**Dear Editor in Chief:**

**Thanks for reviewing our paper. We have extensively revised our paper and below, please see point-to-point response to the critique made by the reviewers as well as by the editor. We hope that this extensive revision of the manuscript will not make the paper acceptable for publication.**

**Best regards.**

**Truly yours,**

**Prof. M. Wasif Saif, MD, MBBS**

**Reviewer A:**

|  |  |
| --- | --- |
| **Comments** | **RESPONSE** |
| This paper deals with the pharmacological management of chronic related fatigue (CRF) in advanced pancreatic cancer patients. In particular with the use of an oral psycho-stimulant agent, namely methylphenidate (MPH). Methylphenidate (MPH) is mainly used for attention deficit hypersensitivity disorders (ADHD).  There are only limited studies available for the control of the CRF mainly in mixed cancer population (eg gynecologic, breast or prostate cancer patients) with inconsistent results.  Therefore, this paper is very important that has enrolled a quite great number  (71 patients) with advanced pancreatic cancer only and resulted in good control of CRF with low dose of MPH. In addition, the use of a simple one-dimensional fatigue scale (Visual analogue fatigue scale -VAFS) (figure 1) which is easily acceptable by the patients and the quite short period of enrollment (June 2011-November 2014) augments the strength of the study. Finally, there are a lot of useful information regarding the mechanisms for cancer related fatigue from the pathophysiology point of view. The possible correlation of CRF with pro-inflammatory cytokines lead to new horizons with the use of anti-inflammatory agents such as Infliximab (discussion line 14). On the other hand this is a non-controlled retrospective study with different stage of pancreatic cancer and different treatment modalities even if most of the patients (63%) received double treatment with gemcitabine. Regarding the side effects it is uncertain whether these side effects are contributed to the underlying pancreatic cancer or to the drug itself but it is very important that there is a comparison with the general MPH users (table 6).  Finally, given the fact that MPH seems to be very useful tool for advanced cancer fatigue overall it would be critical to intensify in the discussion  its  contribution to the maintenance of chemotherapy intensity for this difficult to treat patients. | Added red font wording under introduction: p3  This devastating symptom is also undertreated because of limited treatment options and it often leads to discontinuation or dose reduction of the anti-cancer treatment.  Given the frequency and severity of fatigue in APC patients, and the difficulty to maintain chemotherapy intensity due the fatigue, it is important to test the potential benefit of MPH in the management of fatigue in this patient population. We performed a retrospective chart review to assess the efficacy of MPH in the treatment of fatigue in APC patients.  Add red font wording under discussion: p7  In our study, all patients with grade 2 or above fatigue were started at 5mg PO daily of MPH. The majority of patients were able to achieve the benefit at this dose, though a few required higher doses for benefit. MPH significantly reduced the fatigue level, alleviated depression and anorexia, these symptoms are common reasons causing APC patients to withdraw or reduce chemotherapy intensity. Our study also shows that MPH helped to maintain chemotherapy intensity in APC patients on concomitant chemotherapy. There were no significant side effects and was well tolerated in most of the patients. |
| Minor comments on the paper: It has to be clarified why the duration of the study was terminated to four (4) weeks and not earlier even if we know that the drug action compare to other antidepressants for the chronic pain is immediate within a few days (Pereira J et al. Depression with psychomotor retardation: diagnostic challenges and the use of psychostimulants. J Palliat Med. 2001 Spring;4(1):15-21). | Added below sentences and the reference at P3  ***Response evaluation:***  Response of fatigue was assessed at each visit prior to the next dose of chemotherapy. To correlate the visit schedule and assure the drug effect at equilibrium state10, a trial of at least 4 weeks of MPH was given before discontinuing the drug due to lack of benefit.  Clinical data previously suggested that majority of the patients experience beneficial effects from methylphenidate within a few days of starting the medication, however, it often takes several weeks to get the full effect of the medication [Updated by the College of Psychiatric and Neurologic Pharmacists, January 2016 - See more at: https://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Methylphenidate-Dexmethylphenidate-(Concerta,-Rita#sthash.0UAYCcGY.dpuf]  2- In addition, most chemotherapy cycles are administered q 4 weeks and we wanted to make the assessment uniform in these patients;  and  3- make it convenient for them also to prevent extra visits |
| In addition to that it is not clear enough why the dosage of 5mg has been chosen and under which criteria an escalation to 10mg is decided. | Added below with the two references at P4.  ***Treatment Plan:***  MPH was started small dose at 5mg PO once daily in the morning with related data from previous study 11, 12 and in consideration of our patient population’s age, cardiac risk and cancer related nervousness,  We chose 5mg as initial dose based on the indication from previous studies as listed below as well as keeping in mind side effects potentially attached to the drug in a population already suffering a lot due to pancreatic cancer. In addition, this age of patient population have known cardiac history and cancer related nervousness; therefore, we decided to use 5mg as our initial dose.  Please see related data to support our decision:-  The study by Bruera et al. examined the effect of methylphenidate on CRF in patients with advanced cancer. Mixed types of tumors were included and the largest single group was breast cancer. Methylphenidate 5 mg or matching placebo was given on an ‘‘as needed’’ basis initiated by the patients themselves over a one-week period. The dose could be increased up to 20 mg per day by the patient, depending on response. In both groups, there was an improvement in fatigue scores measured by the FACT-F. However, no statistically significant difference was found between methylphenidate and placebo group on day 8.  Patients undergoing cranial radiotherapy with either primary or metastatic brain tumors were entered into the study of Butler et al. The dose was initiated with methylphenidate 5 mg twice daily or matching placebo and was increased to a maximum of methylphenidate 15 mg twice daily. The primary outcome was the change in fatigue score measured by the FACT-F at eight weeks after the completion of radiotherapy. There was, however, a high dropout rate over time, and the final analysis was conducted on a smaller sample size than the original one. A number of time points were examined and the fluctuation in fatigue scores was observed. However, no fatigue scores between treatment and placebo groups were significantly different at any time points.  1. Butler JM Jr, Case LD, Atkins J, Frizzell B, Sanders G, et al. (2007) A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCL in brain tumor patients receiving radiation therapy. Int J Radiat Oncol Biol Phys 69: 1496–1501 [PubMed]  2. Bruera E, Valero V, Driver L, Shen L, Willey J, et al. (2006) Patient controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 24: 2073–2078 [PubMed] |
| Prepositions  It would be more interesting to stratify patients according to the combination of treatment offered (single, double, triplet or quadruplet) and moreover to stratify them according to the disease stage based on the recent meta-analysis of Moraska AR et al (J Clin Oncol 2010;28(23):3673-3679) in order to point out which stage of pancreatic cancer would benefit from this treatment. | All the patients had stage IV disease and clarified in the revised version.  Made below changes: p3  ***Patient Population:***  We identified a total of 71 stage 4 pancreatic cancer patients who were experiencing fatigue during the treatment from June 2011 – November 2014 at our outpatient clinic as per our institutional guidelines. |
| It would be very useful to extend your study with the use of other agents (eg modafinil). (Qu D et al, Psychotropic drugs for the management of cancer-related fatigue: a systematic review and meta-analysis. Eur J Cancer Care (Engl). 2015 Oct 21). | Under discussion, p6, added below:  Scarce data is available on modafinil to ameliorate cancer-related fatigue, limited study showed negative benefit for CRF40. Also, Modafinil required high copayment and frequent insurance denials41.  Scarce data is available on modafinil to ameliorate cancer-related fatigue. Also, limited data including he study was conducted by Anna Spathis, of Addenbrookes Hospital in Cambridge, United Kingdom, and colleagues in 208 patients with stage IIIa-IV non–small cell lung cancer or recurrent disease after surgery or radiation therapy. Modaﬁnil and placebo both led to a clinically signiﬁcant improvement in fatigue scores. Scores from the Functional Assessment of Chronic Illness Therapy–Fatigue assessment scale improved from baseline to day 28 (mean score change: modaﬁnil, 5.29; placebo, 5.09), with little difference between the 2 groups [ Spathis A, Fife K, Blackhall F, et al. *(2014) Modafinil for the treatment of fatigue in lung cancer: Results of a placebo-controlled, double-blind, randomized trial. J Clin Oncol* ***32****:1882–1888.]*  In addition to the negative data, we also did not chose modafinil due to our previous experience of insurance denials or associated high copayments. One data available showed that the price for one month of modafinil is nearly $1101 [http://www.consumerreports.org/cro/2012/11/where-high-drug-costs-hide/index.htm]. |

 **In conclusion this study is very useful for publication as it shows clearly the benefit of MPH for the control of CRF in patients with advanced pancreatic cancer and secondly as it highlights a lot of interesting fields of molecular biology of cancer which possibly could lead to novel therapeutic options in pancreatic cancer patients.**

**Reviewer B**

|  |  |
| --- | --- |
| **Questions** | **Response** |
| This is an interesting retrospective study.  The number of patients is rather small and the population of patients is rather non-homogenous as they were receiving different regimens of chemotherapy causing different side effects.  Chemotherapy causes severe symptoms in patients with advanced cancer depending on the chemotherapeutic agent used. The treatment was not the same for all patients and it is reasonable to assume that the more the chemotherapeutic agents, the worse the feeling of fatigue for the patients.  Please comment on that. | Added first table  As above, we have provided sub group analysis based on chemo agents and also provide a table of chemo used and incidence of fatigue caused by them from drug insert.   |  |  | | --- | --- | | Agent | % of Fatigue associated with agent | | Gemcitabine | > 30% | | Irinotecan | > 30% | | Oxaliplatin | > 30% | | 5-FU | 10-29% | | Capecitabine | >30% | | Docetaxel | > 30% | | Nab-paclitaxel (Abraxane) | < 10% | | Cisplatin | < 10% | |
| *You should probably compare each group of patients according to the chemotherapy that were receiving (regarding fatigue and its improvement with methylphenidate. I realize this may not be possible now due to the retrospective nature of the study and the poor prognosis of the patients.* |  |
| Page 1 *line 16: associated with.*  *Page 6 line 20: were ~~on~~ receiving chemotherapy… Delete on.*  *Page 11, line 1*: *please explain here* ADHD (do not use only the abbreviation here).  *Page 11, line 2*: *HIV7?* Please correct. 7 is the reference number.  *Page 11, line 7*: Probably better: “… was associated with…”. | We made all changes. |
| Please give more details about the statistical methods used and the software used for statistics. | We calculated the percentage by simple division, no software used for statistics. |
| Please add at the end of the discussion a Summary box mentioning what is already known and what the new findings of the study are. | Last paragraph p7, modified.  In summary, MPH has been shown some mixed results in relieving CRF in mixed cancer population. Our retrospective study shows MPH is benefit in decreasing the severity of CRF and helping maintenance of chemotherapy intensity in APC patients on concomitant chemotherapy, it was well tolerated at a low but effective dose. Large, placebo-controlled prospective trial assessing the safety and efficacy of MPH are warranted in patients with APC. |
| Table 1. Please explain VAFS. Some readers read only the tables.  Table 3. This table is a little complicated but interesting. Please explain VAFS. | Added the full name before the acronym |
| Table 6. Please include the reference for the percentage of side effects in the general population. | Updated |

|  |  |
| --- | --- |
| Editor's comments: |  |
| 1. The abstract should be up to 250 words | Edited to 250 words |
| 2. Each figure and table should stand alone. | Inserted page break between |
| Legends should be more informative and all used abbreviations explained at the bottom | Added all abbreviation at the bottom. |