

Population Thinking as an Adjunct to the Clinical Trial Perspective

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The great evolutionist Ernst Mayr (1) coined the term “population thinking” to encourage biologists to shift their focus from prototypical individual organisms toward the parameters that characterize populations as a whole. Economists are trained to cultivate a similar mind-set, as captured by concepts like “general equilibrium.” Clinicians in psychiatry and psychology may question the relevance of such aggregate-level concepts for their work. But in my research on the analysis of national substance abuse policies, I’ve come to appreciate that population thinking is a valuable adjunct to the more traditional clinical focus on the client or patient. Clinical treatment innovations can have broader social effects, both desirable and undesirable. The clinical trial paradigm is a tremendously powerful engine for medical progress, but as I hope to illustrate through the following brief case studies, this paradigm is not always well suited for exploring these broader consequences.

The European heroin maintenance trials

In the 1990s, Swiss researchers tested a heroin maintenance program as a pragmatic solution to the public health, crime, and disorder problems associated with their hardest-core addict population (2). Clients could receive heroin three times daily, with a massive average daily dose of 500 to 600 milligrams of pure heroin. The heroin could be used only at the clinic, to minimize leakage into the black market. In the original trial design, 250 addicts would receive heroin, 250 would receive morphine, and 200 would receive methadone. For a variety of reasons, attrition was high in the latter two groups, and these treatment arms were largely abandoned. Trial results focused mostly on pre-post comparisons of addicts who received injectable heroin (3,4).

The Swiss trials showed that it is possible to implement a working heroin maintenance program. The researchers were able to provide heroin to more than 800 clients without any reported overdoses or leakage into the black market. The weakened design necessarily limits our confidence in making any inferences about the program’s efficacy (5). However, taken at face value, the simple pre-post comparisons were quite encouraging. Nearly 70 percent of the clients remained in treatment for at least 18 months—a better rate than most methadone programs had achieved. A large proportion of the clients who dropped out moved into other forms of treatment. Arrest records showed a steep drop in criminality. And unemployment among the program participants fell to 20 percent from 44 percent at the start of the trial.

After the completion of these Swiss trials, a test of prescription heroin was initiated in the Netherlands with two more rigorous randomized clinical trials, one involving inhaling addicts and the other involving injectors (6). In each trial, heroin users were randomly assigned to receive methadone alone or methadone plus heroin. Sophisticated intention-to-treat analyses established that, as with the weaker Swiss trial, the Dutch interventions were associated with significant reductions in symptoms of addiction, criminality, and cocaine use.

On its face, heroin maintenance raises troubling ethical and political questions. Still, from a purely empirical, consequentialist standpoint, these converging results clearly establish the feasibility and efficacy of heroin maintenance as an adjunct to methadone for hard-core addicts. But important empirical questions still remain unresolved.

By adopting the traditional clinical trial perspective, the Swiss and Dutch evaluations were client focused rather than community focused. But heroin addicts are active participants in small but intensely hazardous illicit markets. In judging the likely social consequences of heroin maintenance, we need to assess not only the effects on individual participants but the broader market consequences. On one hand, the retail heroin market is dominated by heavy addicts, both users and sellers. Large-scale expansion of heroin maintenance, by reducing addicts' participation in illicit markets, could make heroin less accessible to new users. On the other hand, the availability of heroin maintenance could encourage novice users to escalate their use and could even increase the attractiveness of heroin use for nonusers. Because of their patient focus and limited scale, clinical trials are ill suited for assessing these broader market effects.

Emerging immunotherapies for addiction

Immunotherapies and depot medications currently under development could prevent or greatly curtail relapse—and even addiction itself—in the case of drugs such as tobacco and cocaine (7). These interventions surely hold great promise for the prevention and treatment of substance abuse. Still, they differ in important respects from other pharmacologic treatments for drug addiction and, for that matter, from vaccines used to prevent viral diseases. Immunotherapies and depot medications may significantly alter the complex system of relationships among users, sellers, treatment providers, and social control agents. These actors are likely to change their behavior in both desirable and unintended ways (8).

For example, risk analysts have learned that using a technological innovation to reduce the harmfulness of risky behavior often has the unintended consequence of increasing the prevalence or intensity of that behavior. The total harm produced by a risky activity—for example, addictive drug use—is a function of the average harm per incident multiplied by the total amount of the activity. In theory, if a technological innovation reduces but does not eliminate the riskiness of an activity, and if the risk reduction motivates sufficiently large increases in the frequency or quantity of that activity, then average

harm might fall but total harm might increase (9). There is some evidence for such a scenario in the apparent correlation between increased unsafe sex practices and the availability of highly active retroviral therapy (HAART) for HIV infection and AIDS (10).

The risk of addiction and its attendant social and health consequences is a central message highlighted by antitobacco and antidrug programs and public information campaigns. Conceivably, immunotherapy or depot medication programs for relapse prevention or addiction protection, if widely publicized, may convey—rightly or wrongly—a widespread belief that “addiction has been cured.” If so, current users who are not enrolled in a pharmacologic program may increase their use. And current nonusers may, at the margin, be more willing to begin using the addictive substance.

By changing the behavior of addicted users, immunotherapies and depot medications against addiction might also have important price effects. For illicit drugs such as cocaine, price effects cut both ways. An increase in drug prices discourages use but can also stimulate increases in income-generating crime by addicts. A decrease in prices can reduce street crime, because addicts need less money to finance their use, but such a decrease can also encourage greater use. A successful immunotherapy against cocaine is likely to influence the price of cocaine. Unfortunately, the direction of the effect is unknown, because there are competing predictions under different market theories (11). In any case, by influencing price, a cocaine vaccine could have a mix of beneficial or detrimental effects on initiation of use and on market-related criminality.

Program designers should anticipate the possibility that an immunotherapy or depot medication program might inadvertently encourage nonaddicts to risk becoming addicts, might discourage light users from quitting, and might have broader, more diffuse effects on markets.

Conclusions

All clinical treatments have effects that extend beyond the client—effects on families, on coworkers, and on neighbors; social diffusion effects; and market effects. Arguably, these broader social effects are particularly likely in the case of substance abuse—a domain in which the individual’s condition is largely a product of his or her behavior, and in which that behavior is largely facilitated by economic market transactions. The traditional clinical focus on etiology, pathology, and individually tailored treatment is as important to substance abuse as to any other health condition. But it seems hazardous to rely solely on the clinical trial perspective when assessing dramatic new substance abuse interventions, lest we overlook unintended consequences—both favorable and unfavorable—that extend far beyond existing client populations.

The magnitude of the unintended consequences discussed here is unknown. There is no a priori reason to believe that such effects would be so large as to offset the benefits of reduced drug use among participants. A case in point is syringe exchange for injecting

heroin users. Precisely because it is so controversial—and indeed, because a common criticism is that it “sends the wrong message” and encourages use—evaluators have made a special effort to assess the broader impact of syringe exchange schemes, including heroin use by both addicts and new initiates, patterns of needle sharing, and market-related behavior (12). Although the results of such studies remain controversial (13), the general consensus of mainstream experts is that needle exchange reduces HIV transmission without any offsetting effect in terms of increasing use (14). But clearly, each new intervention needs to be evaluated on its own terms. Doing so will require an interdisciplinary inquiry involving economists, sociologists, epidemiologists, and ethnographers as well as clinical researchers.

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