ADDICTION TREATMENT

Forum

THE QUARTERLY NEWSLETTER FOR CLINICAL HEALTH CARE PROFESSIONALS ON ADDICTION TREATMENT

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There are at least 100 substances that can interact in some fashion to affect patient response to methadone.

IN THIS ISSUE

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Clinical Concepts

Taming Drug Interactions

Serious Concerns

Each year in the U.S. there are more than 2 million *adverse drug reactions*, broadly defined as any unexpected, unintended, undesired, or excessive response to a medicine. Such reactions may require discontinuing or changing medication therapy, or can more seriously result in hospitalization and/or permanent disability. Annually, there are more than 100,000 deaths attributed to reactions involving prescribed medications (Cohen 1999).

Three-fourths of those adverse reactions relate to drug interactions, which occur when two or more drugs react with each other. Avoiding these can be difficult, since the number of potential interactions among diverse drugs used in clinical practice can be overwhelming. More than 2,000 have been described in the literature and new cases appear monthly (Levy et al. 2000). There are at least 100 substances – medications, illicit drugs, OTC products, etc. – that can interact in some fashion to affect patient response to methadone.

There also is the problem of polypharmacy. While multiple drugs are often necessary for treating complex or resistant conditions, side effects of the drugs themselves may induce disease symptoms, rather than any pathological processes (Farrell et al. 2003).

This is of vital importance for patients in methadone maintenance treatment

Continued on Page 6

Beyond Methadone

Drug Relapse: A Detour, Not An End of Recovery

An important goal of methadone maintenance treatment (MMT) is sustained abstinence from illicit opioids and, ideally, all other substances of abuse. However, one of the greatest impediments to treatment success may be viewing drug relapse as an end of the road to recovery, rather than as a temporary detour.

Lapse vs Relapse

Recovery commonly refers to a *process* of initiating abstinence from illicit drug and/or alcohol use, along with necessary life changes to help maintain sobriety over time. The process can be long and arduous – a lifelong progression – with many obstacles and setbacks along the way, including lapses or relapses.

The term *lapse* – often called a "slip" – denotes an initial episode of drug or alcohol use after a period of abstinence. It can end quickly or it may precipitate a more extensive relapse of varying proportions.

Relapse is viewed as a breakdown in the recovery process; a major digression in the individual's attempt to escape the bonds of addiction. Relapse involves both a period during which there are usually observable signs that the person is headed toward trouble as well as the act of resuming extensive substance use, usually at a level equal to or greater than previously. A repeated tendency to relapse is often called "recidivism."

Patients, and sometimes treatment staff, often negatively view relapse as a devastating personal failure indicating that the individual may be incapable of achieving total abstinence. The reality is that drug addiction is now accepted by

Continued on Page 4

Events to Note

For additional postings & information, see: ***www.atforum.com***

January 2004

American Psychoanalytic Association Annual Winter Meeting
January 16-25, 2004
New York, New York
Contact: 212-752-0450

February 2004

6th International Conference on Pain & Chemical Dependency
February 5-7, 2004
New York, New York
Contact: Lorna Gannon 609-275-5030, lorna.gannon@Meditech-media.com; www.painandchemicaldependency.org

American Group Psychotherapy Association Annual Meeting
February 26-28, 2004
New York, New York
Contact: 877-668-2372

National Council for Community Behavioral Healthcare Annual Conference
February 28 - March 2, 2004
New Orleans, Louisiana
Contact: 301-984-6200; neworleans@nccbh.org

March 2004

Anxiety Disorders Association of America 24th National Conference
March 11-14, 2004
Miami, Florida
Contact: 240-485-1001

Society of Behavioral Medicine Annual Meeting
March 24-27, 2004
Baltimore, Maryland
Contact: 608-827-7267

UPCOMING 2004...

35th Annual ASAM Medical-Scientific Conference
April 22-25, 2004
Washington, DC
Contact: 301-656-3920; www.asam.org

American Psychiatric Association Annual Meeting
May 1-6, 2004
New York, New York
Contact: 703-907-7300; apa@psych.org; http://www.psych.org

CPDD (College on Problems of Drug Dependence) 65th Annual Meeting
June 12-17, 2004
San Juan, Puerto Rico
Contact: 1-800-759-5800

[To post your announcement in A.T.Forum and/or our Web site, fax the information to: 847-392-3937 or submit it via e-mail from www.atforum.com]

A.T.F.

Straight Talk... from the Editor

Will Physicians Get The Addiction Message?

The September issue of the *Journal of the American Medical Association* (2003; 290[10]:1299-1303) featured a disquieting article titled "Addiction Poorly Understood by Clinicians."

"For all the lip service paid to the concept of addiction as a medical disease, the idea has yet to gain traction with a large proportion of physicians," wrote Brian Vastag.

Many physicians still believe that *medical* interventions for addiction are inappropriate and ineffective.

Prejudice Permeates Medicine

This is rather astonishing, considering that in 1782 Benjamin Rush, the first U. S. Surgeon General, described substance abuse (alcoholism, in this case) as "a progressive and odious disease." Yet, despite all the advances in other areas of medicine, an understanding of addiction seems rooted in antiquated folklore.

Why? The *JAMA* article notes that merely 1% of the typical medical school curriculum is devoted to drug addiction. Consequently, many physicians still believe that medical interventions for addiction are inappropriate and ineffective. Furthermore, a prejudice that addiction is mainly a consequence of personal willfulness – that is, primarily a moral or behavioral problem – still silently dominates medical thinking.

Addiction Specialists Accountable

Part of the blame for such misunderstandings rests with the addiction treatment community. Nora Volkow, MD, head of NIDA and quoted in the *JAMA* article, suggests that addiction experts must emphasize the disease concept of addiction. They also need to stress that addiction leads to other medical problems. Each year, $133 billion is spent in the U.S. treating the short- and long-term medical complication of addiction.

"We can prevent a lot of other problems by addressing addiction, but somehow we have failed to communicate that," she said.

It is time that the message of addiction – its origins and treatments – reaches the rest of the medical community, and the burden of doing that rests with addiction specialists. One resource, particularly for explaining the treatment of opioid addiction, is *Addiction Treatment Forum.* Share your copy with healthcare colleagues or direct them to http://www.atforum.com.

Respond to Reader Survey

Drug lapses (slips) and relapses are a discouraging facet of addiction treatment, as noted in the feature article in this edition. To help us further explore the extent of these difficulties during methadone maintenance treatment (MMT), ***please respond to the following questions:***

1. What percentage of patients at your MMT clinic experience drug lapses (slips) ____% or full-blown relapses ____%?

2. When are lapses (slips) *most likely* to occur after starting MMT? (check one) __ 1 month; __ 3 months; __ 6 months; __ 1 year; or, __ later.

3. When are relapses *most likely* to occur? (check one) __ 1 month; __ 3 months; __ 6 months; __ 1 year; or, __ later.

4. Which drugs are *most commonly* involved in lapses or relapses? (check all that apply) ❑ cannabis; ❑ heroin; ❑ other opioids; ❑ cocaine; ❑ benzodiazepines; ❑ alcohol; ❑ other _____ (please specify).

5. Are you responding as a ❑ patient, or ❑ clinic staff member?

There are several ways to respond to AT Forum surveys: **A.** provide your answers on the postage-free feedback card in this issue; **B.** write, fax, or e-mail [info below]; or, **C.** visit our web site to respond online. As always, your written comments are important for helping us discuss the results in an upcoming article.

Stewart B. Leavitt, PhD, Editor
stew202@aol.com

Addiction Treatment Forum
P.O. Box 685; Mundelein, IL 60060
Phone/Fax: 847-392-3937
Internet: http://www.atforum.com
E-mail: Feedback@atforum.com

A.T.F.

Practice Pointers: Understanding Methadone Split Dosing

"I nod off at work in the morning but by evening I feel like I'm in withdrawal."

Complaints such as this – of a methadone dose not properly "holding" – frequently occur during methadone maintenance treatment (MMT). Although most MMT patients do well on a once-daily dose of methadone, some do not.

The "not holding" problem typically stems from a sharp rise and then rapid decline in serum methadone level (*SML*, measured in nanograms per milliliter or ng/mL) during the dosing interval. The patient experiences both over- and under-medication during the course of a day. In other cases, patients may feel comfortable most of the day, but the methadone seems to wear off long before the next daily dose.

A solution is to shorten the dosing interval, while maintaining or slightly increasing the total daily amount of methadone.

Staying Within the "Comfort Zone"

Typically, within 4 to 5 days of starting a dose or after a dose increase, methadone reaches a steady-state condition during which the low (trough) and high (peak) SMLs remain about the same from one dosing interval to the next (see ***Figure 1***). During successful MMT, the methadone concentration should eventually reach and stay within a *comfort* zone, which varies among individuals but generally has a trough SML ranging from about 200 to 700 ng/mL. The peak SML should ideally be no more than twice the trough level; that is, a P:T ratio £ 2.

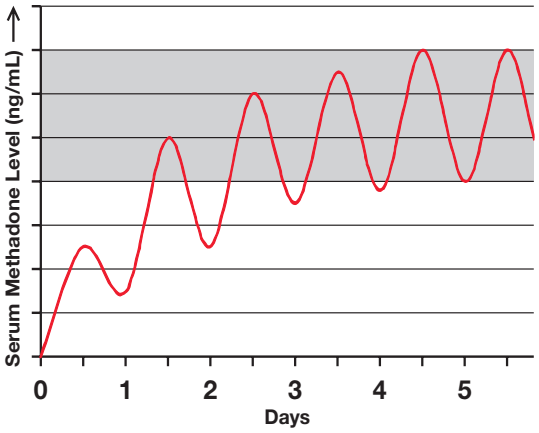


Figure 1: Serum methadone level reaches steady-state in 4-5 days and eventually stays within a "comfort zone" (gray area).

If the SML is within the therapeutic comfort range, the patient will experience no signs or symptoms of methadone overmedication or withdrawal (undermedication). And, at an *adequate* methadone dose, drug craving and illicit opioid use can be abolished.

However, due to individual differences in metabolism or methadone interactions with other substances (e.g., drugs, medications, herbal products, etc.), what is often expected to be a sufficient methadone dose could be inadequate. ***Figure 2*** illustrates methadone being rapidly metabolized, leading to withdrawal prior to the next dose (dotted line). However, simply increasing the dose amount results in overmedication early in the cycle and withdrawal still persists later on (dashed line).

The solution is to adjust the methadone dose interval, rather than the amount. Splitting the dose keeps peak and trough values within the comfort zone (solid red line). The size of the original methadone dose is irrelevant; *whether they are taking 60 or 600 mg/day, certain patients may benefit from splitting their dose.*

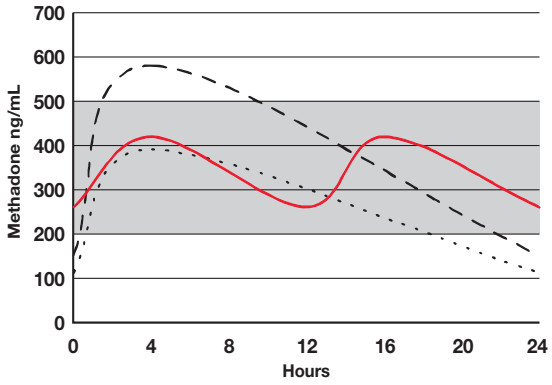


Figure 2: Increasing dose amount results in overmedication, while withdrawal persists. Split dosing is a solution.

Concomitant medications influencing more rapid methadone metabolism also are a common problem. ***Figure 3*** illustrates an interaction effect of the antiseizure medication phenytoin (Dilantin®), which speeds methadone metabolism and greatly lowers the trough SML (P:T = 14.8, dotted line).

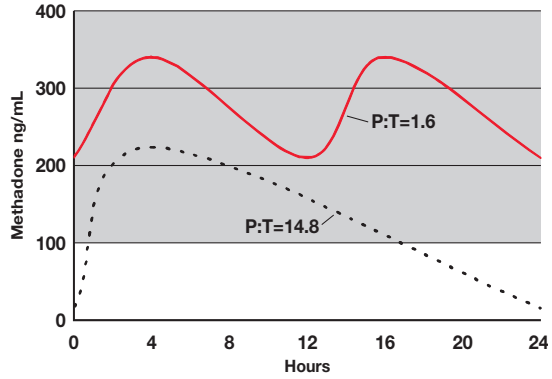


Figure 3: Split dose resolves drug interaction problem.

By splitting the methadone dose, a more consistent methadone concentration within the particular patient's comfort zone is achieved throughout the 24-hour period (P:T = 1.6, red line). Note: the extent of individual reactions to medications may differ; also, if the interacting drug is abruptly discontinued or reduced there could be a steep, possibly unsafe, rise in methadone levels. (Also see the article in this issue on drug interactions.)

Split Dosing Protocol

Measuring peak and trough SMLs can be helpful to verify the extent of fluctuations (with peak occurring on average 2-4 hours after dosing). However, of equal or greater importance, it is necessary to assess clinical signs and patient-reported symptoms of methadone over- or undermedication.

The recommended approach for beginning split dosing is to start with an observed *full* dose of methadone and then administer *half* of that dose 12 hours later (usually given to the patient as a take-home dose). For example: 100 mg in the morning and 50 mg that evening. This means the patient is administered 1.5 doses on day one, but it should not be problematic in an opioid-tolerant patient who is rapidly metabolizing the usual methadone dose. Note: starting the regimen with only a half dose in a patient who is already likely to be in withdrawal is not advised.

On the second day the patient assumes a regular schedule of half doses 12 hours apart. After monitoring the patient's clinical

Continued on Page 4

Practice Pointers
Continued from Page 3

response to the split dose – noting physical signs and patient-reported symptoms of methadone adequacy – the amount can be adjusted if it seems necessary. Doses may be further split into more than two components, but this requires added monitoring and patient compliance becomes more difficult.

Overcoming Limitations

Patient education and cooperation are critical for success. Split dosing regimens are only suitable for otherwise stable and responsible patients; those who have demonstrated an ability to properly handle take-home doses, who are compliant with taking medications properly, and in whom there would not be safety concerns regarding illicit drug or alcohol use.

It is impractical to expect that patients will come to an MMT clinic more than once daily for dosing. Yet, under current federal regulations, it can take a year in continuous treatment before a full week's supply of take-home doses are allowed.

Usually, the need for split dosing becomes apparent after the patient has been in treatment for some time and already qualifies for limited take-homes. Many regulatory authorities will then grant exemptions for patients who need additional take-home privileges for split dosing purposes; however, clinic staff must be prepared to present a medical justification for this, which may include trough and peak SML measurements to support documented clinical signs/symptoms of abnormal methadone metabolism.

AT Forum *thanks* ***J. Thomas Payte, MD*** *(Corporate Medical Director, Colonial Management Group; Orlando, Fla.) for permission to adapt his educational materials for this article, and for his helpful suggestions.*

For more information on adequate methadone dosing see: *Leavitt SB. Methadone dosing and safety in the reatment of opioid addiction. Addiction Treatment Forum. Special Report. 2003. Available at: http://www.atforum.com/SiteRoot/pages/addiction_resources/DosingandSafetyWP.pdf.*

A.T.F.

Beyond Methadone
Continued from Page 1

most medical authorities as a *chronic relapsing disease*, so periodic setbacks should be anticipated and plans established for dealing with them.

Drug addiction frequently has been compared with chronic illness, such as diabetes, hypertension, and asthma. Persons in treatment for any of these may have difficulty adhering to the treatment regimen, may sometimes drop out prematurely, and/or may experience setbacks requiring more intensive care for their conditions.

Staying the Course

Some research studies have reported relapse rates of more than 70% among persons in alcohol- or drug-abuse treatment. Most of those occurred during the first year of treatment, with two-thirds of relapses occurring within the first 90 days. As might be expected, patients remaining in treatment the longest, staying the course, ultimately have the best outcomes.

A belief that one drink or one drug-taking episode inevitably leads to another and a return to total loss of control can be an obstacle to recovery. Clear distinctions must be made between a "lapse" and "relapse"; otherwise, patients may assume that a little bit is just as bad as a lot and turn every sobriety lapse into a relapse, possibly dropping out of treatment entirely.

This has been called the "abstinence violation effect." A person with a strict abstinence goal may view the slightest lapse as a major failure rather than a learning experience, and with a "what the heck, I blew it" attitude proceed to all-out relapse.

Since relapse is a process, slips leading up to it are not purely accidental. Participants in 12-step programs say that SLIP stands for "Something Lousy I Planned." Many small, seemingly irrelevant, decisions may bring about a sampling of drug often leading to relapse, and relapse prevention hinges on learning to recognize those decisions earlier in the chain of thought.

It should be noted that 12-step programs make little distinction between lapse (slip) and relapse; *any* use of an illicit drug or alcohol is forbidden, no matter how fleeting. While this is sound in principle, the practical side is that substance-addicted persons are likely at some point to sample their drug of choice, especially early in recovery, and this need not turn into a catastrophic event.

Readiness to Change

Relapse prevention is essentially about change, as is recovery itself. However, for a person with addiction, change can be a fearful and painful process, and relapse might be viewed as a lost struggle between a person's readiness to change and internal or external factors that fight against it. Some patients prefer to dictate the rules of recovery on their own terms, essentially maintaining the status quo, and they repeatedly relapse.

Psychologists have wrestled with concepts of relapse to better understand the process and develop models for its prevention. An important relapse prevention model was developed by Marlatt and colleagues to extend and enhance therapeutic gains during addiction treatment and to reduce the possibility of recidivism.

A foundation of Marlatt's approach is that it is easier to correct the relapse process early rather than later. If the patient is provided a set of recovery tools, a slip does not necessarily lead to a relapse, and a relapse is not the end of recovery. Some of those "tools" are listed in ***Table 1***.

This notion of developing a set of recovery tools is common to 12-step programs and most addiction therapies. Many of them are directed at overcoming the pain and shame of lapses in sobriety; but foremost is staying with the program no matter what happens.

Continued on Page 5

Table 1: Preventing a Lapse (Slip) from Becoming a Relapse

- Stop consuming the illicit substance(s) as soon as possible.
- Stopping sooner means far less physical and mental anguish due to renewed substance dependence and craving.
- Use the slip as a learning experience.
- Examine the sequence of events leading up to the slip; what could have been done differently to avoid it?
- Do not make excuses but, at the same time, do not beat yourself up.
- Get immediately back into the program of recovery.
- Take pride in renewed efforts to stay "clean"; rather than punishing yourself for past events leading up to the slip.

Adapted from: Volpicelli and Szalavitz 2000

Relapse triggers or cues, whether known or unknown, can be everywhere and intimately woven into the fabric of a person's life. Twelve-step programs, always striving for practical approaches, emphasize that following old habits and patterns of behavior associated with drug use can rekindle cravings leading to slips. They also use the acronym HALT – Hungry, Angry, Lonely, or Tired – to generally represent critical situations and emotions to avoid.

Clinical Interventions

Marlatt classified precipitants of relapse into two broad categories: intrapersonal and interpersonal. Intrapersonal factors include emotional and physical states, a sense of personal control, and urges or temptations. Interpersonal influences include relationship conflicts and social pressures to use substances.

For example, Marlatt found that 19% of heroin addicts who relapsed did so in response to negative emotional states (intrapersonal). On the interpersonal side, some researchers have found that social pressure was identified by 36% of heroin addicts as contributing to their relapses; conversely, more positive social and spousal support predicted a lower risk of relapse. In many cases, addicted persons lacked coping skills for dealing in more positive ways with both the intra- and interpersonal torment in their lives.

Many models of relapse intervention and prevention have been developed and tested over the years. Most of these incorporate strategies from Marlatt's conceptualizations of relapse factors and, in one way or another, focus on the patient's need to develop personal and interpersonal skills along with a broad repertoire of coping strategies for dealing with previously baffling, upsetting, or high-risk situations. Some practical clinical strategies for helping patients are outlined in ***Table 2***.

MMT Road to Recovery

MMT is a well-established, thoroughly studied, and successful model of addiction treatment, combining pharmacotherapy (methadone) with relapse prevention strategies. Yet, there is relatively little scientific literature recommending how clinics can best respond to lapses and relapses among patients.

MMT programs emphasize abstinence from opioids and, usually, all other non-prescribed psychotropic substances. However, methadone is a medication primarily proven useful for treating opioid addiction, even though some research has found that, at adequate doses, methadone curtails cocaine, alcohol, and other substance abuse in certain patients.

A critical factor is providing *adequate* methadone doses. If patients are undermedicated they may be tempted to use other psychoactive substances to overcome uncomfortable symptoms of withdrawal. This then poses the dilemma of how to safely stabilize a patient on methadone who is abusing other substances, some of which may interfere with methadone metabolism or be harmful in themselves.

Relapse prevention strategies during MMT have varied. Some clinics have successfully used reward incentives for continued illicit-drug abstinence, but these can be expensive. Others have tried punishments for even minor lapses, such as loss of take-home dose privileges or reductions in methadone dose, which can be counterproductive. More intensive counseling/therapy has been applied in some cases, which seems like an appropriate strategy but also requires extra time and patient motivation to change.

MMT programs may have an advantage over other addiction treatment modalities in that regular clinic attendance to receive medication is mandatory for an extended period of time – if those patients are retained in treatment. There can be frequent opportunities for patient interactions with staff, even apart from scheduled counseling or group therapy sessions, during which principles expressed in the ***Tables*** above can be reinforced.

As with all other addiction treatment modalities, there are no guaranteed solutions for MMT practitioners to apply when it comes to preventing lapses and relapses. The road to addiction recovery is never ending. Whereas, sobriety lapses or slips might be best viewed as bumps along the way, relapses always pose more difficult challenges.

If patients stumble and fall, it is important that they get back up and move onward, rather than dwell too long on what tripped them up. For some persons, stumbling, but falling in a *forward* direction, is still a meaningful form of progress.

Respond to the survey on lapses/relapses in this edition. Also, tell us how these problems are handled at your MMT clinic. Responses will be published in an upcoming *A.T. Forum* edition,

***Please submit responses* via the feedback card; at http://www.atforum.com; fax: 847-392-3937; or, mail: PO Box 685, Mundelein, IL 60060.**

Table 2: Clinical Interventions for Relapse Prevention

Patients need counseling and guidance in…

- identifying and coping with lapse and relapse warning signs.
- anticipating high-risk relapse situations and in developing coping skills for managing them in appropriate ways.
- identifying feelings and dealing with negative emotional states.
- identifying and preparing to handle social pressures to engage in substance use.
- improving interpersonal communication and relationship-building skills, and in developing a recovery support system.
- understanding and coping with cravings to use substances as well as cues that trigger those cravings.
- identifying and managing patterns of thinking leading to relapse risk.
- working toward more balanced, productive lifestyles.
- interrupting lapses or relapses early to minimize damage caused by setbacks.

Treatment staff also should…

- assess patients for co-occurring psychiatric disorders and facilitate treatment for those conditions.
- combine appropriate medications with psychosocial therapies.
- incorporate strategies that improve patients' adherence to medications and other treatment recommendations.

Adapted from: Daley et al. 2003

For further information see:

Daley DC, Marlatt GA, Spotts CE. Relapse prevention: clinical models and intervention strategies. In: Graham AW, et al. (eds). Principles of Addiction Medicine. 3rd Ed. Chevy Chase, Maryland: American Society of Addiction Medicine; 2003:467-485.

Marlatt GA, Barrett K, Daley DC. Relapse prevention. In: Glanter M, Kleber HD (eds). Textbook of Substance Abuse. 2nd ed. Washington, DC: American Psychiatric Press;1999: 353-365.

Volpicelli J, Szalavitz M. Recovery Options. New York: John Wiley & Sons; 2000

Adequate Methadone During Pregnancy Not Harmful in Neonate

Since the 1970s, methadone maintenance treatment (MMT) has been recognized as beneficial for pregnant opioid-addicted women. However, the recommended daily methadone dose in these patients has been controversial and is often based on attempts to avoid or reduce abstinence syndrome in the neonate, rather than on achieving optimally effective methadone dose in the mother.

Some researchers in the past have recommended that the dose during pregnancy should not exceed 20 mg/day, even though adults usually require at least 80 to 120 mg/d for maintenance therapy, often more. Other research has demonstrated that dose increases may be required during later stages of pregnancy to maintain methadone blood levels and prevent withdrawal in the mother.

Recently, a team of researchers led by Vincenzo Berghella at Jefferson Medical College, Philadelphia, conducted a retrospective review of neonatal records to determine whether maternal methadone dosage correlates with neonatal withdrawal. They identified 100 mother/neonate pairs in whom the women received from 20 to 200 mg/d during their pregnancies.

An objective measure, the neonatal abstinence score (NAS), was used to assess opioid withdrawal in the newborns. Clinical signs and symptoms necessitating treatment for neonatal withdrawal were usually associated with an NAS ≥ 8.0.

As the **Graph** illustrates, average highest NAS measures were actually greater at methadone doses less than 40 mg/d; however, differences between the NAS at any dose were not statistically significant. Also of interest, mean duration of neonatal treatment for withdrawal was longest in the low-dose group (19.6 days) compared with either <80 or 80+ mg/d (13.3 and 13.6 days, respectively). Again, these data were statistically equivalent.

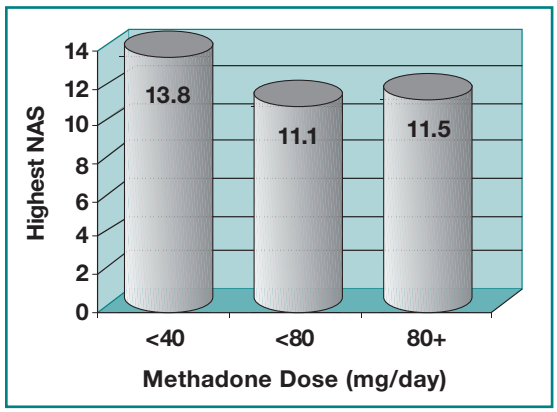
According to Berghella and colleagues, the data offer strong support for the premise that daily methadone dose, at whatever amount is *most adequate* for the mother, does not affect the incidence and severity of neonatal withdrawal. A possible explanation for this is the highly individual and variable metabolism of methadone.

For example, women receiving markedly different doses of methadone may have the same serum levels of the medication in their systems, so fetal exposure to methadone would be equivalent. Earlier research did not take this into account.

Furthermore, other research did not fully consider that subtherapeutic maternal methadone doses may promote illicit drug use, increasing the risk to both mother and fetus. Berghella et al. found that neonates born to mothers who abused benzodiazepines – possibly to quell withdrawal symptoms – required significantly longer withdrawal therapy.

Finally, earlier studies did not use objective scales to rate severity of neonatal withdrawal, such as the NAS. Thus, they failed to discover that the intensity and duration of neonatal withdrawal was not necessarily dependent on methadone.

Berghella and his team conclude that methadone should be given to pregnant opioid addicts during MMT at the most effective dose, which must be individually determined and adequate to prevent withdrawal symptoms in the mother. This, plus a program that includes prenatal care, can reduce the incidence of obstetric and fetal complications, as well as neonatal morbidity and mortality.



See: Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. Am J Obstet Gynecol. 2003;189:312-317.

A.T.F.

Clinical Concepts
Continued from Page 1

(MMT) programs. These individuals often have co-occurring physical and mental disorders requiring multiple medications.

However, it is estimated that 34% of prescriptions written in the U.S. are unnecessary. This trend is fueled by patients' demands for quick and effective medications for even minor ills, although they seldom consider the potential negative consequences (Farrell et al. 2003).

In light of these considerations, MMT practitioners, as well as patients, need strategies for avoiding or managing often unexpected and potentially hazardous drug interactions.

Clinical Action Steps

The potential for certain drugs and drug combinations to interact with methadone requires careful consideration when prescribing comedications. Furthermore, polysubstance abuse may place patients at risk for hazardous interactions of methadone with other opioids and drugs such as alcohol, cocaine, barbiturates, and benzodiazepines.

Clinical experience, intuition, and common sense can be valuable tools for MMT practitioners in taming drug interactions. Following are some suggestions: (Chung 2002; Cohen, 1999; Levy et al., 2000; Piscattelli and Rodvold, 2001)

1. Develop a working knowledge of methadone-drug interactions. Methadone is metabolized by the P450 enzyme system, primarily CYP3A4. The metabolic requirements of other medications can be checked in manufacturers' literature or standard references.
2. Maintain an accurate, updated profile for each patient that includes all prescribed and illicit drugs, and OTC products (including herbal remedies and dietary supplements).
3. Use alternative, non-interacting, drugs whenever possible. Usually, there are differences in the interactive properties of at least some members of any drug class. For example, the macrolide antibiotic erythromycin is a strong CYP3A4 inhibitor, likely to interact with methadone, whereas the macrolide azithromycin does not appear to have this effect. Similarly, divalproex might be substituted for carbamazepine, which is a potent CYP3A4 inducer.
4. If a potentially interacting drug absolutely must be used with methadone,

Continued on Page 7

adjust the methadone dose based on patient response rather than in advance based on an expected interaction. The magnitude of drug interactions varies dramatically from patient to patient, and it is unlikely that the selected methadone dosage adjustment would exactly offset the effect of the second drug.

5. Signs/symptoms of either abstinence syndrome (withdrawal) or overmedication (sedation) can help gauge serum methadone level (SML) adequacy in the presence of an interacting drug. Adjustments of methadone or concomitant drug(s) may be appropriate to overcome such adverse reactions.
6. If there are concerns about adverse effects of increased methadone concentrations, patients should be advised in advance of physical signs/symptoms of overmedication that might occur and what to do. It may be desirable to monitor SMLs.
7. Whenever possible, avoid concurrent administration of drugs with overlapping adverse-effect profiles. Otherwise, signs/symptoms of major variations in methadone concentration may be confused with side effects of concomitantly administered drugs, and vice versa.
8. Consider preexisting disease states. For example, conditions associated with impaired renal or hepatic function may significantly alter drug metabolism and excretion. Patients with preexisting cardiovascular conditions – particularly those with congestive heart failure or left ventricular systolic dysfunction – may be more sensitive to arrhythmogenic effects of certain drugs (including methadone).
9. In some cases, adverse drug reactions can be resolved by prescribing a medication with or without food, by altering dosing schedules, or by splitting doses into smaller increments.
10. Unreported or seemingly inconsequential factors may play a role in drug interactions. For example, grapefruit juice can hinder metabolism and increase methadone serum levels, while large amounts of vitamin C may boost excretion and decrease methadone effects.
11. Patients may not adhere to prescribed medication regimens, which could affect adverse reactions, and the more complicated the regimen the less likely that the patient will adhere to it. This can be important in MMT patients prescribed multiple medications.

Helping MMT Patients Avoid Drug Interactions

- MMT patients should be cautioned to consult healthcare professionals before taking OTC products, herbal remedies, or dietary supplements.
- Patients should provide to their healthcare providers and pharmacist an updated list of all medical products used. (Ideally, this list also will include illicit substance and alcohol use.)
- Patients should understand their prescriptions and the dosage, and be able to cross-check what was prescribed with what they receive from the pharmacist.
- For each prescribed medication, patients should be instructed on what the drug is used for, how to take it, and how to reduce the risk of side effects or drug interactions.
- It cannot be assumed that patients will read or understand product labels or written information provided with medications or other healthcare products.
- Compliance with prescribed medication regimens should be emphasized. Patients need to understand the importance of taking all medications exactly when, how, and in the quantities specified.
- Patients should be educated on the hazards of taking excess medication or sharing medicines with anyone else. They should be reminded about safe storage of medications and proper disposal of unused portions.
- Patients should be counseled on the importance of reporting any sudden or unexpected signs/symptoms of methadone withdrawal or overmedication, as this could indicate a potentially hazardous interaction with another substance.
- Special consideration and instruction will be required for patients with physical conditions that may cause or exacerbate drug interactions, such as: liver or kidney disorders, pulmonary or heart ailments, pregnancy, etc.
- Patients taking multiple medications should be assisted in keeping a journal or chart listing the name, purpose, and dose schedule for each drug.

Adapted from: FDA/CDER 2000; NCPIE 2003.

The traditional advice when adding drugs to a therapeutic regimen is to *start low, go slow, and monitor closely.* This may be especially prudent during MMT, since many commonly prescribed drugs are associated with dose- and concentration-dependent toxicities, and individual response may vary by several orders of magnitude.

Potential adverse reactions also can be minimized by using the smallest effective doses for drugs added to methadone therapy. In many cases, doses of adjunctive medications lower than those recommended by the manufacturer may be sufficient for desired therapeutic effect (Cohen, 1999).

Patient Education is Essential

It has long been recognized that patient education is essential for successful MMT outcomes and this should be initiated early in treatment. Several important points need to be emphasized with patients regarding potential interactions of methadone with other substances and to help them avoid all drug interaction. These are noted in the ***Table.***

Better informed patients can partner more effectively with clinic staff regarding their pharmacotherapy. However, as with all other aspects of MMT, this relies on mutual trust and effective communication.

References:

Chung EP. A review of clinically significant drug interactions. California Pharmacist. 2002 (Summer):56-65.

Cohen JS. Preventing adverse drug reactions before they occur. Medscape Pharmacotherapy [online serial]. 1999. Available at http://www.medscape.com/viewarticle/408588

Farrell VM, Hill VL, Hawkins JB, Newman LM, Learned RE. Clinic for identifying and addressing polypharmacy. Am J Health-Syst Pharm. 2003;60(18):1830-1835.

FDA/CDER (Center for Drug Evaluation and Research). Drug Interactions: What You Should Know. Available at: http://www.fda.gov/cder/.

Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M, eds. Metabolic Drug Interactions. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

NCPIE (National Council on Patient Information and Education). Be MedWise®. 2003. Available at: http://www.bemedwise.org/

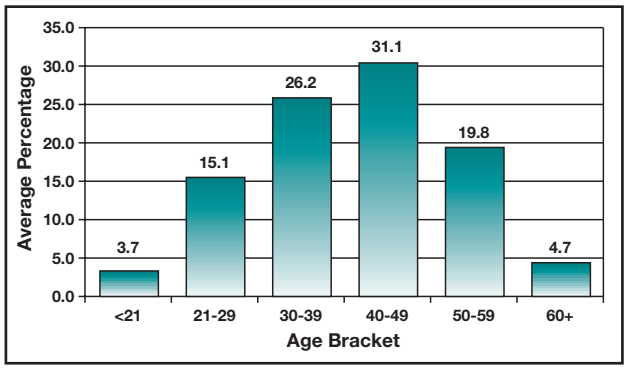
Piscitelli SC, Rodvold KA (eds). Drug Interactions in Infectious Diseases. Totowa, NJ: Humana Press; **2001**.

A.T.F.

As a guide for practitioners, AT Forum will be releasing a special report, **"Methadone-Drug Interactions."** This provides an overview of how drug interactions occur, plus expanded and updated tables listing substances that may alter methadone metabolism and the effects in patients. The report also will be available for downloading at www.atforum.com, under the "Addiction Resources" tab.

Reader Response: "Graying of Methadone"

Last winter, *A.T. Forum* (2003, Vol. 12, No. 1) had a feature article discussing the apparent growth of an older "graying" population in methadone maintenance treatment (MMT) programs. To further examine that trend, all readers were invited to respond to a survey soliciting information about the percentage of patients at their particular clinics within specific age brackets, the total number of patients at each clinic, and years of operation.



Significant Percentage Age 50+

There were a total of 78 valid responses submitted via survey cards or at www.atforum.com, representing different clinics in 25 states. The ***Graph*** shows the average distribution across the 6 age brackets surveyed.

Nearly a quarter (24.5%) of patients in the responding clinics on average were age 50 or greater; so, overall, this group clearly represents a significant proportion of the treatment population. Yet, there was a high degree of variation with percentages of patients in this age group ranging from 0% to 90% across individual clinics.

Broad Clinic Diversity

It was expected that clinics with more years in operation would have the largest percentages of older patients. On average, responding clinics had been in operation for 18.4 years (range 1 to 40 years). There was only a modest, but statistically significant, positive correlation of years in operation with percentage of age 50+ patients ($r = +.29$; $p < 0.01$).

Yet, there was a great deal of variation in this association. In one clinic operating for only a year, 23% of patients were age 50 or older; whereas, only 5% of patients were in that age bracket in another clinic operating for 30 years.

The 78 responding clinics represented a total of about 30,500 patients (average 401 per clinic), and clinic sizes ranged from 14 to 4,400 patients. There was very little correlation of clinic size with percentage of age 50+ patients ($r = +.07$).

Of the 25 states represented in survey responses, those with the most age 50+ patients were: California, Maryland, New Mexico, New York, Ohio, Pennsylvania, Texas, Washington, and Washington DC. At the same time, there was one clinic in Pennsylvania responding with 0% in the 50+ age bracket and one clinic in Maine without any patients older than age 50.

Trend Worth Further Study

This survey was quite limited, representing less than 8% of MMT clinics and only about 15% of patients in the U.S. However, the trend was similar to that reported in the *A.T. Forum* article last winter for Beth Israel Healthcare System in New York City. In 2002, this MMT program – one of the largest and oldest in the country – found that 28.9% of patients were age 50-59 and 6.4% were age 60 or greater (total age 50+ = 35.3%). Similarly, 18 respondents in this *A.T. Forum* survey (23%) indicated at least a third of their population was age 50 or older.

Clearly, there is a need for a more comprehensive survey of this nature; perhaps, sponsored by the federal government or a national organization of treatment providers. However, judging by the limited results of this present survey, there already appears to be reasonable grounds for organizing seminars, conferences, or other efforts focusing on the very special needs of a "graying" MMT population.

A.T.F.

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Drug Lapses/Relapses – Please respond to the following questions:

1. What percentage of patients at your MMT clinic experience drug lapses (slips) ____% or full-blown relapses ____%?
2. When are lapses (slips) *most likely* to occur after starting MMT? (check one) ___ 1 month; ___ 3 months; ___ 6 months; ___ 1 year; or, ___ later.
3. When are relapses *most likely* to occur? (check one) ___ 1 month; ___ 3 months; ___ 6 months; ___ 1 year; or, ___ later.
4. Which drugs are *most commonly* involved in lapses or relapses? (check all that apply) ❑ cannabis; ❑ heroin; ❑ other opioids; ❑ cocaine; ❑ benzodiazepines; ❑ alcohol; ❑ other _____ (please specify).
5. Are you responding as a ❑ patient, or ❑ clinic staff member?

Comments: _____

❑ Please add me to your mailing list (Mailing within U.S. only. Outside U.S. see www.atforum.com).

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