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Psychostimulants in the Treatment of Depression

A Review of the Evidence

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Contents

Abstract

Psychostimulants have euphoric and alerting properties that suggest their usefulness in treating depressive disorders; however, problems with tolerance and dependence with some drugs militate against their widespread therapeutic use where more acceptable licensed alternatives are available. The introduction of modafinil, a stimulant not associated with tolerance and dependence, has re-awakened interest in psychostimulants as antidepressants. The available literature, while containing somewhat inconsistent data of rather poor quality, does suggest that 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.

Psychostimulants (drugs that reduce fatigue and promote alertness and wakefulness) have seen a variety of uses over the past century or so, having been widely used both within and outside the practice of medicine. Following the development of amfetamine in the early part of the 20th century, this and similar drugs were fairly widely employed in the treatment of narcolepsy, fatigue and depressive disorders. Outside medicine, stimulants were an essential part of the war effort on all sides of major conflicts in the middle of the 20th century, being widely taken by members of armed forces and by factory workers.

Because psychostimulants induce euphoria and reduce fatigue they seemed ideal treatments for depression; however, it was soon noticed that patients developed tolerance to these effects, often resulting in dose escalation and sometimes dependence.[1] In the 1950s, MAOIs and TCAs became available for the treatment of depression and relegated stimulants to second- or third-line use. In addition, as illicit use of amfetamines became more widespread, and their supply and possession more strictly controlled, their use declined still further. More widespread use also revealed the propensity of these drugs to induce paranoid psychosis.[2,3] Today, stimulants are used in the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy. They are rarely considered useful or acceptable treatments for depression.

In recent years, the introduction of modafinil, a psychostimulant unrelated to amfetamine, and its safe and effective use in narcolepsy[4] and, to a lesser extent, depression (see below) and ADHD,[5] has reawakened interest in stimulants for the treatment of depression. Although broadly classified as a stimulant, modafinil differs in important respects from amfetamine-like drugs. Unlike such agents, modafinil appears not to cause the release of noradrenaline (norepinephrine) or dopamine, or to induce stereotypy, and probably acts via histamine release and agonism of noradrenaline receptors.[4]

In this article, we review data relating to psychostimulants (classified in the broadest sense as amfetamine and its derivatives, methylphenidate and modafinil) in the treatment of depression. Differences between modafinil and 'true' (amfetamine-related) psychostimulants in mode of action and therapeutic effects are, however, to be noted.

1. Formal Trials of Psychostimulants in Depression

1.1 As Monotherapy

There have been a number of trials examining the effects of psychostimulants as monotherapy in unipolar depression (table I).[6-14] Six of these were placebo-controlled trials[6,8-12] and one compared two stimulants;[7] four trials dealt only with 'mild' depression.[6,8,10,11] None examined the use of modafinil.

Very few of these trials produced results favouring the use of stimulants; three detected no difference in efficacy between psychostimulants and placebo. Failure to detect a difference may reflect an inherent lack of activity in depression or may be explained by methodological shortcomings of the trials. One of these equivocal trials included patients with ADHD-like symptoms[6] and some later studies[15,16] suggest that it is the withdrawn, apathetic patients who respond best to stimulants. Another study[12] found that phenelzine, an MAOI, was more effective in treating anxiety and agitation than dexamfetamine, which itself was not statistically superior to placebo. In fact, neither dexamfetamine nor phenelzine was significantly better than placebo. The duration of this study was only 2 weeks, although dexamfetamine might have been expected to produce a response by this time. This apparent lack of response may, in part, be a consequence of the unvalidated, subjective depression rating scales used, a problem common to many of the studies reviewed. Nonetheless, the overall impression from all studies taken together is that evidence supporting the use of amfetamine-related stimulants as monotherapy in unipolar depression is poor.

1.2 Adjunctive Treatment

Several trials have examined the use of psychostimulants including modafinil as adjunctive agents

Table I. Stimulants as monotherapy in primary unipolar depression

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
Mattes[6]	20 mildly depressed outpatients	Methylphenidate vs placebo	10–60	Double-blind crossover trial, two × 3-wk legs	Third and sixth wk; SAD-C, POMS, HAM-D	Methylphenidate = placebo	Not given	Not given
Little[7]	18 depressed inpatients	Dexamfetamine vs methylphenidate	40; 20	Crossover trial, two × 1-day legs	Daily; HAM-D, GDE-VAS	Dexamfetamine = methylphenidate	66% vs 55% showed a greater than 4-point decrease in HAM-D and increase in GDE-VAS	−2.9 vs −4.3 (p-values not given)
Rickels et al.[8]	101 mildly depressed outpatients with fatigue or apathy	Methylphenidate vs placebo	30–60	4wk double-blind, parallel comparison	Fortnightly; ZDRS, PQ, PDS	Methylphenidate > placebo (ZDRS); methylphenidate = placebo (PDS)	56% vs 33% considered they had improved	NA
O'Donnell[9]	110 acute vs chronically depressed patients	Dexamfetamine vs placebo	10–15	Crossover trial, four × 2-wk legs	Weekly; physician rating of symptom relief	Acute cases – dexamfetamine < placebo; chronic cases – dexamfetamine > placebo	66% vs 58% experienced at least a partial improvement in symptoms	NA
Robin and Wiseberg[10]	43 mild to moderately depressed outpatients	Methylphenidate vs placebo	20–40	4wk double-blind parallel comparison	Fortnightly; MMPI, physician rating	Methylphenidate = placebo	59% vs 48% of patients scored more than the median score when all the rating scale scores were added together	NA
Rickels et al.[11]	120 mildly depressed outpatients	Pemoline vs methylphenidate vs placebo	75; 15	4wk double-blind parallel comparison	Fortnightly; ZDRS, PDS	Pemoline and methylphenidate > placebo	Not given	NA
Hare et al.[12]	43 depressed inpatients	Phenelzine vs dexamfetamine vs placebo	10; 45	Crossover trial, three × 2-wk legs	Fortnightly subjective physician ratings	Phenelzine > dexamfetamine = placebo	Not given	NA
Rudolf[13]	42 depressed outpatients	Methedrine	2.5–30	Open-label trial lasting 1wk–7mo	Subjective physicians ratings	Found to be well tolerated and effective	83% showed a slight to marked improvement	NA
Wilbur et al.[14]	30 depressed patients	Benzedrine (racaemic amfetamine sulfate)	2.5–30	Open-label trial lasting 2wk–8mo	Subjective physician ratings	Found to be well tolerated and effective	70% experienced marked relief of symptoms	N/A

GDE-VAS = Global Drug Effect-Visual Analogue Scale; **HAM-D** = Hamilton Rating Scale for Depression; **MMPI** = Minnesota Multiphasic Personality Inventory; **NA** = not applicable; **PDS** = Physician Depression Scale; **POMS** = Profile of Mood States; **PQ** = Physician Questionnaire; **SAD-C** = Schedule for Affective Disorders and Schizophrenia-Change; **ZDRS** = Zung Self-Rating Depression Scale; **=** indicates equivalent to; **>** indicates more effective than; **<** indicates less effective than.

in depression (table II).[17-25] Only two trials were placebo-controlled.[20,21]

These adjunct studies can be considered in two groups; those that examined evidence for increased efficacy with antidepressant therapy that the patients had not previously received[18,23,24] and those evaluating effects above and beyond that provided by existing antidepressant therapy in patients with treatment-resistant symptoms or those who had only experienced a partial response.[17,19-22,25]

Overall, given the lack of clear superiority over placebo and methodological problems (few trials were randomised and blinded), support for the use of stimulants as adjuncts is flimsy. However, some of the studies that measured fatigue symptom severity found that stimulants were particularly useful in those patients who had been experiencing antidepressant-induced sedation.[17,21,22] In fact, the only clear and unequivocal benefit of using stimulants in these trials was that of reducing symptoms associated with fatigue.

1.3 Depression Associated with Cancer

One of the areas in which psychostimulants are thought to be particularly useful is in the treatment of depression in patients with advanced cancer, where their speed of action may be crucial, and where addiction and tolerance are not concerns. Table III shows data that have been presented from five studies examining this usage.[26-30] These trials seemed to have produced some very positive results (although none of the trials was placebo-controlled); only one trial showed an improvement in <70% of subjects.[26] This particular study reported that only 27% of the participants showed a marked or moderate improvement in symptoms.[26] One possible explanation for this relatively poor response was that the subjects were in the more advanced stages of cancer, with only weeks left to live, unlike other studies in which patients had relatively better prognoses.

Also of note is that many trials showed improvements in symptoms such as anorexia, fatigue, concentration, sedation and pain, as well as depression;[27-30] however, despite their positive findings, the absence of any well conducted, placebo-controlled trials render their findings, at best, tentative.

1.4 Post-Stroke Depression

Four studies have specifically examined the effects of psychostimulants on post-stroke depression (table IV).[31-34] Three of the four trials were uncontrolled and showed reasonable response rates,[32-34] while the one placebo-controlled trial failed to distinguish statistically between placebo and methylphenidate.[31] Differences in baseline characteristics may explain this apparent lack of effect. Nevertheless, the authors of this study[31] concluded that methylphenidate was an effective adjunct treatment for the rehabilitation of acute stroke patients because of the improvements seen in motor functioning and ability to conduct daily activities. However, overall results in this patient group are unconvincing.

1.5 Depression Associated with HIV/AIDS

Two trials have been conducted that evaluated stimulants in depression associated with HIV/AIDs, one of which was placebo-controlled (table V).[15,35] Both studies reported a high response rate and dexamfetamine was statistically superior to placebo, therefore supporting the efficacy of psychostimulants in this group of patients.

1.6 Depression in the Elderly

Elderly patients are less likely than the general adult population to have an adequate response to conventional antidepressants,[36,37] but have a higher mortality rate, particularly when the depression is severe.[38,39] There have been a number of trials examining stimulants in this population, three of which were placebo controlled (table VI).[16,40-44] These elderly patients were often medically ill, yet stimulants appeared to be well tolerated, even in patients with cardiac problems.[44] The majority of these trials produced very positive results, with response rates >50%, including in two of the three placebo-controlled trials.[16,40,43] Two trials evaluated methylphenidate as an adjunctive to citalopram in reducing time to response. In both studies, pa-

Table II. Stimulants as adjunctive therapy in major depression

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
DeBattista et al.[17]	35 outpatients with MDD	Modafinil with a variety of antidepressants	100–400	4wk open-label trial	Fortnightly; HAM-D, BDI, CGI-S, VASF, FSI	Significant improvements seen	42% showed a 50% decrease in HAM-D	−6.5 ($p < 0.001$)
Gwirtsman et al.[18]	20 inpatients with MDD	Methylphenidate with a variety of TCAs	10–30	2wk open-label trial	HAM-D every 3–4 days	Adjunctive use accelerates response to TCAs	63% showed a greater than 50% decrease in HAM-D	−14 ($p < 0.0001$)
Rasmussen et al.[19]	21 outpatients with MDD	Modafinil with a variety of antidepressants	100–400	Addition to existing treatment until condition stabilised	Baseline and endpoint MDI, SCL-92	Led to remission in 43% of patients	43% showed a greater than 50% decrease in MDI	NA
Fava et al.[20]	311 depressed outpatients with a partial response to SSRIs	Modafinil vs placebo with a variety of antidepressants	200	8wk double-blind RCT addition to existing SSRI treatment	Fortnightly; CGI-S, BFI, FSS, ESS, HAM-D	Modafinil > placebo for fatigue and depression	44% vs 36% showed a marked or moderate improvement in CGI-S	−7.2 vs −6.2 ($p < 0.08$)
DeBattista et al.[21]	136 depressed outpatients with a partial response to antidepressants	Modafinil vs placebo with a variety antidepressants	100–400	6wk double-blind parallel comparison trial	HAM-D, CGI-S, SF-36, FSS, ESS at wks 0, 1, 2 and 6	Fatigue: modafinil > placebo; depression: modafinil = placebo	74% vs 61% showed a marked or moderate improvement	−6.94 vs −6.4 (no significant difference)
Schwartz et al.[22]	19 outpatients with MDD and sedation with SSRIs	Modafinil with a variety of antidepressants	50–400	3wk open-label trial	Weekly; SF-12, HAM-D, FSS, ESS	Helped fatigue and mood	71% showed a 50% decrease in HAM-D	−7.3 ($p = 0.0001$)
Fawcett et al.[23]	32 patients with MDD	Pemoline or dexamfetamine with a variety of MAOIs	18.75–112.5; 5–40	6mo open-label trial	CGI every 1–4wk	Well tolerated and effective adjunctives	78% remained symptom free for 6mo post-treatment	NA
Postolache et al.[24]	9 outpatients with MDD	Augmentation of sertraline with methylphenidate	10	Double-blind, placebo-controlled RCT over 9wk	HAM-D	No patients experienced an accelerated or additional response with the combination	0% showed a 50% decrease in HAM-D	Not given
Markovitz and Wagner[25]	27 patients with MDD ± BPAD or personality disorder	Modafinil augmentation of existing antidepressants	200–400	Open-label study over 1–38wk	GAF as a baseline and on recovery	Well tolerated and effective	41% recovered to a GAF greater than 61	NA

BDI = Beck Depression Inventory; **BFI** = Brief Fatigue Inventory; **BPAD** = bipolar affective disorder; **CGI-S** = Clinical Global Impression-Severity; **ESS** = Epworth Sleepiness Scale; **FSI** = Fatigue Scale Inventory; **FSS** = Fatigue Severity Scale; **GAF** = Global Assessment of Functioning; **HAM-D** = Hamilton Rating Scale for Depression; **MDD** = major depressive disorder; **MDI** = Major Depression Inventory; **NA** = not applicable; **RCT** = randomised controlled trial; **SCL-92** = Symptom Checklist; **SF-12** = Medical Outcomes Study Short-Form 12-Item Health Survey; **SF-36** = Medical Outcomes Study Short-Form 36-Item Health Survey; **VASF** = Visual Analogue Scale of Fatigue; **=** indicates equivalent to; **>** indicates more effective than.

Table III. Stimulants as monotherapy for depression in patients with advanced cancer

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement
Macleod[26]	26 hospice inpatients with terminal cancer	Methylphenidate	5–20	Open-label trial for a maximum of 6wk or 3wk post-response	CGI-S	Improvement in mood and energy, although higher doses needed in last wks of life	27% showed a marked or moderate improvement in their CGI-S
Homsi et al.[27]	41 depressed patients with advanced cancer	Methylphenidate	10–30	7-day open-label trial	Subjective physician rating every 2 days	Effective therapy for depression in advanced cancer	73% denied still feeling depressed
Olin and Masand[28]	59 depressed cancer inpatients	Dexamfetamine or methylphenidate	2.5–20; 5–30	Retrospective chart review	CGI-S	Found to be well tolerated and effective treatment options	73% showed marked or moderate improvement
Fernandez et al.[29]	30 depressed cancer patients	Methylphenidate	30–80	Open-label study over 5–70 days	CGI-S	Found to be well tolerated and effective	77% showed marked or moderate improvement
Meyers et al.[30]	30 brain tumour patients	Methylphenidate	20–60	Open-label trial for as long as the drug is tolerated and effective	Neuropsychological tests, including BDI and subjective measures	Methylphenidate improved neurobehavioural functioning, including some improvement in mood at the lower doses	78% at 10mg bid, 85% at 20mg bid, 100% at 30mg bid showed subjective improvements

BDI = Beck Depression Inventory; **bid** = twice daily; **CGI-S** = Clinical Global Impression-Severity.

Table IV. Stimulants as monotherapy for post-stroke depression

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
Grade et al.[31]	21 stroke patients	Methylphenidate vs placebo	5–30	3wk double-blind RCT to establish speed of response	HAM-D, ZDRS, MMSE, FMS, M-FIM	Methylphenidate = placebo for depression but > for motor recovery and independence	Results unclear	Methylphenidate −5.684 vs placebo −6.181 (p-value not given)
Lazarus et al.[32]	10 patients with post-stroke depression	Methylphenidate	5–40	3wk open-label study	Weekly HAM-D	Found to be well tolerated and effective	40% showed a greater than 50% decrease in HAM-D	−10.2 (p-value not given)
Masand et al.[33]	17 patients with post-stroke depression	Dexamfetamine or methylphenidate	2.5–20; 5–15	Retrospective chart review	CGI-S	Found to be well tolerated and effective treatment options	47% showed a marked or moderate improvement	NA
Lingam et al.[34]	25 patients with post-stroke depression	Methylphenidate	15–40	Retrospective chart review	Conservative criteria	Found to be rapidly effective and well tolerated	52% went into complete remission	NA

CGI-S = Clinical Global Impression-Severity; **FMS** = Fugl-Meyer Scale; **HAM-D** = Hamilton Rating Scale for Depression; **M-FIM** = Modified Version of the Functional Independence Measure; **MMSE** = Mini-Mental State Examination; **NA** = not applicable; **RCT** = randomised controlled trial; **ZDRS** = Zung Self-Rating Depression Scale; **=** indicates equivalent to; **>** indicates more effective than.

tients showed a significant response within 2 weeks, more quickly than citalopram alone is thought to act in the elderly.[41,42] However, methodological shortcomings in all trials render inappropriate firm conclusions on the efficacy of stimulants in this group of patients.

1.7 Depression in the Medically Ill

Medically ill patients are another group where a rapid onset of action is advantageous. Five trials have been conducted examining the use of psychostimulants in this population, although only one was placebo-controlled and this study used subjective physician ratings (table VII).[45-49] All of these trials covered a wide range of patients of various ages with various medical conditions or undergoing surgical procedures, and the results were apparently strongly in favour of stimulants as effective antidepressant agents. Nonetheless, the dearth of well conducted, placebo-controlled studies again prevents any firm conclusions being drawn.

1.8 Depression in Other Patient Groups

Table VIII details those reports that examined psychostimulants in other areas not included in sections 1.1–1.7.[50-53]

One study reviewed patients with ADHD who were also experiencing depression. It seems that in this group of patients stimulants did not improve depressive symptoms. This may have been because the dosages of stimulants used were higher than those usually used for depression but not at the maximum adult dosage for ADHD.[50] In other small uncontrolled studies, modafinil was found to be effective for seasonal affective disorder,[51] and methylphenidate was effective in patients with bipolar depression.[52] A larger, but uncontrolled, study of intravenous methedrine in patients with various psychiatric diagnoses demonstrated that treatment was successful in a small number of subjects.[53]

Overall, data are inconclusive at worst, suggestive of activity at best.

Table V. Stimulants as monotherapy for depression in patients with HIV/AIDS

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
Wagner and Rabkin[15]	23 HIV patients with depression and fatigue	Dexamfetamine vs placebo	5–40	2wk RCT, blind for 8wk if responders then open-label trial for 6mo	BHS, BSI, CFS, HAM-D, Q-LES-Q, QLI, VAS, WAIS-R at wks 0, 2, 8, 16 and 26	Dexamfetamine > placebo	73% vs 27% showed marked or moderate improvement	Dexamfetamine −7.7 vs placebo −5 ($p < 0.001$)
Wagner et al.[35]	24 AIDS patients with depression and low energy	Dexamfetamine	5–30	6wk open-label trial	HAM-D and CGI-S at wks 0, 1, 2, 4 and 6	Found to be an effective fast-acting treatment	75% had a CGI-S at least much improved	−11.7 ($p < 0.001$)

BHS = Beck Hopelessness Scale; **BSI** = Brief Symptom Inventory; **CFS** = Chalder Fatigue Scale; **CGI-S** = Clinical Global Impression-Severity; **HAM-D** = Hamilton Rating Scale for Depression; **Q-LES-Q** = Quality of Life Enjoyment and Satisfaction Questionnaire; **QLI** = Quality of Life Index; **RCT** = randomised controlled trial; **VAS** = Visual Analogue Scale; **WAIS-R** = Wechsler Adult Intelligence Scales-Revised; > indicates more effective than.

2. Case Reports

As well as the trials discussed in section 1, there have been a significant number of case series and single case reports published. Although the usefulness of these reports as an evidence base is questionable, the information they provide is sometimes of value. This is particularly true in the treatment of refractory depression where spontaneous remission is rare and placebo effects minimal.

Some of these investigations reported the use of stimulants as adjunctive medications to more conventional antidepressants in treatment-resistant depression. In one case series, a patient did not respond to a trial of imipramine and dexamfetamine, but did respond to fluoxetine and dexamfetamine.[54] Seven cases of bipolar depression responded well, in some respects, to modafinil as an augmenting agent. These patients had residual fatigue prior to modafinil therapy, which responded particularly well to augmentation.[55] An elderly, depressed, medically ill patient responded well to modafinil augmentation of fluoxetine, after experiencing tachycardia with methylphenidate.[56] Four of five patients administered modafinil in addition to previously ineffective antidepressants were shown to respond, to some extent, over a period of approximately 1 month.[57]

Two reports examined stimulants as monotherapy in depression; in the first report, two agitated depressed patients felt calmer and less depressed after administration of dexamfetamine,[58] and in the second report, one man responded well to modafinil within the first week of treatment.[59]

There have been relatively more published case series regarding stimulants in medically ill patients. Two cases reported that methylphenidate was well tolerated in patients with renal failure.[60] Also, in a gravely ill elderly patient who could not swallow, depressive symptoms significantly improved after the addition of dexamfetamine suppositories.[61] In five medically ill patients with neurological disease and major depression, depressive symptoms rapidly went into remission without any apparent adverse effects after the addition of dexamfetamine or methylphenidate to therapy.[62] Four depressed pa-

Table VI. Stimulants for depression in elderly patients

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
Wallace et al.[40]	16 older depressed, medically ill patients	Methylphenidate vs placebo	10–20	Double-blind crossover trial with two 4-day legs	HAM-D and MMSE after each leg	Methylphenidate > placebo	62% of subjects' HAM-D score decreased by more than 55%	Results unclear
Lavretsky et al.[41]	11 elderly depressed outpatients	Methylphenidate and citalopram	5–20; 20–40	10wk open-label trial (both drugs started together)	Weekly HAM-D and CGI-S	Well tolerated and effective way to accelerate citalopram response	55% of subjects' HAM-D score decreased to less than 10	−15.8 (p-value not given)
Lavretsky and Kumar[42]	10 elderly depressed patients	Methylphenidate and citalopram	2.5–20; 10–40	8wk open-label trial, started within 3wk of citalopram therapy	HAM-D and CGI-S at wks 0, 2, 4 and 8	Well tolerated and effective way to accelerate citalopram response	60% of subjects' HAM-D score decreased to less than 10	−11.2 (p-value not given)
Jacobson[43]	54 elderly depressed inpatients	Methylphenidate vs placebo	Range unclear (~20–40)	2–6mo parallel comparison	End of trial; author's global rating	Methylphenidate > placebo	37% vs 15% showed a marked or moderate improvement	NA
Pickett et al.[44]	129 elderly, medically ill, depressed inpatients	Methylphenidate or dexamfetamine	5–20; 2.5–30	Retrospective chart review	CGI-S	Found to be a well tolerated and effective antidepressant	66% showed a marked or moderate improvement in CGI-S	NA
Kaplitz[16]	44 withdrawn, apathetic elderly patients	Methylphenidate vs placebo	20	6wk placebo-controlled RCT	Global evaluations	Methylphenidate > placebo	76% vs 16% were considered improved by the physicians	NA

CGI-S = Clinical Global Impression-Severity; **HAM-D** = Hamilton Rating Scale for Depression; **MMSE** = Mini-Mental State Examination; **NA** = not applicable; **RCT** = randomised controlled trial; **>** indicates more effective than.

Table VII. Stimulants for depression in medically ill patients

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement
Woods et al.[45]	66 depressed medical or surgical patients	Dexamfetamine or methylphenidate	2.5–30; 5–30	Retrospective chart review	CGI-S	Found to be effective and well tolerated in this population	48% showed marked or moderate improvement
Masand et al.[46]	198 depressed medical or surgical patients	Dexamfetamine or methylphenidate	2.5–30; 5–30	Retrospective chart review	CGI-S	Found to be well tolerated and effective in this population	70% showed marked or moderate improvement
Rosenberg et al.[47]	29 depressed medical or surgical patients	Methylphenidate	Dosage unclear (~10)	Retrospective chart review	CGI-S	Found to be well tolerated and effective, although less effective in delirious patients	55% showed marked or moderate improvement
Rothenhausler et al.[48]	7 depressed ICU patients on ventilators	Methylphenidate	2.5–15	Open-label trial to aid weaning from mechanical ventilation	CGI-S	A rapidly effective and well tolerated treatment option	71% showed marked or moderate improvement
Landman et al.[49]	112 medically ill patients with mild depression	Methylphenidate vs placebo	30	Crossover trial with two 4-day legs	Subjective physician ratings	Methylphenidate > placebo	66% exhibited a marked improvement clearly differentiated from the effect of the placebo

CGI-S = Clinical Global Impression-Severity; **ICU** = intensive care unit; **>** indicates more effective than.

tients who could not take TCAs because of cardiovascular problems were administered methylphenidate and underwent a rapid remission of depressive symptoms with no reported adverse effects.[63] Three medically ill depressed patients administered dexamfetamine showed some improvement.[64] There has also been a published report of medically ill depressed patients who could not tolerate TCAs but whose depression went into remission when they received methylphenidate or dexamfetamine.[65] In a report describing five cases where modafinil was used to treat depression in the severely medically ill, four of five patients experienced at least a minimal response.[66] A further case report examining modafinil in post-stroke depression in a patient with a history of bipolar disorder saw her depressive symptoms resolving quickly, allowing her to participate in physical therapy and rehabilitation.[67]

Several case series discussed the use of stimulants in patients with terminal cancer. One reported the successful use of methylphenidate in ten depressed patients with advanced cancer; the depressive symptoms of these patients rapidly improved, as did their concentration, appetite, fatigue and sedation, without severe adverse effects.[68] Eleven fatigued patients with cancer from the same hospice apparently improved rapidly in terms of their depression and fatigue on methylphenidate and some also showed improvement in pain.[69] A further report of dexamfetamine used to treat depression in two terminally ill cancer patients found the advantages of this stimulant over licensed antidepressants to be its therapeutic efficacy, rapid onset of action and rarity of adverse effects.[70]

One author recommended methylphenidate over licensed antidepressants for elderly patients because of its faster onset of action, advantageous adverse effect profile and scarcity of drug interactions.[71] Indeed, it was reported that two extremely elderly patients (104 and 91 years of age) were effectively treated with low-dose methylphenidate for depression. These patients continued stimulant monotherapy therapy for 8 and 9 months, respectively, without experiencing any unpleasant adverse effects, addiction or reduced efficacy.[72]

Overall, these case reports, while lacking scientific rigour, do provide tentative support for the use of stimulants in some specific patient groups.

3. Onset of Action

Psychostimulants might be expected to provide rapid onset of antidepressant action given their prompt euphoric and energising effects. Few studies in the literature examined this possibility in a robust fashion. Those that have provided worthwhile details on time to response are described below (also see tables II, III, IV and VII for details of the studies discussed). All results outlined should be viewed with some caution since in most cases patient and clinician expectation is likely to have provoked a strong placebo response.

A trial of methylphenidate in cancer patients assessed subjects every 2 days, and 21 of 41 patients no longer felt depressed by day 3 and a further five had substantially improved by day 5.[27] Three retrospective reviews of medically ill patients reported a good response (a marked or moderate improvement in Clinical Global Impression-Severity score [CGI-S]) within 2 days of the initiation of dexamfetamine or methylphenidate therapy.[45-47] Methylphenidate use for depression in post-stroke patients produced an early onset of action – a >50% decrease in Hamilton Rating Scale for Depression (HAM-D) score within 3–10 days.[32] In a study of patients with major depression, methylphenidate treatment resulted in baseline HAM-D scores improving by 26% in the first 4 days, 40% after 7 days, 36% after 11 days and 57% after 14 days.[18]

A retrospective review of post-stroke patients reported that improvement in depression with dexamfetamine or methylphenidate occurred rapidly; 29% of patients had shown a marked or moderate improvement on day 1, with the same proportion showing improvement on day 2, while only 18% of responders took longer to show signs of improvement.[33] A study examining the use of stimulants in cancer patients reported time to response to dexamfetamine or methylphenidate in days rather than weeks; 37% of patients had shown marked or moderate improvement on day 1, 15% on day 2 and 5%

Table VIII. Stimulants for depression in other patient groups

Study	Subjects	Drug	Dosage (mg/day)	Study design	Rating scales	Outcome	Percentage of patients who showed improvement	HAM-D outcome
Hornig-Rohan and Amsterdam[50]	17 outpatients with depression and ADHD	Antidepressants vs dexamfetamine or methylphenidate vs a combination of both	7.5–60; 50–60	Retrospective chart review	HAM-D weekly for 4wk, then 2–4 weekly, although not for all patients	Stimulant + antidepressants > antidepressant monotherapy > stimulant monotherapy	88% vs 80% vs 33% had a 50% decrease in HAM-D or a final score of less than 7	Results unclear
Lundt[51]	12 outpatients with SAD	Modafinil	100–200	Open-label study over 8wk	HAM-D, SIGH-SAD, MADRS, CGI and FSS at wks 1, 2, 5 and 8	Well tolerated and effective	67% had a greater than 50% decrease in SIGH-SAD and MADRS	−8.5 ($p < 0.001$)
El-Mallakh[52]	14 patients with BPAD	Methylphenidate	10–20	12wk open-label study	HAM-D every 2wk	Well tolerated and effective	50% had a greater than 50% decrease in HAM-D	−7.1 ($p = 0.019$)
Jonas[53]	72 inpatients with various psychiatric diagnoses	Intravenous methedrine	20	Single dose prior to psychotherapy	Subjective physician rating	Pronounced improvement in progress via psychotherapy	14% had a pronounced improvement in progress	NA

ADHD = attention-deficit hyperactivity disorder; **BPAD** = bipolar affective disorder; **CGI** = Clinical Global Improvement; **FSS** = Fatigue Severity Scale; **HAM-D** = Hamilton Rating Scale for Depression; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **NA** = not applicable; **SAD** = seasonal affective disorder; **SIGH-SAD** = Structured Clinical Interview Guide for the HAM-D, Seasonal Affective Disorder version; **>** indicates more effective than.

on day 3; 10% took 4 or more days to reach this endpoint.[28] An open-label trial of medically ill patients stated that depressive symptoms showed a marked or moderate improvement in CGI within 3–4 days of starting methylphenidate treatment.[48]

Six of 11 elderly patients treated with methylphenidate met the criteria for accelerated response, i.e. they had a HAM-D score of <10 and a CGI-Improvement score of 1 or 2 by day 14.[41] One study using modafinil showed statistically significant improvement in depressive symptoms (a marked or moderate improvement in CGI) after 2 weeks of modafinil treatment, and an improvement in wakefulness after only 1 week.[21] Responders to a dexamfetamine trial reported an early onset of action, as they had all responded after only 2 weeks of treatment (the CGI was at least 'much improved').[35] A study of patients with bipolar depression showed that methylphenidate produced a significant improvement (a 50% decrease in HAM-D score) within 1 week of treatment, both in depressive and global psychiatric symptoms.[52] One study of stimulants in the elderly saw 40% of patients treated with methylphenidate or dexamfetamine responding on day 1, 30% on day 2 and 10% on day 3 or 4 (a marked or moderate improvement in CGI).[44] A maximum response time to methylphenidate of 4 days was achieved in one open-label cancer trial (response was considered to be a marked or moderate improvement in CGI).[29] Remarkably, in a study of intravenous methedrine, patients experienced an improvement in emotional response at psychotherapy within 60 seconds of drug administration.[14]

4. Long-Term Use

The length of time a depressed patient should be prescribed antidepressants is an issue that is often debated, even for the more conventional licensed treatment options. The general consensus is to continue treatment of a single episode for 4–6 months after symptoms have resolved, longer after multiple episodes.[73] The majority of trials of psychostimulants did not examine long-term use, but those that did are discussed in the following paragraphs.

In a modafinil augmentation trial, some of the patients received treatment for up to 1 year, with no adverse effects, including tolerance and dependence, being observed.[19] A study of dexamfetamine in HIV patients observed that 10 of 15 patients maintained their response throughout 6 months of dexamfetamine treatment, although four patients stopped treatment because of adverse effects and one experienced a relapse of his depressive symptoms.[15] A similar trial followed some subjects over an extended trial period of up to 2 years and, although there are no precise data available for this time, the original response to treatment of mood and energy was apparently maintained.[35] Eleven of 30 patients with cancer underwent low-dose methylphenidate treatment for 1 year, apparently without a diminished response or any signs of misuse.[29] A trial of patients with major depression reported that 78% of patients maintained a good response to stimulants and MAOIs for at least 6 months without any signs of tolerance.[23] The authors of a further study claimed that the majority of their patients required no more than 2 months of treatment, but in those who did, methedrine was used safely for up to 7 months.[13]

Only one report described any signs of tolerance, in this case to Benzedrine (racaemic amfetamine sulfate), where, of the 21 patients who received an initial beneficial response, six patients experienced no benefit after the first week, seven stopped after 1 month, three stopped after 3 months and only five patients continued to find the drug beneficial after 6 months had passed.[14]

None of the studies described above reported any adverse effects of long-term use of stimulants, and only one reported signs of tolerance. This might suggest that stimulants may safely be used as longer-term therapy if required, but this goes against accepted understanding of the actions of this group of drugs. This is particularly the case with amfetamine-related drugs where tolerance is an established phenomenon. Indeed, tolerance may also develop with standard antidepressants;[74] therefore, it seems unlikely to be absent in the case of stimulant drugs.

Table IX. Adverse effects of stimulant drugs used to treat depression[a]

	Methylphenidate	Methylphenidate or dexamfetamine	Dexamfetamine	Modafinil	Benzedrine	Methedrine	Total
No. of studies that described adverse effects	18	7	3	5	1	2	36
No. of studies in which adverse effects found	1						1
Adverse effect							
Insomnia	6	1	3	3		1	14
Agitation	9	4			1	1	15
Anxiety	5	2		1	1	1	10
Confusion	1	5					6
Over-stimulation	1	1	2		1		5
Hypomania	2	3					5
Nervousness	2	1		1	1		5
Tachycardia	6	5			1	1	13
Hypertension	3	3		1	1	2	10
Tremor	3				1	1	5
Headache	2		2	4		2	10
Nausea	5	3		2			10
Dry mouth	4			3	1		8
Anorexia and weight loss	2		2		1		5
Gastrointestinal disturbances	3			2			5

a This table outlines the number of reports describing the occurrence of named adverse effects with individual drugs.

5. Adverse Effects

Not all trials reviewed in this article assessed the tolerability and adverse effect profile of the stimulants being evaluated. Common adverse effects that were reported to occur with stimulant therapy are outlined in table IX.[6-35,40-43,45-47] These data are in accordance with the adverse effect profile described by the manufacturers of methylphenidate, dexamfetamine and modafinil (according to their product labelling) and with information included on a commonly used, comprehensive medicines database, Drugdex.[75-80]

Many studies give scant information on the frequency or severity of adverse effects. In the 25 studies reviewed in this article that did provide this information, the percentage of patients experiencing adverse effects ranged from 2.3%[12] to 100%.[41] Trials of modafinil seemed to produce the highest rate of adverse drug reactions,[17,19-22,51,81] but this may simply reflect better monitoring in relatively recent trials. In the few studies that produced a further breakdown of adverse effect data, insomnia and agitation were the most common adverse effects within each trial of the true stimulants. Headaches seemed to be a common adverse effect of modafinil.

Three published evaluations provided enough data to allow comparison of adverse effects with

Table X. Percentage of patients reporting adverse effects in a placebo-controlled trial of methylphenidate in inpatients with mild depression[8]

Adverse effect	Methylphenidate (n = 46)	Placebo (n = 49)
Insomnia	24	14
Excitement	20	16
Tachycardia	20	16
Dry mouth	17	6
Constipation	13	10
Weight loss	13	4
Dizziness	13	10
Headache	13	10
Tremor	7	2
Nausea	7	4
Drowsiness	4	12
Weight gain	4	14

Table XI. Percentage of patients reporting adverse effects in two placebo-controlled trials of modafinil as adjunctive therapy in outpatients with depression

Adverse effect	Fava et al.[20] (n = 311)		DeBattista et al.[21] (n = 136)	
	modafinil and antidepressant (n = 158)	placebo and antidepressant (n = 153)	modafinil and antidepressant	placebo and antidepressant
Headache	13	16	22	12
Nausea	9	2	4	7
Dizziness	7	2		
Dry mouth	6	3		
Rhinitis	6	3	7	6
Insomnia	4	5	19	13
Diarrhoea	4	7	7	7
Infection	3	6	10	12
Hypertension	3	5		
Nervousness			20	4
Anxiety			7	6
Somnolence			7	4
Hypertonia			7	0
Asthenia			3	7
Myalgia			1	6

placebo;[8,20,21] these data are presented in table X and table XI. A further three papers allowed a comparison with placebo of the overall rate of adverse effects, as shown in table XII.[8,11,16]

Some other rarer adverse effects reported in the published literature include atrial fibrillation (true stimulants, not modafinil),[44,46] palpitations (true stimulants),[13-15,29] spasticity (true stimulants),[44,46] shortness of breath and hyperventilation (true stimulants),[23,32,35,53] hypotension (methylphenidate),[18,32] sedation (all drugs, including modafinil),[21,23,24,41] weight gain (true stimulants)[14,23] and excessive sweating (true stimulants).[14,45] Interestingly, no trial reported switching to mania, an important adverse effect previously linked to both amfetamine-like drugs[82,83] and modafinil.[84]

The safety of stimulant drugs has recently been called into question after a US Advisory Panel suggested such drugs should carry warnings about their cardiovascular risks. The US FDA, in a recent hearing, has endorsed this view.[85] This ruling refers mainly to amfetamines and methylphenidate, which potently stimulate the cardiovascular system and the CNS. These drugs increase heart rate and blood pressure, and it is thought that this can induce chronic heart failure, as seen in animal models of dilated cardiomyopathy.[86] Cardiac arrhythmias have also been reported.[87] There have been cases of myocardial infarction, stroke and sudden death in children and adults receiving stimulants for ADHD,[85] but the data from these cases were not thought to be conclusive of causation. The emphasis of the report from the FDA was that these drugs were being over prescribed for ADHD and that more selective use was needed with increasing awareness of their potential risks.[86,88] These serious adverse effects of amfetamine-related drugs clearly limit their clinical utility in depression.

Of course, psychostimulants have long been associated with tolerance and addiction. Interestingly, none of the evaluations cited in this review reported any evidence of addiction occurring, even in those patients who took the drug for long periods. This may simply reflect the paucity of appropriate observation of subjects or inadequate reporting. The variation in rates of tolerance reported is telling in this respect; one study reported tolerance in all its patients, but none of these patients showed any signs of addiction.[53] Data reviewed in this article would suggest that, in practice, at the doses used for depression, psychostimulants are not addictive, al-

Table XII. Comparison of the overall rate of adverse effects (percentage of patients experiencing any adverse effect) of stimulants used to treat depression in placebo-controlled trials

Study	Drug	No. of patients	Rate of adverse effects (%)
Rickels et al.[11]	Methylphenidate	42, 36[a]	26, 25[a]
	Pemoline	35, 32[a]	37, 19[a]
	Placebo	34, 27[a]	21, 7[a]
Kaplitz[16]	Methylphenidate	25	0
	Placebo	19	16
Rickels et al.[8]	Methylphenidate	46	61
	Placebo	49	57

a Results for 2 and 4 weeks, respectively.

though a history of drug or alcohol misuse might be considered a contraindication. In practice, however, clinicians would be right to expect tolerance and dependence in people treated with amfetamine-related drugs in the medium- to long-term. Modafinil may differ in this respect but long-tem data in depression are lacking.

Almost all the trials concluded that the stimulants in question were well tolerated therapeutic options and that their adverse effect profile in fact made them preferable to other treatment options available at the time. Even considering the recent fears surrounding cardiac risks, those trials looking at elderly or medically ill patients often included patients with some form of cardiovascular disease and no author thought that this should be a contraindication to stimulant therapy (see tables VI and VII). A consideration here is the possibility of inappropriately favourable views of advocates of stimulant use. Also notable is the absence of a systematic evaluation of cardiac safety in large numbers of subjects. Clearly, cardiac safety is an important consideration when using amfetamine-like drugs in depression.

6. Data Limitations

Of the reports examined in this article, only 14 were double-blind, placebo-controlled trials. Of these, only six showed clear advantages for psychostimulants. In some of these, statistical analyses were not provided. All trials examined had some limitations, although some in particular were common to many studies. Most important was the frequent use of obscure or unvalidated rating scales, and some studies relied solely on prescriber opinion. The frequency at which this often inadequate monitoring occurred was another limitation, especially considering that one of the potential advantages of the stimulants is their speed of action; the majority of studies did not monitor progress often enough to reveal any advantage. There was a relative lack of longer term studies; thus, there are few data available regarding long-term tolerability and efficacy. In addition, the age of many of these trials is a limitation in itself; older studies were generally those with poor design and using obscure rating scales.

There are a number of examples of study limitations specific to certain trials. One trial recruited subjects with ADHD-like symptoms, even though it is possible that it is the withdrawn, apathetic patients who respond best to stimulants.[6] There was also a trial where the response rate was deceptive since, in those patients who did not respond to the combination of an MAOI and a stimulant or those patients who suffered a relapse, an additional antidepressant such as a TCA or lithium was added, but the positive response that followed was still attributed to the initial combination, and the authors do not state what proportion of subjects needed this additional therapy.[23] Furthermore, one trial allowed prescribing of chlorpromazine at night, which may have counteracted the effects of the methylphenidate administered in the morning.[43]

The most important observation, however, is the absence of any consistent finding of superior antidepressant effect for stimulants compared with placebo, notwithstanding clear effects on fatigue symptoms. This is particularly true of the better conducted trials. Thus, despite the long history of the use of these drugs in depressive orders, their efficacy in depression as true antidepressants remains speculative.

7. Conclusion

Overall, data supporting the use of stimulants in depression are somewhat suggestive of useful activity but lack sufficient scientific rigour and consistency of outcome. Psychostimulants such as dexamfe-

tamine, methylphenidate and modafinil probably remain worthwhile treatment options for depression but only in specific patient groups. Whilst their use as sole agents for uncomplicated major depression cannot be supported given the range of licensed alternatives available (and the paucity of data relevant to their use in depression), they remain important treatment options in resistant depression (although supporting data are less than convincing), depression in the terminally ill, in elderly patients and in other specific patient groups. Their apparently rapid onset of action and good short-tem tolerability and safety make them valuable options where these properties outweigh the known disadvantages of stimulant drugs. However, even in these conditions, stimulants should be considered second- or third-line options given their propensity for tolerance, dependence, cardiac toxicity and psychotic reactions (considerations that may not apply to modafinil). A further restriction on their use is effectively imposed by the quality of research data supporting their use. In this respect and others, however, modafinil stands out; it is better supported by modern research techniques, is probably not liable to misuse, and tolerance and dependence do not seem likely. Nonetheless, available data support the use of modafinil only as an adjunct to standard antidepressants and most studies have identified an effect only on symptoms related to fatigue.

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