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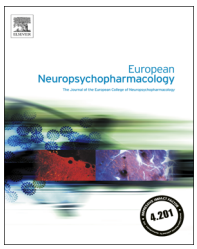

Rapid response to methylphenidate as an add-on therapy to mirtazapine in the treatment of major depressive disorder in terminally ill cancer patients: A four-week, randomized, double-blinded, placebo-controlled study

Ng Chong Guan[a,b,*], **Marco P.M. Boks**[a,c], **Kit C.B. Roes**[a], **Nor Zuraida Zainal**[b], **Ahmad Hatim Sulaiman**[b], **Tan Seng Beng**[d], **Niek J. de Wit**[a]

[a]*Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht, the Netherlands*
[b]*Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[c]*Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre, Utrecht, The Netherlands*
[d]*Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia*

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Abstract
This is a 4 week, randomized, double-blind, placebo-controlled study to examine the effects of methylphenidate as add-on therapy to mirtazapine compared to placebo for treatment of depression in terminally ill cancer patients. It involved 88 terminally ill cancer patients from University of Malaya Medical Centre, Kuala Lumpur, Malaysia. They were randomized and treated with either methylphenidate or placebo as add on to mirtazapine. The change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 3 was analyzed by linear regression. Changes of MADRS and Clinical Global Impression-Severity Scale (CGI-S) over 28 days were analyzed using mixed model repeated measures (MMRM). Secondary analysis of MADRS response rates, defined as 50% or more reduction from baseline score. A significantly larger reduction of Montgomery-Åsberg Depression Rating Scale (MADRS) score in the methylphenidate group was observed from day 3 (B=4.14; 95% CI=1.83–6.45). Response rate (defined as 50% or more reduction from baseline MADRS score) in the methylphenidate treated

*Corresponding author at: Department of Psychological Medicine, University of Malaya Medical Centre, Lembah Pantai, 59100 Kuala Lumpur, Malaysia. Tel.: +6 3 79492068; fax: +6 3 79556477.
E-mail address: chong_guan1975@yahoo.co.uk (C.G. Ng).

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group was superior from day 14. Improvement in Clinical Global Impression-Severity Scale (CGI-S) was greater in the methylphenidate treated group from day 3 until day 28. The drop-out rates were 52.3% in the methylphenidate group and 59.1% in the placebo group (relative risk=0.86, 95%CI=0.54–1.37) due to cancer progression. Nervous system adverse events were more common in methylphenidate treated subjects (20.5% vs 9.1%, $p=0.13$). In conclusions, methylphenidate as add on therapy to mirtazapine demonstrated an earlier antidepressant response in terminally ill cancer patients, although at an increased risk of the nervous system side effects.

1. Introduction

Terminally ill cancer patients experience a lot of distress and psychological suffering, due to physical symptoms and the poor prognosis (Kadan-Lottick et al., 2005; Miovic and Block, 2007; Ng et al., 2011; Tan et al., 2012). As a result depression is highly prevalent in cancer patients, especially in the terminal disease stage (Kadan-Lottick et al., 2005; Miovic and Block, 2007). According to a recent systematic review, there were as many as 10.8% of patients with cancer suffer from depression (Ng et al., 2011). Given the reduced life expectancy of many patients with cancer, fast onset of antidepressant treatment is desirable, especially in the final phase of life. The few randomized trials that assessed the effectiveness and tolerability of antidepressant treatment concluded that the practical use of conventional antidepressants in cancer patients with depression is hampered by the slow response (Rodin et al., 2007).

Methylphenidate, with its relatively rapid onset of action, was suggested as for augmentation of antidepressant treatment in cancer patients (Masand and Tesar, 1995; Challman and Lipsky, 2000; Rozans et al., 2002; Kaminski and Sjogren, 2007) and is currently used in some hospitals for the treatment of depression in terminally ill patients (Huffman and Stern, 2004; Lee et al., 2012).

However, solid evidence for the efficacy of methylphenidate as an antidepressant agent in terminally ill cancer patients is lacking. In a randomized placebo-controlled trial, Wallace et al. demonstrated a rapid improvement of depression in medically ill patients treated with methylphenidate (Wallace et al., 1995). However, interpretation of this study is hampered by the small sample size (16 subjects only) and the short observation period (8 days) (Wallace et al., 1995). Five other non-controlled, open label studies showed a positive effect of methylphenidate on depression in cancer patients (Fernandez and Adams, 1986; Fernandez et al., 1987; Olin and Masand, 1996; Macleod, 1998; Homsi et al., 2001). More evidence regarding both efficacy and tolerability of methylphenidate in cancer patients is needed before implementation in clinical practice can be recommended (Hardy, 2009).

We present the results of a randomized, double-blind, placebo-controlled study of methylphenidate as add on therapy to mirtazapine in the treatment of depression in terminally ill cancer patients. We hypothesize that patients treated with mirtazapine (MTZ) and methylphenidate (MPH) (MTZ+MPH) would have earlier antidepressant response as compared to those receiving mirtazapine and placebo (MTZ+PBO).

2. Experimental procedures

2.1. Study design

We conducted a 4 week, randomized, double-blind, placebo-controlled study between Mac 2011 and June 2012.

2.2. Subjects

We included men and women, 18 years of age and above, with any type of cancer under palliative care in the terminal disease phase (defined as an estimated life expectancy of less than 3 months as judged by the treating physician) at the University Malaya Medical Centre (UMMC). They were under in or outpatient care of either the oncology or surgery departments or the palliative care unit. Patients referred to psychiatric consultancy services who received a primary diagnosis of major depressive disorder as defined in the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition (DSM IV) were approached for participation.

2.3. Ethics

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Medical Ethics Committee of UMMC and all participants provided written informed consent. The trial was registered with ClinicalTrial.gov (ClinicalTrial.gov identifier: NCT01497548).

2.4. Procedures

Before inclusion, eligible patients were interviewed by a consultant psychiatrist (Ng CG) to confirm the DSM-IV based diagnosis of major depressive disorder using the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998). Patients were excluded if they had other co-morbid psychiatric diagnoses, or if they were already treated with antidepressants.

Patients were randomly assigned to either methylphenidate or placebo as add-on therapy to mirtazapine in a ratio of 1:1. A computer-generated table of random numbers (block of 8) was prepared (by AHS) using the Randomization.com program. Patients, researchers and medical staff remained blind to treatment for the duration of the trial.

Patients received a fixed dosage of mirtazapine (30 mg at 10 pm) throughout the entire study period, in line with recommendations (Riechelmann et al., 2010). Methylphenidate was initially dosed at 5 mg twice daily (8 am and 12 noon), but the protocol allowed one dosage increase to 10 mg twice daily from day 3 onwards at the discretion of the treating physician. The placebo treated group were given a twice-daily dosage and allowed adjustment as the methylphenidate treated group. All study medication was handed out by double-dummy administration to maintain blinding: that is,

patients received sealed capsules of identical color and shape twice daily.

Outcome was assessed by a consultant psychiatrist (Ng CG) at baseline (day 1) and at six subsequent follow-up visits during the double-blind treatment period: at day 3, 6, 9, 14, 21 and 28.

2.5. Outcome measures

The primary outcome was the change in depression score at day 3, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). Secondary outcomes were the percentage of patients with a positive response (defined as $\geq$50% reduction of MADRS score from baseline) and the change in Clinical Global Impression-Severity scale (CGI-S).

2.6. Measurements

The MADRS is a clinician-rated scale for the assessment of depression. It consists of 10 items that measure the symptoms of depression. Nine of the items are based on the patient's report, and one (apparent sadness) is based on external observation of the patient. Individual items of the MADRS are rated on a 0–6 scale (0=no abnormality, 6=severe). A decrease in MADRS score indicates improvement in depressive symptoms (Montgomery and Asberg, 1979).

The CGI-S scale is a single-item, clinician-rated scale that reflects global severity of illness at the time of assessment. Scores can range from 1 (normal, not ill at all) to 7 (most extremely ill) (Guy, 1976).

2.7. Safety and tolerability

Safety was assessed on the basis of adverse events (observed by the clinicians or reported by patients) that occurred from the start of treatment until 14 days after cessation of treatment.

2.8. Analyses

Based on the initial power calculation, 120 subjects (60 subjects per group) were required for the study to obtain an effect size of 0.5 with a power of 0.8 (O'Keefe, 2007). However, recruitment was stopped after 88 subjects (44 per group) in accordance with the pre-defined end of the inclusion period.

The analyses were done on a modified intent-to-treat (ITT) basis. All randomized patients with baseline assessment who had at least one follow-up visit were included in the efficacy analyses. Patients who received at least one dose of the study drug were included in the safety analysis.

In the primary analysis, we compared the changes in MADRS score from baseline to day 3 between the treatment and control group using linear regression analysis, with the baseline MADRS and gender as a covariate. For the analysis of MADRS score changes in subsequent visits, we used a mixed model for repeated measures (MMRM). By using MMRM, measurements at irregular time points could be included and drop-out during follow-up could be handled effectively under a missing at random assumption. We used least squares means to estimate the treatment effects from the MMRM analysis using an unstructured covariance model. In the model, fixed effects included treatment, visit and treatment by visit interaction.

As secondary outcome, we analyzed the positive response rate (defined as 50% or more reduction from baseline MADRS scores) (Fantino and Moore, 2009) using Pearson's χ^2 test. The differences of the least square mean changes of MADRS and CGI-S scores between the two groups were analyzed using the nlme package in (Pinheiro et al., 2012).

Effect sizes for MTZ+MPH vs MTZ+PLB were calculated for change in MADRS score from baseline to day 28 using Cohen's *d*-statistic.

Treatment-related adverse events in the two groups were described and categorized according to the body system. The risk difference was evaluated with Pearson's χ^2 analysis. The number of drop outs in each group was determined. The time to discontinuation was calculated and analyzed using Kaplan-Meier Survival analysis. The difference in time to discontinuation between groups was assessed using the Log Rank test in Kaplan-Meier analysis with intervention as the factor.

3. Results

Of the 104 patients that were approached and screened, 6 refused to participate and 10 were excluded (6 because they were too ill to participate and 4 because they were on antidepressant treatment). A total of 88 cancer patients with depression in the terminal disease stage were randomly assigned to double-blind treatment with either methylphenidate (n=44) or placebo (n=44) as add on to mirtazapine (see Figure 1). Table 1 shows the baseline demographic and clinical characteristics of these patients. Excluding breast cancer, there were no statistical differences in the type of cancer between the sexes (p=0.414).

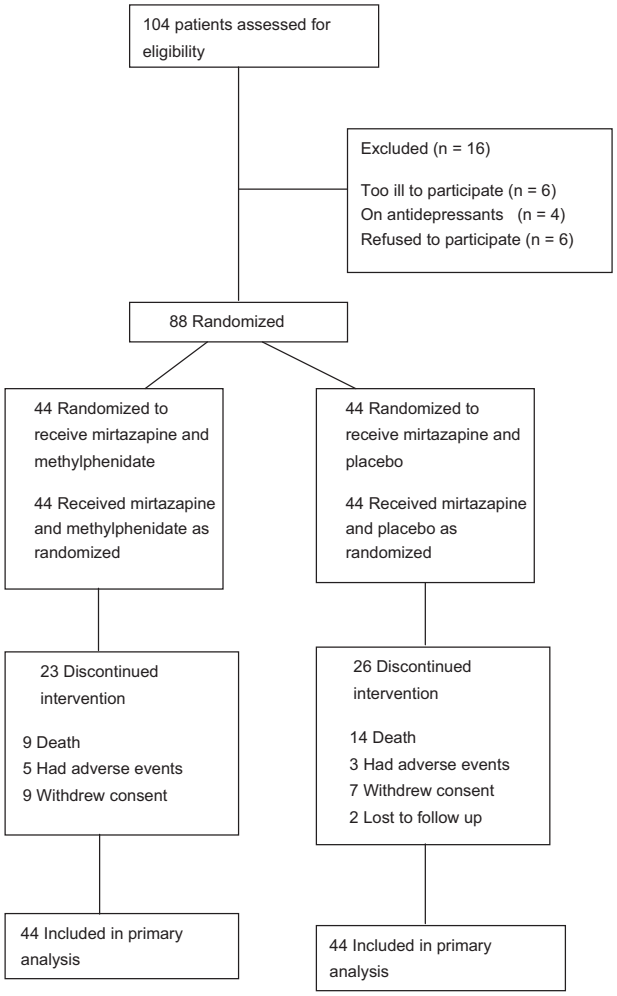

Figure 1 Flow chart of the patients randomised in the study.

All patients that received at least one dose of the study treatment were included in the analysis. 21 (42%) patients in the MTZ+MPH group and 18 (41%) patients in the MTZ+PLB group completed the study ($p=0.52$). Reasons for cessation in the two groups were death [MPH group=9 (20.5%) vs PLB group=14 (31.8%)], adverse events [MPH group=5 (11.4%) vs PLB group=3 (6.8%)] and withdrawn consent [MPH group=9 (20.5%) vs PLB group=7 (15.9%)]

Table 1 Baseline demographics and clinical characteristics of the randomized patients.

Characteristics	MTZ+MPH (*N*=44)	MTZ+PLB (*N*=44)
Male, *n* (%)	10 (23)	20 (46)
Age (years), mean (SD)	59.52 (11.3)	55.89 (11.5)
Etnicity, *n* (%)		
Malay	12 (27.3)	10 (22.7)
Chinese	24 (54.5)	28 (63.6)
Indian	5 (11.4)	5 (11.4)
Other	3 (6.8)	1 (2.3)
Single, *n* (%)	3 (7.0)	6 (13.6)
Inpatient, *n* (%)	37 (84.1)	37 (84.1)
Type of cancer, *n* (%)		
Breast	20 (45.5)	14 (31.8)
Upper gastrointestinal	2 (4.6)	5 (11.3)
Colorectal	1 (2.3)	8 (18.3)
Renal	2 (4.5)	2 (4.5)
Pancreas	4 (9.1)	2 (4.5)
Bone	2 (4.5)	3 (6.8)
Urinary tract and prostate	3 (6.8)	3 (6.8)
Uterine, cervical and ovarian	4 (9.1)	1 (2.3)
Other	6 (13.6)	6 (13.7)
Mean (SD) of baseline depression score		
MADRS	31.89 (6.24)	32.25 (6.14)
CGI-S	4.39 (0.75)	4.43 (0.90)

MTZ=mirtazapine, MPH=methylphenidate, PLB=placebo, MADRS=Montgomery-Åsberg Depression Rating Scale, DT=distress thermometer, CGI-S=clinical global impression-severity scale.

4. Dosage of study medication

All subjects received fixed doses of mirtazapine (30 mg at 10 pm) throughout the study period. In addition they received either methylphenidate starting 10 mg/day or placebo in divided doses.

On day 3, there were equal numbers of patients with dosage increases in the active drug and placebo arms (4/42 in placebo group and 4/41 in methylphenidate group). At follow-up more subjects in the placebo arm required dosage increase. On day 6, 10 out of 33 (30.3%) subjects in the placebo arm required an increase in dosage compared to 7 out of 35 (20.0%) in the methylphenidate arm. On day 28, 5 out of 15 (33%) of the placebo treated subjects were received an increased placebo dose, while only 6 out of 22 (27.3%) methylphenidate treated patients required the 20 mg/day dose.

5. Effectiveness: primary outcome

The MADRS scores at baseline did not differ between the patients in the MTZ+MPH group (31.89, SD=6.24) and MTZ+PLB group (32.25, SD=6.14). The mean reduction of MADRS score from baseline on day 3 was 5.29 (SD=5.20) for the MTZ+MPH group and 1.02 (SD=5.5) for the MTZ+PLB group. Based on linear regression analysis, this estimated difference in mean was was 4.14 (95% CI=1.83-6.45).

Patients in MTZ+MPH group had a greater reduction in MADRS scores at day 28 (the differences of the least square mean changes of MADRS between groups=6.28, $p<0.01$). Differences in MARDS score between the active and the placebo group were significant from Day 3 (difference=−4.87, 95% CI=−2.04,−7.70) (Table 2). As a result, the effect size for changes in MARDS scores from baseline to day 28 (ITT, LOCF) was greater for MTZ+MPH group (0.54) compared to MTZ+PLB (0.16) ($p<0.01$).

Sub-analysis of the individual items in MADRS, demonstrated that improvement was not restricted to somatic symptoms (see Supplementary Table 1).

Table 2 Mean change of MADRS and CGI-S score over 28 days, difference between groups (MTZ+MPH, *N*=44 vs MTZ+PLB, *N*=44). IIT, MMRM analysis.

	MTZ+MPH		MTZ+PLB		Δ MADRS		Δ CGI	
	MADRS Mean (SD)	CGI Mean (SD)	MADRS Mean (SD)	CGI Mean (SD)	Wald	*P*	Wald	*p*
Baseline	31.89 (6.24)	4.39 (0.75)	32.25 (6.14)	4.43 (0.90)	-	-	-	-
Day 3	26.12 (7.56)	3.76 (0.73)	31.24 (7.18)	4.26 (0.99)	−3.39	<0.01	−2.50	0.01
Day 6	20.85 (6.54)	3.15 (0.74)	29.39 (7.47)	3.91 (1.09)	−5.29	<0.01	−3.52	<0.01
Day 9	19.13 (6.91)	3.06 (0.81)	27.63 (7.93)	3.93 (1.14)	−5.24	<0.01	−3.67	<0.01
Day 14	18.41 (7.12)	3.03 (0.94)	26.69 (8.07)	3.72 (1.14)	−5.15	<0.01	−3.39	<0.01
Day 21	17.78 (8.27)	2.91 (1.08)	25.50 (8.27)	3.55 (1.19)	−5.16	<0.01	−3.24	<0.01
Day 28	15.86 (6.65)	2.57 (0.87)	26.73 (8.45)	3.53 (1.25)	−6.28	<0.01	−4.19	<0.01

MMRM=mixed model repeated measures, ITT=intention to treat, SD=standard deviation, MTZ=mirtazapine, MPH=methylphenidate, MADRS=Montgomery-Åsberg Depression Rating Scale, CGI-S=clinical global impression of severity, Δ=the differences of the least square mean changes of MADRS and CGI between the two groups analyzed using the nlme package in R.

Table 3 Number of responders in time in the placebo and intervention group (MTZ+MPH, $N=44$ vs MTZ+PLB, $N=44$).

Intervention	Responders, *N* (%)		RR	95% CI	*p* Value
	Yes	No			
Day 3					
MTZ+MPH	1 (2.3)	43 (97.7)	-	-	1.000[a]
MTZ+PLB	0	44 (100.0)			
Day 6					
MTZ+MPH	3 (6.8)	41 (93.2)	1.049	0.957-1.150	0.616[a]
MTZ+PLB	1 (2.3)	43 (97.7)			
Day 9					
MTZ+MPH	9 (20.5)	35 (79.5)	1.171	0.988-1.388	0.062
MTZ+PLB	3 (6.8)	41 (93.2)			
Day 14					
MTZ+MPH	13 (29.5)	31 (70.5)	1.323	1.075-1.627	0.006
MTZ+PLB	3 (6.8)	41 (93.2)			
Day 21					
MTZ+MPH	13 (29.5)	31 (70.5)	1.29	1.043-1.597	0.015
MTZ+PLB	4 (9.1)	40 (90.9)			
Day 28					
MTZ+MPH	12 (27.3)	32 (72.7)	1.25	1.020-1.532	0.027
MTZ+PLB	4 (9.1)	40 (90.9)			

Response is defined as 50% or more reduction from baseline MADRS score, MTZ=mirtazapine, MPH=methylphenidate, PLB=placebo, CI=confidence interval, RR=relative risk.
[a]Fisher's Exact test.

6. Secondary outcome

The number of responders differed between groups from day 9 onwards. At day 9, nine subjects who received MTZ+MPH had more than 50% reduction from baseline MADRS score compared to three subjects in the MTZ+PLB group (20.5% vs 6.8%, $p=0.062$). On day 14, 13 subjects receiving MTZ+MPH met response criteria compared to three in the MTZ+PLB group (29.5% vs 6.8%, $p=0.006$). By day 28, the MTZ+MPH group had a significantly higher proportion of responders compared to the MTZ+PLB group (27.3% vs 9.1%, $p=0.027$) (Table 3).

There were also significant differences in the changes of CGI-S score between groups from day 3 until the end of study. Within the MTZ+MPH group, effect size changes from baseline to endpoint (ITT, LOCF) were significantly greater at 0.45 compared to 0.13 in the MTZ+PLB group.

6.1. Safety and tolerability

Adverse events were reported in 15 (34.1%) patients in the MTZ+MPH group and 12 (27.3%) patients in the MTZ+PLB group (relative risk, RR=1.103, 95% CI=0.835-1.459).

Adverse events of the nervous system (psychosis, agitation, insomnia, tremor and seizure) were more frequently seen in MTZ+MPH group (9/44 patients versus 4/44) (Table 4). Given the heterogeneity in cancer type and treatment treatments, no conclusion can be drawn about the origin of nervous system adverse events.

Most of the adverse events were mild (55.6%) or moderate (37.0%). All severe side effects (7.4%) could be adequately managed in clinical practice following standard procedures. No adverse effect related deaths were reported.

6.2. Discontinuation

There was a high drop-out rate in the study. 23 (52.3%) subjects in the MTZ+MPH group and 26 (59.1%) subjects in the MTZ+PLB group did not complete the study. The difference was not statistically significant (RR=0.857, 95% CI=0.535−1.373). The median time to discontinuation was 21 days for the MTZ+MPH group and 20 days for the MTZ+PLB group. Log Rank (Mantel-Cox) analysis showed that the difference was not statistically significant ($\chi^2=0.855$, $p=0.355$).

The most common cause of discontinuation was death: 23 (26.1%) of the patients passed away during the study period. There were 9 (39.1%) deaths in the MTZ+MPH group and 14 (53.8%) deaths in the MTZ+PLB group. The difference was not statistically significant ($p=0.225$). There was no gender difference in the death rate (male=33.3% vs female=22.4%, $p=0.269$).

The second most common cause of discontinuation was neuropsychiatric symptoms. 5 patients stopped treatment in the MTZ-MPH group due to seizure, agitation, insomnia, psychosis and confusion whereas three patients in the MTZ+PLB group dropped out due to headache, confusion and psychosis. The difference was not statistically significant (Fischer's Exact test=0.713, $p=0.357$). The remaining subjects dropped-out due to other diverse reasons mostly attributable to their deteriorating medical condition. The decision to discontinue treatment was made by the treating physician in all cases.

Table 4 Incidence of adverse events during treatment ($N=27$).

	MTZ+MPH ($N=44$) n (%)	MTZ+PLB ($N=44$) n (%)	RR	95% CI	p value[a]
Death	9 (39.1%)	14 (53.8%)	1.815	0.689-4.783	0.225
General					
Fever	1 (2.3)	1 (2.3)	0.951	0.833-1.086	0.458[b]
Headache	-	2 (4.5)			
Pain	2 (4.5)	1 (2.3)			
Sepsis	-	1 (2.3)			
Digestive system					
Stomach complaints	2 (4.5)	-	1.024	0.924-1.135	0.645[b]
Diarrhea	-	2 (4.5)			
Vomiting	1 (2.3)	-			
Cardiovascular system					
Hypotension	-	1 (2.3)	-	-	-
Nervous system					
Giddiness	2 (4.5)	2 (4.5)	1.143	0.958-1.364	0.133
Confusion	1 (2.3)	1 (2.3)			
Psychosis	2 (4.5)	1 (2.3)			
Agitation	1 (2.3)	-			
Insomnia	1 (2.3)	-			
Tremor	1 (2.3)	-			
Seizure	1 (2.3)	-			

Percentage is based on the number of subjects in each group ($n=44$).
CI=confidence interval, RR=relative risk.
[a] χ^2 analysis.
[b] Fisher's Exact test.

7. Discussion

The results of this double blind placebo controlled randomized trial demonstrate that addition of methylphenidate to standard treatment of depression in terminally ill cancer patients improves antidepressant response as from the third day of treatment onwards, and results in clinically significant improved response rate from second week onwards. This rapid onset of antidepressant action is of major benefit in clinical practice, particularly in terminal cancer patients with a limited life expectancy. Our study therefore provides a rational for adding methylphenidate to traditional antidepressants in clinical situations where rapid antidepressant response is required.

Although our study included only terminal patients with cancer, the application of methylphenidate in clinical practice may extend beyond cancer patients. Earlier small-scale randomized controlled studies and case studies also reported a positive effect of the use of methylphenidate in terminally ill elderly without cancer with refractory depression (Wallace et al., 1995; Bader et al., 1998; Homsi et al., 2001; Lavretsky et al., 2006; Buhagiar and Cassar, 2007).

The question remains whether the effectiveness is restricted to an enhancing effect to conventional antidepressants, or that methylphenidate may also be effective as a single agent in patients with depression in the terminal phase of life. A previously reported randomized controlled trial demonstrated an enhanced antidepressant effect of methylphenidate as add on therapy to citalopram for elderly non-cancer patients (Bader et al., 1998; Buhagiar and Cassar, 2007; Lavretsky et al., 2006). Some case studies report that methylphenidate augments the effect of other antidepressants or is effective as a single agent in the treatment of depression in the terminal stage cancer patients (Homsi et al., 2000). Well designed and larger scale studies are needed to establish the effectiveness of methylphenidate as a single agent in terminally ill patients with depression.

Although in terminally ill patients the rapid antidepressant action may outweigh the risk of emergent adverse events, there is concern about treatment-related adverse effects in the use of psychostimulants such as methylphenidate (Hardy, 2009). Nervous system related incidents such as psychosis, agitation, seizure, tremor and insomnia are known side effects of psycho-stimulants. In the current study, the risk of treatment-emergent adverse events did not differ between the methylphenidate and the placebo group. This is consistent with the recent systematic review on the use of methylphenidate in the treatment of cancer related fatigue (Minton et al., 2011). However, the absence of a significant increase in adverse events may have been related to the small number of patients. Although methylphenidate can be discontinued at the emergence of side-effects, the impact may potentially be harmful. This is of particular concern in patients with a history of epilepsy or those with preexisting psychosis (Tan and Appleton, 2005; Kraemer et al., 2010). A potential side effect of methylphenidate that we could not take into account is the presence of the rebound phenomenon (Carlson and Kelly, 2003; Cox et al., 2008). Some studies suggest that treatment for a period of months may lead to loss of efficacy or even rebound effects (Carlson and Kelly,

2003; Cox et al., 2008). In terminally ill patients this is unlikely to be a problem.

The results of our study should be interpreted in the light of a number of limitations that are related to the patient group under study. The first one is the high discontinuation rate. Death due to cancer progression was the most common cause of this. Intrinsic in palliative care research is the fact that patients have limited life expectancy, and RCT's in this patient group will always face this limitation (Wilkinson, 1999). At the same time the high death rate in palliative care patients underlines the need for an early antidepressive response and the relevance of methylphenidate co-treatment. As death rates in the methylphenidate and placebo group were comparable we do not believe this affected study outcome. Particularly because the main outcome of this study was antidepressive response of methylphenidate at day three which is well before the large dropout due to death emerges. However, both groups were treated with mirtazapine with its own side effects, among which the impact on mortality remains unknown. Other limitations are that the diagnosis of depression in terminally ill patients may be criticized for the overlap with somatic symptoms such as fatigue, lack of concentration, poor appetite and weight loss (Massie and Popkin, 1998; Cochinov, 2001). We did not reach the preset sample size before the end of the inclusion period, due to the fact that inclusion of these seriously ill patients in their last phase of life is challenging. Local context and family support are other important factors influencing the outcome of depression in palliative cancer patients and they were not being taking into account in the current study (Aishvarya et al., 2013; Maniam et al., 2013; Nik Jaafar et al., 2013). A final limitation is that despite the randomization, the gender distribution in the two groups was skewed: males were over-represented in the placebo group. This may have caused unequal distribution of cancer type and survival in the two groups and there may be differences in efficacy of mirtazapine between sexes. There is however no indication this has affected our results as there were no statistical significant differences in the death rate and cancer type between genders in the current study, and statistical analysis included gender as a covariate.

Given their short life expectancy terminally ill cancer patients need a rapid symptomatic relief of their depression. Overall these results provide evidence that methylphenidate addition can rapidly improve depressive symptoms (Bader et al., 1998; Buhagiar and Cassar, 2007; Lavretsky et al., 2006). We recommend clinical application of methylphenidate as add on therapy in terminal patients with cancer. However, in view of the physical frailty of the terminally ill cancer patient, there is always potential risk of emergent adverse events with the additional treatment of antidepressant or stimulant. It is important to consider the risk-benefit balance when instituting intervention in this group of cancer patients. Further research is needed to establish its effectiveness as a single agent and other treatment domains beyond terminal cancer.

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Contributors

Author NCG, MPMB, AHS, NZZ and NJW designed the study and wrote the protocol. Author NCG, TSB, MPMB and AHS managed the literature searches and analyses. Authors NCG, MPMB and KCBR undertook the statistical analysis, and author NCG wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors have no conflict of interest

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Appendix. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2014.01.016.

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