Cognitive function and chronic opioid use

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Cognitive dysfunction in cancer

- Cerebral metastases
- Electrolyte derangement (e.g. hypercalcemia)
- Metabolic disturbances (e.g. uremia and anemia)
- Humoral factors (TNF, cytokines ect)
- Emotional distress (e.g. anxiety and depression)
- Other symptoms/conditions (e.g. pain and fatigue)
- Antineoplastic treatment (e.g. ”chemobrain”)
- Palliative treatment (e.g. opioids)

”49% of a mixed cancer population complained of problems with concentration and memory”

Cull et al., Br J Cancer 1995

Self-assessment in cancer patients referred to palliative care

Strömgren et al., Cancer 2002

Patients (n=267) were assessed at referral by EORTC, ESAS, MMSE and HADS
(The median number of symptoms: 8 (0-14))

Fatigue	94 %
Inactivity	86 %
Pain	83 %
Anorexia	70 %
Cognitive dysfunction	57 %
Constipation	43 %
Dyspnea	42 %
Sleeplessness	37 %
Nausea/Vomiting	37 %
Diarrhea	21 %
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Anxiety	27 %
Depression	47 %

Mini Mental State Examination (MMSE)

Twenty-one items on orientation to time and place, memory, attention and calculation, and ability to name an object, to follow verbal and written instructions, to write a sentence spontaneously, and to copy a figure

Folstein et al., J Psychiat Res 1975

MMSE in palliative care

- On admission 44 % and prior to death 62 % had abnormal scores

  Pereira et al., Cancer 1997

- On admission 35% had abnormal scores

  Radbruch et al., Palliat Med 2000

- On admission 25 % had abnormal scores

  Strömgren et al., Cancer 2002

Opioid effects

Wanted effects

- analgesia
- sedation
- anti-dyspnoe
- anti-salivation

Unwanted effects

- respiratory depression
- sedation
- constipation
- itching
- nausea/vomitting
- dry mouth
- sweating
- diziness
- sleep disturbance
- difficult micturition
- mood changes
- *cognitive dysfunction*
- *hyperalgesia/allodynia*
- *hallucinations/delirium*
- *myoclonus/seizures*

Long-term consequences of opioid treatment

- Physical dependence
- Tolerance development
- Opioid-induced pain sensitivity
- Addiction
- Cognitive disorders
- Dysfunction of the immune and reproductive systems

Savage, J Pain Symptom Manage 1993
Mitchell et al., Nat Neurosci 2000
Mao, Pain 2002

Sjøgren et al., Eur J Pain 2005
Fecho et al., J Pharmacol Exp Ther 1995
Abs et al., J Clin Endocrinol Metab 2000

Pain management of opioid treated cancer patients in hospital settings in Denmark

Lundorff et al., Acta Anaesthesiol Scand 2008

Side effect	Prevalence	Treatment attempts of side effects
Dryness of mouth	64%	9%
Constipation	63%	81%
Nausea/vomitting	46%	46%
Sweating	39%	2%
Cognitive dysfunction	37%	7%
Sedation	33%	8%
Confusion	17%	9%
Myoclonus	12%	0%
Allodynia	3%	0%

Clinical neuropsychology

”Clinical neuropsychology is an applied science concerned with the behavioral expression of brain dysfunction”

Muriel D. Lezak, ”Neuropsychological Assessment”

Cognitive domains

in cancer and chronic non-cancer pain patients

- Attentional capacity
- Information-processing speed and working memory
- Short-term memory
- Psychomotor speed

Lezak MD, Neuropsychological Assessment 1995
Eccleston and Crombez, Psychol bull 1999
Grace et al., J Clin Exp Neuropsychol 1999
Sjøgren et al., Pain 2000

Opioids and cognition

Study	Design	Opioid treatment (route and dose)	Assessment	Results
Sjøgren and Banning, Pain 1989	Cross-over Controlled	Oral/epidural, Doses:210/80mg	CRT	No-difference
Bruera et al., Pain 1989	Controlled Longitunal	Oral/dose increase	FTT, Memory, Arithmetics	Difference
Banning and Sjøgren, Clin J Pain 1990	Healthy controls Cross-sectional	Oral, Dose=168mg	CRT	Difference
Banning et al., Acta 1992	Controlled, Cross-sectional	Oral, Dose=150mg	CRT	Difference
Vainio et al., Lancet 1995	Controlled, Cross-sectional	Oral, Dose=209mg	Driving ability	No-difference
Clemons et al., Cancer Treat Rev 1996	Controlled Cross-sectional	Oral, Dose=104mg	Arithmetics, Stroop-Colour-Word	Difference
Christrup et al., JPSM 1999	Cross-over Double-blind	Oral morphine vs. oral MST, Dose=120 mg	CRT	No-difference
Sjøgren et al., Pain 2000	Controlled, Cross-sectional	Oral, Doses=120/40mg	CRT, FTT, PASAT	No-difference
Kamboj et al., Pain 2005	RCT, double-blind, cross-over	long-term oral opioids + supplemental morphine doses	Prose recall, Digit span, TMT, FTT	Difference

Exclusion criteria in controlled studies of cancer patients in long-term opioid treatment

1. Metabolic and electrolyte disturbances
2. Cerebral metastasis
3. Other neurological and/or physical dysfunctions interfering with the tests (e.g. dementia, head injury)
4. Use of psychotropic drugs other than opioids
5. Alcohol/drug abuse
6. Anticancer treatment recently (3-4 weeks)
7. Acute progression of disease

Driving ability in cancer patients receiving long-term morphine analgesia

Vainio et al., The Lancet 1995

Methods

1. A computerized test battery consisting of five psychomotor tests designed for professional drivers
2. Reaction times, finger tapping, posture control (eyes open and closed), and thermal discrimination
3. Plasma concentrations of morphine and metabolites
4. The psychological state

Patients

- The morphine group: 24 cancer patients treated with stable doses of slow-release morphine tablets (mean daily dose 209 mg)
- The control group: 25 cancer patients taking no analgesics

The groups were similar regarding age an sex, educational background, duration of illness and performance status

Conclusion

”Long-term analgesic medication with stable doses of morphine does not have psychomotor effects of a kind that would be clearly hazardous in traffic”

Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status

Sjøgren et al., Pain 2000

130 cancer patients were consecutively included and divided in the following categories:

Group 1 (N = 40)	KPS A	- Pain	- Opioids
Group 2 (N = 19)	KPS B	- Pain	- Opioids
Group 3 (N = 19)	KPS B	+ Pain	- Opioids
Group 4a (N = 31)	KPS B	+ Pain	+ Opioids
Group 4b (N = 21)	KPS B	- Pain	+ Opioids

Neuropsychological testing

1) Continuous Reaction Time (CRT): Sustained attention, vigilance, concentration and motivation. 152 auditory signals at random intervals over a period of 10 min

2) Finger Tapping Test (FTT): Psychomotor speed and simple motor coordination using a tapping board

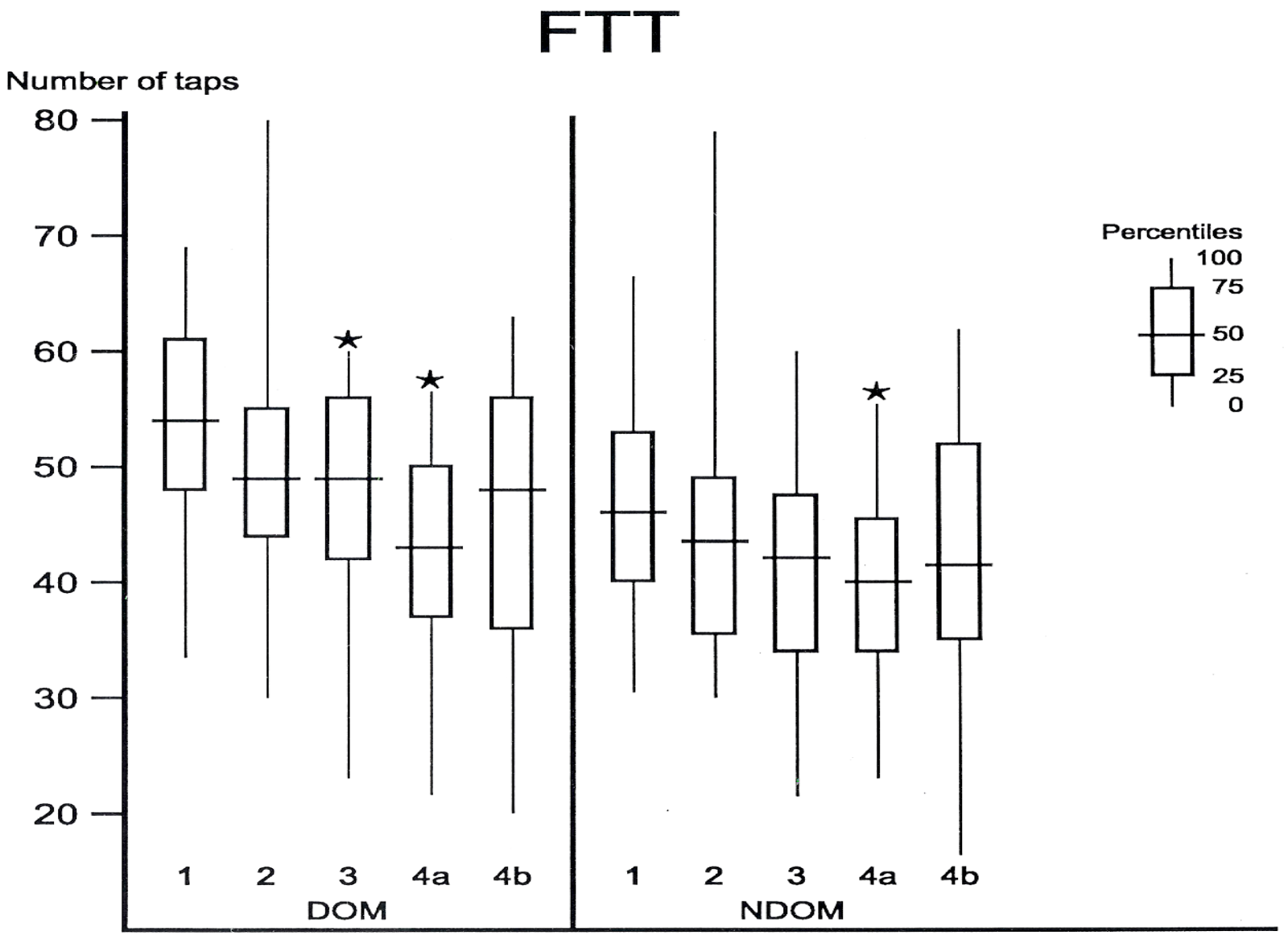
3) Paced Auditory Serial Addition Task (PASAT): Working memory and speed of information processing.
Random digits is presented verbally at timed intervals in series of increasing speed and the patient is instructed continuously to add the last digit to the previous

Results

- CRT: Group 1 > groups 2, 4a and 4b
- FTT: Group 1 > groups 3 and 4a
- PASAT: Group 1 > group 4a (4b > 4a)

The pain-relieved groups (2 and 4b) performed better than the pain-suffering groups (3 and 4a) in PASAT

SVAS and drowsiness was strongly associated with poor performance of CRT and FTT



FTT (range, 25, 50 and 75% percentiles) for dominant (DOM) and non-dominant (NDOM) hands in five patient groups

Conclusions

1. The use of long-term oral opioid treatment did not affect any of the neuropsychological tests

2. Patients being in KPS B had statistically significantly slower CRT than patients being in KPS A

3. Pain itself deteriorated the performance of PASAT

The effects of opioid dose increase and supplemental opioid doses on cognition

Studies	Design	Patients and treatments	Study intervention	Assessments	Results
Bruera et al., Pain 1989	An open-label controlled study	Cancer patients (n=40) on oral and parenteral opioids	A dose increase of 30% in 20 patients Stable doses in 20 controls	ESAS FTT Arithmetics Reverse memory Visual memory	Pain relief Increased sedation and nausea Significant impairment of all cognitive test
Kamboj et al., Pain 2005	Randomized, placebo-controlled, double-blind, cross-over study	Cancer patients (n=14) on long-term opioids	Supplemental morphine doses	PVAS HADS Prose recall Digit span Trail marking FTT	Pain relief Ante- and retrograd memory impairment Attention deficits

...but remember that there are remedies for cognitive dysfunctioning !

Management opioid induced cognitive dysfunction with opioids

1. Co-administrating adjuvant analgesics
2. Reducing the opioid dose whenever possible
3. Circadian modulation with the opioid
4. Administering an alternative opioid
5. Administering the opioid by an alternative route
6. A combination of 4 and 5

Other therapeutic strategies to manage cognitive dysfunction

- Psychostimulants
- Other drugs e.g. antidepressants
- Hydration
- Oxygen supply
- Sleep management

Methylphenidate in opioid-induced cognitive dysfunction and sedation

Studies	Design	Patients and treatments	Study drug	Assessments	Results
Bruera et al., 1987	Randomized, double-blind, cross-over 7 days; cross-over day 4	N=28 Oral opioids	Methylphenidate 10mg+5mg+0	ESAS Sleep	Improvement of pain, activity and drowsiness
Bruera et al., 1992	Randomized, double-blind, cross-over 5 days; cross-over day 3	N=19 Continuous s.c. infusions	Methylphenidate 10mg daily	ESAS FTT Arithmetics Memory	Improvement of drowsiness, confusion, FTT, arithmetics and memory

Modafinil for cognitive dysfunction in advanced cancer: A randomized, controlled, double-blind, cross-over trial

Lundorff et al., submitted to Cancer

- *Aim:* To evaluate the cognitive effects of single-dose Modafinil
- *Methods:* 28 cancer patients (fatigue>50mm on ESAS) received Modafinil 200 mg or placebo and 4 days later they crossed over to the alternative treatment
- *Assessment:* FTT, TMT and ESAS were measured before and 4.5 hours after tablet intake
- *Results:* FTT (dom) and TMT as well as depression and drowsiness measured on ESAS improved statistically significantly on modafinil

Conclusions

1. The cognitive effects of stable long-term oral opioid treatment seem to be modest
2. Driving ability seems to be preserved in patients treated with stable doses of opioids
3. Dose increase as well supplemental opioid doses may temporarily deteriorate cognitive function
4. Pain itself seems to deteriorate some aspects of neuropsychological performance
5. Poor performance status seems to deteriorate some aspects of neuropsychological performance
6. Psycho-stimulants may counteract cognitive dysfunction and sedation, however, more studies are needed