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Abbreviated Class Update: Long-Acting Opioids (LAOs)

Month/Year of Review: September 2013
New drug(s): tramadol ER (Ultram ER™, Conzip™, & generics)

End date of literature search: July 2013
Manufacturers: Janssen Pharmaceutical, Inc. Vertical Pharmaceuticals Inc., & various

Oregon PDL status	Drug	Trade name(s)	Forms evaluated in review	Recommended usual dosing frequency (times per day)
N	buprenorphine	Butrans™	ER transdermal film	Every 7 days
Y	fentanyl	Duragesic™	ER transdermal film	Every 72 hours
N	hydromorphone ER	Exalgo™	ER oral tablet	1
N	levorphanol	generic	Oral tablet	3-4
N	methadone	generic, Dolophine™	Oral tablet	2-3
N	morphine sulfate ER	generic	ER oral capsule	1
N		Avinza™	ER oral capsule	1
N		Kadian™	ER oral capsule	1-2
N		generic	ER oral capsule	1-2
Y		generic	ER oral tablet	2-3
Y		MS Contin™	ER oral tablet	2-3
N	morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
N	oxycodone ER	OxyContin™	ER oral tablet	2
N	oxymorphone ER	Opana ER™	ER oral tablet	2
N	tapentadol ER	Nucynta ER™	ER oral tablet	2
	tramadol ER	generic	ER oral tablet	1
		Ultram ER™	ER oral tablet	1
		Conzip™	ER oral capsule	1

Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release.

There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims.

Research Questions:

- Is there any evidence about comparative effectiveness of tramadol extended release (ER) versus the different long-acting opioids, in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
- Is there any new evidence about comparative harms (including addiction and abuse) of tramadol ER versus the different long-acting opioids in adult patients being treated for chronic non-cancer pain?
- Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic non-cancer pain for which tramadol ER is more effective or associated with less harm?

Conclusions:

- There is insufficient comparative evidence to establish differences in effectiveness of tramadol ER versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of tramadol ER versus the other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate tramadol ER from the other LAOs.

Recommendations:

- Tramadol ER should be evaluated in executive session for relative cost.
- Set maximum daily dose to 300mg per the drug label.

Reason for Review: Oregon reviewed the literature in this class in July 2013 and recommended adding tramadol extended release products to complete the class.

Previous P&T Conclusions:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among the LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo per DynaMed. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All LAOs carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.

Background: Tramadol ER is a weak opioid μ-agonist and thus differs from the other drugs in this class which are strong opioid μ-agonists. It also weakly inhibits norepinephrine and serotonin reuptake. It is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of pain for an extended period of time (at least 3 to 6 months).[1,2] Tramadol ER is recommended after non-opioids have failed and prior to initiation of full opioid μ-agonists by the Canadian Pain Society,[3,4] the National Institutes if Clinical Excellence[5] guidelines and the World Health Organization's (WHO) "analgesic ladder."[6] Potential off-label uses include premature ejaculation[7] and restless leg syndrome.[8]

Methods:
A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) that compared tramadol to long-acting opioids in head to head trials for chronic pain was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. After review of the citations from Medline and the manual searches, three systematic reviews[9,10,11] comparing tramadol to opioid treatments and two updated chronic pain treatment guidelines[3,4,5] were included in this review.

Systematic Reviews:
The DynaMed[9] review notes that not only is the comparative evidence lacking for this class but, that evidence of efficacy of the individual opioids is weak overall, with the best evidence for morphine ER tablets and transdermal fentanyl. DynaMed reports Level 1 Evidence (likely reliable) based upon a single Cochrane Review[12] that tramadol provides small degree of pain relief in osteoarthritis of knee and/or hip over placebo but insufficient evidence of benefit over active controls. Another Cochrane review provided Level 2 Evidence (mid-level) tramadol was effective over placebo for neuropathic pain but there was insufficient evidence against morphine.

A Clinical Evidence review of postherpetic neuralgia treatments found low-quality evidence that tramadol was likely be beneficial when compared to placebo (n=149).[10]

Another Clinical Evidence review of opioids in people with cancer-related pain found insufficient evidence to assess the equivalence, in terms of analgesic benefit and adverse effects, of morphine compared with codeine, dihydrocodeine, fentanyl, hydromorphone, methadone, oxycodone, or tramadol.[11]

New Guidelines:

The National Institute of Clinical Excellence published guidance on the use of strong opioids for pain in palliative care in 2012 and recommends they only be used for patients not controlled on codeine or tramadol.[5]

The Canadian guidelines[3,4] for chronic nonmalignant pain were updated and published in 2011. The guidelines include recommendations on opioid indications, selection, titration, precautions and monitoring. Only selection recommendations are reported here. After a failed trial of either codeine or tramadol, morphine is recommended for patients without renal impairment.

References:

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12. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database of Systematic Reviews*. 2009;(1). Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD005522.pub2/abstract. Accessed August 21, 2013.

Appendix 1: Specific Drug Information

PHARMACOKINETICS[1,2]

Parameter	Result
Oral Bioavailability	85-90%
Protein Binding	20%
Elimination	Renally excreted: 30% unchanged and 60% as metabolites
Half-Life	10-11 hours
Metabolism	P450 CYP2D6, 3A4 and conjugation

DOSE & AVAILABILITY[1,2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
100mg, 200mg, 300mg	PO	Q24H	Initially 100mg Q24H, with titration of 50mg Q5D to desired effect or maximum dose of 300mg Q24H	Not recommended if Cr. Clearance is <30ml/min	Do not use in patients with severe hepatic impairment (Child-Pugh class C)	The use of tramadol in children is not recommended.	On Beers watch list but no adjustments in label for normal renal and hepatic function	ADEs experienced at higher frequency in elderly.

DRUG SAFETY[1,2]

Serious (REMS, Black Box Warnings: No Black Box Warnings or REMS

Warnings and Precautions: Seizures have been reported within the normal dose range. Concomitant use with drugs affecting the serotonin system or in patients with increased seizure risk is not recommended. Serotonin syndrome may occur. Do not prescribe for patients who are suicidal or addiction prone.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

TraMADol may be confused with tapentadol, Toradol, Trandate, traZODone, Voltaren

Ultram may be confused with Ultane, Ultracet, Voltaren