Can mirtazapine assist recovery from crystal meth addiction?

20 December 2011

Stimulants such as amphetamine and its more potent form, crystal methamphetamine (crystal meth, tina, ice), quickly accumulate in the brain when ingested. This drug causes the brain to release chemical signals called neurotransmitters—dopamine, norepinephrine and serotonin—that cause users to experience feelings of pleasure and temporary relief from feelings of fatigue, anxiety and depression. In part, crystal meth can have these effects because it changes the perception of users and temporarily heightens a person’s:

- alertness
- concentration
- energy
- sense of well-being

The high concentration of neurotransmitters that are released in the brain due to crystal meth can significantly raise a person’s blood pressure and heart rate. This can sometimes result in a heart attack.

Crystal meth can cause users to experience delusions, hallucinations and paranoia. People undergoing crystal-meth-induced psychosis can become emotionally unstable and even hostile.

Addiction and its discontents

Crystal meth usage can quickly become addictive; repeated use appears to rewire circuits in the brain, intensifying a person’s craving for this substance. Moreover, a major problem associated with the use of crystal meth is that it appears to diminish the capacity of some addicted people to have insight into their condition.

As with many addictive drugs, crystal meth can impair a person’s judgment and critical thinking. Not surprisingly, there have been reports of users engaging in unprotected sex and subsequently becoming infected with HIV and other sexually transmitted infections (STIs).

Attempts to break free of crystal meth are not easy because of highly unpleasant withdrawal symptoms, including:

- a profound lack of energy
- difficulty falling asleep
- irritability
- loss of interest in everyday activities
- anxiety
- depression

There are currently no medical therapies approved to treat crystal meth addiction. Recovery efforts involve psychological therapy. Research teams around the world have been testing different strategies in an attempt to treat crystal meth addiction, with limited success.

Enter mirtazapine

Mirtazapine (Remeron) is an antidepressant. Experiments with rats addicted to crystal meth suggest that it has potential for help with addiction recovery.
Some small and short-term studies of mirtazapine in people addicted to crystal meth have produced hints of promising activity. So researchers with the San Francisco Department of Public Health conducted a 12-week randomized, placebo-controlled study of mirtazapine in people using crystal meth, about half of whom were HIV positive. The researchers also selected mirtazapine partly because, unlike some other antidepressants, it is unlikely to cause problems getting and maintaining an erection.

All participants received counselling designed to help overcome addiction. The San Francisco researchers found that participants given mirtazapine had fewer crystal-meth-positive urine tests. Importantly, engagement in unprotected sexual activities also decreased significantly among participants taking mirtazapine. Larger and longer clinical trials are needed to confirm and extend this study’s findings.

**Study details**

Researchers recruited 60 gay and bisexual men who were dependent on crystal meth. All of the men expressed an interest in either breaking free from meth or reducing their intake of this drug. The men also disclosed that they had used the drug in the recent past to enhance the feeling of pleasure when having sex.

The researchers sought participants who fit this description:

- did not have severe depression
- had used antidepressants in the past
- had a CD4+ count of at least 200 cells, if they were HIV positive
- were currently using crystal meth

Researchers offered all participants standard counselling designed for people addicted to drugs. This included one 30-minute session every week for 12 weeks (the duration of the study). Researchers also provided participants with HIV risk-reduction counselling. Participants were randomly assigned to one of two groups, or arms, and received one of the following interventions:

- mirtazapine 15 mg per capsule taken at bedtime for the first week, followed by 30 mg (two capsules) nightly for the rest of the study
- identical-looking placebo capsules taken in the same quantities and according to the same schedule

The average profile of participants who enrolled in the study was as follows:

- age – 40 years
- 38% had a college degree
- 60% were unemployed
- 40% used meth two or less days each week
- 43% used meth three to six days each week
- 17% used meth daily
- 53% of participants were HIV positive

Participants took meth in the following ways (note that some people used more than one method so the percentages do not add up to 100):

- injected – 45%
- inserted rectally – 30%
- snorted – 40%
- swallowed – 17%

In total, 60 people were recruited and 93% (or 23 people) in each arm completed the study.

**Results**

The proportion of participants in each arm of the study whose urine samples tested positive for crystal meth at the start and end of the study were as follows:
Mirtazapine

- 73% had meth-positive urine tests at week zero
- 44% had meth-positive urine tests at week 12

Placebo

- 67% had meth-positive urine tests at week zero
- 63% had meth-positive urine tests at week 12

This difference in decreased rates of meth use between study arms was statistically significant.

At the end of the study, two participants disclosed that they had been taking “psychiatric medications” during the study. Removing the data of these two participants from the study did not change the significance of its findings.

Adherence

The ability to take medication exactly as directed is critical to the success of clinical trials. In the present study, adherence was assessed in two ways:

- a medication event monitoring system (MEMS) was used to electronically record when participants opened the pill bottles
- self-reports of adherence

The adherence rates that were assessed electronically were as follows:

- mirtazapine – 48%
- placebo – 49%

The adherence rates assessed by self-report were:

- mirtazapine – 76%
- placebo – 73%

When researchers asked participants why they did not adhere to the study protocol, participants gave these reasons:

- “simply forgot” – 61%
- “slept through [the time to take my] dose” – 54%
- “busy with other things” – 45%
- “change in daily routine” – 45%

Sexual risk behaviours

Sexual risk behaviours decreased faster among participants who took mirtazapine than among participants who took the placebo. Decreased risk behaviours included the following:

- fewer sexual partners
- fewer episodes of unprotected anal sex with partners of a different or unknown HIV status

Also, participants who received mirtazapine generally engaged less in these behaviours than participants on placebo. This difference was statistically significant.

There was a link between testing negative for meth use and having fewer episodes of unprotected intercourse.

None of the participants who enrolled in the study had severe, prolonged bouts of depression. Mirtazapine’s ability to help reduce participants’ intake of crystal meth did not occur because it reduced feelings of even mild depression. There were no differences in rates of depression between mirtazapine and placebo users during the study.

Safety
Overall, there were no differences in the frequency of side effects reported by participants in either mirtazapine or placebo arms.

Two serious adverse events occurred—a case of methamphetamine psychosis in the mirtazapine arm and a bone fracture in a person who received placebo. However, these were judged to be unrelated to the use of study medications.

Lab tests detected elevated levels of the liver enzyme ALT (alanine aminotransferase) in the following proportion of participants in each group:

- mirtazapine – 23%
- placebo – 30%

Lab tests detected elevated levels of another liver enzyme, AST (aspartate aminotransferase), in the following proportion of participants in each group:

- mirtazapine – 17%
- placebo – 27%

As expected, mirtazapine can cause some side effects. The following side effects were reported by participants who took this drug:

- drowsiness in the daytime – 43%
- increased appetite – 13%
- weight gain – 10%

One participant taking mirtazapine gained 13 kg (29 pounds) during the study, while another gained 10 kg (22 pounds). After gaining 8 kg (nearly 18 pounds) in the first month of the study, a third participant refused to disclose further changes in his weight.

**Unblinding the study**

In placebo-controlled studies, participants sometimes attempt to unblind, or unmask, the study—to find out if they are receiving an active drug or placebo. At the end of the study, researchers asked participants to “guess” what they had been receiving—50% in the mirtazapine arm and 56% in the placebo arm did so correctly. This difference was not statistically significant.

**Bear in mind**

The San Francisco study has provided some promising results: Overall, mirtazapine was significantly associated with a reduction in the use of crystal meth over 12 weeks. A similar result was found by researchers in Sweden who conducted a placebo-controlled study of the drug naltrexone to help treat addiction in people using amphetamines. However, in the Swedish study, participants were required to have ceased the use of amphetamines prior to entering the study.

**Limits**

Mirtazapine was somewhat effective in the San Francisco study, though participants had less-than-ideal levels of adherence. It is possible that future studies that include an intensive program of adherence support may have better results. The San Francisco researchers did not include adherence support because they wanted to see what might happen in the average clinical setting where such support programs are likely not available.

Larger studies are needed to confirm and extend the mirtazapine results from San Francisco, at least with some of these issues:

- Would taking mirtazapine for longer periods ensure that at least some participants would quit crystal meth?
- Would more intensive psychological therapy with mirtazapine improve quit rates? The present study was designed to merely assess differences in the use of crystal meth between participants given mirtazapine and participants given a placebo. It was not designed to test mirtazapine’s ability to help people quit crystal meth or
to assess how long they could remain free from crystal meth. This should be explored in a future study.

People who had severe depression were not enrolled in this study because the research team did not want the possibility of such people being given a placebo (mirtazapine is an antidepressant). So, in the future, clinical trials need to find ways to assess the impact of mirtazapine (or other therapies) in depressed people who are addicted to crystal meth.

—Sean R. Hosein

REFERENCES:

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Production of this content has been made possible through a financial contribution from the Public Health Agency of Canada.

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