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# Evaluation of dosage, safety and effects of methylphenidate on posttraumatic brain injury symptoms with focus on mental fatigue and pain

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**Abstract**

Objective: The neurobehavioral symptoms and pain following traumatic brain injury (TBI) can be long-lasting. The condition impairs the persons' ability to function in their work, studies and gatherings with family and friends. The aim of this study was to investigate dosage, safety and effects of methylphenidate on mental fatigue and pain.

Methods: Twenty-nine physically-well rehabilitated, TBI victims, 28 with a mild TBI and one with TBI and also with pain in the neck, shoulders and head were included in the study. Methylphenidate was tested in each patient using three treatment strategies: no medication, low dose (5mg x 3) and normal dose (20mg x 3) for four weeks using a randomized cross-over design.

Results: Twenty-four patients completed the three treatment periods. Five participants discontinued, four females due to adverse reactions and one male due to attenuated motivation. Only minor adverse events were reported. Methylphenidate significantly decreased mental fatigue as evaluated by the Mental Fatigue Scale ($p<0.001$), and the effects on mental fatigue were dose-dependent. No effect on pain was detected.
Conclusions: Methylphenidate decreased mental fatigue for subjects suffering a traumatic brain injury, the treatment is considered to be safe and we recommend starting with a low dose.

## INTRODUCTION

Annually, about 100-300/100 000 sustain a TBI and most of the injuries are mild (1). A majority of patients recover within one to three months after a mild TBI (2, 3), but a minority will suffer from the symptoms of long-lasting post-concussion syndrome (4). Fatigue is one of the most important long-lasting symptoms interfering with the ability to work. Improvement in fatigue has been reported during the first year following TBI, after which time the improvement has been limited (5). In follow-up studies, the frequency of prolonged fatigue varies from 16 up to 73 % (6-8). Mental activities are reported to be more energy-demanding. The person is able to perform mental effort for short periods. A considerable tiredness can appear suddenly, and in that situation the affected person is not able to continue the activity. It will be too much for the person to handle and organize large amounts of information at the same time. For many persons, this mental fatigue is the dominating factor which limits the person's ability to take part in a normal life with work and social activities. Other symptoms, such as irritability, emotional instability and headache, which are common in association with the mental fatigue, further impair social interactions (9, 10). This mental fatigue is defined within the diagnosis, Posttraumatic brain injury/post-concussion syndrome (ICD10 F07.2). Long-term pain in the neck, shoulders and head may also be a prominent and disabling symptom following TBI (11).

Mental fatigue seems to depend, to some extent on attenuated attention and concentration capacity over time. It has been proposed that mental fatigue after TBI correlates to poor performance in attention tests and reduced processing speed (12-15). It is also well-known that dopaminergic and noradrenergic signaling are important as they are responsible for the performance of these functions. Methylphenidate has been used for many years and is currently mainly used in clinical practice in the treatment of ADHD in children, in the first instance to increase wakefulness, attention and concentration capacity. Methylphenidate inhibits dopamine and noradrenalin reuptake resulting in an increased extracellular concentration of dopamine and noradrenalin (16).

Methylphenidate has been tested on TBI victims with positive effects on information processing speed and, to some extent on working memory and attention (17-23). The design of these studies has varied. Patients suffering from mild or more severe brain injuries have been included. In addition, patients were included within a 3-month period following an injury and patients were also included several years after an injury. Moreover, most of the studies have been short-term studies and the effects of methylphenidate have been studied during a period of between one day and up to 6 weeks with a focus on cognitive function. Guidelines for use of methylphenidate for deficits of attention and processing speed after TBI have been suggested (24), while no such guidelines exist for fatigue or emotional symptoms following TBI.

Methylphenidate is suggested to be a safe drug for treatment of cognitive symptoms after TBI (Willmott, Ponsford, Olver, & Ponsford, 2009; Alban et al., 2004). Adverse reactions at normal therapeutic treatment, or to some extent a mild overdose, can include nervousness, insomnia, hypersensitivity, anorexia, nausea, dizziness, palpitations, headaches, dyskinesia, drowsiness, changes in blood pressure and tachycardia (16). In general, the risk for serious cardiovascular events seems low. However, caution is advised in patients with risk factors of cardiovascular disease (25).

There are, at present no studies that report on the effects of methylphenidate specifically on mental fatigue or pain following TBI. According to our clinical experience, patients with TBI report positive effects of methylphenidate. In the present study, with focus on feasibility, we tested whether methylphenidate in two different dosages was safe and would alleviate mental fatigue and pain after TBI. The importance of dosage was evaluated, as many TBI patients are sensitive to psychotropic medications (26). Safety of methylphenidate treatment in terms of general and cardiovascular side-effects, i.e. heart rate, blood pressure and electrocardiography (ECG) changes was assessed. The rationale for the inclusion of pain was to evaluate whether pain interacts with fatigue, as many patients experience both fatigue and pain after a TBI.

## MATERIALS AND METHODS

Before the start of the study, medical examination, including ECG, heart rate (HR), blood pressure (BP), body weight and general blood screening were performed on each subject.

### Inclusion criteria

1. Subjects who suffer from mental fatigue and pain due to head trauma >12 months earlier, with the intention to minimize the influence of spontaneous recovery. The participants were diagnosed with post-concussion syndrome (ICD10 F07.2). The participants were recruited from a series of referrals to by the Kungälv´s Pain Centre (27 patients), or by the Department of Neurology, Sahlgrenska University Hospital, Gothenburg (2). No specific mild head injury clinic exists in the area. 2. Age: 18 – 65. Glasgow Outcome Scale (extended) moderate disability (5 or better). 4. Subjects were reported healthy before they suffered TBI. 5. Patients were free from language and motor problems, but suffered from mental fatigue and associated post-concussive symptoms including pain in the head, neck or shoulders. 6. At study start each person had reached a steady state level concerning social and functional performance. The participants were assessed at the clinic before inclusion.

### Exclusion criteria

1. Persons, where pain was the main problem (i.e. persons with pain of other genesis as well as pain-prone persons or persons with a high degree of somatization). 2. Major psychiatric disorder such as depression (according to DSM IV) prior to the trauma and at admission. 3. Organic personality disorder or other organic CNS disorder. 4. Heavy analgesic medication with high possible risk of interaction with methylphenidate treatment such as opioids (i.e. high dose of morphine, Morphine Equivalent Daily Dose; MEDD >60mg). 5. Women of child-bearing age not on contraceptives. 6. Pregnant women. 7. Alcohol or drug abuse. 8. Untreated cardiovascular disease.

Medication that is known not to interfere with the substance tested, methylphenidate, was permitted. Such medications could include acetyl salicylic acid, lipid-lowering agents or drugs prescribed to lower blood pressure levels, routinely used non-heavy analgesics or other similar substances.

### Study design

This was an open study, on 29 subjects. All had suffered a mild TBI, except one who had suffered a moderate TBI. The subjects were randomized into three groups (Table 1). All groups received 3 treatment periods, in a balanced order according to the Latin square design. One third of the included study subjects started with a regime of no medication (Group 1).

This was referred to as “period 1”. Thereafter they were moved into “period 2” and were given methylphenidate according to a low-dose scheme. The subjects then attended “period 3” according to ordinary, standard doses. Another 1/3 of the included study subjects followed the scheme known as group 2 and the last 1/3 of the subjects followed the regime according to group 3, as shown in Table 1. According to this design, all subjects were treated as follows: 1) no active substance, 2) methylphenidate at a low dose, and 3) normal-dose methylphenidate and treatment was continued for 4 weeks in each period. Methylphenidate was gradually increased to the intended dose. Low-dose methylphenidate: Week 1: 5mg x 1; week 2: 5mg x 2; week 3 and 4: 5mg x 3. Normal dose: Week 1: 10mg x 2; week 2: 20mg+10mg+10mg; week 3: 20mg+20mg+10mg and week 4: 20mg x 3. No washout period was included as short-acting Ritalin® was used.

Table 1. Treatment of study subjects

| **Group** | **Period 1, 4 weeks** | **Period 2, 4 weeks** | **Period 3, 4 weeks** |
|---|---|---|---|
| **1** | No medication | Low dose | Normal dose |
| **2** | Low dose | Normal dose | No medication |
| **3** | Normal dose | No medication | Low dose |

Twelve of the participants were prescreened 5 to 8 months before start of the study (mean 5.7 months). They were once again screened at start of the study. Their level of mental fatigue (MFS) was, at prescreening 25.7 and at start of the study 23.9, indicating mental fatigue to be a fairly stable condition long-term after a brain injury.

The trial was conducted in compliance with the protocol, GCP and the Declaration of Helsinki. The study was approved by the Ethical Review Board in Gothenburg and the Swedish Medical Products Agency. All participants gave written informed consent before inclusion.

**Outcome measures**

The outcome measures were done at the final visit for each treatment period. Adverse events were assessed at each visit throughout the study, defined as any negative event the subject experienced during the study. Blood pressure, heart rate, and 12-lead electrocardiography (ECG) were recorded at all visits. In addition to the online ECG review made by the study team, a blinded manual ECG analysis was performed by an independent cardiologist.

The therapeutic effects of methylphenidate were measured by the Mental Fatigue Scale (MFS). Mental fatigue Scale is based on common activities and it relates the estimation to exemplified alternatives (27). The questions included in this self-assessment scale are based on symptoms described after longitudinal studies of patients with TBI, tumors, infections, vascular diseases, and other brain disorders (28-30). We also measured pain according to VAS (visual analog scale) (31). An experience of pain above 3 on VAS was considered significant pain (32). Depression and anxiety were measured according to the Comprehensive Psychopathological Rating Scale (CPRS)(33). The CPRS depression scale is identical to the Montgomery Åsberg Depression Rating Scale (MADRS) (34). The CPRS items are shown in figure 2. MADRS and BDI are highly intercorrelated and MADRS focuses on core depression symptoms and do not include fatigue (35) .

**Statistics**
A cross-over design was used and repeated treatment analysis was performed (36, 37). The analysis was done with an ANOVA for a special three-factor Latin squares design. SPSS 16.0 for Windows was used for data analysis. The Bonferroni test was used for post-hoc analysis. Bonferroni adjustment was done for multiple comparisons.

## RESULTS

**Effects on symptoms**
A total of 29 subjects were enrolled in the study and 24 completed the study. Five subjects withdrew from the study; four females due to adverse events and one man due to lack of motivation (Table 2).

Table 2. Baseline characteristics

| | Study patients | Study withdrawal |
|---|---|---|
| Number of subjects | 24 | 5 |
| Age (mean ± standard deviation/sd) | 38.6 ±11.1 | 41.8 ± 11.0 |
| Age range | 22-63 | 32-57 |
| Gender, females/males | 12/12 | 4/1 |
| Mild TBI/TBI | 23/1 | 5/0 |
| VAS below 3/VAS 3 and above* | 4/20 | 3/2 |
| Education (years ± sd) | 12.1 ± 2.1 | 12.6 ± 2.0 |
| Time since injury (years ± sd) | 8.6 ± 5.1 | 8.8 ± 4.3 |
| More than one injury | 8 | 2 |
| Full time sick leave or disability pension | 10 | 3 |
| Part time sick leave or disability pension | 7 | 2 |
| In active work (100%) | 7 | 0 |

* experience of pain above 3 on VAS was considered significant pain
sd= standard deviation
TBI= Traumatic Brain Injury
VAS= Visual Analog Scale for pain

**Mental fatigue, depression and anxiety**
Treatment with methylphenidate significantly improved mental fatigue measured by the MFS ($F=21.7$, $p<0.001$, Figure 1). There was also a significant difference due to dosage of methylphenidate on MFS, with a significant difference between no medication and low-dose treatment, between no medication and a normal dose, and also between low and normal dose. The CPRS depression ($F=8.6$, $p=0.001$) and anxiety ($F=4.9$, $p=0.010$) scales also improved significantly. Pain was not significantly changed due to treatment ($F=0.127$, $p=0.881$). The mean VAS rating was, with no medication 5.6 and with normal dose 5.2. The measurements relating to pain levels from the CPRS anxiety scale showed a similar result with no significant effect due to treatment ($F=0.325$, $p=0.723$). An experience of pain above 3 on VAS was considered significant pain (32). No significant effects were detected due to order of treatment

(no medication, low or normal dose) in any of the analyses done, indicating no carryover effect.

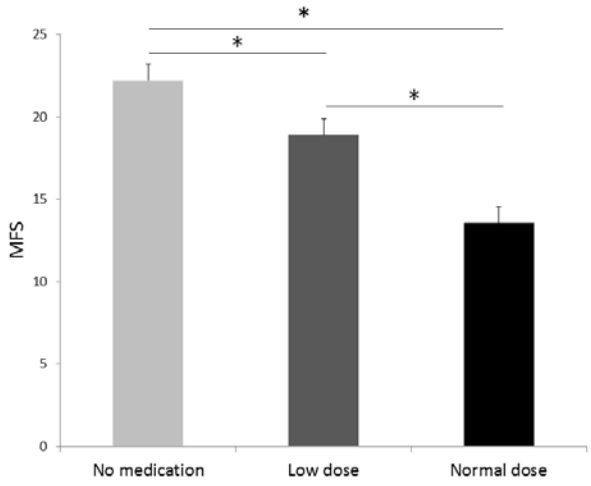


Figure 1.
The figure shows changes in Mental Fatigue Scale (MFS) due to dosing level of methylphenidate (mean ± standard error of mean, $p<0.001$); * indicates significant differences between doses according to post-hoc test, a p-value of $<0.05$ is indicated.

When analyzing single items from the three scales, symptoms connected to the MFS improved significantly with methylphenidate treatment. These items included the following: Fatigue in general, Mental fatigue, Concentration difficulties, Lack of initiative, Slowness of thinking, and Sensitivity to stress (Figure 2, Bonferroni correction was used to adjust for multiple comparisons and p-values of $<0.002$ were considered significant). As overlapping items exist and are identical in the MFS and CPRS and may confound the result, an analysis without the overlapping items (concentration difficulties, lack of initiation, irritability, and decreased sleep) was done. The result now showed a significant effect between treatments for MFS ($F=19.0$, $p<0.001$), while the significant effect was no longer present for CPRS depression ($F=2.9$, $p=0.064$) and CPRS anxiety ($F=2.4$, $p=0.10$).

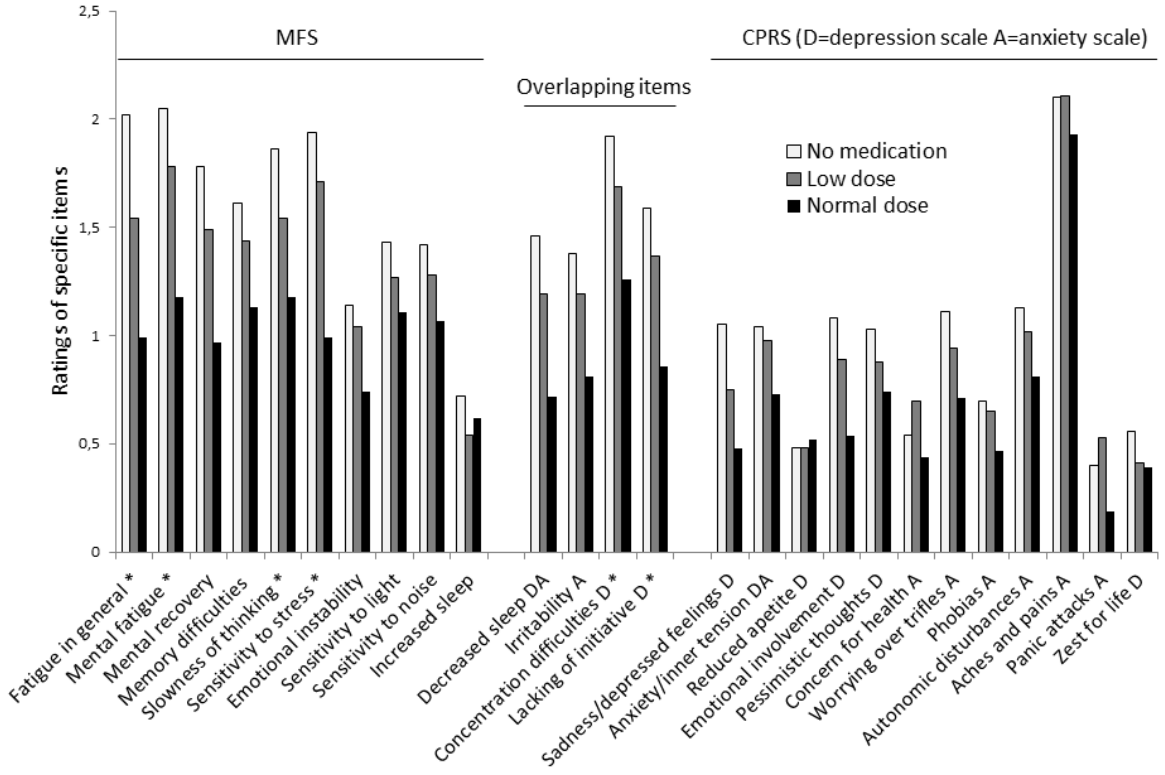


Figure 2.

Ratings of items from the Mental Fatigue Scale (MFS) and the Comprehensive Psychopathological Rating Scale (CPRS). Four items are overlapping and identical in both scales. * indicates a significant difference due to methylphenidate treatment. Bonferroni adjustment was made for multiple comparisons. After correction, the accepted p-value was set to $p<0.002$.

**Cardiovascular effects**

Seven subjects had borderline hypertension (blood pressure ≥140/90) at baseline. None of them were on pharmacological treatment. Three of these subjects increased the blood pressure during the study. Two of them started pharmacological treatment. One normalized the blood pressure and continued the study, while the other was excluded after 1 week pharmacological treatment because of hypertension. The third subject increased the blood pressure at the end of the study and never received any treatment for hypertension. One patient had at baseline pharmacological treatment against hypertension and was normotensive during the whole study.

**Electrocardiographic results**

All ECGs were manually analyzed due to incorrect computer derived annotation of interval data. Twenty-one subjects had ECGs from all study periods, including baseline. Eight subjects had missing ECGs from at least one period. Flat ST (already at baseline) in one subject and noise in other subject made QT analysis unreliable. With manual ECG analysis no

arrhythmias were observed and no significant changes in any heart-rate corrected QT intervals were detected. There was a slight, but significant, increase in HR during periods of methylphenidate treatment (Table 3). Four subjects developed supraventricular tachycardia above 100 beats per minute (102-111 bmp) during treatment with methylphenidate. Two of these subjects developed slight (<1mm), non-symptomatic, ST depression. Morphology at baseline was within normal limits without clinical significance. Two subjects underwent normal ergometer bicycle test, one of them due to flat T-wave which hampered measurement of QT-time and the other one had high ST junction (both already at baseline).

Table 3. Cardiovascular effects (mean and standard deviation).

| | No treatment | Low dose | Normal dose | F-value | p-value |
|---|---|---|---|---|---|
| Body weight (kg) | 85±18 | 85±19 | 85±18 | 0.016 | 0.984 |
| Systolic blood pressure | 127±14 | 127±13 | 131±12 | 0.629 | 0.537 |
| Diastolic blood pressure | 77±10 | 78±9 | 80±7 | 0.580 | 0.563 |
| Heart rate | 72±12 | 71±10 | 81±15 | 4.635 | 0.013 |

**Safety**

Methylphenidate was well-tolerated by 86 % of subjects (25/29). Four women withdrew from the study due to adverse effects. These subjects did not experience positive effects of any significance. The adverse effects reported for these subjects included high blood pressure, depressive mood, anxiety, increased heart rate and fatigue. One or more adverse events were reported for four subjects receiving a low dose and 16 subjects on the normal dose. Adverse events among those who completed the study were reported as mild and were reversible after a dose decrease. The most commonly reported adverse events were restlessness, anxiety, headache, and increased heart rate (Table 4). No serious adverse events were reported. A significant increase in heart rate was detected, while no changes in body weight or blood pressure were detected during treatment with methylphenidate (Table 3).

Table 4.
Number of reported adverse events (the number of subjects who reported adverse reactions is given in brackets). Thirteen subjects did not report any adverse events and 16 reported one or more adverse events.

| **Adverse events** | Withdrawn (n=4) | No effect of methylphenidate (n=3) | Positive effect of methylphenidate (n=9) |
|---|---|---|---|
| Restlessness | 1 | 1 | 4 |
| Anxiety | 2 | | 2 |
| Headache | 1 | 1 | 1 |
| Tachycardia | 2 | | 2 |
| Hypertension | 2 | | 1 |
| Hand tremor | 1 | 1 | 1 |
| Dry mouth | 1 | | 1 |
| Depressed mood | 2 | | |
| Aggression | | 1 | |
| Irritability | | | 1 |
| More emotional | | | 1 |
| Fungal infection in the | | | 1 |

| | | | |
|---|---|---|---|
| mouth | | | |
| Lump-like sensation in the throat | 1 | | |
| Concentration difficulties | | 1 | |
| Fatigue | 1 | | |
| Paraesthesia of the skin | 1 | | |
| Muscle twitches | | 1 | |

## DISCUSSION

### Clinical effect

Methylphenidate significantly improved mental fatigue as assessed with MFS. The effect of treatment was dose-dependent; the most prominent effect with methylphenidate was found for MFS at a normal dose with a regime of 20 mg three times/day. A significant improvement was also detected between no medication and a low dose and between a low and normal dose, showing a dose-dependent effect. The rating on MFS decreased from 22 points with no medication to 14 points with methylphenidate at a normal dose. In comparison, healthy controls reported a MFS rating of about 4.5; this rating was never above 10 points (10). In addition, methylphenidate has previously been reported to improve performance at work and school for patients with chronic difficulties following a severe TBI (38).

Methylphenidate also improved depression and anxiety as assessed with the CPRS. However, when the overlapping items were excluded from the CPRS depression and anxiety scales, no significant effect remained for the CPRS depression and anxiety scales. In previous studies, methylphenidate has been reported to have a positive effect on mood and depression following TBI (38, 39), and methylphenidate and sertraline administered early after TBI had a positive effect on depressive symptoms, while methylphenidate had a positive effect on daytime sleepiness and cognitive functioning (39). However, the item, fatigue was not considered in these studies. Since depression, anxiety and mental fatigue can appear after a TBI, either in isolation, or simultaneously, it is necessary to include fatigue as an important factor, and also to examine these as separate items from the assessment scales. The reason for this is that overlapping symptoms can confound the interpretation of the result.

The item, pain was rated high by most of the subjects in this study. However, no significant changes were reported for pain levels as a result of methylphenidate treatment, neither on VAS nor from the pain rating on the CPRS anxiety scale. However, it is important to note that pain can hide posttraumatic brain injury symptoms which are not always connected to the pain itself. This was detected for many of the participants in this study. We also found that pain did not interact with mental fatigue when the participants were treated with methylphenidate. These findings indicate the need to treat patients, not only for the pain they primarily are referred to the clinic for, but also for mental fatigue and post traumatic brain symptoms if these symptoms are present.

### Safety

Methylphenidate was well-tolerated by 86 %. A significant increase in heart rate was found. No significant changes in blood pressure or QT intervals. Four women (14 %) were withdrawn from the study due to adverse effects. This is in accordance with previous reports

with methylphenidate treatment for TBI symptoms. The safety issue with methylphenidate for moderate to severe TBI subjects was evaluated following a two-week study design (40). The participants were inpatients with a mean post-injury time of 68 days. In their study, it was concluded that methylphenidate was a safe drug, with side-effects within the mild range. Slight increase in pulse, diastolic blood pressure and mean arterial pressure were reported. Alban and co-authors also reported methylphenidate to be a safe drug for use in adults who had suffered a moderate to severe TBI at least 3 months prior to enrolment. Poor appetite was the only significant adverse effect reported by them. Increases blood pressure and heart rates were relatively insignificant. One woman withdrew due to adverse effects (17). According to the results in the present study and our clinical routine it is feasible to use regular 12-lead ECG assessments.

The safety of the extended-release formulation of methylphenidate used in ADHD adults was extensively reported by Adler and co-authors (41).There were a number of subjects (14.5 %) who were withdrawn from their study due to adverse events. They further concluded that methylphenidate was well-tolerated and no serious adverse events were reported. Most of the adverse events were mild or moderate in intensity. Adverse events that led to discontinuation included irritability, increased blood pressure, anxiety, and depressed mood. These results conform to our results. Furthermore, cohort studies reported no increased risk of serious cardiovascular events among adults up to 64 years of age with ADHD being treated with methylphenidate (42).

**Limitations**

One major limitation was the lack of a placebo-controlled treatment. However, in the present feasibility study, we first wanted to evaluate dosage and safety before doing a placebo controlled study, as many TBI patients are sensitive to psychotropic medications (26). Our study had a small sample size and was performed during a short period, and is considered to be a hypothesis generating study. Further analysis needs to be carried out to determine the long-term effects and possible adverse effects. It will also be important to analyze social and quality of life effects methylphenidate may have for subjects treated over a longer period.

**Conclusion**

Methylphenidate was well-tolerated by TBI subjects. No major adverse effects and no cardiovascular effects were detected in the present study. We detected a dose-response effect and the normal dose had the best effect on mental fatigue for most of the participants. However, tolerance of methylphenidate differed between subjects and we recommend starting with a low dose. Further placebo-controlled studies of a longer duration are warranted.

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**Declaration of interest**

The authors report no declarations of interest.

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