

F. Leclercq

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Dr. Francis C. Colpaert
Janssen Pharmaceutica
Beerse, Belgium B-2340

Dear Dr. Colpaert,

It has been a number of years since I was directly involved in studies of narcotics and narcotic antagonists, so that your questions came as somewhat of a surprise. Nevertheless, I shall try to answer as best as I can.

When we gave subjects repeated doses of heroin intravenously, the timing was so spaced that we did not observe tolerance. When we gave oral doses of methadone, tolerance developed rapidly, and when we gave such subjects injections of heroin, we were able to observe cross-tolerance. Depending on time after oral dose of methadone and ~~time~~, subjects either could or could not distinguish placebo from heroin. They generally used as cues their subjective feelings of relaxation ("high") plus the change in skin tingling, respiratory slowing and occasionally the relief of irritability. When we gave patients levomethadyl, they developed tolerance as they did to methadone, and the same pattern of cross tolerance to heroin, with a different time course. When patients who are tolerant are given a single dose of naloxone or cyclazocine, a severe withdrawal syndrome is precipitated. These are the types of experiments we carried out, and based on these observations I would think the answers to your questions are as follows.

1. The discrimination of a narcotic from a placebo is dependent on dose of the narcotic, state of the subject (tolerant or 'clean'), and time in the withdrawal period that the narcotic is given. If repeated administration is rapid (doses within a few hours of each other, as in three or four times a day) then tolerance is seen easily.

2. Users discriminate active from inactive material from their central effects mainly: relaxation, euphoria, drowsiness, decreased irritability; and to a lesser extent from peripheral cues. They also use the relief of withdrawal symptoms if these have been allowed to develop.

3. The euphoric effects of opiates are subject to tolerance.

I trust these comments are helpful. Some years ago, 1970 or 1971, I visited Beerse seeking some undeveloped narcotic antagonists as we were then hoping to find an improvement on cyclazocine. I remember with pleasure the cooperation of the laboratory personnel, and I am pleased that your work has continued.

My work at the New York Medical College continues under the leadership of the chairman of the Department, Professor Alfred M. Freedman. Should you wish some additional information regarding their recent experience with heroin, naltrexone, etc. you may wish to write to him.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry