Methylphenidate (Ritalin) and other psychostimulants in adults and the elderly

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Executive Summary

This is an abstract of the literature on the use of psychostimulants to treat psychiatric conditions in adults and the elderly. The results are presented primarily in two sections: the first section reports on studies in which psychostimulants, primarily methylphenidate (MPH) were used as first-line therapy or monotherapy. This section is broken down into five tables: randomized controlled trials; open label trials; case series, retrospective chart reviews, and case reports. The subsequent section lists studies of psychostimulants used as adjunctive therapy, usually as add-ons to either conventional antidepressants or the newer SSRIs and SNRIs.

While the mechanism of action of psychostimulants in treating depression or depressive symptoms such as apathy remains speculative, my hypothesis is that the effect of psychostimulants on reducing sleep, and especially reducing REM sleep when given early in the morning, is responsible for improving depressive symptoms. There is a considerable body of literature on the use of sleep deprivation or partial sleep deprivation to treat depression (please see the talks I have given on this topic, eg: http://henry.olders.ca/wordpress/?p=192). That MPH is effective at suppressing sleep is briefly discussed in the section “MPH and sleep”.

My clinical impression, after treating hundreds of elderly patients with methylphenidate, including many at Ste. Anne’s Hospital, is that better results in treating depressive symptoms are obtained by giving the first dose of the medication early in the morning, when it is likely to suppress what would otherwise be the longest period of REM sleep. A later dose of MPH, at 8h for example, is not as effective as a 6h or 6h30 dose.

Several review articles, abstracted in the section “Reviews”, typically emphasize that psychostimulants result in rapid improvement with few side effects.

In conclusion, the scientific literature suggests that methylphenidate and other stimulants have been widely used as first-line treatment for a number of conditions affecting the elderly, and continue to be so used because they are effective and safe. Additionally, these medications find application as add-on treatment, especially in depressions resistant to treatment with traditional or newer generations of antidepressants.

Future studies on the use of psychostimulants should include measurements of their effects on sleep, particularly duration, timing, and REM sleep; and effects on circadian rhythms.

Randomized controlled trials			
16-week randomized double-blind placebo-controlled trial for geriatric depression in 143 older outpatients diagnosed with major depression	three treatment groups: methylphenidate plus placebo (N=48), citalopram plus placebo (N=48), and citalopram plus methylphenidate (N=47). Daily doses ranged from 20 mg to 60 mg for citalopram (mean=32 mg) and from 5 mg to 40 mg for methylphenidate (mean=16 mg).	All groups showed significant improvement in depression severity and in cognitive performance.	(Lavretsky et al. 2015)
double-blind, randomized, placebo-controlled trial (144 patients)	ambulatory patients with HIV disease and persistent and severe fatigue	MPH and pemoline were equally effective at reducing fatigue, compared to placebo. Also, improved quality of life and decreased levels of depression and psychological distress	(Breitbart et al. 2001)
Five "N of 1" trials (individual cross-over, double-blinded, randomized trials)	nursing home patients: 2 depressed due to a medical condition; 1 treatment-resistant depression; 2 chronic apathy in dementia	MPH (5 mg bid) or placebo, crossed over. ⅔ depressed pts improved; 1 apathy pt improved; the other apathy pt trial stopped as test instrument could not be completed	(Jansen et al. 2001)
prospective, randomized, double-blind, placebo-controlled study (21 stroke patients consecutively admitted to a community-based rehabilitation unit)	Three-week treatment of methylphenidate (or placebo) in conjunction with physical therapy	MPH started at 5 mg/day, increased gradually to 15 mg bid: significantly more mprovement on HAM-D, Zung Depression Scale, motor functioning, and functional independence for MPH compared to placebo	(Grade et al. 1998)
8-day double-blind, randomized, placebo-controlled crossover trial	16 older medically ill patients with depression	13/16 completed the trial; statistically and clinically significant treatment responses were found	(Wallace et al. 1995)
randomized, double-blind, comparative trial (20 patients)	HIV antibody-positive patients with depression, assigned to either desipramine or MPH	individual dose titration; mean daily dose of desipramine: 150 mg; MPH: 30 mg. No statistically significant differences in responses or in speed of response.	(Fernandez et al. 1995)

Randomized controlled trials			
randomized, double-blind 2-day crossover trial (18 inpatients)	depressed patients, drug-free for at least one week	given either 20 mg d-amphetamine or 40 mg MPH in one dose, then crossed over to the other drug: many patients improved on one or the other, but few improved equally on both	(Little 1993)
double-blind placebo-controlled randomized trial	44 withdrawn, apathetic geriatric patients treated with MPH or placebo	MPH 10 mg bid led to significantly better outcomes after 6 weeks cf. placebo, in the MSCL test, NOSIE scale, in 4 target symptoms, and in nurses' and physicians' global evaluations	(Kaplitz 1975)

Open label trials			
open-label prospective study (41 patients with advanced cancer)	41 depressed ("are you depressed?") patients enrolled; 30 completed the study	21/30 responded to 5 mg bid MPH after 3 days; a further 9 to 10 mg bid after 5 days.	(Homsi et al. 2001)
12-week open-label study (23 DAT patients with apathy)	initial scores >40 on the Apathy Evaluation Scale	significant improvement in apathy, depression, MMSE scores, and functional status	(Padala et al. 2010)
pilot study (10 patients)	patients with CRF	fatigue and depression scores improved rapidly to day 9, minimal improvement thereafter. 5 mg bid was optimal dose.	(Hardy et al. 2010)
open prospective trial (31 patients)	patients with advanced cancer and fatigue	MPH self-dosed up to 20 mg daily. Anxiety, appetite, pain, nausea, depression, and drowsiness all improved significantly ($P < .05$).	(Bruera et al. 2003)
pilot study of consecutive admissions (12 AD, 15 vascular dementia)	dementia patients with negative symptoms	Negative symptoms and cognitive scores improved significantly with MPH treatment	(Galynker et al. 1997)

Case series			
Case series (4)	apathy, treated with MPH	significant improvement in apathy and subdomains of motivation, novelty, and persistence	(Padala et al. 2007)
case series (30)	patients with primary brain tumours	improvements in cognitive function, gait, stamina and motivation to perform activities	(Meyers et al. 1998)
case series (26 patients)	hospice inpatients with terminal cancer, diagnosed with major depressive disorder	MPH from 10 to 20 mg/day for up to 6 weeks: a therapeutic response was obtained in 46% (but only in 7% of those patients who died within the 6 weeks)	(Macleod 1998)
case series (28 MPH, 30 nortriptyline)	elderly stroke patients with major depression	remission: 53% MPH; 43% nortriptyline. speed of response: 2.4 days MPH, 27 days nortriptyline	(Lazarus et al. 1994)

Retrospective chart reviews			
retrospective chart review (82 patients)	all patients who had received MPH for cancer-related fatigue (CRF) in two prospective trials	50/82 (61%) responded to MPH (>/ = 7 points of FACIT-F). Better response predicted by higher initial fatigue.	(Yennurajalin gam et al. 2011)
retrospective chart review (16 patients)	patients receiving MPH in a bipolar disorder clinic	mean treatment duration: 14 months. ADHD: 5 pts; depression: 11 pts. Two pts stopped MPH because of side effects.	(Lydon and El-Mallakh 2006)
retrospective chart review (10 patients)	patients with stroke in an inpatient rehabilitation program	7/10 patients treated with methylphenidate for depression improved	(Johnson et al. 1992)
retrospective chart review (29 patients with depression, adjustment disorder, organic mood disorder)	all medical/surgical inpatients during 2 years treated with MPH	Of the 29 patients, 16 (55%) had moderate or marked improvement, all within 2 days of commencing treatment with the maximal dose of MPH	(Rosenberg et al. 1991)
retrospective chart review (25 patients)	poststroke depression	13/25 (52%) had complete remission with MPH, with mood improvement typically within 48 hours. 3 patients had side effects.	(Lingam et al. 1988)

Case reports			
case report (1 patient with melanoma)	interferon-alpha induced depression	MPH effective in rapidly improving neurovegetative symptoms in severe protacted depression	(Camacho and Ng 2006)
case reports (2 women with advanced cancer in palliative care)	hypoactive delirium treated with MPH	delirium improved on MPH, worsened when MPH stopped, improved again when MPH restarted	(Keen and Brown 2004)
case report (1 woman with pulmonary disease and heart failure, admitted for pneumonia)	no psychiatric history; became very depressed in a Montreal hospital	responded after 2 days on MPH 5 mg qam.	(Roy and Bernier 1999)
case report (1 patient with prominent apathy after multiple subcortical infarcts)	38 y-o male, cocaine abuse; infarcts caused a frontotemporal syndrome	MPH 5 mg bid led to a marked increase in interest and improved social behavior, personal hygiene, and participation in activities.	(Watanabe et al. 1995)
case reports (2 women, aged 91 and 104 years)	elderly with medical problems and depression	very small doses of MPH (1.25 and 5 mg daily) produced responses for > 8 months	(Gurian and Rosowsky 1990)

Table 2. Psychostimulants as adjunctive therapy

Psychostimulants as adjunctive treatment			
16-week randomized double-blind placebo-controlled trial for geriatric depression in 143 older outpatients diagnosed with major depression	three treatment groups: methylphenidate plus placebo (N=48), citalopram plus placebo (N=48), and citalopram plus methylphenidate (N=47). Daily doses ranged from 20 mg to 60 mg for citalopram (mean=32 mg) and from 5 mg to 40 mg for methylphenidate (mean=16 mg).	All groups showed significant improvement in depression severity and in cognitive performance.	(Lavretsky et al. 2015)
4-week, randomized, double-blind, placebo-controlled study (60 patients)	treatment-resistant depression; pts taking antidepressants	extended-release MPH (Concerta) (18-54 mg/d) was added to unchanged antidepressant dose; no difference between placebo and MPH on HAM-D or BDI scores, although the proportion of responders was significantly higher with MPH cf placebo.	(Patkar et al. 2006)
10-week double-blind, randomized, placebo-controlled trial (16 elderly outpatients with major depression)	patients received either citalopram plus MPH or citalopram plus placebo. Doses titrated up to 20 mg/day MPH, 40 mg/day citalopram	citalopram plus MPH had a faster and better improvement compared to citalopram plus placebo	(Lavretsky et al. 2006)
open study of MPH in bipolar patients (14) with depression	MPH added to a stable mood stabilizing regimen	HAM-D scores dropped from 16.9 +/- 1.79 SD at baseline to 9.4 +/- 9.73 on week 12 ($p = 0.12$, $t = 1.84$, $df= 6$)	(El-Mallakh 2000)
case series (8 patients, 5 with bipolar I disorder, 3 with bipolar II)	residual depression and medication-induced sedation	moderate clinical improvement in their target symptoms and substantial improvement of overall bipolar illness (mean change in CGI-BP overall score 2.9).	(Carlson et al. 2004)
case series (7 patients with major depressive disorder suboptimally responsive to 2nd-gen antidepressants	augmentation with psychostimulant	marked improvement in clinical symptoms of depression was noted in all cases, with particular improvement in apathy and feelings of fatigue	(Masand et al. 1998)

Psychostimulants as adjunctive treatment			
case series (5 consecutive cases of DSM-IIIR major depression)	open-label trial to augment SSRI treatment	Self-reported symptom reduction was achieved rapidly in all cases, with MPH dosages ranging from 10 to 40 mg/day	(Stoll et al. 1996)
case report (1 patient in his 6th episode of bipolar depression	had failed adjunctive repetitive transcranial magnetic stimulation and electro-convulsive therapy (24 treatments); was taking fluoxetine 80 mg/day, duloxetine 360 mg/day, mirtazapine 60 mg/day, and sodium valproate 1,000 mg/day, with no improvement.	10 mg/day early morning MPH led to mild improvement after 1 week; then 20 mg/day extended-release MPH gave significant improvement, stable over one year	(Adida and Azorin 2014)
case report (1 patient)	partial response to 60 mg/day of fluoxetine	10 and then 20 mg/day of MPH added to Rx improved apathy but not HAM-D scores	(Padala et al. 2005)
case report (1 patient with multiple medical conditions)	bipolar pt, in ICU for respiratory failure.	sertraline 50 mg begun; MPH 5 mg started 5 days later; same-day response. Worsened when MPH stopped. Responded when MPH restarted. Response maintained for over 9 months.	(Ayache and Junior 2001)

MPH and sleep

MPH suppresses REM sleep (Baekeland 1966). MPH reduces total sleep and REM sleep, but does not decrease slow wave sleep (Nicholson and Stone 1980).

Stimulant drugs are effective in the treatment of hypersomnia (Taub 1978).

The time of day when MPH is taken has an important influence on effectiveness in improving depressive symptoms (Swift 1989).

Partial sleep deprivation acts to increase the effect of MPH on subjective fatigue and on attentional performance. It also increase the preference of subjects for taking MPH (Roehrs et al. 1999),

In dementia patients, neither sertraline nor mirtazapine was better than placebo in improving symptoms of depression after 13 weeks of treatment (Banerjee et al. 2011)

MPH keeps people awake (increased mean latency on the Multiple Sleep Latency Test (MSLT) in both sleep deprived and sleep replete conditions) (Bishop et al. 1997)

Reviews

“Psychostimulants have useful antidepressant properties and are usually well tolerated. They may be useful as adjuncts to standard antidepressants in refractory depression, but have particular utility in conditions where a prompt therapeutic effect is desired and where tolerance and dependence are less of a concern. Such conditions include the treatment of depression in terminal illness and in extreme old age.Psychostimulants, although now largely discarded as treatment options for depression, deserve careful consideration as potential therapeutic agents in specific patient subgroups.” (Orr and Taylor 2007)

“173 studies were screened. Five studies on methylphenidate and 1 study on caffeine met inclusion criteria and were included in this review. Two studies were case reports, 2 were open-label trials, and 2 were double-blind, crossover randomized placebo-controlled trials. Three studies were conducted with hypoactive delirium patients and all studies were conducted in an advanced cancer patient population. CONCLUSIONS: The reviewed studies support the use of methylphenidate to improve end-of-life patient cognitive functions, particularly in the case of hypoactive delirium. Caffeine seems to have beneficial effects on psychomotor activity.” (Elie et al. 2010)

“Randomised controlled trials (RCTs) assessing the effectiveness of PS (psychostimulants) were included. The trial population comprised adults of either sex with a diagnosis of depression. …Twenty-four RCTs were identified. The overall quality of the trials was low. Five drugs were evaluated; dexamphetamine, methylphenidate, methylamphetamine, pemoline and

modafinil. Modafinil was evaluated separately as its pharmacology is different to that of the other PS. PS were administered as a monotherapy, adjunct therapy, in oral or intravenous preparation and in comparison with a placebo or an active therapy. Most effects were measured in the short term (up to four weeks). Thirteen trials had some usable data for meta-analyses. Three trials (62 participants) demonstrated that oral PS, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.40, -0.33, with non-significant heterogeneity. A similar effect was found for fatigue. In the short term PS were acceptable and well tolerated. Tolerance and dependence were under evaluated. No statistically significant difference in depression symptoms was found between modafinil and placebo." (Candy et al. 2008)

"Despite antidepressant therapy of appropriate trial duration and dose optimization, …only 35-40% achieve remission. …18 RCTs reporting on the use of psychostimulants in the treatment of adult patient populations, suffering from moderate-severe depression and having no other concomitant medical illnesses, were included in this review. 14 articles provided results for unipolar depression, two for bipolar depression, whereas two articles presented mixed samples of unipolar and bipolar patients. RESULTS: Five different psychostimulants were evaluated: modafinil, methylphenidate, dexamphetamine, methylamphetamine and pemoline. Two studies examining modafinil demonstrated significant ameliorating characteristics pertaining to symptoms of depression. No clear evidence for the effectiveness of traditional psychostimulants in the therapeutic management of MDD was found. In general the quality of included trials was poor since the majority was of short-term duration, comprising relatively small sample sizes and some, especially older studies, were methodologically flawed." (Abbasowa et al. 2013)

"A total of 19 controlled trials of methylphenidate in medically ill older adults or patients in palliative care were identified. Unfortunately, their conflicting results, small sample sizes, and poor methodologic quality limited the ability to draw inferences regarding the efficacy of methylphenidate, although evidence of tolerability was stronger. The available evidence suggests possible effectiveness of methylphenidate for depressive symptoms, fatigue, and apathy in various medically ill populations." (Hardy 2009)

This review looked at the pharmacology of psychostimulants and their uses in a range of conditions. It looked at both retrospective and prospective studies in depression, medical illness, cancer, fatigue, obsessive-compulsive disorder, drug-induced sedation, hiccups, Parkinson's disease, epilepsy, incontinence, mania, narcolepsy, pain, opiod-induced respiratory depression, physical disability, traumatic brain injury, and syncope. Psychostimulants were helpful in many of these conditions, although there were differential effects in some cases, eg dextroamphetamine was helpful, but MPH was not, in OCD (Homsi et al. 2000).

A MEDLINE search from 1986 to 1995 was done to identify literature on the use of methylphenidate for depression in the medically ill elderly. The references of articles found were evaluated for other relevant articles. CONCLUSIONS: Depression in the medically ill elderly occurs frequently and is underdetected in part because of the difficulty in diagnosing depression in this population. Methylphenidate has been found to be a safe and effective treatment of depression in the medically ill elderly. A potential advantage of methylphenidate over other antidepressants is its relatively quick onset of action, usually within 2-5 days. (Emptage and Semla 1996)

Survey

All 245 psychiatrists registered in Alberta in Feb 1995 were sent a survey (2 mailings); 230 (94%) responded. 204 out of this group treated adult patients. 95/204 (47%) prescribed psychostimulants; 73/95 (77%) prescribed MPH. 55/95 (58%) prescribed psychostimulants for unipolar depression for 296 patients; 12/95 (13%) for bipolar depression (36 patients), and 4/95 (4.2%) for dementia (17 patients). (Beck et al. 1999)

Side effects

To evaluate MPH-associated symptoms or side effects in frail adults with advanced cancer, data was collected from 2 published prospective cohort series and a phase 2 study of MPH for symptom control in advanced cancer. Initial doses were MPH 5 mg bid at 8h and 12h, titrated up to a maximum of 30 mg/day. 62 patients were enrolled. Fifty completed 7 days of MP with a median age of 69 (range 30-90) years. Thirty-five received MPH 10 mg/day. Most (96%) had improvement in depression and/or fatigue. Among the 62 patients, new symptom prevalence throughout the study was agitation (16%), insomnia (16%), dry mouth (15%), nausea (10%), tremors (6%), anorexia (5%), headache (3%), palpitations (2%), and vomiting (2%). Patients could have more than 1 symptom simultaneously. Seven (11%) withdrew due to MPH S/E. (Lasheen et al. 2010)

Forty percent of bipolar patients treated with psychostimulants for either ADHD or bipolar depression developed mania or hypomania, in a retrospective chart review of patients with bipolar disorder (137 randomly selected patients) evaluated at the Emory Bipolar Disorder Specialty Clinic (Wingo and Ghaemi 2008)

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