitoring. Also, it is recommended that patients avoid eating for at least 2 hours and drinking for at least 30 minutes prior to use to decrease nausea risk.

**Effectiveness:**

**Short-term study:** In a 4-week study, esketamine in conjunction with a newly initiated oral antidepressant (AD) showed statistical superiority in reducing the Montgomery-Asberg Depression Rating Scale (MADRS) total score as compared to placebo plus an oral AD (least squares mean difference 4.0 [95% CI -7.3 - -0.6]).

**Long-term study:** Patients considered stable responders or remitters at least 16 weeks of esketamine use were randomized to either continued esketamine or placebo. All subjects were taking concomitant oral AD. The primary endpoint was time to relapse, specified by MADRS score or other clinically relevant indication of relapse. Relapse was significantly delayed in the esketamine group compared to the placebo group. In the stable responders, the estimated hazard ratio of esketamine relative to placebo was 0.30 [95% CI 0.16 - 0.55]. In remitters, the estimated hazard ratio was 0.49 [95% CI 0.29 - 0.84], though noted this ratio was inconsistent throughout the trial.

**Safety:** Esketamine carries potential for misuse, and therefore was approved as a C-III drug with a risk evaluation and mitigation strategy (REMS).

**Boxed warnings:** Dissociation, sedation, and suicidal thoughts

**Adverse effects:** Impaired attention, judgment, thinking, reaction speed, and motor skills; nausea; dizziness; anxiety; transient blood pressure elevations (warranting monitoring before and after administration)

**Contraindications:** Aneurysmal vascular disease or arteriovenous malformation, intracerebral hemorrhage, or known hypersensitivity to ketamine. Esketamine should not be used in pregnant or breastfeeding women.

**Place in Therapy:** Esketamine may decrease depression symptoms and delay time to relapse when used as an adjunct to an oral AD in patients with treatment-resistant major depression. Clinical trials indicate that esketamine may provide benefit in those who have failed at least two other antidepressant therapies, and it is notable that careful adherence to REMS criteria is warranted. Cost is also likely to play a role in place in therapy, as Reuters predicts a cost of $590 for a 56 mg dose and $885 for an 84 mg dose.

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