The Impact of Narcotics on Cognitive Functioning in Patients at the Ann Arbor VA

by

Kathryn L. Swanson

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Advisor: Dr. Linas Bieliauskas

Abstract

The present study examined the impact of narcotics and the dosage on cognition. Participants included 289 patients from a database of those previously staying in the Community Living Center at the Ann Arbor VA. These patients included in the study scored greater than 23 on the Mini-Mental Status Exam, scored less than 8 on the Memorial Delirium Assessment Scale, were ages 60 and older, and had not been administered sedatives the day of testing with a neuropsychology testing battery. The patients' scores on several different cognitive tests were compared between those who were administered narcotics on the day of testing and those who were not. Scores were also correlated with morphine equivalent doses of narcotics to see if higher doses of narcotics had greater impairment on cognition. Neither administration of narcotics nor the dose of narcotics had a significant impairment on cognition. The results of the study indicated that the prescribed doses of narcotics in the current setting do not have impairing effects on patients' performance on cognitive testing.

The Impact of Narcotics on Cognitive Functioning in Patients at the Ann Arbor VA

During an extended stay at the Veterans Affairs hospital, patients recovering from a surgery, participating in physical therapy, or spending the last period of life as comfortably as possible are often administered narcotics to help with pain, anxiety, and defensiveness. All patients in the Community Living Center (nursing home unit) are required to complete a neuropsychological testing battery that assesses memory, executive functioning, and signs of depression. This battery is given early in the patient's stay, so their performance can be compared to their score at a later time if doctors suspect the patient is experiencing further problems. A lower score on the testing battery may be evidence of infection or other complications.

Narcotics, also called opioid analgesics, are used to treat moderate to severe acute and constant pain. Unfortunately, the serious side effects of narcotics outweigh the desired level of pain relief for some patients, so a less than adequate dose is usually administered (Ersek, Cherrier, Overman, Irving, 2004). Death caused by respiratory depression can also occur at too high of doses (Zacny, 1995). Another very problematic, but less serious side effect is cognitive impairment. These cognitive effects can make other conditions like dementia more debilitating. Therefore, administration of narcotics to the elderly can especially alter their ability to function normally and live independently (Ersek et al., 2004).

According to Lawlor (2002), cognitive functioning can be described as the "brain's acquisition, processing, storage, and retrieval of information." Patients on narcotics describe feeling confused and being in a dream-like state. In self-reports conducted by McCracken and Iverson (2001), patients most commonly report "forgetfulness", "minor accidents", and difficulty paying attention for finishing a task. Patients who are less educated, male, on opioid analgesics,

and having sleeping problems report more cognitive complaints. Pain severity is also correlated with more complaints. Many patients at the Veterans hospital are males who have only graduated high school on average and also report changed sleeping patterns during their stay as a result of the high activity of the hospital environment. The research by McCracken and Iverson (2001) indicate that patients at the VA could potentially be more at risk for cognitive impairments if taking narcotics.

Narcotics can also cause mental slowness, confusion, and hallucinations, so a patient's performance on a testing battery may not accurately reflect their cognitive abilities while on narcotics (Zablocki, 2004). Narcotics act as depressants on the brain by slowing down the nervous system, so signals to and from the brain do not move as fast as they should (Stronach, 2004). This in turn slows down a person's mental and emotional processes, halting physical and emotional pain. Studies have shown that cognition may be impaired while on narcotics due to other factors also, such as endorphins.

Opiates lead to an excess of endorphins, which can impair cognitive functioning, alter mood and behavior, and lead to symptoms of schizophrenia including hallucinations (Ganguli, 1984). Martin (1993) also found that narcotics used in pain therapy affected one's quality of life with effects on patients' memory, cognitive performance, mood, and behavior. Furthermore, the narcotics used for medical purposes may have more serious side effects than narcotics of abuse. In a study by Davis and Templer (1988) children exposed to methadone in utero experienced more pathological effects than those exposed to heroin later in life. Also, the children exposed to narcotics performed worse on IQ and other performance tests. It was interesting that those exposed to methadone faired worse in pathological assessments since this is a common drug prescribed while in the Community Living Center.

In the present study, the burden of different dosages of narcotics was assessed to determine if a greater dose has more of an impact on cognitive functioning. Bruera, Macmillan, Hanson, and MacDonald (1989) tested two comparative groups of patients, including patients who had been receiving stable doses of narcotics for a week and patients who received a higher dosage of narcotics just prior to the study. The group who received a higher dosage experienced greater sedation and nausea from the medication. These symptoms affected the patients' performance on cognitive tests, which included finger tapping, arithmetic, digit span, and visual memory tests. This study showed that an increase in narcotic dosage might result in impairment on cognition and also more impairment if it is a patient's first time taking the drug the day of testing.

Although narcotics have been shown to cause mental slowness, the physical activity resulting from mental processes while on narcotics may not be significantly impaired. Some cognitive tests require the patient to have psychomotor abilities. Fortunately, different doses of morphine do not seem to alter one's psychomotor activity (Zacny, Lichtor, Thapar, & Coalson, 1994). This reveals that scores on cognitive tests may show different levels of impairment depending on the importance of psychomotor abilities. Psychomotor performance was important on the Frontal Assessment Battery included in this study.

A common problem for the elderly receiving opioids in hospitals to treat acute pain is delirium that can affect cognitive functioning. Delirium is described as an abrupt disturbance in consciousness that affects one's ability to focus and pay attention and may fluctuate throughout the day (American Psychiatric Association, 2002). However, a study by Schor et al. (1992) found that advanced age and previous cognitive problems were more strongly associated with cognitive impairments than use of narcotics. Patients in the present study were not considered delirious

according to the Memorial Delirium Assessment Scale but were of advanced age making them more susceptible to cognitive impairments.

Other studies suggest that pain itself causes cognitive impairments, but administering opioids improves cognitive functioning due to pain relief. In a study by Haythornthwaite, Menefee, Quatrano-Piacentini, and Pappagallo (1998), patients reported cognitive impairment due to chronic pain from cancer. After administration of opioid therapy, their impairment due to pain improved and pain decreased. Cognitive function did not decline even after long-term administration of opioids. Emotional distress from pain and disruption in daily routines may also cause problems with cognition. McCracken and Iverson (2001) found that antidepressant use and sleep disruption due to pain were predictive of patients' self-reports of cognitive impairment. Many of the patients in the Community Living Center experience disruptions in their sleep pattern due to their pain and the busy hospital environment, waking due to nurses' or their roommate's activity. Their study also found a non-significant relationship between opioid use and cognitive complaints. However, the study was based on self-report measurement instead of direct measurements from a battery like that used at the Ann Arbor VA. Patients, especially elderly suffering from early signs of dementia, may not realize they are experiencing cognitive impairments.

Another study by Sjogren, Olsen, Thomsen, and Dalberg (2000) also found that pain might actually worsen working memory more than oral opioid treatment for pain. When pooling patients in their study who were in pain and received opioid treatment versus those who experienced pain but no opioid treatment, the only significant result was that those experiencing pain with no treatment did worse on tests assessing working memory. Additionally, the study

was not able to show any significant results indicating that the opioid treatments negatively affected cognitive performance.

Furthermore, a study by Klepstad, Hilton, Moen, Fougner, Borchgrevink, and Kaasa (2002) found that self-reports of cognitive function and sedation in cancer patients taking narcotics were not always valid assessments when comparing results of neuropsychological testing and observations of sedation between complainers and noncomplainers of impairment. These two groups did not score differently on objective tests measuring cognition and sedation administered by trained psychologists.

Previous research has demonstrated that is unclear if narcotics negatively affect cognition and how the dosage of narcotic medications impact cognitive ability. The present study was conducted to see if narcotics significantly impair cognitive performance of patients at the VA and whether the level of impairment depends on the dosage. This study hypothesized that those on narcotics would experience significantly more cognitive impairment than those not on narcotics. Additionally, with increasing narcotic burden (due to high dosages and/or multiple medications) the level of cognitive impairment would also increase.

Method

Participants

This study used a database of 289 patients who had been tested with a neuropsychological testing battery required for all patients staying in the Community Living Center at the Veterans Affairs Hospital of Ann Arbor. Patients in the database were ages 60 to 100 years old (*M*=72.66, *SD*=8.36). The patients were educated from 4 to 22 years (*M*=12.42, *SD*=2.55). The database included 274 males and 15 females.

Measures

A neuropsychological testing battery was administered to every patient. This screen tested executive functioning, memory, intelligence, general mental status, and depression. The measures assessed in this study are described below:

The Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) measures general mental status and is also used to screen for dementia. The test has 30 items that check short-term memory, orientation, attention, language, and visuospatial skills. Scores range from 0-30.

The Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000) assesses the possibility of frontal lobe dysfunction. There are six subtests that test conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibition, and environmental autonomy. Scores can range from 0-18.

Neurobehavioral Cognitive Status Exam Judgment Subtest (Kiernan, Mueller, Langston, & Van Dyke, 1987) asks patients to respond to everyday life problems. The test assesses judgment and verbal reasoning. Scores range from 0-6.

The Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlan, Groninger, & Brandt, 1998) contains 12 words that the examinee is asked to recall three times in a row. After a 20 minute delay the examinee is asked to recall as many items as possible again. Two variables of interest are immediate recall, which is the total recall for the first three trials, and delayed recall after the 20-minute period. Immediate recall scores range from 0-36. Delayed recall scores range from 0-12.

In the Forward and Backward Digit Span Tests (Wang, Xiao, Zhang, Liang, and Zhang, 2008) examinees were asked to recall a series of digits in the same order as presented or

backward after the digits are read. This test is a measure of short term working memory. Each trial correctly recalled leads to a one-increment increase in the examinee's score.

The Peabody Picture Vocabulary Test-III (PPVT; Dunn & Dunn, 1997) is a measure of intelligence. It is a picture vocabulary test that assesses premorbid verbal intellectual ability. A standardized IQ score can be derived from the raw score of this exam.

The short form of the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) contains 15 self-report items assessing depression. Scores of 5 and above are significant for depression. This test is designed for the geriatric population but is given to all patients in the Community Living Center.

The Memorial Delirium Assessment Scale (MDAS; Breitbart, Rosenfeld, Roth, Smith, Coehn, & Passki, 1997) contains a 10-item rating scale measuring delirium. It includes disorientation, disorganized thinking, delusions, perceptual disturbances, decreased psychomotor activity, and sleep-wake cycle disturbances. Scores of 8 and above are considered delirium.

Procedure

The original sample of patients in the database was narrowed down to exclude patients with suspected delirium (i.e. a MDAS score of less than 8), patients with suspected dementia (i.e. an MMSE score greater than 23), and patients who were administered sedatives on the day of testing. For each patient, the medications that were taken on the day of the neuropsychological screen were documented. Dosages of all narcotic medications were translated into a morphine equivalent dosage using an opioid calculator designed by Agency Medical Directors' Group (2007) and narcotic dose equivalencies used in a previous study (Jaffe and Martin, 1990). Morphine equivalency can be defined as "a conversion of a given dose of an opioid to an approximate equianalgesic dose" of morphine taken orally (Zacny, 1995). These morphine

equivalencies allowed us to take dosage and multiple medications into account by providing an overall burden score. Scores on the FAB, Judgment, MMSE, HVLT, and Forward and Backward Digit Span Tests from the testing battery were compared to patients' morphine equivalency doses. Control variables included age and scores on GDS and PPVT.

Results

Morphine equivalency dose was not significantly correlated with MDAS scores, $r = -.05$, $p = .39$. The morphine equivalency doses had a range of 0 to 8000 mg and a median dose of 4.75 mg ($M=51.56$, $SD=478.22$).

It was hypothesized that patients administered narcotics on the day of testing would be more impaired on cognitive tests than those not on narcotics. To test this, two groups, those on narcotics and those off narcotics, were compared using a Multivariate Analysis of Covariance test, adjusting for age and scores on the PPVT and GDS. Patients' test scores on the MMSE, HVLT immediate recall total, HVLT delayed recall, Forward/Backward Digit Span, Judgment, and FAB were compared between the two groups. An alpha level of .01 was used for all analyses. No statistical significance was found between the patients' test scores of those on narcotics and those not taking narcotics (see Table 1).

It was also hypothesized that narcotic burden would be correlated with cognitive functioning. Test scores on the MMSE, HVLT immediate recall total, HVLT delayed recall, Forward/Backward Digit Span, Judgment, and FAB were included in the correlation. Age and scores on PPVT and GDS served as partial controls in a partial correlation. The results of a partial correlation showed no significant correlation between morphine equivalency dose and patients' scores on each of the cognitive tests in the battery (see Table 2).

Discussion

Previous research had demonstrated that narcotics have an impact on cognition in humans. At the Ann Arbor VA, many patients are administered narcotics daily during their recoveries from illnesses and surgeries and are often administered a neuropsychology testing battery while on these narcotics. This study hypothesized that those on narcotics while taking the battery would have significantly more cognitive impairment than those not on narcotics. Also, those on higher doses of narcotics would be significantly more impaired than those on lower doses. The results showed that neither having been administered narcotics on the day of testing nor being on higher doses significantly impaired cognition. Morphine equivalency was also not correlated with delirium.

These results show that physicians at the Ann Arbor VA may not be administering doses of narcotics that are large enough to affect their cognitive functioning but still give the necessary analgesic effects desired by the patients. The doses of morphine equivalency ranged from 0 to 8000 mg but with a median dose of only 4.75 mg (M=51.56, SD=478.22). The few very high doses, including 8000 mg, were outliers that threw off the mean morphine equivalent dose. Our results are consistent with previous studies that have also not shown significant impairment on higher cognitive functions including logical reasoning and working memory with oral morphine of doses up to 45 mg (Walker & Zacny, 1998). Since the patients were not administered high enough doses of narcotics to affect their cognition, their results of the testing battery were also not affected and were more likely to be an accurate representation of the patients' cognitive abilities.

There were possible limitations of this study that could have affected the results. Bruera, Macmillan, Hanson, and MacDonald (1989) found that patients receiving a stable dose of narcotics showed tolerance to the cognitive effects after three to five days. From the database

used in this study, we do not know whether patients had received an increase in narcotic dose, if it was their first time being administered narcotics, or whether the patient had been on narcotics at stable doses for consecutive days. Future studies may want to include this information in the database and remove those patients having been receiving stable doses of narcotics.

This study did not take into account the time of administration of the narcotics and duration of each patient's dose of narcotic. Lowery (2005) demonstrated that narcotics' effect on cognition decreases more quickly than the analgesia. Some patients in the database may not have been administered their narcotic medications at a time prior to testing that they would still be experiencing the cognitive impairments to affect their results. We only know the narcotics were administered during the same day as testing. However, the study by Lowery (2005) also suggested that narcotics administered to older adults require a longer elimination time, which may mean longer duration of cognitive impairment effects. The present study did not factor in elimination time of each narcotic. This may also influence results since by the time a patient was tested, the narcotic(s) in his system could almost already be eliminated. Future studies should include the narcotic dose effects after time of administration, but also take into account the age of each patient at the VA that affects elimination time.

Generalizing all of the patients' narcotic medications as a morphine equivalency could also be considered a limitation of this study. Although many of the narcotics were given orally, opioids with different routes of administration and pharmacokinetics may have resulted in different declines in cognitive functioning. Previous studies found no significant results when testing the effects of routes of administration and pharmacokinetics on cognitive functioning, but these were done on healthy volunteers, unlike the majority of patients in the Community Living Center (Ersek, Cherrier, Overman, & Irving, 2004). Future studies on patients staying in

Community Living Center may want to include these aspects of the narcotics administered to see if they impair cognition in patients recovering from illness.

Previous research showed that pain can impair cognition, but administration of narcotics improves cognition due to pain relief (Haythornthwaite, Menefee, Quatrano-Piacentini, & Pappagallo, 1998). However, McCracken and Iverson (2001) found that reductions in pain severity might only result in cognitive improvements if there are emotional improvements as well. Therefore, future studies on patients in the Community Living Center may want to include scores on tests measuring mood and self-reports on pain severity in addition to various cognitive tests both before and after administration of opioid analgesics. This would show whether a decrease in pain severity resulting in emotional improvements is actually what maintains cognitive functioning in patients at the VA and provide further insight as to why this study's results may have not been significant. Nevertheless, the failure to find significant effects of narcotics on cognition at the dosages utilized at the Ann Arbor VA is encouraging in that it alleviates at least gross concerns of their adverse impact in patients requiring similar courses of treatment.

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Author Note

Table 1

Cognitive Performance of Patients On and Off Narcotic Medications

Test	On Narcotics Mean (*SD*)	Off Narcotics Mean (*SD*)	p-value Mean (*SD*)
MMSE	26.95 (1.81)	26.63 (1.82)	.54
HVLT IMM	16.42 (5.68)	15.91 (5.53)	.83
HVLT Delay	4.98 (2.89)	4.60 (3.16)	.92
DigFwd	4.90 (.31)	5.00 (.68)	.10
DigBkwd	3.53 (.89)	3.64 (.80)	.25
Judgment	5.31 (1.14)	5.30 (1.15)	.86
FAB	13.70 (2.67)	13.53 (2.78)	.80

Note. MMSE = Mini-Mental Status Exam; HVLT IMM = Hopkins Verbal Learning Test immediate recall; HVLT Delay = Hopkins Verbal Learning Test delayed recall; DigFwd = Forward Digit Span Test; DigBkwd = Backward Digit Span Test; Judgment = Neurobehavioral Cognitive Status Exam Judgment Subtest; FAB = Frontal Assessment Battery

Table 2

Correlation Between Narcotic Burden and Patients' Test Scores

	Morphine Eq.	
Test	Correlation	Significance (2-tailed)
MMSE	.09	.18
HVLT IMM	.07	.29
HVLT Delay	.10	.13
DigFwd	-.02	.75
DigBkwd	.00	.97
Judgment	-.09	.16
FAB	.00	1.00

Note. MMSE = Mini-Mental Status Exam; HVLT IMM = Hopkins Verbal Learning Test immediate recall; HVLT Delay = Hopkins Verbal Learning Test delayed recall; DigFwd = Forward Digit Span Test; DigBkwd = Backward Digit Span Test; Judgment = Neurobehavioral Cognitive Status Exam Judgment Subtest; FAB = Frontal Assessment Battery