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## Topical administration of psychotropic medications in pluronic lecithin organogel to treat patients with dementia: A retrospective observational study

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## **Topical administration of psychotropic medications in pluronic lecithin organogel (PLO) to treat patients with dementia: a retrospective observational study**

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**Abstract:**

**Objective:** Treatment of mood and behavioral symptoms in geriatric patients with advanced dementia may be impeded by poor compliance with oral medications. Pluronic lecithin organogel (PLO) is a compounding substrate that can be used for the topical administration of psychotropic medications.

**Methods:** Charts of patients treated with psychotropic medications compounded with PLO cream were reviewed for treatment outcomes. All patients were treated by a nursing home outreach service.

**Results:** Records from twenty-four patients, mean age  $86.8 \pm 5.9$ , were reviewed. Common psychiatric symptoms included agitation, aggressive behavior, and depression. Medications most commonly administered as a PLO cream included quetiapine and venlafaxine. All patients had mild to marked improvement in psychiatric symptoms.

**Conclusions:** Pluronic lecithin organogel (PLO) may be an effective option for the topical administration of psychiatric medications in geriatric patients with dementia who are not compliant with oral medications.

**Keywords:** pluronic lecithin organogel, PLO, pharmacotherapy, geriatric, dementia

## **Introduction:**

More than eighty percent of geriatric patients with dementia develop mood and behavioral symptoms during the course of their illness.<sup>1,2</sup> Psychotropic medications can effectively treat these symptoms. However, patients with dementia may not comply with oral medications due to behavioral issues, paranoia or swallowing difficulty. Alternative routes for administering medications are needed to increase compliance and improve outcomes.

During the past 20 years, several drugs have been formulated for topical administration including scopolamine, nitroglycerin, nicotine, rivastigmine and fentanyl. These drugs are combined with permeation enhancers to increase passive transdermal diffusion through the skin into the circulation. Currently, selegiline and methylphenidate are the only psychotropic medications available in a transdermal formulation.

Pluronic lecithin organogel (PLO) is a synthetic compound developed in the 1990s as a transdermal drug delivery substrate.<sup>3,4,5</sup> When combined with a therapeutic agent, PLO forms drug micelles in a thermodynamically stable cream. The FDA permits the mixing and physical modification (compounding) of medications by a pharmacist upon receipt of a prescription from a licensed practitioner to meet the unique needs of an individually identified patient. Compounding psychotropic medications with PLO can offer new treatment options for geriatric patients with dementia.

PLO has three major components; lecithin, isopropyl palmitate, and poloxamer (Pluronic). All three components act as skin permeation enhancers. Lecithin is a naturally occurring fatty substance which is a surfactant and acts as an emulsifier. Isopropyl palmitate is a palm oil based moisturizer and thickening agent. Both lecithin and isopropyl palmitate are commonly used in various topical products and can effectively dissolve lipophilic drugs. Poloxamer is a copolymer of polyoxypropylene and polyoxyethylene, and is FDA approved for human use. The structure of poloxamer promotes the formation of drug micelles when mixed with lecithin and isopropyl palmitate. A thermodynamically stable cream is formed when the three components are mixed together.

At this time, there are very few studies evaluating the clinical effectiveness of medications applied topically using PLO. Two recent prospective trials reported improvement in nausea and vomiting induced by chemotherapy when patients were treated with lorazepam, diphenhydramine and haloperidol compounded with PLO.<sup>6,7</sup> These trials concluded that administering medications topically via PLO reduces gastrointestinal side effects and improves patient compliance, without significant skin irritation. However, in a study evaluating the plasma concentrations of lorazepam (2mg), diphenhydramine (25mg) and haloperidol (2mg) administered topically using PLO; lorazepam and haloperidol were not detectable, and only five of the 10 subjects had detectable plasma levels of diphenhydramine.<sup>8</sup>

To our knowledge, there are no studies assessing the effectiveness of topically applied psychotropic medications compounded with PLO cream for the treatment of psychiatric symptoms. For a number of years, we have used PLO creams to administer psychiatric medications in elderly patients who are unable or unwilling to take oral medications. For this

study, we reviewed the records of 24 geriatric patients who were treated with psychiatric medications applied topically using PLO cream. All patients had advanced dementia with psychiatric symptoms that significantly impacted the patient's quality of life or caretakers' ability to provide basic care, and were unwilling or unable to take oral medications.

### **Methods:**

A retrospective chart review was carried out by the authors on all geriatric psychiatry patients treated with topical psychotropic medications using PLO. A structured data collection form was used to collect data including age, gender, living situation, medications, medical and psychiatric diagnoses, psychiatric/behavioral symptoms and the Mini Mental State Exam score (MMSE).<sup>9</sup> The authors assessed response to therapy by reviewing the medical record, which contained the nursing staff and physician's clinical assessment of patients. Response was rated on a 4 point scale; (1) no improvement, (2) mild improvement, (3) moderate improvement, or (4) marked improvement. Statistical analysis was carried out using SPSS for descriptive variables.

### **Results:**

Twenty-four geriatric psychiatry records were reviewed. Demographic and clinical variables are shown in Table 1. All patients had severe dementia and resided in skilled nursing facilities. Psychiatric diagnoses included major depression ( $n = 17$ , 70.8%) and mood disorder secondary to general medical condition ( $n = 3$ , 12.5%). Medical conditions included hypertension ( $n = 17$ , 70.8%), stroke ( $n = 12$ , 50%), coronary artery disease ( $n = 8$ , 33.3%), hyperlipidemia ( $n = 6$ , 25%), diabetes ( $n = 2$ , 8.3%), hypothyroidism ( $n = 5$ , 20.8%), seizure disorder ( $n = 3$ , 12.5%) and osteoarthritis ( $n = 5$ , 20.8%).

**Table 1.** Demographics, Clinical Characteristics and Outcomes

Demographics	
Age, years [mean (SD)]	86.8 (5.9)
Female	20 (83.3%)
Male	4 (16.7%)
Type of dementia	
Alzheimer's	12 (50%)
Vascular	7 (29.2%)
Alzheimer's and Vascular	5 (20.8%)
MMSE, previous 6 months, 9 pts [mean (SD)]	2.7 (5.7)
MMSE, previous 2 years, 15 pts [mean (SD)]	12.8 (8.6)
Psychiatric symptoms	
Depressed mood [number (%)]	15 (62.6%)
Aggression and agitation	19 (79.2%)
Decreased appetite	10 (41.7%)
Insomnia	5 (20.8%)
Wandering	3 (12.5%)
Psychosis	2 (8.3%)
Anxiety	2 (8.3%)
Outcome	
No improvement	0 (0%)
Minimal improvement	4 (16.7%)
Moderate improvement	14 (58.3%)
Marked improvement	6 (25%)

Reasons for starting PLO psychiatric medications included: physical aggressiveness and agitation ( $n = 19$ , 79.2%), depressive symptoms ( $n = 15$ , 62.5%), decreased appetite ( $n = 10$ , 41.7%), insomnia ( $n = 5$ , 20.8%), and psychotic symptoms ( $n = 2$ , 8.3%). Six different psychiatric medications were used in PLO formulation: quetiapine, venlafaxine, trazodone, buspirone, escitalopram and lorazepam.

Quetiapine was used in eighteen patients at an individual dosage range from 12.5 mg to 100 mg (mean =  $57.6 \pm 34.9$ ), given one to four times a day, for a total daily dose of 25 mg to 300 mg (mean =  $136.1 \pm 97.5$ ). Mean duration of treatment was  $5.3 \pm 4.6$  months.

Venlafaxine was used in fifteen patients at an individual dose range of 37.5 mg to 100 mg (mean =  $66.6 \pm 17.6$ ). Venlafaxine was administered twice a day in fourteen patients and three times a day in one patient. Total daily dose of venlafaxine ranged between 75 mg to 200 mg (mean =  $135.7 \pm 37.9$ ), and mean duration of treatment was  $5.5 \pm 4.4$  months at time of review. Nine patients were treated with both quetiapine PLO cream and venlafaxine PLO cream.

Five patients received trazodone PLO cream at a dose of 50 mg to 100 mg at bedtime for insomnia (mean =  $70 \pm 27.4$ ). The mean duration of treatment with trazodone was  $3 \pm 1.4$  months at time of chart review. Four patients who were treated with topical trazodone also received topical quetiapine and two received topical venlafaxine. Two patients received topical

buspirone at a dose of 5-10 mg (mean =  $7.5 \pm 3.5$ ). Buspirone was administered three times a day with a total daily dose between 15-30 mg (mean =  $22.5 \pm 10.6$ ). One hospice patient received 1mg lorazepam PLO cream four times a day. One patient received 20mg escitalopram PLO cream daily for 11 months.

Before starting PLO medication, all patients had been non-compliant with or unable to take oral medications. PLO compounded medications were applied to the inner aspect of the forearm in all patients except one who had PLO cream applied to his back due to physical aggressiveness. No side effects were reported in any of the patients.

All patients benefited from PLO medications as shown in Table 1. Improvement in symptoms were as follows: 12 patients (50%) were more compliant with oral medications, 13 of 19 (68.4%) patients with severe agitation improved, 11 of 15 (73.3%) patients with depressive mood improved, 6 of 10 (60%) patients had improved appetite, and 2 of 5 (40%) had improvement in sleep. Two patients who received PLO for psychotic symptoms were rated as moderately improved.

The following two clinical vignettes illustrate the use of psychotropic PLO cream.

## **Case Vignettes**

### **Subject 1**

Ms. A was a 78 year-old woman with vascular dementia, who was referred for evaluation of depression, behavioral disturbance and poor appetite. Ms. A stated that her mood was “not too good”, and she was irritable, anxious and uncooperative with care by nursing home staff. Mini-Mental State Examination was 7/30. She was treated with oral venlafaxine extended-release 75mg daily with improvement of appetite and mood, however she continued to be anxious and was uncooperative. Buspirone 5mg bid was used with good results. Over the following year, her cognitive impairment progressed and she became uncooperative with all oral medication. Her depressive and behavioral symptoms returned. She was started on venlafaxine 50mg PLO topical cream bid and buspirone 10mg PLO topical cream bid. Four weeks after starting PLO cream, the nursing home staff reported significant improvement in her depressive and behavioral symptoms.

### **Subject 2**

Mr. B was an 84 year-old man diagnosed with mixed type (Alzheimer’s and Vascular) dementia, who was referred for evaluation of insomnia and severe aggression toward staff and other residents. MMSE was 0/30. Eventually, the patient was treated with a medication regimen of quetiapine 100mg bid, valproic acid syrup 750mg bid and trazodone 50mg qhs, with marked improvement in his behavior. However after 2 years, he became uncooperative with oral medications and experienced recurrence of aggression. Strategies to improve compliance were unsuccessful and oral medications were discontinued. PLO quetiapine cream 100mg bid and trazodone 50mg PLO cream qpm were begun. He was compliant with PLO medications and within two months his behavior markedly improved.



## Discussion:

Patients with advanced dementia frequently do not comply with oral medications due to behavioral issues, paranoid thoughts about treatment intentions, or difficulty with swallowing pills. Transdermal administration of medications in this patient population offer many advantages including improved tolerability, ease of administration, and steady continuous delivery rate. Pluronic lecithin organogel (PLO) is a synthetic compound that has been developed as a substrate for the topical administration of therapeutic agents.

A limited number of studies have evaluated the bioavailability of medications administered topically when combined with PLO cream. Finding from these studies typically reveal low or undetectable serum levels of medications, however, the doses of medications used in these studies may be too low for adequate transdermal absorption.<sup>10,11</sup> For example, Glisson et al. administered promethazine 50mg compounded with PLO in 15 subjects; blood samples were collected over a 6 hour period.<sup>12</sup> Only 65% of the blood samples had measurable serum concentrations of promethazine, and only 39.2% of these samples contained quantifiable concentrations of the drug equal to or greater than 1 ng/mL. Interestingly, eleven of the fifteen subjects in this study experienced drowsiness. In another study, methadone (dose range 10mg to 45mg) compounded with PLO was administered topically to ten subjects.<sup>13</sup> Only one subject who received the 45mg dose of methadone achieved measurable serum levels. These studies suggest that when compounding a medication with PLO for topical application, a higher dose of medication is needed in order to obtain serum levels similar to that observed with oral administration. The reduced absorption of medications when administered transdermally is reflected by the fact that currently available transdermal therapeutic patches are formulated with significantly higher doses of the therapeutic agent when compared to oral formulations. For example, methylphenidate patch contain between 27.5mg to 82.5mg per patch, selegiline patch contain between 20mg to 40mg per patch, and rivastigmine patch contains 9mg to 27mg per patch.

In our case series, a variety of psychotropic medications were administered topically using PLO cream in patients unwilling or unable to take oral medications. Based on our retrospective chart reviews, all patients demonstrated some clinical improvement in their psychiatric symptoms. This case series was limited to geriatric patients with dementia; however other groups of patients with psychiatric disorders may benefit from PLO compounded medications.

Our study has a number of limitations, including the retrospective observational design and small sample size. Because of the observational design, we cannot rule out the possibility that the observed improvements were due to placebo effect of PLO cream application. Also, we assessed the effectiveness of several different psychotropic medications applied topically with PLO cream, which limits the conclusions that can be draw concerning the effectiveness of any specific agent. However, the goal of this study was to demonstrate that compounding medications with PLO for topical application may offer an effective alternative for treatment of complex geriatric patients. There may be concerns about the patient population in this study; however clinical trials have not consistently revealed any significant differences in transdermal absorption of medications when comparing young and old patients.<sup>14</sup>

In conclusion, compounding psychotropic medications with pluronic lecithin organogel (PLO) provides the opportunity for topical application of a wide range of medications. However, more research is needed to determine the absorption rates and bioavailability of different medications when administered with PLO cream. Although our series was limited to the use of six medications, we expect that other psychiatric medications could be effectively administered as a PLO creams, thereby expanding the treatment options for geriatric patients, as well as psychiatric patients in general.

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