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Update from DDW: Part 3

Alan Franciscus, Editor-in-Chief

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The final report on the DDW 2004 conference will focus on various reports issued, including practice patterns of liver specialists in the United States, managing treatment related anemia and the effect of estrogen replacement therapy on treatment outcome.

PRACTICE PATTERNS

Sean P. Hurley and colleagues studied the practice patterns of gastroenterologists and hepatologists to assess whether clinicians followed an acceptable approach to treatment and management of treatment side effects. In this national study, 5000 gastroenterologists were mailed a 31 question survey of whom 17.8% responded. It was generally found that most clinicians followed established management patterns but there were still many who did not. In 77% of respondents the therapy of choice was pegylated interferon plus ribavirin, the current standard of care. Seventy-five percent of the respondents followed the 12 week rule and discontinued medical therapy in patients who did not achieve a 2 log or greater reduction in viral load.

Key Points:

- Initially 45% of physicians would dose reduce HCV medications to manage severe fatigue and cytopenias (blood disorders).
- Growth factors were used to manage side effects, but insurance reimbursement limited the use of growth factors more than 50% of the time in 14% of the respondents.
- Twelve percent would use pharmaceutical agents to treat muscle/joint paint and fatigue.
- Thirteen percent would start patients on antidepressants before treatment.
- Most (74%) would manage interferon induced depression themselves with SSRI's, listed as the treatment of choice.

Of interest, the researchers found that physicians in high-volume practices were less likely to dose reduce or discontinue therapy when managing treatment side effects. Finally, the researchers reported that according to their study patients were less likely to complete therapy when a physician used a dose reduction approach to manage fatigue and cytopenias.

TREATMENT INDUCED ANEMIA

Ribavirin is associated with a hemoglobin (Hb) decline which may require the use of adjunct therapies or a reduction in the ribavirin dose.

Anouk T. Dev and colleagues reported on a study they conducted to find out if the drop in Hb is predictive of sustained virological response (SVR). In this retrospective study, the investigators identified 349 patients from two hospital databases. Hb levels were measured at baseline, and at weeks 4 and 8 of therapy. No patient in this study had a ribavirin dose reduction during the 8 week period.

The patient characteristics in this study were: male (75%), genotype 1 (83%), Caucasian (66%). Sixty two percent received pegylated interferon plus ribavirin and 38% received standard interferon plus ribavirin.

The authors reported that an Hb drop of 3g/dl levels or more occurred in 32% of the patients during the first 8 weeks of therapy. But it was found that a decline in

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Injection Drug Users and Hepatitis C

Liz Highleyman

Because hepatitis C and B are transmitted efficiently through contaminated needles and other injection equipment, infection rates are high among injection drug users (IDUs). Various studies have found HCV prevalence rates as high as 80-90% among IDUs, while incidence (new infection) rates are estimated at 10-30% per year. Although incidence in IDUs has decreased dramatically since the 1980s, drug injection still accounts for about 60% of new HCV infections. HBV is more often sexually transmitted, but drug injection still accounts for an estimated 17% of new infections, and about 60% of IDUs show evidence of HBV infection. Further, IDUs have high rates of HIV/HCV, HBV/HIV, and HCV/HBV coinfection.

Unfortunately, IDUs have been excluded from most hepatitis C and B studies, so there is little data about the natural history of the diseases or how well HCV and HBV treatment works in this group.

Until recently, many experts felt that IDUs were not good candidates for viral hepatitis treatment. In particular, it was thought that IDUs would adhere poorly to therapy, were more likely to experience psychiatric side effects related to interferon, and if treatment was successful were at high risk of reinfection due to continued drug use. The 1997 National Institutes of Health (NIH) consensus guidelines recommended that IDUs should not be offered HCV therapy until they had abstained from drugs and alcohol for at least six months.

But with IDUs accounting for such a large proportion of HCV patients, experts increasingly recognize the need to find ways to manage this population. The latest NIH consensus guidelines, revised in 2002, recommend that "treatment of active injection drug use be considered on a case-by-case basis, and that active injection drug use in and of itself [should] not be used to exclude such patients from antiviral therapy." Furthermore, "methadone treatment has been shown to reduce risky behaviors that can spread HCV infection, and it is not a contraindication to HCV treatment."

What few studies there are show that IDUs and people on methadone can benefit from hepatitis C treatment. Brian Edlin of Cornell presented an overview of this data at the June 2002 NIH consensus meeting on the management of hepatitis C.

A study by Markus Backmund and colleagues (reported in the July 2001 issue of *Hepatology*) looked at 50 heroin injectors starting opiate detoxification treated with standard interferon monotherapy or interferon plus ribavirin. The overall SVR rate was 36% (26% for genotype 1; 48% for genotypes 2 or 3), comparable to that seen in nonusers treated with this regimen. Patients who relapsed to drug use during the study (80%) were offered methadone or dihydrocodeine maintenance (which 30% accepted) and allowed to continue HCV treatment. SVR rates were 24% in patients who relapsed to drug use and did not resume drug treatment, 53% in patients who relapsed and started opiate maintenance, and 40% in those who did not relapse to drug use (not a statistically significant difference). The authors concluded that, "HCV-infected drug addicts with chronic HCV infection can be treated successfully with interferon alfa-2a and ribavirin if they are closely supervised by physicians specialized in both hepatology and addiction medicine."

Diana Sylvestre from Oakland's OASIS program found that among 66 methadone patients treated with standard interferon plus ribavirin, the overall SVR rate was 29%. Patients reporting a psychiatric diagnosis (about two-thirds) had a lower SVR rate than non-psychiatric patients (24% vs 35%). During HCV treatment, one-fifth reported drinking alcohol and one-third reported using drugs. Those who did not use drugs during HCV treatment had an SVR rate of 32%, compared with 29% for those who used rarely, 33% who used intermittently, and none who used daily. "Relapse to drug use during HCV treatment should not prompt HCV treatment discontinuation," Sylvestre concluded, "but rather an early and aggressive attempt to intervene before the drug use becomes regular."

In the July 2004 issue of *Hepatology,* Stefan Mauss and colleagues reported data from a study of 100 subjects with HCV, 50 on methadone

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HealthWise:

Spiritual Health

Lucinda K. Porter, RN, CCRC

The origin of the word "health" is from Old English meaning "wholeness." Merriam-Webster defines health as "the condition of being sound in body, mind, and spirit." Most of us have a general idea of how to cultivate a sound body and mind. We know we ought to eat well, exercise, refrain from substance use, engage in stress reduction techniques, etc. But when it comes to spiritual health, many do little or nothing. This is especially true for those who associate spirituality with an uncomfortable or negative religious experience.

The word "spirit" can be traced back to spirare meaning "to breathe." As we know, breathing is central to life. Stop breathing and we stop living. For those who maintain a spiritual practice it can be as essential as breathing. Those who are not engaged in a spiritual discipline may feel "out of sorts" or have a sense of emptiness.

Meditation and prayer are the cornerstones of spiritual health. One way to describe the difference between prayer and meditation is that prayer is asking or addressing, while meditation is listening. Meditation can be either secular or religious in nature. Atheists can practice meditation. Prayer, on the other hand, is usually associated with a belief in some sort of divine power.

Patients from all religious faiths may turn to prayer to help cope with chronic illness. Prayer has been studied at major hospitals throughout the United States. The National Institutes of Health has awarded a grant to study the effects of prayer on cancer and AIDS patients. Therapeutic or healing prayer is offered in both denominational and non-denominational settings. Alcoholics Anonymous and other 12-step programs use prayers such as the Serenity Prayer during meetings.

The practice of prayer is deeply personal. There is no right, wrong or single way to pray. Who you pray to is personal. Some people are uncomfortable with the word "God" and prefer to use "Higher Power" or other meaningful terminology. Prayers can be short or long. It has been said that under certain conditions, the shortest prayers are "Help" and "Thank You."

Meditation is a broad concept and can encompass a variety of approaches. Some people meditate for stress relief while others meditate as part of a spiritual practice. In general, meditation is a tool to help quiet the mind while promoting awareness and a sense of well-being. Meditation is sometimes described as the practice of mindfulness or living in the present. Because of its positive effect, meditation is used as a tool to help manage illness—chronic hepatitis C, for example.

Meditation is simple to learn, although not necessarily easy to practice. Here are a few suggestions to help get you started:

Practice regularly, but start small - Initially practice for 5 minutes daily and gradually increase to 15-30 minutes. Some people find it helpful to meditate more frequently but for short intervals.

Set aside time to meditate - Schedule a regular time to meditate. Meditating in the morning has the added advantage of setting a relaxing tone for the day.

Dress comfortably - Wear loose fitting, comfortable clothes. Make sure the temperature in the room is also comfortable.

Location - Choose a quiet and relaxing location. You can sit in a comfortable chair or on the floor with a cushion. Lying down is alright if you can avoid the temptation to fall asleep. Walking meditation is another alternative.

Sitting - You can sit in a comfortable straight-backed chair with hands resting on your legs and feet gently touching the floor. You may prefer sitting crossed-leg on the floor, chair or cushion. Comfort is essential. In this application, meditation is meant to alleviate health problems, not to create them.

Managing distractions - Distraction and resistance are as much a part of meditation as breathing is. The mind will continue to think, the ears will continue to hear, and the body will continue to feel. It is perfectly acceptable to have thoughts and to notice sounds. The tricky part is not letting these occurrences dominate and call your

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Hb during the first 8 weeks of combination therapy is not predictive of an SVR. Further studies are required to assess whether longer initial levels of Hb affect treatment response, including early and sustained virological response.

In another report, long term use of epoetin was studied. In this study conducted by Paul Packros and colleagues, 185 patients who developed anemia during therapy were randomized to receive either once-weekly epoetin (93 patients) or a placebo (92 patients) during the first 8-week double-blinded phase of the study. After the double-blinded phase of the study was completed, all patients received epoetin for the remainder of their treatment. Patient characteristics were similar in the two groups.

The authors found that 84% of the total patient population in this study maintained their ribavirin dose and that epoetin therapy was well-tolerated and maintained over the entire course of HCV therapy. Furthermore, it was found that the use of epoetin did not adversely affect HCV clearance. The authors also noted that more studies are needed to determine whether maintaining higher ribavirin doses with epoetin increased sustained virological response rates.

Improving the efficacy of epotein alfa was the objective of a retrospective study conducted by Aijaz Ahmed and colleagues. In this study, the medical records of 56 consecutive patients with HCV who were treated with weight-based ribavirin dosing and peginterferon alfa-2a or peginterferon alfa-2b were analyzed. The patients were identified during a 12 month period between 6/1/02 and 6/1/03 at a university hospital satellite clinic. Patients with pre-existing anemia, platelet count less than 50,000, or decompensated cirrhosis were excluded. Baseline blood counts were obtained and a weekly complete blood count performed for the first 12 weeks of treatment. New onset of anemia was defined as hemoglobin less than 12 g/dl, hemoglobin decline more than 3 g/dl or hemoglobin decline more than 2 g/dl with significant fatigue. Patients with new onset of anemia were treated with epoetin alfa 40,000 units/week until 2 weeks after their counts returned to baseline. Patients treated with 40,000 units/week who developed severe anemia (10-11 g/dl) were prescribed 60,000 units/week until their hemoglobin levels returned to baseline.

> ***The authors concluded that ERT appeared to have little impact on the response to HCV treatment outcome and that there may be another cause which may explain the higher treatment response rates among pre-menopausal women.***

Four patients out of the 56 patients were excluded from the study data due to failure to complete 12 week of treatment. Of the 52 remaining patients, 34 met the study criteria for therapy-related anemia. Thirty of the 34 patients were treated with epoetin, of whom 90% were managed on 40,000 units/week and 10% required higher dosing of epoetin at 60,000 units/week. Seven percent required additional supplementation of ferrous sulfate (iron-deficiency anemia). Twelve percent were dose reduced because they did not qualify for insurance coverage of epoetin. An additional 7% of patients required ribavirin dose reduction of 200 mg due to delays of insurance authorization and delivery of the drug.

The authors found that the average patient developed anemia during the first 12 week period. As expected there were no complications associated with epoetin treatment during the study period.

The authors concluded that early identification of treatment-related anemia can prevent ribavirin dose reductions, which should increase the percentage of patients who stay on HCV therapy and thereby increase the chances of a successful treatment outcome.

The authors made the following recommendations which they considered crucial to improving the efficacy of epoetin:

- Weekly complete blood counts
- For those patients identified as anemic, folate and iron studies
- For those patients identified as anemic, repeat complete blood counts weekly to follow progress on epoetin alfa and identify those that may need higher doses of epoetin alfa
- Ferrous sulfate for those with low iron on iron studies

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attention away from your breathing. One way to manage distractions is by acknowledging and incorporating them into your awareness. For instance, if you find yourself thinking about an errand you want to attend to, try saying "thinking," and gently turn your attention back to breathing.

How to meditate

There are many types of meditation and you may want to experiment with different techniques before settling on any one particular style. Meditation can be self-taught or learned from a teacher. Some meditation centers offer classes in various disciplines, such as Insight, Transcendental or Zen meditation. Books and tapes can provide instruction on the art of meditation. Here are a few simple techniques you can try:

- *Breathing* - close your eyes and concentrate on your breath. Feel your breath as it moves into and out of your lungs. You may want to count each breath until you reach four and then repeat. Try to relax into your breath and feel your stress melt away.
- *Candle* - Light a candle in a dark, draft-free area and place it at eye level. Gaze at the flame and concentrate on your breath. Soon you will find your mind relaxed and still. **Note:** This should not be practiced if you suffer from migraines or seizures.
- *Meditation of Loving Kindness* - Relax and concentrate on your breath. As you are breathing in say, "May I be well." As you breathe out say, "May others be well".
- *Chanting* - You can use a Mantra to chant while meditating. Practitioners of Transcendental Meditation (TM) are given a word (mantra) when initiated into TM. Others may simply use "OM" or "peace" while meditating. Christian and other religious contemplative practices may use meaningful words. Try sitting comfortably and repeat a word or sound. Feel the vibration while you breathe out. Stretch it out as long as you can. If you stay with it, you may soon feel relaxed and tranquil.

These are but a few techniques out of many ways to meditate. Give it a try…you literally have nothing to lose but stress and tension.

The Serenity Prayer

"God, grant me the serenity to accept the things I cannot change, courage to change the things I can, and wisdom to know the difference."

Resources

- *Kitchen Table Wisdom*, by Rachel Naomi Remen
- *A Path with Heart*, by Jack Kornfield
- *Start Where You Are*, by Pema Chodron
- *Soul Food*, by Jack Kornfield and Christina Feldman
- *Stillness Speaks*, by Eckhart Tolle
- *The Miracle of Mindfulness*, by Thich Nhat Hanh
- *Wherever You Go There You Are*, by Jon Kabat-Zinn
- *Zen Mind, Beginner's Mind*, by Shunryu Suzuki

- The Transcendental Meditation Center - www.tm.org
- Vipassana Meditation - www.dhamma.org
- World Wide Online Meditation Center - www.meditationcenter.com
- Zen - www.do-not-zzz.com

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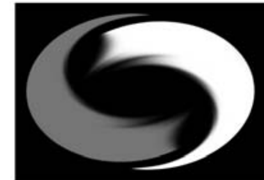

Executive Director
Editor-in-Chief,
HCSP Publications
Alan Franciscus
alanfranciscus@hcvadvocate.org

Managing Editor, Webmaster
C.D. Mazoff, PhD
cdmazoff@hcvadvocate.org

Contributing Authors
Liz Highleyman
Lucinda K. Porter, RN, CCRC

Design and Production
Paula Fener
Blue Kangaroo Design
blueroodesign@aol.com

Contact information:
Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142-7037

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IDU's

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maintenance for at least six months and 50 who had not used street drugs or opiate substitution for at least five years; about 60% in both groups had genotype 1 HCV. All were treated with Peg-Intron plus ribavirin. During the first eight weeks of treatment, methadone patients were five times more likely than non-methadone subjects to either request stopping HCV therapy or to discontinue due to nonadherence (22% vs 4%). After eight weeks, however, rates of discontinuation for these reasons were similar (10% vs 8%). At the end of follow-up, SVR rates were 42% in the methadone groups and 56% in the nonuser group (because relatively few patients completed a full course of therapy, the difference did not reach statistical significance). The researchers concluded that HCV treatment is "reasonably safe and sufficiently effective" in patients on methadone maintenance.

There is evidence from other diseases (including HIV) that some IDUs can adhere well to therapy, especially if they receive regular monitoring and support. IDUs do have higher rates of psychiatric diagnoses, including depression, bipolar disorder, and anxiety disorders. Some studies show that people with a history of psychiatric conditions are more likely to experience depression as a side effect of interferon, but this does not always happen, and often can be treated if it does. All HCV patients IDUs and nonusers alike should be screened for depression before starting interferon, monitored during therapy, and given antidepressants if appropriate.

Research also suggests that HCV reinfection rates in IDUs appear to be low. In Backmund's study, no reinfections were detected during the 24-week post-treatment follow-up period among the 10 SVR patients who resumed drug injection. Another study by Olav Dalgard and colleagues looked at outcomes five years after the end of treatment in 27 Norwegian IDUs who had an SVR to HCV therapy. Although nine relapsed to drug use, only one was reinfected.

Because addiction is a chronic, recurring condition, all active IDUs and people in drug treatment or on methadone maintenance should be counseled about ways to prevent viral hepatitis transmission and reinfection, including not sharing needles or other injection equipment, and, for people who must share, cleaning works with bleach (although bleach has not been proven to kill HCV or HBV in syringes). Research shows that HCV and HBV can be transmitted via cookers, cotton filters, and even water used for rinsing syringes or mixing a drug solution. In addition, all IDUs should receive the hepatitis A and B vaccines if they have not already been exposed.

Individuals in recovery from injection drug use face special challenges when using interferon, since the medication must be injected. Some people find that the act of preparing and injecting interferon rekindles the urge to use drugs. However, both Roche's prefilled Pegasys syringes, and Schering's Peg-Intron Redipen, which mixes and delivers the medication without a syringe, may help lessen the association between drug injection and medication administration.

To help IDUs achieve the best treatment outcomes, Edlin recommends establishing a climate of mutual respect between patients and physicians, including patients in decision-making, and educating patients about their medical status, proposed treatment, and side effects. According to the NIH consensus panel, IDUs with HCV are best managed by a multidisciplinary team that includes both hepatologists and substance use treatment specialists. In addition, all IDUs should be offered drug treatment. Opiate maintenance can help IDUs maintain stable lives and, because it requires regular visits, provides an opportunity for directly observed therapy and regular support around adherence and management of side effects.

Finally, more research is needed on the course of HCV disease progression and its optimal treatment in IDUs. Because this group makes up the majority of people with HCV, Edlin emphasizes, "Controlling hepatitis C in the U.S. population, therefore, will require developing, testing, and implementing effective prevention and treatment strategies for persons who inject drugs."

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• Insurance carrier policies on the use of epoetin alfa

• Nursing staff familiarity with use of epoetin alfa, criteria for its use in patients with ribavirin and peginterferon related anemia, as well as familiarity with requesting insurance authorization for epoetin alfa.

ESTROGEN REPLACEMENT THERAPY

It has been suggested that women (especially pre-menopausal) respond better to interferon based therapies than men. It has been speculated that estrogen may improve treatment outcome because of its immunomodulatory properties. In order to test this hypothesis, Matthew J. Hepburn and colleagues retrospectively analyzed data from five multi-center treatment studies. All patients included in the analyses were previously treated with weight-based ribavirin plus standard interferon or pegylated interferon. The medication lists for all women over 45 years old were reviewed for oral or transdermal preparations of estrogen. Women over 45 years old receiving estrogen replacement therapy (ERT) were compared to women not receiving ERT. A total of 179 women over 45 years old were available for analysis. The patient characteristics were similar between both groups

The authors reported that no differences existed in treatment outcome with or without ERT, except that treatment response in patients treated with pegylated interferon were higher in the group of women who were not receiving ERT. The authors concluded that ERT appeared to have little impact on the response to HCV treatment outcome and that there may be another cause which may explain the higher treatment response rates among pre-menopausal women.

However, the authors also pointed out that there were limitations in their study design:

• ERT compliance was not monitored

• Other factors that may influence response to therapy were not controlled

• Data was measured across different trials

• The definition of post-menopausal women (age greater than 45 yo) was imprecise.

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