Acentra HEALTH

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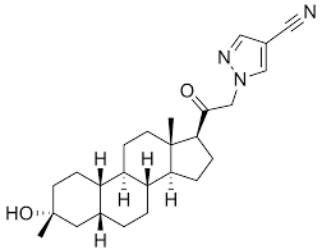
2024 Quarter 1 Newsletter

FDA APPROVAL SPOTLIGHT

ZURZUVAE®
(zuranolone) capsules CIV
20 mg • 25 mg • 30 mg



Postpartum depression (PPD) is a form of depression that effects approximately 7-15% of women in the first three months of the postpartum period. Its etiology is unclear, but theories include the significant fluctuation of hormones and cortisol during this period. It is characterized by depressive symptoms for greater than two weeks with moderate to severe dysfunction in daily life, including suicidality, aggressive thoughts towards the infant, sleep disorders, etc. Previously, selective serotonin reuptake inhibitors (SSRIs) have been first-line for the treatment of PPD due to their side effect profiles and the possibility for concurrent breastfeeding.

Zurzuvae (zuranolone) is a gamma-aminobutyric acid (GABA) A receptor positive modulator, also known as a neuroactive steroid, that was approved August 4, 2023 for the treatment of postpartum depression. This is currently the only oral treatment on the market specifically indicated for postpartum depression. Another GABA-A receptor positive modulator, Zulresso (brexanolone), is an intravenous solution that is indicated for postpartum depression.
Zurzuvae is dosed as 50 mg by mouth once daily in the evenings with a fatty meal for a total duration of 14 days with an option to decrease the dose to 40 mg in the event of significant CNS depression. It is also recommended to decrease to 30 mg by mouth once daily for eGFR of 15-59 mL/min/1.73 m^2 and for Child-Turcotte-Pugh (CTP) Class C

There were two phase three clinical trials performed for Zurzuvae. The first compared a 30 mg once-daily dose to placebo. When researchers saw benefit and tolerability with this dose, the second trial was performed comparing a 50 mg once-daily dose to placebo. The was a randomized, double-blind, placebo-controlled study, and the results of this second phase 3 trial are discussed below. The study group consisted of 196 adult female patients randomized 1:1 to either zuranolone 50 mg once daily or placebo for 14 days. The study found a statistically significant improvement in the primary endpoint of Hamilton Depression Rating Scale (HAM-D) scores with least squares mean (LSM) change from baseline of -15.6 vs. -11.6 (difference -4.0, 95% CI of -6.3,-1.7). It also found a statistically significant improvement in the secondary endpoint of Clinical global Impressions – Severity (CGI-S) score. CNS depressant effects (dizziness, somnolence, and sedation) were the most common adverse drug effects (ADEs) during both of these trials.

As a once-daily oral tablet, Zurzuvae is superior to Zulresso's 60-hour intravenous infusion both in time and cost. Additionally, its short-term treatment duration of 14 days is beneficial when compared to the more extensive titration and tapering dosing regimens of SSRIs. However, it can also be combined with

SSRIs if the effect is suboptimal at maximally tolerated dosing. Also, while there is no current data on the effects of zuranolone with breastfed infants, it is distributed into breast milk at lower levels than most SSRIs and is, therefore, likely tolerated. Given these considerations, Zurzuvae is an excellent option in the treatment of PPD and will likely increase in popularity and use for this indication.

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2023 GUIDELINE UPDATES

On November 30 2023, a joint committee of the American Heart Association (AHA) and American College of Cardiology (ACC) published updated guidelines for the diagnosis and management of atrial fibrillation (AF). This served as an update to the previously published 2014 comprehensive guidelines, as well as the

2019 guideline update. These new guidelines are based on a comprehensive literature search from May 12, 2022 to November 3, 2022.

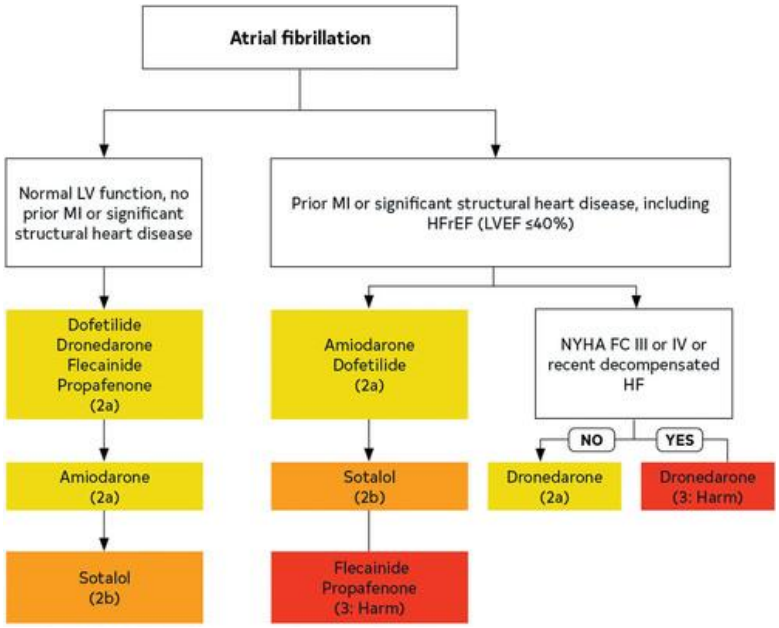
These new guidelines emphasize shared decision-making with patient in AF management, lifestyle and risk factor modifications, prevention of thromboembolism, rate and rhythm control, and management of comorbid heart failure (HF). The mainstays of pharmacotherapy management from the 2023 guidelines are outlined in Table 1.

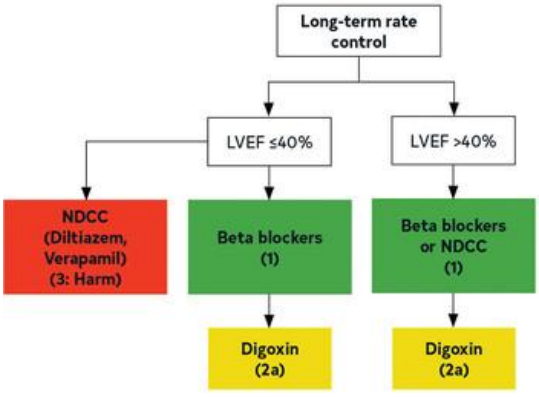
Table 1: ACA/AHA 2023 Atrial Fibrillation Highlighted Guideline Updates

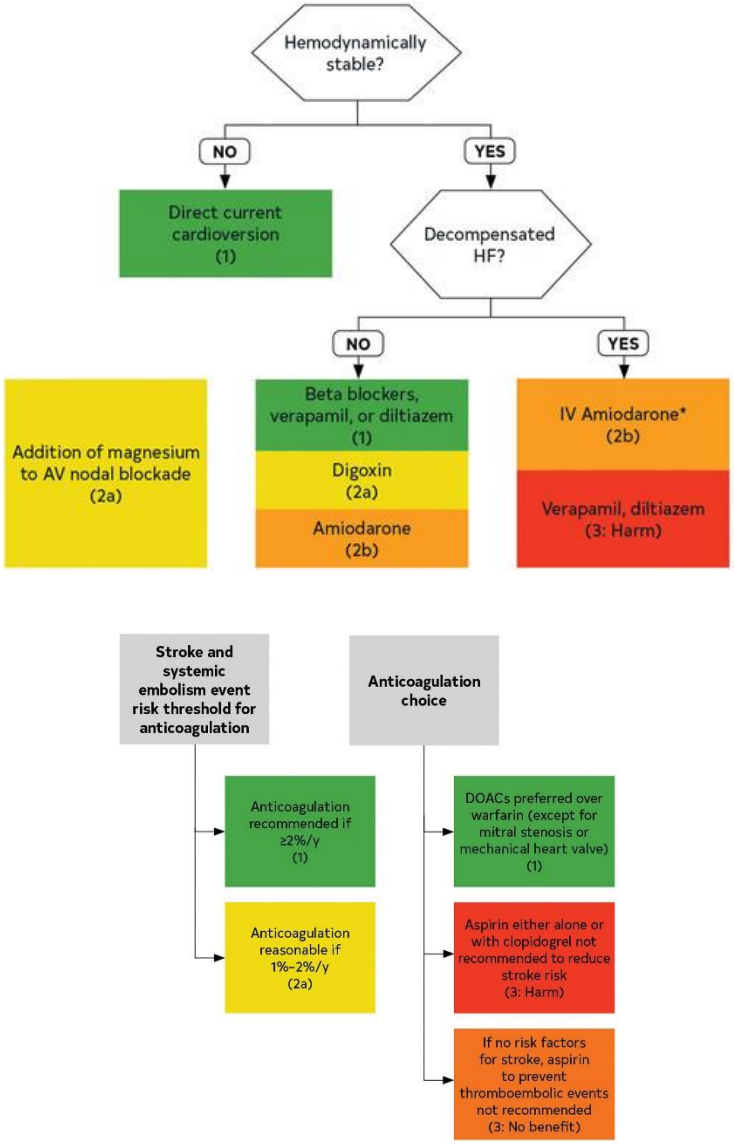
Guideline Topic	2023 Recommendations
Anticoagulation	Anticoagulation recommended for CHA_2DS_2-VASc score of ≥2 in men and ≥3 in women.
	DOACs recommended over warfarin unless history of moderate-severe rheumatic mitral stenosis or mechanical heart valve is present.
	Target INR of 2-3 in most patients taking warfarin.
	Warfarin or low-dose apixaban preferred for ESRD patients.
Rate Control	Goal resting HR of <100-110 bpm.
	BBs and non-DHP CCBs are preferred for hemodynamically stable patients with AF with RVR for acute and long-term rate control. For acute settings, may be used in combination with IV magnesium
	Digoxin may be considered for acute rate control if BBs or non-DHP CCBs are contraindicated. IV amiodarone may be considered if first-line measures are ineffective or patient is not hemodynamically stable.
Rhythm Control	Rhythm control recommended for reduced LV function, comorbid HF, and/or symptomatic AF.
	Pharmacological cardioversion compared to electrical cardioversion is reasonable in patients that are hemodynamically stable.
	Ibutilide and IV amiodarone are reasonable cardioversion. Single-dose flecainide or propafenone is also reasonable for cardioversion in

	recurrent AF, if previously tested in an inpatient setting.
	Pharmacological cardioversion compared to electrical cardioversion is reasonable in patients that are hemodynamically stable.
	Long-term rhythm control with dofetilide or amiodarone is reasonable for patients with comorbid HFrEF (<40%).
	Long-term rhythm control with flecainide/propafenone, low-dose amiodarone (100-200 mg/day), dofetilide, dronedarone, or sotalol is reasonable in patients with no other significant CV comorbidities.

Some of the most notable recommendations include the preference of cardio-selective beta-blockers and non-DHP calcium channel blockers to target a resting heart rate of <100-110 bpm, pharmacological cardioversion over electrical cardioversion in hemodynamically stable patients, and DOACs recommended over warfarin for anticoagulation in most patients. The figures below show the algorithms including several of these recommendation with their corresponding level of evidence. With this information, these guidelines will continue to inform practitioners in the most appropriate and evidence-based therapies for the treatment of atrial fibrillation.







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LEGISLATIVE NEWS

As of August 28, 2023, the Drug Enforcement Administration's (DEA) rule on the transfer of electronic prescriptions for controlled substances became effective. This rule was initially published on July 27, 2023 and servse to enhance current policy on electronic prescribing of schedule II-V controlled substances.

This policy allows for electronic prescribing of controlled substances one a one-time bases between retail pharmacies if the following requirements are met:

- The prescription is for a drug in schedules II-V.
- The transfer is upon request from the patient.
- The transfer is for an initial fill only.
- Any authorized refills for medications in schedule II-V are transferred with the original prescription.
- The transfer occurs between two licensed pharmacists.
- The prescription remains in electronic form.
- The contents of the prescription are unaltered.
- The transfer is otherwise allowable under state or local law.

One of the major purposes of this ruling, as stated by the DEA, is that "allowing the electronic transfer of controlled substance prescriptions will decrease the potential for duplicate prescriptions and thus reduce the opportunity for diversion or misuse." Previously, schedule II substances could only be filled with a written prescription with few exceptions and no allowable refills. Additionally, schedules III-V substances could be dispensed following the provision of a written or electronic prescription (including facsimiles of written prescriptions) with a maximum refill number of five times or refill timeframe of six months.

These previous stipulations are unchanged by the new regulations. Rather, the policy has been simply updated to clarify the procedure on the transferring of electronic prescriptions for controlled substances where there has been room for interpretation previously. As discussed by the DEA, the hope is that this new ruling will limit errors and confusion for the electronic prescribing and dispensing of controlled substances to allow for transfer of these prescription when a pharmacy is out of stock of the required drug or otherwise unable to refill the requested drug.

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