# Therapeutic Reviews

***Series Co-Editors: Andrew Wilcock, DM, FRCP, and Robert Twycross, DM, FRCP***

*Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. The content is also available on www.palliativedrugs.com and will feature in future editions of the Hospice and Palliative Care Formulary USA and its British and Canadian counterparts. The series editors welcome feedback on the articles (hq@palliativedrugs.com).*

## *Psychostimulants* *AHFS 28.20.92*

Paul Howard, BMedSci, BM, BS, MRCP, John Shuster, MD, Robert Twycross, DM, FRCP, Mary Mihalyo, BS, PharmD, RPh, and Andrew Wilcock, DM, FRCP
*Duchess of Kent House (P.H.), Reading, United Kingdom; Vanderbilt University (J.S.), Nashville, Tennessee, USA; Oxford University (R.T.), Oxford, United Kingdom; Mylan School of Pharmacy (M.M.), Duquesne University, Pittsburgh, Pennsylvania, USA; and University of Nottingham (A.W.), Nottingham, United Kingdom*

**Indications:** Licensed indications vary between products; consult Prescribing Information for details. Attention deficit hyperactivity disorder; daytime drowsiness due to narcolepsy, obstructive sleep apnea or chronic shift work-related sleep disorder; †depression when prognosis <3 months; †opioid-related drowsiness; †fatigue refractory to correction of underlying contributory factors.

**Contraindications:** Amphetamines and other psychostimulants should not be prescribed concurrently or within 14 days of the use of a monoamine oxidase inhibitor (MAOI) because of the risk of precipitating a hypertensive crisis (characterized by severe hypertension, headache and hyperpyrexia). Psychostimulants also should not be used in patients receiving procarbazine (an antineoplastic drug) because this is a weak MAOI.

### Pharmacology

Psychostimulants increase alertness and motivation, and have antidepressant and mood-elevating properties.[1–4] This drug class includes combined dextroamphetamine/amphetamine salts, lisdexamfetamine, dexmethylphenidate, and armodafinil. However, this review will focus on dextroamphetamine, methylphenidate, and modafinil, which have the best evidence base to support use in palliative care.[5] Further, the newer alternatives are generally significantly more expensive, and have no proven additional pharmacological benefit.

Caffeine is a time-honored traditional psychostimulant widely used in the community. It is an adenosine type-1 receptor antagonist. It blocks the sleep-promoting GABAergic and antidopaminergic effects of adenosine, which accumulates during wakefulness.[2] However, medicinal psychostimulants are used when traditional measures are inadequate.

*Address correspondence to:* Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, United Kingdom. E-mail: andrew.wilcock@nottingham.ac.uk

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Although the specific mechanisms of action may vary, medicinal psychostimulants generally appear to act directly or indirectly via dopamine.[2–4,6,7] Dopamine has an important role in the mesolimbic and mesocortical systems, which are concerned with reward, motivation, attention, and arousal. It is released in response to relevant stimuli and thoughts, particularly those associated with reward. These effects are mediated by $D_1$ and $D_2$ receptors.[2,8]

Dopaminergic dysfunction in the mesolimbic and mesocortical systems is implicated in several disorders. In attention-deficit hyperactivity disorder, psychostimulants may improve attention by correcting a deficit in dopamine release in response to relevant stimuli.[9] Conversely, in psychoses, dopamine excess ("over-attention") may cause hallucinations and delusions, and may account for the beneficial effects of $D_2$ antagonists.[8] There is also interest in inhibiting dopamine-mediated "reward" systems in addiction disorders.

Methylphenidate is probably the most widely used psychostimulant in palliative care.[10,11] However, dextroamphetamine has a potential advantage because it is more often effective with once daily dosing.[12] Sustained-release preparations, though more expensive, may be worth the extra cost if the convenience of prolonged duration of effect without repeat administration is desired. Sustained-release preparations also have more risk of insomnia, particularly if taken later in the day.

About half or less of a dose of dextroamphetamine is excreted renally and largely unchanged; there is thus a theoretical risk of increased toxicity in renal impairment.[10] For selected pharmacokinetic data, see Table 1.

## Cautions

*For full list, see manufacturers' Prescribing Information.*

Psychostimulants may exacerbate cardiovascular disease (e.g., severe hypertension, arrhythmia, and angina); psychiatric illness (e.g., anxiety, agitation, psychosis, and addiction disorders); epilepsy (possible lowering of seizure threshold); hyperthyroidism and closed-angle glaucoma (not modafinil).

## Drug Interactions

*For full list, see manufacturers' Prescribing Information.*

Pharmacodynamic interactions include those with sympathomimetics (e.g., MAOI, see contraindications) and antipsychotics (reduced stimulant effect).

Methylphenidate and modafinil may increase plasma concentrations of tricyclic antidepressants, phenytoin, and warfarin (check INR at least weekly until stabilized). Modafinil also may increase the plasma concentrations of diazepam.

Modafinil induces CYP3A4/5 (reduced efficacy of cyclosporine, HIV-protease inhibitors, midazolam, calcium channel blockers, statins, and hormonal contraception). Modafinil also inhibits CYP2C19 and thus may decrease the plasma concentrations of the active metabolites of clopidogrel.

## Undesirable Effects

*For full list, see manufacturers' Prescribing Information.*

Undesirable effects have been reported in up to 30% of patients.

*Table 1*
**Pharmacokinetic Details for Selected Psychostimulants[13–16]**

| | Oral Bio-availability (%) | Time to Peak Plasma Concentration (h) | Half-Life (h) | Metabolism |
|---|---|---|---|---|
| Dextroamphetamine | No data | 2–4 | 7–17 | Multiple routes; ≤50% renally excreted unchanged |
| Methylphenidate | 30[a] | 1–3 | 2 | Non-CYP carboxylesterase[b] |
| Modafinil | ≥40 | 1.5–3 | d-modafinil 3; l-modafinil 10–16 | CYP3A4; non-CYP esterase[b] |

[a]Almost completely absorbed but undergoes extensive first pass hepatic metabolism.
[b]Metabolites are inactive.

***Neuropsychiatric:*** insomnia, agitation, and anorexia (generally settle after 2–3 weeks if the drug is continued or resolve after 2–3 days if the drug is discontinued), psychosis, movement disorders.
***Cardiovascular:*** tachyarrhythmias, hypertension, and angina (rare).
***Other:*** headache, common and responds to slower dose titration; *very rarely cerebral arteritis occurs with methylphenidate.* Mild rashes are common with modafinil; serious skin reactions occur in 1% of children.

**Use of Psychostimulants in Palliative Care**

A psychostimulant is probably prescribed to less than 5–10% of patients receiving palliative care. Consider warning patients about possible jitteriness, anxiety, insomnia, and/or anorexia.

***Depression***

Psychostimulants are used where a prompt response to treatment is required and tolerance to long-term use is irrelevant. A consensus panel concluded that they were the drugs of choice for treating depression in patients with a prognosis of <3 months.[17] If daily review is practical, it is often possible to achieve a response in a few days, increasing the dose every 1–2 days until a response is obtained or undesirable effects prevent further escalation (Box 1).[11,17] However, published trials are generally of poor quality, short duration, and with outcome measures of uncertain clinical significance. Thus, conventional antidepressants are the drugs of choice for a patient with a sufficient prognosis for a response to manifest, e.g., ≥2–3 months.[5,17,18] Concurrent use with a conventional antidepressant has been reported, and may hasten the response compared with the latter alone, particularly in relation to fatigue.[18]

Methylphenidate is probably the most commonly used psychostimulant for depression in palliative care. With cautious dosing and attention to response, psychostimulants are generally well tolerated (Box 1). Although undesirable effects are similar for all psychostimulants, some patients benefit by switching to an alternative if the first choice is ineffective or poorly tolerated.

***Fatigue***

Psychostimulants may be considered for the treatment of fatigue when other approaches are insufficient.[19–21] These include, when feasible, the correction of underlying causal factors (e.g., anemia, depression, and electrolyte disturbance) and modification to the patient's daily routine (e.g., gentle exercise, energy conservation, and practical help to aid adjustment to changing circumstances).[19] However, RCTs yield conflicting results and the routine use of psychostimulants for fatigue remains controversial.

In cancer patients, methylphenidate[22] and dextroamphetamine[23] were ineffective for cancer-related fatigue, although results of trials of dexmethylphenidate for chemotherapy-related fatigue were conflicting.[24,25] A single-dose study found modafinil improved drowsiness, psychomotor speed and attention in patients with advanced cancer.[26] Further trials of modafinil in cancer patients are underway.

RCTs examining modafinil for fatigue in myotonic dystrophy, Parkinson's disease, and traumatic brain injury found little or no effect.[1,27] Fatigue in multiple sclerosis improved in a small cross-over RCT[28] but not in a larger parallel group study.[29] Benefit was shown in amyotrophic lateral sclerosis (motor neuron disease).[30] A lack of clear benefit may relate, in part, to the large placebo response seen in many trials. Further, some have suggested that the b.i.d. drug regimen may have interfered with sleep and thus exacerbated fatigue in some patients.[31]

***Opioid-Related Drowsiness***

Drowsiness is common when opioids are commenced or the dose is increased; it is generally transient. Persistent drowsiness may indicate opioid toxicity; a trial dose reduction should be made and other drug and non-drug approaches considered to provide adequate analgesia.[32] However, some patients experience persistent drowsiness despite adjusting the opioid dose. In this circumstance, switching to an alternative opioid may be of benefit.[33]

Psychostimulants are sometimes used for opioid-related drowsiness refractory to these measures. They improve psychomotor performance and allow opioid dose escalation to a higher level than would otherwise be possible.[34] This can be particularly helpful for patients experiencing break-through (episodic) pain.[35–38]

**Box 1. Guidelines used at some centers for psychostimulants in depressed patients**

A psychostimulant is the drug of choice for treating depression in patients with a prognosis of <3 months because they may not live long enough to benefit maximally from a conventional antidepressant. It is often possible to achieve a response in a few days by increasing the dose progressively until benefit or undesirable effects occur. Psychostimulants are generally considered *not* as effective as conventional antidepressants, and these should be considered instead or concurrently in patients with a sufficient prognosis for a response to manifest, e.g., ≥2–3 months.

**Advantages**
Well tolerated and generally effective.
No lag time to effect.
Rapid clearance from the body.
Paradoxically improve appetite in the physically ill.

**Disadvantages**
Can only be given by mouth.
May precipitate/exacerbate delirium.
Undesirable effects include restlessness, hallucinations, insomnia, tachycardia, hypertension.
Tolerance may develop.
Withdrawal depression if stopped abruptly after prolonged use.

**Management strategy**
Start with recommended doses (see below).
Re-assess after 2–3 hours to observe maximum benefit and undesirable effects.
Because of the rapid onset of effect, adjust the dose every 1–2 days by the smallest practical amount until:
- the depression resolves *or*
- unacceptable undesirable effects occur *or*
- the maximum recommended dose is reached.

**Drugs of choice**
Methylphenidate:
- start with 2.5–5 mg b.i.d. (early morning and noon)
- if necessary, increase progressively every 1–2 days to 20 mg b.i.d.

Dextroamphetamine:
- start with 2.5–5 mg each morning
- if necessary, increase progressively every 1–2 days to 20 mg each morning
- some patients may require b.i.d. dosing (early morning and noon) if the effect wears off too quickly.

Modafinil:
- start with 100 mg each morning
- if necessary, increase to 200 mg each morning after 1–2 days
- doses up to 400 mg have been used.

**Supply**
Psychostimulants are controlled substances in the USA. Amphetamines and methylphenidate are Schedule II and modafinil Schedule IV. Sustained-release formulations are available for some stimulants (see below).

**Dextroamphetamine** (generic)
***Tablets*** 5 mg, 10 mg, 28 days @ 10 mg once daily = $50.

**Methylphenidate** (generic)
***Tablets*** 5 mg, 10 mg, 20 mg, 28 days @ 10 mg b.i.d. = $23.

Methylin® (Mallinckrodt)
***Tablets*** 5 mg, 10 mg, 20 mg, 28 days @ 10 mg b.i.d. = $23.
***Tablets chewable*** 2.5 mg, 5 mg, 10 mg, 28 days @ 10 mg b.i.d. = $58.
***Oral solution*** 1 mg/mL, 5 mg/mL, 28 days @ 10 mg b.i.d. = $27.

Ritalin® (Novartis)
***Tablets*** 5 mg, 10 mg, 20 mg, 28 days @ 10 mg b.i.d. = $51.

Sustained-release
Concerta® (Ortho-McNeil-Janssen)
***Tablets*** 18 mg, 27 mg, 36 mg, 54 mg, 28 days @ 36 mg once daily = $142.

Metadate® CD (UCB)
***Capsules*** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 28 days @ 20 mg once daily = $109.

Daytrana® (Shire)
***Transdermal patch*** 10 mg, 15 mg, 20 mg, 30 mg, 28 days @ 20 mg once daily = $151.

**Modafinil**
Provigil® (Cephalon)
***Tablets*** 100 mg, 200 mg, 28 days @ 200 mg once daily = $80.

***Other Psychostimulants***
**Armodafinil**
Nuvigil® (Cephalon)
***Tablets*** 50 mg, 150 mg, 250 mg, 28 days @ 150 mg once daily = $293.

**Dexmethylphenidate**
Focalin® (Novartis)
***Tablets*** 2.5 mg, 5 mg, 10 mg, 28 days @ 5 mg b.i.d. = $54.

Sustained-release
Focalin XR® (Novartis)
***Capsules*** 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 28 days @ 10 mg once daily = $133.

**Dextroamphetamine/amphetamine salts**
Adderall® (Shire)
***Tablets*** 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg, 28 days @ 10 mg b.i.d. = $190.

Sustained-release
Adderall XR® (Shire)
***Capsules*** 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 28 days @ 20 mg once daily = $218.

**Lisdexamfetamine**
Vyvanse® (Shire)
***Capsules*** 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 28 days @ 50 mg once daily = $135.

*This is not a complete list.*

## *Abbreviations/Key*

| | | | |
|---|---|---|---|
| † | Off-label indication | GABA | Gamma-aminobutyric acid |
| CYP | Cytochrome P450 | INR | International normalized ratio |
| $D_1$, $D_2$ | Dopamine-1, Dopamine-2 receptors | RCT | Randomized controlled trial |

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