Nucynta ER C-II Formulary Monograph

Generic Name:	**Tapentadol extended-release tablets C-II**
Brand Name:	**Nucynta ER® C-II**
Manufacturer:	**Janssen Pharmaceuticals, Inc.**
Date of Review:	**January 15, 2013**

Available Therapeutic Alternatives:

Prescription Benefit	
Preferred/Formulary	**Non-Preferred/Non-Formulary**
Amitriptyline (generic) Gabapentin (generic) Carbamazepine (generic) Tramadol (generic) [moderate to severe pain indication] Acetaminophen/Codeine (generic) [moderate to severe pain indication] Acetaminophen/Hydrocodone (generic) [moderate to severe pain indication]	Pregabalin (Lyrica®) Lamotrigine (Lamictal®) Oxycodone CR (Oxycontin®) [moderate to severe pain indication] Tapentadol extended-release tablets (Nucynta ER® CII)

TABLE OF CONTENTS:

Abbreviations used in this monograph:

ANCOVA: Analysis of co-variance	**LAO**: Long Acting Opioid(s)
BIA: Budget Impact Analysis	**MAOI**: Monoamine Oxidase Inhibitor
CDS: Controlled Dangerous Substance	**NE:** Norepinephrine
CHF: Congestive Heart Failure	**NSAID**: Nonsteroidal Anti-Inflammatory Drug
CKD: Chronic Kidney Disease	**OA**: Osteoarthritis
CNS: Central Nervous System	**PAC-SYM**: Patient Assessment of Constipation Symptoms
COWS: Clinical Opiate Withdrawal Scale	**PGIC**: Patient Global Impression of Change
CR: Controlled Release	**QALY:** Quality Adjusted Life Year
CR_{CL}: Creatinine clearance	**SNRI**: Serotonin-Norepinephrine Reuptake Inhibitor
CUA: Cost Utility Analysis	**SSRI**: Selective Serotonin Reuptake Inhibitor
CYP: Cytochrome P450 Enzyme	**TCA**: Tricyclic Antidepressant
DPN: Diabetic Peripheral Neuropathy	**TEAE**: Treatment-emergent adverse events
ER: Extended Release	**T_{MAX}**: Time to maximum serum concentration
FDA: Food and Drug Administration	**WHO**: World Health Organization
5-HT: Serotonin (5-Hydroxytryptamine)	**WOMAC**: Western Ontario and McMaster Universities Index of Osteoarthritis Questionnaire

Reason for Review:

To determine the appropriate formulary status for Tapentadol extended-release tablets (Nucynta ER® C-II) in the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults.

EXECUTIVE SUMMARY

Key Questions/Issues and Results of Investigation:

Issue 1: What is the evidence of efficacy from clinical trials?

Multiple studies suggest Tapentadol (Nucynta ER) is non-inferior to opioid analgesics and Tramadol for the treatment of chronic musculoskeletal and/or OA (osteoarthritis) pain. For neuropathic pain, especially diabetic peripheral neuropathy (DPN), preliminary data, in the form of animal models and a few placebo controlled trials, suggests Nucynta displays some degree of efficacy.[1, 2] However, to date no major studies have been performed to directly compare Nucynta to non-opioid agents (e.g. duloxetine, gabapentin) used in the treatment of neuropathic pain.

Issue 2: Is there sufficient evidence to assess real world comparative effectiveness?

Based on Phase III clinical trials and follow up studies comparing Nucynta to Oxycontin/LAO, evidence suggests that Nucynta ER is non-inferior in terms of its comparative effectiveness. That said, LAO are used as second line agents in the treatment of neuropathic pain. Since the only other pertinent clinical trials conducted thus far in patients with neuropathic pain have compared Nucynta to a placebo, it is premature to conclude that Nucynta's efficacy translates into real world effectiveness.

Issue 3: What is the evidence of safety?

Nucynta exhibits adverse effects common to both opioids and norepinephrine reuptake inhibitors; nevertheless, its side effects tend to be less pronounced than those of Oxycontin and other LAOs. Relatively few cases of overdose have been reported with Nucynta. Because Nucynta is a mu opioid receptor agonist, it may enhance the effects of other agents capable of producing CNS and/or respiratory depression, especially other opioids, benzodiazepines and barbiturates. Patients taking Nucynta should avoid alcoholic beverages as well as the herbal supplement St. John's Wort, due to the risk of serotonin syndrome. Nucynta exhibits relatively few drug-drug interactions, in large part due to minimal Phase I metabolism by CYP450 enzymes and near total renal clearance. Nucynta is absolutely contraindicated in patients taking MAOIs or for 14 days after discontinuing an MAOI because the combination may trigger a life threatening hypertensive crisis. Nucynta is classified as a category C drug in pregnancy and has not been approved for pediatric use.[5]

Issue 4: What is the value proposition for this product?

In addition to a more tolerable side effect profile than controlled release (CR) formulations of oxycodone, Nucynta ER is ostensibly less expensive than Oxycontin on a per dose basis. As will be discussed later, data from both wholesale and retail pharmacy websites largely debunks the claim that Nucynta is a more cost effective drug than Oxycontin. One major reason for its high cost is that Tapentadol will remain on patent as Nucynta for at least another 5 years before a

generic formulation becomes available.[6] Alternative medications for DPN tend to be more attractive in terms of their cost and ease of prescribing. Only Nucynta has C-II drug status; none of the alternatives has a CDS schedule, with the exception of Pregabalin, a C-V drug.

Issue 5: Are there identifiable patient subgroups in which this treatment will be most cost-effective?

Targeting

Patients who experience inadequate pain relief from alternative drugs, especially Oxycontin and Tramadol, or who experience intolerable side effects or hypersensitivity to long acting opioids represent the subgroups for whom this treatment will be the most cost effective.

RECOMMENDATIONS TO THE COMMITTEE

Therefore, the following P&T action is recommended:

Our team recommends that Nucynta ER remain on formulary as a brand name, non-preferred drug for patients with neuropathic pain or DPN, who either experience inadequate pain relief or who cannot tolerate alternative agents such as duloxetine, gabapentin, or pregabalin.

In the realms of safety, efficacy, and effectiveness Nucynta is at least non-inferior to comparably dosed opioid analgesics; nevertheless, two major drawbacks remain: the drug's Schedule-II status and the lack of a generic formulation. Taken together, these factors make it unlikely that Nucynta ER will come into widespread use for the foreseeable future.

ISSUE DETAILS

ISSUE 1: What is the level and quality of evidence for efficacy from clinical trials?

- Analgesic efficacy for Nucynta in the treatment of chronic musculoskeletal or OA pain in adults is well established.
- Nucynta is FDA approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults. However, head to head studies comparing Nucynta to SNRIs and other non-opioid treatments for DPN/neuropathic pain have yet to be performed.
- Phase 3 clinical trials show that the Nucynta ER achieves its analgesic efficacy via the μ-opioid receptor and as a norepinephrine reuptake inhibitor in patients with low back pain, osteoarthritis and DPN. It turns out that Nucynta ER demonstrated non-inferior efficacy in relieving pain especially for DPN compared to other widely accepted non-preferred μ-opioid receptor agonists such as oxycodone and tramadol. Results from the Phase 3 clinical trials.

- Number Rating Scale (NRS) from patients with pain in osteoarthritis, chronic pain and DPN that shows improvement in alleviating pain using statistical figures.
- Limitation of the data collected from the subjective point of view due to the nature of NRS system.
- Possibility of developing a new method of measuring pain other than the NRS system.
- Comparison and contrast with other non-preferred μ opioid receptor agonists such as Oxycodone and Tramadol in terms of efficacy and potency.

- Nucynta may have additional efficacy by relieving pain through its second mechanism of action as a norepinephrine reuptake inhibitor. There is, however, a risk in accepting the NRS data collected from the patients' subjective point of view as an absolute marker for the results of clinical trials and it might be necessary to develop a more objective standard to measure the drug's efficacy, and, in turn, for the results to be validated in multiple trials.

ISSUE 2: Is there sufficient evidence to assess real world comparative effectiveness?

Initial trials show that Nucynta ER has comparable analgesic effectiveness. Nucynta ER is indicated for the management of moderate to severe chronic pain and also neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Nucynta ER seems to be more effective in the sense that studies show fewer adverse events compared to other LAOs, in turn leading to fewer discontinuations of treatment.

A chronic pain treatment review in Europe reached a similar result. It compared Nucynta ER to the likes of transdermal buprenorphine, transdermal fentanyl, hydromorphone, morphine, and oxymorphone. Nucynta showed favourable results over oxycodone for pain intensity, 30% and 50% pain relief, and quality of life. Furthermore, some of the most common adverse events of chronic opioid treatment were significantly less frequent with Nucynta as compared to oxycodone, i.e. constipation, nausea, and vomiting; discontinuations due to these adverse events were found significantly reduced with Nucynta. (http://www.ncbi.nlm.nih.gov/pubmed/21905968)

In another study, the incidence of gastrointestinal effects leading to discontinuation of treatment was 2.5 times lower in the Nucynta ER group. This is likely due to the dual synergistic mechanism of action of Nucynta ER, where appreciable levels of analgesia are achieved with a lesser degree of mu receptor activation. The ability of Nucynta ER to suppress neuropathic as well as somatic pain suggests it will offer a broader spectrum of efficacy than the currently available ER analgesics. Opioid agonists are not considered a first line because they are limited in their clinical effectiveness, whereas analgesic medications with a combined mechanism of action, including norepinephrine reuptake inhibition, are effective against chronic pain.
(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3160834/#b49-jpr-4-211)

ISSUE 3: What is the level and quality of evidence for safety?

Nucynta demonstrates a more favorable safety and tolerability profile compared to oxycodone CR in assessments including gastrointestinal-related and central nervous system adverse effects as well as pruritus (itching). Two Phase 3 clinical trials showed that the percentage of patients with TEAE of gastrointestinal disorders, especially in regards to constipation, nausea, and vomiting, was lower compared to oxycodone CR (Afilalo *et al.,* 2010 and James *et al.,* 2010). The lower percentage of these TEAEs led to less frequent study discontinuation as shown in the trial data.

- *Gastrointestinal disorders*. The LSM change from baseline was significantly lower in the tapentadol ER group than the oxycodone CR group for the overall PAC-SYM score ($p<0.001$) (Afilalo *et al*., 2010).
- *Opioid withdrawal*. Clinical trial by *Afilalo et al*. also evaluated opioid withdrawal severity at treatment discontinuation for patients who did not use opioids following discontinuation of study medication. COWS was applied in all treatment groups for all time periods, showing that patients in the tapentadol ER groups have a higher percentage of experiencing no opioid withdrawal (98.6% and 85.7%), but a lower percentage experiencing mild to moderate opioid withdrawal (1.4% and 11.9%; 0% and 2.4%) than the oxycodone CR groups (Afilalo *et al*., 2010). Another Phase 3 clinical trial by James *et al* also showed COWS total scores during all time periods were less than 25, indicating that there was no moderately severe or severe withdrawal in either treatment group for patients who did not take opioids after the last dose of study medication (James *et al*., 2010).
- Nucynta is not listed on the 2012 Beers Criteria. Patients over 65 years of age should still be cautioned about the potential for dizziness and falls while taking Nucynta or other opioids.
- Nucynta is classified as a category C drug in pregnancy and has not been approved for pediatric use.
- *Renal impairment.* Nucynta needs to be dose adjusted in patients with significant renal impairment. Specifically, the dose of Nucynta should be decreased by 50% in patients with mild to moderate renal disease (CR_{CL} between 30-60 mL/minute), and the drug should be avoided altogether in patients with Stage 4 or 5 CKD. This is a routine precaution suggested whenever it would be impractical or unethical to test a new drug in patients with moderate to severe renal disease.
- *Hepatic disease*. No dosage adjustments are necessary in patients with mild liver dysfunction. Practically no safety data exists about the use of Nucynta in patients with advanced liver disease or fulminant hepatic failure. As such, the manufacturer recommends against using Nucynta in these patients.
- *Absolute contraindications.* Nucynta is absolutely contraindicated in patients taking an MAOI and for 14 days after discontinuing an MAOI. Additional contraindications include patients with paralytic ileus/bowel obstruction or severely compromised pulmonary function, e.g. respiratory depression or severe asthma.
- Other disease states in which Nucynta must be used with extreme caution - or avoided altogether - include intestinal obstruction, acute pancreatitis, as well as any patient with severely compromised pulmonary function, e.g. uncontrolled asthma, severe COPD, or respiratory failure.

ISSUE 4: What is the value proposition for this product?

Summary of Product Value

Nucynta's major advantage over other opioid analgesics lays in its dual mechanism of action and relatively mild side effect profile. As a mu receptor agonist and NE reuptake inhibitor, Nucynta can potentially treat both nociceptive pain (OA) in addition to neuropathic pain (DPN). By inducing fewer cases of gastrointestinal upset or CNS side effects, Nucynta represents a viable alternative for patients who otherwise might not tolerate opioid analgesics and avoid them altogether in spite of their therapeutic effects.

Manufacturer-Submitted Modeling

Budget Impact Analysis: The manufacturer's BIA begins with the premise that the HMO is operating on a fixed budget and can add Nucynta to its formulary if and only if it decreases expenditures on other drugs, in this case Oxycontin. This economic model rests on one critical assumption: that, on average, Nucynta ER costs $0.90 less per dose than Oxycontin. As an added bonus, Nucynta's milder side effect profile means fewer patients would require prescriptions for the laxatives and antiemetics they might have needed had they been prescribed Oxycontin. These lower costs translate into an annual savings of $144,048 in "pharmacy costs" according to the dossier. Finally, fewer serious side effects with Nucynta translates into fewer emergency room visits and subsequent hospitalizations, resulting in an annual savings of an additional $4,549 in "medical costs".

Cost-Utility Analysis: CUA was not included in the dossier. Calculating Cost Effectiveness Ratios for Nucynta vs. Oxycontin and other LAO would be extremely difficult. First, there is the issue of cost per tablet. The prices quoted in the dossier are biased in favor of Nucynta and may not reflect current market trends. As the report will discuss at length, a careful search of wholesale and retail websites revealed the vendors' prices to be consistently *higher* for Nucynta than for equivalent dosage strengths of Oxycontin. Second, and even more importantly, analgesics may improve outcome parameters such as productivity and the number of days lost from work, but these numbers simply do not equate to quality adjusted life years (QALY).

ISSUE 5: Are there identifiable patient subgroups in which this treatment will be most cost-effective?

[Discussion of patient subgroups and the evidence that would indicate improved incremental cost-effectiveness ratio (ICER) for them. Include a description of relevant biomarkers or other companion diagnostics that would be used to identify these target populations, and the feasibility of using these markers in routine clinical practice.]
The main subgroups for whom this treatment will be most cost effective include: a) patients with a history of adverse reactions or hypersensitivity to Oxycontin or other LAO and b) opioid experienced patients who have developed a high degree of tolerance to pure mu receptor agonists. Factors such as gender, age, and racial background are less of a concern in the realm of cost effectiveness for analgesics as a whole; however, this is merely our group's opinion.

<table>
<tr><th>Ref. and Evidence Grade</th><th>Drug Regimens</th><th>N</th><th>Time</th><th></th><th>Demographics</th><th>Design*</th><th>End Points/Results/Comments</th></tr>
<tr>
<td>ilalo et al., Trial: CT00421928
ade: A</td>
<td>randomized, double-blind, active- and placebo-controlled parallel-arm, multicentre, phase 3 study.

Tapentadol ER 100-250mg po bid
Oxycodone HCl CR 20-50mg po bid
Placebo</td>
<td>1,023</td>
<td>3-week titration period followed by a 12-week maintenance period total 15 weeks</td>
<td></td>
<td>Baseline Characteristics
<table>
<tr><th></th><th>Tapentadol ER</th><th>Oxycodone CR</th><th>Placebo</th><th>Total</th></tr>
<tr><td>#</td><td>344</td><td>342</td><td>337</td><td>1023</td></tr>
<tr><td>Age, y Mean (SD)</td><td>58.4 (10.09)</td><td>58.2 (10.29)</td><td>58.2 (9.15)</td><td>N/A</td></tr>
<tr><td>≥65 y</td><td>95 (27.6)</td><td>93 (27.2)</td><td>77 (22.8)</td><td>265</td></tr>
<tr><td><65y</td><td>249 (72.4)</td><td>249 (72.8)</td><td>260 (77.2)</td><td>758</td></tr>
<tr><td>Male</td><td>128 (37.2)</td><td>140 (40.9)</td><td>137 (40.7)</td><td>405</td></tr>
<tr><td>Female</td><td>216 (62.8)</td><td>202 (59.1)</td><td>200 (59.3)</td><td>618</td></tr>
<tr><td>White</td><td>260 (75.6)</td><td>245 (71.6)</td><td>267 (79.2)</td><td>772</td></tr>
<tr><td>Black</td><td>49 (14.2)</td><td>45 (13.2)</td><td>38 (11.3)</td><td>132</td></tr>
<tr><td>Hispanic</td><td>21 (6.1)</td><td>37 (10.8)</td><td>20 (5.9)</td><td>78</td></tr>
<tr><td>Other</td><td>14 (4.1)</td><td>15 (4.4)</td><td>12 (3.6)</td><td>41</td></tr>
</table></td>
<td>IVRS, NRS, PGIC, WOMAC, PAC-SYM, COWS, SOWS, ANCOVA,</td>
<td>TEAE reported by ≥5% of patients (safety analysis populatio
<table>
<tr><th></th><th>Tapentadol ER</th><th>Oxycodone CR</th><th>Placebo</th></tr>
<tr><td>Incidence of TEAEs</td><td>75.9% (261/344)</td><td>87.4% (299/342)</td><td>61.1% (206/337)</td></tr>
<tr><td>Constipation (p<0.001)</td><td>18.9% (65/344)</td><td>36.8% (126/342)</td><td>6.5% (22/337)</td></tr>
<tr><td>Nausea (p<0.001)</td><td>21.5% (74/344)</td><td>36.5% (125/342)</td><td>6.8% (23/337)</td></tr>
<tr><td>Vomiting (p<0.001)</td><td>5.2% (18/344)</td><td>17.8% (61/342)</td><td>3.3% (11/337)</td></tr>
<tr><td>Somnolence</td><td>10.8% (37/344)</td><td>19.6% (67/342)</td><td>4.2% (14/337)</td></tr>
<tr><td>Pruritus</td><td>7.0% (24/344)</td><td>12.6% (43/342)</td><td>1.2% (4/337)</td></tr>
</table>
COWS assessments completed ≥5 days after last intake of stu medication:
<table>
<tr><th></th><th>Tapentadol ER</th><th>Oxycodone CR</th><th>Placebo</th></tr>
<tr><td>No opioid withdrawal</td><td>98.6% (69/70)</td><td>85.7% (72/84)</td><td>91.5% (45/59)</td></tr>
<tr><td>Mild opioid withdrawal</td><td>1.4% (1/70)</td><td>11.9% (10/84)</td><td>8.5% (5/59)</td></tr>
<tr><td>Moderate opioid withdrawal</td><td>0% (0/70)</td><td>2.4% (2/84)</td><td>0% (0/59)</td></tr>
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ild *et al*., Trial: CT00361504 ade: B	randomized, open-label phase 3 study Tapentadol ER (100 to 250mg bid) Oxycodone HCl CR (20 to 50mg bid)	1117	Up to 1 year study period including screening period, washout period, 1-week titration period, 51-week maintenance period, and a follow-up period.		Demographic and Baseline Characteristics (Safety Population): Tapentadol ER (n=894) / Oxycodone CR (n=223) Age, y Mean (SD): 56.8 (12.51) / 58.1 (11.83) <65 y: 649 (72.6%) / 156 (70.0%) ≥65y: 245 (27.4%) / 67(30.0%) Female: 515 (57.6%) / 125 (56.1%) Male: 379 (42.4%) / 98 (43.9%) White: 792 (88.6%) / 203 (91.0%) Black: 60 (6.7%) / 13 (5.8%) Hispanic: 26 (2.9%) / 4 (1.8%) Other: 16 (1.8%) / 3 (1.3%)	PAC-SYM, COWS;	TEAE reported by ≥5% of patients in either treatment group population) Tapentadol ER / Oxycodone CR Incidence of patients experienced at least 1 TEAE: 85.7% (766/894) / 90.6% (202/223) Constipation: 22.6% (202/894) / 38.6% (86/223) Nausea: 18.1% (162/894) / 33.2% (74/223) Vomiting: 7.0% (63/894) / 13.5% (30/223) Dizziness: 14.8% (132/894) / 19.3% (43/223) Pruritus: 5.4% (48/894) / 10.3% (23/223) Tapentadol ER / Oxycodone CR TEAEs leading to study discontinuation: 22.1% (198/894) / 36.8% (82/223) COWS assessments completed ≥5 days after treatment discor for patients who did not take opioids after treatment discontir Tapentadol ER (n=166) / Oxycodone CR (n=50) No opioid withdrawal: 88.0% (146/166) / 84.0% (42/50) Mild opioid withdrawal: 10.8% (18/166) / 14.0% (7/50) Moderate opioid withdrawal: 1.2% (2/166) / 2.0% (1/50)

BACKGROUND INFORMATION

DISEASE BACKGROUND

Neuropathic pain is caused by direct nerve damage or may arise from a disease process affecting the nervous system. Neuropathic pain is usually burning, tingling, sharp, or stabbing. People may have the pain all the time, or the pain can come and go (Neuropathic pain, Lexicomp online). There are three main conditions underlying most cases of neuropathic pain: Diabetic neuropathy, Postherpetic neuralgia, and Stroke (Neuropathic pain, Lexicomp online). Pain and other symptoms often appear symmetrically at the sites most distant from the brain and the spinal cord, eventually progressing toward the central part of the body (Peripheral Neuropathy Fact Sheet). In general, people with diabetic neuropathy experience a pain pattern consistent with ascending nerve damage (Peripheral Neuropathy Fact Sheet). Peripheral neuropathy may be inherited or acquired following physical injury (trauma) to a nerve; it may also be associated with tumors, toxins, autoimmune responses, nutritional deficiencies, alcoholism, and vascular and metabolic disorders (Peripheral Neuropathy Fact Sheet).

Disease Burden

With the incidence of diabetes mellitus rising at an alarming rate, it stands to reason that millions of people in the U.S. and abroad will eventually develop painful DPN. An estimated 25.8 million Americans currently have some form of diabetes.[18] Over time as many as 50% of these people will go on to develop microvascular complications of diabetes, including DPN. As with any form of chronic pain, DPN can exacerbate comorbid disease states including hypertension, CHF, obesity, and depression.
The total costs of DPN are unknown, but estimates range from $4.6 to $13.7 billion in the U.S. annually[19] once factors such as days lost from work, lost productivity, and overall decreased quality of life are taken into account.

Pathophysiology

The pathophysiology of DPN is complex; a host of factors including oxidative stress, increased sorbitol deposition, decreased nitric oxide production, and increased homocysteine are thought to be involved (Head, 2006). Much of the damage is believed to stem from chronically elevated blood glucose levels. Long standing hyperglycemia results in an increased numbers of glycosylated proteins, such as Hgb_{A1C}, which are easily damaged by free radicals (Onge and Miller, 2008). These proteins are also sticky and tend to combine with fats to produce advanced glycosylated end-products that have been linked to abnormalities in vascular tissue, lipid metabolism, and platelet function (Duby 2004 and Head 2006). Evidence suggests that following the entry of excessive glucose into neuronal cells, some glucose is converted into sorbitol, which accumulates and eventually forms insoluble deposits that ultimately damage the neurons (Onge and Miller, 2008). Studies of diabetic rats suggest that deficiency of nitric oxide may result in decreased blood flow, which is another major contributor to tissue dysfunction and damage observed in DPN (Onge and Miller, 2008). Finally, elevated homocysteine levels, a well-known marker of endothelial damage, are present in many patients with diabetes mellitus (Head 2006).

Treatment Alternatives for Painful DPN

- Pregabalin (Lyrica, Pfizer) is an anticonvulsant structurally similar to its pioneer drug, gabapentin (Onge and Miller, 2008). Several clinical trials have studied pregabalin since it's one of the few medications approved by the FDA for the treatment of DPN (Onge and Miller, 2008). The doses of pregabalin studied ranged from 75 mg up to 600 mg/day, in which, the doses of 300 mg to 600 mg/day were proved to be required to produce significant improvements in mean pain scores (Onge and Miller, 2008). According to Onge and Miller's 2008 review article, pregabalin was concluded by each clinical trial to be safe and effective for patients with DPN.
- Lamotrigine as another anticonvulsant agent, which has been studied in patients with DPN with mixed results (Onge and Miller, 2008). It has been compared with placebo as well as with amitriptyline in two identical clinical trials that were being processed simultaneously, yet with opposite results with two different doses (Onge and Miller, 2008). Some other small trials have shown that lamotrigine was as effective as amitriptyline. However, the inconsistency of clinical trials is not a strong evidence for using lamotrigine as a preferred therapy (Onge and Miller, 2008).
- Duloxetine (Cymbalta) is an SNRI antidepressant. As of 2010, it became FDA approved for the treatment of pain arising from DPN or fibromyalgia.
- Oxycodone is an opioid analgesic that produces decreased perception of and response to pain signals by binding to and activating mu opioid receptors throughout the central nervous system (CNS). There is much evidence supporting the use of oxycodone to treat moderate-to-severe pain, however, there are limited clinical trials to demonstrate the effectiveness of oxycodone for pain with DPN (Onge and Miller, 2008).

Preferred Existing Therapy

- Amitriptyline is the most studied TCA for DPN and has been compared to placebo, imipramine, and desipramine. Compared to placebo, amitriptyline reduced pain to a significant degree, and evidence of pain relief was shown as early as the second week of the therapy, with greater pain relief noted at higher doses (at a mean dose of 90 mg) (Onge and Miller, 2008).
- Gabapentin, originally developed as an anticonvulsant agent, has also been used to treat DPN. It has been compared with placebo as well as with amitriptyline. When compared with placebo, gabapentin 900 to 3,600 mg/day was required to produce significant changes in pain scores. In comparative trials, gabapentin was at least equivalent to amitriptyline in treating pain associated with DPN (Onge and Miller, 2008).
- Tramadol is a "non-narcotic" analgesic that binds to mu-receptors in the CNS, causing a change in the perception of and response to pain. Tramadol also inhibits the reuptake of NE and 5-HT, thereby further altering the pain pathway. It has been studied alone and in combination with acetaminophen. In a six-week double-blind, placebo-controlled portion of the study, the author concluded that tramadol provided effective relief of DPN pain over a six-month period. The authors also concluded that tramadol plus acetaminophen was effective and well tolerated for pain relief for patients with DPN pain (Onge and Miller, 2008).

Other Therapeutic Alternatives

Several alternative pharmacologic treatments for neuropathic pain exist including capsaicin cream, which depletes Substance P stores in peripheral nerves; the antiepileptic drug carbamazepine, which may reduce pain by blocking voltage gated sodium channels; and injections of short acting anesthetics such as lidocaine to act as nerve blocks. Many non-pharmacologic therapies have also been tried including massage, acupuncture, biofeedback, and hypnosis; however, a full discussion of these modalities is beyond the scope of this monograph.

PRODUCT BACKGROUND

Pharmacology

Nucynta is believed to exert its effects by a dual mechanism of action. First, it is a mu receptor agonist, albeit significantly less potent than morphine or most other opioids. Second, Nucynta inhibits the reuptake of norepinephrine, exerting analgesic effects similar to SNRI drugs like duloxetine and TCA drugs like amitriptyline. This dual mechanism of action raises the possibility that Nucynta may provide analgesia not only in patients suffering from chronic musculoskeletal pain but also those experiencing neuropathic pain. Relatively few analgesics are effective at treating both types of pain.

Pharmacokinetics Hoy SM, *Drugs* 2012: 72(3): 375-393

Route of Administration:	**Oral**
Bioavailability:	**32%**
Time to Peak (T_{MAX}):	**1-2 hours**
Elimination half life:	**4-5 hours**
Multiple dosing:	**Twice daily**
Clearance:	**99% renal; estimated at 1530-1603 mL/min.**

Adverse Effect Profile

The most commonly reported adverse effects of Nucynta are constipation, nausea, vomiting, and pruritus. These side effects often lead to treatment discontinuation of opioid therapy. Among these side effects, constipation is one the most common since it is caused by the interaction of exogenous opioids with receptors in the GI tract, resulting in inhibition of gastrointestinal motility and secretion (Candiotti and Gitlin, 2010). Opioid-associated adverse events affecting the central nervous system include somnolence, cognitive impairment, dizziness, and respiratory depression (Candiotti and Gitlin, 2010).

The figure below was taken from a 2012 review comparing the most common adverse effects in patients taking Tapentadol ER (Nucynta) vs. Oxycodone CR (Oxycontin) vs. a placebo.

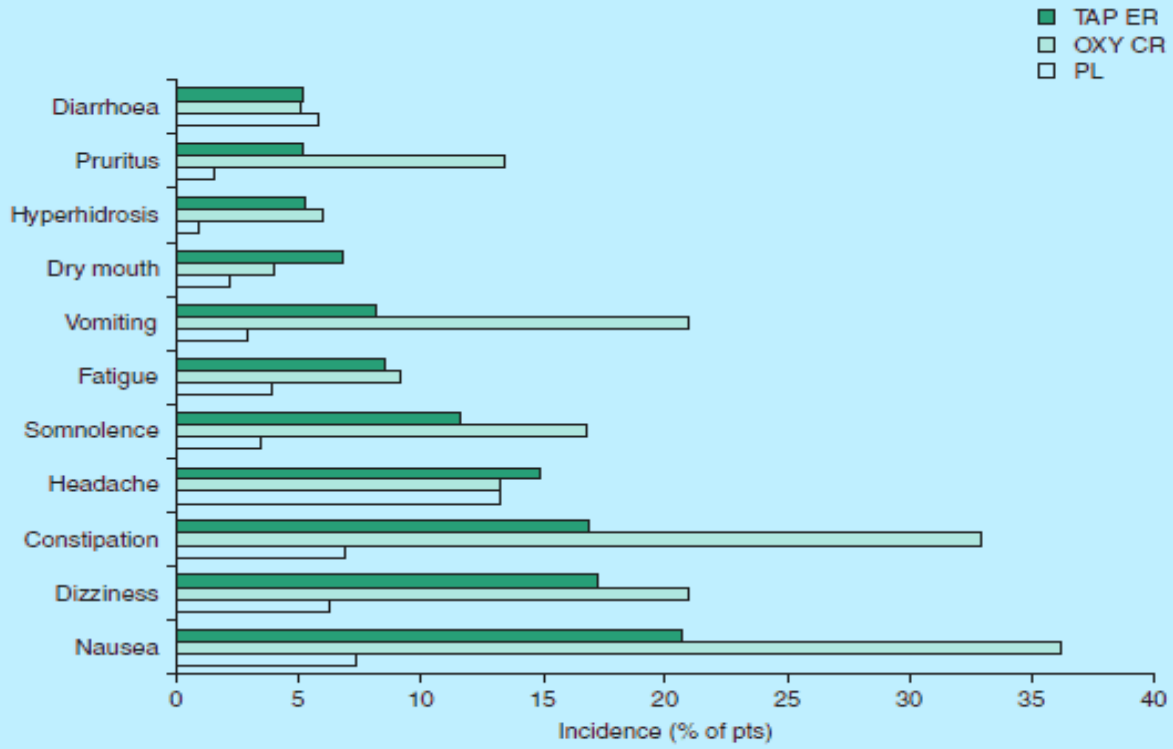

Fig. 1. Tolerability profile of oral tapentadol extended release in the shorter-term treatment of adult patients with moderate to severe chronic pain associated with knee osteoarthritis or the lower back. Incidence of treatment-emergent adverse events affecting ≥5% of patients in a pooled analysis[43] of three randomized, double-blind, multinational, phase III studies.[21-24] Patients received twice-daily tapentadol extended release 100–250 mg (n = 980), oxycodone controlled release 20–50 mg (n = 1001) or placebo (n = 993) for 15 weeks; see section 4 for study design and full treatment regimen details. **OXY CR** = oxycodone controlled release; **PL** = placebo; **pts** = patients; **TAP ER** = tapentadol extended release.

Hoy SM (2012) *Drugs*; 72(3) 375-393

Drug Interactions

MAOIs are absolutely contraindicated with Nucynta. Use of Nucynta within 14 days of discontinuing an MAOI is also contraindicated.
Relatively contraindicated drugs include opioids (especially meperidine and dextromethorphan), SNRIs, SSRIs, TCAs, triptans (migraine headache medication), trazodone, and lithium. [from Lexi-comp]
Drug-Food Interactions: Ethanol should be avoided.
Herbal supplements: St. John's Wort raises the risk of serotonin syndrome and should be avoided.

METHODOLOGY OF THIS REVIEW

DATABASES SEARCHED:
Ovid MEDLINE
PubMed

SECONDARY SOURCES:
FDA.gov
Who.int

SEARCH STRATEGY:

- **Search Terms**: tapentadol, acetaminophen, naproxen, drug interactions, chronic pain, oxycodone CR, efficacy and safety, opioid analgesics, diabetic peripheral neuropathy
- **Exclusion/limits**: English Language

INCLUSION CRITERIA:

Search Results:

Study Type	**N**
Randomized controlled trials (RCT)	X
Meta-analyses of RCTs	
Systematic reviews	X
Randomized pragmatic Trials	
Prospective cohort studies	
Retrospective cohort or case-control studies	
Economic modeling studies	
Case Series	
RCT abstracts, not peer-reviewed	
Other abstracts, posters, etc., not peer-reviewed	

Articles Excluded from Evidence Synthesis: None

Reason for Exclusion	**N**

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