

*Review Article*

# Methylphenidate and Its Under-recognized, Under-explained, and Serious Drug Interactions: A Review of the Literature with Heightened Concerns

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## Abstract

*Methylphenidate arguably is the most successful psychiatric medication in history. Response rates in some studies are as high as 78%, and, despite opposition to medicating children with psychostimulants, the use of methylphenidate in the treatment of Attention-Deficit/Hyperactivity Disorder in both pediatric and adult populations has dramatically increased over the last decade. Along with this increased use, and in conjunction with black box warnings on antidepressants and psychostimulants, has come an increased awareness of the risks associated with the use of methylphenidate and other stimulants including seizures, heart attacks, strokes, and precipitation of mania or psychosis. Serious drug-drug interactions, with the exceptions of interactions with monoamine oxidase inhibitors, warfarin, and meperidine, rarely are attributed to methylphenidate, possibly due to its success and longevity. Many Cytochrome P450 isoenzyme (CYP450) drug interaction charts generally do not list methylphenidate either as a substrate or an inhibitor of particular enzymes. Yet, this review reveals a number of CYP450 interactions, many potentially serious, between methylphenidate and commonly prescribed medications in nearly every class. Further, these interactions and their known or hypothesized mechanisms imply that more such interactions will come to light in the near future. Such interactions can be more carefully anticipated and are predictable from the known pharmacodynamics and pharmacokinetics of methylphenidate (German J Psychiatry 2013; 16(1): 29-42).*

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## Introduction

**M**ethylphenidate is a central nervous system stimulant that appears to exert its therapeutic effects by increasing synaptic concentrations of dopamine and norepinephrine through antagonism of dopamine and norepinephrine transporters (Findling, 2008; Volkow et al., 1998). Methylphenidate also appears to cause dopamine transporters to reverse causing a re-release of recently re-

uptaken dopamine into synapses in the brain stem, mesolimbic pathways, and prefrontal and frontal cortices (Stahl, 2005). There also is evidence that methylphenidate increases cortical concentrations of acetylcholine secondarily through this enhanced dopaminergic and noradrenergic transmission (Leonard et al., 2004). We view this as a primary pro-dopaminergic, secondary pro-noradrenergic, and tertiary pro-cholinergic mechanism. Additionally, methylphenidate also appears to act as an agonist at the  $\mu$  opioid receptor which may account for some of the euphoria experienced by

those who abuse it, making this mechanism a pharmacological target for prevention of stimulant abuse (Zhu et al., 2011).

Methylphenidate presently is approved for the treatment of narcolepsy and, in combination with behavioral and systems management therapies, is effective in addressing symptoms associated with Attention-Deficit/Hyperactivity Disorder (ADHD), including distractibility, inattention, hyperactivity, emotional lability, impulsivity, and aggression in children, adolescents, and adults (Jensen et al., 2001; Nevels et al., 2010; Pelham et al., 1987). More recently, methylphenidate has been purported to act as a neuroprotective agent in disease states ranging from methamphetamine toxicity (Kim et al., 2000) to Parkinson's disease (Devos et al., 2007). It also has been studied and promoted for treating post-stroke depression (Lazarus, et al., 1994; Lingam et al., 1988; Masand & Chaudhary, 1994; Masand et al., 1991; Ramasubbu & Goodyear, 2008; Robinson, 2003), weaning patients from mechanical ventilation (Johnson et al., 1995), treating giggle incontinence (Sher & Reinberg, 1996), and ameliorating the psychological distress related to both cancer and human immunodeficiency virus infection (Challman & Lipsky, 2000; Fernandez & Adams, 1986; Fernandez et al., 1995; Viganò et al., 1995; Volz, 2008; White et al., 1992).

Pharmacokinetic studies have shown that methylphenidate is almost completely absorbed and primarily metabolized by de-esterification to ritalinic acid (carboxylesterase 1 is a critical enzyme in this cascade—see below). In animals, peak plasma concentrations occur 1–3 hours after an oral dose with a plasma half-life of 1.5–2.5 hours. In the currently available preparations, methylphenidate contains a racemic mixture of D, L-threo-methylphenidate, the D-isomer apparently being more pharmacologically active than the L-isomer, confirmed by experimental studies in which the D-isomer increases the extracellular concentration of dopamine more potently than the L-isomer. Similar results have been reported in PET studies in man (Leonard et al., 2004). The long-term effects of methylphenidate largely remain unknown. Growth suppression has been reported with chronic stimulant administration in rats (Greeley & Kizer, 1980) and chronic use in humans (Kramer, 2000; Satterfield et al., 1979; Shader et al. 1999; Vitiello et al., 2001). Evidence suggests that methylphenidate and other psychostimulants act to lower the seizure threshold (Erdemoglu et al., 2003; Wroblewski et al., 1992). Other reported potential adverse short to medium term reactions include visual disturbances, nervousness, insomnia, anorexia, nausea, dizziness, headache, dyskinesias, drowsiness, changes in blood pressure and pulse, angina, cardiac arrhythmias, abdominal pain, and weight loss (Findling et al., 2001; Novartis Pharmaceuticals, 2001; Pelham et al., 2001; Stahl, 2008). Effects on blood glucose levels appear to be minimal (Lewis et al., 2001); however, there have been reports of increased glucose with methylphenidate and other sympathomimetics (Sund & Zeiner, 2005; Wender, 2001). In addition to potentially life-threatening side effects (e.g., cardiac arrhythmias and seizures), methylphenidate has been linked to the precipitation and/or exacerbation of mental illness, including onset of mania (with and without psychosis), depression, agitation, aggression, and suicidality (DelBello et al., 2001; Ross, 2006; Soutullo et al., 2002).

As the use of methylphenidate for treating ADHD and other syndromes has increased, so has its illicit use and abuse. Aside from relatively well understood effects associated with primary pro-dopaminergic and secondary pro-noradrenergic activity, it had been theorized that endogenous opiate activity also was involved in producing the euphoria associated with methylphenidate and other stimulant abuse. Using a mouse model, Zhu et al. (2011) showed that supra-therapeutic doses of methylphenidate produced rewarding effects in a conditioned place preference paradigm and greatly increased mu ( $\mu$ ) opioid receptor (MOPR) activity (occupancy) in the reward circuitry of the striatum and nucleus accumbens. They also found that co-administration of the opioid receptor antagonist naltrexone prevented methylphenidate induced activation of the  $\mu$  receptor and obviated its rewarding effects. Interestingly, the rewarding effect required activation of dopamine D1 (excitatory) receptors but not D2 (inhibitory) receptors. These findings identify the mu opioid receptor as a potential target for attenuating the rewarding effects of methylphenidate and suggest that combining naltrexone or other opioid antagonists with methylphenidate possibly could reduce the abuse potential of methylphenidate and other stimulants.

## Methylphenidate Drug Interactions

From a review of recent literature, it appears that methylphenidate drug interactions remain under-reported or poorly explained. This is coupled with increasing use of this agent to address a widening range of conditions. For example, use of methylphenidate to address the neurobehavioral deficits associated with various neurological disorders (e.g., stroke, traumatic brain injury) has increased substantially during the past 15 years. Results have varied across investigations, but there have been documented improvements with methylphenidate for these conditions on tests of memory and motor functioning, tests of vigilance and sustained attention, measures of information processing speed, and observational ratings of mood and behavior (Pelham et al., 2001; Sund & Zeiner, 2005; Whyte et al., 2002).

Thus, as neurobehavioral improvement and other uses for methylphenidate have increased, so has the potential for drug interactions. Many of these patients are middle-aged to older adults and are more likely to be on polypharmacy. Simple pharmacodynamic interactions are to be expected, and the likelihood of more complex pharmacodynamic interactions increases with the number of medications administered. The majority of drug interactions, however, are pharmacokinetic in nature (Markowitz & Devane, 2000; Markowitz & Patrick, 1996, 2001). The literature is replete with methylphenidate studies, but relatively little mention of methylphenidate interactions. When interactions are reported, satisfying kinetic/dynamic explanations often are lacking. In part, methylphenidate's long-term success likely is a factor. As mentioned, the pharmacotherapy of ADHD with methylphenidate has received the largest empirical support

of any pharmacological treatment in the history of psychiatry (Boxtel et al., 2001; Julien et al., 2008; Stahl, 2008).

## CYP450 Interactions

In both children and adults, the majority of drug interactions involve the CYP450 (sometimes shortened to P450) isoenzyme system. These enzymes are subject to induction and inhibition by drugs, certain foods, and/or metabolites and are located in the liver, gut, kidneys, lungs, brain, and heart. The capacity of these enzymes is regulated by genes in response to environmental triggers. P450 enzymes metabolize toxins and medications and help to synthesize endogenous hormones, vitamins, and other homeostatic substances. Drugs or toxins may induce or increase drug metabolism by enzymatic receptor binding and/or gene activation or deactivation resulting in either the increased or decreased production of enzymes or other proteins (Preskorn & Flockhart, 2009).

In inhibitory interactions, P450 isoenzymes are inhibited by the drug tightly binding to the P450 heme-iron complex of the enzyme and competitively reducing the metabolism of other substrates of that enzyme. Additionally, some substrates have metabolites that complex the heme-iron and render it catalytically inactive. Again, these drugs, substrates, and metabolites bind to the heme-iron receptor and inactivate the enzyme, which causes inhibition. This inhibition can be reversible, quasi-reversible, and irreversible. Thus, higher levels of the substrate (up to three times more than normally would be expected) can be in the patient's serum and be active (Preskorn & Flockhart, 2009). Methylphenidate inhibits the P450 metabolism of substrates with which it interacts, with subsequent substrate serum concentration elevations.

The Physicians' Desk Reference Guide to Drug Interactions (Thomson Healthcare, 2012) cautions about interactions between methylphenidate and antidepressants, particularly tricyclics (TCAs), which often are substrates for CYP2C9. Such interactions are noted to be methylphenidate-initiated inhibitory interactions in which the serum concentrations of the TCAs in question are increased significantly. Among these TCAs are drugs such as imipramine, doxepin, desipramine, amitriptyline and triptyline. Methylphenidate interactions with selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, and serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, in which levels of these antidepressants are increased significantly, also are highlighted (Breggin & Scruggs, 2001). Therefore, methylphenidate may inhibit several other CYP450 isoenzymes (e.g., 2C19, 2D6, and 3A4), and inhibitory interactions among methylphenidate and other drug substrates for those isoenzymes are to be expected. It also appears that methylphenidate is a substrate for 2D6 as well as a weak inhibitor of 2D6. Thus, inhibitory interactions might be possible between methylphenidate and drugs that are potent or even moderate inhibitors of 2D6 (e.g., fluoxetine, paroxetine, bupropion) in which serum levels of methylphenidate would increase. Additionally, as a weak inhibitor of an isoenzyme for which it is a substrate, methylphenidate could inhibit its own metabolism. As a result, a slight upward dos-

age adjustment periodically might be needed even in some patients on monotherapy.

## Cyclosporine Interaction

Lewis et al. (2001) reported a case of a 10-year-old boy with a heart transplant who experienced a potentially life-threatening decrease in his cyclosporine blood levels during administration of bupropion. Subsequently, he had an increase in cyclosporine levels while receiving methylphenidate. Prior to 2001, these drug interactions had not been documented in the literature. The authors state that cyclosporine-bupropion and cyclosporine-methylphenidate interactions merit further investigation because such agents often are prescribed in combination with immunosuppressants in transplantation patients of all ages. The authors offered little explanation other than that these interactions are significant and appear to be pharmacokinetic in nature.

## Antidepressants and Methylphenidate

Reported and/or warned-against methylphenidate interactions include antidepressants, especially TCAs, SSRIs, monoamine oxidase inhibitors (MAOIs), and bupropion. MAOI interactions are well understood, are relatively straightforward, and are the quintessential model of drug interactions. They result from methylphenidate's mediated increases in possibly all of the monoamines, but specifically norepinephrine and dopamine, which can lead to a hypertensive crisis. More specifically, monoamine oxidase is prevented from degrading intracellular monoamines resulting in synaptic hyper-availability. Interestingly, both linezolid and methylene blue now are categorized as reversible MAOIs. Other antidepressant interactions typically are not pharmacodynamically or pharmacokinetically explained and leave the clinician or pharmacist to guess at the mechanism(s) that might be involved. As most of the available antidepressants result in an increase in the synaptic availability of one or all of the monoamines, specifically serotonin and norepinephrine, and methylphenidate also increases monoamines postsynaptically, increased additive or synergistic agonistic effects of monoaminergic transmission with very high rates of postsynaptic receptor occupancy and increased adverse reactions would seem likely. There are many reports of the inhibition of antidepressant metabolism, however, which would lead to higher serum levels, greater areas under the curve, and longer durations of activity (longer half-lives) of these agents that functionally would be equivalent to the administration of higher doses of the medication in question, namely overdose levels with increased side effects and adverse reactions (Breggin & Scruggs, 2001; Wolraich et al., 2008; Zhu et al., 2008).

TCAs are metabolized by multiple CYP450 isoenzymes. Major pathways of TCA metabolism leading to pharmacologically active products include *N*-demethylation and ring hydroxylation (Skjelbo et al., 1991). *N*-demethylation to desipramine is mediated by CYP1A2, CYP3A4, and CYP2C8; whereas, aryl hydroxylation primarily proceeds

through CYP2D6 (Lemoine et al., 1993; Skjelbo et al., 1991). A number of early reports have implicated methylphenidate as an inhibitor of TCA metabolic clearance. Wharton et al. (1971) reported significantly elevated imipramine plasma concentrations in several patients following the addition of methylphenidate 20 mg/day. Zeidenberg et al. (1971) found that 2 of 6 adult patients treated with imipramine may have had TCA plasma concentrations rise as a result of methylphenidate treatment. Cooper and Simpson (1973) reported significantly higher imipramine and desipramine concentrations following the addition of methylphenidate in a patient treated with imipramine 300 mg/day. In contrast, other reports have found no effects of methylphenidate on TCA metabolism. Drimmer et al. (1983) found a small decline in serum desipramine concentration when methylphenidate 40 mg/day was added to a patient's regimen of desipramine 250 mg/day. In a double-blind cross over study in children, Pataki et al. (1993) reported greater adverse effects in 10 patients treated with desipramine plus methylphenidate than with methylphenidate alone, although no significant influences of methylphenidate on desipramine blood concentrations were found. Flemenbaum (1972) reported three cases of hypertensive episodes occurring in patients treated with TCAs following the addition of methylphenidate. It should be noted, however, that all patients had a history of labile blood pressure. These episodes abated upon discontinuation of methylphenidate, and two of the patients had repeat episodes upon drug rechallenge. Burke et al. (1995) cautioned of an additive effect of methylphenidate to blood dyscrasias associated with imipramine therapy, although no plasma sampling was performed. Grob and Coyle (1986) also described two cases of suspected methylphenidate-imipramine interactions in children who developed increased agitation, aggression, and violence. These behaviors subsided when both medications were discontinued.

McGlohn and Bostwick (1995) reported the development of visual hallucinations and confusion in a 61-year-old male patient several days after adding methylphenidate 10 mg/day to an existing regimen of sertraline 100 mg/day. Symptoms resolved within 24 hours of the discontinuation of methylphenidate. This patient previously had tolerated methylphenidate at 5 mg/day in conjunction with the sertraline without adverse effects, so this may have been the result of a higher methylphenidate dosage rather than a true drug interaction. Feeney and Klyklyo (1997) described a case of a 13-year-old patient treated with methylphenidate 80 mg/day for seven months who experienced a tonic-clonic seizure approximately one week after the addition of sertraline 50 mg/day. The following day, sertraline was discontinued and the patient remained seizure-free on the methylphenidate regimen. Sertraline and other SSRIs have been associated with induction of seizures, making specific causality difficult to establish in this case. A number of reports have documented the well tolerated use of SSRIs with methylphenidate. Gammon and Brown (1993) reported successfully treating 32 patients with ADHD (9 to 17 years of age) with comorbid mood disorders using a combination of fluoxetine and methylphenidate. Findling (1996) also described successfully treating four children and adolescents (11 to 16 years of age) for comorbid depression and ADHD

with either fluoxetine (mean dosage 46.7 mg/day) or sertraline (mean dosage 37.5 mg/day) in combination with methylphenidate 10 to 40 mg/day. No significant adverse effects were indicated. Findling also described successfully treating one adult patient with sertraline 100 mg/day and three adult patients with fluoxetine 20-40 mg/day in combination with methylphenidate. Furthermore, Stoll et al. (1996) have reported that SSRIs can be combined safely with methylphenidate in adults.

#### *Serotonin Syndrome by Methylphenidate Augmentation of SSRI in an Elderly Female*

Augmentation of SSRI therapy with methylphenidate is one form of combination polypharmacy for patients with treatment resistant major depression, especially elderly patients (Julien et al., 2008; Stahl, 2005). Motoyasu et al. (2008) reported the case of a 62-year old woman hospitalized for severe, unremitting depression who had no history of neurologic disorders and had normal serum studies, including thyroid function tests. Magnetic resonance imaging (MRI) disclosed multiple subcortical infarcts, but neurological examinations detected no abnormalities. Neither paroxetine at 40 mg/day, milnacipran at 100 mg/day, nor nortriptyline at 225 mg/day could alleviate her depression, and electroconvulsive therapy also was ineffective. On day 111 of hospitalization, sertraline was started and the dose was increased to 100 mg on day 122, but the patient remained treatment resistant. On day 125, 10 mg of methylphenidate was added as augmentation to the sertraline. On day 130, the patient suddenly developed profuse diaphoresis and muscle rigidity. Body temperature elevated to 37.4°C, and heart rate and blood pressure increased to 100/min and 154/109 mmHg, respectively. She had marked mydriasis (9 mm) and symmetrical potentiation of deep tendon reflexes in all limbs. Blood leukocyte count was 5200/ml, and creatine kinase was 281 IU/L. Repeat MRI showed no new brain abnormalities. Medication was discontinued immediately and all neurological symptoms resolved within 10 days. Methylphenidate + SSRI serotonin syndrome, a first in the literature, was reported.

In summary, data suggests that some patients who receive co-administration of antidepressants with methylphenidate will experience a drug interaction. For example, methylphenidate with imipramine can result in increased concentrations of imipramine. The research is mixed, however, so caution is advised and extraordinary justification would be needed in today's pharmacological zeitgeist to justify TCA and methylphenidate combination therapy. The narrow safety margin for all TCAs is an ongoing concern, especially for a methylphenidate mediated inhibitory interaction. As for SSRIs, SNRIs, NDRI, SARI, NRI, mirtazapine, and newly approved viloxodone (a 5HT<sub>1A</sub> partial agonist and SRI), though safety margins in regard to inhibition by methylphenidate is much less of a concern than for TCAs, still there is the potential for multiple types of interactions.

## Anticonvulsants and Methylphenidate

Anticonvulsant agents commonly are co-administered with psychostimulants in both the treatment of comorbid psychiatric conditions and epilepsy. Present clinical practice frequently involves the use of carbamazepine, valproic acid, gabapentin, or lamotrigine for a variety of psychiatric disorders. Consequently, the risk for drug-drug interactions (DDIs) is considerable. An early report implicated methylphenidate as an inhibitor of phenytoin metabolism, and current methylphenidate prescribing information continues to warn of this effect. Garrettson et al. (1969) reported a early case in which a 5-year-old receiving phenytoin and primidone with methylphenidate 20 mg/day developed ataxia following an increase in methylphenidate to 40 mg/day. Therapeutic drug monitoring revealed an approximately 4-fold increase in the serum concentrations of phenytoin and primidone over baseline values. Additionally, concentrations of phenobarbital, a metabolite of primidone, increased by approximately 50% over baseline. These values returned to normal following methylphenidate discontinuation. Ghofrani (1988) reported a case of phenytoin toxicity in a 10-year-old child, possibly precipitated by the addition of methylphenidate 20 mg/day to an existing regimen of phenytoin 8 mg/kg/day. The baseline plasma phenytoin concentration was 11.9 mg/L, while the follow-up concentration after symptoms of toxicity was 50 mg/L. Phenytoin concentrations reportedly declined after methylphenidate was discontinued. Larger, more systematic studies have not found methylphenidate to influence the disposition of phenytoin (Kupferberg et al., 1972; Mirkin & Wright, 1971).

A double-blind crossover study was conducted by Gross-Tsur et al. (1997) to assess the safety and efficacy of methylphenidate versus placebo in the treatment of children with epilepsy and ADHD. Anticonvulsant concentrations from 27 patients were compared before and after methylphenidate 0.3 mg/kg or placebo. Prior to initiating methylphenidate therapy, 18 patients were receiving valproic acid only, five carbamazepine only, and one phenytoin only. The remaining three patients received a combination of valproic acid and carbamazepine, valproic acid and ethosuximide, and carbamazepine and vigabatrin. Significant changes were not detected in any anticonvulsant plasma concentration measured. Furthermore, none of the 25 patients who were seizure-free prior to the research had any ictal events while taking methylphenidate. There have been at least two case reports of purported carbamazepine-induced reductions of methylphenidate plasma concentrations. Behar et al. (1998) reported a case in which a 7-year-old patient failed to respond to escalating doses of methylphenidate (up to 35 mg every four hours) in combination with carbamazepine 1000 mg/day. Notably, neither methylphenidate nor ritalinic acid could be detected in plasma at two hours (typical time of peak concentration after the methylphenidate dose). Carbamazepine doses also were escalated during this period, which could have attenuated the therapeutic effects of methylphenidate.

Schaller and Behar (1999) reported a single case in which a patient's methylphenidate plasma concentration decreased by over 50% following the initiation of carbamazepine. In this

case, it became necessary to prescribe larger dosages of methylphenidate to maintain therapeutic effects. This would be consistent with carbamazepine's induction of most CYP450 isoenzymes. In contrast, however, Gross-Tsur (1999) reported no loss of methylphenidate activity in patients treated with carbamazepine.

## First Generation Antipsychotics and Methylphenidate

First generation antipsychotic medications frequently have been co-administered with psychostimulants (Connor et al., 1997; Wilens et al., 1995). Even though it has long been recognized that moderate to large doses of stimulants may worsen or precipitate psychosis (Janowsky & Davis, 1976), there also is concern as to whether the co-administration of antipsychotic medication (primarily dopamine antagonists) with psychostimulants (dopamine agonists) may titrate the therapeutic effects of one or both medications as a pharmacodynamic interaction (Julien et al., 2008; Olson, 2006). Wald et al. (1978) evaluated the activating and euphoric properties of methylphenidate in 10 euthymic adult patients on long-term prescription lithium. Each was given two intravenous infusions of methylphenidate 30 mg separated by several days. Five minutes prior to the methylphenidate injection, the patients received either intravenous haloperidol 5 mg or IV saline by random assignment. Patients were rated using a stimulant effects scale. The group receiving saline displayed marked activation and euphoric response in spite of lithium treatment. In the group receiving haloperidol, there was a reduced response in three patients and total abolishment of the euphoric and activating response in the other seven patients. This is consistent with a dopaminergic mechanism of methylphenidate-induced activation and euphoria and its blockade by antipsychotic medication. Levy and Hobbes (1988) conducted a double-blind study in 12 patients with ADHD to assess the effect of methylphenidate 0.3 mg/kg on vigilance tasks after pretreatment with haloperidol 0.04 mg/kg. After methylphenidate was administered without haloperidol, there was an improvement in scores on a continuous performance test with fewer errors of commission and omission, shorter mean reaction times, and better discriminant function. When haloperidol was administered before methylphenidate treatment, there was no statistically significant improvement in any of these measures of attention.

## Atypical Antipsychotics and Methylphenidate

The use of atypical antipsychotics concurrently with stimulants in children and adolescents is becoming more frequent as clinicians attempt to treat comorbidities involving ADHD, conduct disorder, oppositional defiant disorder, mental retardation, and pediatric bipolar disorder (Nevels et al., 2010). Stimulant and atypical antipsychotic medications often are used concurrently with little concern, despite their potentially opposing pharmacological mechanisms. Yanofski

(2010) labels this “the dopamine dilemma” based on an examination of dopamine pathways and receptors which suggests that concerns regarding interactions between these two classes are justified and relevant complex dopamine mechanisms are considered to explain the dilemma. Benjamin and Salek (2005) reported three cases of stimulants and antipsychotics having been used together and the induction of dystonic reactions upon stimulant discontinuation in these patients who had no history of extrapyramidal symptoms (EPS). In one of these, a 9-year-old boy with history of ADHD, bipolar disorder, and mental retardation was admitted for inpatient evaluation and treatment following the onset of acute dystonias immediately after discontinuation of methylphenidate while concurrently taking risperidone. Hollis and Thompson (2007) reported a case of acute and transient dyskinesia occurring within hours of the initiation of time-release methylphenidate (Concerta) in a stimulant-naïve, 7-year-old boy who had recently discontinued risperidone. McLaren et al. (2010) described a case of acute dystonia induced by aripiprazole after discontinuation of methylphenidate. The mechanism of these interactions appears to be between supersensitive, upregulated basal ganglia dopamine receptors, specifically the D2-D4 superfamily, and either prolonged and discontinued, or acute exposure to an agent that increases synaptic levels of dopamine. Clinicians need to be aware of these potential EPS side effects, and exercise caution when using the combination of psychostimulants with all antipsychotics.

### **Coumadin-Related Anticoagulant Therapy Interaction; Glipizide Interaction**

Methylphenidate also is reported to inhibit the metabolism of Coumadin (warfarin) and other related anticoagulants possibly through several P450 pathways, but specifically through 2C9 for which the most active Coumadin enantiomer, S-warfarin, is a substrate. Warfarin is a racemic mixture, and the R enantiomer is a substrate of CYP1A2; however, it is the more potent S enantiomer (a CYP2C9 substrate) that accounts for most of the clinical effects of warfarin (Ansell et al., 2004). This frequently mentioned interaction can lead to hyper-anticoagulation with potential for serious hemorrhaging. 2C9 inhibition appeared to be involved in a significant decrease in glucose levels in a 38-year-old female patient with diabetes mellitus who was placed on methylphenidate post cerebellar tumor resection and who also was being treated with glipizide, a 2C9 substrate (Gontkovsky et al., 2007). By inhibiting the metabolism of her usual dose of glipizide, methylphenidate led to an increase in glipizide serum levels and half-life, thus increasing its anti-hyperglycemic (hypoglycemic) activity. There was no indication of this interaction in the literature, and little mention of methylphenidate as either a substrate or inhibitor of CYP450 enzymes according to these authors.

### **Genetic Polymorphism Associated with Methylphenidate Metabolism by Carboxylesterase 1**

Many formulations of methylphenidate (e.g., Metadate CD, Focalin and Focalin XR, Ritalin LA, and Concerta) are utilized for the treatment of ADHD. It has continued to puzzle clinicians as to why some individuals seem to be unusually sensitive to methylphenidate products, while others require high dosages. It is well-known that carboxylesterase 1 is the primary enzyme that metabolizes methylphenidate; however, there is evidence that polymorphisms of this gene can lead to unexpectedly high levels of methylphenidate (Zhu et al., 2008). This finding has particular importance in light of Food and Drug Administration (FDA) indications of possible adverse effects of psychostimulants on the cardiovascular system. In the future, individuals with these genetic alterations may be at risk to develop serious cardiovascular side effects associated with their high blood levels of methylphenidate. These higher serum levels of methylphenidate may substantially contribute to the P450 interactions already noted. Carboxylesterase 1 is a serine esterase governing both metabolic deactivation and activation of numerous therapeutic agents. During the course of the above noted study, Zhu et al. (2008) found that the pharmacokinetics of the methyl ester racemic psychostimulants profoundly elevated methylphenidate plasma concentrations when there was an extremely rare mutation in the human carboxylesterase 1 (CES1) gene that encodes for this enzyme. This rare polymorphism results in a severe deficiency of the enzyme. In such a situation, hemodynamic measures, such as blood pressure and heart rate, increase significantly.

### **Guanethidine, Guanfacine, Beta-Blockers, and Other Pressor Agents**

Clonidine and guanfacine may be useful in the treatment of certain subgroups of children with ADHD and is commonly used in combination with methylphenidate and other psychostimulants. The psychotherapeutic mechanism of clonidine may be based on decreasing norepinephrine tone in the locus ceruleus. Concern has been expressed over the possible adverse cardiovascular effects of combining methylphenidate with clonidine (Swanson et al., 1995). Ritalin may increase the hypotensive effects of guanethidine (Leikin & Paloucek, 2008), which is explained as an antagonistic interaction as methylphenidate acts to increase norepinephrine. Guanethidine depletes norepinephrine from postganglionic sympathetic nerve terminals and inhibits the release of norepinephrine in response to norepinephrine stimulation, thus reducing cardiac output and vascular resistance. As methylphenidate increases norepinephrine and sympathetic stimulation, guanethidine's depletion of norepinephrine stores and inhibition of norepinephrine release are magnified resulting in significantly decreased blood pressure and a plethora of associated adverse hemodynamic effects (Wells et al., 2009). Additionally, beta-blockers and other antihypertensives (e.g., alpha 2 agonists, such as guanfacine

and clonidine) all would potentially have antagonistic relationships with methylphenidate. Thus, there are drug interaction cautions for the use of a psychostimulant, such as methylphenidate, with pressor agents. Human pharmacological studies have shown that Ritalin may inhibit the metabolism of coumarin-related anticoagulants, anticonvulsants (e.g., phenytoin, phenobarbital, diphenylhydantoin, primidone, phenylbutazone), and TCAs (e.g., imipramine, desipramine, and clomipramine). Also, as mentioned previously, methylphenidate has been shown to increase the therapeutic effects or toxicity of cyclosporine. A decreased dosage of these drugs often will be necessary when they are administered concomitantly with methylphenidate.

### Alpha 2 Agonist Interaction

Serious adverse reactions have been reported with clonidine when given concomitantly with methylphenidate (Goldman et al., 1998; Miller et al., 2001; Perring, 1997), but the pharmacological nature of this interaction has not been investigated and no causality for this relationship has been established. Similarly, the effects of using methylphenidate with other centrally acting alpha-2 agonists has yet to be systematically explored. Moreover, there has been an exponential increase in the number of medications since then. Carbamazepine also has been noted to induce the metabolism of methylphenidate which can reduce its effectiveness (i.e., methylphenidate is a 2D6 substrate and likely may be a substrate for one or more other CYP450 isoenzymes). As with all sympathomimetics, the combination of methylphenidate with a non-selective MAOI absolutely is contraindicated. The use of caffeine (or OTC psychostimulants including pseudoephedrine or phenylpropanolamine) can have additive effects with methylphenidate and also is contraindicated (Olson, 2006; Preston et al., 2008). Medications containing these ingredients recently have been scheduled in some states.

### Class IB Antidysrhythmics – Phenytoin and Indirectly Mexilitine; Class III-Amiodarone

Class IB antidysrhythmic medications (e.g., lidocaine, mexilitine, phenytoin, tocainide) are used to treat life-threatening ventricular dysrhythmias. Ineffective against atrial dysrhythmias, for example, lidocaine treats ventricular fibrillation and wide-complex ventricular tachycardia even though amiodarone, a class III antidysrhythmic, now is the first line treatment for these cardiac abnormalities. Methylphenidate, as noted elsewhere in this article, inhibits the metabolism of phenytoin thereby increasing its serum levels. Phenytoin induces the metabolism of mexilitine, reducing mexilitine's serum concentrations. Thus, methylphenidate singly interacts with phenytoin and, in the case of happenstance co-administration of methylphenidate with both phenytoin and mexilitine, high levels of phenytoin could result in significantly decreased levels of mexilitine (McGuistion & Gutierrez, 2007). Consequences of either the former or latter could be

catastrophic, resulting in fatal arrhythmias. Moreover, it is possible that methylphenidate also could inhibit the metabolism of amiodarone with a similar potentially serious and life-threatening result. This is inductive reasoning but consistent with recommendations for rational polypharmacy involving thoughtful anticipation of possible DDIs.

### Disulfiram and Methylphenidate

Disulfiram inhibits dopamine-beta-hydroxylase production, and low dopamine-beta-hydroxylase activity has been associated with various psychiatric disorders and pathological phenomena, such as ADHD, psychosis, and mood swings (Stahl, 2005). Caci and Bayle (2007) report a case of a DDI between disulfiram and methylphenidate in the treatment of comorbid alcohol abuse and ADHD possibly based on this phenomenon in a 33-year-old male with alcohol abuse. After one month of inpatient treatment for alcohol abuse, he was transferred to the psychiatric unit where he received a comorbid diagnosis of ADHD. During the inpatient addiction treatment, he was placed on disulfiram, 400 mg/day, without any noticeable adverse effects. The patient was discharged, returned home, and prescribed OROS-methylphenidate, 36 mg/day, as an outpatient. After the first dose of methylphenidate, he rapidly experienced a psychotic-like episode that lasted most of the day. He denied any alcohol intake and described the experience as similar to acute cocaine intoxication with visual hallucinations. Methylphenidate was discontinued, disulfiram and vitamins continued, and the patient recovered fully. Three months later, the disulfiram was discontinued and OROS-methylphenidate, 36 mg/day, was restarted and the dose titrated up to 54 mg/day over the next three months with no adverse effects.

### Psychiatric Patients, the Elderly, Polypharmacy, Poly-DDIs, and Methylphenidate

Psychiatric patients have an increased risk of being on complex polypharmacy with consequent drug interactions relative to age-matched non-psychiatric patients (Leonard et al., 2004; Preskorn & Flockhart, 2009). Similarly, aging populations increasingly are poly-medicated and have poorer and diminishing pharmacokinetic parameters, especially due to decreased hepatic and renal functioning. A careful psychopharmacologist often has to consider a plethora of medications from different classes for both of these populations.

A common mistake made by prescribers of drugs like methylphenidate is to see possible interactions as simple additive or synergistic psychodynamic effects of the involved medications; whereas, methylphenidate and most other psychiatric drugs interact primarily through pharmacokinetic properties. The rational informed approach to drug interactions, based on understanding both the kinetics and dynamics of, say methylphenidate, too infrequently is practiced clinically.

## General Safety of Methylphenidate and Recent FDA Warnings

Methylphenidate is considered relatively safe when administered at recommended dosages (Rappley, 1997; Teo et al., 2003; Wax, 1997). Despite these findings, methylphenidate and all other stimulants and the non-stimulant atomoxetine, received an FDA Black Box Warning in February of 2007. This warning detailed an increased risk of cardiovascular events and an exacerbation of pre-existing symptoms, including increased aggression, hostility, and treatment-emergent mania and psychosis.

## Conclusions and Rational Polypharmacy

This brief review of the literature indicates professionals should be more alert to potential methylphenidate interactions and do so as an extension of the “rational” polypharmacy often advocated by the leading psychopharmacologists (Julien et al., 2008; Preskorn & Flockhart, 2009; Preston et al., 2008; Stahl, 2008). These possible methylphenidate DDIs may have serious or life-threatening consequences (e.g., serotonin syndrome, hemodynamic abnormalities, increased levels of cyclosporine with toxic effects, significantly decreased glucose levels for some on antihyperglycemic medications). Table 1 provides an overview of some known and potential methylphenidate drug interactions. For a more complete listing, drugs.com provides 18 major (mostly with other sympathomimetics), 206 moderate, and 15 minor methylphenidate drug interactions. Again, many of these are combinations involving the same medications (e.g., phenylephrine, phenylephrine/acetaminophen, phenylephrine/ibuprofen, tramadol, tramadol/acetaminophen,

tramadol/ibuprofen). Interestingly, no DDI warnings currently are posted for methylphenidate with glipizide or other antihyperglycemics.

Why, as proposed here, would under-reporting of methylphenidate interactions be common? Among reasons would be the success of methylphenidate, which may have led many prescribers to be less vigilant about the possibility of a methylphenidate DDIs in three related ways: 1) The patient is doing well on the medication, and the untreated ADHD is dangerous. In such a case, there may exist no other viable option but to treat with methylphenidate; 2) Except for the obvious sympathomimetic and antidepressant interactions, most interactions are minor and/or would have been sufficiently communicated to clinicians; and, 3) Most methylphenidate interactions are pharmacodynamics, so if a side effect such as decreased glucose levels occur, it is an idiosyncratic anomaly not worth reporting. Further, the era in which methylphenidate frequently began to be prescribed (the 1950s) was one in which interactions were poorly understood and monitoring and reporting of interactions inadequate. Medicine has been notoriously traditional and slow to change. Additionally, thousands of agents have come to market since the introduction of methylphenidate, exponentially increasing the possibility of interactions.

This tendency towards less vigilance in regard to methylphenidate interactions appears to be changing, and reporting mechanisms such as the FDA Drug Watch now make it simple to report any possible interaction. Greater numbers of prescribers are being educated about CYP450 and other metabolic interactions. Hopefully, this review will be part of this ongoing educative process. In summary, as we have indicated, methylphenidate therapy should be monitored more closely and potential drug interactions, specifically CYP450 interactions, can be more thoughtfully anticipated based on current knowledge of this widely used, highly effective psychostimulant.



Table 1. Methylphenidate Drug Interactions

Drug	Effect	Mechanism of action
<b>Antihypertensive agents</b>	Effectiveness of antihypertensive agent may be decreased	Pharmacodynamic (e.g., methylphenidate increases norepinephrine, which is competitive at adrenergic receptors with beta blockers and, as a stimulant sympathomimetic, methylphenidate raises blood pressure in both normotensives and hypertensives)
<b>Bupropion</b>	Serum concentrations of MPH may be increased; synaptic concentrations of norepinephrine and dopamine may be increased by additive dynamics	Bupropion is a 2D6 inhibitor, which may inhibit the metabolism of methylphenidate; both methylphenidate and bupropion increase post-synaptic availability of norepinephrine and dopamine
<b>Carbamazepine</b>	Serum concentration of methylphenidate may be decreased	Carbamazepine is an inducer of metabolism at almost all of the major CYP450 isoenzymes
<b>Clonidine</b>	Severe toxic reactions have been reported	As an alpha 2 agonist, clonidine affects cardiovascular functioning as does methylphenidate, thus concerns about cardiotoxicity as a result of antagonistic pharmacodynamics; however, mechanisms are not well understood in some cases of toxicity
<b>CYP2D6 inhibitors (e.g., chlorpromazine, delaviridine, fluoxetine, miconazole, paroxetine, pergolide, quinidine, quinine, ritonavir, and ropinirole)</b>	Serum concentration of methylphenidate may be increased	Through 2D6 inhibition of methylphenidate metabolism and increased serum levels of methylphenidate
<b>CYP2D6 substrates (e.g., desipramine, flecainide, fluoxetine, haloperidol, imipramine, metoprolol, nortriptyline, paroxetine, propafenone, risperidone, sertraline, thioridazine)</b>	Serum concentrations of these substrates may be increased; caution	Methylphenidate also is a 2D6 inhibitor which would result in increased serum levels of these agents
<b>Class IB antidysrhythmics (phenytoin; mexilitine)</b>	Increase in phenytoin; coadministration of phenytoin with mexilitine results in reduced mexilitine levels; dysrhythmias possible with former or latter	Methylphenidate inhibits the metabolism of phenytoin thereby increasing its serum levels; phenytoin induces the metabolism of mexilitine, reducing mexilitine's serum concentrations
<b>Cyclosporine</b>	Increase in CSA levels; toxicity	Cyclosporine-methylphenidate combination can increase cyclosporine levels through several possible pharmacokinetic mechanisms
<b>Disulfiram</b>	Possible psychotic episodes; caution with alcoholics on Antabuse	Disulfiram inhibits dopamine-beta-hydroxylase production, and low dopamine-beta-hydroxylase activity has been associated with various psychiatric phenomena including ADHD and psychosis; methylphenidate possibly inhibits the metabolism of disulfiram, though exact mechanism not completely understood

Table 1 (continued)

<b>Drug</b>	<b>Effect</b>	<b>Mechanism of action</b>
<b>Glipizide (Other hypoglycemics)</b>	Reduced serum glucose levels due to inhibition of metabolism	Methylphenidate is a 2C9 substrate inhibitor; glipizide and other oral hypoglycemic are 2C9 substrates, thus their serum levels and half-lives would be increased
<b>Linezolid</b>	Concurrent use with methylphenidate should generally be avoided	Linezolid is an MAOI and could lead to serotonin syndrome as well as hypertensive crises if combined with methylphenidate, which increases all monoamines though favoring DA/NE
<b>MAO inhibitors</b>	Severe hypertensive episodes have occurred when used in patients receiving nonselective MAO inhibitors and methylphenidate; methylphenidate may be less likely to interact or reactions may be less severe; use with caution; wait 14 days following discontinuation of MAO inhibitor	See above
<b>N-methyl-3, 4,-methylenedioxy-methamphetamine(MDMA or "Ecstasy")</b>	MDMA (Ecstasy) is a 2D6 substrate and levels could increase = toxicity and hyperthermia, dehydration, seizures, coma, death	Methylphenidate is a 2D6 inhibitor and decreases metabolism of its substrates; also, it is a stimulant and would have at least additive effects with the stimulant component of MDMA
<b>Phenobarbital</b>	Serum levels may be increased	Methylphenidate is an inhibitor of phenytoin thus phenobarbital metabolism
<b>Phenytoin</b>	Serum levels may be increased (also see class IB antidysrhythmias [mexilitine])	See above
<b>Pseudoephedrine</b>	Hemodynamics increased (e.g., BP/HR)	Additive sympathomimetic effects
<b>Phenylpropanolamine Psychostimulants as a class Selegiline</b>	See pseudoephedrine above Above When selegiline is used at low dosages (<10 mg/day), an interaction with methylphenidate is less likely than with nonselective MAO inhibitors	Selegiline becomes nonselective for MAO inhibition at doses above 10 mg per day; see above
<b>Selective serotonin reuptake inhibitors (SSRIs)</b>	Possible serotonin syndrome; increased levels of SSRIs due to inhibition of metabolism	Possible additive or synergistic effects due to methylphenidate increasing 5HT; increased levels of SSRIs due to inhibition of metabolism
<b>Sibutramine</b>	Potential for reactions noted with amphetamines (severe hypertension and tachycardia) appears to be low	Possible additive or synergistic effects due to methylphenidate increasing 5HT and other monoamines
<b>Tramadol</b>	Caution advised: may increase risk of seizures (additive effects)	Tramadol is an SNRI as well as an opiate agonist; increases in both 5HT and NE could be convulsogenic
<b>Tricyclic antidepressants</b>	May increase serum concentrations of tricyclic agents with higher SEs; clinical reports of toxicity are limited; dosage reduction of tricyclic antidepressants may be required	Through methylphenidate inhibition of TCA metabolism
<b>Venlafaxine</b>	NMS has been reported	Possibly due to increased dopaminergic activity at dopamine superfamily two inhibitory receptors (D2-D4) from high dose SNRI becoming SNDRI and increased dopamine from methylphenidate
<b>Tamoxifen, cyclophosphamide</b>	Potential interactions with these antineoplastics increasing toxic SEs including hepatotoxicity, renal damage, agranulocytosis, anemia, pancytopenia	Methylphenidate is inhibitor of metabolism of these agents through P450 isoenzymes (e.g., especially 2C9)

Table 1 (continued)

Drug	Effect	Mechanism of action
<b>Statin drugs</b>	Potential reduction of effectiveness	Methylphenidate may have antagonistic effects on lipid levels through sympathomimetic hepatic mechanisms; rare and poorly understood interaction
<b>Benzodiazepines (e.g. midazolam, alprazolam, diazepam)</b>	increased sedation/tranquilization	Inhibition of metabolism
<b>Expected Other: Including antineoplastics (e.g., Avastin, Temodar) other than tamoxifen or cyclophosphamide, antibiotics, antifungals, antiviral/retrovirals (e.g., nevirapine), class III antidysrhythmics (e.g., amiodarone), many drugs in multiple drug classes</b>	Expected and unexpected reactions congruent with dynamics and kinetics of these agents	Mechanism = General and individual CYP450 inhibitory DDIs, especially, Whites or Asians with 2D6 or 2C9 polymorphisms; Also possible competitive substrate interactions
<b>Herbals/Foods: St. John's Wort (hypericum), Kava Kava, grapefruit juice, ephedra, caffeine, other</b>	Photosensitivity; serotonin syndrome; HTN; seizures; sedation	Hypericum perforatum interacts with wide range of medications due to activation of the Pregnane X receptor detoxification pathway, as well as causing photosensitivity; grapefruit juice is a potent inhibitor of isoenzymes, which also are inhibited by methylphenidate; Kava Kava/MPH antagonize therapeutic effects; ephedra and MPH = additive sympathomimetic effects - HTN, increased HR; caffeine also could have additive stimulant effects

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