Marek Kaminski[1], Per Sjøgren[2]
[1]Department of Anaesthesiology, Vejle Hospital, Vejle, Denmark
[2]Multidisciplinary Pain Centre, National Hospital, Copenhagen, Denmark

The use of psychostimulants in palliative and supportive treatment of cancer patients

Abstract

Psychostimulants have been used in psychiatric and medically ill patients. The need to control and counteract the multiple distressing symptoms related to cancer and its treatment has brought this group of medications into palliative and supportive care of cancer patients. Psychostimulants have been studied and used in symptoms like cancer-related fatigue, cognitive dysfunction, depression and sedation. This review discusses the pharmacology of methylphenidate, amphetamine and pemoline and other psychostimulants like caffeine and the novel wake-promoting drug, modafinil. Studies evaluating use of these drugs in cancer patients have been reviewed.

Key words: pychostimulants, cancer, palliative care

Introduction

A psychostimulant is a drug, which by inducing certain brain activities causes a sense of well being, decreases fatigue and depression, improves cognitive and intellectual function and enhances motivation. Different drugs belonging to various pharmacological groups are defined as psychostimulants. Among those are naturally occurring substances like cocaine and caffeine and synthetic drugs like amphetamine or methylphenidate. Naturally occurring substances with psychostimulating properties has been consumed through centuries in different cultures. For example cocaine obtained from coca plant were used for its stimulating properties by ancient peoples of Peru and other pre-Columbian Andean societies. It was also one of the original ingredients of Coca-Cola until its highly addictive properties were recognized, and it was replaced by caffeine in 1903. Currently, cocaine is illicit all over the world and its legal use is limited to local analgesia in ophtalmic surgery. Caffeine, the most commonly used psychostimulant is consumed worldwide in coffee, tea and variety of soft drinks, and is also a component of many popular medications as well. Amphetamine, which was synthetized in 1887, was used by military forces in twentieth century to improve alertness during sustained war operations. In sixties and seventies amphetamine abuse became epidemic and restrictions of its availability in majority of European countries were accomplished. Novel drugs — like modafinil — with less abuse potential has been developed recently. Modafinil acts more selectively on the sleep-wake cycle instead of promoting generalized activation of CNS. Commonly accepted indications for psychostimulants include attention deficit/ /hyperactivity syndrome (ADHD) and narcolepsy. Moreover, psychostimulants have been used to treat

Address for correspondence: Marek Kaminski
Department of Anaesthesiology
Vejle Hospital, Kabbeltoft 25, 7100 Vejle, Denmark
tel: +45 79406200, fax: +45 79406875
e-mail: marek_kam@yahoo.dk

Advances in Palliative Medicine 2007, 6, 23–31

a variety of symptoms accompanying different diseases. They have been used i.e. for the treatment of fatigue in patients with multiple sclerosis or HIV disease or as a adjuvant medication for major depression.

Cancer diseases and anticancer treatments are accompanied by various severe and prevalent symptoms, which diminish quality of life of the patients, and are usually difficult to combat. These include fatigue, sedation and cognitive dysfunction.

Several authors have investigated psychostimulants in cancer patients. The aim of this article is to review the available literature on psychostimulants in palliative and supportive treatment of cancer patients.

Pharmacology of psychostimulants and their use in cancer patients

Methylphenidate

Pharmacology

Methylphenidate (MP) is a piperidine derivative and like amphetamine and catecholamines it has a phenylethyloamine structure [1–3]. Because the MP molecule has two chiral centers it exists as four enantiomers: d- and l-threo-metylphenidate and d- and l-erythro-methylphenidate [4]. Most of clinically used preparations of MP contains a mixture of d- and l-isomers of threo- form [1, 5]. An exception is Focalin™ (Novartis Pharmaceuticals) which contains primarily a d-isomer [1]. MP is well absorbed from the gastrointestinal tract and achieves peak blood levels within 1 to 2 hours [6]. Absorbed drug undergoes extensive first-pass metabolism and has an elimination half-life of 2 to 7 hours [6]. Its major metabolite, ritalinic acid, is mainly excreted in the urine [6]. Clinical effect of MP has duration of 3 to 5 hours. Several commercially available products include also sustained-release preparations with duration of action up to 12 hours [1,6].

The exact mechanism of action of MP is not fully elucidated. Evidence from animal and human studies indicates that MP increases extra-cellular dopamine levels in the brain by blocking dopamine re-uptake and by facilitation of dopamine release into the synaptic cleft [1, 7]. It has also been shown that MP blocks dopamine re-uptake by binding to the dopamine transporters in the presynaptic cell membrane [8, 9]. This differs from the main mechanism of action of amphetamine, which releases newly synthesized cytosolic dopamine from the nerve terminal [10]. The dopamine transporters is thought to be a critical regulator of dopamine homeostasis [8, 11]. At oral therapeutic doses (0.3–0.6 mg/kg), methylphenidate is estimated to occupy more than half of brain dopamine transporters. Studies using single-photon emission tomography have shown that the striatum is the area of highest methylphenidate uptake in the human brain [6, 12, 13]. MP blocks also re-uptake of norepinephrine and binds weakly to the serotonine transporters, but the effect on these two neurotransmitters, particularly serotonine, appears to be weaker compared with the effect on dopamine [14]. Recent research has shown another possible mechanism of action: methylphenidate can increase prefrontal cortex excitability by activation of alpha-2-adrenoreceptors in inhibitory interneurons [15].

MP is a relatively safe drug and few side effects have been demonstrated in clinical trial settings. The most common side effects include insomnia, nervousness, tachycardia, hypertension and anorexia [1, 2]. In adults anorexia is not observed as side effect [16].

An overdose of MP is associated with symptoms of CNS overstimulation and sympathomimetic effects, and can usually be treated symptomatically [1].

MP potentiates effects of tricyclic antidepressants, MAO inhibitors and coumarin anticoagulants. Effects of central adrenergic blockers are antagonised by MP [2].

MP has abuse potential as it can induce euphoria. However, abuse of oral MP seems not to be an important problem in medically ill population [2]. Used intravenously or intranasally MP has a cocaine-like effect with clinically important abuse potential [17].

The majority of clinical experience with MP comes from its use in patients with attention-deficit/hyperactivity disorder (ADHD) [18, 19].

The Food and Drug Administration (FDA, United States regulative body for drugs) has approved MP for the treatment of ADHD and narcolepsy. The same diseases are officially approved indications for the use of MP in Denmark, and in Poland MP is only approved for the treatment of ADHD.

Use in patients with cancer

MP has been investigated as a remedy to relieve several symptoms associated with cancer and its treatment. These include very frequent and serious symptoms and side effects as depression, opioid-induced sedation, cognitive dysfunction and fatigue. The potential of MP as an adjuvant drug in cancer patients has been evaluated in several studies.

Opioid-induced sedation. Many patients with advanced cancer require high doses of opioids to control their pain. Sedation is a well-described and frequent side effect of opioid drugs that may be

present for long periods of time and may be associated with poor quality of life. Moreover during opioid treatment sedation can be a limiting factor for achieving desirable analgesia. The prevalence of opioid induced sedation was 33% in a mixed population of hospitalised cancer patients [20]. MP effect can counteract opioid-induced sedation.

Open-label studies. In a non-randomised study involving 15 patients with incident cancer pain 10 mg MP was administered at 08.00 h a.m. and 5 mg at 12.00 h a.m. in order to counteract opioid-induced sedation [21]. This allowed for higher doses of opioids, which, in turn resulted in better pain control and less drowsiness. In another non-randomised study involving 50 patients with advanced cancer and opioid-induced sedation MP was started at a dose of 15 mg/day [22]. The majority (91%) of 48 evaluated patients reported improvement in sedation after 48 hours of treatment and continued on MP for mean 39 ± 20 days. However, due to development of tolerance, the doses of MP were increased the following month. The mean maximal daily dose of MP in this study reached 42 ± 6 mg.

Randomised controlled trials. The effects of MP in opioid-induced sedation were also investigated in three randomised, double-blind, placebo controlled, cross-over studies.

In the first study, 32 patients with advanced cancer receiving opioids were randomised to receive MP (10 mg in the morning and 5 mg at noon) or placebo. Patients receiving MP showed improvement in pain, activity and sedation scores [23]. The second study evaluated effects of MP (20 mg daily) compared to placebo on sedation and cognitive function in twenty patients receiving a continuous infusion of opioids for cancer pain. Cognitive functions were assessed by means of several tests like finger tapping speed, arithmetic tests, and memory for digits and visual memory. MP resulted in significant improvement in drowsiness, confusion and cognitive functions [24].

The third study involved 43 cancer patients receiving stable doses of oral opioids . Patients were randomised to receive 5 days of MP followed by 5 days placebo, or vice versa. The dose of MP used in this study was 10 mg in the morning and 5 mg at noon (5 mg in the morning and 5 mg at noon for patients aged 70 years or over). Thirty-four patients completed all 10 days of double-blind assessment. Data from this study did not demonstrate statistically significant benefit of methylphenidate, but suggested that this drug could mildly decrease opioid-induced drowsiness and improve night-time sleep [25].

Depression. Depression is frequently seen in patients with advanced cancer [26]. The prevalence of major depression in palliative care cancer patients have recently been found to be 47% [27]. Treatment of these patients with antidepressants is hampered by the slow onset of effects seen in relation to the short life expectancy. Psychostimulants may have antidepressant effects and may be advantageous due to the rapid onset of action.

Open-label studies. MP has been evaluated as a remedy for depression in a number of non-randomised studies. In a case series of five organically impaired and depressed patients with head and neck cancer, rapid remission of depressive symptoms and improvement in cognition was reported after initiating MP therapy [28]. In another study 59 hospital charts of oncology patients, who were treated for depression with either dextro-amphetamine or MP, were reviewed retrospectively. Eighty-three percent of the patients showed at least some improvement, while 73% had marked or moderate improvement of depressive symptoms following psychostimulant treatment. There was no significant difference in efficacy between the two psychostimulants [29].

An open-label study evaluated efficacy of MP (5–20 mg daily) in 26 depressed hospice patients with end-stage cancer. In 46% a moderate and in 7% a pronounced improvement of depression was described. The author concluded, that higher doses of psychostimulants may be indicated in terminal phase of cancer [30].

In another case series MP (10–20 mg daily) was used to treat depression in 10 patients with advanced cancer. Rapid improvement in depressive symptoms was noted in all patients [31].

In more recent, open-label, prospective study MP was used to treat depression in 41 patients with advanced cancer. Out of 30 patients, who completed the study, 21 responded to 10 mg/day and 9 responded to 20 mg/day. Improvement occurred within three days [32].

Cognitive dysfunction. Cognitive dysfunction is prevalent and serious in patients with advanced cancer, particularly, in patients with brain tumours. In palliative care using Mini Mental State Examination (MMSE) a study by Pereira et al. comprising 348 inpatients showed a prevalence of cognitive dysfunction of 44% on admission, whereas 68% had abnormal MMSE scores prior to death [33]. Strömgren et al. investigated 267 patients referred to three palliative care functions: Inpatient, outpatient and palliative home care. The overall prevalence of cognitive dysfunction on admission showed that 24% had abnormal MMSE scores [27].

Open-label studies. In an open-label, prospective study involving 30 patients with malignant gliomas, improvement in cognitive domains like attention, memory, graphomotor speed or verbal fluency was observed in 50 percent of patients receiving MP (10–30 mg/day) despite progressing brain lesions documented by MRI [34].

In another open-label, prospective study including 14 patients with advanced cancer and hypoactive delirium, cognitive function measured by MMSE improved after treatment with MP in all patients [35].

Randomised controlled trials. MP's capability of improving cognition has been evaluated in three randomised, placebo-controlled studies.

In an older study, discussed previously in the context of opioid-induced sedation, MP (10 mg in the morning) also improved cognitive function (assessed by finger tapping speed and arithmetic and memory tests) in most patients receiving opioid infusions [24].

Another randomised, double-blind, placebo-controlled study evaluated the cognitive effects of MP (0.6 mg/kg) in 32 long-term survivors of childhood acute lymphoblastic leukaemia or malignant brain tumours. Using Conner's Continuous Performance Test patients receiving MP showed significant improvement in sustained attention and overall index reflecting learning capabilities. However, there was not significant improvement in reaction times or verbal memory [36].

The largest study involved 83 children with long-term survival of acute lymphoblastic leukaemia or brain tumors [37]. The children were randomised to receive MP (0.3 mg/kg or 0.6 mg/kg) or placebo. Use of MP resulted in improved cognitive function and social functioning. The children were evaluated by parents and teachers using Conner's Rating Scales and Social Skills Rating System. There was no significant advantage of higher dose (0.6mg/kg) of MP.

Cancer-related fatigue. Fatigue is among the most frequent and among the most distressing symptoms experienced by cancer patients. In palliative care the prevalence of fatigue among cancer patients is > 90% in most populations [27].

Open-label studies. The effectiveness of MP in this symptom has been assessed in a number of non-randomised studies in cancer patients. In a small, prospective, open-label study MP relieved fatigue in nine out of eleven patients with advanced cancer. In most of the patients 10 mg methylphenidate daily in two divided doses was effective [38]. In a study involving 31 cancer patients, the patients could use 5 mg of MP as needed every 2 hours for fatigue. Patients were allowed to take a maximum of four tablets per day. Fatigue was measured using 0 to 10 point scale. Significant improvement from 7.2 ± 1.6 score to 3.0 ± 1.9 score was noticed after seven days of treatment with MP. Most patients preferred to take three or four doses daily [39].

In another open-label study MP was used for treatment of fatigue in 37 patients with history of breast cancer treated with surgery and/or chemotherapy and/or radiotherapy. The patients included were disease-free for at least 6 months from the last treatment sequence. Fatigue level was assessed using Brief Fatigue Inventory (BFI). Treatment with MP (10–20 mg/daily) resulted in improvement of fatigue measured as a decrease in BFI scores greater than two points in 54% of the patients [40].

Randomised controlled trials. Two randomised, double-blind, placebo-controlled studies assessed effectiveness of MP for cancer-related fatigue.

A study was a follow up from a pilot study [39], in which Bruera et al. assessed patient-controlled MP (10–20 mg/daily) versus placebo in 112 cancer patients. In contrast to the results of the pilot study, MP was not found to be more effective than placebo in relieving cancer-related fatigue [39, 41]. In another study d-isomer of MP was compared to placebo in 152 post-chemotherapy cancer patients. The average dose of d-MP in the study was 27.7 mg, which is comparable to a dose of approximately 55 mg of racemic mixture. Significant relief of fatigue and improved memory was observed in d-MP group compared with placebo [42].

Amphetamine and dextroamphetamine

Pharmacology

Amphetamine is a racemic mixture of levo- and dextrorotatory isomers. Its molecule shares a phenyloethyloamine structure with catecholamines and MP [2, 3]. The dextrorotatory form (dextroamphetamine) is three to four times more potent than the l-isomer. Due to its high lipophilicity, amphetamine is rapidly and completely absorbed from the gastrointestinal tract and easily crosses blood-brain barrier. Peak plasma levels are achieved in 3 to 4 hours after oral administration. Amphetamine is partially metabolised in the liver, but a considerable fraction may be excreted in the urine unchanged. No active metabolites are produced. The elimination half-life is approximately 12 to 20 hours and is dependent on urinary pH. Acidification of the urine promotes the clearance of amphetamine. Pharmacodynamic responsivity to amphetamine is variable and there is no good correlation between plasma levels and clinical response. The exact mechanism of action of amphetamine is unknown [3, 10].

In animals, it facilitates catecholamine release from neurons, reduces their reuptake and inhibits monoamino oxidase activity. The central psychostimulant actions are primarily dependent on interaction with dopaminergic fibers in ventral tegmentum, mesolimbic system and particularly in the nucleus accumbens. Anorexic and locomotor effects depend to greater extent on central release of norepinephrine. In addition amphetamine exerts mild peripheral α- and β-sympathomimetic effect leading to elevation of heart rate and blood pressure. Amphetamine like other structure-related psychostimulants is capable of producing a range of central nervous system, cardiovascular and gastrointestinal side effects. Insomnia, agitation, palpitations and dry mouths are among the most common. In most cases these side effects are transient and diminish with the development of tolerance. Cardiac arrhythmias, hypertension and delirium are relative, but not absolute contraindications to a low dose amphetamine trial. The tolerance and abuse potential of amphetamine seems to be related to several factors like treatment indications, patient selection and supervision of administration. Clinical experience with cancer patients and other medically ill patients suggest little if any tendency towards abuse. In contrast uncontrolled use for fatigue and//or as a mood enhancer tolerance, drug abuse and chronic toxicity will develop rapidly and frequently. Several studies confirm effectiveness of dextroamphetamine for depression secondary to medical illness [43–46]. It has been also found helpful in counteracting sedation resulting from opioids in postoperative patients [47]. Few studies have assessed the usefulness of amphetamine in cancer patients. In Denmark and Poland amphetamine is not available legally. In the USA amphetamine is available for treatment of ADHD, narcolepsy and refractory obesity.

Use in patients with cancer

Only a few older publications can be found describing the use of amphetamines in cancer patients. In a clinical note Yee and Berde presented experience with 4 terminally ill cancer patients, who received dextroamphetamine as adjuvant to opioid analgesics [48]. Using 5 or 7.5 mg dextroamphetamine daily the authors achieved decreased somnolence and improved interaction in 3 patients. In a formerly cited retrospective study [29] in which hospital charts of oncology patients were reviewed, 44 cancer patients received dextroamphetamine for depression. The daily dose of dextroamphetamine ranged from 2.5 to 20 mg. Seventy percent of treated patients demonstrated marked or moderate improvement of depressive symptoms. Mood improved quickly, usually within the first two days of treatment.

Pemoline

Pharmacology

Pemoline is oxazolidinone derivative that is structurally dissimilar to methylphenidate and amphetamine. The mechanism and site of action is not known. Animal studies suggest blockage of presynaptic neuron dopamine reuptake. Pemoline is readily absorbed from the gastrointestinal tract. It is partially metabolised in the liver and is excreted in the urine as both unchanged drug and metabolites [3]. In spite of short elimination half-life ($t_{1/2}$ = 9 to 14 hours), the onset to peak clinical effectiveness may be a matter of days to weeks [2].

The side effect profile of pemoline is similar to that of MP and amphetamine. From 1971 to 1985 there have been reported approximately hundred cases of pemoline-associated hepatic toxicity [2, 49]. In the USA pemoline has been used to treat ADHD and narcolepsy [2]. It has also been tested and demonstrated to be efficacious against fatigue in patients with multiple sclerosis and HIV disease [50, 51]. There are no available studies of pemoline in cancer patients. In 2005 FDA withdrew approval for pemoline due to public pressure and in the same year Abbot Laboratories discontinued the production of pemoline.

Caffeine

Pharmacology

Caffeine is a mild CNS stimulant consumed every day by millions of people all over the world, mainly in coffee, tea and a variety of soft drinks. Chemically caffeine is a methylxantine and is structurally unrelated to other psychostimulants [3]. After oral ingestion caffeine is rapidly and almost completely absorbed from gastrointestinal tract and easily passes through blood-brain barrier [52]. Peak plasma concentration is reached in 30–60 min after oral intake and elimination half-life is approximately 3–6 hours [3, 52]. Caffeine is almost completely metabolised in the liver [3]. Its mechanisms of action are not fully understood. The presumed mechanism of action of caffeine is an antagonism of adenosine receptors, but an interaction with dopamine systems within the CNS has also been postulated [52]. Nausea, vomiting, diarrhoea, gastrointestinal bleeding, insomnia, headache, restlessness, tremor and palpitations are possible side effects of caffeine [3]. Prolonged high intake may lead to tolerance and withdrawal symptoms after abrupt discontinuation, but addiction is extremely rare [3, 52].

Use in patients with cancer

Only one study could be found assessing the use of caffeine in cancer patients [53]. In a double-blind, placebo-controlled, crossover study Mercadante et al. assessed effects of caffeine infusion on cognitive function in cancer patients receiving morphine. Twelve patients participated in the study, and their psychomotor performance was assessed using finger tapping test, arithmetic tests, memory for digits and visual memory. Only finger tapping speed improved significantly compared with placebo.

Modafinil

Pharmacology

Modafinil (2-[(diphenylmethyl) sulphinyl]acetamide) is a novel, vigilance and wakefulness promoting CNS stimulant. It is chemically unrelated to other psychostimulants [54]. Following oral administration, modafinil is rapidly and completely absorbed from gastrointestinal tract, and achieves peak plasma level in two to four hours [55]. It is extensively metabolised in the liver. The main metabolite is modafinil acid, which is pharmacologically inactive. Less then 10% of a modafinil dose is excreted in urine unchanged. The elimination half-life after a single oral dose is between 10 and 13 hours. With multiple daily dosing steady-state plasma levels are reached after three days. Modafinil is moderately bound to plasma proteins, therefore drug interactions originating from competitive protein binding are unlikely [45, 56]. Important interactions of modafinil are connected to activation or inhibition of CYP450 enzymes in the liver. CYP3A4 is induced by Modafinil at doses > 400 mg/d. This may reduce serum concentration of co-administered drugs (i.e. carbamazepine, phenobarbital, ketoconazole, cyclosporine) that are dependent on this enzyme for their metabolism. Two enzymes from CYP450 family (CYP2C19, CYP2C9) have been identified as being inhibited by modafinil. This may be of clinical importance, since these enzymes are involved metabolism of tricyclic antidepressants, warfarin, diazepam and phenytoin [54, 56].

Although various neurotransmitter systems have been proposed to be involved in the actions of modafinil, little is still known about the molecular mechanisms by which modafinil increases wakefulness. It is likely that modafinil selectively enhances catecholaminergic signalling in the CNS like amphetamine and methylphenidate, but its site of action is different. Modafinil acts primarily in the anterior hypothalamus, an area of brain involved in the regulation of normal wakefulness, whereas amphetamine and methylphenidate generally act throughout the striatum and cortex [56–59]. Therefore modafinil interacts with sleep-wake cycle, rather than inducing generalized excitation, such as that seen with seen with other psychostimulants. The fact that modafinil acts more locally within the CNS seems to be responsible, at least in part, for its relatively low incidence of side effects and low abuse potential [56]. Contra-indications comprise patients with left ventricular hypertrophy, mitral valve prolapse or history of psychosis. Modafinil is registered in many countries including Denmark for the treatment of narcolepsy. It has been found effective for excessive sleepiness associated with obstructive apnoea/hypopnoea syndrome [60] and against fatigue accompanying a variety of diseases including multiple sclerosis and fibromyalgia [61–63]. Modafinil has also been investigated for the treatment of ADHD [64], and as a main or adjunctive medication in certain forms of depression [65–67]. Usefulness of modafinil against opioid-induced sedation has been tested in patients with chronic non-malignant pain [68]. Modafinil may be found useful in the treatment of symptoms associated with cancer and its treatment. The number of studies addressing this problem is still very limited.

Use in patients with cancer

Open label studies. Modafinil has been tested for persistent fatigue in patients who completed breast cancer treatment. [69]. In an open-label study 51 patients received 200 mg modafinil (Provigil®) in the morning. Fatigue severity level was measured using 0–10 scale, where 0 = "not present" and 10 = "as bad as you can imagine". The mean fatigue severity level for the 51 participating patients was reduced statistically significant. Furthermore majority of patients reported improvement in general activity, mood and normal work ability. Patient reported global effectiveness of modafinil was mean 5.0 during this study (1 = "no benefit" and 7 = "great improvement"). The study has been followed by a randomised controlled study, which has not been published yet.

Randomised studies. The only currently available randomised study assessing effects of modafinil regarding cognition and fatigue was presented in 2006 at the Annual ASCO Meeting [70]. The study involved thirty patients with brain tumours treated with neurosurgical resection, radiotherapy, and/or chemotherapy. Cognitive dysfunction and depression were assessed using Trail Making (TM) A and B, Symbol Digit Modalities (SDM), Verbal Fluency (VF),

and Hamilton Depression Scale (HAM-D). Fatigue was measured with Fatigue Severity Scale (FSS), Visuals Analogue Fatigue Scale (VAFS), and Modified Fatigue Impact Scale (MFIS). Patients were randomised in the double-blind, dose-controlled design to receive 200 or 400mg modafinil daily for 3 weeks. After 1 week washout the study was continued for 8 weeks in open-label fashion. Statistically significant improvement in all measured parameters was observed with greatest improvement 8 weeks after baseline.

Discussion

Cancer patients experience multiple distressing symptoms. Pain has long been recognized as a common burden for patients with cancer. Tremendous efforts have focussed on understanding the mechanisms of pain and developing effective drug and interventional approaches for its management. Just as pain itself received inadequate attention from cancer clinicians in the past, other symptoms than pain are often under-assessed and under-treated. Other symptoms, like cancer related fatigue, sedation and cognitive dysfunction, have only within recent years received attention by clinicians and researchers. Research in epidemiology, mechanisms and interventions is still in its infancy and for that reason the interventions are still not specified.

Psychostimulants offer new possibilities in managing symptoms related to cancer and its treatment. Out of the three "classical" psychostimulants (amphetamine, MP and pemoline) MP has been most thoroughly evaluated in cancer patients. Because amphetamine is feared for its abuse potential and pemoline production has been stopped, MP remains the classical and "gold-standard" psychostimulant, which seems to have a future in palliative and supportive treatment of cancer patients.

MP may potentially be effective in reducing sedation, when used as adjuvant to strong opioids. However, the three randomised studies [23–25] in this area do not convincingly specify, that it is opioid induced sedation and not sedation of other aetiologies, which is antagonised. Furthermore, the findings need to be confirmed by larger randomised, controlled studies.

MP has also been proposed as an antidepressant in cancer patients, however, until now this has only been studied in open non-randomised trials. As the indications for fast acting antidepressants are obvious in cancer patients with short life expectancy randomised trials are hardly needed.

The use of MP seems also to improve cognition in cancer patients. However, due to the fact, that randomised, controlled studies mostly were carried out in children with leukaemia or brain tumours, more evidence from patients with other malignancies are needed.

A number of open-label studies have indicated a possible usefulness of MP for the treatment of cancer-related fatigue. However, randomised, controlled studies have not unambiguously confirmed that methylphenidate is effective against cancer-related fatigue [40, 41]. Discrepancy in results from the two studies in treatment of fatigue may be related to differences in study design, however, most likely the doses of MP may have caused different outcomes. In the first study a maximum of 20 mg of racemic MP was used daily [41], whereas the other study the average dose of d-MP in the study was 27.7 mg, which is comparable to a dose of approximately 55 mg of the racemic mixture. Significant relief of fatigue and improved memory was observed in d-MP group compared with placebo [42]. Thus, higher doses of MP may be needed to improve cancer-related fatigue. More evidence from dose-respond trials could help to resolve this issue.

Modafinil, the novel vigilance and wake-promoting agent, may be potentially effective in some symptoms that accompany cancer and its treatment. This may include cancer-related fatigue, cognitive dysfunction and opioid induced sedation. Results from studies investigating the efficacy of modafinil in fatigue originating from multiple sclerosis and HIV disease have encouraged for further studies in cancer patients. Current data are limited, but results of currently ongoing studies are awaited. The lower abuse potential and more specific effects seem to be the main advantage of modafinil, when comparing it to "classical" psychostimulants.

Conclusion

Opioid induced sedation, depression, cognitive dysfunction and fatigue are very frequent and severe symptoms in patients with cancer. The psychostimulants are becoming increasingly important as pharmacological options in the treatment of these symptoms, however, both classification and understanding of the patophysiological mechanisms of the symptoms as well as the specificity of available psychostimulants make targeted treatments difficult. MP is still the "golden standard" within the psychostimulants in palliative medicine due to the level of evidence and a modest side effect profile. However, new and exciting psychostimulants may be awaited in the near future.

References

1. Sood A, Barton DL, Loprinzi CL. Use of methylphenidate in patients with cancer. Am J Hosp Palliat Care 2006; 23: 35–40.
2. Masand PS, Tesar GE. Use of stimulants in the medically ill. Psych Clin North Am 1996; 19: 515–547.
3. Homsi J, Walsh D, Nelson KA. Psychostimulants in supportive care. Support Care Cancer 2000; 8: 385–397.
4. Ding YS, Fowler JS, Volkow ND, Dewey SL, Wang GJ, Logan J et al. Comparison of the pharmacokinetics of [11C]d-threo and L-threo-methylphenidate in the human and baboon brain. Psychopharmacology (Berl) 1997; 131: 71–78.
5. Seeman P, Madras BK. Anti-hyperactivity medication: methylphenidate and amphetamine. Mol Psychiatry 1998; 3: 386–396.
6. Kimko HC, Cross TC, Darrell RA. Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinet 1999; 37: 457–470.
7. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention deficit hyperactivity disorder: a review and integration. Behav Brain Res 1998; 94: 127–152.
8. Challman TD, Lipsky JJ. Methylphenidate: Its pharmacology and uses. Mayo Clin Proc 2000; 75: 711–721.
9. Sonders MS, Zhu SJ, Zahniser NR, Kavanaug MP, Amara SG. Multiple ionic conductances of the human dopamine transporter: The actions of dopamine and psychostimulants. J Neurosci 1997; 17: 960–974.
10. Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. The Pharmaceutical Basis of Therapeutics. Goodman & Gilman's, 9th ed., New York 1996: 220.
11. Gaidentinov RR, Jones SR, Fumagalli F, Wightman RM, Caron MG. Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis. Brain Res Rev 1998; 26: 148–153.
12. Ding YS, Fowler JS, Volkov ND, Gatley SJ, Logan J, Dewey SL et al. Pharmacokinetics and in vivo specifity of [11C]dl-threo-methylphenidate for the presynaptic dopamine neuron. Synapse 1994; 18: 152–160.
13. Volkov ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley JS et al. Is methylphenidate like cocaine? Studies on pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry 1995; 52: 456–463.
14. Gatley SJ, Pan D, Chen R, Chaturvedi G, Ding YS. Affinities of methylphenidate derivatives for dopamine, norepinephrine and serotonine transporters. Life Sci 1996; 58: 231–239.
15. Andrews GD, Lavin A. Methylphenidate increases cortical excitability via activation of alpha-2 noradrenergic receptors. Neuropsychopharmacol 2006; 31: 594–601.
16. Masand P, Pickett P, Murray GB. Psychostimulants for secondary depression in medical illness. Psychosomatics 1991; 32: 23–28.
17. Parran TV Jr, Jasinski DR. Intravenous methylphenidate abuse. Prototype for prescription drug abuse. Arch Intern Med 1991; 151: 781–783.
18. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005; 366: 237–248.
19. Leonard BE, McCartan D, White J, King DJ. Methylhenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharacol Clin Exp 2004; 19: 151–180.
20. Lundorff L, Peuckmann V, Sjogren P. Pain management of opioid treated cancer patients in hospital settings. A preliminary study. Accepted by Acta Anaesth Scand.
21. Bruera E, Fainsinger R, MacEachern T, Hanson J. The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminare report. Pain 1992; 50: 75–77.
22. Bruera E, Brenneis C, Paterson AH, MacDonald RN. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. J Pain Symptom Manage 1989; 4: 3–6.
23. Bruera E, Chadwick S, Brenneis C, Hanson J, MacDonald RN. Methylphenidate associated with narcotics for the treatment of cancer pain. Cancer Treat Rep 1987; 71: 67–70.
24. Bruera E, Miller MJ, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain 1992; 48: 163–166.
25. Wilwerding MB, Loprinzi CL, Mailliard JA, O'Fallon JR, Miser AW, van Haelst C et al. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 1995; 3: 135–138.
26. Massie MJ, Popkin MK. Depression. In: Holland J, Rowland J (ed.). Handbook of psycho-oncology. Oxford University Press, New York 1998: 518–540.
27. Stromgren AS, Goldschimdt D, Groenvold M, Petersen MA, Jensen PT, Pedersen L et al. Self-assessment in cancer patients referred to palliative care: a study of feasibility and symptom epidemiology. Cancer 2002; 94: 412–520.
28. Fernandez F, Adams F. Methylphenidate treatment of patients with head and neck cancer. Head Neck Surg 1986; 8: 296–300.
29. Olin J, Masand P. Psychostimulants for depression in hospitalized cancer patients. Psychosomatics. 1996; 37: 57–62.
30. Macleod AD. Methylphenidate in terminal depression. J Pain Symptom Manage 1998; 16: 193–198.
31. Homsi J, Walsh D, Nelson KA, LeGrand S, Davies M. Methylphenidate for depression in hospice practice: A case series. Am J Hosp Palliat Care 2000; 17: 393–398.
32. Homsi J, Nelson KA, Sarhill N, Rybicki L, LeGrand SB, Davis MP et al. A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care 2001; 18: 403–407.
33. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997; 97: 835–842.
34. Mayers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol 1998; 16: 2522––2527.
35. Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. J Psychiatry Neurosci 2005; 30: 100–107.
36. Thomson SJ, Leigh L, Christensen R, Xiong X, Kun LE, Heideman RL et al. Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. J Clin Oncol 2001; 19: 1802–1808.
37. Mulhern RK, Khan RB, Kaplan S, Helton S, Christensen R, Bonner M et al. Short-term efficacy of methylphenidate: A randomized, double-blind, placebo controlled trial among survivors of childhood cancer. J Clin Oncol 2004; 22: 4795–4803.
38. Sarhill N, Walsh D, Nelson KA, Homsi J, LeGrand S, Davis MP. Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. Am J Hosp Palliat Care 2001; 18: 187–192.
39. Bruera E, Driver L, Barnes EA, Willey J, Shen L, Palmer JL et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. J Clin Oncol 2003; 21: 4439–4443.

40. Hanna A, Sledge G, Mayer ML, Hanna N, Einhorn L, Monahan P et al. A phase II study of methylphenidate for the treatment of fatigue. Support Care Cancer 2006; 14: 210–215.
41. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006; 24: 2073–2078.
42. Lower E, Fleishman S, Cooper A, Zeldis J, Faleck H, Manning D. A phase III, randomised placebo-controlled trial of the safety and efficacy of d-MPH as new treatment of fatigue and "chemobrain" in adult cancer patients. 41st ASCO Annual Meeting, 13–17 May 2005, Orlando, FL, USA. J Clin Oncol 2005; 23 (suppl): 8000.
43. Woods S.W., Tesar G.E., Murray G.B., Cassem N.H. Psychostimulant treatment of depressive disorders secondary to medical illness. J Clin Psychiatry 1986; 47: 12–15.
44. Holmes VF, Fernandez F, Levy JK. Psychostimulant response in AIDS-related complex patients. J Clin Psychiatry 1989; 50: 5–8.
45. Pickett P, Masand P, Murray GB. Psychostimulant treatment of geriatric depressive disorders secondary to medical illness. J Geriatr Psychiatry Neurol 1990; 3: 146–151.
46. Masand P, Pickett P, Murray GB. Psychostimulants for secondary depression in medical illness. Psychosomatics 1991; 32: 203–208.
47. Forrest WH Jr, Brown BW Jr, Brown CR, Defalque R, Gold M, Gordon HE et al. Dextroamphetamine with morfine for the treatment of postoperative pain. N Engl J Med 1977; 296: 712–715.
48. Yee JD, Berde CB. Dextroamphetamine or methylphenidate as adjuvant to opioid analgesia for adolescents with cancer. J Pain Symptom Manage 1994; 9: 122–125.
49. Nehra A, Mullick F, Ishak KG, Zimmerman HJ. Pemoline-associated hepatic injury. Gastroenterology 1990; 99: 1517–1519.
50. Weinshenker BG, Penman M, Bass B, Ebers GC, Rice GP. A double-blind, randomised, crossover trial of pemoline in fatigue associated with multiple sclerosis. Neurology 1992; 42: 1468–1471.
51. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001; 161: 411–420.
52. Lorist M, Tops M. Caffeine, fatigue, and cognition. Brain Cogn 2003; 53: 82–94.
53. Mercadante S, Serretta A, Casuccio A. Effects of caffeine as an adjuvant to morphine in advanced cancer patients: a randomised, double-blind, placebo-controlled, crossover study. J Pain Symptom Manage 2001; 21: 369–372.
54. Provigil (Modaginil). Product monograph. Cephalon UK Limited 1999.
55. Wong YN, King SP, Watson BL, Simcoe D, Laughton W, McCormick GC et al. Open-label, single-dose pharmacokinetic study of modafinil tablets: Influence of age and gender in normal subjects. J Clin Pharmacol 1999; 39: 281–288.
56. Cox JM, Pappagallo M. Modafinil: A gift to portmanteau. Am J Hosp Palliat Care 2001; 18: 408–410.
57. Lin J-S, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunochemistry in the cat. Proc Natl Acad Sci USA 1996; 93: 14128–14133.
58. Ferrano L, Antonelli T, O'Connor WT, Tanganelli S, Rambert FA, Fuxe K. Modafinil: An antinarcoleptic drug with a different neurochemical profile to amphetamine and dopamine uptake blockers. Biol Psychiatry 1997; 42: 1181–1183.
59. Engber TM, Dennis SA, Jones MS, Miller MS, Contreras PC. Brain regional substrates for the actions of the novel wake-promoting agent modafinil in the rat: comparison with amphetamine. Neuroscience 1998; 87: 905–911.
60. Keating GM, Raffin MJ. Modafinil: A review of ist use in excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome and shift work sleep disorder. CNS Drugs 2005; 19: 785–803.
61. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Nagaraja HN. Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple slerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 2002; 72: 179–183.
62. Rosenberg JH, Shafor R. Fatigue in multiple sclerosis: a rational approach to evaluation and treatment. Curr Neurol Neurosci Rep 2005; 5: 140–146.
63. Pachas WN. Modafinil for the treatment of fatigue of fibromyalgia. J Clin Rheumatol 2003; 9: 282–285.
64. Lopez FA. ADHD: new pharmacological treatments on the horizon. J Dev Behav Pediatr 2006; 27: 410–416.
65. DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003; 64: 1057–1064.
66. Lundt L. Modafinil treatment in patients with seasonal affective disorder/winter depression: an open label pilot study. J Affect Disord 2004; 81: 173–178.
67. Vaishnavi S, Gadde K, Alamy S, Zhang W, Connor K, Davidson JR. Modafinil for atypical depression: effects of open_label and double-blind discontinuation treatment. J Clin Psychopharmacol 2006; 26: 373–378.
68. Webster L, Andrews M, Stoddard G. Modafinil treatment of opioid-induced sedation. Pain Med 2003; 4: 135–140.
69. Morrow GR, Gillies LJ, Hickok JT, Roscoe JA, Padmanaban D, Griggs JJ. The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed. 41st ASCO Annual Meeting, 13––17 May 2005, Orlando, FL, USA. J Clin Oncol 2005; 23 (suppl): 8012.

70. N, Triaspolitica. "Mengenal Penyakit Kangker, Jenis, Gejala, Penyebab Berikut Pengobatan Kangker." Nanya Dong Dok. Blogger, 20 June 2017. Web. 20 June 2017. <http://nanyadongdok.blogspot.com/2017/06/mengenal-penyakit-kangker-jenis-gejala.html>.