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March 19, 2008

To: Treating Physician

From: Dane A. Higgins, Pharm.D., M.B.A.

Subject: **Pharmacotherapy of ------------**

I have conducted a pharmacotherapy review of the medication utilization pattern of --------. A full review with evidence-based recommendations for therapeutic modifications is attached. A summary of key recommendations are listed below.

SUMMARY OF KEY RECOMMENDATIONS

The patient has not been treated for her original injury since 4/23/2007. However, the patient recently received prescriptions for Lyrica®, Lidoderm®, Ibuprofen and Skelaxin® after almost a year without any medication for her pain.

Drug	Recommendation	Rationale
Lyrica® 75 mg BID	The clinical value of Lyrica® relative to generic gabapentin should be questioned and Lyrica® costs about $1,200 more per year in this patient. Please consider switching the patient to generic gabapentin or simply discontinuing Lyrica® due to questionable effectiveness at the 150 mg per day dose.	Evidence-based reviews have suggested that Lyrica® and gabapentin are equally effective and safe. However, meta-analysis data comparing NNH data from clinical trials does suggest that gabapentin may actually be better tolerated (NNH for gabapentin of 26.1 for versus 7.4 to 11.7 for pregabalin). The patient's current dose (150 mg/day) has been shown to be no more effective than placebo in multiple clinical trials.
Skelaxin®	Consider limiting Skelaxin® therapy to a short-term treatment (i.e., only 1 prescription). If a long-term treatment is desired, consider generic tizanidine as it would provide equivalent, or possibly even superior, therapeutic results for $800 less per year.	Skelaxin® acts as a systemic CNS depressant and does not reduce muscle spasticity. The only agents that have actually been shown to reduce muscle spasticity chronically are baclofen, tizanidine and dantrolene. An alternative therapy to Skelaxin® would be tizanidine (as baclofen may cause muscle weakness).

Drug	Recommendation	Rationale
Lidoderm®	Consider switching the patient to an alternative oral medication (e.g., gabapentin, nortriptyline) or topical medication (e.g., lidocaine jelly, dibucaine ont). Switching the patient to one of these alternatives would save between $2,000 and $2,500 per year at the patient's current Lidoderm® dose.	An evidence-based review of Lidoderm® (in *Pain*) has suggested that it may be considered as a first-line agent (on par with gabapentin, nortriptyline, etc), yet they also suggest that… "Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use." Multiple generic alternatives could provide similar therapeutic results at a significantly reduced cost.

Thank you for your time and consideration,

Dane A. Higgins, Pharm.D., M.B.A.

MEDICATION REVIEW (DUR)

Patient Name: ------------ DOB: ------ Sex: -

DIAGNOSES:

Injury Related

1) Neck/Arm Injury from Flipping Mattress

CURRENT MEDICATIONS:

Rx Name	Rx Strength	Rx Qty	Rx Cost Per Month	Rx Cost Per Year (12 Rx/Yr)
Lyrica® (pregabalin)	75 mg	60	$121.08	$1,452.96
Lidoderm® (lidocaine patch)	5%	30	$227.24	$2,726.88
Ibuprofen	800 mg	60	$4.37	$52.43
Skelaxin® (metaxalone)	800 mg	30	$78.00	$936.00

SUMMARY OF RECOMMENDATIONS:

Drug	Recommendation(s)	Supporting Clinical Evidence	Potential Savings Per Year
Lyrica®	Consider discontinuation	Data suggests that 150 mg per day is no more effective than placebo.	$1,452
	If chronic therapy is required, consider generic gabapentin.	Data suggests that Lyrica® and gabapentin produce very similar results (see data below).	$1,200
Skelaxin®	Consider discontinuation	Therapy is only recommended for short periods of time (<14 days).	$936
	If chronic therapy is required, consider generic tizanidine.	Tizanidine has been shown to be effective with chronic therapy.	$800
Lidoderm®	Consider lidocaine gels, creams and ointments.	The generics will be as effective, but require more frequent application.	$2,250

CLINICAL AND ECONOMIC EVIDENCE FOR CHANGE

The patient has not been treated for her original injury since 4/23/2007. However, she recently received prescriptions for Lyrica®, Lidoderm®, Ibuprofen and Skelaxin® after almost a year without any medication for her pain. The origination of this pain flare and any relationship to the original injury (versus some other injury that has occurred in recent months) should be considered. If therapy is deemed related to the original injury, then please consider the following review of her medications. Lyrica®, Lidoderm® and Skelaxin® all have equally effective, and in some cases safer and more effective, alternatives that are significantly less expensive. As she has not been stabilized on these drugs for months or years, conversions would likely be less problematic.

Lyrica® (pregabalin)

Lyrica® (pregabalin) is a structural congener of gabapentin or a "second-generation gabapentin".[1-4] Pregabalin and gabapentin display similar pharmacology, mechanisms of action and therapeutic effects. In clinical trials involving diabetic peripheral neuropathy, 300 mg of pregabalin daily was associated with only modest improvements in pain scores (e.g., 1.7 point placebo adjusted reduction in pain score at 8 weeks);

however, **<u>150 mg per day was found to be no more effective than placebo</u>** (patient's current dose).[5,6] The 150 mg and 300 mg per day doses were found to be no more effective than placebo in a trial involving patients with fibromyalgia.[7] In one trial involving post-herpetic neuralgia, the 150 mg/day dose was found to be minimally effective (0.88 point placebo adjusted reduction in pain).[8] Therefore, based on current clinical trial data, the effectiveness of Lyrica® 75 mg twice daily is questionable. This could represent a very expensive "placebo" at a cost of $1,452 per year.

In general, the value of Lyrica® relative to generic gabapentin should be questioned. An evidence based review on the treatment of neuropathic pain was very recently published in *Pain*.[9] This review suggested that either gabapentin or Lyrica® may be considered for first-line status. The review stated "the potential for twice daily dosing and the linear pharmacokinetics of Lyrica® may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar". The linear pharmacokinetics may allow for more rapid onset of action when first titrating a patient; however, this difference is minimal (e.g., several weeks) and will not represent an advantage once patients are titrated to effective doses.

Two other evidence based reviews have concluded that the number-needed-to-treat (NNT) and number-needed-to-harm (NNH) for gabapentin and pregabalin were similar, if not favorable towards gabapentin.[10-11] The NNT for gabapentin was 3.8 versus 3.7 to 4.2 for pregabalin. However, NNH was 26.1 for gabapentin versus 7.4 to 11.7 for pregabalin.

Overall, it appears that Lyrica® and gabapentin are basically equivalent. However, Lyrica® costs about $1,200 more per year in this patient. Therefore, please consider switching the patient to generic gabapentin or simply discontinuing Lyrica® therapy due to questionable effectiveness at the 150 mg per day dose.

<u>Skelaxin® (metaxalone)</u>

Skelaxin® acts as a systemic CNS depressant and does not reduce muscle spasticity per se.[1,12-13] Clinical trial data supporting the safety and efficacy of Skelaxin® in patients with acute muscle spasms dates back to the mid-1960s.[12-13] Assumptions regarding the efficacy and safety of Skelaxin® based on these trials may not be accurate considering the many study limitations.[12-13] These trials were of short-duration (i.e., <10 days), poorly controlled, patient selection was not clearly defined, methods for determining the presence of muscle spasms was not established, objective parameters were not used, and concomitant medication and physical therapy were either allowed or not addressed in these studies.[12-13] Clinical trial data, package insert recommendations and expert opinions all suggest that Skelaxin® should only be employed as an adjunctive therapy for acute conditions (e.g., < 14 days of therapy).[1,12-13] Therefore, consideration should be given to limiting Skelaxin® therapy to a short-term duration (only 1 prescription).

The only skeletal muscle relaxants that have actually been shown to reduce muscle spasticity chronically are baclofen, tizanidine and dantrolene.[13] An excellent alternative therapy to Skelaxin® for muscle spasticity would be tizanidine (as baclofen is more prone to cause muscle weakness). Switching the patient to more effective generic tizanidine would save more than $800 per year.

<u>Recommendations for Skelaxin®</u>

1) Consider limiting Skelaxin® therapy to a short-term treatment (i.e., only 1 prescription).
2) If a long-term treatment is desired, consider switching to generic tizanidine as it would provide equivalent, or possibly even superior, therapeutic results at a cost of $800 less per year.
3) If tizanidine is not considered, other generic alternatives include low-dose cyclobenzaprine and orphenadrine; however, like Skelaxin®, these agents have not been shown to reduce muscle spasticity on a chronic basis.

Lidoderm® (lidocaine jelly)

Although Lidoderm® has been shown to be effective for short-term use (generally used for 2 to 4 weeks in clinical trials) in patients with postherpetic neuralgia, it has not been shown to be effective for long-term administration in treating other neuralgias.[14] The evidence-based review of neuropathic pain does suggest that Lidoderm® may be considered as a potential first-line treatment option on par with generic gabapentin.[9] However, it also states that…

> "Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use."

If 12 prescriptions of Lidoderm® are filled every year the cost would exceed $2,700 at the current frequency of administration and as much as $8,000 if maximum doses are used. Therefore, the value of Lidoderm® relative to alternative oral medications (e.g., gabapentin, nortriptyline) and topical medications (e.g., lidocaine jelly, dibucaine ont) is questionable. Switching the patient to one of these alternatives would save between $2,000 and $2,500 per year at the patient's current Lidoderm® dose. The only disadvantage for the topical lidocaine and dibucaine products is that they have to be reapplied two to three times daily.

Neuropathic Pain Considerations

Although Lyrica® and Lidoderm® are both effective and considered potential first-line treatments in the management of neuropathic pain, equally effective and lower cost alternatives should be considered. Many of these alternatives have already been stated in this review; however, the alternatives with their approximately monthly cost include the following:

- Generic gabapentin at $20/month
- Lidocaine jelly, lotion, cream or ointment – cost varies, but ranges from $5-$50 per month
- Dibucaine ointment at $5 per month
- Nortriptyline at <$20/month
- Desipramine at <$20/month

These agents are highly effective, have decades of evidence supporting their use and are very inexpensive. Please consider a trial on one or more agents.

References:

1. Facts and Comparisons. Wolters Kluwer Health, Inc. 2007.
2. Guay DR. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? *Am J Geriatr Pharmacother*. 2005;3(4):274-87.
3. Bialer M. New antiepileptic drugs that are second generation to existing antiepileptic drugs. Expert Opin Investig Drugs. 2006;15(6):637-47.
4. Zareba G. Pregabalin: a new agent for the treatment of neuropathic pain. Drugs Today (Barc). 2005;41(8):509-16.
5. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110(3):628-38.
6. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain*. 2005;6(4):253-60.
7. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52(4):1264-73.
8. van Seventer R, Feister HA, Young JP Jr, Stoker M, Versavel M, Rigaudy L. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Curr Med Res Opin. 2006;22(2):375-84.
9. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;237-51.
10. Finnerup NB, et al. Algorithm for neuropathic pain treatment: An evidence based proposal. *Pain*. 2005. 118:289-305.
11. Finnerup NB, Otto M, Jensen TS, Sindrup SH. An evidence-based algorithm for the treatment of neuropathic pain. MedGenMed. 2007;9(2):36.
12. Toth PP, Urtis J. Commonly used muscle relaxant therapies for acute low back pain: a review of carisoprodol, cyclobenzaprine and metaxalone. *Clin Therap*. 2004;26(9):1355-67.
13. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and muscloskeletal conditions. *Jour Pain Symp Mgmt*. 2004;8(2):140-75.
14. Davies PS, et al. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drug*s. 2004;64(9):937-47.

Physician Response Form

DUR – ---------------

Dear treating physician,

After reviewing the DUR on ------------------, please fill-in and sign the response form below:

Drug	**Recommendation(s) from DUR**	**Physician Response**	**Logic Supporting Rejection**
Lyrica®	Consider discontinuation	☐ Accept ☐ Reject	
	If chronic therapy is required, consider generic gabapentin.	☐ Accept ☐ Reject	
Skelaxin®	Consider discontinuation	☐ Accept ☐ Reject	
	If chronic therapy is required, consider generic tizanidine.	☐ Accept ☐ Reject	
Lidoderm®	Consider lidocaine gels, creams and ointments.	☐ Accept ☐ Reject	

Additional Documentation (if required): ____________________

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Physician Signature: ____________________ **Date:** __________