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Current Landscape of the Antidepressant Class: First Line Agents, Newer Agents, and Safety Risks

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The antidepressants class is comprised of a variety of agents with different clinical characteristics and within the past few years three new agents have been approved by the United States Food and Drug Administration (FDA). Generally, second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are the most commonly utilized and recommended medications for the management of major depressive disorder (MDD) due to their safety profile.[1-4] However, the choice of antidepressant should be individualized for each patient based on evidence for safety and efficacy while taking cost into consideration.[2,4] The purpose of this newsletter is to review first line agents, evaluate comparative data for newer agents, and assess safety risks with SSRIs in pediatric patients.

Guidelines

The National Institute for Health and Care Excellence (NICE) guidelines for treatment of depression in adults recommend generic SSRIs as first line treatment for most patients.[2] In addition to SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion are also recommended as first line options by the American Psychiatric Association and the Department of Veterans Affairs (VA) and Department of Defense (DoD) MDD guidelines.[3,4] Patient-specific considerations of safety risks and drug interactions are also emphasized in the guidelines.[2-4]

Oregon Health Plan Policy

Drugs for mental health conditions in Oregon Health Plan (OHP) Medicaid patients are exempt from the traditional Preferred Drug List (PDL) and prior authorization requirements. Therefore, OHP relies on prescribers to voluntarily prescribe antidepressants with high value. Preferred agents are listed below and have demonstrated safety and efficacy (Table 1).

Table 1. Preferred Agents on Voluntary Mental Health PDL

Preferred Agents		
Atypical	Bupropion tablets & 12H ER tablets	Mirtazapine tablets & rapidly disintegrating tablets
SNRI	Venlafaxine tablets & 24H ER capsules	
SSRI	Citalopram tablets & solution	Escitalopram tablets
	Fluoxetine capsules, tablets & solution	Fluvoxamine tablets
	Paroxetine tablets	Sertraline tablets & oral concentrate
Tricyclic	Amitriptyline tablets	Anafranil™ (brand only) capsules
	Desipramine tablets	Doxepin capsules & oral concentrate
	Imipramine tablets	Maprotiline tablets
	Nortriptyline capsules & solution	Protriptyline tablets
	Trimipramine capsules	

Abbreviations: ER = extended release; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; 12H = 12-hour; 24H = 24-hour

Newer Agents Compared to Other Second Generation Antidepressants

Levomilnacipran, vilazodone, and vortioxetine are three newer agents approved by the FDA for the treatment of MDD between 2011 and 2013.[5-7]

In April 2017, the Drug Effectiveness Review Project (DERP) published a review on second-generation antidepressants with an emphasis on levomilnacipran, vilazodone, and vortioxetine.[1] The report focused on MDD and generalized anxiety disorder in adults and seven head-to-head trials were included.[1] A pre-specified network meta-analysis studying response to treatment on the Hamilton Depression Rating Scale was also completed which utilized 119 placebo- and active comparator-controlled randomized controlled trials (RCTs).[1] All trials included in the network meta-analysis were double-blinded and focused on the outpatient MDD population.[1] However, as the network meta-analysis reflects indirect evidence, results should be interpreted with caution.

For MDD, limited direct comparative evidence is available for levomilnacipran, vilazodone, or vortioxetine compared with other second-generation antidepressants.[1] Moderate quality evidence shows similar response rates for both vilazodone and citalopram as well as vortioxetine and venlafaxine XR, and vortioxetine had similar or lower response rates compared to duloxetine depending on the trial.[1]

Low quality network meta-analyses showed overall similar response rates for all three agents versus other second-generation antidepressants.[1]

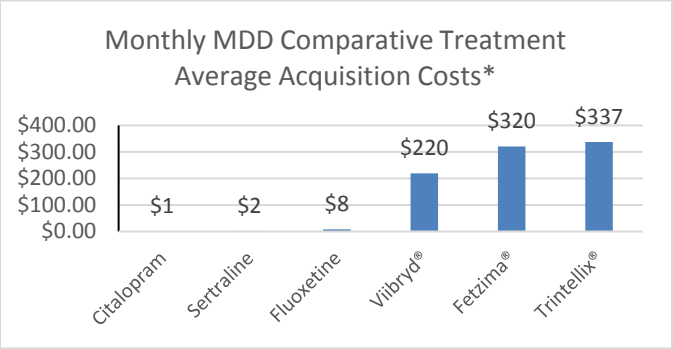
Safety outcomes were evaluated in the DERP report as well.[1] Low strength of evidence found differences in adverse effects which included higher rates of diarrhea (26.5% vs. 10.6%) and vomiting (6.6% vs. 1.8%) with vilazodone versus citalopram (one fair quality RCT; n=580), statistically non-significant yet numerically lower rates of discontinuation due to adverse events with vortioxetine versus venlafaxine XR (7.0% vs. 14.2%; one fair quality RCT; n=320), and significantly lower rates of sexual dysfunction (25% vs. 46% and 36% vs. 53%; two fair quality RCTs; n=288) and somnolence (5% vs. 12%; one fair quality RCT; n=310) with vortioxetine versus duloxetine.[1] Meta-analyses demonstrated lower risks with vortioxetine compared to duloxetine for dry mouth (9.6% vs. 13.1%; RCT=3).[1] Other safety outcomes evaluated in the DERP report demonstrated no statistically significant difference between levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants.[1]

Levomilnacipran, vilazodone, and vortioxetine are voluntary non-preferred agents on the Oregon Medicaid voluntary mental health PDL.

Cost Comparison

The newer agents of levomilnacipran (Fetzima®), vilazodone (Viibryd®), and vortioxetine (Trintellix®) have significantly higher costs per 30 days of MDD treatment compared to common SSRIs which are recommended as first line treatment for most patients (Chart 1).[2-4] Many patients can be treated with older, more established agents for the same cost of treating one patient with a newer agent.

Chart 1: Comparative Costs of Common SSRIs & Newer Agents



*Based on commonly prescribed maintenance doses

Safety Reminder: SSRIs in Pediatric Patients

When prescribing antidepressants in pediatric or young adult patients, special consideration should be given to the potential safety risks. Antidepressants have a boxed warning regarding the increased risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.[8] In SSRIs specifically, dose-related safety risks have been demonstrated.[9]

One large, well-designed retrospective cohort study (n=21,305) from 2014 revealed a dose-related increase in deliberate self-harm among pediatric, adolescent, and young adult patients initiated on high-dose SSRIs for MDD.[9] The risk of deliberate self-harm in the high dose group was found to be approximately double that of the modal dose group (HR 2.2; 95% CI, 1.6-3.0).[9] As a result of this study, a 2014 Oregon Medicaid drug use evaluation was completed which found that 27% of patients aged 5-24 years were initiated on high-dose SSRI therapy, potentially putting them at risk for deliberate self-harm.[10]

To improve safety for pediatric patients initiating on SSRI therapy, it is recommended to prescribe SSRIs at recommended initial doses or not higher than the age-specific maximum initiation doses (Table 2). Additionally, patients should be monitored closely for clinical worsening, suicidality, and unusual changes in behavior, especially in the initial few months of therapy and at times of dose changes.[8]

Table 2. Recommended Initial SSRI Doses in Younger Patients

SSRI	Recommended initial dose (mg)*[11]	Age – specific maximum initiation dose (mg)**[10]			
		Age range [years]			
		5 – 9	10 – 15	16 – 19	20 – 24
escitalopram	5 – 10	5	10	10	10
fluoxetine	5 – 20	10	10	10	20
sertraline	12.5 – 50	25	25	50	50

*Doses for MDD or depression were used if listed and other indication doses were used if no MDD or depression dose was available. Citalopram excluded due to lack of FDA-approved pediatric indications.[12] Paroxetine excluded due to lack of FDA-approved pediatric indications as well as safety and efficacy concerns in this population.[13,14]
**Based on modal doses determined in a 2014 Oregon Medicaid drug use evaluation.[10]

Avoid high doses to limit risk of deliberate self-harm when prescribing initial antidepressant therapy with SSRIs in pediatric, adolescent, or young adult populations and evaluate risks versus benefits.

Conclusion

Levomilnacipran, vilazodone, and vortioxetine lack established efficacy or safety advantages over first line MDD agents that have been in clinical use for many years yet have significantly higher comparative costs. Evidence shows these drugs are similar or less effective than other second generation antidepressants and as they are still relatively new, the full long term safety profile may not be established. Safety concerns in the antidepressants class such as high initial doses of SSRIs in pediatric patients also continue to be of importance. Risks and clinical need with any treatment should be weighed and evaluated. If multiple agents are determined to be equally appropriate for a patient, utilizing the most cost-effective medication can assist in managing Oregon Medicaid resources in the most effective manner possible.

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