

## Methylphenidate: Its Pharmacology and Uses

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Methylphenidate is a commonly used medication in the United States. This central nervous system stimulant has a mechanism of action distinct from that of amphetamine. The Food and Drug Administration has approved methylphenidate for the treatment of attention-deficit/hyperactivity disorder and narcolepsy. Treatment with methylphenidate has been advocated in patients with traumatic brain injury and stroke, cancer patients, and those with human immunodeficiency virus infection. Placebo-controlled trials have documented its efficacy as an adjunctive

agent in the treatment of depression and pain. This article reviews the current understanding of the mechanism of action and efficacy of methylphenidate in various clinical conditions.

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ADHD = attention-deficit/hyperactivity disorder; AIDS = acquired immunodeficiency syndrome; FDA = Food and Drug Administration; HIV = human immunodeficiency virus

Methylphenidate (Ritalin) is a commonly used medication in the United States. First synthesized in 1944, methylphenidate was initially used as an analeptic for reversal of barbiturate-induced coma.<sup>1</sup> It is now primarily used as treatment of attention-deficit/hyperactivity disorder (ADHD). Estimates are that more than 2 million Americans, mostly children, are currently being treated with methylphenidate.<sup>2</sup> While concerns regarding overuse have been raised,<sup>3</sup> methylphenidate clearly has utility in several clinical situations. Recent articles have reviewed 1 or more aspects of methylphenidate use.<sup>4-10</sup> The goals of this article are to provide a focused review for the clinician regarding what is known about the mechanism of action and pharmacology of methylphenidate and to appraise critically its therapeutic uses. Particular emphasis is given to newer uses in the adult population.

### CHEMISTRY AND MECHANISM OF ACTION

Methylphenidate is a piperidine-derived central nervous system stimulant. The methylphenidate molecule possesses 2 centers of chirality; thus, a total of 4 enantiomers of this drug exist (Figure 1). The earliest marketed preparations of methylphenidate contained all 4 enantiomers. Subsequent study revealed, however, that the *erythro* isomers were devoid of any major central nervous system stimulant effect.<sup>11</sup> As a result, currently available prepara-

tions of methylphenidate contain a racemic mixture of only *d,l-threo*-methylphenidate. As discussed later, the pharmacological activity is attributable to just the *d-threo* isomer.<sup>12</sup>

The complete mechanism by which methylphenidate exerts its behavioral effect remains unknown. Early animal studies indicated that methylphenidate increased efflux of dopamine from neurons<sup>13</sup> and inhibited dopamine reuptake from the synaptic cleft.<sup>14-16</sup> It was subsequently shown that methylphenidate binds to the dopamine transporter in the presynaptic cell membrane, blocking reuptake of dopamine and causing a resultant increase in extracellular dopamine levels.<sup>17-21</sup> This is in contrast to the primary mode of action of amphetamine, which causes the release of newly synthesized cytosolic dopamine from the nerve terminal.<sup>22</sup> The dopamine transporter is thought to be a critical regulator of dopamine homeostasis.<sup>23</sup> At oral therapeutic doses (0.3-0.6 mg/kg), methylphenidate is estimated to occupy more than half of brain dopamine transporters.<sup>24</sup> The gene encoding this transporter has been cloned from both rats<sup>25</sup> and humans,<sup>26</sup> and in humans it is located on chromosome 5p15.3.<sup>27</sup> Associations between polymorphisms of the dopamine transporter gene and various neuropsychiatric conditions, including ADHD, have been explored.<sup>28,29</sup> In the rat, methylphenidate inhibits dopamine reuptake in the striatum, nucleus accumbens, olfactory tubercle, and prefrontal cortex.<sup>17,30,31</sup> Microdialysis studies have confirmed the *in vivo* ability of methylphenidate to increase extracellular dopamine levels in the striatum and nucleus accumbens.<sup>20,32-35</sup> The more recent application of single-photon emission computed tomography<sup>36</sup> has helped to confirm that the highest area of methylphenidate uptake in humans is in the striatum.<sup>12,37,38</sup>

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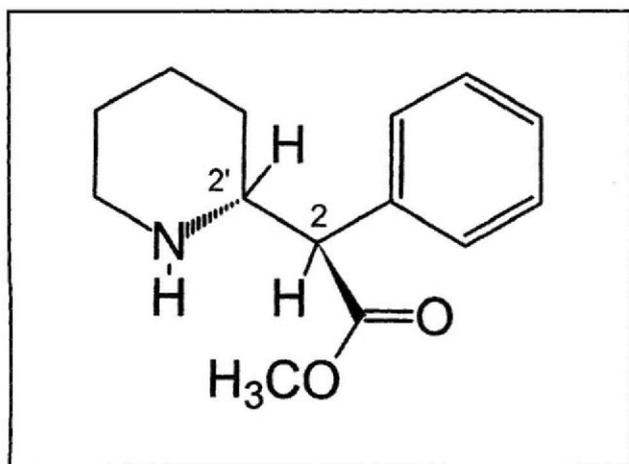


Figure 1. The structure of *d-threo* (2R,2'R)-methylphenidate, the pharmacologically active enantiomer.

Because of these observations, the prevailing theory has been that methylphenidate influences hyperactivity and behavior largely via a direct effect on key dopaminergic areas of the brain.<sup>9</sup> However, methylphenidate has appreciable effects on norepinephrine reuptake<sup>14,21,35,39,40</sup> and also binds (albeit weakly) to the serotonin transporter.<sup>21,41</sup> The possibility that methylphenidate causes its behavioral effects by influencing multiple neurotransmitters has been suggested.<sup>42</sup> A mouse knockout model was recently developed in which the gene for the dopamine transporter was disrupted.<sup>43</sup> These mice exhibited significantly higher levels of baseline locomotor activity compared with wild-type mice and interestingly showed impaired learning.<sup>44</sup> Despite the fact that these mice do not possess any neuronal dopamine transporters, administration of methylphenidate still reduced their hyperactivity. Increasing brain serotonin levels in these mice also had a similar effect.<sup>44</sup> Therefore, investigators have postulated that methylphenidate may work via serotonergic neurons to reduce hyperactivity by restoring a lost balance between certain dopaminergic and serotonergic neuronal circuits.<sup>44</sup> In an earlier study, however, methylphenidate had no effect on extracellular serotonin levels,<sup>35</sup> and since the dose of methylphenidate used in the aforementioned dopamine transporter knockout mouse study was 50 to 100 times the usual therapeutic ADHD dose, the direct applicability of these results to humans remains uncertain.

#### PHARMACOKINETICS AND PHARMACODYNAMICS

After oral administration, methylphenidate is almost completely absorbed and is primarily metabolized via de-esterification to ritalinic acid.<sup>45</sup> Peak plasma concentrations ( $C_{max}$ ) occur 1 to 3 hours ( $T_{max}$ ) after an oral dose of stan-

dard methylphenidate, with a plasma half-life ( $T_{1/2}$ ) of 1.5 to 2.5 hours.<sup>45-48</sup> Absorption seems to be enhanced when methylphenidate is taken with food.<sup>49</sup> Protein binding of methylphenidate is low,<sup>50,51</sup> which may contribute to its relatively brief  $T_{1/2}$ . The metabolism of the enantiomers of methylphenidate is stereoselective. As previously mentioned, the currently available preparations of methylphenidate contain a racemic mixture of *d,l-threo*-methylphenidate. After oral administration of methylphenidate, blood levels of the *d*-isomer are significantly higher.<sup>52-54</sup> No difference is seen in the plasma levels or renal clearance of the isomers in the first 1.5 hours after intravenous administration, indicating that there is enhanced presystemic metabolism of the *l*-isomer after oral administration.<sup>55</sup>

Methylphenidate is available in 5-, 10-, and 20-mg tablets, as well as a 20-mg sustained-release tablet in which the drug is embedded in a wax matrix.<sup>56,57</sup> This formulation has been used for once-daily morning dosing in children with ADHD who would rather not take a noon dose of methylphenidate at school. Pharmacokinetic studies of sustained-release methylphenidate have shown a somewhat longer  $T_{max}$  (3 to 4 hours) and  $T_{1/2}$  (4 hours).<sup>58,59</sup> Additionally, the  $C_{max}$  of sustained-release methylphenidate is lower than that of standard methylphenidate.<sup>59</sup> Because of the nature of the wax-matrix tablet, halving these tablets increases the rate of dissolution,<sup>60</sup> and chewed tablets behave pharmacokinetically similar to an equivalent dose of standard methylphenidate.<sup>55</sup> Adverse effects have been noted in children who chew, instead of swallow whole, sustained-release methylphenidate tablets.<sup>61</sup>

There is an important difference in the pharmacological activities of the 2 enantiomers of *threo*-methylphenidate. Studies in rats indicated that the *d*-isomer is more active in the induction of locomotion than is the *l*-isomer.<sup>62</sup> A subsequent double-blind, 4-way randomized crossover study in humans compared each individual isomer with the racemic mixture and placebo, using computer-based tests of attention.<sup>63</sup> This study showed no difference between the activities of *l-threo*-methylphenidate and placebo and no difference between a 5-mg dose of *d-threo*-methylphenidate and a 10-mg dose of *d,l-threo*-methylphenidate. The clinical effect, therefore, seemed to be entirely attributable to the *d*-isomer. Further microdialysis studies in rats confirmed that *d-threo*-methylphenidate binds stereospecifically in the striatum<sup>64</sup> and increases striatal extracellular dopamine levels substantially more than does *l-threo*-methylphenidate.<sup>65</sup> A more recent study using positron emission tomography in humans showed that the highest uptake of labeled *d-threo*-methylphenidate is in the basal ganglia, whereas *l-threo*-methylphenidate exhibits nonspecific uptake throughout the brain.<sup>12</sup> Therefore, it seems that *d-threo*-methylphenidate is the main pharmacologically ac-

tive isomer. Differences in the plasma concentrations of these isomers in "responders" vs "nonresponders" to methylphenidate<sup>66</sup> indicate that the determination of variation in drug metabolism among individuals may eventually help identify those patients most likely to benefit from treatment with racemic methylphenidate. Clinical trials of a chirally pure preparation of *d-threo*-methylphenidate are in progress.<sup>67</sup>

### CLINICAL USES

The Food and Drug Administration (FDA) has approved methylphenidate for the treatment of ADHD and narcolepsy. Its usefulness in many other conditions has been investigated, including such diverse situations as autonomic failure,<sup>68</sup> giggle incontinence,<sup>69</sup> and weaning patients from mechanical ventilation.<sup>70</sup> A larger body of literature suggests possible therapeutic uses for methylphenidate in medically ill elderly patients with depression, those with traumatic brain injury and stroke, cancer patients, and those with human immunodeficiency virus (HIV) infection.

### Attention-Deficit/Hyperactivity Disorder

Psychostimulants were first used to treat disruptive behavior in children in 1937.<sup>71</sup> Since that era, further research and diagnostic refinement have led to the recognition of ADHD as a distinct clinical entity, with an estimated prevalence in children between 3% and 5%.<sup>72</sup> Methylphenidate is the most widely used medication for the treatment of ADHD. While dilemmas remain in the accurate diagnosis of ADHD,<sup>73</sup> a myriad of studies support the efficacy of methylphenidate and other psychostimulants in the treatment of the symptoms of ADHD in children.<sup>74-77</sup> Methylphenidate may also have a role in the treatment of neurobehavioral symptoms in patients with other developmental disabilities. Its use for hyperactivity in patients with autism,<sup>78</sup> Williams syndrome,<sup>79,80</sup> and Prader-Willi syndrome<sup>81</sup> has been reported, although data from large controlled studies of these conditions are lacking. Other studies have indicated that methylphenidate may be a useful part of the overall therapeutic approach in children with mental retardation and severe behavioral problems.<sup>82-90</sup> Several studies (including 2 double-blind, placebo-controlled trials) have shown comparable short-term efficacy between sustained-release and standard methylphenidate for the management of ADHD.<sup>91-93</sup> One study (also double-blind, placebo-controlled), however, has shown an apparent advantage of standard methylphenidate over the sustained-release formulation in certain behavioral measures.<sup>94</sup>

The persistence of ADHD into adulthood is now recognized.<sup>95</sup> Several studies have examined the efficacy of methylphenidate in treating the symptoms of adults with

ADHD. An early double-blind, placebo-controlled trial of methylphenidate in 11 adult patients with "minimal brain dysfunction" showed significant improvement in measures such as concentration, temper, or calmness in 8 patients.<sup>96</sup> Later studies (also double-blind, placebo-controlled) indicated therapeutic response rates to methylphenidate in 25% to 57% of adults with ADHD-like symptoms.<sup>97-99</sup> This response rate is less than that typically seen in children with ADHD. Potential explanations for this disparity include clinical heterogeneity of the study populations or inadequate dosing.<sup>100</sup> A subsequent controlled trial of methylphenidate in adults with ADHD using more rigid diagnostic criteria showed a beneficial response in 78%.<sup>100</sup>

### Narcolepsy

Another FDA-approved indication for methylphenidate is for the treatment of narcolepsy. An early trial of methylphenidate (dose range, 20-60 mg/d) in 106 patients with narcolepsy revealed a dose-related improvement in sleepiness and sleep attacks, as well as a beneficial effect on "psychic tension."<sup>101</sup> Later controlled trials confirmed that methylphenidate improved the patient's ability to stay awake and had beneficial subjective effects in narcoleptic patients.<sup>102,103</sup>

### Medically Ill Elderly Patients

Among the earliest uses of methylphenidate was as an antidepressant.<sup>104,105</sup> As newer antidepressants were developed, the use of psychostimulants as first-line agents for depression was questioned and is now mainly of historical importance.<sup>106</sup> Interest has persisted, however, in the use of stimulants for depression in certain clinical situations—particularly as a supplemental agent in treatment-refractory depression<sup>107-110</sup> and in medically ill elderly patients. While the usefulness of stimulants in the former situation has been questioned,<sup>111</sup> a body of evidence suggests that methylphenidate and other psychostimulants may have a role in the management of neurobehavioral symptoms in the medically ill elderly population.

Several recent articles have reviewed the uses of stimulants in medically ill patients.<sup>10,112,113</sup> Certain specific clinical situations (brain injury, cancer, acquired immunodeficiency syndrome [AIDS]) will be discussed subsequently in detail. The use of methylphenidate in the geriatric population dates to the 1950s. An early double-blind, placebo-controlled trial of methylphenidate indicated no positive effect on the behavior of a group of elderly, cognitively impaired institutionalized patients.<sup>114</sup> Nevertheless, stimulants were used to treat depression and apathy in geriatric patients. Uncontrolled studies of a combination medication available at the time (Ritonic) containing methylphenidate,

methyltestosterone, ethinyl estradiol, and vitamins supported such use.<sup>115,116</sup> A subsequent double-blind, placebo-controlled trial of methylphenidate in 44 withdrawn, apathetic elderly patients showed an apparent beneficial effect of the medication on cognition and functional status.<sup>117</sup> A similar study, however, could not confirm a positive effect of methylphenidate on cognitive functioning in moderately impaired elderly persons.<sup>118</sup>

A series of case reports and retrospective studies have advanced the theory that methylphenidate and other psychostimulants may be useful in particular settings, especially in alleviating depressive symptoms in patients with various medical illnesses.<sup>119-124</sup> A double-blind, placebo-controlled trial of methylphenidate in depressed, medically ill elderly patients subsequently revealed that moderate or dramatic improvement in depressive symptoms was achieved in 10 of 13 patients without serious adverse effects.<sup>125</sup> More recent uncontrolled studies suggest potential uses for methylphenidate in apathy due to various etiologies,<sup>126</sup> as treatment of negative symptoms in patients with dementia,<sup>127</sup> and for treatment of depression and cognitive symptoms in liver transplant recipients.<sup>128</sup>

### Brain Injury

Psychostimulants including methylphenidate have been evaluated for use in the treatment of the sequelae of brain injuries due to both trauma and stroke.<sup>129</sup> The results of studies using methylphenidate in the treatment of neurobehavioral symptoms after traumatic brain injury have been mixed. A role for psychostimulants in improving memory and attention in brain-injured patients has been proposed.<sup>130</sup> Double-blind, placebo-controlled studies have shown both positive effects of methylphenidate on neurobehavioral symptoms<sup>131-133</sup> and no pronounced effect.<sup>134,135</sup> Heterogeneity of the study populations, particularly the time elapsed since the injury, confound the interpretation of these results. The possibility of carryover effects encountered during placebo-controlled crossover trials has also been identified.<sup>131</sup> Psychostimulants may have a role in alleviating certain neurobehavioral symptoms in patients immediately after a brain injury,<sup>132,136,137</sup> whereas their effect may be less dramatic when administered at a later time.<sup>131,134</sup> Case reports have indicated that methylphenidate may be useful in the acceleration of recovery from coma,<sup>138</sup> although further controlled studies are needed to determine its efficacy for this indication. Specific use of methylphenidate in treating posttraumatic narcolepsy<sup>139</sup> and brain injury-related anger<sup>140</sup> has also been reported. Concerns about the possibility of increased risk of seizures in brain-injured patients who are taking methylphenidate have not been substantiated. In fact, the only study addressing this issue showed a reduction in seizure frequency in

brain-injured patients with seizure disorders who were taking methylphenidate.<sup>141</sup>

Case reports and retrospective analyses have pointed toward a role for psychostimulants in stroke patients with depression<sup>120,123</sup> and in treating hemineglect after stroke.<sup>142</sup> Retrospective studies have indicated response rates from 52% to 70% in depressed patients who have had a stroke and are being treated with methylphenidate.<sup>143-145</sup> Improvement was generally rapid (within 48 hours). An open trial of methylphenidate for depression in patients who had had a stroke resulted in full or partial response in 8 of 10 patients.<sup>146</sup> Adverse effects occurred in half of the patients but were mild and did not interrupt therapy. A recent double-blind, placebo-controlled trial showed that methylphenidate may be helpful in the early recovery period after a stroke has occurred.<sup>147</sup> Twenty-one patients who had had a stroke were given either methylphenidate or placebo after admission to a rehabilitation unit. Significant reductions in depression rating scales and enhancements in motor and functional scores were seen in the methylphenidate-treated patients compared with the placebo controls.

### Cancer

Cancer patients commonly experience cognitive changes, and as many as 50% will develop a depressive disorder during the course of their illness.<sup>148,149</sup> Both the disease itself (as in the case of central nervous system tumors) and the various treatments (radiation therapy, chemotherapy, opiates) can contribute to neurobehavioral changes. Methylphenidate has been evaluated as a potential therapy for improving mood, cognition, and pain control in cancer patients.

While several case reports<sup>150,151</sup> have suggested a possible role for methylphenidate in improving mood and reducing sedation in cancer patients, few controlled studies have investigated this issue in detail. A series of 5 patients with head and neck cancers were reported to have improvement in mood, appetite, and energy when treated with methylphenidate.<sup>152</sup> These patients were thought to have depression due to their medical illnesses, and, in 1 patient, cognitive changes from radiation therapy delivered to the right hemisphere. A larger study evaluated the response to methylphenidate in 30 cancer patients with depressive symptoms.<sup>153</sup> These patients needed a rapid response, were at high risk of adverse reactions to tricyclic antidepressants, or had a contraindication to the use of tricyclic antidepressants. Of these 30 patients, 23 had a moderate or substantial improvement in their depressive symptoms with the use of methylphenidate, with most showing a response within a few days after initiation of treatment. A retrospective study of 15 hospitalized cancer patients treated with methylphenidate for depression showed

that 80% had a positive response.<sup>154</sup> Five patients had an improvement in their appetite. Minor side effects were seen in 3 patients. As in the earlier studies, the depressive symptoms improved rapidly (1 to 2 days) in most patients. A less dramatic response rate was seen in a study of 26 hospice patients with advanced malignancies treated with methylphenidate for depression; 46% of these patients showed a therapeutic response.<sup>155</sup> Only 7% of patients in the last stages of their illness (within 6 weeks of death) showed improvement in their depressive symptoms.

Interest has arisen in the use of methylphenidate in patients with brain tumor who routinely experience neuropsychiatric effects from both the tumor and the various treatment strategies. Improvement in neurobehavioral slowing was seen in 3 patients with brain tumors treated with low-dose methylphenidate.<sup>156</sup> In 30 patients with malignant gliomas treated with methylphenidate, improvements in cognitive functioning and performance status were demonstrated despite ongoing neurologic injury due to disease progression or radiation therapy in half of these patients.<sup>157</sup> In a series of 12 children with brain tumors or acute lymphocytic leukemia and consequent tumor- or therapy-induced neurologic injury, 10 showed improvement in attention, academic performance, language skills, memory, or behavior when treated with methylphenidate.<sup>158</sup>

Psychostimulants can potentiate the effects of opioid analgesics.<sup>159,160</sup> Methylphenidate has been studied as adjuvant therapy for cancer patients receiving narcotics. In a randomized, double-blind, placebo-controlled crossover trial of 32 patients with advanced cancer receiving chronic opiate therapy, statistically significant reductions in pain intensity and sedation were seen with the use of methylphenidate.<sup>161</sup> A more recent study of methylphenidate showed no added benefit in patients taking narcotics for cancer pain but suggested some improvement in sedation.<sup>162</sup> In a study of 50 patients with advanced cancer and opiate-induced sedation, 44 had a decrease in sedation after initiation of methylphenidate.<sup>163</sup> Tolerance to this effect was seen over a period of 1 month. Patients with incident cancer pain (mild or no pain at rest, severe pain during movements) showed better pain control, and they tolerated higher doses of narcotics when supplemented with methylphenidate.<sup>164</sup> A placebo-controlled trial demonstrated that the addition of oral methylphenidate resulted in improved cognitive function in 20 patients receiving continuous subcutaneous narcotics for cancer pain.<sup>165</sup> Similarly, 5 of 11 adolescent cancer patients receiving opiates exhibited improved interaction with family or decreased somnolence when methylphenidate was added to their medication regimen.<sup>166</sup>

### HIV Infection

Cognitive impairment and neuropsychiatric symptoms are common in people infected with HIV-1. Impaired memory, decreased attention, and related neurobehavioral symptoms are typical features. These features have prompted interest in the use of psychostimulants in this group of patients.<sup>167</sup> Case reports have indicated the potential role for methylphenidate in addressing cognitive difficulties and depression in patients with AIDS.<sup>168,169</sup> Uncontrolled trials of methylphenidate, amphetamine, or both in patients with HIV-related cognitive decline or depression have shown a positive effect of these agents on both subjective and objective neurobehavioral factors,<sup>170-172</sup> although the lack of a control group in these studies limits their usefulness. A comparative trial of methylphenidate and desipramine showed similar efficacy between the 2 drugs in alleviating depressive symptoms.<sup>173</sup> A double-blind, placebo-controlled trial of methylphenidate in a single AIDS patient demonstrated improved scores concerning depression and possibly enhanced cognitive functioning.<sup>174</sup> More recently, however, a double-blind, placebo-controlled crossover trial of sustained-release methylphenidate in HIV-1-infected drug abusers failed to show that methylphenidate was superior to placebo in the treatment of cognitive impairment.<sup>175</sup> Small sample size and the effects of time, medical treatment, and drug abstinence on the results of neuropsychological testing are factors that may preclude generalization of these results. Larger, longer-term studies are needed.

### DOSING, ADVERSE EFFECTS, AND RISK OF ABUSE

Methylphenidate is FDA-approved for use in children older than 6 years and in adults. Typical dosing schedules for various indications are shown in Table 1. Potential adverse effects of methylphenidate are listed in Table 2. Several issues regarding possible adverse effects deserve special mention. Anorexia is a common adverse effect of stimulant use, and there have been concerns that methylphenidate may suppress growth in children being treated for ADHD. Whether growth alterations are a direct methylphenidate effect<sup>176-178</sup> or related to ADHD itself,<sup>179</sup> the cause and importance of these decreases in growth velocity remain unresolved. Another lingering issue is the role of stimulants in precipitating or exacerbating tic disorders.<sup>180</sup> Recent studies have indicated that methylphenidate, in usual doses, does not cause tics in most children or worsen tics in children with mild to moderate tic disorders.<sup>181,182</sup> Observation for the development or exacerbation of tics in patients taking methylphenidate is still recommended, however, because some patients may be susceptible.

The abuse potential of methylphenidate is another issue that has received considerable attention. Methylphenidate

Table 1. Dosing Regimen for Methylphenidate

Age group	Indication	Typical initial dose	Usual maximal daily dose
Children (>6 y)	Attention-deficit/hyperactivity disorder	Regular release: 5 mg twice daily, with or after breakfast and lunch Sustained release: 20 mg once daily	60 mg
Adults	Attention-deficit/hyperactivity disorder, narcolepsy	Regular release: 5 to 20 mg 2 to 3 times daily, with or after meals Sustained release: 20 mg 1 to 3 times daily, at 8-h intervals	90 mg
	Depression due to medical illness	Regular release: 5 to 10 mg 2 to 3 times daily	30 mg

and cocaine both bind to the dopamine transporter and compete for the same binding sites in the striatum.<sup>38</sup> When given intravenously, methylphenidate can induce a sensation of euphoria.<sup>38</sup> Methylphenidate has been abused both intravenously<sup>183</sup> and intranasally.<sup>184,185</sup> Despite these facts, methylphenidate has a much lower abuse potential than cocaine, possibly related to other pharmacological differences between the 2 drugs.<sup>186</sup> Numerous studies in adults have shown no indication that the use of oral methylphenidate in the medically ill population leads to problems of abuse.<sup>10</sup> It is prudent, however, to always remember the possibility of abuse or diversion of the drug, keep careful records, and consider using nonstimulant medications in patients who have a personal or family history of current or past substance abuse problems.<sup>8</sup>

### CONCLUSIONS

Methylphenidate is widely used in the United States. Its mechanism of action and pharmacology, which are distinct from those of other central nervous system stimulants such as amphetamine, illustrate the increasing importance of understanding issues of stereospecificity in drug action. While appropriate concerns have been raised regarding the possible long-term effects and abuse potential of methylphenidate, there is evidence that its utility may extend beyond solely the treatment of ADHD (Table 3). Studies support a role for methylphenidate in the treatment

of depressive symptoms in medically ill elderly patients and stroke patients. Psychostimulants may be most beneficial in patients in whom a rapid response in the depressive symptoms is desired or in whom potential adverse effects of standard antidepressants would be undesirable. Depressive symptoms and cognitive functioning in cancer patients may be improved by the addition of methylphenidate, although the absence of controlled trials limits conclusive recommendations. Stronger evidence exists showing the usefulness of psychostimulants in potentiating the analgesic effects of opiates and in reducing opiate-induced sedation. Currently, there is no conclusive evidence that methylphenidate accelerates recovery in patients with traumatic brain injury or ameliorates cognitive impairment in patients with HIV infection; thus, further controlled studies are needed to help further define its usefulness in these patients.

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Table 2. Selected Methylphenidate Adverse Effects

System	More frequent	Less frequent
Cardiovascular	Hypertension, tachycardia	Angina, dysrhythmias
Central nervous system	Insomnia, nervousness	Headache, dizziness, dyskinesia
Gastrointestinal	Anorexia	Nausea, abdominal pain, weight loss
Dermatologic	...	Rash, urticaria

Table 3. Some Proven and Unproven Uses of Methylphenidate

Clinical use	Efficacy supported by double-blind, placebo-controlled trial	References
Attention-deficit/hyperactivity disorder	Yes	8, 73
Narcolepsy	Yes	102, 103
Depression in medically ill (including stroke) elderly persons	Yes	125, 147
Alleviation of neurobehavioral symptoms after traumatic brain injury	Mixed	131-135
Improvement in pain control, sedation, or both in patients receiving opiates	Yes	159-166
Treatment of cognitive impairment in patients with human immunodeficiency virus infection	No	175

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