

Anticipating Unintended Consequences of Vaccine-Like Immunotherapies for Addictive Drug Use

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Immunotherapy or depot medication (henceforth, “I/DM”) programs that would prevent addiction or relapse to drugs like tobacco or cocaine are largely unprecedented. These interventions differ in important respects from other pharmacological treatments for drug addiction, and, for that matter, from vaccines used to prevent viral diseases. I/DM’s 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.

Given the novelty of such interventions and uncertainty about how they might be implemented, it is not possible to forecast either the likelihood or the magnitude of unintended behavioral responses. Nevertheless, it is desirable to design I/DM interventions that might minimize such risks. In this essay, I identify plausible mechanisms by which I/DM’s might produce unintended consequences, and I review available evidence on the effects of these mechanisms in the research and clinical literatures on drug use and on other risky behaviors. I define “plausible” as something more than simply possible, but not necessarily “more likely than not.”

Judgments about whether and how to implement I/DM programs should not necessarily be based solely on worst-case scenarios. Economists and risk analysts have long noted the opportunity costs in foregone benefits that can result from extreme risk aversion (e.g., Viscusi, 1992; cf. Shrader-Frechette, 1991).¹ But the literature on technological risks also documents the dangers posed by excessive optimism on the part

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¹ The argument that risk averse choices impose opportunity costs is analytical; the question of whether we should be more risk neutral is a value judgment. Rational choice theory predicts the consequences of risk preferences but it does not dictate those preferences.

of enthusiastic program designers (e.g., Janis, 1983; MacCoun, 1998a; Tenner, 1996; Vaughan, 1996). Thus, in the spirit of “devil’s advocacy,” I have chosen to err on the side of caution; giving greater attention to arguments in support of various unintended consequences than to possible counterarguments (which are nevertheless noted).

CONCEPTUAL FRAMEWORK

Program Prototypes

The Committee has identified three types of immunotherapy or depot medication treatment protocols: Overdose treatment, relapse prevention, and protection from addiction. *Overdose treatment* appears to be less susceptible than the other two categories to unintended consequences created by behavioral responses to the intervention, at least with respect to the mechanisms considered here. And to the extent that overdose treatment might operate via those mechanisms, its effects are likely to be similar to those of a relapse prevention program, only weaker. Thus, this essay focuses primarily on *relapse prevention*, and secondarily on the somewhat more remote prospect of *addiction protection*.

For simplicity, I focus my analysis to interventions targeting tobacco and cocaine use. Tobacco illustrates issues involved in pharmacological treatments for a legal, commercially available drug, and cocaine exemplifies issues posed for an illicit, recreational drug without a legitimate prescription market.

Relevant Actors and Drug-Use States

Psychoactive drug use is a multidimensional behavior, characterized by many continuous parameters: Age of onset, length of using career, variety of drugs used, frequency of use, quantity consumed per use, and so on. To simplify the discussion, I will abstract away all this detail and characterize drug use in terms of four mutually exclusive states. Figure 1 presents a stochastic flow diagram, modified from a similar diagram used by Everingham and Rydell (1994). The figure depicts drug using careers as patterns of movement among four “states”: Never used, light use, heavy use, and former use. Among users, I will further distinguish program participants from non-participants,

and use of the target drug vs. use of other drugs. And at the end of the essay, I will briefly consider behavioral effects on drug dealers, politicians, and the general public.

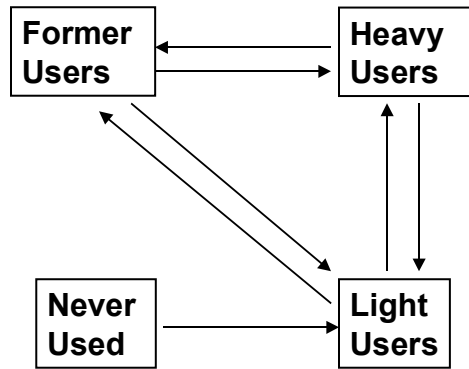


Figure 1. Drug use conceptualized in terms of flows among four distinct drug-use states

Presumably a relapse prevention program would target some fraction of heavy users. If effective, it should increase the flow of heavy users into non-use and reduce the flow of non-users back into use. An addiction protection program would target some fraction of light users, and perhaps (not shown) newly heavy users and (more controversially) those at high risk who have never used. If effective, it should increase the flow of light users into non-use and reduce the flow of non-users into use.

In addition to these flows, it is important to consider the “stocks” – the distribution of individuals across these states. The distribution of consumption across users is strongly positively skewed for most drugs (see Everingham & Rydell, 1994; Skog, 1993) – though less dramatically so for tobacco than for cocaine. As a result, the harmful consequences of substance use are not uniform, but are disproportionately concentrated among the heaviest users.

The relative viability of targeting the median user vs. hard-core users in the right tail of the distribution will probably vary as a function of several factors (Edwards et al., 1994; MacCoun, 1998b; Rose, 1992). Everything else being equal, it will be more

effective to target typical users when the dose-response curve for various harms rises very quickly with small doses, and when typical users account for a large fraction of total consumption. It will be more effective to target heavy users when the dose-response curve for various harms rises slowly at low doses, and when the statistical distribution of consumption is heavily skewed. Relapse prevention I/DMs would disproportionately target right-tail users; addiction protection I/DM's would presumably include individuals from the whole range of the use distribution (even including some who would never use anyway), depending on their recruitment process and our accuracy at predicting whom is "at risk" for addiction. But of course the choice of users to target for a pharmacological intervention will also be determined by legal, ethical, economic, and political considerations not considered in this chapter .

Voluntary vs. Mandated Participation

The consequences of an I/DM program are likely to differ depending on whether participation is solely voluntary vs. mandated by legal or other authorities (e.g., employers). The voluntary-mandatory distinction hinges in part on the legal status of the drug in question. MacCoun and Reuter (2001; MacCoun, Schelling, & Reuter, 1996) examine the effects of a drug's legal status on its prevalence and harmful consequences. Here I summarize a few key points of relevance to the comparison of pharmacological interventions for a licit drug (e.g., tobacco) vs. an illicit drug (e.g., cocaine).

- Prohibition almost certainly raises the price of a prohibited substance, probably substantially (MacCoun & Reuter, 2001; Manski et al., 2001; cf. Miron, 2003). This is one reason why cocaine users might be more likely than tobacco users to commit income-generating crimes, even in the absence of any pharmacologically mediated disinhibition or aggression.
- Prohibited drugs are marketed quite differently from licit drugs; there is less quality control and far greater violence. The lack of quality control may make it more difficult to determine appropriate pharmacological dosages for cocaine addicts than for tobacco addicts. And the nature of black markets creates a risk that pharmacological interventions for illicit drugs might have non-pharmacological effects on violence.

- Prohibition increases the stigma associated with a drug, although stigma can have both desirable and undesirable consequences (see the section on “Social norm effects” below).

In addition to a drug’s legal status, a related consideration is whether participation in a pharmacological program would be voluntary or mandatory.² Voluntary relapse prevention for either drug seems most feasible, and would face few ethical and legal obstacles. For cocaine, mandatory participation would pose thorny ethical, legal, and political questions, but the drug’s illicit status makes such programs plausible. (See Manski et al., 2001, Chapters 6, 8, and Appendix E). On the other hand, *mandatory* participation in a relapse or addiction prevention seems implausible for tobacco, a licit drug.

Although the distinction between voluntary and mandatory programs has legal and political relevance, it may have less clinical and behavioral relevance. Many experts contend that mandatory treatment is as effective as voluntary treatment,³ and that conclusion seems even more plausible for these pharmacological interventions than for more traditional psychotherapeutic modalities. The behavioral mechanisms examined here seem as applicable to voluntary as to mandatory programs, given the severe self-control problems involved in drug addiction. Indeed, the very concept of “voluntariness” is problematic in the case of addictions, which are often characterized as “diseases of will” (see Elster & Skog, 1999; Vucinich & Heather, in press).

EFFECTS OF PRICE CHANGES

The first mechanism I consider involves the behavioral effects (on use and on criminality) of a change in drug prices brought about by I/DM programs.

² I use the term “mandatory” to refer to a program in which clients are required to participate under threat of formal legal sanctions. The term “coerced” is commonly used in the treatment literature, but is ambiguous because many clients are “coerced” into treatment via the threat of *informal* sanctions – divorce, the loss of a job, expulsion from school.

³ For evidence on this point, see Anglin & Hser, 1990; Farabee et al., 1998; Inciardi et al., 1997; Lawental et al., 1996; Maxwell, 2000; Miller & Flaherty, 2000; Nishimoto & Roberts, 2001. Manski et al. (2001) raise concerns about the methodologies used in these studies (Chapter 8) and also the possibility that mandated treatment has a “net-widening” effect on the scope of criminal justice activity (Chapter 6 and Appendix E).

Price Elasticity of Demand

Some readers may question the relevance of a drug's price for the behavior of a consumer who is addicted. Traditionally, many have assumed that addicts, by the very nature of their addiction, are oblivious to price changes – they will obtain their drug no matter the cost, committing income-generating crime if needed to finance their habit. Thus, it has been surprising to learn that illicit drug use is in fact fairly sensitive to price variations.

Economists estimate sensitivity to prices in terms of the “price elasticity of demand”—the percentage change in consumption for a 1 percent change in price. Estimates for the price elasticity of cigarette demand are in the -0.3 to -0.5 range (Chaloupka & Pacula, 2000; Manning et al., 1991), suggesting that a 10% increase in the price of cigarettes would only reduce overall consumption by 3% to 5%. Thus tobacco users are in fact somewhat unresponsive to price, but not completely unresponsive. Cocaine users are more price sensitive; low estimates are around -0.4 but some studies find elasticities of -1.0 or more (see reviews by Caulkins & Reuter, 1996; Chaloupka & Pacula, 2000). A drawback is that most estimates are based on users in the household population, and may overrepresent casual users. But Reuter and Kleiman (1986, p. 300) argue that if anything, budget constraints tend to make heavy users more rather than less price sensitive. And Caulkins (2001) has shown that trends in emergency room incidents involving cocaine are highly responsive to trends in cocaine price, suggesting that heavy users are also price sensitive.

Assumptions Underlying a Shift in Demand

The analysis of drug price effects presented here is premised on four “best-case” assumptions about the effectiveness of I/DM programs. Later mechanisms will challenge each of these four assumptions; to the extent that these assumptions are false, any price effects will probably be smaller than those contemplated here. Specifically, assume that:

1. Targeted users cooperate fully with the intervention program.
2. The intervention completely discourages use of the target drug among program participants.
3. Participants do not substitute other psychoactive drugs.

4. The program has no direct effect on the behavior of non-participants, and any *indirect* effects are benign.

Under these conditions, a successful psychopharmacological relapse or addiction prevention program ought to shift the demand curve downward, such that less cocaine (or tobacco) is demanded at any price. The magnitude of the demand shift would be determined by the number of users targeted and their previous levels of consumption.

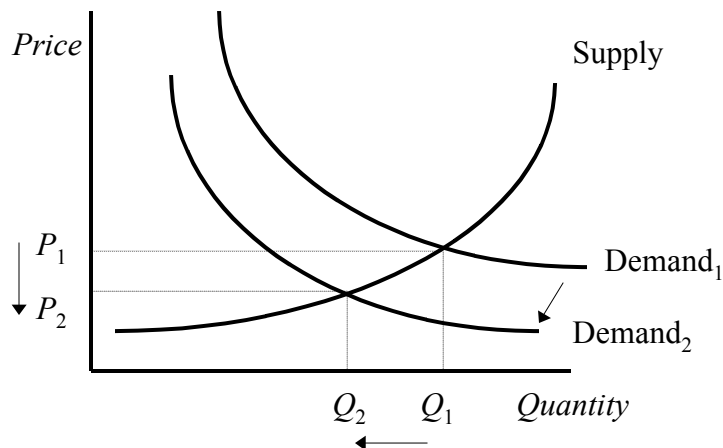


Figure 2. Price and quantity decreases following a downward shift in demand, assuming a traditional supply curve (Note: P_1 = initial price, P_2 = new price; Q_1 = initial quantity supplied, Q_2 = new quantity supplied)

Effects Predicted by a Traditional Model of Supply and Demand

Figure 2 presents a rudimentary “comparative statics” analysis of the implications of this shift in drug demand. In this type of microeconomic analysis, a product’s price and quantity supplied are inferred from the equilibrium point where the supply curve (reflecting supplier responses) and demand curve (reflecting consumer responses) intersect. *Ceteris paribus*, a downward shift in the demand curve ought to produce a reduction in the quantity supplied, and a drop in the equilibrium price of the drug.⁴

⁴ Jon Caulkins and Rick Harwood each suggested that the I/DM effect could be modeled as a downward shift in the supply curve – supply reduction rather than demand reduction -- in the sense that these treatments block the supply of the drug to the brain. But it seems preferable to model the effects with respect to demand, for two reasons. First, the supply function is usually conceptualized with respect to supplier behavior rather than consumer physiology or phenomenology. Second, I/DM programs, if

In the short run, this reduced price should not in itself lead to increased use; by definition, the equilibrium price and quantity already reflect consumer and supplier preferences. But in the long run, reduced prices pose a risk of increased consumption, for two reasons. First, existing drug users may be more responsive to price changes over the long run than the short run (e.g., Reuter & Kleiman, 1986, p. 299; Caulkins, 2001, p. 1447). Second, adolescents may be more likely to initiate use if they perceive the drug as inexpensive rather than expensive. This latter effect may be qualitative as well as quantitative; the reputation of a drug as “cheap” vs. “expensive” can change over time – compare cocaine’s reputation in the late 1970s vs. the late 1980s.

On the other hand, a consequence of reduced cocaine demand is that any “psychopharmacological” criminality -- produced by the direct effects of the drug (Goldstein, 1985) – should be reduced.⁵ Moreover, a price drop might reduce crime even among users not enrolled in an I/DM program. Presumably, some fraction of those non-participant cocaine users commit income-generating crimes to finance their use – what Goldstein (1985) calls “economic-compulsive” criminality. A reduction in price means that they might be expected to reduce their criminal involvement – a collateral benefit of a successful program. The effects of a price change on criminality, if any, will depend in part on whether the users who participate in I/DM programs differ from non-participants in their price sensitivity. If the two classes of users differ, then I/DM programs might alter the slope of the demand function by changing the composition of the remaining user pool.

Predicted Effects If the Supply Function is Downward Sloping

The traditional analysis in Figure 2 is plausible as a qualitative depiction of the tobacco market. But several experts (e.g., Kleiman, 1993; Reuter & Kleiman, 1986; Reuter, Crawford, & Cave, 1988; Rydell & Everingham, 1994) argue that the illicit

effective, will reduce the demand of participants, but will not necessarily affect the supply to non-participant users, at least not directly.

⁵ Of course, neither of these crime-reduction benefits seem very likely for a tobacco program. Tobacco has not been causally linked with significant increases in psychopharmacological criminality, and because prices are lower (and the average user is more socially integrated), few users commit crimes to buy cigarettes.

nature of the cocaine business might produce a supply curve that is downsloping, as seen in Figure 3. This conclusion follows if:

- the marginal cost of producing a kilogram of cocaine does not increase with the total number of kilograms produced; and
- the per-unit risk of seizures and other enforcement actions falls with the total quantity of cocaine that is produced.

The assumption of a downward sloping cocaine supply curve is controversial (see Caulkins, Chiesa, & Everingham, 2000; Manski et al., 1999), but it is important to consider because it has implications for the effect of a downward shift in the demand curve.

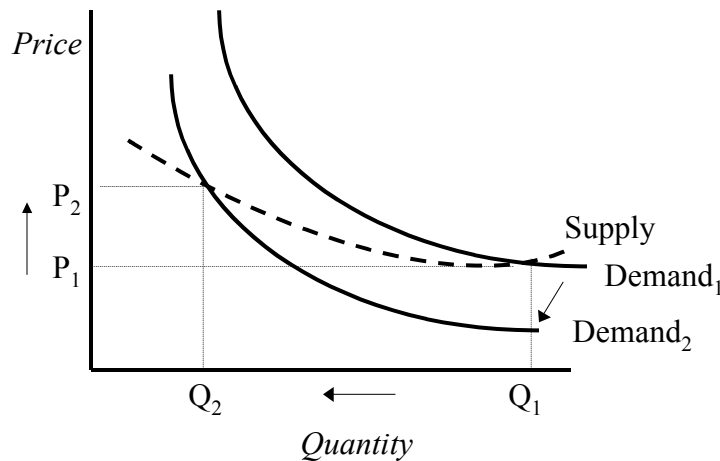


Figure 3. Price increase and quantity decrease following a downward shift in demand, assuming a downsloping supply curve (Note: P_1 = initial price, P_2 = new price; Q_1 = initial quantity supplied, Q_2 = new quantity supplied)

Figure 3 indicates that with a downsloping supply curve, a downward shift in the demand curve would still produce a reduction in the quantity supplied, but prices would actually rise. This is obviously a desirable effect if users not receiving a I/DM intervention are price sensitive, because they can be expected to reduce their consumption *even though they are not in the program*. Moreover, the higher prices should discourage potential users from initiating drug use.

On the other hand, if those still using cocaine are relatively price-insensitive, they might increase their rate of income-generating crime to maintain their preferred level of

consumption – clearly an unintended consequence of the program. This effect would be mitigated to the extent that those users targeted for the program were the users most heavily involved in criminal activity – as might occur through a court-mandated program.

This discussion of price and criminality effects suggests the importance of additional empirical research on users' responsiveness to price changes. To accurately predict the consequences of an I/DM intervention on drug markets, we need better information on short- vs. long-run price elasticities, and on differences in the price sensitivity of likely participants vs. other users.

NON-PARTICIPATION AND NON-COMPLIANCE

The analysis of price effects presented above was premised on the best-case assumption that I/DM programs produce their intended shift in demand. The remaining mechanisms I consider each challenge that assumption. The simplest and least speculative challenge to the best-case scenario is the likelihood that some non-trivial fraction of targeted users will fail to participate.

It may be difficult to enroll targeted participants at high rates, and sustain their participation for the desired length of time. In the Drug Abuse Treatment Outcome Study (DATOS), a nationwide naturalistic examination of non-experimental treatment settings, median retention in treatment ranged from 29 to 177 days across 18 long-term residential programs, and from 42 to 144 days for 16 outpatient drug-free programs (Joe, Simpson, & Broome, 1998). Methadone clinics fared somewhat better, with a median of 117 to 583 days across 13 programs; across these programs, half of all clients participated for at least a year. But an examination of the evidence from a variety of at least partially analogous interventions suggests that high dropout rates are the norm:⁶

⁶ These high dropout rates do not necessarily imply that those dropping out receive no treatment (see Simpson, Joe, & Brown, 1997, p. 305) or do not stop using on their own (see Shadish et al., 1998); they simply suggest that high levels of participation in a vaccine program cannot be taken for granted.

Evidence From Partially Analogous Programs

Smoking cessation programs. The smoking cessation evaluation literature has largely ignored the question of program attrition; e.g., dropout rates are not analyzed in many major meta-analyses of this literature (e.g., Cepeda-Benito, 1993; Viswesvaran & Schmidt, 1992). In a recent methodological analysis of 7 carefully controlled clinical trials (Shadish et al., 1998), the dropout rate ranged from 0% to 30%, with a mean of 13%. But Borrelli et al. (2002, p. 23) suggest that “proactive recruitment and population-based studies demonstrate no-show rates approaching 50%.”

Pharmacological treatment of cocaine dependence. Table 1 summarizes data from 45 clinical trial arms on the effects of 15 different pharmacological interventions for cocaine dependence, computed from data presented in a recent meta-analysis by Silva de Lima et al. (2002). Discouragingly, the meta-analysis found no significant effects of any of these interventions. But the participation rates were also discouraging, with dropout rates ranging from 15% to 79%, with an overall rate of 48%; the same rate was observed across placebo conditions. High attrition rates are also common in psychosocial cocaine treatments (Gottheil, Sterling, & Weinstein, 1997; Siqueland et al., 1998; Van Horn & Frank, 1998; White, Winn, & Young, 1998).

Table 1.

Dropout rates in pharmacological treatment trials for cocaine dependence.

Active drug	# studies	Active drug condition			Placebo condition			Relative Risk
		Dropouts	N	Rate	Dropouts	N	Rate	
Bupropion	1	11	74	15%	13	75	17%	0.86
Desipramine	8	72	185	39%	39	136	29%	1.36
Fluoxetine	1	8	16	50%	15	16	94%	0.53
Gepirone	1	9	20	45%	11	21	52%	0.86
Imipramine	1	24	59	41%	27	54	50%	0.81
Ritanserin	1	11	40	28%	13	40	33%	0.85
Amantadine	6	68	144	47%	55	140	39%	1.20
Bromocriptine	3	32	70	46%	31	72	43%	1.06
Pergolide	1	111	156	71%	89	153	58%	1.22
Carbamzaepine	4	92	152	61%	110	161	68%	0.89
Disulfiram	2	14	47	30%	6	40	15%	1.99
Mazindol	2	10	40	25%	12	40	30%	0.83
Naltrexone	1	18	24	75%	15	22	68%	1.10

Phenytoin	1	23	29	79%	25	31	81%	0.98
Risperidone	1	23	30	77%	42	45	93%	0.82
TOTAL		526	1086	48%	503	1046	48%	1.01

DATA SOURCE: Adapted from Silva de Lima et al. (2002). Pharmacological treatment of cocaine dependence: A systematic review. *Addiction*, 97, 931-949.

Methadone maintenance. One might hope participation rates would be higher for a more effective pharmacological intervention. But dropout rates computed from data on 22 controlled methadone maintenance trials (reported in Farré et al., 2002) range from 13% to 80%, with a mean of 43% and a median of 46%. As might be expected, dropout rates are lower in programs with higher daily methadone doses (see Figure 4), but even at the highest studied doses (100 mg/day), a quarter of participants dropped out. (Participants receiving a placebo or another treatment are excluded from this analysis.)

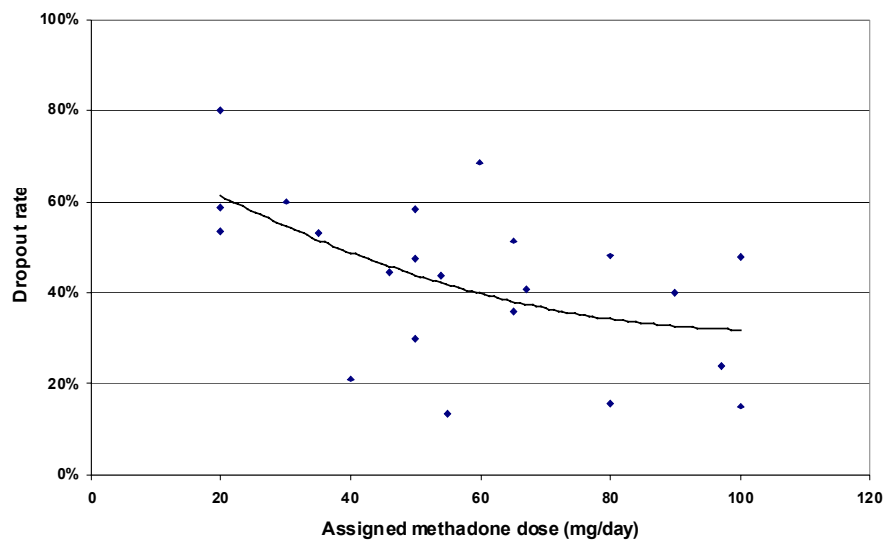


Figure 4. Declining dropout rates as a function of increased doses in methadone trials (data reported in Farré et al., 2002)

Drug court graduation rates. One might also assume that participation rates might be higher in mandatory, court-administered programs, where clients face possible criminal sanctions for non-compliance. But the drug court literature suggests that as many as half of assigned participants fail to “graduate” (averaging 47% in studies

reviewed by Belenko, 2001, p. 26). This low rate may seem to contradict the notion of a “mandatory” program, but Belenko (1998, p. 25) notes that in a recent Department of Justice survey, “only 25% of probationers reported that they were required to undergo drug testing” and “[o]ne quarter of felony probationers had had no contact of any type with their probation officer during the past month.”⁷

Disease vaccine programs. Finally, non-participation is a serious problem in vaccination programs for many serious diseases (Szilagyi et al., 2000). For example, Carter et al. (1986) found that only a quarter to a third of high-risk patients who were actively urged to get influenza shots actually did so. Moore-Caldwell et al. (1997) report that compliance with a hepatitis B vaccine series was reduced because “most teens perceived their risk of acquiring hepatitis B infection as slight or none,” yet Lawrence and Goldstein (1995) report that the hepatitis B immunization has been hampered by the inability of medical providers to identify high-risk individuals. On the other hand, in a recent intervention targeting over a thousand heroin addicts in Italy, 88% completed a full hepatitis B vaccine series (Quaglio et al., 2002). So high compliance is possible even in heavy drug-using populations.

Conclusion

Neither a voluntary nor a compulsory vaccination program can be expected to achieve high rates of compliance without aggressive recruitment and followup. A variety of roughly comparable interventions each routinely lose about half of their clients. Perhaps if I/DM programs are perceived to be less onerous (or more efficacious) than traditional substance abuse treatments, they may fare better. But not necessarily. High treatment dropout rates probably have less to do with treatment management than with the inherent difficulty of changing addictive behavior (De Leon, 1998; Joe et al., 1998). Most addiction treatment clients are at best ambivalent about the prospect of total abstinence, and for that reason, these interventions may be both encouraging and somewhat threatening. Indeed, addicts at risk of coerced treatment may even volunteer for traditional psychosocial programs to avoid participating in pharmacological programs.

⁷ Perhaps unsurprisingly, mandatory treatment compliance is much higher in in-patient psychiatric institutions (Zito et al., 1991).

Program designers will have to attend to a variety of factors that might increase participation:

- Confronting fear and distrust of a novel and intrusive medical technology that has both medical and social control objectives.
- Minimizing logistical barriers to participation (location, hours, etc.).
- Carefully crafted persuasive appeals and outreach for voluntary programs.
- Monitoring and clear sanctioning of court-mandated clients (see Kleiman, 1997).

INCREASED CONSUMPTION TO “SWAMP” THE TREATMENT

The previous section examined incomplete participation – a prevalence effect across people. In this section, I consider the effects of an only partially effective intervention – a within-client effect. Thus, rather than (or in addition to) only a fraction of targeted people participating, I consider what would happen if:

- participating clients experience no reduction, or only a partial reduction, in drug craving; and/or
- participating clients are able to produce the same subjective drug effects by significantly increasing their consumption (frequency and/or quantity) – in essence, “swamping” the treatment.⁸

The results of such a scenario are potentially quite serious. We might not expect to the downward shift in the demand curve plotted in Figure 2 above. Users who maintain their previous level of consumption will experience fewer drug effects. From a clinical perspective, this may produce a significant improvement in functioning, but from a market perspective there may be no observable behavioral change. This is particularly troubling for an illicit drug like cocaine, because many of the harms associated with illicit drug use are primarily attributable to illicit markets rather than the effects of the drug per se (MacCoun, Reuter, & Schelling, 1996; MacCoun & Reuter, 2001). Worse yet, participating users may well simply increase their consumption of their drug of dependency in an attempt to achieve the same subjective effects. (To the extent that this

⁸ Pentel (in this volume) uses the label “compensation” for this effect, but I prefer to avoid that term because of potential confusion with a different behavioral mechanism discussed below, called “compensatory behavioral response” in the risk literature.

happened it would reduce the magnitude of reduction in demand, and in theory could even produce a net increase in demand.

Although the analogies are not perfect, experiences with existing pharmacological treatments for addiction are not comforting. Positive urine tests for illicit opiates are found in methadone maintenance clinical trials in anywhere from 16% to 71% of the clients, with a median rate of 53% (Farre et al., 2002). Figure 4 plots the results of 15 such trials as a function of experimentally assigned methadone dose. As one might expect, illicit opiate use declines with increasing maintenance dose, but even at the highest observed dose, 100 mgs/day, over a quarter of all clients continued using street opiates. Clinical trials for pharmacological treatment of tobacco dependence -- bupropion SR and nicotine gums, inhalers, nasal sprays, and patches -- routinely find that a majority of clients continue smoking (see Fiore et al., 1994, 2000).

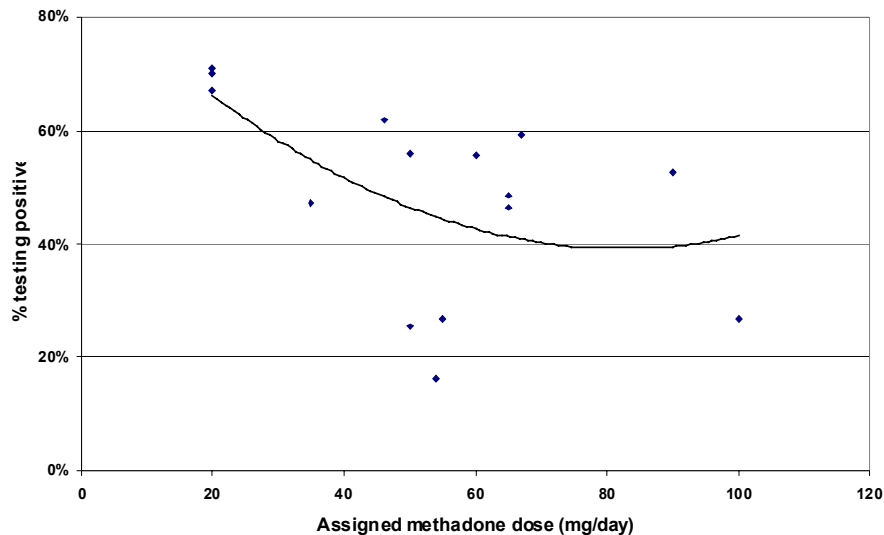


Figure 5. Decreasing illicit opioid use with increases in methadone dose in methadone trials (data reported in Farré et al., 2002).

Of course, studies of these interventions provide no indication that users actually *increase* their consumption. And the immunotherapies and depot medications under consideration here surely differ from these other interventions in important ways. But some of the differences could make the picture less rather than more encouraging.

A key consideration is the extent to which these interventions *reduce the motivation to use the targeted drug*, rather than (or in addition to) simply blocking the

physical and/or subjective effects of the drug. Methadone and nicotine treatments do so, but the proposed I/DM interventions do not, at least not directly. They do not provide a substitute or maintenance substance, nor do they directly alter the brain mechanisms thought to be responsible for craving and/or withdrawal.

Still, Pentel (in this volume) suggests that “The hope in using this strategy is to reduce the rewarding effects of the drug which lead to and sustain addiction. For example, a cocaine addict who is vaccinated would feel little effect and therefore have little reason to continue using it.” [VERIFY THAT THIS QUOTE APPEARS IN FINAL VERSION] One way to characterize this argument is in terms of what behavior analysts call “extinction.” In classical conditioning, extinction occurs when a conditioned stimulus is no longer paired with unconditioned stimuli. In operant conditioning, extinction occurs when a learned behavior no longer receives a positive reinforcement. Treatments that prevent an addictive drug from crossing the blood-brain barrier are likely to produce both types of extinction.

Extinction can produce lasting behavior change, but it has other predictable consequences (Azrin et al., 1966; Neuringer et al., 2001; Skinner, 1953; Sulzer-Azaroff & Mayer, 1977):⁹

- The target behavior does not cease immediately; responding may temporarily increase in frequency and in variability.
- Occasional re-pairing behavior and the reinforcer changes the extinction non-contingency to an intermittent schedule of reinforcement, which can encourage persistent responding.
- During extinction, conditioned associations are not unlearned so much as they are “forgotten,” or put into competition with newly learned alternative contingencies, which means that even in the absence of further reinforcement, the response can “spontaneously recover” (Bouton, 1994).

⁹ Very similar predictions are made reached based on different arguments and evidence in the reactance theory and control theory literatures (see Carver & Scheier, 1998). Time-discounting accounts of addiction (see Elster & Skog, 1999 and Vuchinich and Heather, in press) also predict that I/DM treatments should reduce drug use, by eliminating, at least temporarily, the temptation posed by immediate reinforcers and encouraging the user to invest in alternative behaviors with larger but more delayed payoffs (work, sports, family, etc.).

- Increased responding may be accompanied by aggressive behavior – the so-called “vending machine phenomenon” (Sulzer-Azaroff & Mayer, 1977).
- *Ceteris paribus*, extinction produces a net reduction in positive reinforcement, which if not replaced by substitute rewards can produce lethargy, apathy, and depression.

Moreover, a traditional extinction account may fail to capture important subtleties of addictive drug use. Classical and operant conditioning have long been implicated in drug addiction, but they do not account for many aspects of the phenomenon (Robinson & Berridge (2003). There is increasing evidence that chronic drug use can produce enduring changes in the brain’s sensitivity to drug-related cues, producing a heightened motivational state that may persist long after drug use has been stopped (see Gardner & David, 1999; Robinson & Berridge, 2003).¹⁰ Gardner and David (1999, p. 117) suggest that “strong and persistent drug craving may outlast drug detoxification and withdrawal by months or years.”

Thus, there are reasons to be concerned that these new interventions will fail to fully block drug taking. Users may attempt to “swamp” the treatment by increasing their consumption. These effects may be temporary, but they could be extremely serious.

For example, the immunotherapeutic effects are expected to dissipate between treatments (Pentel, this volume). If so, the effects of a given dose of the targeted drug will vary over time; a dose that produces no response or a mild response soon after a treatment may produce a very large response if attempted some weeks later. It seems unlikely that users will be able to accurately anticipate such effects and titrate their doses accordingly. Thus, users who attempt to overcome the I/DM blocking effect will be at serious risk of extreme psychiatric reactions, cardiac failure, respiratory failure, or other reactions to toxicity.

Consider also the implications if the user’s previous consumption level was already at the outer limits of what he or she could afford. (This is more plausible for cocaine than for tobacco.) If so, efforts to “swamp” the treatment with high doses could motivate increased income-generating “economic compulsive” criminality.

¹⁰ Note that widespread application of these new treatments will provide important new evidence about the relative merits of competing theories of drug addiction.

For all these, reasons, *it is crucial to use monitoring and counseling to discourage users from attempting to “swamp” the treatment by increasing their consumption.* I/DM treatments should not be viewed as a “cure” for addiction, but rather a prolonged respite from it – an opportunity for the addict to regain control of his or her life and invest in a repertoire of alternative activities.

Later in this chapter, another mechanism will be identified that might produce heightened risk behavior in response to a vaccine (Blower & McLean, 1994). The mechanism there is somewhat different, involving compensatory responses to perceived risk reduction.

DRUG SUBSTITUTION

Another major concern is whether a pharmacological relapse prevention or addiction protection program would inadvertently motivate participants to increase their use of *other* drugs – a substitution effect. Note that the substitute drug may have either more or less harmful physical and behavioral effects than the targeted drug.

Psychopharmacological researchers often study drug substitution using a drug discrimination paradigm (Kamien et al., 1993), which is useful for studying agonist and antagonist mechanisms. But while a client in a cocaine relapse prevention program may substitute another drug based on its similar pharmacological properties, the choice might be influenced as much or more by situational factors – availability, price, peer use, etc. Moreover, the closer two drugs are in pharmacology, the more likely it is that I/DM treatments may at least partially block the effects of the substitute (see Pentel, this volume). Thus, it is worthwhile to construe the notion of a “substitute” more broadly rather than in the drug discrimination tradition.

Economists have a purely behavioral way of operationalizing substitutes and complements that has been adapted by the behavioral economic research community in psychology (e.g., Petry & Bickel, 1998). Two goods are considered *substitutes* if an increase in the price of the first good leads to an increase in demand for the second good – a positive “cross-price elasticity.” Two goods are considered *complements* if an increase in the price of the first good leads to a decrease in demand for both goods – negative price and cross-price elasticities.

One might reasonably ask whether evidence on “cross-price elasticities” is relevant for understanding I/DM effects. Is an increase in the preferred drug’s price analogous to decreases in the preferred drug’s effects on the brain? Several arguments suggest the answer is probably yes. First, laboratory experiments have established that manipulations of effort, price, available income, and reinforcement magnitude have roughly equivalent effects on rates of drug consumption (e.g., DeGrandpre & Bickel, 1995). Second, some of the econometric studies of substitution operationalize “price” using proxies like drug enforcement risk, marijuana eradication, and variations in state drinking ages, all of which involve reduced availability to the consumer.

In econometric studies, substitution and complementarity can be estimated *in situ*, capturing actual behavior outside the laboratory, though the relevant data are often sparse and poor, and there are serious concerns about endogeneity and spurious correlation (Manski et al., 2001). Bickel and his colleagues (Bickel et al., 1995; Petry & Bickel, 1998) have developed a laboratory paradigm that avoids these problems by manipulating prices in a simulated market, but their participants, though experienced addicts, are nevertheless “behaving” in an artificial setting that may distort their choices. Because there are inevitable tradeoffs between statistical control and realism, both approaches seem necessary (see Mook, 1983).

Relevant Evidence

Marijuana-alcohol link. The most studied linkage has been between marijuana and alcohol – a relationship that has little bearing for the interventions examined here. Still, that literature illustrates the methodological challenges to correctly estimating the relationship. Some studies find a substitution relationship between marijuana and alcohol use (Chaloupka & Laixuthai, 1994; DiNardo & Lemieux, 1992), while others suggest the relationship is complementary (Pacula, 1998; Williams et al., 2001). Chaloupka and Pacula (2000, p. 105) argue that: “The mixed evidence with respect to alcohol and marijuana can be attributed to differences in the level of aggregation of the data as well as to differences in the populations being studied. When individual-level data are employed, and demand equations for marijuana can also be estimated, the findings are generally supportive of the complementary relationship between alcohol and marijuana.

Until good measures of the money price of marijuana are obtained, however, this cannot be known with certainty.”

Marijuana-tobacco link. Econometric studies of the relationship between marijuana and cigarette consumption suggest a complementary relationship (Cameron & Williams, 2001; Chaloupka et al., 1999; Farrelly et al. 2001; Pacula, 1998). If so, this implies that a successful pharmacological tobacco intervention ought to bring about a some reduction in marijuana use.

Alcohol-tobacco link. The evidence on the alcohol-tobacco relationship is similarly ambiguous. Cameron and Williams (2001) find an inverse association between the price of cigarettes and alcohol consumption, while alcohol prices are positively but insignificantly associated with cigarette consumption. Decker and Schwartz (2000) find that increases in the price of cigarettes are associated with increases in the prevalence of drinking and the amount consumed by drinkers.

Marijuana-hard drug link. Model's (1993) analysis of Drug Abuse Warning Network (DAWN) emergency room data for the years 1975-1978 found higher rates of marijuana incidents, and lower rates of hard drug incidents, in states that had depenalized marijuana. She interpreted this as evidence for a substitution effect, in which users shifted from harder drugs to marijuana after its legal risks decreased. A laboratory study of hypothetical drug purchase choices by heroin addicts also suggest that marijuana and heroin are substitutes (Petry & Bickel, 1998). On the other hand, Saffer and Chaloupka (1995) found that marijuana had a complementary relationship with cocaine and with heroin, but their data source (the National Household Survey on Drug Abuse) captures only a small and possibly unrepresentative fraction of cocaine and heroin users. The methodological differences across these studies are so great that the contradictory findings are difficult to resolve without more research.

Relationships among hard drugs. It appears that only one econometric study has examined the cross-price elasticities between hard drugs (Saffer & Chaloupka, 1995), finding that cocaine and heroin were complements rather than substitutes. Again, their household sample may be quite unrepresentative of hard drug users. Petry and Bickel's (1998) simulation experiments using heroin addicts suggest that valium and cocaine substituted for heroin; mock “purchases” of these drugs rose with simulated rises in

heroin prices. Heroin purchases were unresponsive to rises in the price of valium. Unfortunately for our purposes, cocaine prices were not manipulated. Despite the obvious limitations of the simulation (no legal risks, no actual consumption), a conceptual replication of this paradigm using cocaine addicts and manipulated cocaine prices might provide valuable insights into possible substitutes for cocaine.

In addition to these economic studies, there are also large clinical literatures on cocaine-alcohol (Pennings, Leccese, & de Wolff, 2002) and cocaine-heroin (Leri, Bruneau, & Stewart, 2003) poly-drug use. Popular lore suggests that a cocaine-heroin mix (a speedball) has particularly attractive effects for addicts, which would suggest complementarity, but Leri et al. (2003, p. 7) argue that “clinical and preclinical experimental evidence indicates that the simultaneous administration...does not induce a novel set of subjective effects, nor is it more reinforcing than either drug alone...”.

Effects of methadone maintenance on use of other drugs. Methadone maintenance provides a partial analogy to the pharmacological treatments at issue here. Methadone itself is a substitute for heroin, in the empirical sense that it is inversely related to heroin use among former heroin users. Though methadone at adequate doses significantly reduces heroin use (e.g., Farre et al., 2002), use of other street drugs is common among methadone clients (Leri et al., 2003; Preston et al., 1998). For example, in one study (Nirenberg et al., 1996, p. 225) report that “more than half of the sample tested positive at least once for opiates (61%) other than methadone, almost half tested positive for cocaine (48%), almost half tested positive for benzodiazepines (46%), and more than three quarters tested positive for cannabis (78%).”

Naturally, there is a concern that the use of these other drugs reflects a substitution effect of the methadone maintenance regimen. Clients do not appear to be substituting cocaine for heroin. Longitudinal studies suggest that many clients were already using cocaine prior to starting methadone, and that participation in the maintenance program is associated with a decline in cocaine use (see Dunteman, Condelli, & Fairbank, 1992; Fairbank, Dunteman, & Condelli, 1993; Shaffer & LaSalvia, 1992; but see Compton et al., 1995, p. 109). Indeed, Kidorf and Stitzer (1993) were able to reduce cocaine use among clients by making methadone contingent on cocaine-free urine for 7 weeks (also see Caulkins & Satel, 1999).

Cigarette smoking is also common among methadone clients (Frosch et al., 2000), but experimental manipulations of methadone dose levels have produced inconsistent effects on smoking levels (Schmitz, Grabowski, & Rhoades, 1994; Stark & Campbell, 1993). On the other hand, buprenorphine maintenance appears to increase tobacco consumption, at least among concurrent opiate and cocaine users (Mutschler et al., 2002).

Conclusion

At present, the only substitution effect that can be predicted with any confidence for a tobacco relapse prevention or addiction prevention intervention involves *food*, as weight gain is a common consequence of smoking cessation (Cabanac & Frankham, 2002). Tobacco appears to have a complementary relationship with marijuana, but there is evidence for both complementarity and substitution between tobacco and alcohol. For cocaine cessation, there is mixed evidence for a possible substitution effect involving marijuana, and simply too little evidence to predict effects on the consumption of amphetamines, opiates, or alcohol. Pharmacologically, the use of stimulants seems plausible, but again, social and economic factors may be more determinative (price, availability, peer use).

It is apparent that additional research on drug substitution effects in natural, clinical, and experimental settings ought to be considered a high priority for the addiction research community. In the meantime, in the face of such scanty evidence, a conservative assumption would be that some sort of substitution is a plausible response to these interventions. Use of other drugs should be closely monitored, and appropriate preventive counseling should be provided.

COMPENSATORY RESPONSES TO RISK REDUCTION

Unlike the previously discussed mechanism, the remaining mechanisms suggest unintended effects on *drug use by those not receiving I/DM treatment*.

Risk analysts have learned that technological risk reduction often has the unintended consequence of increasing the prevalence and/or intensity of that behavior. According to MacCoun and Reuter (2001, p. 392)

When technological innovations successfully reduce the probability of harm given unsafe conduct, they make that conduct less risky. And if the perceived risks were motivating actors to behave somewhat self-protectively, a reduction in risk should lead them to take fewer precautions than before, raising the probability of their unsafe conduct to a higher level. This notion has been variously labeled compensatory behavior, risk compensation, offsetting behavior, or in its most extreme form, risk homeostasis—a term that implies efforts to maintain a constant level of risk (Wilde, 1982).

Compensatory behavioral responses to risk reduction are now well established in a number of risk domains (see reviews in MacCoun, 1998b; Stratton et al., 2001, Chapter 2). For example, people drive faster and more recklessly in cars with seat belts and air bags (Chirinko & Harper, 1993; Stetzer & Hofman, 1996). Similarly, smokers compensate for filters and low-tar tobacco by smoking more cigarettes, inhaling more deeply, or blocking the filter vents (Hughes, 1995; Stratton et al., 2001). In both domains, some of the safety gains brought about by a reduction in the probability of harm given unsafe conduct have been offset by increases in the probability of that conduct.

The total harm produced by a risky activity (e.g., addictive drug use) is a function of the average harm per incident, multiplied by the total amount of the activity (MacCoun, 1998b; MacCoun & Reuter, 2001, Chapter 15). 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.

In many settings, technological risk reduction provides little evidence that behavioral responses produce net increases in harm, or even the constant level of harm predicted by Wilde's (1982) "homeostatic" version of the theory. Rather, such effects are sufficiently small relative to the benefits of the intervention that they reduce, but do not eliminate, the gains in safety (MacCoun, 1998a; Stratton et al., 2000).

But there are some important cautionary tales. For example, in 1994, Blower and McLean published epidemiological simulations suggesting that an HIV vaccine, unless perfectly prophylactic, could actually exacerbate the San Francisco AIDS epidemic. This

would occur if individuals behaved less cautiously in response to their increased sense of safety.

In the decade that has followed, it has become increasingly clear that a similar scenario is playing out in response to highly active retroviral therapy (HAART) (see Blower, 2001; Katz et al., 2002; Ostrow et al., 2002; Stolte et al., 2002). Katz et al. (2002) report that the percentage of San Francisco men who have report unprotected anal sex increased from 24 percent to 45 percent between 1994 and 1999. The authors present correlational and anecdotal evidence linking this increase in risky sex to reduced fears of HIV since the advent of HAART. Survey reported by Ostrow et al. (2002) also show a correlation between unsafe sex and perceptions that HAART reduces the harmful consequences of HIV infection.

Immunotherapies or depot medications for drug dependence are potentially vulnerable to compensatory behavioral responses. The decision to take risks is influenced by the expected outcome of an activity, but also by perceived worst-case scenarios (March & Shapira, 1992; Slovic, Fischhoff, & Lichtenstein, 1979). Thus, the perceived *risk of becoming addicted* is an important predictor of the decision to initiate and/or escalate recreational drug use (e.g., Benthin, Slovic, & Severson, 1993; Goldberg & Fischhoff, 2000). As such, this risk is a major focus of the curriculum of primary drug prevention activities (Manski et al, 2001, Chapter 8).

Compensatory responses to I/DM might well be larger than that observed in studies of seat belts, needle exchanges, and other interventions. The reason is perceptual: those other interventions are at best seen as ways to reduce the relevant risks at the margin. But existence of immunotherapy or depot medication program for relapse prevention or addiction protection, if widely publicized, may convey – rightly or wrongly – a widespread belief that “addiction has been cured” (see MacCoun, in press). Psychologically, the perceived elimination of a small risk has much larger impact than perceived reductions of equivalent magnitude elsewhere in the risk distribution (Kahneman & Tversky, 1984). If so, current users who are not enrolled in a pharmacological program may increase their consumption. And current non-users may, at the margin, be more willing to begin using the addictive substance.

The magnitude of such effects is unknown. There is no *a priori* reason to believe that such effects would be so large as to offset the benefits of reducing drug use among participants. But program designers should anticipate the possibility that an immunotherapy or depot medication program might inadvertently encourage non-addicts to risk becoming addicts.

SOCIAL NORM EFFECTS

Another way that I/DMs might influence drug use by non-program participants is by altering networks of social influence. One such effect is beneficial. A reduction in use by light users could have “social multiplier” effects on non-users and current light users (see Caulkins, Rydell, Everingham, Chiesa, & Bushway, 1999, pp. 31-34). This follows under the assumption that current users socially reinforce, encourage, and facilitate use among those around them. There is much correlational evidence for this assumption, at least among adolescents (e.g., Elliott, Huizinga, & Ageton, 1985), although the correlation conflates a social influence effect with a selection effect, since high-risk peers tend to select each other as friends (Bauman & Ennett, 1996; Kandel, 1996).

But it is possible that this social influence effect would be inverted in the case of hard-core dependent users.¹¹ Musto (1971/1987) and Johnston (1991) each offer versions of a “generational forgetting” model of drug epidemics, in which the increasing visibility of the deleterious effects of addiction trigger a reduction in initiation.¹² Behrens and her colleagues (1999, 2000, 2002) have incorporated this process into Everingham and Rydell’s (1994) model of the cocaine epidemic. Their analyses lead to the disturbing prediction that if Musto and Johnston are correct, widespread drug treatment early in an epidemic could actually exacerbate the epidemic by slowing the social learning process. Similarly, if the generational forgetting model is correct, then *ceteris paribus*, reducing

¹¹ Caulkins et al. (1999) included negative feedback from heavy use to initiation in their modeling of a social multiplier effect for primary prevention, but they concluded that the desirable multiplier effects would be larger than any negative effects.

¹² In Musto’s account, the predicted effect is cyclical, because as the number and visibility of users declines over time, initiation begins to rise again. The models developed by Behrens and her colleagues (1999, 2000, 2002) allow for other possibilities (e.g., damped oscillation).

the visibility of the harms of addiction might reduce a social deterrent to drug use. This prediction is admittedly speculative. The generational forgetting model remains largely untested; there are simply too few "cycles" of data to test the cyclicity of drug epidemics. Still, this line of reasoning bolsters the concern that depot medications or immunotherapies might well encourage drug use by reducing its perceived risks.

UNINTENDED EFFECTS ON DRUG MARKETING

Putting aside the unintended consequences discussed thus far, assume again for the sake of argument that a successful pharmacological intervention is widely implemented and reduces the prevalence and severity of tobacco or cocaine addiction. This would almost certainly threaten the profitability of tobacco or cocaine production and sales. Producers and sellers, whether licit or illicit, may well respond in a compensatory fashion.

Illicit Drug Sellers

Sellers of cocaine or other targeted street drugs may respond in various ways:

- Drug sellers may move into the production and/or sales of other psychoactive drugs (e.g., Constantine, 1995; Thompson, 2002), or develop new synthetics that mimic the targeted drug without being blocked by I/DM pharmacologies.
- At least in the short run, each dealer may act more aggressively to protect and expand their share of the diminishing market. We might see (at least temporarily) an upsurge in violence as sellers compete for a shrinking pool of addicts.
- Drug selling organizations may also attempt to expand into regions where the relevant I/DM interventions are less available or less widely used. It has long been rumored that urban cocaine trafficking organizations expanded into rural areas as urban drug enforcement became more aggressive in the 1990s (Butterfield, 2002; Johnson, 2003; National Alliance of Gang Investigators Associations, 2000; cf. Maxson, 1998).

The Tobacco Industry

If I/DM interventions against tobacco addiction become popular, the tobacco industry may also seek new users who are not currently targeted for these interventions

(e.g., the young, rural communities, other nations) and seek to establish or strengthen these alternative markets. For example, as U.S. tobacco consumption has declined, tobacco companies have become more aggressive in international markets, especially in developing nations (WHO, 2001). We might also see new forms of advertising, perhaps subtly hinting that tobacco addiction is now a more manageable risk of their product.

The Pharmaceutical Industry

For manufacturers of immunotherapeutics or depot medications, the largest market will involve addiction protection rather than relapse prevention, simply because the population of potential clients is so much larger – there are many more potential addicts than actual addicts, especially if “at risk” is defined broadly. (This is especially likely to be true for the tobacco market, which is roughly an order of magnitude larger than the market for illicit drugs other than marijuana.¹³) Many parents may feel a moral (or perhaps social) obligation to protect their children against the risks of future addiction. The industry may market the treatments in a manner that reinforces or amplifies this sense of responsibility.

Much may depend on the decision by public and private health insurance providers about whether to reimburse I/DM addiction protection, and by any professional guidelines for off-label use established by professional medical societies (e.g., the American Medical Association). Broad coverage of youth addiction protection is likely to be socially inefficient. If parents and physicians define “addiction risk” too broadly, there will be a “moral hazard” problem of excessive utilization of the intervention. On the other hand, if insurers set strict limits on coverage (ex ante), they may face lawsuits if some youth who were denied coverage later became addicted.

¹³ According to the National Household Survey on Drug Abuse, in 2001 there were 7.0 million current users of illicit drugs other than marijuana vs. 66.5 million current users of a tobacco product. See <http://www.samhsa.gov/oas/nhsda.htm#NHSDAinfo>.

UNINTENDED SOCIAL AND POLITICAL CONSEQUENCES

Again, assuming that a pharmacological intervention is widely implemented and is at least perceived to be successful in reducing addiction, other actors may also respond in unintended ways:

- Non-users may further stigmatize or ostracize existing smokers and drug users who have not availed themselves of a pharmacological relapse intervention. While this stigma may help to discourage initiation and escalation by casual users, the labeling theory tradition in sociology suggests that it could actually intensify the drug involvement of heavy users (MacCoun, 1993).
- Law enforcement officials may demote cocaine offenses as an enforcement priority, increasingly viewing cocaine as a medical problem rather than a social control problem. This would be particularly troubling if these officials overestimated the actual “capture” or effectiveness rates of the pharmacological intervention.
- Politicians and the general public may be less willing to actively support more traditional forms of treatment, primary prevention, and law enforcement. This would be particularly troubling if in fact a large fraction of existing users were ineligible for such a pharmacological intervention. Also, a reduction in support could have pernicious effects on substance abuse control efforts involving drugs for which no pharmacological intervention is available.
- There may be a political backlash against the coercive use (by legal authorities or by parents) of this invasive technology. This seems particularly likely if mandated clients are disproportionately drawn from ethnic and racial minority groups, which is not implausible given the disproportionately high rates at which those groups are apprehended for drug use (MacCoun & Reuter, 2001, Chapter 6).

CONCLUSIONS

This essay has raised a number of potential unintended consequences of a depot medication or immunotherapy program for addiction, including:

- Increased use of the target drug by some program clients (if the treatment is only partially effective and fails to reduce drug motivation).
- Increased use of other drugs by program clients (a substitution effect).

- Increased use of the target drug by those not in the program (through reductions in the perceived riskiness of the drug).
- Increased dealer violence (through increased competition for fewer customers and/or effects of the program on prices).

There is little basis for estimating the likelihood of these potential outcomes, other than to suggest that their probabilities are non-trivial (i.e., below 1.0 but closer to .50 than to 0).

Of course, these effects are not the only factors to consider when evaluating such a program. Even if all these consequences occurred, they may well be completely offset by the program's benefits. A full analysis of the desirability of an I/DM program should consider other factors assessed elsewhere in this volume, including:

- the ethical obligation to treat drug dependence if possible;
- the ethical, legal, and political objections to the intervention;
- the administrative and medical costs of the program;
- the cost-effectiveness of the program relative to other interventions;
- and the program's benefit-cost ratio.

Nevertheless, the scenarios considered here are not implausible on their face. Each is based on familiar theoretical mechanisms, evidence from at least partially analogous interventions, or both. Program designers have an obligation to take these risks seriously and to minimize them through careful program implementation, monitoring, and evaluation.

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Table 1.
Dropout rates in pharmacological treatment trials for cocaine dependence.

Active drug	# studies	Active drug condition			Placebo condition			Relative Risk
		Dropouts	N	Rate	Dropouts	N	Rate	
Bupropion	1	11	74	15%	13	75	17%	0.86
Desipramine	8	72	185	39%	39	136	29%	1.36
Fluoxetine	1	8	16	50%	15	16	94%	0.53
Gepirone	1	9	20	45%	11	21	52%	0.86
Imipramine	1	24	59	41%	27	54	50%	0.81
Ritanserin	1	11	40	28%	13	40	33%	0.85
Amantadine	6	68	144	47%	55	140	39%	1.20
Bromocriptine	3	32	70	46%	31	72	43%	1.06
Pergolide	1	111	156	71%	89	153	58%	1.22
Carbamzaepine	4	92	152	61%	110	161	68%	0.89
Disulfiram	2	14	47	30%	6	40	15%	1.99
Mazindol	2	10	40	25%	12	40	30%	0.83
Naltrexone	1	18	24	75%	15	22	68%	1.10
Phenytoin	1	23	29	79%	25	31	81%	0.98
Risperidone	1	23	30	77%	42	45	93%	0.82
TOTAL		526	1086	48%	503	1046	48%	1.01

DATA SOURCE: Adapted from Silva de Lima et al. (2002). Pharmacological treatment of cocaine dependence: A systematic review. *Addiction*, 97, 931-949.