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In this issue…

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.

The PCSK9 Inhibitors: What You Need to Know

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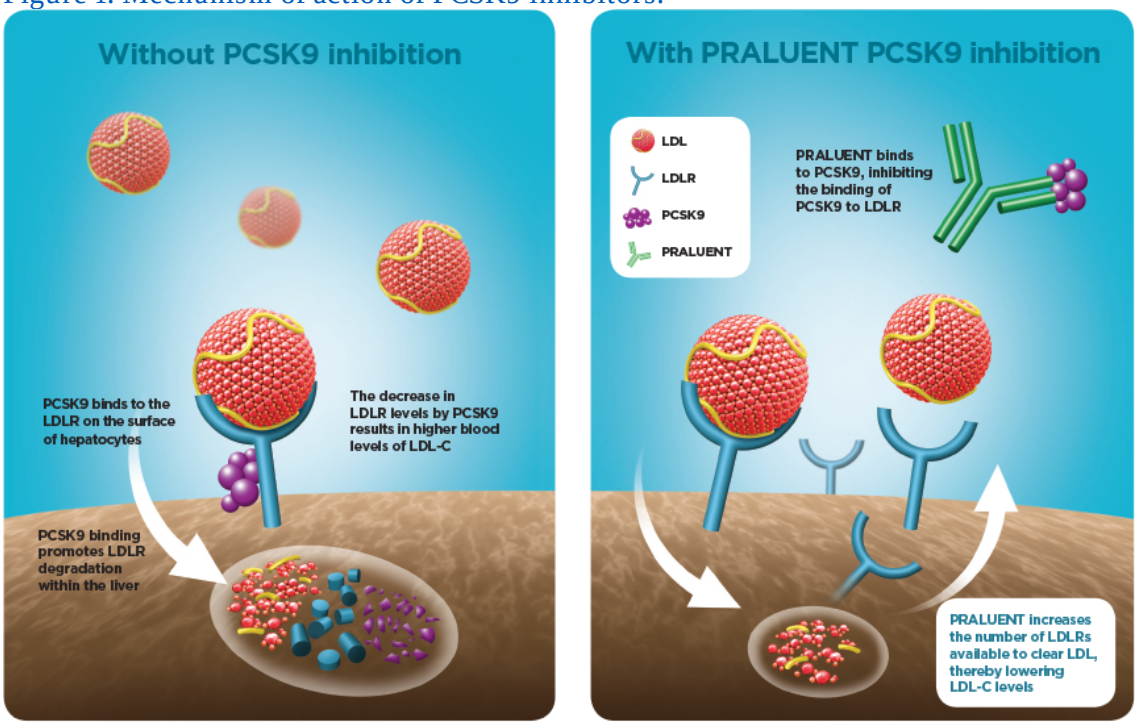
When one used to think of atherosclerotic cardiovascular disease (ASCVD) and risk reduction, management of cholesterol levels was the primary focus.[1] However, the American College of Cardiology/American Heart Association (ACC/AHA) 2013 Blood Cholesterol evidence-based guideline moved away from the idea of focusing on target cholesterol levels and instead encouraged holistic assessment of the patient in order to reduce ASCVD risk.[2] Based on data from randomized controlled trials, the ACC/AHA 2013 guideline identified 4 statin benefit groups in whom statin therapy should be used to reduce the risk of ASCVD. The guideline also defined statin therapy intensities, or doses at which there is an expected percentage of reduction in low-density lipoprotein (LDL) cholesterol. However, if patients cannot tolerate or do not respond adequately to statin therapy, what is next?

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibodies, evolocumab (Repatha®) and alirocumab (Praluent®), are medications of a relatively new class that have shown significant impact on LDL cholesterol reduction with further effects on total cholesterol, non-high-density lipoprotein (non-HDL) cholesterol, and apolipoprotein B (ApoB).[3,4] As shown in Figure 1, these products consist of human monoclonal

antibodies that bind to PCSK9. PCSK9 binds to the low-density lipoprotein receptors (LDLRs) on hepatocytes to promote their degradation within the liver. LDLR is the primary receptor that clears circulating LDL cholesterol; thus, by inhibiting the binding of PCSK9 to LDLRs, these medications increase the number of receptors available to clear circulating LDL.

Figure 1. Mechanism of action of PCSK9 inhibitors.[5]



Evolocumab (Repatha®) is approved by the Food and Drug Administration (FDA) as an adjunct to diet and other lipid-lowering therapies to treat patients with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH), who require additional reduction in LDL cholesterol.[4] For established cardiovascular disease or primary hyperlipidemia (including HeFH) the recommended dosage is either 140 mg by subcutaneous injection (SC) every 2 weeks or 420 mg SC every month. For HoFH, 420 mg SC every month is the approved dosage. In clinical trials of patients with primary hyperlipidemia including HeFH, on average and in adjunct to maximally tolerated statin therapy, the manufacturer reports that evolocumab lowered LDL cholesterol by approximately 47 to 63 mg/dL, non-HDL cholesterol by 40 to 55 mg/dL, and ApoB by 40 to 50 mg/dL over 12 weeks. For those with HoFH, evolocumab lowered LDL cholesterol by 22 mg/dL, non-HDL cholesterol by 20 mg/dL, and ApoB by 17 mg/dL over 12 weeks.

In December 2017, the FDA approved an additional indication for evolocumab: reduction of the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.[6] This approval was based on findings from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial.[7] This trial was a randomized, double-blind, placebo-controlled, multinational study involving patients 40 to 85 years of age who had clinically evident ASCVD with LDL cholesterol of at least 70 mg/dL or greater while taking optimized lipid-lowering therapy. Patients were assigned 1:1 to receive evolocumab (either 140 mg every 2 weeks or 420 mg every month, SC) or placebo. The primary efficacy endpoint was major cardiovascular events, defined as a composite of

cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Safety was assessed through reports of adverse events.

A total of 27,654 patients were randomized: 13,784 patients in the evolocumab group and 13,780 patients in the placebo group.[7] Patients were followed for a median duration of 26 months. The baseline characteristics were similar between groups: the mean age was 63 years, and 75% of participants were male. Most of the patients (81.1%) had a history of myocardial infarction, 19.4% had a history of non-hemorrhagic stroke, and 13.2% had a history of symptomatic peripheral artery disease. Approximately 69.3% were taking a high intensity statin at baseline and 30.4% were taking a moderate intensity statin. With regard to the primary endpoint, evolocumab significantly reduced the risk compared to placebo. These events occurred in 9.8% of patients in the evolocumab group and 11.3% of patients in the placebo group (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.79 to 0.92). In terms of the individual events, significant differences were observed between groups favoring evolocumab for the following outcomes: myocardial infarction (HR 0.73, 95% CI 0.65 to 0.82), stroke (HR 0.79, 95% CI 0.66 to 0.95), and coronary revascularization (HR 0.78, 95% CI 0.71 to 0.86). Evolocumab also significantly lowered LDL cholesterol levels compared to placebo with a least-squares mean percentage reduction of 59% (95% CI 58 to 60) at 48 weeks. For safety, there were no significant differences between groups in the overall rates of adverse events, serious adverse events, and treatment-related adverse events. There were nominally significant differences in the rates of injection-site reactions; however, the incidences were rare (2.1% vs. 1.6%, evolocumab vs. placebo, respectively, $p<0.001$).

Alirocumab (Praluent®) is FDA-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with clinical ASCVD or HeFH.[3] The approved dosages include either 75 mg SC every 2 weeks or 300 mg SC every month. Per the manufacturer, efficacy trials involving patients with primary hyperlipidemia including HeFH have shown that on average and in adjunct to maximally tolerated statin therapy, alirocumab lowered LDL cholesterol by approximately 47 to 58 mg/dL, total cholesterol by 30 to 36 mg/dL, non-HDL cholesterol by 42 to 49 mg/dL, and ApoB by 40 to 50 mg/dL over 24 weeks.

The effects of alirocumab on cardiovascular outcomes were investigated in the Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY Outcomes) trial.[8] The ODYSSEY Outcomes trial has not yet been published but the methods and results were presented at the March 2018 ACC Annual Scientific Session. Patients who were 1 to 12 months status-post an acute coronary syndrome event were randomized to alirocumab every 2 weeks SC or placebo. The drug was titrated between 75 and 150 mg to maintain LDL cholesterol levels between 25 and 50 mg/dl but above 15 mg/dl. The primary efficacy endpoint was major cardiovascular events, defined as a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.

A total of 18,924 patients were evaluated in ODYSSEY Outcomes: 9,462 patients in the alirocumab group and 9,462 patients in the placebo group.[8] Patients were followed for a median duration of 48 months. The baseline characteristics were similar between groups: the mean age was 58 years, and 75% of participants were male. A subset of the patients (18.9 to 19.5%) had a history of myocardial infarction; approximately 88.6% were taking a high intensity statin at baseline, and 8.8% were taking a moderate intensity statin. With regard to the primary endpoint, alirocumab significantly reduced the risk compared to placebo. These events occurred in 9.5% of patients in the alirocumab group and 11.1% of patients in the placebo group (HR 0.85, 95% CI 0.78 to 0.93). In terms of the individual events, significant differences were observed between groups favoring alirocumab for the following outcomes: non-fatal myocardial infarction (HR 0.86, 95% CI 0.77 to 0.96), ischemic stroke (HR

0.73, 95% CI 0.57 to 0.93), and unstable angina (HR 0.61, 95% CI 0.41 to 0.92). Though there was a lower occurrence of coronary heart disease death with alirocumab compared to placebo, the difference was not statistically significant (HR 0.92, 95% CI 0.76 to 1.11).

Overall and as shown above, the PCSK9 inhibitors, evolocumab (Repatha®) and alirocumab (Praluent®), have demonstrated significant benefits in terms of lipid-lowering effects and cardiovascular outcomes.[7,8] Following the publication of FOURIER, the ACC Expert Consensus published a focused update pertaining to non-statin lipid lowering therapies for LDL reduction and the National Lipid Association (NLA) also updated their recommendations on the use of PCSK9 inhibitors.[9,10] Specifically, when given SC at biweekly or monthly increments, both organizations suggest that patients with a diagnosis of hyperlipidemia who have had an acute coronary syndrome event or need further ASCVD risk reduction may benefit from this medication class and recommend PCSK9 inhibitors as viable adjunctive agents. In conclusion, in patients who are intolerant to or on maximum statin therapy, have a suboptimal response in LDL reduction while on statin therapy, and/or have evident cardiovascular disease or risk, PCSK9 inhibitors can be considered in addition to other lipid-lowering therapies.

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Antihypertensives and Prevention of Dementia and Alzheimer's Disease

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Alzheimer's disease is a growing public health issue in the United States (US).[1] As the population ages, the prevalence of Alzheimer's also increases. As of 2018, approximately 5.7 million adults in the US are living with Alzheimer's dementia; 5.5 million of these cases are in patients aged 65 or older.[2] Alzheimer's disease is the sixth leading cause of death in the US and causes significant burden on both patients and caregivers.[3] In order to care for family members with Alzheimer's disease, caregivers often experience substantial financial, physical, and emotional burdens. Alzheimer's disease also places a burden on the entire healthcare system as it is 1 of the costliest conditions to society.[4] With no known cure, and treatments that have, at best, limited evidence for efficacy and effectiveness, prevention of the disease is essential to overcome this public health dilemma. Over decades of research, it is clear that prevention of Alzheimer's involves reducing risk factors that span across several domains.

When examining the currently limited treatment options for Alzheimer's, it becomes clear that the prevention of the disease is the best treatment. Treatment of Alzheimer's dementia revolves around 2 classes of medications: acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists.[5] The choice of agent(s) depends largely on the severity of the disease. All agents in these classes (donepezil, galantamine, rivastigmine, and memantine) have displayed paltry evidence for efficacy and effectiveness in randomized controlled trials and systematic reviews. Instead, these agents are known for their wide-ranging adverse effects (especially gastrointestinal [GI]-related) that often render them intolerable. The Alzheimer's pharmaceutical pipeline for 2018 looks promising; there are drugs with novel treatment approaches undergoing phase III trials.[6] Unfortunately, these agents are still years away from being approved (if they are approved at all).

The modifiable risk factors for Alzheimer's disease are related to lifestyle and diet.[7] Addressing these risk factors has guideline support based on evidence from the medical literature.[7,8] Population-based studies have revealed an association between elevated blood pressure in midlife and an increased risk of Alzheimer's and dementia development later in life.[9,10] Studies on body mass index (BMI) have revealed a bidirectional association: higher BMI in midlife can lead to increased risk of Alzheimer's and dementia, but a low BMI or BMI loss in advanced age may be related to the development of dementia.[11,12] Studies on cholesterol and risk of dementia and Alzheimer's disease have also shown a mixed effect, with elevated cholesterol levels in midlife increasing the risk of dementia and Alzheimer's disease and declining cholesterol levels in the late stages of life conferring a higher dementia risk.[13,14] Current cigarette smoking is another major risk factor for Alzheimer's dementia; notably, it is thought that as much as 14% of Alzheimer's cases can be attributed to this behavior.[15]

The future of preventing Alzheimer's disease may focus on using medication treatment to address the modifiable risk factors. An abstract of a meta-analysis presented at the Alzheimer's Association International Conference (AAIC) in July 2018 discussed the use of blood pressure-lowering drugs and their association with Alzheimer's and dementia incidence.[16] This meta-analysis examined long-term, prospective studies of community-dwelling adults at least 55 years of age. These studies included baseline data on blood pressure and the use of blood pressure-lowering drugs. Additionally, all adults included were initially dementia-free. The specific drug classes analyzed were: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and diuretics. There were 6 studies included in this meta-analysis involving 31,090 adults. Participants were followed anywhere from 7 to 22 years. In total, 3728 adults were diagnosed with dementia and 1741 were specifically diagnosed with Alzheimer's disease. In subjects who had a high baseline blood pressure, the use of blood pressure medications was associated with a reduced risk for all-cause dementia when compared to those who were not on blood pressure medication (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.79-0.98). The risk for Alzheimer's dementia specifically was significantly lower in the blood pressure treatment group (HR 0.85, 95% CI 0.74-0.99). When stratified by APOE-ε4 carrier status, it was revealed that only those who carried the gene showed a statistically significant association between blood pressure-lowering agents and lower incidence of dementia.

The association was significant for those on ACE-inhibitors (HR 0.75, 95% CI 0.57-0.98), ARBs (HR 0.65, 95% CI 0.47-0.91), and diuretics (HR 0.75, 95% CI 0.59-0.94). Subjects with a normal baseline blood pressure did not show an increased risk for development of dementia. This meta-analysis showed that prevention of Alzheimer's may necessitate drug treatment aimed at modifiable risk factors. Similar findings were also found in a separate meta-analysis, which found that antihypertensive drugs were associated with a reduced risk of dementia (albeit, not a reduced risk of Alzheimer's).[17] Additionally, another meta-analysis found that ACE-inhibitors may reduce dementia risk.[18]

Despite some support from meta-analyses, guidelines assert there is limited evidence to support use of antihypertensives in prevention of dementia. For example, the British Association for Psychopharmacology (BAP) briefly discusses pharmacological treatment as a way to prevent dementia.[19] The BAP states there is currently limited evidence to support the use of antihypertensives in dementia prevention and that more research is needed to determine causality. This general consensus is repeated in a practice guideline from the European Federation of the Neurological Societies.[20]

Current treatment modalities for Alzheimer's dementia have shown limited efficacy and effectiveness. Thus, the best treatment continues to be prevention of the disease. Medication treatment aimed at modifying certain risk factors for Alzheimer's may prove to be beneficial in disease prevention. The recent meta-analysis presented at the AAIC 2018 supports use of antihypertensives as a potential means of preventing Alzheimer's in patients who have elevated blood pressure.[16] However, treatment guidelines assert there is a lack of evidence supporting use of antihypertensives for prevention of dementia.[19,20] As such, additional research is needed to determine whether antihypertensives are effective in dementia prevention. Additional considerations include which antihypertensive agents should be used, what risk factors should be targeted, and which patients would benefit from treatment.

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Updates on FDA Recall of Valsartan-Containing Products

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Valsartan is an angiotensin receptor blocker (ARB) that is widely used in the treatment of hypertension and heart failure.[1] It works to lower blood pressure by preventing the binding of angiotensin II to the angiotensin II type-1 receptor, thus preventing angiotensin II-mediated vasoconstriction of vascular smooth muscle. Valsartan (Diovan®) is available as an oral tablet formulation in 40 mg, 80 mg, 160 mg and 320 mg strengths. Valsartan is also available as a combination product with the thiazide-type diuretic, hydrochlorothiazide (Diovan HCT®), with the calcium channel blocker, amlodipine (Exforge®), with the beta-blocker, nebivolol (Byvalson™), with the neprilysin inhibitor, sacubitril (Entresto®), and as a triple combination product with both hydrochlorothiazide and amlodipine (Exforge HCT®).[2-6] Combination products are available in several different dosages and, with the exception of Byvalson™ and Entresto®, all valsartan-containing products are available in generic formulations.[7] On July 13, 2018, the Food and Drug Administration (FDA) announced the voluntary recall of certain valsartan-containing products in the United States.[8] The recall was prompted by the identification of an impurity called N-nitrosodimethylamine (NDMA) in certain valsartan products containing active pharmaceutical ingredients (API) supplied by the manufacturer Zhejiang Huahai Pharmaceuticals, Linhai, China.

The Environmental Protection Agency (EPA) describes NDMA as a "semi-volatile organic chemical" that can be produced naturally or unintentionally through certain chemical reactions or industrial processes.[9] According to the EPA, NDMA has been shown to cause cancerous tumors after experimental exposure in animals and is thus listed as a probable human carcinogen. In addition to its carcinogenic potential, the EPA also lists liver damage as a possible consequence of excessive NDMA exposure in humans. The EPA reports that NDMA exposure can occur from consuming certain foods and drinks including contaminated water, through use of certain cosmetic products and through inhalation of cigarette smoke. Although dangerous in certain amounts, the FDA reports that exposure to or consumption of smaller amounts of NDMA (up to 96 nanograms per day) is considered to be safe in humans.[10]

According to the FDA, the unexpected presence of NDMA in certain valsartan products is thought to have resulted from changes in the manufacturing process of the valsartan API used by certain companies; however, these changes have not been specified.[11] Although the presence of this NDMA impurity was only recently discovered and the recall has only been effective in the United States since July, the FDA reports that valsartan-containing products supplied by affected manufacturers for the past 4 years could have potentially been contaminated with NDMA.[10] In addition, the FDA reports that the amount of NDMA contained in the affected products is greater than the amount considered safe for human exposure or consumption; therefore, the affected products do not meet safety standards. As a result of this discovery, the FDA has implemented inspection of several additional valsartan-containing products from various manufacturers to identify if any other contaminated products exist. In an updated safety statement released in August, the FDA stated that it will be working closely with manufacturers of valsartan API to ensure that the processes used to make the product do not or will not result in the unintentional formation of NDMA now or in the future.[12] In addition, the FDA has imposed an import alert on Zhejiang Huahai Pharmaceuticals that will prevent API and finished drug products made by the company from entering the United States.[13]

The original recall released on July 13 included certain valsartan-containing products manufactured by Teva Pharmaceuticals Industries Ltd., Major Pharmaceuticals, and Solco Healthcare, which all reportedly obtained valsartan API from Zhejiang Huahai Pharmaceuticals.[8] Since the original press release, the FDA has subsequently added more valsartan-containing products from additional generic manufacturers to the list of recalled products.[14-15] In order for patients and healthcare providers to stay informed on the most recent updates to the ongoing recall, the FDA has created a list of products that are currently affected as well as a list of products not affected by the recall that are still considered safe for use.[16,17] Both of these lists can be found on the FDA website and are regularly updated as valsartan-containing products continue to be evaluated for safety and purity.[13,15-18] The FDA has recommended that patients and healthcare providers continue to check these lists on a regular basis. Readers will also note on the above-linked page a recent FDA alert regarding the recall of certain irbesartan products. Similar to the valsartan recall, this irbesartan recall came about due to the presence of a contaminant in affected products, although it is a different contaminant than the NDMA in recalled valsartan products.[19] Although beyond the scope of this article, practitioners can stay informed about both recalls by using the above link to the FDA website.

As the recall of valsartan-containing products continues, it is likely that questions from both patients and healthcare providers will continue to arise regarding the issue. It is important to remember that not all manufacturers, lots, or strengths of valsartan and valsartan-containing products are affected by the recall.[16] Patients and healthcare providers should be directed to the lists on the FDA website as mentioned previously to verify whether their specific products are safe for continued use. Patients prescribed valsartan-containing products can also be referred to the dispensing pharmacy if they are uncertain if their product is affected. Per the FDA, patients whose valsartan or valsartan combination products are affected by the recall should be counseled to continue their medication until a replacement product is obtained.[16]

Patients using recalled products can either be switched to an alternative manufacturer not affected by the recall, or, if not available, patients can be transitioned to an equivalent dose of an alternative ARB medication.

The information in Table 1 below, obtained from Pharmacist's Letter™/Prescriber's Letter™, provides a reference on equivalent doses of various ARB medications that can be used to help guide healthcare providers transitioning patients to alternative medications, if needed.[20] All of the ARB medications listed in Table 1, with the exception of azilsartan, are also supplied as combination products with hydrochlorothiazide.[7] Patients using recalled valsartan-hydrochlorothiazide combination products can either be switched to an alternative ARB at an equivalent dose and hydrochlorothiazide at the same dose as separate products or utilize 1 of the other available ARB and hydrochlorothiazide combination products. A triple combination product of amlodipine, hydrochlorothiazide and olmesartan (Tribenzor®) is also available. Patients using recalled amlodipine, hydrochlorothiazide and valsartan products can either be switched to an alternative ARB at an equivalent dose plus amlodipine and hydrochlorothiazide as 3 separate products or Tribenzor® at an equivalent dose.

Healthcare providers and patients can continue to check the FDA website for additional updates on the topic as they become available. The FDA has also encouraged healthcare providers and patients to report any adverse events potentially related to the valsartan recall to the FDA's MedWatch Program.[8]

Table 1. ARB antihypertensive dose comparison, adapted from Pharmacist's Letter/Prescriber's Letter™.[20]

Drug	**Comparable dose based on therapeutic interchange studies, comparative clinical trials, and manufacturers' recommended dosing for hypertension**				
Valsartan (Diovan®)	**40 mg daily or 20 mg BID**	**80 mg daily or 40 mg BID**	**160 mg daily**	**320 mg daily**	**---**
Azilsartan (Edarbi®)	40 mg daily	40 mg daily	40 mg daily	40 mg daily	80 mg daily
Candesartan (Atacand®)	4 mg daily	8 mg daily or divided BID	16 mg daily or divided BID	16 mg daily or divided BID to 32 mg daily or divided BID	---
Eprosartan (Teveten®)	400 mg daily	600 mg daily	800 mg daily or divided BID	800 mg daily or divided BID	---
Irbesartan* (Avapro®)	75 mg daily	150 mg daily	300 mg daily	300 mg daily	---
Losartan (Cozaar®)	25 mg daily	50 mg daily or divided BID	100 mg daily or divided BID	---	---
Olmesartan (Benicar®)	10 mg daily	20 mg daily	20 mg daily to 40 mg daily	40 mg daily	---
Telmisartan (Micardis®)	20 mg daily	40 mg daily	40 mg daily to 80 mg daily	80 mg daily	---

*Readers should note that certain irbesartan products are also under recall per the FDA
ARB=angiotensin receptor blocker; BID=twice daily

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2018 American Academy of Pediatrics Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and Ongoing Management – A Review

Charisse Chehovich, PharmD

Background

According to data from the 2016 National Survey on Drug Use and Health, 12.8% of adolescents aged 12-17 years had experienced at least 1 major depressive episode (MDE) during the past year.[1] An MDE was defined as a period of at least 2 weeks when there was either a "depressed mood or a loss of interest or pleasure in daily activities," along with other symptoms such as "problems with sleep, eating, energy, concentration and self-worth." Of the adolescents who experienced an MDE in the past year, only 40.9% received treatment for depression.

Depression can result in increased morbidity and mortality due to an increase in suicide risk.[2] Suicide has been identified as the second leading cause of death in adolescents aged 10-21 years.[3] Depression can also lead to academic failure, increases in both smoking and substance abuse, as well as obesity.[4-6] It is for these reasons that early diagnosis and treatment of adolescent depression is of grave importance.[4] Only 50% of adolescents with depression sought treatment before adulthood, with the first onset of depression occurring during adolescence.[7]

Primary care (PC) is often the setting in which adolescents receive treatment for depression.[8] While major depressive disorder (MDD) management guidelines, such as those of the American Academy of Child and Adolescent Psychiatry, are available for specialty care settings, these guidelines cannot be transferred to the PC setting. GLAD-PC was first published in 2007 to address this deficit, and has since been updated to reflect current treatment, management and follow-up recommendations.[9]

GLAD-PC is a 2-part guideline; the first part focuses on preparation of a PC practice, identification of depression, assessment, and initial management of depression, while the second part focuses on treatment and ongoing management of adolescent depression.[9] Adolescents are defined as individuals aged 10 to 21 years in the context of this guideline. This article will primarily focus on part 2.

Guidelines

Recommendations in treatment and management of depression in adolescents in the PC setting were classified based on evidence from the literature as well as the expert opinion of the Steering Committee.[9]

After the initial diagnosis in patients with mild depression, prescribers should decide if a period of active support and monitoring before starting evidence-based treatment is appropriate.[9] If an adolescent with moderate or severe depression is identified or if the patient has complex issues and/or conditions, which can include substance abuse or psychosis, consultation with a mental health specialist should be discussed. The mental health clinician and PC provider should communicate and agree in regards to co-management of the patient. The family and patient should approve of the multidisciplinary team approach and all roles. The treatments can include psychotherapy or antidepressant therapy.

Psychotherapy includes both cognitive behavioral therapy (CBT) as well as interpersonal psychotherapy for adolescents (IPT-A).[9] Both have been shown to be effective in this patient population, even in community settings. Positive effects have been found with the use of CBT in the PC setting; preliminary support has also been found for greater efficacy when used in combination with medication than when used alone.

Antidepressant therapy is appropriate in certain adolescents with depression.[9] Selective serotonin reuptake inhibitors (SSRIs) should be used in patients who have a diagnosis of MDD without any comorbid conditions, if the patient and/or family are in favor of pharmacotherapy. Choice of an SSRI should be based on both safety and efficacy. It is recommended to start antidepressant therapy at normal starting doses, not higher doses, due to the risk of self-harm and/or suicide. It is of great importance to counsel the patient and family on adverse effects, which can include suicidal thought or behaviors, behavioral activation, or switching to mania. A patient should be given an adequate trial of the antidepressant, up to the maximum dose and duration. Table 1, below, includes a list of the recommended antidepressants and their doses for adolescent depression treatment. Effective doses in adolescents are typically lower than those in adults. It is important to recognize that fluoxetine is the only antidepressant approved by the Food and Drug Administration (FDA) in both child and adolescent depression, and escitalopram is the only FDA-approved drug for depression in patients who are at least 12 years of age. When an SSRI is discontinued, it should be tapered over time due to risks of withdrawal effects. All SSRIs are contraindicated in patients using monoamine oxidase inhibitors.

Table 1. SSRI titration schedule. Adapted from GLAD-PC.[9]

Medication	Starting Dose (qd/od), mg	Increments, mg	Effective Dose, mg	Maximum Dose, mg
Citalopram	10	10	20	60
Fluoxetine	10	10-20	20	60
Fluvoxamine	50	50	150	300
Paroxetine*	10	10	20	60
Sertraline	25	12.5-25	50	200
Escitalopram	10	5	10	20

qd/od=every day once daily
*Not recommended to be started in PC

There are several recommendations the guidelines discuss in terms of ongoing management for adolescents with depression.[9] A patient's goals and outcomes from treatment should be monitored regularly, including assessment of depressive symptoms and the patient's functioning in different settings, such as home, school, and peer situations. Diagnosis and initial choice of therapy should be reassessed if no improvement is noted after 6 to 8 weeks of treatment. For patients achieving only partial improvement after PC diagnostic and therapeutic approaches have been exhausted, a mental health consultation should be considered. These therapeutic approaches would include evaluation of poor adherence, ongoing issues of abuse, as well as comorbid disorders. In ongoing management of adolescent depression, PC clinicians should actively follow-up on, and provide support to, adolescents with depressive episodes who are referred to mental health services to ensure adequate management. PC clinicians may also consider sharing care with mental health agencies and/or professionals where possible, and appropriate roles and responsibilities regarding the provision and co-management of care should be communicated and agreed upon by the PC and mental health clinicians.

Discussion

GLAD-PC provides information for PC providers regarding empiric antidepressant and psychotherapy treatment in adolescent depression.[9] Follow-up should be a routine part of the management of depression, especially considering the FDA's boxed warning on the use of antidepressants in adolescents. The FDA recommends that all pediatric patients should be monitored closely following initiation of an antidepressant to assess if the patient is worsening clinically, having increased suicidality, or any unusual or changed behavior especially within the first few months of therapy as well as after any changes in therapy. In addition to pharmacotherapy, another first-line treatment for adolescent depression is psychotherapy, which has been shown to improve care in this patient population. However, better adolescent depression care cannot take place without the proper training of PC providers.

For PC clinicians who are challenged by the lack of mental health resources available to adolescents, GLAD-PC gives them the basic tools needed to treat adolescent depression confidently.[9] GLAD-PC combines evidence from the literature with recommendations from expert consensus. With current undertreatment of adolescent depression in PC, it is invaluable to have GLAD-PC available to PC clinicians.

Limitations

The updated guidelines do not include recommendations on specific augmenting treatment options or the treatment of subthreshold symptoms.[9] Some of the recommendations made within these guidelines are made in the absence of data or in response to little evidence.

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