# Meperidine: Second-Line Agent with First-Line Prescribing Practices

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Pharmacologic options for pain management have increased significantly over the past two decades. Newer agents, convenient dosing and novel delivery systems have made it possible to meet a variety of individual patient requirements. Nevertheless, many second-line agents continue to be the first-line choices of prescribing physicians. The most notable second-line agent with first-line choice is meperidine.

Meperidine is a synthetic opioid introduced in 1939.[1] Although meperidine exhibits some of the pharmacological effects of morphine in man it is chemically quite dissimilar. It is a prototype of the phenylpiperidine opioids which include fentanyl and its derivatives diphenoxylate (Lomotil®) and loperamide (Immodium®). Like other opioids it binds to opioid receptors, exerting its primary pharmacological actions on the central nervous system and the neural elements of the bowel. There is some evidence that it also exerts an effect on the kappa opioid receptors.

Meperidine is metabolized chiefly by the liver. It is hydrolyzed to meperidinic acid and is then partially conjugated. It is then N-demethylated to normeperidine which is then hydrolyzed to normeperidinic acid and subsequently conjugated. Meperidine is excreted through the renal system.

Meperidine shares unique thermoregulatory effects when compared to other opioids. This appears to result from its kappa-receptor activity.[2,3] It is also believed to have less effect on the sphincter of oddi. However the evidence for this is controversial.[4] Some local anesthetic properties have been identified which are beneficial in epidural analgesia.[5]

These positive features, however, do not offset the significant problems that result from continued use of meperidine as a first-line agent across practice specialties. Because of this concern, the pain service in a 500-bed facility in New England surveyed the knowledge base supporting the use of meperidine by house officers in the specialties of medicine and surgery.

**Abbreviations Used:**

| | |
|---|---|
| AHCPR | Agency for Health Care Policy and Research |
| CNS | central nervous system |

## Methodology

Following Institutional Board Approval, 259 house officers in adult services were asked to complete a questionnaire regarding their current meperidine-prescribing practice. Survey questions were drafted from the queries chronicled by the pain service over the previous twelve months. Responses were ranked on a five point Likert scale, from strongly agree to strongly disagree. The targeted specialties included house officers from internal medicine (186) and surgical services (73). A nominal incentive of a drawing for a gift certificate to a local restaurant was offered to those who returned surveys by a designated date. Fifty-four people (20%) responded.

*...many second-line agents continue to be the first-line choices of prescribing physicians*

## Pain Questionnaire

**1. Meperidine (Demerol) is the first line agent for post-operative pain.**
**Correct response: disagree or strongly disagree**
**Percent who responded correctly: 75%**

Meperidine should be reserved for very brief courses in healthy patients or for those who have unusual reactions or allergic responses to other opioids. Of all the opioids meperidine has the shortest duration of action. In addition it has a neurotoxic metabolite that accumulates with repeated doses even in healthy individuals with normal renal function.[6] For post-operative patients requiring multiple doses of opioids or for those with renal or hepatic impairment meperidine should be considered a second-line agent.[5]

**2. Meperidine is not recommended for use in elderly patients, or in patients with renal or hepatic dysfunction.**
**Correct response: agree or strongly agree**
**Percent who responded correctly: 85%**

Patients who are elderly, or those with renal or hepatic failure are particularly vulnerable to the neurotoxic effects of normeperidine. With advancing age, hepatic and renal blood flow diminishes, increasing the risk of poor metabolism of meperidine and its metabolite as well as accumulation due to impeded renal elimination. Production of albumin declines also in the elderly, increasing the risk of drug toxicity from higher concentrations of unbound drug.[7] Because of the unique neurotoxicity and the extended terminal half-life (35 hours) of its metabolite, meperidine should be avoided in those with impaired capacity to eliminate the drug.[7,8] Oxidation of opioids is reduced in patients with hepatic cirrhosis, alcoholic hepatitis and acute viral hepatitis. These disease states alter the pharmacokinetics and result in the accumulation of normeperidine with repeated dosing.[9,10]

**3. The interval between meperidine doses ranges from 2-4 hours, with 3 hours as the average.**
**Correct response: strongly agree or agree**
**Percent who responded correctly: 69%**

The common postoperative meperidine order of "75mg parenterally every 4 hours as needed" is inadequate. Meperidine produces clinical analgesia

for only 2-3 hours.[11] Meperidine would need to be dosed more frequently to achieve acceptable analgesia for patients with acute pain. More frequent dosing intervals increase the risk of potential adverse effects thus limiting its utility in patients who require repeated administration.

Pain Service Survey

Please answer the following questions according to your current prescribing practice.

1. Meperidine (Demerol) is the first line agent for post-operative pain management.

   Strongly agree agree neutral disagree strongly disagree

2. Meperidine is not recommended for use in elderly patients, or in patients with renal or hepatic dysfunction.

   Strongly agree agree neutral disagree strongly disagree

3. The interval between meperidine doses ranges from 2-4 hours, with 3 hours as the average

   Strongly agree agree neutral disagree strongly disagree

4. Vistaril® is given in combination with meperidine because it significantly increases the efficacy of meperidine.

   Strongly agree agree neutral disagree strongly disagree

5. As with all pure mu-agonists (like morphine), there is no maximum recommended daily dose associated with its use.

   Strongly agree agree neutral disagree strongly disagree

6. The recommended IV dosing for which meperidine is safe and effective are doses not to exceed 600mg/day for up to a 48 hour period.

   Strongly agree agree neutral disagree strongly disagree

7. Chronic use of meperidine is safe and effective provided renal function is monitored.

   Strongly agree agree neutral disagree strongly disagree

8. Although oral doses of meperidine have approximately ¼ the analgesic efficacy of parenteral doses, the toxic metabolite is produced in approximately equal amounts on a mg per mg basis.

   Strongly agree agree neutral disagree strongly disagree

9. Naloxone is used to reverse all CNS effects caused by meperidine and its metabolite.

   Strongly agree agree neutral disagree strongly disagree

10. Seizures related to meperidine use are associated with the accumulation of the metabolite normeperidine. Accumulation only occurs in renally impaired patients in doses over 100mgs every two hours.

    Strongly agree agree neutral disagree strongly disagree

**4. Vistaril® is given in combination with meperidine because it significantly increases the efficacy of meperidine.**

Correct response: strongly disagree or disagree

Percent who responded correctly: 67%

Hydroxyzine (Vistaril®) is commonly prescribed with meperidine as "Meperidine 50-75mg and Vistaril 25mg IM q4hrs prn." Clinical data do not support the belief that it has opioid-sparing effects. Hydroxyzine has mild sedative, antiemetic and antihistamine effects and lasts from 4-6 hours. Meperidine lasts from 2-3 hours. In doses that may contribute to pain relief, hydroxyzine demonstrates a significant potential for causing respiratory depression which is additive to that of opioids, but not reversible with naloxone. In addition to the respiratory depressant effect of hydroxyzine other adverse reactions have been observed.[12] The combination of meperidine and hydroxyzine does not appear to be efficacious as few data support the merits of this combination.

**5. As with all pure mu-agonists (like morphine), there is no maximum recommended daily dose associated with its use.**

Correct response: strongly disagree or disagree

Percent who responded correctly: 44%

Dose limiting features of opioids are based on the patient's analgesic response and side effects. Given the toxic effects of meperidines metabolite the maximum recommended daily dose for acute pain management, even in healthy individuals, is restricted. Other opioids are dosed to effect without the same ceiling limitation.

**6. The recommended IV dosing for which meperidine is safe and effective are doses not to exceed 600mg/day for up to a 48 hour period.**

Correct response: strongly agree or agree

Percent who responded correctly: 42%

Normeperidine, the major metabolite of meperidine has a longer half-life (15-30 hrs) than meperidine (3-4 hrs) and accumulates faster. The intensity of central nervous system excitation is highly correlated with the plasma concentration of normeperidine. The circulating normeperidine/meperidine ratio increases with time in patients receiving successive meperidine doses. For this reason meperidine should not be used for more than 48 hours for patients in acute pain or at doses greater than 600mg/day for up to a 48 hour period.[14,15,16]

**7. Chronic use of meperidine is safe and effective provided renal function is monitored.**

Correct response: strongly disagree or disagree

Percent who responded correctly: 70%

Meperidine should be considered

QUESTION 1:

*Meperidine (Demerol) is the first line agent for post-operative pain.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | | 2 | 1 | 17 | 7 |
| | Emergency Medicine | | 2 | | 4 | 1 |
| | Neurology | | | 1 | | |
| Surgery | General Surgery | | | | 5 | 1 |
| | Orthopedics | | 2 | 3 | 2 | 1 |
| | Neurosurgery | | 1 | 1 | 2 | |

QUESTION 2:

*Meperidine is not recommended for use in elderly patients, or in patients with renal or hepatic dysfunction.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 12 | 13 | 2 | | |
| | Emergency Medicine | 1 | 5 | | 2 | |
| | Neurology | 1 | | | | |
| Surgery | General Surgery | 1 | 3 | 1 | 1 | |
| | Orthopedics | 1 | 6 | | 1 | |
| | Neurosurgery | 3 | | 1 | | |

QUESTION 3:

*The interval between meperidine doses ranges from 2-4 hours, with 3 hours as the average.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 1 | 16 | 5 | 3 | |
| | Emergency Medicine | 1 | 3 | 2 | 2 | |
| | Neurology | | 1 | | | |
| Surgery | General Surgery | | 5 | | 1 | |
| | Orthopedics | 1 | 4 | 1 | 2 | |
| | Neurosurgery | | 4 | | | |

QUESTION 4:

*Vistaril® is given in combination with meperidine because it significantly increases the efficacy of meperidine.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | | 8 | 2 | 11 | 6 |
| | Emergency Medicine | | 2 | 1 | 4 | 1 |
| | Neurology | | | | 1 | |
| Surgery | General Surgery | | | 1 | 5 | |
| | Orthopedics | | 2 | 1 | 5 | |
| | Neurosurgery | | 1 | | 1 | 2 |

QUESTION 5:

*As with all pure mu-agonists (like morphine), there is no maximum recommended daily dose associated with its use.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 3 | 10 | 1 | 8 | 5 |
| | Emergency Medicine | | 4 | 1 | 2 | 1 |
| | Neurology | | | | 1 | |
| Surgery | General Surgery | | 3 | 1 | 1 | 1 |
| | Orthopedics | | 3 | | 4 | 1 |
| | Neurosurgery | | 3 | 1 | | |

QUESTION 6:

*The recommended IV dosing for which meperidine is safe and effective are doses not to exceed 600mg/day for up to a 48 hour period.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | | 8 | 11 | 7 | 1 |
| | Emergency Medicine | | 5 | 2 | 1 | |
| | Neurology | | 1 | | | |
| Surgery | General Surgery | | 2 | 2 | 1 | |
| | Orthopedics | | 3 | 4 | 1 | |
| | Neurosurgery | | 3 | 1 | | |

QUESTION 7:

*Chronic use of meperidine is safe and effective provided renal function is monitored.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 1 | 3 | 4 | 12 | 7 |
| | Emergency Medicine | | 1 | 1 | 6 | |
| | Neurology | | | | 1 | |
| Surgery | General Surgery | | | 1 | 4 | 1 |
| | Orthopedics | | | 2 | 3 | 3 |
| | Neurosurgery | | 3 | | | 1 |

QUESTION 8:

*Although oral doses of meperidine have approximately ¼ the analgesic efficacy of parenteral doses, the toxic metabolite is produced in approximately equal amounts, on a milligram per milligram basis.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 1 | 10 | 14 | 2 | |
| | Emergency Medicine | | 5 | 3 | | |
| | Neurology | | 1 | | | |
| Surgery | General Surgery | | 3 | 3 | | |
| | Orthopedics | 1 | 3 | 4 | | |
| | Neurosurgery | | 3 | 1 | | |

QUESTION 9:

*Naloxone is used to reverse all CNS effects caused by meperidine and its metabolite.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | | 7 | 7 | 10 | 3 |
| | Emergency Medicine | 1 | | 1 | 4 | 1 |
| | Neurology | | 1 | | | |
| Surgery | General Surgery | | 2 | | 4 | |
| | Orthopedics | | 1 | 2 | 4 | 1 |
| | Neurosurgery | 1 | 2 | | 1 | |

QUESTION 10:

*Seizures related to meperidine use are associated with the accumulation of the metabolite normeperidine. Accumulation only occurs in renally impaired patients in doses over 100mg every two hours.*

| | | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|---|
| Medicine | General Medicine | 1 | 3 | 4 | 13 | 6 |
| | Emergency Medicine | | 2 | | 5 | 1 |
| | Neurology | | | | 1 | |
| Surgery | General Surgery | | | 1 | 5 | |
| | Orthopedics | | | 3 | 4 | 1 |
| | Neurosurgery | | 1 | 1 | 2 | |

a second-line agent for acute pain. For chronic pain the risk of adverse effects outweighs any benefit. Chronic pain management would require oral administration. The oral route has extensive first pass metabolism with only 50-60% reaching systemic circulation. In order to achieve equianalgesia oral doses must be greater than parenteral doses. Chronic use would result in a significant accumulation of the neurotoxic metabolite.

8. Although oral doses of meperidine have approximately 1/4 the analgesic efficacy of parenteral doses, the toxic metabolite is produced in approximately equal amounts, on a milligram per milligram basis.

Correct response: Strongly agree or agree

Percent who responded correctly: 50%

After oral administration, meperidine undergoes extensive hepatic first pass metabolism in which only 50-60% of a dose reaches the systemic circulation unchanged. Meperidine undergoes metabolism in the liver by two pathways. The major pathway is hydrolysis to meperidinic acid, followed by conjugation and renal elimination. The other pathway is demethylation to normeperidine, the only active metabolite, which is then hydrolyzed to normeperidinic acid, further conjugated, and renally excreted. Only a frac-

tion of the parent compound is eliminated unchanged in the urine. Due to first pass metabolism, oral administration of meperidine is associated with more extensive production of normeperidine than equianalgesic doses given parenterally. Normeperidine enters the systemic circulation faster than meperidine leading to rapid attainment of peak normeperidine blood concentrations. A dose of 300mg given orally is equianalgesic with 75mg parenterally. On a milligram per milligram basis, there is approximately four times the amount of normeperidine produced with oral administration than with parenteral administration.[1,5,11,14]

**9. Naloxone is used to reverse all CNS effects caused by meperidine and its metabolite.**
**Correct response: strongly disagree or disagree**
**Percent who responded correctly: 53%**

Normeperidine has a longer half-life than meperidine and accumulates faster than meperidine. When normeperidine levels rise and meperidine levels fall, central nervous system excitability results. Naloxone does not reverse normeperidine induced central nervous system excitability. It may actually exacerbate it by blocking the depressant effect of meperidine and allowing the convulsant activity of normeperidine to become manifest.[1,14,16]

**10. Seizures related to meperidine use are associated with the accumulation of the metabolite normeperidine. Accumulation only occurs in renally impaired patients in doses over 100mgs every two hours.**
**Correct response: strongly disagree or disagree**
**Percent who responded correctly: 70%**

Normeperidine produces marked central nervous system stimulation evidenced by nervousness, agitation, hyperreflexia, myoclonus, tremors and seizures. These symptoms are associated with elevated normeperidine concentrations. Accumulation of normeperidine is not limited to those with renal insufficiency. Even in healthy individuals the circulating normeperidine to meperidine ratio increases with time in patients receiving successive doses. This accumulation may occur at any dose if the patient is either susceptible or sensitive.[5,14,15,16]

## Summary

Results from this survey need to be viewed within the context of the small number of responses (20%), which may not fully represent the knowledge base of all house officers. Recommendations established by the Agency for Health Care Policy and Research (AHCPR) define standards of care for acute and chronic pain management and address many of the problems seen nationally with meperidine and its metabolite, normeperidine. Data from this survey have assisted us in providing educational programs which are in line with these guidelines for house officers.


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