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# A Review of Aldosterone Antagonists in Diastolic Heart Failure

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Heart failure (HF) affects an estimated 5.1 million individuals living in the United States. The occurrence of HF in patients older than 65 is approximately 10 per 1000 individuals. In 2009, HF was responsible for more than 660,000 ED visits and 270,000 deaths.[1] Development of HF is strongly associated with various risk factors including hypertension, coronary heart disease, smoking, and chronic kidney disease.[2] The total cost of HF is expected to rise to $70 billion by 2030 – an increase from the 2013 estimated total cost of $32 billion.[1]

Differentiating between systolic and diastolic HF is important because prognosis and management may depend on the underlying pathophysiology that is causing the symptoms. HF due to systolic dysfunction is characterized by a decrease in the myocardial contractility leading to reduced left ventricular ejection fraction (LVEF). Patients with HF due to diastolic dysfunction typically have normal LVEF but myocardial relaxation is impaired causing incomplete filling of the heart. Evidence of left ventricular hypertrophy can be seen in patients with diastolic HF; however, the remolding process is much slower since the main causes of diastolic HF are hypertension and diabetes.[3] Typically affecting the older population, an estimated 50% of HF patients older than 70 years have preserved LVEF. As the population continues to age, diastolic HF may eventually become the most common form of HF.[4]

The introduction of aldosterone antagonists provided clinicians with another option in the management of HF. Currently, the two aldosterone antagonists FDA approved for use in patients with HF are spironolactone (Aldactone®) and eplerenone (Inspra®). Aldosterone, a neurohormone stimulated by the renin-angiotensin-aldosterone system (RAAS), is thought to play an important part in the pathophysiology of HF.[5] The benefits of aldosterone antagonists in systolic HF are well established; however, strong interest exists in determining whether these benefits also extend to diastolic HF.

This article will review the utility of aldosterone antagonists in the management of diastolic heart failure and compare their role in systolic heart failure. The pharmacological characteristics of aldosterone antagonists will also be discussed as well as a comparison between spironolactone and eplerenone. Lastly, several clinical trials that assessed aldosterone antagonists' role in therapy will be evaluated.

## Current Guidelines on Heart Failure

The American College of Cardiology (ACC) and American Heart Association (AHA) jointly publishes guidelines for the management of patients with heart failure. According to the most recent ACC/AHA guidelines,[6] patients with HF due to reduced LVEF should be managed with a combination of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) and a beta blocker. Diuretics may be

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considered in patients with overt fluid retention to improve symptoms. Aldosterone antagonists are recommended in patients with New York Heart Association (NYHA) class II – IV HF and LVEF of 35% or less. They are also recommended for use in patients who develop HF following an acute myocardial infarction (MI) with an LVEF of 40% or less. These recommendations are based on clinical trials showing benefit with the addition of an aldosterone antagonist to recommended therapy.[7-9] Management of HF associated with preserved ejection fraction is much less clear due to the lack of clinical trials performed in patients with this form of HF. Current guidelines state that treatment is guided by management of physiological factors such as blood pressure, heart rate, blood volume, and myocardial ischemia, and the use of diuretics, beta -blockers, ACE inhibitors, ARBs, or calcium channel blockers may be effective in reducing symptoms.[6] The use of aldosterone antagonists for the management of diastolic HF is much less clear and is under investigation.

## Pharmacology and Pharmacokinetics

Aldosterone antagonists act by competitively inhibiting aldosterone at the mineralocorticoid receptor (MR). Although both spironolactone and eplerenone bind to the MR, significant differences in the pharmacology and pharmacokinetics exist between the two drugs **(Table 1)**. Spironolactone was the first aldosterone antagonist developed and has similar characteristics to progesterone, which is thought to be the cause of its progestogenic and antiandrogenic side effects. Eplerenone is a derivative of spironolactone and has a three to ten-fold higher selectivity for the MR than progesterone and androgen receptors.[10, 11]

Both aldosterone antagonists are extensively metabolized by the liver; however, spironolactone has active metabolites with prolonged half-lives. Eplerenone is metabolized by cytochrome P450 isoenzyme 3A4 (CYP3A4) and does not have an active metabolite. Concurrent use with potent inhibitors or inducers of CYP3A4 may have significant effects on epelerenone concentration.[12, 13]

The beneficial effects of aldosterone antagonists are believed to be through two mechanisms: increasing serum potassium and magnesium levels, and blocking aldosterone's action on the heart. The increase in serum potassium and magnesium reduces the risk of arrhythmias by preventing hypokalemia and hypomagnesia, respectively.[14, 15] Aldosterone is believed to promote myocardial fibrosis which facilitates the remolding process.[16] A positive correlation is seen between high serum levels of collagen synthesis and rates of death and hospitalization.[17] Aldosterone antagonists are able to reduce the serum concentrations of collagen and possibly have a beneficial effect on mortality.[18] Aldosterone's other detrimental actions include decreasing the reuptake of norepinephrine, reducing endothelial function, and increasing plasminogen activator inhibitor levels. These actions promote the occurrence of ischemic events which can lead to arrhythmias and sudden cardiac death.[5, 16] Thus, the benefits of aldosterone antagonists may extend beyond just preventing the cardiac remolding process.

## Clinical Trials

*Clinical trials in patients with HF and reduced LVEF (systolic HF)*

The benefits of aldosterone antagonists when added to standard therapy in patients with HF and reduced LVEF were investigated in three major clinical trials **(Table 2)**: RALES,[7] EPHESUS,[8] and EMPHASIS-HF.[9] RALES and EPHESUS both investigated the benefits of aldosterone antagonists in patients with moderate to severe HF and reduced LVEF (defined as LVEF ≤ 35 percent). The severity of symptoms was described using the New York Heart Association (NYHA) classification of HF. Patients were enrolled in the studies if they had NYHA class III or IV HF. A majority of the patients were concurrently on medical therapy for HF which included an ACE inhibitor, ARB, beta-blocker, or diuretic. EPHESUS differed from RALES in that the patient population had a documented acute myocardial infarction (MI).[8] In both trials, a significantly higher mortality rate was seen in patients in the placebo group compared to the study group. The authors concluded that the addition of aldosterone antagonists to medical therapy reduces the risk of morbidity and death in patients with systolic HF with or without previous MI.[7, 8]

EMPHASIS-HF was designed to study the benefits of eplerenone in systolic HF patients with mild symptoms (NYHA class II). Enrolled patients were on medical therapy for HF at baseline that included an ACE inhibitor, ARB, or beta-blocker. Eplerenone significantly reduced the risk for the primary outcome, death from cardiovascular causes or hospitalization for HF, compared to placebo. The authors noted that the addition of eplerenone to standard medical therapy for systolic HF in patients with mild symptoms reduced the risk of death from cardiovascular causes or hospitalization due to HF.[9]

**Table 1 | Pharmacodynamics and Pharmacokinetics of Spironolactone and Eplerenone [11-13]**

| | Spironolactone (Aldactone®) | Eplerenone (Inspra®) |
|---|---|---|
| MR affinity (aldosterone =1) | $1.1 \times 10^{-1}$ | $5.1 \times 10^{-3}$ |
| Absorption | Increased with food | No effect with food |
| Absolute bioavailability (%) | Unknown | ~69% |
| Half-life (h) | 1.4 | 4-6 |
| Protein binding (%) | 90 | 49 |
| Metabolism | Hepatic | CYP3A4 |
| Metabolites (half-life) | TMS (13.8)<br>HTMS (15)<br>Canrenone (16.5) | Inactive |
| Excretion (%) | Urine: 53<br>Feces: 20 | Urine: 66<br>Feces: 32 |

CYP4A4 = cytochrome P450 isoenzyme 3A4; HTMS = 6-β-hydroxy-7-α-(thiomethyl) spironolactone; MR = mineralocorticoid receptor; TMS = 7-α-(thiomethyl) spironolactone

**Table 2 | Summary of Aldosterone Antagonists Clinical Trial Data in Patients with HF and Reduced LVEF**

| Study (Year) | Design | Intervention | Primary Outcome | Results |
|---|---|---|---|---|
| RALES[7] (1999) | • RCT, MC, DB<br>• Mean follow-up: 24 mo.<br>• Inclusion: NYHA class III or IV, treated with loop diuretic and/or ACEI, LVEF≤35% | • Spironolactone 25 mg/d (N=822)<br>• Placebo (N=841)<br>• After 8 wk., dose could be increased to 50 mg/d if tolerated | • Death from any cause | • Spironolactone (35%) vs. placebo (46%); RR 0.7, 95% CI 0.6-0.82; p<0.001 |
| EPHESUS[8] (2003) | • RCT, MC, DB<br>• Mean follow-up: 16 mo.<br>• Inclusion: documented acute MI, LVEF≤40%,<br>• Pts received ACEI, ARBs, diuretics, or BB | • Eplerenone 25 mg/d (N=3319)<br>• Placebo (N=3313)<br>• After 4 wk., dose could be increased to maximum of 50 mg/d | • Death from any cause<br>• Death from CV causes or first hospitalization for CV event | • Eplerenone (14.4%) vs. placebo (16.7%); RR 0.85, 95% CI 0.75-0.96; p=0.008<br>• Eplerenone (26.7%) vs. placebo (30%); RR 0.87, 95% CI 0.79-0.95; p=0.002 |
| EMPHASIS-HF[9] (2011) | • RCT, MC, DB<br>• Mean follow-up: 21 mo.<br>• Inclusion: NYHA class II, LVEF≤30%, treatment with ACEI, ARB, or BB | • Eplerenone 25 mg/d (N=1364)<br>• Placebo (N=1373)<br>• After 4 wk., dose could be increased to 50 mg/d | • Composite of death from CV causes or first hospitalization for HF | • Eplerenone (18.3%) vs. placebo (25.9%); HR 0.63; 95% CI 0.54-0.74; p<0.001 |

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CI = confidence interval; CV = cardiovascular; DB = double-blind; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction ; MC = multicenter; MI = myocardial infarction ; mo. = months; NYHA = New York Heart Association ; pts = patients ; RCT = randomized, controlled trial; RR = relative risk; wk. = weeks

*Clinical trials in patients with HF and preserved LVEF (diastolic HF)*

Evidence-based therapy for patients with diastolic HF is insufficient due to the small number of clinical trials in this patient population. Due to the detrimental role that aldosterone appears to play in HF, the use of aldosterone antagonists has become a target for medical therapy in diastolic HF. Two smaller clinical trials, RAAM-PEF[19] and Aldo-DHF,[20] studied the use of aldosterone antagonists in patients with HF and preserved LVEF; however, neither evaluated mortality as an outcome. The TOPCAT trial is a large clinical trial investigating the mortality benefit of aldosterone antagonists in patients with diastolic HF.[21] The trial is currently in progress with the results expected to be completed by the end of the year. A summary of the clinical trials is listed in Table 3.

In RAAM-PEF, patients with NYHA class II or III HF and preserved LVEF (defined as LVEF ≥50%) were randomized to receive either eplerenone (N= 23) or placebo (n=23). The initial starting dose of 25 mg daily of eplerenone was given for 2 weeks followed by 50 mg daily for the next 22 weeks. A majority of the patients were currently on either an ACE inhibitor or ARB. The outcomes of the study were a change in

**Table 3 | Summary of Aldosterone Antagonists Clinical Trial Data in Patients with HF and Preserved LVEF**

| Study (Year) | Design | Intervention | Outcomes | Results (study drug vs. placebo) |
|---|---|---|---|---|
| RAAM-PEF[19] (2011) | • RCT, SC, DB<br>• Total tx duration: 24 wk<br>• Inclusion: NYHA class II or III, LVEF≥50%, current use of ACEI or ARBs | • Initial 2-wk open label period of eplerenone 25 mg/d<br>• Eplerenone 25 mg/d (N=23) for 2 wk., then 50 mg/d for 22 wk.<br>• Placebo (N=23) | • Primary: 6-MWD (meters) change from baseline<br>• Secondary: ECHO measures of diastolic dysfunction (change in E/E')<br>• Biomarkers of collagen turnover and B-type natriuretic peptide | • Primary: No difference in change in 6-MWD (+39.30 vs. +37.3; p=0.91)<br>• Secondary: significant improvement in diastolic function (-1.77 vs. 1.23; p=0.01)<br>• Significant decreases in PINP (-7.22 vs +2.27; p=0.009) and CITP (-0.47 vs 0.86; p=0.026) |
| Aldo-DHF[20] (2013) | • RCT, MC, DB<br>• Total tx duration: 12 mo.<br>• Mean follow-up: 11.6 mo.<br>• Inclusion: NYHA class II or III, LVEF≥50%<br>• Current use of ACEI/ARB, BB, Diuretic, or CCB | • Spironolactone 25 mg/d (N=213)<br>• Placebo (N=209) | • Primary: diastolic function (change in E/E')<br>• Maximal exercise capacity (peak $VO_2$) | • Significant improvement in diastolic function (-0.6 vs. +0.8; p<0.001)<br>• No difference in the change in peak $VO_2$ (+0.5 vs +0.5; p=0.81) |
| TOPCAT[21] (ongoing) | • RCT, MC, DB<br>• Inclusion: NYHA class II-IV, LVEF≥45%, age≥50<br>• Exclusion: SBP>160 mmHg, SCr≥2.5 mg/dL, history of hyperkalemia | • Spironolactone 15 mg/d, then 30 mg/d after 4 wk., then optional up-titration to maximum 45 mg/d on or after the 4-mo. visit | • Primary: First occurrence of the composite of CV death, hospitalization for the management of HF, or aborted cardiac arrest<br>• Secondary: all-cause mortality, all-cause hospitalization, QOL | • Results not yet released (expected at the end of 2013) |

6-MWD = 6-minute walk distance; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium-channel blocker; CITP = carboxy-terminal telopeptide of collagen type I; CV = cardiovascular; DB = double blind; E/E' = measure of LV filling pressure; MC = multi-center; mo. = months; NYHA = New York Heart Association ; peak $VO_2$ = maximal oxygen capacity; PINP = procollagen type I; QOL = quality of life; RCT = randomized, controlled trial; SBP = systolic blood pressure; SC = single-center; SCr = serum creatinine; ; tx = treatment; wk. = weeks

6-minute walk distance, echocardiographic measures, biomarkers related to HF, and quality of life. Echocardiographic measures were used to assess improvement in diastolic function. The E/E' ratio was calculated as a measure of left ventricular filling pressure. This ratio has been considered a useful index for the detection of diastolic dysfunction in patients with HF and preserved LVEF.[22] Various biomarkers for collagen turnover were tested including amino-terminal peptide of procollagen type I (PINP) and type III (PIIINP), carboxy-terminal telopeptide of collagen type I (CITP), and carboxy-terminal peptide of procollagen type I (PICP).[19]

Eplerenone was not associated with a significant change in the 6-minute walk distance compared to placebo; however, it demonstrated significant reductions in PINP and CITP serum levels, and a significant difference in the change in E/E' ratio. Further investigation is required to determine whether the changes in collagen turnover and diastolic function translate into long-term benefits on morbidity and mortality.[19]

The ALDO-DHF trial investigated the use of spironolactone in patients with NYHA class II or III HF and LVEF of 50% or greater. Patients were randomly assigned to receive either spironolactone (N=213) at a dose of 25 mg daily or placebo (N=209). Improvement of diastolic function and maximal exercise capacity were investigated as the primary outcomes of the study. Similar to RAAM-PEF, a change in E/E' was used as a measure of diastolic function. Maximal exercise capacity was measured through cardiopulmonary testing and calculating the peak $VO_2$.[20]

Spironolactone produced significant changes in the E/E' ratio and significantly improved cardiac remolding; however, it did not affect maximal exercise capacity (no difference in the change in peak $VO_2$), patient symptoms, or quality of life. The authors concluded that additional studies are required to investigate the effect of improving diastolic function on clinical end points such as morbidity and mortality.[20]

Results from RAAM-PEF and ALDO-DHF indicate that despite having no effect on exercise capacity in HF patients with preserved LVEF, aldosterone antagonists were able to improve diastolic function and cardiac remolding. The TOPCAT trial is an ongoing clinical study evaluating the effect of spironolactone on morbidity and mortality in patients with HF with preserved LVEF.[21] Patients with symptomatic HF (NYHA class II-IV) and preserved LVEF (defined as ≥45%) were randomly assigned to receive spironolactone 15 mg daily or placebo. The dose of spironolactone could be up-titrated to a maximum of 45 mg daily. The primary end point is the time to first occurrence of the composite of cardiovascular death, hospitalization for HF, or aborted cardiac arrest. Secondary endpoints included all-cause mortality, all-cause hospitalization, and quality of life. According to statistical analysis, an estimated sample size of 3,515 patients would be required to detect a 20% reduction in event rate in the spironolactone group with at least 80% power.[21]

## Adverse Events and Safety

Although spironolactone and eplerenone have slightly different side effect profiles, both can increase serum potassium levels. In clinical trials, a higher proportion of patients on aldosterone antagonists had elevated serum potassium levels compared to patients on placebo.[7, 9, 20] In the kidneys, antagonism of the aldosterone receptors decreases the excretion of $K^+$ into the distal convoluted tubules and collecting ducts through modulation of the apical $Na^{+2}$-$K^+$-ATPase pump and luminal $K^+$ channel.[12] Severe hyperkalemia has the potential to destabilize the cardiomyocyte membrane potential and precipitate unstable ventricular arrhythmias.[23]

Aldosterone antagonists should not be initiated in patients with hyperkalemia or impaired kidney function. Spironolactone can only be started in patients with serum potassium ≤ 5 mEq/L and serum creatinine ≤ 2.5 mg/dL.[24] Eplerenone is contraindicated in patients with serum potassium >5.5 mEg/L, creatinine clearance ≤ 30 mL/min, and concurrent use with strong CYP3A4 inhibitors.[25] Recommendations for monitoring serum potassium include obtaining a serum potassium level at 1 week and 1 month after start of therapy, and then obtain a level at each subsequent visit. If serum potassium is between 5.5 and 6.0 mmol/L in the first month, the dose can be decreased. The drug may be discontinued if the serum potassium level is greater than 6.0 mmol/L.[16]

Spironolactone has a higher incidence of sexual side effects than eplerenone. In RALES, the incidence of spironolactone-related breast tenderness and gynecomastia was reported to be 10% for men.[7] Typically these side effects occur at doses greater than 50 mg per day and tend to resolve after discontinuation of the drug.[12] Spironolactone is also associated with decreased testosterone levels, erectile dysfunction, and menstrual irregularities. These side effects may be intolerable to some patients and may increase the rates of noncompliance.[10]

## Dosing & Cost

Spironolactone is available as 25 mg, 50 mg, and 100 mg tablets, and is indicated for various conditions including primary hyperaldosteronism, hypertension, and HF. The dosing may differ depending on the indications. For the treatment of severe HF (NYHA class III or IV), the initial dose is 25 mg daily. The dosage may be increased to 50 mg daily if the patient is able to tolerate the lower dose, shows improvement in signs and symptoms of HF, and has no evidence of hyperkalemia.[24-] The cost of a 30-day supply of spironolactone is relatively cheap and is included on many pharmacies' $4 generic list.

Eplerenone is indicated for both hypertension and HF, and is available in two strengths, 25 mg and 50 mg. In the management of HF post-MI with reduced LVEF, patients are started on a dose of 25 mg daily. This dose may be titrated to a maximum of 50 mg daily within four weeks.[25] The cost of a 30-day supply of eplerenone ranges from $96.41 to $124.95.

## Summary

The use of aldosterone antagonists in the management of diastolic HF is still controversial. Clinical trials have established the benefits of aldosterone antagonists when added to standard therapy in the treatment of systolic HF. Whether these benefits translate to patients with HF and preserved LVEF remains to be seen. Smaller trials show that the short-term use of aldosterone antagonists improve diastolic function and reduce serum markers of cardiac remodeling in HF patients with preserved LVEF. The results of TOPCAT are expected to be released near the end of this year and may give insight as to whether aldosterone antagonists have a mortality and/or morbidity benefit in diastolic HF.

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# Tapentadol Extended-Release for Painful Diabetic Peripheral Neuropathy

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Neuropathies are one of the most common complications of diabetes mellitus (DM), eventually affecting approximately 50% of patients.[1-3] Neuropathies are defined by a progressive loss of nerve fiber function that can manifest in a variety of ways, commonly including pain, tingling, and numbness in extremities. More severe cases are associated with pain described as a constant "burning," "electrical," and "stabbing with deep aching," and generally being more intense at night.[4] While the mechanisms which cause neuropathies are not completely understood many hypotheses exist, including chronic excess glucose concentration in the nerves, advanced glycation end products, and increased oxidative stress.[5-7] While tight glycemic control can reduce neuropathy by ~60%[8] other studies show that despite long-term glycemic control (glycosylated hemoglobin < 8%) a ~20% chance of developing painful neuropathy remains.[9]

Painful diabetic peripheral neuropathy (PDPN) is a chronic and progressive condition that typically develops initially in the feet and may eventually be manifested throughout the body. The condition has the potential to affect every organ system.[10] PDPN affects virtually all areas of the patient's life, including (but not limited to) mood, sleep, self-worth, independence, ability to work, and interpersonal relationships.[11] The economic impact of PDPN is also significant: neuropathy associated with DM and its complications account for nearly 27% of the direct medical costs of DM.[12] As of March 2013, the total cost of diagnosed diabetes in the United States was approximately $245 billion[13] and it is estimated that neuropathies account for ~$50 billion, representing a large financial cost to society. While the actual contribution of symptomatic PDPN is unknown, it is assumed to be a significant portion of this percentage.

Historically, the first step in controlling PDPN has been tight glycemic control, which decreases the incidence of neuropathy and significantly slows the progression of the condition.[8] When tight glycemic control alone does not provide adequate relief the symptoms of PDPN are treated with a variety of medications including antiepileptics, antidepressants, or opioid analgesics. These medications should always be viewed as adjuncts to tight glycemic control as they only control the symptoms and have no effect on the incidence or progression of the condition. The American Academy of Neurology published evidence-based guidelines in 2011 including recommendations for treatment of PDPN **(Table 1)**.[14] Their recommendations include 2 levels (Level A and Level B) with pregabalin being the only first-line, Level A recommendation. Beyond pregabalin, the choice of second-line medication becomes muddled and is dependent on patient-specific factors as well as the clinical judgment of the provider.

In August 2012 Janssen Pharmaceuticals announced that the FDA had approved Nucynta ER® (tapentadol extended-release) for use in the treatment of neuropathic pain associated with diabetic

**Table 1 | Summary of American Academy of Neurology Guidelines for Painful DPN**

| Recommendation Level | Medication Name | Recommended Daily Dose |
|---|---|---|
| Level A | Pregabalin (Lyrica®) | 300-600 mg |
| Level B | Gabapentin (Neurontin®) | 900-3600 mg |
| | Sodium Valproate (Depacon®) | 500-1200 mg |
| | Venlafaxine (Effexor®) | 75-225 mg |
| | Duloxetine (Cymbalta®) | 60-120 mg |
| | Amitriptyline | 25-100 mg |
| | Dextromethorphan | 400 mg |
| | Morphine Sulfate | 120 mg |
| | Tramadol (Ultram®) | 210 mg |
| | Oxycodone | Mean 37mg; max 120 mg |
| | Capsaicin | 0.075% applied four times |
| | Isosorbide Dinitrate Spray | No specific recommendation |

DPN: diabetic peripheral neuropathy

peripheral neuropathy requiring continuous, around-the-clock analgesia.[15] The immediate-release formulation had been approved for treatment of acute moderate to severe pain since 2008, but this new indication made tapentadol ER the first, and only, opioid with a specific indication for use in PDPN. This review will discuss the pharmacology, pharmacokinetics, adverse effect profile, abuse potential, cost, and potential place in therapy of tapentadol ER in the treatment of PDPN.

## Pharmacology & Pharmacokinetics

Tapentadol ER is a centrally-acting, synthetic opioid analgesic acting primarily through mu-receptor stimulation and norepinephrine reuptake inhibition (NERI). While the complete mechanism for analgesia is unknown, preclinical studies show that both of these properties are associated with producing analgesia.[16] Activation of the mu-receptors in the spinal cord ($mu_2$ receptors) along with stimulation at higher levels in the CNS ($mu_1$ receptors) leads to analgesia as well as an altered emotional response to painful impulses.[16] The NERI properties also lead to a degree of analgesia, but this effect has not been measured outside of *in vitro* studies. One trial found that tapentadol had similar NERI potency as venlafaxine, and suggested that the effects on reducing neuropathic pain are comparable between the two treatments.[17] Modulation of norepinephrine can lead to altered emotional response to pain as well as possible reduction of the transmission of pain signals through the spinal cord, both beneficial in PDPN. Tapentadol ER has no effect on acetylcholine, gamma-aminobutyric acid (GABA), adenosine, or dopamine uptake in animal studies. However, it does show some affinity for sigma-2 receptors, muscarinic receptors (weak antagonist effect), and serotonin receptor subtype 3 (moderate dose-dependent antagonist effect).[17] These additional effects have not been associated with the analgesic efficacy of the medication.

Tapentadol is a Schedule II controlled substance and possesses significant potential for abuse, misuse, and diversion. These concerns must be considered when weighing the risks and benefits of tapentadol ER as an analgesic option. The risk for abuse is increased in patients with a personal and/or family history of substance abuse (any substance) or mental illness (e.g., major depression). Routine monitoring for signs of misuse, abuse, possible diversion, and addiction is necessary since these patients are a risk for addiction even under appropriate medical use and administration.

Tapentadol ER is administered orally, having a relatively low bioavailability of 32% due to a high degree of first-pass metabolism **(Table 2)**. Tapentadol ER is highly metabolized (97%) with metabolism facilitated via three primary pathways: conjugation, methylation, and hydroxylation. Conjugation through glucuronic acid to produce glucuronides is responsible for the majority of the metabolism (~70%). Other pathways include metabolism by the cytochrome p-450 (CYP) enzymes, specifically CYP2C9, CYP2C19, and CYP2D6. While the CYP enzymes play a role in metabolism, administration with CYP enzyme inducers or inhibitors does not necessitate tapentadol ER dose adjustment. The metabolites produced are not active,

**Table 2 | The Pharmacokinetic Properties of Tapentadol ER[16]**

| Property | Data |
|---|---|
| Bioavailability | ~32% |
| Time to $C_{max}$ | 3-6 hours |
| Time to Steady-State | After third dose if dosed twice daily (~36 hours after first dose) |
| $T_{1/2}$ | ~5 hours |
| Volume of Distribution | 540 ± 98 L |
| Protein Binding | 20% |
| Metabolism | Conjugation via UGT (70%), methylation via CYP2C19 and CYP2C9 (13%), hydroxylation via CYP2D6 (2%), unknown pathways (12%), excreted unchanged (3%) |
| Pro-drug | No activation required |
| Active metabolites | None |
| Excretion | 99% urinary excretion (active drug and metabolites) |

Cmax – maximum concentration, CYP – cytochrome p-450, $T_{1/2}$ – half-life, UGT - UDP glucuronosyltransferase

and virtually all of the active drug and metabolites are excreted renally (~99%).[16]

Tapentadol ER has no potential to induce or inhibit CYP enzymes. Drug interactions with medications dependent on these enzymes for metabolism are unlikely. Interactions with medications that alter gastric pH are highly unlikely as the bioavailability is not affected by gastric pH. Free concentration is unaffected by any drug-drug interactions resulting in displacement from the protein binding site.[16] Clinical trials measuring efficacy and safety did not include patients with severe renal or hepatic disease, and therefore tapentadol ER is not recommended in patients with such conditions.[16]

## Clinical Trials

There are several clinical trials supporting the safety and efficacy of tapentadol ER in patients suffering from chronic low back pain, pain from osteoarthritis, and PDPN. Two of these clinical trials specifically studied the analgesic efficacy off tapentadol ER in patients with PDPN **(Table 3)**. The studies are similar in design, have the same inclusion/exclusion criteria **(Table 4)**, and measure the same primary and secondary outcomes.

In a randomized-withdrawal, double-blind, placebo-controlled Phase III study Schwartz et al. evaluated the efficacy and safety of tapentadol ER in the management of moderate to severe chronic PDPN.[18] The population included opioid-naïve and opioid-experienced patients **(Table 4)**. Patients began with a three week, open-label phase where they were first categorized as responders or non-responders to treatment. During this "Pain Intensity Evaluation" period patients were qualified as responders if their pain intensity score (a 11-point numerical rating scale with 10 being the worst pain and 0 being no pain) improved by ≥ 1 point on over the course of the first 3 days of open-label period. During the open-label phase patients were initiated on tapentadol ER 50 mg twice daily for three days, then doses were increased to 100 mg twice daily (minimum dose allowed). Upward titration was allowed every 3 days up to a maximum dose of 250 mg twice daily while downward titration was allowed without time restrictions in decrements of 50 mg twice daily. Those who responded to treatment were studied in the subsequent double-blinded phase and were given either tapentadol ER or placebo treatment for a 12 week maintenance period. The primary endpoint of the study was to evaluate reduction of the pain intensity score at the end of the maintenance period as compared to the patient's baseline pain score. Secondary endpoints included evaluating how the patient's pain affected their quality of life through use pain surveys, including the brief pain survey (BPI), EuroQol – 5 Dimensions (EQ-5D), and 36-item Short-Form Health Survey (SF-36).[18]

The study started with 1,131 participants, 389 of them eventually being evaluated for safety and efficacy. There was no significant difference in time to discontinuation between placebo and the study group during the double-blind maintenance phase, but there was no comment on whether there was a significant difference during the open-label titration phase. At the end of the maintenance period, the patients treated with tapentadol ER had a significant reduction of 1.3 on the pain intensity score while patients in the placebo arm had no significant change in the pain score. A greater percentage of patients in the tapentadol ER arm achieved ≥ 50% reduction in pain intensity as compared with the patients in the placebo arm (37.8% vs. 27.6% of patients, respectively; p=0.028).[18]

In a randomized-withdrawal, double-blind, placebo-controlled, Phase III study Vinik et al. evaluated the efficacy and safety of tapentadol ER in opioid-naïve and opioid-experienced patients with moderate to severe chronic pain due to DPN.[19] The study design for this trial was similar to that of

**Table 3 | Summary of Efficacy Data for Tapentadol ER**

| | | Primary Outcomes | Secondary Outcomes | | | | |
|---|---|---|---|---|---|---|---|
| Design: | # of participants and dosing | Mean change in average pain intensity at week 12; LSMD vs. placebo | BPI total score | SF-36 physical component summary | SF-36 mental component summary | EQ-5D health status index | Comments |
| Schwartz et al. 2011[18] randomized-withdrawal, placebo-controlled trial | Tapentadol ER (100mg – 250mg) n = 1,131 initial phase; 395 maintenance phase | -1.3 [-1.70 to -0.92] | -0.2 | -0.2 | 0 | 0 | Tapentadol ER group was significantly different from placebo at week 12 of maintenance phase for the primary outcome (p<0.001) |
| | Placebo group (n = 193) | --- | 0.7 | -2.3 | -1.2 | -0.1 | |
| Vinik et al 2012[19] Design: randomized-withdrawal, placebo-controlled study | Tapentadol ER (100mg – 250mg) n = 1,131 initial phase; 320 maintenance phase) | -0.95 [-1.42 to -0.49] | 0.2 | -3.0 | -0.1 | 1.26 | Tapentadol ER group was significantly different from placebo at week 12 of maintenance phase for the primary outcome (p<0.001) |
| | Placebo group (n = 193) | --- | 1.4 | -2.6 | 0.8 | 10.10 | |

BPI: Brief Pain Inventory, EQ-5D: EuroQol – 5 Dimensions, LSMD: least-squares mean difference, SF-36: 36-item Short-Form Health Survey

**Table 4 | Inclusion and Exclusion Criteria for Schwartz et al[18] and Vinik et al[19]**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • DM 1 or 2 with chronic PDPN<br>• Age ≥ 18 years<br>• Moderate to severe pain, defined as an average baseline pain intensity score of ≥ 5 on an 11-point numerical rating scale (NRS) over the 3-day pain intensity evaluation period<br>• HbA1c ≤ 11%<br>• Use of analgesic therapy for ≥ 3 months; if receiving opioids, total daily opioid-equivalent dose ≤ 160 mg oral morphine<br>• Dissatisfaction with current analgesic | • History of malignancy within the past 2 years, lifelong history of seizures, traumatic brain injury, brain neoplasm, stroke/ transient ischemic attack within the past year, alcohol or substance abuse, chronic hepatitis B or C infection<br>• Moderate or severe hepatic or severe renal impairment, significant cardiac or vascular disease, hypersensitivity to study medication<br>• Other clinically significant diseases or conditions<br>• Significant diabetic ulcers, amputation of the limbs, or Charcot joints.<br>• Use of other analgesics, neuroleptics, anticonvulsants, antiparkinsonian drugs, MAOIs, TCAs, SNRIs, or systemic corticosteroids |

DM – diabetes mellitus, HbA1c – glycosylated hemoglobin, MAOI – monoamine oxidase inhibitor, NRS – numerical rating scale, PDPN – painful diabetic neuropathy, SNRI – serotonin/norepinephrine reuptake inhibitor, TCA – tricyclic antidepressants

Schwartz et al[18], consisting of a 3-week open-label titration period, a 3 day pain intensity evaluation period, and a 12 week double-blind maintenance period. Inclusion/exclusion criteria along with primary and secondary outcomes were identical to Schwartz et al **(Table 4)**.[18] To reach the maintenance period patients must have responded to treatment during the three day pain intensity evaluation period of the open-label phase. Responders were identified as patients reporting an improvement of ≥ 1 point on their pain intensity score with tapentadol ER. The open-label portion of the study included 917 patients, 318 of these patients were evaluated for efficacy in the maintenance phase.[19] During the open-label phase patients were initiated on tapentadol ER 50 mg twice daily for three days, then doses were increased to 100 mg twice daily (minimum dose allowed). Upward titration was allowed every 3 days up to a maximum dose of 250 mg twice daily while downward titration was allowed without time restrictions in decrements of 50 mg twice daily

Results showed that tapentadol ER was superior to placebo in reducing pain (-0.95 compared to placebo), superior in reducing the physical and mental components of the SF-36 scale, and increased the percentage of patients achieving 50% reduction of pain intensity as compared to placebo (40.4% vs 28.9% respectively; p=0.015).[19]

While the key clinical trials regarding safety and efficacy show that tapentadol ER provides analgesia to the patients with PDPN superior that of placebo,[18,19] there are no studies comparing efficacy against other medications use in PDPN. Many of the large trials measure efficacy solely against placebo and included an open-label phase to ensure that the only patients to be evaluated in the double-blinded phase were already known responders. This pre-selection of responders may not accurately reflect a truly randomized patient population. Comparisons to other medications for PDPN (gabapentin, pregabalin, venlafaxine, etc) would be helpful to establish a true place in therapy for tapentadol ER, however such comparisons are not currently available.

## Adverse Events and Safety

A summary of the adverse effects of tapentadol ER are summarized in Table 5, including adverse drug reactions reported by ≥ 5% of patients from pooled clinical trials. The data is based on two randomized withdrawal, double-blind, placebo-controlled 12-week studies of tapentadol ER in patients suffering from PDPN.[16] The average age across both studies was 60 years, 40% of patients were female and 60% were males. The most common adverse drug events reported (incidence ≥ 10%) were nausea, constipation, vomiting, dizziness, somnolence, and headache.

**Table 5 | Summary of Adverse Events from Two Pooled Placebo Studies[16]**

| | Tapentadol ER, 50 to 250 mg twice daily (n=1040) | Placebo (n=343) |
|---|---|---|
| Nausea | 27% | 8% |
| Dizziness | 18% | 2% |
| Somnolence | 14% | <1% |
| Constipation | 13% | <1% |
| Vomiting | 12% | 3% |
| Headache | 10% | 5% |
| Fatigue | 9% | <1% |
| Pruritus | 8% | 0% |
| Dry mouth | 7% | <1% |
| Diarrhea | 7% | 5% |
| Decreased appetite | 6% | <1% |
| Anxiety | 5% | 4% |

Wild et al. studied the safety and tolerability of tapentadol ER against oxycodone CR (controlled-release) for a one year period.[20] The patient's dose of either agent was titrated to a therapeutic dosage during week one of the study and subsequently maintained for 51 more weeks (maintenance phase). Of the 1,458 patients entering the first week of the study, 1,095 entered the maintenance phase. In the maintenance phase 894 patients received tapentadol ER and 223 received oxycodone CR.

The most common treatment emergent adverse events (TEAEs) in patients taking tapentadol ER were constipation, nausea, vomiting, somnolence, dizziness, headache, fatigue, and pruritus. The tapentadol ER group showed no clinically relevant treatment-related effects on lab values, vital signs, or ECG results. Patients treated with tapentadol ER had a longer time to onset of gastrointestinal (GI) adverse events (nausea, vomiting, or constipation) than those treated with oxycodone CR ($p < 0.001$). Less patients discontinued treatment due to GI adverse events in the tapentadol ER group (8.6%) than in the oxycodone CR group (21.5%). In those who reported constipation at the end of the study, tapentadol ER was associated with less severe constipation compared to oxycodone CR as measured by the overall Patient Assessment of

Constipation Symptoms (PAC-SYM) score. Patients in the tapentadol ER group showed a slightly higher percentage of withdrawal symptoms 3 days after study completion compared to the patients in the oxycodone CR group (2.5% compared to 1.3%).[20]

Beyond the adverse effect profile, there are other aspects of tapentadol that warrant caution. Due to the inhibition of serotonin/norepinephrine reuptake, there have been case-reports of life-threatening serotonin syndrome in patients with concomitant use of other serontonergic medications including selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs,) triptans, and monoamine oxidase inhibitors (MOAIs). As with other opioid analgesics, fatal respiratory depression may occur with high doses. A dose titration strategy of increasing by 50 mg twice daily (maximum dose of 250 mg twice daily) is recommended to avoid severe respiratory depression. Concomitant intake of ethanol can cause increased plasma levels of tapentadol and cause additive CNS depressant effects which both may increase the risk of fatal respiratory depression. Contraindications to tapentadol ER include significant respiratory depression, acute or severe bronchial asthma, known or suspected paralytic ileus, hypersensitivity reaction, and concurrent use (or use within 14 days) of any MAOI.

## Cost

Currently there is no generic form of tapentadol ER available on the US market. Table 6 summarizes the cost of Nucynta® ER on various insurance plans (commercial and Medicare), average copayments, and cash prices at popular commercial pharmacies in the Gainesville area. The manufacturer has a savings card available through their website where eligible patients will pay no more than $25 for their prescription co-pay. The card is valid for up to 14 prescriptions per calendar year with a cap of $100 savings per fill. In order to be eligible, patients must not be enrolled in Medicare and Medicaid.

**Table 6 | Patient cost of Nucynta® ER Including Commercial Plans, Medicare plans, and cash price21**

| | Price for monthly supply* | Placebo (n=343) |
|---|---|---|
| Commercial Insurance Plans | $31 | 8% |
| Medicare Insurance Plans | $18 | 2% |
| Cash Price | $203.58 [$186.54 – 221.99] | <1% |

*monthly supply determined as 60 tablets; medication taken twice daily for therapeutic effect

## Summary

The role of tapentadol ER for PDPN is not clearly defined. Neuropathic pain has traditionally been difficult to control with opioids, making tapentadol ER an intriguing option due to its NERI quality. The American Academy of Neurology has determined opioid medications as level B agents for PDPN, but the dual action of tapentadol ER may make this a nebulous classification. Clinical trials have shown efficacy vs. placebo, but have not included comparisons with active agents. The adverse effects are similar to that of other opioid analgesics including risk of fatal respiratory respiratory depression, abuse potential, GI adverse effects, but with the possibility of serotonin-syndrome. There is no generic currently available which may make it difficult for patients who are not insured to pay for the medication long-term.

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