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Association of Neuromyelitis Optica With Severe and Intractable Pain

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Abstract

Objective—To contrast differences in pain and treatment outcomes between neuromyelitis optica (NMO) and multiple sclerosis (MS).

Design—Retrospective, cross-sectional cohort study.

Setting—Academic MS center.

Patients—Complete ascertainment of an academic MS center cohort of NMO and an MS comparison sample cohort.

Main Outcome Measures—Current pain was quantified by a 10-point scale and the McGill Pain Questionnaire. Expanded Disability Status Scale score and number of involved spinal cord levels were collected in addition to testing for cognition, fatigue, depression, and quality of life. Number and types of pain medications were tabulated.

Results—Current pain was more common in subjects with NMO (n=29) vs MS (n=66) (86.2% vs 40.9%; $P<.001$) and more severe on a 10-point scale (5.38 vs 1.85; $P<.001$). Pain remained more common after controlling for disability and number of spinal cord segments ($P=.03$). Prescription pain medication was used more frequently in subjects with NMO compared with subjects with MS (75.9% vs 37.8%; $P<.001$), often requiring more than 1 medication (65.5% vs 15.2%; $P<.001$). No subject with NMO taking pain medication (22 of 29) rated their current pain as 0 of 10, whereas almost half of those taking pain medication with MS were currently free of pain (0% vs 48%; $P=.006$).

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Conclusions—Neuromyelitis optica is frequently associated with severe pain that appears insufficiently controlled by pharmacologic interventions. Future studies should evaluate the efficacy of a multidisciplinary and multimodal approach to pain management.

Longitudinally extensive transverse myelitis from neuromyelitis optica (NMO) may result in poor recovery, severe disability, and decreased survival.[1,2] Neuromyelitis optica is associated with extensive spinal cord injury, and autopsy series have noted axonal loss, cavitation, and necrosis.[3,4] Multiple sclerosis (MS) commonly affects the spinal cord, as noted in 83% by magnetic resonance imaging (MRI) and up to 99% at autopsy.[5,6] However, transverse myelitis from MS is typically not as fulminant compared with NMO, with less motor involvement and greater chance for recovery.[7] At autopsy, myelitis from MS is characteristically partial, is associated with fewer spinal levels, and demonstrates relative axonal preservation.

Pain in demyelinating and inflammatory central nervous system diseases can be disabling, lead to a lower quality of life, and result in an increased health care burden.[8,9] We hypothesized that, in comparison with MS, the more severe spinal cord injury in NMO would be associated with increased prevalence and severity of neuropathic pain syndromes. We also hypothesized that pain would be associated with a lower quality of life, polypharmacy, and a greater chance for medication adverse effects. This cross-sectional study compared a cohort of subjects with NMO spectrum disorder with subjects with MS and aimed to describe and compare the prevalence, severity, characteristics, treatment, and consequences of pain between the 2 disorders while accounting for differences in overall disability and the number of affected spinal cord levels.

METHODS

STANDARD PROTOCOL APPROVALS AND PATIENT CONSENTS

All subjects provided informed consent, after approval by the Washington University Human Research Protection Office/institutional review board.

STUDY PROTOCOL AND PATIENTS

Subjects with NMO met criteria for NMO spectrum disorder by 3 or more of the 4 following criteria: (1) clinical events involving the optic nerve or spinal cord, (2) longitudinally extensive transverse myelitis, (3) NMO IgG positivity, and (4) brain MRI normal or nondiagnostic of MS.[10] All 29 patients with NMO followed up at Washington University were included, resulting in complete ascertainment through January 2011. Neither subjects with NMO nor MS were required to have documented spinal cord lesions by MRI, because the number of spinal cord lesions was added to the linear model to evaluate pain across the complete clinical spectrum. A 1:2 ratio of subjects with NMO to subjects with MS was selected for recruitment, resulting in prospective selection of 66 patients with MS confirmed by McDonald criteria from the same center.[11] All visits were performed by a single nonblinded examiner (P.Q.) using a standard interview and face-to-face structured questionnaires.

PAIN SCALES AND QUESTIONNAIRES

Pain was defined per World Health Organization pain treatment guidelines as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Current pain from NMO or MS was scored on a scale of 0 to 10. When current pain was 1 or more, the McGill Pain Questionnaire quantified the most concerning current pain that was directly attributable to NMO or MS by descriptors, location, and temporal characteristics.[12] The McGill Pain Questionnaire pain rating index is

the sum of the rank value of the words chosen by the patient from 20 groups of word descriptors, with a maximum value of 78. Subjects were instructed not to describe or include pain syndromes not directly due to central nervous system injury in NMO or MS (eg, migraine or arthritis).

In addition to current pain, prior demyelinating pain syndromes were collected based on categorizations of retro-orbital (Did you have pain in or around your eye that could have been made worse with light or eye movement?), peripheral dysesthesias (Did you have pain associated with numbness, tingling, heaviness, or burning?), girdle or bandlike (Did you have numbness, burning, tightness, or squeezing that wrapped around your trunk?), Lhermitte sign (Did you feel an unpleasant or shocklike sensation when you flexed your neck?), neuralgias (Did you have any brief, repetitive, shock-like pain that may have been exacerbated by movement or touch?), and tonic spasms (Did you have transient cramps or stiffness in arms or legs that were associated with sustained involuntary movement?).

DISABILITY SCALES AND OTHER FUNCTIONAL MEASURES

Disability measures included the Expanded Disability Status Scale (EDSS) (range, 0–10) and the Multiple Sclerosis Functional Composite. The Quality of Life Short Form 36 (SF-36) is based on the prior 4 weeks; higher scores are indicative of better quality of life. The form is divided into physical and mental summary scales, and these summary scales are further divided into 8 subscales. Additional measures included the Modified Fatigue Impact Scale (21 items based on prior 2 weeks; range, 0–84) and the Center for Epidemiologic Studies Depression Scale (CES-D) (20 items based on prior week; score of 15–21 may be consistent with mild or moderate depression; score >21 may be consistent with major depression).

SPINAL CORD MRI

Spinal cord MRIs were available to determine number of involved spinal cord segments for all subjects with NMO and 49 of the 66 subjects with MS, and these images were reviewed by a neurologist (P.Q.) and a radiologist. The total numbers of involved T2 hyperintense segments were quantified based on sagittal T2-weighted sequences.

CURRENT PRESCRIPTION PAIN MEDICATIONS

Prescription pain medications were tabulated and categorized into opioids (hydrocodone, methadone hydrochloride, oxycodone, hydromorphone, and fentanyl citrate), neuropathic pain medications (tricyclic antidepressants, gabapentin, pregabalin, and duloxetine hydrochloride), sodium-channel antagonizing antiepileptics (phenytoin, carbamazepine, sodium valproate, and lamotrigine), and antispasticity medications (baclofen, tizanidine hydrochloride, and cyclobenzaprine hydrochloride).

STATISTICAL ANALYSES

Group differences were evaluated by *t* test, Wilcoxon rank sum test, or χ^2 analysis. Spearman or Kendall correlation coefficients assessed the association between variables. Linear modeling controlled for differences in age, sex, EDSS score, and involved spinal segments. All tests were 2-sided and $P<.05$ was considered significant.

RESULTS

DEMOGRAPHICS

Subjects with NMO (n=29) and MS (n=66) were similar in age, sex, and disease duration (Table 1). The MS cohort comprised 58 subjects with relapsing-remitting MS, 5 with

secondary progressive MS, and 3 with primary progressive MS (eTable, http://www.archneurol.com). Subjects with NMO included a higher proportion of African American individuals and a greater number of involved spinal cord levels. Neuromyelitis optica was associated with higher disability levels (EDSS score), more functional impairments (Multiple Sclerosis Functional Composite score), worse physical quality-of-life scores (SF-36 score), and worse depressive symptoms (CES-D score). The 2 groups reported similar pain severities for common conditions (ie, worst toothache, headache, and stomachache), suggesting no major difference in pain tolerance and experience.

PAIN AFFECTS PATIENTS WITH NMO MORE FREQUENTLY AND SEVERELY

Current pain was more common in NMO when compared with MS (86.2% vs 40.9%; $P < .001$) and more severe on a 10-point scale (5.38 vs 1.85; $P < .001$) (Table 2). Severe current pain, defined by a score of 7 or more of 10, was present in approximately half of subjects with NMO, as opposed to the minority of subjects with MS (51.7% vs 10.6%; $P < .001$). The pain was constant for the majority with both conditions (64% for NMO vs 51.8% for MS; $P = .22$). No difference was observed between pain in subjects with MS with confirmed (n = 41) or no confirmed (n = 8) spinal cord lesions by MRI for current pain prevalence (39% vs 50%; $P = .15$) or severity (score ≥7) (12.5% vs 14.6%; $P = .69$).

A history of predefined central nervous system pain syndromes was more frequent in those with NMO compared with MS, including tonic spasms (89.7% vs 39.3%; $P < .001$), dysesthesias (82.8% vs 62.1%; $P = .046$), banding/girdle pain (69% vs 21.2%; $P < .001$), Lhermitte sign (65.5% vs 42.4%; $P = .04$), and retro-orbital pain (55.2% vs 30.3%; $P = .02$) (Table 2).

Neuromyelitis optica was associated with a higher McGill Pain Questionnaire pain ranking index compared with MS (38.7 vs 17.2; $P < .001$), and this index demonstrated high correlation with the 10-point scale ($r = 0.86$; $P < .001$). Neuromyelitis optica pain was frequently characterized as “hot” (72%) and “exhausting” (56%), whereas MS pain was frequently “shooting” (55.6%) and “cramping” (55.6%). Similar descriptors between the groups included “sharp” (80% NMO vs 81.5% MS), “sickening” (60% NMO vs 77.8% MS), and “wretched” (60% NMO vs 66.7% MS).

Because of imbalances between the groups for disability (EDSS score) and number of involved spinal cord segments, modeling with these 2 additional covariates confirmed that current pain severity remained significantly higher in NMO compared with MS ($P = .03$). Nonetheless, subjects with higher EDSS scores remained at greater risk for more severe pain for both diseases after controlling for the number of involved spinal segments ($P < .001$). For example, severe pain was present in 55.2% with an EDSS score of 6 or more vs 9.1% for an EDSS score less than 6. The number of involved spinal cord segments by T2 hyperintensity on MRI was not a strong predictor of current pain ($r = 0.35$; $P < .01$) for the entire cohort. In evaluating subgroup associations between length of spinal cord level and pain for each disease, NMO was associated with a modest trend for greater pain with more extensive lesions ($r = 0.34$, $P = .09$) whereas the association was not apparent with MS ($r = -0.013$; $P = .93$).

PAIN CONTROL WAS CHALLENGING DESPITE MULTIPLE MEDICATIONS

Prescription medication for pain was more frequently required by those with NMO compared with MS (75.9% vs 37.8%; $P < .001$), and those with NMO often required more than 1 medication (65.5% vs 15.2%; $P < .001$). Notably, sodium-channel blocking antiepileptic medication was prescribed in 7 times more patients with NMO (65.5% vs 9.1%; $P < .001$), likely reflecting the differing incidence of tonic spasms and other

paroxysmal pain syndromes. Opioids were prescribed to more than 2.5 times more subjects with NMO (31% vs 12.1%; $P = .006$). Similarly, other neuropathic pain and antispasticity medications were prescribed for twice as many subjects with NMO as subjects with MS (Table 3).

Despite the use of multiple medications in NMO, current pain was not controlled. No subject with NMO taking pain medication (22 of 29) rated their current pain as 0 of 10, whereas almost half of those with MS taking pain medication were currently free of pain (0% vs 48%; $P = .006$). Three subjects with NMO noted current pain but were not taking medication: 1 had a current pain of level 2 of 10 and did not think this was severe enough to treat; the other 2 had level 8 of 10 current pain but did not tolerate amitriptyline hydrochloride, pregabalin, or gabapentin because of adverse effects.

PAIN MEDICATIONS WERE ASSOCIATED WITH ADVERSE EFFECTS

The number of current pain medications used by those with NMO had a positive correlation with the severity of current pain by the 10-point pain scale ($\tau = 0.43$; $P = .003$) in distinction to the current pain and number of medications in MS ($\tau = 0.20$; $P = .06$). Perhaps of concern, the number of pain medications in NMO correlated negatively with the cognitive Paced Auditory Serial Addition Test ($\tau = -0.38$; $P = .02$). Similarly, the number of pain medications in NMO corresponded to worse scores for fatigue by the Modified Fatigue Impact Scale ($r = 0.42$; $P = .002$) and depression by the CES-D ($r = 0.39$; $P = .006$). Current pain in NMO was higher for those whose CES-D score suggested clinically significant depression (CES-D score <15: current pain score, 4.41; CES-D score ≥15: current pain score, 6.75; $P = .02$). Severe current pain (score ≥7 of 10) in NMO was associated with a CES-D score suggestive of clinically significant depression (≥15) in 60% and a CES-D score suggestive of major depression (≥21) in 53.3%.

PAIN NEGATIVELY IMPACTED QUALITY OF LIFE

Current pain intensity was associated with worse scores on both physical ($r = -0.64$; $P < .001$) and mental ($r = -0.39$; $P < .001$) components of the SF-36. Current pain also correlated moderately to highly with all 8 SF-36 subscales (physical functioning: $r = -0.624$; $P < .001$; role physical: $r = -0.50$; $P < .001$; bodily pain: $r = -0.73$, $P < .001$; general health: $r = -0.362$; $P < .001$; vitality: $r = -0.48$; $P < .001$; social functioning: $r = -0.56$; $P < .001$; role emotional: $r = -0.52$; $P < .001$; mental health: $r = -0.35$; $P < .001$).

Pain remained a significant predictor of quality of life after controlling for disability by EDSS score ($P = .001$), with the 2 variables explaining 54% of the variability in SF-36 physical component score and only 13% of the variability in SF-36 mental component score. Number of involved spinal segments by imaging was not a significant predictor in the model ($P = .54$), nor was sex ($P = .57$) or age ($P = .76$). As expected, the negative impact of pain on quality of life was observed for both NMO and MS, and the type of demyelinating disease was not a significant predictor in the model.

COMMENT

This study indicates that pain in NMO is more common and more severe compared with MS, and pain adversely affects quality of life. Pain is a major symptom in NMO, affecting more than 85% of patients with NMO in this cohort from an academic center. To provide further context, cancer pain has been identified as a major health care problem and patient concern, and a review of pain prevalence in advanced/metastatic/terminal cancer was noted to be 64%.[13] Pain in NMO deserves special attention during each office visit, and pain management should be a treatment goal in addition to disease control.

Unfortunately, this study reveals that pain intensity remained unacceptably high despite frequent use of pain medication. Notably, these subjects were seen at a multi-disciplinary MS center where all symptoms were assessed in a comprehensive manner. While these patients were treated by several different physicians, a consistent pain management strategy included assessment and sequential titration of pain medication to effect.[14] If neuropathic pain agents were not sufficient, both long- and short-acting opioids were frequently used. Despite this standard approach, current pain in NMO was twice as prevalent and 3 times more severe compared with a random sampling of patients with MS, despite a 4-fold more frequent use of combination pain medications in NMO. Most concerning, a greater number of pain medications in NMO was not associated with being pain free, and pain medication polypharmacy was associated with greater cognitive dysfunction and fatigue. This suggests that additional adjuvant strategies to pain control should be explored, because pharmacologic interventions may be insufficient.

Multiple sclerosis likewise frequently affects the spinal cord and is associated with pain; thus, crucial differences must exist between NMO and MS spinal cord lesions in terms of size, location, and substance. Surprisingly, the number of involved spinal cord levels was not a strong predictor of pain. The association between affected spinal cord levels was more apparent for NMO than it was for MS, perhaps because MS lesions within the brain and brainstem can also lead to pain.[15–17] Intraspinal lesion location may be an important factor, because previous studies have shown that spinal cord MRI lesions in patients with NMO occupied more than half of the cord area and mainly involved the central gray matter.[18] In distinction, more than 80% of the lesions in MS were localized in the lateral and posterior white matter of the cord.[18] Aquaporin 4 is densely expressed in the foot processes of astrocytes, and these are highly concentrated in the central cord gray matter.[19] Central gray matter is involved in the inhibition of pain input, and high densities of opiate receptors are found in periaqueductal gray, a location also preferentially affected by NMO.[20,21] The more damaging pathology of NMO and more frequent gray matter involvement may help explain the severe pain and poor response to opioid treatment.[22]

Painful tonic spasms were frequently noted, which is important because this pain category may respond to sodium-channel blocking antiepileptic agents.[23–25] Spinal cord–generated tonic spasms may be due to loss of inhibitory motor neurons within central gray matter.[26] Also, severe trunk/girdle pain may be seen in NMO, and several of our patients have been evaluated for an acute abdomen.

We cannot be certain whether depression leads to pain, is a consequence of pain, or both.[27] Depression scores were higher in NMO, despite MS perhaps leading to more organic depression due to cerebral plaques. Depression and disability were highly correlated even after controlling for pain ($r^2 = 0.46$; $P < .001$). Nonetheless, recognition and treatment of significant depression seems to be a reasonable approach in the management of both diseases.

One prior study of pain in a Japanese NMO cohort likewise found the pain to be more frequent and severe compared with MS. The present study confirms this finding on a US-based NMO cohort, which is important because differences may exist between North American and East Asian variants of disease.[8,28] Our study also expands the literature by investigating the role of disability, involved spinal cord levels, outcomes of pain medication, and other important symptoms. For MS pain prevalence, 41% found in the present study is similar to the range reported in the literature.[9,29–32]

Several caveats are important to consider. This NMO cohort was referred to an MS center for treatment and may not reflect patients with NMO who receive treatment from

community practitioners. The MS comparator group was chosen from the same center to help minimize referral bias, and inclusion bias was minimized by complete ascertainment of the available adult cohort of NMO spectrum disorder. A single evaluator administered all the questionnaires and assessments by a standardized protocol, but this person was not blinded to the diagnosis. To reduce recall bias, we selected current pain as our main outcome measure. While current pain can serve as a surrogate for past pain, it may not necessarily reflect precisely the type of pain people experienced in the past.

In summary, pain should be assessed and aggressively treated in NMO. While therapies may help reduce pain levels, many continue to have severe pain despite treatment. Not a single patient with NMO taking pain medications reported no current pain. While pain medications remain a cornerstone of therapy for reducing pain levels, future studies should explore the efficacy of a multimodal and multidisciplinary approach to pain management.

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Table 1

Subject Characteristics[a]

	Mean (SD)		
	NMO (n = 29)	MS (n = 66)	*P* Value
Age, y	44.7 (13.3)	43.6 (10.2)	.67
Sex			
F	24	52	.66
M	5	14	
Disease duration, y	8.5 (9.4)	8.9 (7.3)	.85
Race, No. (%)			
White	14 (48.3)	56 (84.8)	<.001
African American	14 (48.3)	10 (15.2)	
Asian	1 (3.4)	0	
NMO IgG Ab positive, No. (%)	24 (79.3)	NA	
Clinical manifestations, No. (%)			
LETM	29 (100)	9 (13.6)	<.001
ON	18 (62.1)	21 (31.8)	.006
Any spinal cord involvement by MRI, No./total No. (%)	29/29 (100)	41/49 (83.7)	.03
Spinal segments involved	9.6 (5.1)	3.2 (4.5)	<.001
EDSS score	5.0 (2.4)	3.1 (1.9)	<.001
T25-FW, s[b]	15.2 (17.3)	8.2 (5.8)	.08
9HPT score, dominant, s[c]	34.2 (18.6)	24.5 (9.5)	.03
9HPT score, nondominant, s[c]	30.5 (12.3)	26.5 (13.1)	.21
PASAT score	34.6 (15.7)	44.4 (14.8)	.009
SF-36 score, physical component	30.4 (10.9)	37.3 (9.5)	.002
SF-36 score, mental component	43.5 (8.2)	43.9 (8.5)	.82
CES-D score[d]	16.7 (14.5)	5.9 (4.9)	<.001
Modified Fatigue Impact Scale score	43.4 (20.2)	38 (20.0)	.23

Abbreviations: Ab, antibody; CES-D, Center for Epidemiologic Studies Depression Scale; EDSS, Expanded Disability Status Scale; 9HPT, 9-Hole Peg Test; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; NMO, neuromyelitis optica; ON, optic neuritis; PASAT, Paced Auditory Serial Addition Test; SF-36, Quality of Life Short Form 36; T25-FW, Timed 25-Foot Walk.

[a] Analyses included *t* test of means and χ^2 test, as appropriate.

[b] The T25-FW was unable to be performed in 5 subjects with NMO and 2 subjects with MS because of inability to ambulate. Means included those able to perform the test.

[c] Four subjects with NMO were unable to perform the test on either the dominant or nondominant hand.

[d] A score less than 15 indicates no depression; 15 to 21, mild to moderate depression; and more than 21, major depression likely.

Table 2

Pain Characteristics

	No. (%)		
	NMO (n=29)	**MS (n=66)**	***P* Value**
Patients with pain	25 (86.2)	27 (40.9)	<.001
Current pain on 10-point scale, mean (range)	5.38 (0–9)	1.85 (0–10)	<.001
Categorized pain severity			
None (0)	4 (13.7)	39 (59.1)	<.001
Mild (1–3)	3 (10.3)	11 (16.7)	
Moderate (4–6)	7 (24.1)	9 (13.6)	
Severe (7–10)	15 (51.7)	7 (10.6)	
Temporal pattern (% of those with current pain)			
Constant	16 (64.0)	14 (51.8)	.22
Intermittent	6 (24.0)	12 (44.4)	
Transient	3 (12.0)	1 (3.7)	
Pain syndrome[a]			
Tonic spasm	26 (89.7)	26 (39.3)	<.001
Dysesthetic pain	24 (82.8)	41 (62.1)	.046
Banding/girdle	20 (69)	14 (21.2)	<.001
Lhermitte sign	19 (65.5)	28 (42.4)	.04
Retro-orbital pain	16 (55.2)	20 (30.3)	.02
McGill Pain Questionnaire score, mean (SD) [range][b]	38.7 (18.4) [0–68]	17.2 (22.0) [0–60]	<.001
Description (% of those with current pain)			
Sharp	20 (80.0)	22 (81.5)	
NMO: hot/MS: sickening	18 (72.0)	21 (77.8)	
NMO: exhausting/MS: wretched	16 (56.0)	18 (66.7)	
NMO: sickening/MS: shooting	15 (60.0)	15 (55.6)	
NMO: wretched/MS: cramping	15 (60.0)	15 (55.6)	
Intensity of pain score, mean (SD), (range, 1–5)			
Now	2.3 (1.1)	1.8 (0.9)	.03
Worst	4.6 (0.8)	3.9 (1.2)	.01
Least	1.6 (0.9)	1.3 (0.5)	.10

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica.

[a] Pain syndromes include both current and past pain.

[b] McGill Pain Questionnaire score rates severity of pain descriptors based on current pain with maximum score of 78.

Table 3

Current Pain Medications and Pain Control

	No./Total No. (%)		
	NMO	**MS**	***P* Value**
Pain medications	22/29 (75.9)	25/66 (37.8)	<.001
≥2 Pain medications	19/29 (65.5)	10/66 (15.2)	<.001
Neuropathic medications[a]	17/29 (58.6)	16/66 (24.2)	.005
Antiepileptic (sodium-channel blocking) medications[b]	19/29 (65.5)	6/66 (9.1)	<.001
Antispasticity medications[c]	11/29 (37.9)	12/66 (18.2)	.03
Opioids[d]	9/29 (31.0)	8/66 (12.1)	.006
Current pain level while taking pain medication			
Pain free (0)	0/22 (0)	12/25 (48.0)	.001
Mild pain (1–3)	2/22 (9.1)	4/25 (16.0)	
Moderate pain (4–7)	7/22 (31.8)	4/25 (16.0)	
Severe pain (8–10)	13/22 (59.1)	5/25 (20.0)	

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica.

[a]Neuropathic: tricyclic antidepressants, gabapentin, pregabalin, and duloxetine hydrochloride.

[b]Antiepileptic: phenytoin, carbamazepine, sodium valproate, and lamotrigine.

[c]Antispastic: baclofen, tizanidine hydrochloride, and cyclobenzaprine hydrochloride.

[d]Opioids: hydrocodone, methadone hydrochloride, oxycodone, hydromorphone, and fentanyl citrate.