Use and abuse of methylphenidate in attention-deficit/hyperactivity disorder

Beware of legitimate prescriptions being diverted

Charity Evans, BSP; David Blackburn, BSP, PharmD; Peter Butt, MD; Dan Dattani, MD

The role of stimulants in treating children with attention-deficit/hyperactivity disorder remains controversial within the community. However, the evidence in their favour is still sound. Objections based on potential diversion to illegitimate black-market use need to be considered on a case-by-case basis, but in most instances should not be used to deprive children of proven therapy.

Background

The American Academy of Pediatrics[1] and the American Academy of Child and Adolescent Psychiatry[2] have recently released practice guidelines for the management of children with attention-deficit/hyperactivity disorder (ADHD). Although both reports recommend stimulants (e.g., methylphenidate [MPH]) as first-line therapy, many people remain skeptical about the role of these drugs in children and adolescents.

On one hand, MPH is promoted as a safe and effective treatment for children, on the basis of extensive evidence and expert consultation. On the other hand, it is a well-known and problematic drug of abuse across North America. The purpose of this paper is to clarify this apparent dichotomy by summarizing two recently published practice guidelines, reviewing the fundamental characteristics of MPH, and investigating its abuse potential.

Stimulants to treat ADHD

The use of stimulants in treating behavioural disorders dates back to the 1930s, when it was discovered that these drugs led to better academic performance and reduced motor activity in hyperactive children.[2] Since then, stimulants have been extensively studied and are now considered first-line therapy for the treatment of ADHD.[1,2]

In terms of benefits and adverse events, MPH's actions are virtually identical to other available stimulants (e.g., dextroamphetamine). However, because of individual variability in responsiveness, patients may respond favourably to one drug but not the other.[1-3] Therefore, patients whose symptoms fail to improve and those who experience side effects while taking one stimulant should be tried on the other, as approximately 80% of patients will respond to at least one of these agents.[1]

Methylphenidate

Numerous studies have shown the efficacy of MPH in reducing the core symptoms of ADHD: inattention, hyperactivity, and impulsivity.[1] For many patients, MPH also improves the ability to follow rules, decreases emotional overreactivity, and facilitates improvements in relationships with peers, teachers, and parents.[1,3] In the classroom setting, MPH has been shown to decrease fidgeting and interrupting, while increasing on-task behaviour.[2] These beneficial effects appear in patients of all age groups, from preschoolers to adults, regardless of ethnic background, sex, family income, functionality of the family, and parents' marital status.[3] In many cases, dramatic improvements in behaviour are seen almost immediately after MPH therapy has been initiated.[3]

Few non-stimulant medications have evidence supporting their use as second-line treatment for ADHD. In addition to tricyclic antidepressants (imipramine and desipramine) and bupropion,[1] clonidine is occasionally used in the treatment of ADHD, mainly for patients with coexisting sleep disturbances.[1]

Several different products for the treatment of ADHD are available in the United States and will likely be approved in Canada within the next few years. Most are just refined formulations of existing products, which provide the advantage of once-daily dosing. However, the US Food & Drug Administration has recently approved a non-stimulant medication, atomoxetine, for the treatment of ADHD. A brief overview of new products for the management of ADHD is presented in Table 1 (but a detailed review of these agents is beyond the scope of this article).

***Charity Evans**, BSP, is a primary care pharmacist at Stueck Pharmacy in Leader, SK. **David Blackburn**, BSP, PharmD, is Assistant Professor, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon. **Peter Butt**, MD, is Associate Professor in the Department of Family Medicine, University of Saskatchewan. **Dan Dattani**, MD, is a general practitioner in Saskatoon who has experience in the management of patients with ADHD; he also has an appointment to the Department of Family Medicine, University of Saskatchewan.*

MECHANISM OF ACTION

Currently available preparations of MPH contain a racemic mixture of both D-*threo*-methylphenidate and L-*threo*-methylphenidate isomers, the D-*threo* isomer being the more pharmacologically active.[4] The complete mechanism of action by which MPH exerts its behavioural effects remains unknown, although it is believed that the drug binds to the dopamine transporter, resulting in an increase in synaptic dopamine levels.[2,4] It has also been suggested that MPH binds weakly to serotonin transporters; however, this theory remains controversial because the supporting evidence has not been directly applied to humans.[4] Tolerance to the actions of MPH is not commonly observed.[2]

Safety

When used appropriately, MPH is an extremely safe therapeutic modality for children with ADHD.[1,2,5] Of the mild side effects that occur during therapy, most respond to simple dose modification.[1,2,5-7] Severe side effects such as growth impairment, tics, seizures, and other serious events have also been reported, but rarely and these are usually considered improbable in otherwise healthy children.[1,2,5,8-12]

TABLE 1 — **New products for the management of attention-deficit/hyperactivity disorder**

Product	Active ingredient	Comments
Strattera	Atomoxetine	• Selective NE reuptake inhibitor • Low abuse potential (non-stimulant) • Potential for drug interactions via the CYP 2D6 pathway • Not available in Canada
Adderall	3:1 ratio of D-amphetamine and L-amphetamine salts	• Extended-release formulation (Adderall XR) allows once-daily dosing • Available in Canada (Shire Biochem Inc.)
Metadate	MPH	• Capsules containing immediate- and sustained-release pellets • Pellets may be sprinkled on applesauce • Not available in Canada
Concerta	MPH	• Special-release formulation of MPH (22% of dose released immediately, 78% of dose released over 10 hours) • Available in Canada (Janssen-Ortho Inc.)
Attenade (Focalin in US)	Dexmethylphenidate	• Contains only the active isomer of MPH • To be marketed in Canada by Biovail Pharmaceuticals

NE = norepinephrine; MPH = methylphenidate.

Common side effects

The most commonly reported side effects of MPH, occurring in more than half of all children treated,[6] include insomnia, anorexia, stomach aches, jitteriness, and headaches.[1,2,6,7] In some cases, the side effects of MPH closely resemble the symptoms of ADHD. For example, MPH-induced irritability is thought to result from high peak levels and therefore occurs soon after a dose is administered. However, irritability at the end of a dosage interval is more likely the result of the wearing off of drug effects (a rebound effect).[2] "Dulling" or depressive effects may also result from high peak levels of MPH, but must be distinguished from depressive symptoms that represent a comorbid condition.[1,2]

Fortunately, many of these side effects can be minimized with simple alterations in the dosing schedule (Table 2). To distinguish ADHD-induced behaviours from drug-induced behaviours, caregivers must carefully document the type and timing of all suspected adverse effects. This information will enable caregivers to determine the best course of action to minimize undesirable symptoms.

Growth suppression

MPH has been reported to delay growth in children with ADHD.[5,13,14] This effect may result solely from the anorexic effects of MPH, or it may result from some unknown effect on endogenous substances such as growth hormone or prolactin.[13] Fortunately, growth delays associated with MPH treatment appear to be short-lived and reversible. Available evidence suggests that, despite continued treatment, initial growth delays are followed by periods of accelerated growth that appear to neutralize any significant effects on final height attained.[1,2,5,13] Still, caregivers must closely monitor the appetite and nutrient intake of all children receiving MPH to minimize any effects on weight gain or physical development (Table 2).

Other safety concerns

Serious adverse events related to the use of MPH are rare.[5] Psychosis, mood disturbances, and obsessive-compulsive disorder have been reported, but most cases resolved upon discontinuation of the drug.[1,2,10-12] Considering the substantial numbers of children in North America who take MPH daily, the small number of serious adverse events reported from therapeutic use suggests that MPH is very safe when used appropriately.[2]

Many people fear that children receiving MPH may become addicted. Although there is virtually no evidence that therapeutic MPH acts as a gateway to substance abuse, the evidence is inconsistent and is complicated by higher rates of substance abuse within the ADHD population (see below).[15-18] Practically speaking, responsible provision of MPH therapy should not lead to abuse or addiction problems.

Cont'd on p. 32

TABLE 2 — **Tactics for dealing with stimulant-associated side effects***

Side effect	Action
Appetite suppression	• Give stimulants with meals. • Provide a high-calorie drink or snack late in the evening, when stimulant effects have worn off.
Insomnia	• Distinguish cause: side effect of MPH or oppositionality related to the attention-deficit/hyperactivity disorder or separation anxiety. • If insomnia is drug-induced, reduce the last stimulant dose of the day or move it to earlier in the day.
Sadness	• Evaluate for possible coexisting cause. • If sadness is drug-induced, reduce the dose or change to sustained-release formulation, because the peak of immediate-release stimulant may be causing more depressive effects.
Behavioural rebound	• Overlap the stimulant dosing pattern, switch to longer-acting stimulants, combine immediate-release with sustained-release formulations, or add other medications (e.g., bupropion).
Irritability	• Assess onset of behaviour (may represent behavioural rebound if irritability occurs at end of dosage interval). • Reduce the dose.

*Adapted from American Academy of Child and Adolescent Psychiatry.[2]

Contraindications

As with all medications, there are contraindications to the use of MPH. Those listed below have clinical relevance.[2]

- Concomitant use of monoamine oxidase inhibitors (MAOIs) with any stimulant is strongly contraindicated because of the increased risk of severe hypertension and cerebrovascular accidents.
- Stimulants are known to produce a psychotomimetic effect in patients with schizophrenia and should therefore be avoided in such patients.
- Because MPH is a sympathomimetic, there is a risk for increased intraocular pressure; therefore, the drug should be avoided in patients with glaucoma.
- Although drug dependence is not an absolute contraindication, patients with a history of substance abuse should be closely monitored when being treated with MPH.
- Although several randomized controlled trials have shown the efficacy of MPH in preschoolers, more research is needed before the treatment of children <6 years old becomes evidence-based practice.

Motor tics or a personal or family history of Tourette's syndrome are listed as contraindications to MPH therapy.[19] However, these contraindications have recently been challenged by the American Academy of Pediatrics[1] and the American Academy of Child and Adolescent Psychiatry.[2] Seizure disorders have also been considered a contraindication for MPH therapy. However, it appears that epileptic children may safely receive MPH therapy after they have been stabilized on anticonvulsant therapy.[1,2,20] Although MPH appears safe in these situations, children should be referred to a physician with expertise in managing these conditions.

Drug interactions

The concurrent use of MPH and MAOIs or pressor agents significantly increases the chance for hypertensive crisis and should be avoided.[2,19] MPH may inhibit the metabolism of coumarin anticoagulants and some anticonvulsants (e.g., phenobarbital, diphenylhydantoin, primidone), necessitating downward dosage adjustments in some patients.[19] Alcohol may exacerbate the adverse central nervous system effect of MPH; therefore, patients should be advised to abstain from alcohol during MPH treatment.[19]

Prescribing MPH

Because the effects of MPH are not weight dependent,[1] the drug should be initiated at a low dose and titrated upward as needed.[1] However, the first dose that improves symptoms may not necessarily represent the maximal effect, so dose titration may be continued in an attempt to achieve a superior response.[1] Dose titration should be stopped or reversed if side effects occur or if no further improvement is seen.[1,2] Not only are side effects troublesome, but they may also decrease both the patient's and the parent's willingness to continue with therapy. Ultimately, the best dose is the one that results in optimal effects with minimal side effects.[1]

Dosing schedules vary with the patient's target outcomes.[1] One patient may need MPH on weekdays only, to control symptoms at school, whereas another may require continuous daily dosing to achieve symptom relief at home as well as at school. Given the problems associated with MPH diversion and theft, reducing the need for school-time doses may be a significant advantage. Modified and immediate-release formulations are often combined to increase the effectiveness and duration of effect of MPH, which allows for more flexible dosing.[2] When a combination of formulations is taken in the morning, the short-acting formulation will take effect before the child's first class, and the intermediate formulation will begin working in mid-morning and last through the rest of the day. Although this strategy is intended to eliminate the need for the patient to take the drug while at school, the overall duration of MPH effect varies considerably, and the effect of the sustained-release preparation is not always more prolonged than that of the standard preparations.[3]

Therefore, more research is needed to determine the efficacy of such combined MPH regimens.

Follow-up and monitoring

Once a patient's condition has been stabilized with MPH, he or she should be periodically evaluated for effectiveness of and adherence to therapy, as well as emergence of side effects.[1] The frequency of monitoring depends largely on degree of dysfunction, presence of complications, and suspicions of non-adherence.[1] Generally, an office visit every three to six months allows for assessment of learning, behaviour, and side effects such as headache, insomnia, decreased appetite, or alterations in growth.[1] Although follow-up should include regular physician visits, the clinician cannot be expected to work alone in the treatment and monitoring of the patient. Continual communication with parents, teachers, and other health care professionals is vital in determining the efficacy of MPH therapy.[1] Community pharmacists are in an excellent position to initiate dialogue about side effects, effectiveness, and dosing issues when refilling prescriptions.

DRUG HOLIDAYS

Questions still surround the idea of a "drug holiday" for patients receiving MPH. For these patients, a drug holiday is the regular interruption of therapy for a certain period to promote weight gain, reduce possible long-term effects, or assess the ongoing need for medication. It is not known if drug holidays improve the safety of MPH therapy. However, MPH works only while it is being administered, so stopping the drug usually results in a rapid return of symptoms.[2] Therefore, if a drug holiday is attempted, it should not be when the patient is attending school or is involved in important social activities.[2]

Abuse-related issues

Although MPH is a drug of choice for patients with ADHD,[1-3] there are widespread concerns about its abuse potential. Unlike many other drugs that can be manufactured illicitly, MPH is available only through pharmaceutical diversion, which includes drug thefts, illegal sales, prescription forgery, and "polydoctoring."[21] Since MPH is produced from legitimate sources, it is a commonly sought drug of abuse because of its reliability, quality, and stimulant action. In addition, for those who are taking MPH legitimately, urine drug screening is useless for detecting abuse (i.e., dosing at greater than prescribed levels). Although the significant increase in MPH prescriptions over the past five years may be due to greater awareness and physician recognition of ADHD, it is feared that the greater volume of MPH will create more opportunities for diversion.

Public perception has historically been that MPH is a "mild" stimulant. However, Volkow et al.[22,23] have discovered that the pharmacological potency of MPH is very similar to that of cocaine. Cocaine inhibits dopamine transporters, increasing the amount of dopamine in the synapse, which results in a "hit" of pleasure.[24,25] This action has been linked to the reinforcing and addictive effects of cocaine.[24] MPH and cocaine share a similar affinity for dopamine transporters, have an almost identical regional distribution in the brain, and have a peak uptake in the brain that is comparable after intravenous administration.[22]

Although MPH and cocaine share certain pharmacodynamic properties, the abuse and addiction potential of MPH appear to be lower than those of cocaine.[23] It has been suggested that the pharmacokinetic differences between the two drugs (duration of action and clearance from the brain) may account for this difference in addiction potential.[22] Fast onset and short duration of action are two common characteristics of addicting drugs.[22] When administered intravenously, both MPH and cocaine have a quick onset of action (four to 10 minutes and two to eight minutes, respectively),[22] but cocaine is cleared from the brain more than four times faster than MPH.[22] This slower clearance from the brain with MPH may be responsible for differences in abuse potential relative to cocaine.[22] However, intravenously administered MPH is still associated with strong and persistent drug-seeking behaviour, and abusers will often inject themselves more than once a day.

Because MPH is water soluble, it is easily manipulated into an injectable form. Both the sustained- and immediate-release tablets are used in this way. Sustained-release tablets are heated with water until the core dissolves and the wax can be removed; the remaining suspension is then injected. Immediate-release tablets are crushed, dissolved in water or urine, and then injected. Although the suspension is sometimes filtered through cotton, contaminants such as insoluble fillers, talc, and cornstarch binders are often present. As a result, emboli can lodge in the capillaries of the lung, eyes, spleen, kidneys, and brain and lead to further complications, including retinopathy, panlobular emphysema, and multiple organ failure.[26] Other documented effects of intravenous MPH use include cardiac arrhythmias,[27] normochromic and normocytic anemia, hallucinations, paranoia, and syncope.[28] Case reports describing morbidity and mortality are most commonly related to pulmonary complications such as pulmonary hypertension, cor pulmonale,[29] and pulmonary fibrosis.[28]

Many MPH abusers believe the high-dose brand-name tablets (Ritalin SR 20 mg) have the lowest amount of insoluble incipient constituents and therefore a lower risk of potential pulmonary complications.[28] Markets exist for both the sustained- and immediate-release forms of MPH. In the authors' experience, the relative popularity of each agent appears to vary geographically.

MPH is also abused in combination with pentazocine (Talwin). The tablets are crushed, mixed together, and dissolved, and the resulting solution is injected intravenously to produce a euphoric state.[30] MPH is also commonly

Cont'd on p. 34

injected intravenously after injection of an opioid, particularly morphine or hydromorphone. In this situation, MPH reduces the "nodding" or sedative effects resulting from the narcotic.

Intranasal use, or snorting, of crushed MPH tablets is becoming an increasingly common method of abuse. Intranasal use of MPH rapidly delivers a euphorigenic dose to the brain, thus increasing the addictive potential of the drug.[31] Cases describing intranasal abuse of doses of 60–200 mg have been reported.[31-33] The euphoric state reportedly lasts six hours and is often accompanied by increased activity, insomnia, and anorexia.[31]

Although uncommon, there have been reports of oral misuse of MPH by children to induce euphoria.[34,35] A variety of doses ranging from 15 to 200 mg daily were used to reach the desired "high."[34,35] However, oral administration of MPH at therapeutic doses rarely leads to euphoria, probably because of the slow rate of brain uptake of MPH taken orally (about 60 minutes) relative to that of MPH taken by intravenous or intranasal administration.[36]

Like other prescription drugs that have potential for abuse, a balance between controlling drug access and maintaining clinical availability of a highly efficacious agent is essential. A significant amount of diversion occurs at the parent or caretaker level, and adults frequently use children, with or without ADHD, to obtain their supply. Accurate physician, pharmacist, and patient education about ADHD, its diagnosis, and its management, and an understanding of the appropriate use and abuse potential of MPH are vital to preventing illegitimate use. In addition, some practical interventions can be applied to ensure that MPH prescriptions are used properly (see box). However, these interventions are not necessarily easy to implement, nor are they infallible.

The best solution would be an alternative medication with equivalent efficacy to MPH but without abuse potential. Only time and further study will reveal whether newer agents such as atomoxetine can eliminate the use of stimulants in ADHD. Until then, continued patient and prescription monitoring, recognition of drug-seeking behaviour, and specific precautions will help to ensure the appropriate use of MPH and decrease the diversion and abuse of this effective therapeutic modality.

PRACTICAL INTERVENTIONS TO REDUCE METHYLPHENIDATE DIVERSION AND ABUSE

- Random urine screening of the patient may indicate that a caregiver or other acquaintance is diverting the MPH supply. Screening could be implemented with parental consent as part of the treatment contract.
- Initiate drug administration through the patient's school if the parental or home situation is unsuitable or the behaviour is not improving.
- Institute random pill counts to ensure a match between number prescribed and number used.
- Consider examining parents for track marks if there is a strong suspicion of abuse.
- Instruct parents, children, teachers, and other caregivers to refrain from informing others about a child's stimulant therapy. If this information ends up in the wrong hands, patients' homes may become targets for break-ins or children may become targets on the playground.

Conclusion

MPH provides important benefits to patients with ADHD. These benefits can be safely achieved if a few simple precautions are exercised. It is important for all health care professionals to encourage objective dialogue about this legitimate treatment option and provide support to patients receiving it. ■

REFERENCES

1. American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108:1033-44.
2. Greenhill LL, Pliska S, Dulcan MK, et al, for the American Academy of Child and Adolescent Psychiatry. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;41:26S-49S.
3. Elia J, Ambrosini PJ, Rapoport JL. Treatment of attention-deficit-hyperactivity disorder. *N Engl J Med* 1999;340:780-8.
4. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000;75:711-21.
5. Rappley MD. Safety issues in the use of methylphenidate. An American perspective. *Drug Saf* 1997;17:143-8.
6. Barkley RA, McMurray MB, Edelbrock CS, et al. Side effects of methylphenidate in children with attention-deficit/hyperactivity disorder: a systematic, placebo-controlled evaluation. *Pediatrics* 1990;86:184-92.
7. Ahman PA, Waltonen SJ, Olson KA, et al. Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993;91:1101-6.
8. Feeney DJ, Klyklo WM. Medication-induced seizures [letter]. *J Am Acad Child Adolesc Psychiatry* 1997;36:1018-9.
9. Schteinschnaider A, Plaghos LL, Garbugina S, et al. Cerebral arteritis following methylphenidate use. *J Child Neurol* 2000;15:265-7.
10. Kotsopoulos S, Spivak M. Obsessive-compulsive symptoms secondary to methylphenidate treatment [letter]. *Can J Psychiatry* 2001;46:89.
11. Kouris S. Methylphenidate-induced obsessive compulsiveness [letter]. *J Am Acad Child Adolesc Psychiatry* 1998;37:135.
12. Adrian N. Explosive outbursts associated with methylphenidate [letter]. *J Am Acad Child Adolesc Psychiatry* 2001;40:618-9.
13. Satterfield JH, Cantwell DP, Schell A, et al. Growth of hyperactive children treated with methylphenidate. *Arch Gen Psychiatry* 1979;36:212-7.

14. Gittelman R, Klein RG, Manuzza S. Hyperactive boys almost grown up. *Arch Gen Psychiatry* 1988;45:1131-4.

15. Manuzza S, Klein RG. Long-term prognosis in attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Clin North Am* 2000;9:711-26.

16. Lambert NM, Hartsough CS. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J Learn Disabil* 1998;31:533-44.

17. Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics* 1999;104:e20.

18. Manuzza S, Klein RG, Bonagura N, et al. Hyperactive boys almost grown up v. replication of psychiatric status. *Arch Gen Psychiatry* 1991;48:77-83.

19. Prescribing information: Ritalin® (methylphenidate hydrochloride) 10 mg and 20 mg tablets Novartis standard and Ritalin® SR (methylphenidate hydrochloride extended-release tablets) 20 mg tablets Novartis standard. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 1999 Dec 15. Available: www.pharma.ca.novartis.com/downloads/e/ritalin_scrip_e.pdf (accessed June 21, 2004).

20. Gross-Tsur B, Manor O, Van der Meere J, et al. Epilepsy and attention-deficit/hyperactivity disorder: is methylphenidate safe and effective? *J Pediatr* 1997;130:40-4.

21. DEA congressional testimony. Statement by Terrance Woodworth before the Committee on Education and the Workforce: Subcommittee on Early Childhood, Youth and Families (electronic). Alexandria (VA): US Drug Enforcement Administration; 2000 May 16. Available: www.usdoj.gov/dea/pubs/cngrtest/ct051600.htm (accessed June 21, 2004).

22. Volkow ND, Yu-Shin D, Fowler JS, et al. Is methylphenidate like cocaine? *Arch Gen Psychiatry* 1995;52:456-63.

23. Volkow N, Wang GJ, Fowler JS, et al. Methylphenidate and cocaine have a similar in vivo potency to block dopamine transporters in the human brain. *Life Sci* 1999;65:7-12.

24. Ritz MC, Lamb RJ, Goldberg SR, et al. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* 1987;237:1219-23.

25. Bergman J, Madras BK, Johnson SE. Effects of cocaine and related drugs in nonhuman primates. III Self-administration by squirrel monkeys. *J Pharmacol Exp Ther* 1989;251:150-5.

26. Liana ME, Crismon ML. Methylphenidate: Increased abuse or appropriate use? *J Am Pharm Assoc* 1999;39:526-30.

27. Lucas PB, Gardner DL, Wolkowitz OM, et al. Methylphenidate-induced cardiac arrhythmias [letter]. *N Engl J Med* 1986;315:1485.

28. Parran TV, Jasinski DR. Intravenous methylphenidate abuse. Prototype for prescription drug abuse. *Arch Intern Med* 1991;151:781-3.

29. Lewman LV. Fatal pulmonary hypertension from intravenous injection of methylphenidate (Ritalin) tablets. *Hum Pathol* 1972;3:67-70.

30. Carter HS, Watson WA. IV pentazocine/methylphenidate abuse - the clinical toxicity of another Ts and blues combination. *J Toxicol Clin Toxicol* 1994;32:541-7.

31. Garland EJ. Intranasal abuse of prescribed methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1998;37:573-4.

32. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991;30:773-5.

33. Massello W 3rd, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin®). *J Forensic Sci* 1999;44:220-1.

34. Corrigall R, Ford T. Methylphenidate euphoria [letter]. *J Am Acad Child Adolesc Psychiatry* 1996;35:1421.

35. Goyer PF, Davis GC, Rapoport JL. Abuse of prescribed stimulant medication by a 13-year-old hyperactive boy. *Am Acad Child Psychiatry* 1979;18:170-5.

36. Volkow ND, Wang GJ, Fowler JS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry* 1998;155:1325-31.