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The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

Spravato™ (Esketamine) Nasal Spray

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Background

In March 2019, the United States (US) Food and Drug Administration (FDA) approved Spravato™ (esketamine) nasal spray as adjunctive therapy to an oral antidepressant for treatment-resistant depression.[1] Symbyax® (a fixed-dose combination of fluoxetine and olanzapine) had previously been the only agent approved for treatment-resistant depression.[2] There are various definitions for treatment-resistant depression in the literature;[3] the definition utilized by the manufacturers of Spravato™ and Symbyax® (the FDA regulatory definition) is an episode of major depressive disorder unresponsive to at least 2 different antidepressants of adequate dose and duration.[4,5] Nearly one-third of the 300 million people living with depression worldwide fail to respond to currently available antidepressants.[3,6-8] Treatment-resistant depression accounts for the largest burden of disease and represents a critical need for new treatment options.[3,6] Practice guidelines recommend different strategies for managing patients with incomplete response to treatment; 1 strategy is to change to a different antidepressant, either from the same class or from a different class.[9,10] Addition of a second antidepressant from a different pharmacological class may also be considered. Somatic treatment options such as transcranial magnetic stimulation or electroconvulsive therapy (ECT) and psychotherapy are also recommended as alternatives or adjuncts to medication therapy.

Esketamine is considered a groundbreaking advancement in the treatment of depression, given its novel mechanism of action and the short timeframe in which it produces clinically meaningful improvements.[6] Esketamine may improve depression symptoms in as little as hours or days, as opposed to standard antidepressants which take weeks to reach full effect. Esketamine has also demonstrated clinically meaningful outcomes in elderly patients who often have greater disability and lower response rates.

Esketamine is the S-enantiomer of ketamine.[4] Ketamine, also known by its street name "Special K," is an FDA-approved anesthetic.[2] Esketamine works on the N-methyl-D-aspartate (NMDA) receptor in the brain as an antagonist, facilitating glutamate release which activates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.[2,11] AMPA receptor activation increases signaling of neurotrophic factors, resulting in rapid onset and long-term antidepressant effects.[11]

Clinical Trials

Janssen Pharmaceuticals submitted 5 phase 3 studies to the FDA as part of its new drug application for esketamine: 3 short-term studies (TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3), 1 maintenance of effect study (SUSTAIN-1), and 1 long-term safety study (SUSTAIN-2).[11-13] At the time of this writing, only 1 of these studies has been published (TRANSFORM-2);[14] details pertaining to the other phase 3 trials are limited to poster presentations, press releases, manufacturer resources, and the FDA briefing document.[1,2,4,6,11-13,15-17] Among the trials, TRANSFORM-2 and SUSTAIN-1 were considered pivotal to FDA approval and are discussed below.[11,13]

TRANSFORM-2 was a double-blind, active-controlled, multi-center study conducted at 39 sites in the Czech Republic, Germany, Spain, Poland, and the US.[13,14] This study included adults aged 18 to 64 years with moderate-to-severe, non-psychotic, recurrent or persistent depression meeting the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) diagnostic criteria, and history of non-response to ≥2 antidepressants in the current episode of depression, with 1 of them assessed prospectively. Key exclusion criteria included suicidal ideations within the past year, major depressive disorder with psychotic features, bipolar or related disorders, uncontrolled hypertension, history of moderate-to-severe substance use disorder within the past 6 months or lifetime history of ketamine use disorder, and positive urine test results for selected drugs of abuse (e.g., opioids). Patients were randomized (1:1) to flexibly-dosed intranasal esketamine (56 mg or 84 mg twice weekly) plus a newly initiated oral antidepressant or to placebo nasal spray plus a newly initiated oral antidepressant (duloxetine, venlafaxine extended-release, escitalopram or sertraline). The primary endpoint was change from baseline to day 28 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. (Total MADRS scores range from 0 to 60 with higher scores indicating more severe depression). Response rates, defined as ≥50% improvement in MADRS from baseline, and remission rates, or MADRS scores ≤12, were also assessed. MADRS sustained response, which was the onset of clinical response by 24 hours post-dose, maintained through day 28, was evaluated as a secondary endpoint. All MADRS assessments were performed by independent raters who were blinded to the study protocol

A total of 223 subjects was randomized; 109 subjects were randomized to the treatment arm and 114 subjects were randomized to the placebo arm.[13,14] Baseline MADRS total scores were comparable between esketamine and placebo groups, with mean scores of 37.0 and 37.3, respectively, suggesting similar baseline illness severity. However, lifetime suicidal behavior was higher in the placebo arm than in the esketamine arm (13% vs. 8%). The placebo group was older, with a mean age of 46.4 years ± 11.1, versus the esketamine group, with a mean age of 44.9 years ± 12.6. In terms of efficacy, esketamine plus an oral antidepressant demonstrated statistically significant improvement in patients' depressive symptoms versus the comparator as measured by MADRS scores at day 28 (least square [LS] mean difference -4.0, 95% confidence interval [CI] -7.31 to -0.64) and at earlier time points (24 hours post-dose and days 8 and 22, p≤0.009). Response rates and remission rates at 28 days were notably higher in esketamine users versus non-users (esketamine vs. placebo response rates: 69.3% vs. 52.0%; odds ratio [OR]=2.4, 95% credible interval 1.30 to 4.54; remission rates: 52.5% vs. 31.0%, OR not reported). The secondary endpoint, however, did not meet statistical significance (p=0.161). In

terms of safety, there were more adverse events reported in the esketamine group compared to the placebo group. The most common adverse events occurring in >2% of the esketamine group and ≥2-fold higher frequency than the comparator group were dysgeusia, nausea, vertigo, and dizziness (incidences: 20.9 to 26.1%).

SUSTAIN-1 was a randomized, double-blind, multi-center study that assessed relapse prevention in adults with treatment-resistant depression who were enrolled or transferred from other esketamine phase 3 studies.[13,15-17] All patients had been treated with esketamine nasal spray plus an oral antidepressant for 16 weeks prior to this study (4-week induction phase followed by 12-week optimization phase) and were either in stable remission, or had a stable response but were not in stable remission. Stable remission was defined as MADRS total score ≤12 for at least 3 of the last 4 weeks of the optimization phase. Stable response was defined as ≥50% reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission. In SUSTAIN-1, patients were randomized to receive esketamine nasal spray (56 mg or 84 mg) or placebo nasal spray, plus the oral antidepressant they had been using in the optimization phase. Time to relapse among patients who were in stable remission following the optimization phase was the primary endpoint.

In SUSTAIN-1, a total of 90 subjects were randomized to the treatment arm and 86 were randomized to the placebo arm.[13] Baseline characteristics were similar across the 2 groups for the stable remitters. With regard to efficacy, the results significantly favored esketamine plus an oral antidepressant in delaying relapse. During the maintenance phase, 26.7% of stable remitters in the esketamine group experienced a relapse event versus 45.3% of stable remitters in the placebo group. The difference between groups in time to relapse was clinically and statistically significant (twenty-fifth percentile: 153 days vs. 33 days, respectively; p=0.003). Investigators determined that esketamine with an antidepressant reduced the risk of relapse among stable remitters by 51% (hazard ratio [HR]=0.49, 95% CI 0.29 to 0.84). Among those with stable response but without remission, 25.8% of the esketamine group versus 57.6% of the placebo group experienced a relapse event. The difference between groups for the time to relapse was also clinically and statistically significant (twenty-fifth percentile: 217 vs. 24 days, respectively; p<0.001). Among these stable responders, esketamine with an antidepressant reduced the risk of relapse by 70% (HR=0.30, 95% CI 0.16 to 0.55).

With regard to safety, there were higher incidences of certain adverse events among patients in the esketamine group compared to the control group, including sedation (41.4% vs. 9.7%, maintenance phase; p=not reported) and hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg; 4.4% vs. 1.2%; p=not reported).[11] Serious adverse events attributed to study treatment were reported in 6 subjects (1.4%); adverse events included disorientation, suicidal ideation, sedation, autonomic nervous system imbalance, and hypothermia. Notably, treatment-emergent suicidal ideation was higher among patients who did not receive esketamine compared to those who received esketamine (4.5% vs. 2.4%, p=not reported). There was no significant difference in impaired cognition between esketamine and control groups.[13]

The results of TRANSFORM-2 and SUSTAIN-1 demonstrated clinically and statistically significant superiority of esketamine in combination with an oral antidepressant to an oral antidepressant with placebo in improving symptoms of depression and delaying relapse in patients with treatment-resistant depression.[13,14]

Contraindications

Contraindications to esketamine include aneurysmal vascular disease, intracerebral hemorrhage, and hypersensitivity to esketamine, ketamine, or any of the excipients.[4]

Warnings and Precautions

Esketamine is classified as a controlled substance (Federal Schedule III) and is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS).[4,18] The strict

regulation of esketamine is prompted by the risk of serious adverse outcomes resulting from sedation and dissociation, as well as the potential for abuse and misuse of the drug. Spravato® REMS requires the patient to make arrangements to safely leave the healthcare setting and to not drive or use heavy machinery for the rest of the day on which they received the drug.

There is a boxed warning for sedation and difficulty with attention, judgment and thinking (i.e., dissociation), abuse and misuse, and suicidal thoughts and behaviors after administration of esketamine.[4] Patients must be monitored by a healthcare provider for at least 2 hours after receiving esketamine, given the risk of sedation and dissociation.

Other Safety Concerns

The most common adverse reactions (>5%) reported in patients treated with esketamine and an oral antidepressant in clinical trials, occurring at >2-fold higher frequencies compared to the control groups, include dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, elevated blood pressure, vomiting, and feeling drunk.[4] Most adverse events and associated symptoms were seen predominantly on the day of dosing and generally resolved later that day.[6]

Dosing and Administration

Esketamine should be administered by the patient under the supervision of a healthcare provider in a certified treatment center.[4] Pharmacies must also be certified in the Spravato™ REMS in order to dispense the medication.[18] Once delivered for a patient specific order or obtained for a healthcare setting's bulk supply, esketamine should be stored at room temperature, 20° to 25°C (68° to 77°F) and should be kept in a secure place per State and Federal Drug Enforcement Agency (DEA) laws and regulations for Schedule III controlled substances.[4,19] Products dispensed for patient specific orders must be administered within 14 days after receipt by the healthcare setting per DEA requirements, and may not be returned to the general inventory of the healthcare setting or pharmacy.[19] The healthcare provider should instruct the patient on proper administration technique and monitor the patient prior to, during, and after each use of the nasal spray device. More details regarding administration, including illustrations, are available in the esketamine label.[4] The device cannot be taken home. Due to the risk of sedation and dissociation, patients are required to stay in the provider's office for at least 2 hours after their dose and are not permitted to drive for 24 hours after their dose. Baseline blood pressure must be obtained prior to administration. If elevated (>140 mmHg systolic, >90 mmHg diastolic), risks versus benefits should be considered. Blood pressure should be reassessed 40 minutes after administration of esketamine and then as clinically needed. If blood pressure is decreasing and the patient appears clinically stable for at least 2 hours, he/she may leave the provider's office; if not, the patient should continue to be monitored.

During the induction phase (weeks 1 to 4), esketamine should be administered twice weekly.[4] The recommended starting dose (day 1) for all patients is 56 mg. Subsequent doses may be increased to 84 mg based on efficacy and tolerability. At the end of the induction phase, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. During the maintenance phase (weeks 5 to 8), esketamine should be administered once weekly. At week 9 and onward, the manufacturer recommends individualizing the frequency of dosing (e.g., every 2 weeks or weekly) to the lowest frequency needed to maintain remission.

Each nasal spray device delivers 2 sprays (1 spray for each nostril) containing a total of 28 mg of esketamine.[4] For a 56 mg or 84 mg dose, 2 devices or 3 devices are required, respectively. Patients should wait 5 minutes between uses of each device to allow medication to be absorbed.

Food and Drug Interactions

Prior to administration of esketamine, patients should avoid food for at least 2 hours and avoid drinking liquids for at least 30 minutes, due to possible nausea and vomiting.[4] If required on a dosing day, nasal corticosteroids or nasal decongestants should be administered at least 1 hour prior to esketamine.

Pregnancy/Lactation

Esketamine is not recommended during pregnancy.[4] The esketamine label includes warnings for embryo-fetal toxicity, as esketamine may cause fetal harm. Pregnancy planning and prevention in females of reproductive potential should be considered. Currently, there are no data on the effects of esketamine on the breastfed infant or milk production. Animal data suggest a potential for neurotoxicity. Since esketamine is present in human milk, and because of the potential for neurotoxicity, breastfeeding during treatment with esketamine is not recommended.

Summary

Esketamine is a newly approved drug reserved for those with treatment-resistant depression who have not responded to standard antidepressants.[4] Patients need to have failed at least 2 antidepressants during their current episode of depression. Esketamine should not be used as monotherapy: patients should take esketamine in addition to a standard antidepressant. Access to esketamine is restricted given its safety profile. In addition, limited experience with esketamine precludes widespread use at this time.

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Statins and Risk of Developing Diabetes

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Background

β-Hydroxy β-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are cited in the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease to reduce atherosclerotic cardiovascular disease (ASCVD) risk in multiple patient populations.[1] Despite this benefit, research has emerged revealing that these medications can increase a patient's risk of incident diabetes.[2-4]

Meta-analyses

A number of meta-analyses have been published on this topic. A review of some of the more recent studies is included here.

A systematic review and meta-analysis by Khan et al evaluated the relationship between lowering low-density lipoprotein cholesterol (LDL-C) with statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and risk of developing diabetes mellitus.[5] Randomized controlled trials (RCTs) published through November 15, 2018 were included. The RCTs all included ≥100 patients receiving either statins or PCSK9 inhibitors compared to a placebo or active control for ≥12 weeks, and reported ≥1 clinical event for incident diabetes. High-intensity statins (atorvastatin 80 mg, simvastatin 80 mg, or rosuvastatin 40 mg) and low-intensity statins (atorvastatin 10 mg, simvastatin 20-40 mg, and rosuvastatin up to 20 mg) were evaluated. Exclusion criteria consisted of studies investigating other dyslipidemia therapies such as fibrates, niacin, and cholesteryl ester transfer protein inhibitors, studies which showed that other interventions (bile acid sequestrants, ileal bypass surgery, exercise, and diet) had a concomitant effect on diabetes, studies without full-text publication available, and trials investigating bococizumab.

In total, 33 RCTs were included in the analysis: 21 studies of statins (124,755 patients) and 12 of PCSK9 inhibitors (38,933 patients).[5] The mean follow-up duration was 4.2±1.2 years. The metaregression analysis did not demonstrate a significant association between absolute reduction in LDL-C (for every 1 mmol/L [38.67 mg/dL][6]) and incident diabetes for more intensive lipid-lowering therapy (risk ratio [RR]=0.95; 95% confidence interval [CI] 0.87-1.04; P=0.30), for statins (RR=1.02; 95% CI 0.91-1.14; P=0.67), or for PCSK9 inhibitors (RR=1.09; 95% CI 0.60-1.99; P=0.74).[5] The meta-analysis of the study population showed that 6.1% of patients had incident diabetes with the more intensive lipid-lowering therapy as compared to 5.8% with the less intensive lipid-lowering therapy. More intensive lipid-lowering therapy was associated with a higher risk of incident diabetes compared with less intensive therapy (RR=1.07; 95% CI 1.03-1.11; P<0.001). The authors stated that these results were due to the higher risk of diabetes with statins (RR=1.10; 95% CI 1.05-1.15; P<0.001), not the risk with PCSK9 inhibitors (RR=1.00; 95% CI 0.93-1.07; P=0.96).

Thakker et al performed a network meta-analysis of RCTs of statins that reported data on incidence of diabetes, with the intent of evaluating a potential link between statins and diabetes.[7] The investigators searched for studies published between August 2010 and June 2014. They also identified studies published before August 2010 by reviewing previously published meta-analyses. Twenty-nine trials (163,039 participants) were included in the pair-wise meta-analysis (direct comparisons of statin vs. placebo or any other active agent). The median duration of the trials was 4.8 years with a range of 3 months to 6.1 years. The investigators reported that there was a significantly increased risk of incident diabetes with statins (pooled odds ratio [OR]=1.12; 95% CI 1.05-1.21; I^2=36%; P=0.002; 18 RCTs). Of the individual statins, only rosuvastatin was associated with an increased risk of diabetes (OR=1.18; 95% CI 1.04-1.33; I^2=0%; P=0.009; 4 RCTs).

Twenty-seven studies were included in the network meta-analysis which included a combination of direct and indirect comparisons.[7] The investigators reported that atorvastatin 80 mg was associated with the highest risk of diabetes (OR=1.34; 95% CI 1.14-1.57) followed by rosuvastatin (OR=1.17; 95% CI 1.02-1.35). These were followed by simvastatin 80 mg (OR=1.21; 95% CI 0.99-1.49), simvastatin (OR=1.13; 95% CI 0.99-1.29), atorvastatin (OR=1.13; 95% CI 0.94-1.34), pravastatin (OR=1.04; 95% CI 0.93-1.16), lovastatin (OR=0.98; 95% CI 0.69-1.38), and pitavastatin (OR=0.74; 95% CI 0.31-1.77). The researchers also found that lipophilic statins (atorvastatin, lovastatin, simvastatin) had a 14% higher risk of diabetes compared to placebo (OR=1.14; 95% CI 1.02-1.28) but did not demonstrate an increased risk compared to hydrophilic statins (OR=1.05; 95% CI 0.9-1.23). Thakker et al noted that due to the lack of head-to-head studies, indirect comparisons between statins were performed; therefore, the outcomes have limitations. The trials included had a relatively short follow-up time, which could lead to an underestimation of the risk of diabetes.

Casula et al performed a meta-analysis of observational studies to evaluate the risk of new-onset diabetes with statin medications.[8] Studies from inception to June 2016 were included; the studies all examined the risk of diabetes with statins versus without statins, included ≥1,000 participants, had a follow-up period ≥1 year, and reported a risk estimate and associated 95% CI. Tests for between-study heterogeneity and publication bias were performed; $P<0.05$ was considered statistically significant.

Twenty observational studies were included in the meta-analysis.[8] The median duration of the studies was 7.2 years with a range of 2-20 years. An overall statistically significantly greater risk of new-onset diabetes was found in users of statin therapy compared to those not on statin therapy (relative risk=1.44; 95% CI 1.31-1.58). An analysis of individual statins revealed that rosuvastatin (relative risk=1.61; 95% CI 1.30-1.98) and atorvastatin (relative risk=1.49; 95% CI 1.31-1.70) carried the greatest risk. A limitation of the study was publication bias for atorvastatin when using Egger's test ($P=0.03$); no publication bias was noted for other statins.

Additional Studies

Multiple studies have been published on incident diabetes associated with statins. The following studies are examples of those that were recently published and not included in the above meta-analyses.

A case-control study by Kim et al, published in April 2019, evaluated an association between statin therapy and new-onset diabetes.[9] Data were used from the National Health Insurance Service National Sample Cohort database in South Korea. The study period was from 2009 to 2013. Patients who took statins at any point in the 3 years before the study period, and those who were prescribed a statin only once were excluded. Controls were assigned through 1:5 propensity score matching with age and sex. There were 6,417 cases with new-onset diabetes and 32,085 controls without diabetes. The average age was 51.1 years and both groups were 67.7% male.

After propensity score matching and adjusting for age and sex, there was a statistically significant increased risk for new-onset diabetes in statin users compared to non-statin users (OR=1.44; 95% CI 1.31-1.59).[9] Another model was created which included additional adjustments (for drinking, smoking, exercise, body mass index [BMI], high-density lipoprotein cholesterol [HDL-C], LDL-C, triglycerides, waist circumference, and hypertension) and no significant increase in new-onset diabetes was observed during the study period (OR=1.03; 95% CI 0.93-1.14). The investigators also reported results according to the duration of statin therapy; when the full model was used, none of the results were significantly elevated. Using the larger model, a statistically significant increase in incident diabetes was reported in patients who were prescribed statins for a period <6 months and within the last 6 months compared to non-statin users (OR=1.48; 95% CI 1.21-1.82).

A strength of this study was that it included data such as cholesterol values, alcohol and tobacco use, and waist circumference for subjects.[9] A limitation of the study was that it did not include glycosylated hemoglobin (HbA1c) values or the type or dose of statin.

A prospective cohort study by Ahmadizar et al, published in March 2019, provided additional evidence regarding increased risk of incident diabetes associated with statins.[10] The authors used subjects from the Rotterdam study, a prospective population-based cohort study, as their intervention and control cohorts. The Rotterdam study included an initial cohort from 1989 and 2 cohort extensions: from 2000 and 2006. The

intervention group consisted of patients who were statin users, and the control group were patients who were never prescribed a statin. Patients who had a diagnosis of type 2 diabetes mellitus (T2DM) or cardiovascular disease were excluded from the study. Patients who were on a statin medication at baseline were also excluded. If a patient was diagnosed with T2DM within the timeframe a statin was prescribed, he/she was classified as a current user and stratified into a group based on statin therapy duration. Patients who were diagnosed with T2DM but were no longer on a statin were defined as past users. "Ever" use was defined as current use or past use. The T2DM diagnosis was defined as a fasting serum glucose of ≥7.0 mmol/L (126 mg/dL[11]), a non-fasting serum glucose of ≥11.1 mmol/L (200 mg/dL[11]), or use of blood glucose-lowering medications.

There were 8,567 patients in the cohort, with 716 cases of incident T2DM.[10] Simvastatin was used by 58% of subjects, atorvastatin by 25.5% of subjects, pravastatin by 10.3% of subjects, and fluvastatin by 7.1% of subjects. The median follow-up was 4 years. The adjusted risk (adjusted for age, gender, cohort, smoking, alcohol consumption, physical activity and education level, BMI, and hypertension) of incident diabetes was significantly higher with ever statin use compared with never statin users (hazard ratio [HR]=1.38; 95% CI 1.09-1.74). The adjusted risk was significantly higher for current but not past statin users (HR=1.52; 95% CI 1.15-2.00). The results showed that the risk of incident diabetes was significantly higher in intermediate (31-365 days) and long-term (>365 days) users of statins (adjusted HR=1.70; 95% CI 1.13-2.56 and adjusted HR=1.37; 95% CI 1.04-1.81, respectively). When the data were stratified by baseline BMI, the association between statin use and incident T2DM was statistically significant in those who were overweight or obese as compared to those with normal BMI (HR=1.42; 95% CI 1.10-1.83 and HR=1.18; 95% CI 0.69-2.02, respectively). It should be noted that obesity and dyslipidemia themselves are associated with the risk of T2DM.[12]

There were some drawbacks to this study. Importantly, HbA1c values were not obtained at any point.[10] While imperfect, the diagnosis of diabetes can be determined based on HbA1c (≥6.5%).[13] Some commonly prescribed statin medications, rosuvastatin and lovastatin, were not evaluated in this study. The authors noted that reverse causation may be occurring, as patients who are high risk (obese, fatty liver) are prescribed statins to prevent ASCVD. Ninety-five percent of the patients enrolled were Caucasian and the study was completed in Europe, which limits the generalizability of this study.

The study had strengths, which include its prospective design, which mitigates selection and information biases.[10] The study enrolled a large number of subjects and the study follow-up was a median of 4 years. Detailed data on the type, dose, and duration of statin use were available to the researchers. The data were then analyzed using multiple models which were adjusted for many different confounders.

Implications in Pharmacy Practice

Statins are currently first-line medications for patients with moderate or high ASCVD risk.[1] Although current research has shown a link between statin therapy and new-onset diabetes, it is understood that patients with dyslipidemia will be at a higher risk for developing the disease.[11] When a statin is prescribed, patients should be educated on the importance of measures such as diet and exercise in preventing both ASCVD and T2DM. For those who are statin resistant or intolerant, PCSK9 inhibitors may not have an increased risk for the development of diabetes, based on the meta-analysis by Khan et al.[5]

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Measles Outbreaks in the United States

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The presence of measles was first described dating back to the ninth century.[1] Measles is a highly contagious illness caused by a single-stranded ribonucleic acid virus in which humans are the only reservoir.[2] Although vaccination efforts led to measles being declared eliminated from the United States (US) in the year 2000, it still remains common in many other developing countries worldwide, including areas of Africa, Europe, Asia and the Pacific. As a result, travel to these countries by unvaccinated individuals can reintroduce the disease to the US. Each year, small outbreaks of measles are noted throughout different parts of the US when these travelers return and spread the disease to other unvaccinated individuals. However, in recent years there has been a significant increase in the number of outbreaks and confirmed measles cases in the US, with 2019 already seeing the most cases of measles since it was declared eliminated.

The measles virus is very contagious; if exposed, up to 90% of those not immune to it could become infected.[3] The virus survives within the mucous of the nose and throat of those infected, and therefore can be easily spread from person to person through coughing and sneezing. In addition, respiratory droplets released from an infected individual contain measles virus that remains active for up to 2 hours. Therefore, touching contaminated objects or breathing contaminated air, even if the infected individual is no longer present, can allow for transmission of the virus to susceptible individuals. Those infected with measles are considered to be contagious for the 4 days both preceding and following the development of the classic maculopapular rash.

Once introduced to the human body, the measles virus undergoes an incubation period that typically lasts anywhere from 10-12 days, with symptoms generally appearing between days 7 and 14.[4,5] The initial symptoms classically associated with measles occur in what is known as the prodrome period and include fever, cough, runny nose and conjunctivitis.[2,5] About 48-72 hours after initial symptoms appear, many patients develop Koplik spots, which present as small white lesions inside the mouth.[5] Following the development of initial symptoms and Koplik spots, the next phase of measles infection presents, characterized by the development of a red maculopapular rash that typically starts at the hairline and face and then spreads down from the head to the rest of the body. Development of this rash can also be associated with a high fever, in some cases over 104°F.

The rash associated with measles infection typically lasts for 5-6 days and then fades; other symptoms start to resolve as well.[4] However, up to 30% of patients who develop measles also develop complications of the disease, with the most common being otitis media and diarrhea.[4,6] Other more serious complications can include development of encephalitis or pneumonia.[6] Those <5 years of age and >20 years of age are most likely to develop measles complications if infected with the virus. Although very rare, a long-term complication of measles called subacute sclerosing panencephalitis (SSPE) is also possible in some individuals and typically presents 7-10 years after the initial measles infection. SSPE is an incurable and predominantly fatal disorder of the central nervous system that can develop even if the individual has made a full recovery from the initial measles infection.

Currently there is no antiviral treatment available for measles; treatment of the disease is mainly supportive and may include anti-pyretics and fluids.[2] Antibiotics may be necessary to treat secondary complications such as otitis media and bacterial pneumonia if they arise. Vitamin A may also be given to children hospitalized with severe infections, as measles can lead to acute deficiency.[7] This can be problematic, as low levels of vitamin A can prolong recovery time, increase the rate of complications, and lead to xerophthalmia.

Although measles remains a major source of morbidity and mortality in many developing countries, vaccination efforts have drastically decreased the number of measles cases and outbreaks in the US.[2] The first vaccine against the measles virus was developed in 1963 by John Enders and colleagues and was later updated in 1968.[1] Today, there are 2 vaccines licensed for use in the US that protect against measles as well as other viral diseases: the measles, mumps, and rubella virus (MMR) vaccine and the measles, mumps, rubella, and varicella virus (MMRV) vaccine.[8,9] Both vaccines contain live-attenuated viruses of their respective components and therefore should not be given to those who are pregnant, have a weakened immune system, have had a recent blood transfusion, have tuberculosis, have received another vaccine in the past 4 weeks or are moderately to severely ill.

The Centers for Disease Control and Prevention (CDC) recommend children receive their first dose of MMR or MMRV vaccine at 12-15 months and a second dose between the ages of 4 and 6 years.[10] Adults without evidence of immunity to measles, mumps, or rubella who were born after the year 1957 are also recommended to receive 1 dose of the MMR vaccine, although adult dosing schedules may vary depending on the presence of special situations including pregnancy, severe immunocompromising conditions, students at postsecondary institutions, international travelers and healthcare personnel.[11] Those born before the year 1957 are presumed to be immune to measles. The vaccine has been proven both safe and effective against measles, with 1 dose providing protection against the virus in 93% of cases and 2 doses providing 97% protection.[8]

Since the year 2000, the annual number of measles cases in the US has ranged anywhere from 37 cases (2004) to 667 cases (2014).[2] However, in just the first 5 months of 2019, the number of measles cases in the US has already surpassed the highest annual number of cases since 1992, reaching a total of 981 confirmed cases in 26 states as of May 31, 2019.[12] Outbreaks (defined as 3 or more cases) have been reported in California (Butte County, Los Angeles County and Sacramento County), Georgia, Maryland, Michigan, New York (Rockland County and New York City), Pennsylvania, and Washington. These outbreaks have largely been linked to international travel to countries such as Israel, Ukraine, and the Philippines, which are all currently experiencing large measles outbreaks. Although no deaths have been reported as of April 26, 2019, over 60 hospitalizations due to the disease have been reported and the vast majority of cases seen have been in unvaccinated individuals.[13]

The recent hesitancy and refusal of individuals to get vaccinated and for parents to have their children vaccinated is also thought to have contributed to the increase in measles cases and outbreaks throughout the country.[14,15] According to experts, the reasons for not vaccinating may vary. Some common reasons for not vaccinating include incorrect information regarding the safety of vaccines, the belief that vaccines are not necessary due to decreased experience and exposure to vaccine preventable diseases, religious beliefs that deter individuals from medical care, and the belief that lawmakers should not have the right to take away patients' rights to make their own medical choices.[14] While all states require routine vaccinations for school children, there are exemptions to this rule.[16] Only 3 states (California, West Virginia, and Mississippi) allow for vaccine exemptions strictly for medical reasons. All other states allow for medical and/or religious exemptions, and 16 states allow for vaccine exemptions for medical, religious, and philosophical reasons. These exemptions have allowed many individuals to bypass the vaccination requirements for children and have likely contributed to the current outbreak, as well.

Several states have taken steps to improve vaccination rates and prevent future spread of the disease. A bill in the state legislature of Oregon proposes to eliminate all non-medical vaccine exemptions, if passed.[17] Similarly, states such as Colorado and Maine are considering bills to tighten vaccine laws and remove certain non-medical exemptions. The state of Washington recently removed philosophical reasons from the list of vaccine exemptions to promote increased vaccination rates. Given the numerous outbreaks in New York City, government officials in New York have taken several steps to help increase vaccination rates, especially among the ultra-Orthodox Jewish community where the majority of measles cases have occurred.[18,19] At first, educational outreach was employed but did not appear to make an impact on the intended communities. This led to more drastic efforts, including the banning of unvaccinated children from attending school, the declaration of a public health emergency in the Williamsburg neighborhood of Brooklyn (that would require those unvaccinated to receive the vaccine or receive a $1,000 fine), and the proposal to require unvaccinated individuals, those with confirmed measles, or those ≤18 years of age who have been exposed to the virus, living

in Rockland County to remain at home in isolation for 21 days. Although later overruled and halted by a judge, Rockland County also placed a ban on unvaccinated children in public places.

In light of the recent measles outbreaks occurring across the country, it is imperative for healthcare providers to ensure that patients, especially children, are vaccinated against the disease if not otherwise contraindicated. Healthcare providers should also be prepared to discuss vaccine safety and efficacy with those who may be hesitant about getting the vaccine. In addition, those traveling internationally, especially to countries where measles remains common or where outbreaks are occurring, should ensure they are properly protected against the disease prior to travel to avoid contracting the virus and potentially spreading it to others.[2] Full immunization recommendations regarding the MMR vaccine for adults and children, including international travelers, can be found on the CDC website. As the number of cases continues to rise across the country, extra vigilance should be taken by patients as well as healthcare providers to promptly recognize potential cases of measles and respond appropriately to avoid further spread of the highly contagious disease. Patients who believe they may have measles should contact their healthcare providers immediately for further evaluation. Patients with confirmed measles should be placed in isolation for at least 4 days after development of rash and healthcare facilities should take airborne precautions for any individuals with suspected or confirmed measles.

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2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

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Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death both globally and in the United States (US).[1] Multiple chronic health conditions have been identified which increase the risk for ASCVD; however, appropriate treatment of these conditions may allow for a reduction in ASCVD risk. Some of these conditions include obesity, diabetes, hypertension, and hyperlipidemia. In addition to the above, comprehensive, patient-centered discussions between patients and clinicians should be undertaken to successfully optimize therapy and encourage a shared decision-making process that will keep the patient involved in his/her care. The recently published American College of Cardiology (ACC)/American Heart Association (AHA) guideline addresses the primary prevention of cardiovascular disease in adults with the goal of reducing negative outcomes related to ASCVD, congestive heart failure, and atrial fibrillation through both pharmacologic and non-pharmacologic interventions. The overall objective of the guideline was to consolidate existing guideline recommendations, consensus statements, and expert opinions for type 2 diabetes, hyperlipidemia, and hypertension and to provide new recommendations regarding aspirin, exercise/physical activity, and tobacco use.

Overview

First and foremost, the 2019 ACC/AHA guideline on primary prevention of cardiovascular disease revisits the 10-year ASCVD risk score, which is an estimate of a patient's overall expected cardiovascular event risk, and provides guidance and standardization on preventive interventions.[1] For adults 20 to 39 years of age, it is reasonable to assess ASCVD risk factors every 4 to 6 years; an ASCVD risk score calculation should be performed routinely thereafter, starting at 40 years of age until approximately 75 years of age. Following calculation of a patient's 10-year ASCVD score, placement into a particular ASCVD risk group occurs,

indicating the risk for an ASCVD event: low (<5%), borderline (5% to <7.5%), intermediate (7.5% to <20%), or high (≥20%). For patients who are considered borderline or selected patients with intermediate risk with an unclear indication for preventive treatment (e.g., statins), obtaining a coronary artery calcium (CAC) is reasonable. This involves a non-invasive computed tomography (CT) scan of the heart that calculates ASCVD risk by measuring the amount of calcified plaque in the coronary arteries.[2] Based on the CAC results, ASCVD risk can either be reclassified upwards (if score is ≥100) or downwards (if score is 0).

Using the results from the ASCVD risk calculator with or without CAC, the patient-clinician discussion can also include identification of factors that could increase a patient's risk of an ASCVD event.[1] These can be found in Table 1. Addressing lifestyle factors that could improve ASCVD risk is also imperative; these include a well-rounded diet consisting of vegetables, fruits, whole grains, and dietary monosaturated/polysaturated fats, with less refined carbohydrates, sweetened beverages, sodium, cholesterol (animal proteins), and saturated/trans fats. Furthermore, adults are recommended to engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity to reduce ASCVD risk. Overall, the goal is to encourage weight loss (≥5% initial weight) in those who are deemed overweight or obese based on their body mass index (≥25 kg/m^2) since increased body weight and waist circumference can increase overall cardiometabolic risk.

Table 1. Risk-enhancing factors for clinician–patient discussion.[1]

Risk-Enhancing Factors	Comments
Family history of premature ASCVD	Males, age <55 years; females, age <65 years
Primary hypercholesterolemia	LDL-C, 160-189 mg/dL; non-HDL-C, 190-219 mg/dL
Metabolic syndrome	Increased waist circumference, elevated triglycerides (>150 mg/dL, nonfasting), elevated blood pressure, elevated glucose, and low HDL-C (<40 mg/dL in men; <50 mg/dL in women) are factors; a tally of 3 makes the diagnosis
Chronic kidney disease	eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation
Chronic inflammatory conditions	Examples: psoriasis, RA, lupus, or HIV/AIDS
History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase ASCVD risk	Example: preeclampsia
High-risk race/ethnicity	Example: South Asian ancestry
Lipids/biomarkers	Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, nonfasting) If measured: • Elevated high-sensitivity C-reactive protein (≥2.0 mg/L) • Elevated Lp(a) (≥50 mg/dL or ≥125 nmol/L) • Elevated apoB (≥130 mg/dL) • ABI (<0.9)

ABI=ankle-brachial index; AIDS=acquired immunodeficiency syndrome; apoB=apolipoprotein B; ASCVD=atherosclerotic cardiovascular disease; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; HIV=human immunodeficiency virus; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); RA=rheumatoid arthritis.

Following these general interventions, the 2019 ACC/AHA guideline presents recommendations based on disease state or condition.[1] These conditions will be briefly discussed below.

Type 2 Diabetes

The development and progression of type 2 diabetes are heavily influenced by dietary patterns, physical activity, and body weight; therefore, the interventions which were discussed above are important for these patients.[1] Type 2 diabetes remains a highly prevalent disease and a major ASCVD risk factor. After lifestyle modifications are attempted, or in conjunction with these modifications, metformin therapy is supported by the guideline as a first-line agent due to its ability to decrease hepatic gluconeogenesis and increase peripheral insulin sensitivity. Furthermore, according to the United Kingdom Prospective Diabetes Study, intensive metformin treatment, when compared to conventional treatment (primarily diet modifications), resulted in a 32% reduction in microvascular and macrovascular diabetes-related outcomes, a 39% reduction in myocardial infarction (MI), and a 36% reduction in all-cause mortality rate.[3] Following metformin therapy, if patients require further therapy for glucose control, the ACC/AHA acknowledges 2 other drug classes which have shown to provide ASCVD risk reduction and benefit in primary prevention: glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g., empagliflozin).[1,4-6]

Hyperlipidemia

The 2019 ACC/AHA guideline adopted the 2018 ACC/AHA multisociety guideline recommendations for management of elevated blood cholesterol.[1,7] The guideline recommends statins for specific groups of patients (i.e., statin benefit groups) based on ASCVD risk scores, disease states, or lipid panel results. These groups are explained in Table 2.

Table 2. Statin benefit groups.[1,7]

Benefit Group	Recommendations
Age 20 to 75 years, LDL-C ≥190 mg/dL	High-intensity statin or maximally tolerated statin
Diabetes and age 40 to 75 years	Moderate-intensity statin Risk assessment to consider high-intensity statin*
Age 40 to 75 years, LDL-C ≥70 but <190 mg/dL without diabetes	<5% "Low Risk"** – emphasize lifestyle
	5% to <7.5% "Borderline Risk" – risk discussion for moderate-intensity statin
	≥7.5% to <20% "Intermediate Risk" – risk discussion for statin therapy to reduce LDL-C by ≥30% (i.e. moderate-intensity statin) CAC scores may be used to further assess
	≥20% "High Risk" – statin to reduce LDL-C ≥50% (i.e. high-intensity statin)
Age ≥75 years	Clinical assessment, risk discussion

*Multiple atherosclerotic cardiovascular disease (ASCVD) risk factors including long duration of type 2 diabetes (≥10 years) or type 1 diabetes (≥20 years), albuminuria ≥30 mcg albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, ankle brachial index <0.9.
**Percentages (%) refer to calculated ASCVD risk.
CAC=coronary artery calcium; eGFR=estimated glomerular filtration rate; LDL-C=low-density lipoprotein cholesterol.

Hypertension

The 2019 ACC/AHA guideline adopted the 2017 ACC/AHA hypertension clinical practice guideline recommendations for management of elevated blood pressure.[1,8] Non-pharmacologic treatments are always recommended as previously explained, including healthy diet, reduction in sodium intake, enhanced intake of potassium, weight loss, physical activity, and moderation in alcohol consumption. The 2017 guideline did

introduce a new threshold for stage 1 (130-139/80-89 mm Hg) and stage 2 (≥140/90 mm Hg) hypertension. The recommendations on when to initiate blood pressure-lowering therapy are explained in Table 3.

Table 3. Blood pressure thresholds and recommendations for treatment.[1,8]

Blood Pressure	Range (mm Hg)	Recommendations
Normal	<120/80	Lifestyle modifications
Elevated	120-129/<80	Lifestyle modifications
Stage 1	130-139/80-89	Estimate ASCVD Risk: ≥10% - lifestyle modifications PLUS pharmacotherapy <10% - lifestyle modifications
Stage 2	≥140/90	Lifestyle modifications PLUS pharmacotherapy

ASCVD=atherosclerotic cardiovascular disease

For patients with hypertension, chronic kidney disease, and/or type 2 diabetes, a blood pressure goal of <130/80 mmHg is recommended.[1,8]

Tobacco Use

Tobacco use is known to increase the risk of all-cause mortality and ASCVD; this even involves secondhand smoke exposure.[1] In addition to traditional tobacco products, electronic nicotine delivery systems (ENDS) are a new class of tobacco products that may increase the risk of both cardiovascular and pulmonary diseases. It has been reported that ENDS can lead to arrhythmias, hypertension, oxidative stress, and sympathetic stimulation. The 2019 ACC/AHA guideline adopted the US Public Health Service clinical practice guideline recommendations for treating tobacco use and dependence, which encourages clinicians to advise patients to quit smoking/smokeless tobacco in a firm but nonjudgmental fashion.[1,9] Strategies of tobacco cessation are discussed briefly within the primary prevention guideline and include both behavioral interventions and pharmacotherapy options.[1] The guideline additionally recommends that assessment of tobacco use status be treated like a vital sign, which would allow for screening at every office visit. Seven medications are available to assist with smoking cessation and have been approved by the Food and Drug Administration (FDA); these medications include nicotine replacement therapy (patch, gum, lozenge, nasal spray, oral inhaler), bupropion (Zyban®), and varenicline (Chantix®). Lastly, the primary prevention guideline recommends that clinicians counsel on precautions against exposure to secondhand smoke, including ENDS, by restricting exposure inside all homes or vehicles and within 25 feet of all entryways, windows, and building vents.

Aspirin

Aspirin has been a long-standing therapy for ASCVD prevention, with a more well-established role in secondary prevention of ASCVD.[1] Aspirin's role for primary prevention is less clear; the guideline recommends that clinicians discuss the risk of bleeding versus the benefit of treatment with patients. In addition, ACC/AHA does not recommend use of low-dose aspirin routinely in patients >70 years of age or in those at an increased risk of bleeding. However, in patients 40 to 70 years of age with an increased ASCVD risk (≥10%) with a low risk of bleeding, aspirin therapy at doses of 75 to 100 mg/day can be considered, especially if the patient cannot modify or is having trouble adjusting other contributing ASCVD risk factors.

Conclusion

The 2019 ACC/AHA guideline on primary prevention of cardiovascular disease encompasses the numerous areas that contribute to an increased risk of ASCVD including diabetes, hyperlipidemia, hypertension, obesity, and tobacco use, as well as lifestyle factors.[1] The objective of the guideline was to consolidate existing guideline recommendations, consensus statements, and expert opinions into a single document. The ACC/AHA guideline also includes new recommendations regarding aspirin, exercise/physical activity, and tobacco use. At the

forefront of the guideline and continuously mentioned throughout, effective patient-clinician interactions, calculation of the ASCVD risk score, and emphasis on both non-pharmacologic (i.e., lifestyle management) and pharmacologic treatments are mainstays that are essential to implement the changes that will truly impact ASCVD risk and improve preventive care for identified patients.

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