Use of Methylphenidate for Treatment of Depression in Cancer Patients - A Literature Review

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The prevalence of depressive disorder in persons with cancer ranges from 3.2% to 50%. Most systematic reviews have concluded that 25% of cancer patients are likely to meet criteria for major depression or adjustment disorder with depressed mood. It has been established that depression adversely affects length of survival, compliance with therapy, self-care, perception of pain and quality of life. Goldberg and Mor found that only 3% of patients with terminal cancer were being treated, which highlights “under-diagnosis” and failure to treat as major concerns.

In general, somatic symptoms such as fatigue, appetite and weight loss become less helpful in making a diagnosis of major depression in cancer patients, because these symptoms can be caused by the patients' medical illness. Endicott's substitution criteria, which remove somatic symptoms from the diagnostic criteria and replace them with other psychologic features of depression identify much the same group of depressed individuals as an approach in which somatic symptoms are included. This finding should caution underestimation of depression in cancer patients and encourage medical intervention.

Psychostimulants work by interacting with dopaminergic fibres in the brain. Through the central nervous system, amphetamines act to produce wakefulness, alertness, elevation of mood and self esteem. Although amphetamines suppress normal appetite, poor appetite is normalized. In addition psychostimulants in depression have been shown to have potentiating effects on blood levels of tricyclic antidepressants. Psychostimulants are highly desirable to treat depression in the medically ill, since they have a rapid onset of action, few side effects and have been shown to significantly increase the quality of life in palliative care patients. They have been successfully used in conditions such as HIV, cancer, fatigue, pain and mood disorders.

Psychostimulants have been shown to have an important role in the management of depression in cancer patients. Effective psychostimulant treatment breaks a cycle of hopelessness and inactivity by renewing the patient's energy. Reactivation promotes a renewed sense of competence, hopefulness and motivation that leads to further activity and involvement. The rapid onset of action (usually with first 24-72 hours of treatment), the low incidence of side effects, the augmentation of opioid analgesia, the reversing of opioid induced sedation and the enhancement of appetite in cachectic patients all add to the usefulness of psychostimulants in palliative care. The delay of onset of action (3-4 weeks) of the standard antidepressants (tricyclics, selective serotonin reuptake inhibitors and novel antidepressants such as venlafaxine, bupropion, as well as poorly tolerated side effects for tricyclics may limit their usefulness in cancer patients. Electroconvulsive therapy may be contraindicated by anesthetic risks. Although psychotherapeutic approaches may be useful, they may also take longer to achieve therapeutic effect.

Widely used psychostimulants include dextroamphetamine, methylphenidate (MPD) and Pemoline. MPD is perhaps the most widely used psychostimulant in cancer patients. It is rapidly absorbed after oral administration, achieves peak blood levels within 1 to 2 hours, and the metabolic products are inactive. MPD has a short elimination half-life (t1/2 = 2 to 7 hours) requiring repeat administration two to four times per day. It releases intra-neuronal dopamine from granular rather than newly synthesized cytosolic pools. In general, uncontrolled cardiac arrhythmias, hypertension and delirium are relative but not absolute contraindications to a low-dose MPD trial. The risk of adverse effects is greater in such patients; cardiac rhythm may be aggravated, further elevation of heart rate or blood pressure may occur and confusion is more likely. The starting dosage of MPD is 5 to 10 mg at 8 AM and noon. When a rapid antidepressant response is critical, however, cautious use of MPD, titrating upward from a test dose of 2.5 mg, is worth considering. The perceived safety of MPD is probably a function of the low doses and brief courses of treatment used in the depressed medically ill. However, rebound depression is possible after cessation and habituation and abuse have occurred, as well as some precipitation of paranoid reactions due to their mechanism of dopamine agonism.

Katon and Raskind were among the first to provide published evidence of psychostimulant efficacy in depressed patients with documented medical illness. Initiation of MPD, 10 mg twice a day, was followed by rapid improvement of depressive symptoms over 2 to 3 days in three patients aged 73, 82, and 85, respectively. Natenson reported on 26 patients with various cancers (including esophageal and breast cancer) whom he treated with MPD in doses up to 60 mg/d for up to 26 weeks. Twenty-two of the 26 patients had an excellent response and 1 had a poor response. None developed tolerance or habituation to the psychostimulants. Two patients developed insomnia during the 1 year follow-up period. Fernandez et al treated 30 depressed cancer patients with MPD. Patients were started on 10 mg three times a day; the dose was increased by 5 to 10 mg every 2 to 3 days until a maximum of 80 mg/d or improvement occurred. Psychiatric diagnoses for...
these patients included adjustment disorder with depressed mood, major depression, dementia with depressed mood, organic affective syndrome and organic personality disorder. The different cancers included head and neck, hematologic, melanoma, sarcoma, thoracic and breast. Seventy-seven percent experienced a marked or moderate response. The average duration of treatment was 38 days. An attempt was made to decrease the dose of the psychostimulant 1 week after remission of depressive symptoms; unfortunately, 11 out of 30 patients had a relapse on discontinuation of MDP. Side effects included nervousness, palpitations, nausea, confusion and psychosis, constipation, chest pain, tachycardia and blood pressure changes, each of which was present in one patient. There was no evidence of tolerance or abuse, and the psychostimulant had to be discontinued because of side effects in only two patients. Stiebel and Kemp described successful treatment with MDP (at a dose of 25 mg/d) of a 47-year-old white male with carcinoma of the colon and an organic mood disorder. The patient was also able to decrease its dose of narcotic analgesics. He continued on MDP for 1 year without relapse, side effects, evidence of tolerance or dependence. Kraus and Burch described a 65-year-old man with squamous cell cancer of the larynx and Parkinson’s disease who was treated with MDP (at a dose of 30 mg/d) and showed a moderate response to treatment. His psychiatric diagnosis was adjustment disorder with depressed mood. The patient experienced no side effects. Olin and Masand in a retrospective chart review of 59 hospitalized oncology patients treated with MDP for depression during a 5-year period in a large urban general hospital found that 83% of the patients showed at least some improvement following psychostimulant treatment. Seventy-three percent of all patients treated with a psychostimulant demonstrated a marked or moderate improvement in symptomatology. No significant differences in efficacy were noted between the two psychostimulants or across psychiatric diagnostic categories for depression. Most patients improved within the first 2 days of treatment. Nineteen percent of the patients experienced side effects (e.g., agitation, hypomania, sinus tachycardia, paranoid delusions and confusion). The psychostimulant had to be discontinued because of side effects in 10% of cases. The average daily dose was 8 mg/d. There were no cases where appetite was suppressed owing to psychostimulant treatment. In fact, 41% of patients had a moderate-to-marked improvement in their appetite following treatment with psychostimulants.

The above data are based on retrospective reviews and naturalistic clinical observations. The individuals recording that data were not blinded to the treatment given, and in many cases were already biased in favor of psychostimulant efficacy and thus caution must be exercised in interpretation. On the other hand, randomized, placebo controlled trials in the terminally ill are ethically difficult to conduct, particularly in end stage disease.

In an open label study, MacLeod et al. diagnosed and treated 26 patients with major depression and advanced malignancies for 2 years with a mean dose range of 17.7 mg of MDP. The duration of MDP administration was 5 days to 6 weeks. There was a significant response as assessed by the Clinical Global Impression Scale in 46% of the sample. Symptoms rated included depressed mood, energy, appetite and ambulation. Responders benefited from enhanced interest in their remaining life, improved quality time with relatives and an easing of fears of impending death. Energy levels were not improved in responders. Marked responses were achieved by 50% women and only 12% men. This trend of gender specificity in the efficacy of psychostimulants has also been suggested by Akinzio et al. In a single subject study by Pereira et al., a patient with advanced pancreatic cancer demonstrated an observed and self-reported improvement of mood and psychomotor retardation following the initiation of MDP treatment.

MDP has also been shown to have a synergistic effect when combined with SSRIs in more serious depression. In a study by Stoll et al., self reported symptom reduction was achieved rapidly in all cases with MDP doses of 10-40 mg/d. MDP added to ineffective SSRI treatment in a rapid and efficacious manner, with particular improvement in apathy and fatigue.

In short, despite small study size and lack of randomized controlled trials, the above literature clearly demonstrates that depressive symptoms dramatically improve with the use of psychostimulants in cancer patients. These improvements are observed regardless of the specific psychiatric depressive diagnosis. However, larger, controlled trials using specified criteria to diagnose depression are warranted to elucidate the role of psychostimulants in treating depression in palliative care patients. Future studies of stimulants should evaluate efficacy at 24 to 72 hours rather than after 1 to 2 weeks (which is the traditional period for follow-up in controlled clinical trials) to demonstrate quick onset of action.

MDP appears effective across a multitude of cancer types, requiring low mean doses (abuse and tolerance issues are negligible), across age ranges from 47-85 and across genders. Side effects are largely nonproblematic. Although these general trends exist, the physician must always tailor each patient’s care on the basis of his or her own unique personal style and needs. It has been suggested that psychostimulants are extraordinarily underused and warrant more careful consideration in the pharmacological armamentarium used in palliative medicine. Although death may be inevitable in many cancer patients, the process of “dying with dignity” may and ought to be more often facilitated by the use of psychostimulants.

References