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The use of incentives to reinforce medication adherence

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Abstract

Objective—Poor medication adherence is a longstanding problem, and is especially pertinent for individuals with chronic conditions or diseases. Adherence to medications can improve patient outcomes and greatly reduce the cost of care. The purpose of the present review is to describe the literature on the use of incentives as applied to the problem of medication adherence.

Methods—We conducted a systematic review of peer-reviewed empirical evaluations of incentives provided to patients contingent upon medication adherence.

Results—This review suggests that incentive-based medication adherence interventions can be very effective, but there are few controlled studies. The studies on incentive-based medication adherence interventions most commonly feature patients taking medication for drug or alcohol dependence, HIV, or latent tuberculosis. Across studies that reported percent adherence comparisons, incentives increased adherence by a mean of 20 percentage points, but effects varied widely. Cross-study comparisons indicate a positive relationship between the value of the incentive and the impact of the intervention. Post-intervention evaluations were rare, but tended to find that adherence effects diminish after the interventions are discontinued.

Conclusions—Incentive-based medication adherence interventions are promising but understudied. A significant challenge for research in this area is the development of sustainable and cost-effective long-term interventions.

Introduction

The success of any pharmacotherapy depends critically on adherence to the prescribed medication regimen. Many treatments for chronic conditions and diseases require daily action on the part of the patient for the entirety of their lives, and even single-dose treatments require patient participation. Failure to adhere to a pharmacotherapy can have catastrophic effects for the patients, which in turn leads to greater cost of care. Increases in hospital admissions due to poor medication adherence cost an estimated $100 Billion per year in the United States alone (Osterberg and Blaschke, 2005). The problem is widespread, and the World Health Organization (Sabaté, 2003) estimates that in developed nations only 50% of patients with chronic conditions adhere to (i.e., take at least 80% of) their prescribed medicines. The potentially severe health consequences and the enormous economic burden

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of medication non-adherence make developing highly effective means to improve medication adherence as a top priority for behavioral science.

Several high-profile reviews have concluded that there is an urgent need to develop effective interventions for medication adherence, that no single method or type of intervention is detectably superior to all other interventions, and that the best interventions evaluated to date have produced only small to moderate effects (McDonald et al., 2002; Osterberg and Blaschke, 2005; Kirpalani et al., 2007; Culter and Everett, 2010). A similar conclusion was drawn in a Cochrane review on the topic (Haynes et al., 2008), which also noted that a taxonomy of the interventions attempted thus far was not feasible because of the complexity and multi-component nature of most of the interventions that have been evaluated.

The principles of operant conditioning are the basis for many highly effective behavioral interventions. These interventions emphasize the importance of targeting specific, observable, and measurable behavior, and as such may be especially well suited as a means of improving medication adherence. Perhaps the most common kind of operant intervention is the reinforcement procedure, in which the availability of an incentive is contingent upon the occurrence of a target behavior. Such interventions are effective in the treatment of drug addiction (Lussier et al., 2006; Higgins, Silverman and Heil, 2008), in improving the lives of individuals with developmental disabilities and autism (Fischer, Piazza, & Roane, 2011), and in improving safety and productivity in the workplace (Austin and Carr, 2000), among other applications. These kinds of interventions can also promote medication adherence, though attempts to address medication adherence via patient incentive programs has been relatively uncommon. The purpose of the present review is to describe the literature on the use of incentives as applied to the problem of medication adherence. A review of the relevant principles and procedures of operant conditioning is beyond the scope of the present review, but interested individuals should consult a comprehensive text (e.g., Cooper, Heron, & Heward, 2007).

Methods

Studies were identified by searching the electronic databases MEDLINE, PsycInfo, and Academic Search Complete. The search engine employed SmartText searching. The following search terms were combined using Boolean operators OR or AND as appropriate: Drug, Medication, Adherence, Compliance, Incentives, Reinforcement, Contingency, and Intervention. Searches were limited to peer-reviewed articles, but no other restrictions were applied. Relevant articles, including reviews, were hand-searched for additional references. The first author conducted all searches, reviewed all search findings, and selected articles for inclusion. The second author reviewed all search findings and created an independent list of articles for inclusion.

Articles selected for inclusion in this review were required to be peer reviewed empirical evaluations of incentives provided to patients contingent upon medication adherence. Only interventions that featured material incentives were included. Studies in which the incentives were not described precisely or in which the incentives were not delivered by the study team or a service provider were excluded. Any studies that featured incentives as part of a multifaceted approach to promoting medication adherence and that did not specifically evaluate the role of incentives in the success of the intervention were excluded. Studies involving immunization or vaccination were excluded. Also excluded were any studies in which the target behavior was attendance at any kind of health services event (e.g., a doctor’s appointment, physical therapy, counseling, or health screening), and studies in which the target behavior was a health-related behavior other than taking a medication (e.g., the self-monitoring of blood glucose level by diabetics, exercising). After removal of

redundant titles, searches yielded a combined total of 692 abstracts for review. Abstracts for all titles were evaluated by both authors, who independently applied the exclusion criteria. The criteria were applied in a serial order and review of a given abstract was stopped once a single exclusion criterion was satisfied. Any title that was not unequivocally excluded by both authors was obtained, and the complete manuscripts were independently evaluated by both authors. During the abstract review process, 324 articles were excluded because they were not research articles involving an intervention designed to affect patient behavior. Then 125 articles were excluded because they did not involve incentives. Next, the requirement that incentives be contingent upon medication adherence resulted in the exclusion of 117 articles. The requirement that incentives be given to patients resulted in the exclusion of six articles, and then another nine articles were excluded because the target behavior was vaccination or attendance at a health related event. The remaining 48 manuscripts were obtained. Of these, further inspection resulted in exclusion of an additional 18 articles for one of the reasons specified above. An additional nine articles were then excluded because the incentives were either not specified or not quantified (Lundervold et al., 1989; Koch et al., 1993; da Costa et al., 1997; Anderson and Collier, 1999; Laidlaw et al., 1999; Bartlett et al., 2002; Watt et al., 2003; Chaney et al., 2004; Staring et al., 2010). Finally, eight articles were excluded because the incentives were included as part of a treatment package and the effects of the incentives were not isolated (Rapoff et al., 1998; Morisky et al., 2001; Molassiotis et al., 2003; Javanbahkt et al., 2006; Nunes et al., 2006; Kirby et al., 2008; Penica and Williams, 2008; Hser et al., 2011). After independent review, final decisions on discrepant conclusions (two of 48 articles) were reached by mutual agreement after brief discussion. The literature search yielded 13 manuscripts, a review of the reference sections of these manuscripts and of medication adherence review papers found during the literature search was conducted by the first author and yielded an additional five manuscripts. With the inclusion of one hand-picked article (DeFulio et al., 2012), a final list of 19 titles to be included in the present review was created. In reviewing the results of the included articles, the use of the term “significant” indicates that $P \leq .05$. Data reported here were selected on the basis of priority given to the data by the original authors, with consideration given to consistency of presentation across articles in this review. Table 1 summarizes the methods and results of the studies that were included in the review.

Results

Naltrexone

Naltrexone is an opiate antagonist that blocks the physiological and reinforcing of opioids (Martin et al., 1973; Mello et al., 1981), and its lack of abuse potential and overall safety (Schecter et al., 1974) make it pharmacologically ideal for the treatment of opioid dependence. However, adherence to naltrexone has been very poor and as a result it is rarely prescribed (Kosten and Kleber, 1984).

Naltrexone pharmacotherapy for opioid dependence may be an especially difficult target for adherence interventions. Induction onto naltrexone is difficult because the patient must first be completely detoxified. Insufficient opioid detoxification can lead to precipitation of withdrawal symptoms. In all of the studies reported below, the participants were opiate dependent adults who had already completed detoxification, and thus focus on naltrexone maintenance. Even during maintenance, naltrexone pharmacotherapy is distinct from most other chronic medication regimens in that opioid blockade is likely to be undesirable to patients. Side effects may disrupt adherence to some medications, but primary effects typically do not. For example, patients are unlikely to stop taking asthma medication because they wish to avoid breathing, and when a patient fails to adhere to their statin prescription no one seriously entertains the idea that it is because the inhibition of HMG-CoA reductase is unappealing. Naltrexone’s blockade of the reinforcing effects of opiates is

fundamental to its therapeutic potential but may present a special challenge for adherence interventions; patients may actively avoid naltrexone because the loss of reinforcement is aversive (Kaufman and Baron, 1968).

Incentive-based interventions designed to address the problem of naltrexone adherence are especially well studied. This is likely a direct function of the rich lineage of operant research in drug abuse treatment (Silverman, 2004). The first recommendation to develop contingencies of reinforcement to promote naltrexone self-administration was made in the earliest stages of clinical testing (Meyer et al., 1975), and the first attempt to do so followed shortly thereafter (Meyer et al., 1976).

The first peer reviewed evaluation of an incentive-based intervention for naltrexone adherence involved nine patients who selected naltrexone from a range of available treatments for opiate use, and who completed induction and were stabilized on the medication (Grabowski et al., 1979). Patients were required to attend the clinic and ingest naltrexone in order to qualify for the payments. Planned payments equaled $10.05 per week and $3.35 per visit. Patients receiving the intervention were substantially more likely to be retained through one month of treatment than the previous 126 patients who received naltrexone but no incentives at the same clinic (89% and 60% retained, respectively). By the fourth study month 44% of the adherence incentive patients were retained in naltrexone treatment, compared to less than 10% of the patients who did not receive incentives. These differences were not evaluated for statistical significance. The authors concluded that monetary reinforcement may increase the duration of naltrexone adherence and that regular ingestion of naltrexone occurred whenever it was required by the contingency.

Interest in incentives for naltrexone adherence resumed in the late 1990s with the publication of a controlled trial of incentives in which participants were randomly assigned to one of three study groups (n = 57; Preston et al., 1999). In the contingent group, participants received monetary vouchers contingent upon oral naltrexone ingestion. The voucher intervention was modeled after the “escalating schedule” developed by Higgins et al. (1991) for the treatment of cocaine dependence.[1] In a yoked non-contingent control group, participants were matched to a participant in the contingency group and received vouchers whenever that participant received vouchers, independent of their own naltrexone consumption. In the no voucher group no incentives were available. All participants received free naltrexone and weekly counseling. Contingent group participants could earn up to $1155 for total adherence over 12 weeks, with thrice weekly naltrexone consumption required under observation. Contingency participants consumed a significantly greater number of doses on average [21.4 (59%)] compared to the non-contingent voucher group [11.3 (31%)] and the usual care control group [4.4 (12%)]. The groups were not significantly different with respect to opiate use, though the contingent group showed the highest overall rate of opiate-negative urine samples.

Carroll et al. (2001) described a similar randomized controlled trial of an incentive-based intervention for naltrexone adherence (n = 127). Participants were randomly assigned to usual care, incentives, or incentives plus significant other involvement. This study differed importantly from the Preston et al. (1999) study in two respects. First, participants in the incentives groups were paid separately for naltrexone adherence (confirmed by direct observation of pill consumption) and drug abstinence (confirmed by urinalysis) according to independent escalating schedules. Second, the value of incentives available for naltrexone

[1]In escalating schedules, the monetary value of the vouchers starts at a base value, and is increased after each incentive delivery up to a maximum value. Importantly, the incentive value is reset to the base level if the participant fails to meet the criteria for earning an incentive. In addition, bonus vouchers are provided for meeting the criteria on three consecutive opportunities.

adherence was substantially lower. Perfect naltrexone adherence and drug abstinence resulted in $561 in items over 12 weeks. Statistics in this study were conducted on the basis of contrasts between intervention elements rather than direct group comparisons, and show that the incentives did not produce a significant effect on naltrexone adherence. However, participants who received incentives submitted a significantly greater number of drug-free urine samples compared to usual care.

Carroll et al. (2002) reported a three-group randomized controlled trial of incentives for naltrexone adherence in that included usual care, and low- and high-magnitude incentive groups (n = 55). Participants in the incentive groups were paid separately and independently for naltrexone adherence and drug abstinence. Participants in low-magnitude group could receive up to $561, and participants in the high-magnitude group could receive up to $1,152, for perfect adherence to naltrexone and total drug abstinence over 12 weeks. The mean number of naltrexone doses consumed and the number of drug free urine samples submitted did not differ in comparisons between participants who did and did not receive incentives, or between participants who received high- versus low-magnitude incentives. However, there was a significant time x incentives interaction in self-reported days of opiate use per month, indicating that participants who received incentives improved more over time. The authors conclude that the lack of any significant findings based on magnitude of incentives suggests, “no relative value of higher- over lower-value incentives in this population.” However, given the relatively narrow range of incentive values explored in this study, and the brief duration of the intervention, this conclusion seems premature.

More recently, naltrexone for extended-release injectable suspensions (XR-NTX) have been developed to reduce the frequency of dosing and improve adherence (Comer et al., 2007). However, the motivational issues inherent in antagonist treatments for drug abuse, and the previous studies of incentives for oral naltrexone adherence, suggest that an incentive intervention may be useful in promoting long-term adherence to XR-NTX. Everly et al. (2011; n = 35) and DeFulio et al., (2012; n = 38) describe randomized controlled trials of an incentive-based intervention designed to promote long-term XR-NTX adherence. The intervention investigated in both studies was employment-based reinforcement. Under employment-based reinforcement interventions, the opportunity to work to earn wages is the incentive. This arrangement facilitates the use of high-value incentives, may enhance the feasibility and acceptability of incentives, and may be ideal for the delivery of long-term intervention (Silverman, 2004). The primary difference between the two studies was that each study featured a different formulation of XR-NTX. The formulation of XR-NTX used in Everly et al. study had a three-week inter-dose interval (Depotrex®), and the formulation of XR-NTX used in the DeFulio et al. study had a four-week inter-dose interval (Vivtrol®). Each study featured a two group design in which the contingency group received paid job training (~$10 per hour, for up to 20 hours per week) contingent upon acceptance of XR-NTX doses and the prescription group received the same training and payments independent of their acceptance of XR-NTX. All participants in both studies were offered a six-dose course of XR-NTX at no cost. In both studies the contingency group accepted a significantly higher proportion of doses than the prescription group (see Table 1), and a significantly higher proportion of contingency participants completed the entire six-dose course of medication (e.g., 74% versus 26% in DeFulio et al.). Opiate abstinence was not significantly different between the groups in either study, but a greater proportion of urine samples submitted by the contingency group were opiate negative in both studies (see Table 1).

Taken together, the naltrexone studies illustrate the potential for incentive interventions to promote medication adherence under especially unfavorable conditions, including a refractory patient population that is likely to have ongoing problems with drug use, and a medication for which the primary effect is undesirable to many patients. It is also

noteworthy that the simplified and less frequent dosing offered by XR-NTX relative to oral naltrexone appears insufficient to maintain long-term adherence to the medication, and that an incentive-based intervention can greatly improve adherence to a long-acting medication.

Disulfiram

Disulfiram is a medication used in the treatment of alcohol dependence that makes the adherent patient physically sick (e.g., nausea and headache) upon consumption of alcohol by interfering with the enzymes that are essential to the second stage of the metabolization of alcohol. Like naltrexone, the primary effect of disulfiram is unattractive to its intended patient population, and poor adherence has severely curtailed its clinical utility. Liebson et al. describe two studies in which methadone was used as an incentive for disulfiram adherence in methadone patients who were experiencing severe problem drinking that was interfering with their participation in methadone treatment. The first of these studies (Liebson et al. 1973) included six methadone patients who were abusing alcohol. After 14 days of stabilization on disulfiram, participants were randomly assigned to receive methadone contingent upon disulfiram adherence or independent of whether they took disulfiram. All participants received disulfiram at no cost. No adherence data were presented, but the contingent-methadone participants had substantially and significantly fewer drinking days than their non-contingent counterparts. In all cases, participants had a lower percentage of drinking days under the contingent condition relative to the non-contingent condition (see Table 1). The follow-up report (Leibson et al., 1978) was very similar, but included 25 participants. This study showed similar results (see Table 1) and also reported that the disulfiram contingency reduced arrest rates in addition to reducing drinking days. Similar to the studies of naltrexone compliance, these disulfiram studies indicate that incentives can be effective in enhancing medication adherence to a medication that has minimal clinical impact due to notoriously poor adherence that is likely a result of its undesirable effects in the patient.

Antiretroviral Medication

Adherence interventions are especially important in the treatment of human immunodeficiency virus (HIV), because a high level of adherence to antiretroviral medication is required to maintain virologic suppression (Pham, 2009). All of the studies we found that specifically evaluate the role of incentives in antiretroviral adherence have been conducted in HIV patients with co-occurring substance abuse disorders, possibly due to the aforementioned rich operant research tradition among substance abuse treatment researchers. There is at least one randomized controlled trial of incentives as part of a medication adherence intervention for a general population of HIV patients, but that study did not specifically evaluate the role of incentives (Javanbakht et al., 2006).

Rigsby et al. (2000) describe a pilot study in which an incentive-based antiretroviral adherence intervention was administered to VA patients. Participants were on stable anti-retroviral treatment for HIV, and 80% had histories of drug use. Participants were randomized to usual care, cue-dose training (i.e., teaching patients to link medication-taking with other activities that they do every day), or cue-dose training plus incentives. At the time that this study was conducted, many HIV patients were required to take a variety of separate pills as part of their antiretroviral regimen. In order to simplify the incentive intervention, one medication (zidovudine) served as the target for the intervention, and as the cue in the cue dose training. Medication adherence was measured with MEMS caps (electronic pill bottle caps that record and time stamp bottle openings). The MEMS caps results were occasionally corroborated with blood tests for zidovudine. Participants earned incentives under an escalating schedule. Earnings were delivered on a weekly basis for four weeks, and a total of $280 could be earned for perfect adherence. Viral loads were measured at baseline

and at 8-weeks post-intervention. During the incentive period participants in the cue-dose training plus incentive group were significantly more likely to adhere to the medication than controls, and adherence in the cue-dose training alone group was not significantly different from controls. No statistical comparisons between the cue-dose training plus incentive group and the cue-dose training alone group were presented. There were no differences in viral loads across groups at any time point, and differences in adherence rates did not persist after the intervention was withdrawn.

Rosen et al. (2007) reported the full-scale randomized trial that followed the pilot study by Rigby et al (2000). Fifty-six HIV+ adults with histories of drug use who were prescribed antiretroviral medication but who took less than 80% of prescribed doses during a 4-week baseline period were randomly assigned to receive counseling or counseling plus incentives for antiretroviral adherence for 16 weeks. All participants were followed for an additional 16 weeks thereafter. The incentive intervention was prize-based (i.e., incentives of differing value were delivered based on a lottery drawing; see Petry et al., 2000) and participants could earn up to an average of $800 in prizes. Adherence was measured by MEMS caps. During the intervention, the incentive group participants were significantly more likely to adhere to their medication than controls, and the incentive group had a significantly higher proportion of patients who viral load below the assay sensitivity threshold (i.e., <400 HIV-RNA/mL) (see Table 1). These effects were not maintained during the 16-week follow up period.

Finally, there has also been a randomized controlled trial of incentives for antiretroviral adherence in methadone patients (n = 66) (Sorensen et al., 2007; and see Barnett et al., 2009 for an analysis of the cost effectiveness of the intervention). After a 4-week baseline, participants were randomly assigned to an incentive group or a control group, both of which received medication coaching. The incentive intervention in this study featured up to $1172 in vouchers according to an escalating schedule over 12 weeks for antiretroviral adherence as measured by MEMS caps. During the baseline period, group mean percentage of doses taken was similar for the two groups (50% in the incentives group; 52% in the control group). During the incentives intervention, participants in the incentives group took a significantly greater percentage of their doses of antiretroviral medication than the control group (see Table 1). There were no differences in viral load or associated health measures at any point in the study (see Table 1) and no difference in antiretroviral adherence during follow-up.

Overall, incentives show substantial promise in the area of antiretroviral adherence, but the interventions tested to date have not shown an effect on viral load and suggest that long-term intervention may be required to produce lasting increases in adherence, at least in HIV+ adults with a history of substance abuse. Future studies should be directed toward enhancing the effect on viral load, supporting long-term antiretroviral adherence, and targeting a broader sample of HIV+ adults.

Latent Tuberculosis Infection Medication (e.g. Isoniazid)

Isoniazid is a front line treatment for latent tuberculosis, and must be taken for at least six months and preferably nine months to achieve maximum benefit (American Thoracic Society, 2000). In two early uncontrolled studies that included an isoniazid adherence intervention for methadone patients, daily doses of methadone were contingent upon isoniazid consumption. In the first of these reports, 9 of 11 participants were 100% adherent to their isoniazid treatment, (Elk et al., 1993), and in the second report, the overall isoniazid adherence rate was 97.6% (Elk et al., 1995). The first controlled trial of isoniazid adherence included a general population of homeless adults who were prescribed isoniazid (n = 118) (Tulsky et al., 2000). In this study, participants were randomly assigned to receive usual care

at the TB clinic, directly observed treatment by a peer health advisor, or directly observed treatment with a $5 incentive for each of two planned instances of isoniazid consumption each week. The peer health advisor group and the usual care group were not different on any adherence measure. The incentives group were retained isoniazid treatment significantly longer on average (five months) compared to the peer health advisor group (two months) and the usual care group (two months). Isoniazid treatment completion was also significantly higher, with 44% of incentive group participants completing treatment, compared to 19% of the peer health advisor group and 26% of the usual care group (see table). Overall, the very low cost incentive intervention used in this study produced moderate gains in isoniazid adherence in homeless adults.

Cass et al. (2005) reported a retrospective study (n = 841) of a low-cost intervention designed to enhance adherence to isoniazid in children receiving treatment for latent TB at a public clinic. At their first visit to the clinic, children were given a prescription to a 1-month supply of isoniazid to be taken daily, a calendar of the upcoming month, and a set of stickers (one for each day). Children who returned the following month with a calendar that had one sticker affixed for each day were allowed to select a small toy from a “Treasure Chest.” Treatment was recommended for nine months, but considered complete after six months. Treatment completion was significantly higher (see Table 1) when the incentive intervention was in place (91.6%) compared to when the clinic did not offer incentives (82.3%). Another study of low-cost incentives for adherence to TB medication was conducted in Timor-Leste (Martins et al., 2009). Participants were randomly assigned to receive usual care at clinics that used directly observed treatment methods to deliver medications (including isoniazid) to patients with latent TB, or to receive usual care plus food incentives over an eight month study period. This intervention did not affect any adherence or treatment completion measure, with 93% adherence in both study groups.

Overall, the studies on incentive-based interventions for isoniazid adherence involve low-value incentives for vulnerable populations. Given the finite nature of treatment for latent tuberculosis, the low cost of the interventions, and the importance of latent tuberculosis as a public health problem, it seems likely that incentive-based medication adherence interventions could be easily adopted and become part of the normal practice in the treatment of latent tuberculosis, especially in clinics where services are tailored to the needs of low-income populations.

Individual Studies on Other Medications

Hypertension Medication—Dapcich-Miura and Hovell (1979) conducted a combination multiple-baseline and reversal single-subject design study of incentives for medication adherence in a hypertensive elderly man with angina. The participant was non-adherent with three prescribed medications and other medical recommendations. An incentive-based intervention that included precise descriptions of specific behaviors and detailed instructions was implemented first for exercising, then for orange juice drinking, and finally for medication adherence. The incentives for medication adherence were subsequently withdrawn then reinstated. Relatives monitored medication adherence by counting the pills or directly observing medication consumption. When the complete intervention was in place, the participant earned up to three tokens per day, one for successful completion of each of the three targets. The participant could select the menu of the following night’s dinner at a cost of five tokens, or have a weekend dinner at the restaurant of his choosing at a cost of 25 tokens. All targeted behaviors improved substantially as a result of the incentive intervention as evidenced by visual inspection of the adherence data. The results of the reversal and reinstatement of the contingency for medication adherence indicated clear control of medication adherence by the token incentive intervention.

Warfarin—Volpp et al., (2008) describe two pilot studies (n = 10 in each study) of an incentive-based intervention designed to improve adherence to warfarin, an anticoagulant medication that is prescribed to patients who have medical conditions that increase the risk of thromboembolism. This medication is typically prescribed for chronic, long-term administration. Participants in these studies were recruited from a specialty outpatient clinic. The intervention used in these studies featured a lottery system in which participants were assigned a particular number for the three month duration of the study. Drawings occurred every day, and those participants whose numbers matched the drawn number were eligible for a cash prize if they had opened their pill bottle at the correct times on that day, as measured by MEMS caps. After a draw, participants whose number was drawn were informed of the result independent of whether they qualified for the cash prize. The two studies differed only in the probability of winning the $10 prize. The probability of winning $10 was 0.4 in one study and 0.2 in the other study, and the probability of winning $100 was 0.01 in both studies. Primary outcomes were percent of days of adherence to the prescribed warfarin regimen, as measured by MEMS caps, and proportion of blood coagulation tests that were out of therapeutic range. No statistical tests were reported, because the studies were not scaled to achieve significance. However, both studies showed that participants were, on average, more adherent to their medication, and had fewer blood tests out of range during the intervention relative to historical comparisons.

Nicotine Gum—Nicotine replacement therapy can effectively promote smoking cessation, but compliance rates reported in medication trials range from 16% to 55%, suggesting that non-adherence could be compromising the effectiveness of this pharmacotherapy. Mooney et al. (2005) described a three-group randomized controlled trial in which smokers who were prescribed nicotine gum received the standard treatment, the standard treatment plus brief feedback, or the standard treatment plus brief feedback and contingency management. Participants in the former two conditions were paid $70 on the 15th day of the intervention if they had attended required sessions and refrained from smoking as confirmed by breath and urine samples on the 7th and 15th day of the intervention. In the contingency management condition, participants had the additional requirement of chewing at least 12 pieces of nicotine gum on at least 10 of 15 intervention days as verified by self-reports in a daily nicotine gum consumption diary. Participants in the contingency management group were compliant a significantly greater percentage of days (66%) of days than the feedback group (25%) or standard treatment group (14%). However, no differences were obtained between any study groups with respect to smoking status as measured by point prevalence one week after the end of treatment. Thus, similar to studies on naltrexone, incentives can effectively increase adherence to nicotine replacement therapy, but this does not appear to translate to higher rates of smoking cessation.

Discussion

Incentive-based medication adherence interventions are promising but understudied. Studies that are well controlled or that feature large sample sizes are rare and no single study offers both of these features. Overall, the studies that include at least moderate value incentives (i.e., >$100/month) suggest that incentives confer substantial benefit in increasing medication adherence. In studies where the base rate adherence was moderate (e.g., Sorenson et al., 2007), incentives increased adherence by at least 20 percentage points. In studies where the base rate adherence was low (e.g., DeFulio et al. 2012), incentives increased adherence by at least 30 percentage points. Even low-value incentive interventions can be effective under some circumstances (e.g., Tulsky et al., 2000).

In addition to the need for more and higher-quality evaluations of the effectiveness of these interventions, there is also a need to determine the conditions under which these

interventions are most effective. Carroll et al., (2002) is the only controlled attempt to evaluate the relationship between a parameter of these interventions and their effectiveness. This lone study evaluated only a narrow range of the incentive value (i.e., reinforcement magnitude) parameter, and showed no effect of incentive value. Much more work remains in determining how incentive value relates to intervention effectiveness across a variety of patient populations, and this is just one of many potentially important variables that merit investigation.

Even the most effective intervention is of limited utility unless it can be delivered to a large number of people who would benefit from it. Incentive researchers in the operant tradition have generally prioritized effectiveness but do not ignore scalability. Other groups may reverse these priorities. Diversity in the balance between effectiveness and scalability across research teams working on the problem of medication adherence is most certainly a good thing. Nevertheless, extreme movement toward one end or the other is unlikely to yield useful results. Providing $500 per day contingent upon adherence to a medication might produce very high rates of adherence, but such an arrangement is unlikely to be economically feasible. Similarly, we may easily deliver gold star stickers to thousands of adults contingent upon their medication adherence, but this arrangement would be unlikely to maintain their behavior.

It is important, whatever our approach, to create interventions that can be maintained over the long term. Medication adherence is of greatest concern when the medication is prescribed for a chronic disease or condition (WHO, 2003). Five studies in the current review evaluated medication adherence after the incentive intervention was discontinued (see Table 1), and all showed that the effects of the interventions dissipated after the incentives were discontinued. Thus, similar to medication for a chronic condition that is only effective when taken consistently, incentive-based medication adherence interventions will probably need to be maintained in order for their effects to be sustained over time. The high cost of non-adherence and the absence of effective alternatives suggest that incentive-based medication adherence interventions that are integrated into the normal delivery of pharmacotherapy for chronic conditions may be cost-effective under a variety of circumstances. Identifying such circumstances is of critical importance to the dissemination of these interventions, and thus should be a focus of future research.

Note that some of the interventions presented here could be construed as failures (e.g., Carroll et al., 2002; Martins et al., 2009). In the face of such failures it is important to remember that the theoretical and empirical basis for these interventions includes much more than the few studies presented here. Decades of research on every aspect of operant psychology is relevant to incentive-based medication adherence interventions. The well demonstrated generality of behavioral processes suggests that if an intervention fails then the safest and most productive assumption is that it was a design failure. Design failures do not demarcate the scope of applicability of incentives for medication adherence to particular populations or settings. Interpreting a failure as a signal to abandon the use of incentives rather than as an opportunity to improve our designs could seriously jeopardize the development of effective medication adherence interventions (see Baer et al.1987 pp 17–21 for a thorough discussion of this point). The road to technological achievements of all kinds is littered with failures, and there is no reason to suspect that the development of behavioral interventions would be any different. Be that as it may, the studies reviewed here provide a solid basis for the view that incentive-based medication adherence interventions have a bright future.

Conclusions

Incentive-based medication adherence interventions can effectively promote medication adherence under a variety of conditions. A significant challenge for research in this area is the development of sustainable and cost-effective long-term interventions.

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HIGHLIGHTS

- Incentives for medication adherence are promising but understudied.
- Available evidence suggests these interventions can be very effective.
- Sustainability and scalability are key challenges for future interventions.

Table 1

Summary of reviewed manuscripts.

Drug	Source	Study N	Population	Study Duration	Dosing regimen	Study Design	Incentives and maximum possible total value	Primary Adherence Outcome	Adherence Outcome Value Incentive v. Control	Incentive v. Control Adherence P < .05 (Y/N)	Secondary Outcome	Secondary Outcome Value Incentive v. Control	Incentive v. Control Secondary P < .05 (Y/N)
Oral Naltrexone for Opioid Dependence	Grabowski et. al (1979)	9	Treatment seekers who chose naltrexone	4 months	3 times per week	Incentives v. Historical comparison	$3.35 per dose, $174.20 total	Retained through month 4 (Y/N)	44% v 10%	NR	-	-	-
	Preston et al. (1999)	57	Post-detox treatment seekers	12 weeks	3 times per week	RCT, contingent v. non-contingent	Escalating vouchers $1155 total	# doses taken	21.4 v 11.3	Y	% of opiate free urine samples	86% v 73%	N
	Carroll et al. (2001)	127	Post-detox treatment seekers	12 weeks	3 times per week	RCT, incentives v. usual care[a]	Escalating independent vouchers for adherence & drug abstinence $561 total	# doses taken	17.8 v 14.2	N[b]	# of drug free urine samples	13.6 v 8.9	Y[b]
	Carroll et al. (2002)	55	Post-detox treatment seekers	12 weeks	3 times per week	RCT, incentives v. usual care [c]	As in Carroll et al. (2001), with $561 or $1152 total	# doses taken	22.4 v 14.4	N[b]	# of drug free urine samples	18.8 v 11.0	N[b]
Injectable Naltrexone for Opioid Dependence	Everly et al. (2011)	35	Post-detox treatment seekers	18 weeks	Once every 3 weeks; nurse administered	RCT, contingent v. non-contingent	Access to paid job training (~ $10/hr, 20 hrs/ week), $3600 total	% injections accepted	80.6% v 42.2%	Y	% of opiate free urine samples	74% v 62%	N
	DeFulio et al. (2012)	38	Post-detox treatment seekers	24 weeks	Once every 4 weeks; nurse administered	RCT, contingent v. non-contingent	Access to paid job training (~ $10/hr, 20 hrs/ week), $4800 total	% injections accepted	86.6% v 51.8%	Y	% of opiate free urine samples	72% v 65%	N
Disulfiram for Alcohol Dependence	Leibson et al. (1973)	6	Methadone patients addicted to alcohol	Variable, mean 107 days	Daily	Crossover	Methadone	-	-	-	% of days drinking	1% v 17%	Y
	Leibson et al. (1978)	25	Male Methadone patients addicted to alcohol	6 months	Daily	RCT, contingent v. non-contingent	Methadone	-	-	-	% of days drinking	2% v 21%	Y
Antiretrovirals for HIV	Rigsby et al. (2000)[d]	55	HIV positive VA patients	4 weeks	Variable, but at least daily	Pilot RCT Cue training & Incentives v. Cue training[e]	Escalating cash from $2 to $10 per dose, $280 total	On-time MEMS cap openings	90% v 73%[f]	NR	Change in viral load	0.64 log increase v. 0.29 log decrease	NR
	Rosen et al. (2007) [d]	56	Non-adherent HIV patients with history of drug use	16 weeks	Variable, but at least daily	Incentives & counseling v. counseling only	Prize-based raffle, $800 average total	On-time MEMS cap openings	76% v. 44%	Y	% w/viral loads <400 ng/ml	72% v. 48%	N
	Sorensen et al. (2007) [d]	66	HIV positive methadone patients	12 weeks	Twice daily	Medication coaching & incentives v. medication coaching only	Escalating vouchers, $1172.40 total	On-time MEMS cap openings	78% v. 56%	Y	Mean HIV- 1 RNA levels [median levels]	6880 v. 5550 [0 v. 0]	N
Isoniazid for Latent Tuberculosis	Elk et al. (1993)	Two studies, 11total	Methadone treatment applicants	24 weeks	Daily	Uncontrolled demonstration	Methadone	% adherence (nurse observed)	97.2%[g]	-	-	-	-
	Elk et al. (1995)	5	Methadone treatment applicants	Determined by prescription	Daily	Uncontrolled demonstration	Methadone	% adherence (nurse observed)	97.6%	-	-	-	-

Drug	Source	Study N	Population	Study Duration	Dosing regimen	Study Design	Incentives and maximum possible total value	Primary Adherence Outcome	Adherence Outcome Value Incentive v. Control	Incentive v. Control Adherence P < .05 (Y/N)	Secondary Outcome	Secondary Outcome Value Incentive v. Control	Incentive v. Control Secondary P < .05 (Y/N)
	Tulsky et al. (2000)	118	Homeless adults	6 months	Twice weekly	RCT, incentives v. usual care	$5 per dose, $260 total	Treatment completion	44% v. 26%	Y	-	-	-
	Cass et al. (2005)	841	Children at a public health clinic	9 months	Daily, adherence evaluated monthly	Incentives v. Retrospective comparison	One small toy per evaluation	Treatment completion (6 months)	91.6% v. 82.3%	Y	-	-	-
	Martins et al. (2009)	270	Adults in Timor-Leste	Two phases, 8 & 24 weeks, respectively	Daily in Phase 1; fortnightly in Phase 2	RCT, incentives v. usual care	One adult sized meal per scheduled dose	Treatment completion	76% v 78%	N	Weight gain (Y/N)	10.1% v 7.5%	Y
Hypertension medication	Dapcich-Miura & Hovell (1979)[d]	1	82-yr old retiree	35 days	Three different medications, each thrice daily	Multiple baseline across behaviors and reversal	Tokens exchangeable for meal selection	Pills consumed per day	8.5 v. 4.1[f]	-	Exercise (walks per day)	2.4 v. 0.1[f]	-
Warfarin for anti-coagulation	Volpp et al. (2008)[d]	Two studies, 20 total (10 in each)	Adults with home phones	3 months	Varied by prescription, evaluated daily	Pilot comparisons w/historic means	Cash lottery; $450 avg in study 1; $270 avg in study 2	% incorrect doses	2.3% (Study 1) 1.6%, (Study 2) v. 22.0%	NR	Coagulation tests out of range	12.2% v. 35% (study 1) ; 40.4% v 65% (study 2)	NR
Nicotine Gum for Smoking Cessation	Mooney et al. (2005)	97	Adult smokers	15 weeks	At least 12 times per day	RCT, incentives, feedback, and standard treatment	$70	% days adherent	66% v. 25%	Y	Smoking status at one week post-intervention	24% v. 23%	N

RCT = randomized controlled trial, NR = the relevant statistical analysis was not reported.

[a] three group design, only usual care and incentives group data are shown, incentives plus significant other involvement group excluded.

[b] the statistical tests included data not represented in the value columns, see original manuscript for full explanation.

[c] three group design, only usual care and low-magnitude incentives are shown, high-magnitude incentives group excluded.

[d] study included assessment of post-intervention adherence.

[e] three group design, only values from cue training and cue training plus incentives groups are shown, usual care group excluded.

[f] values calculated from figure.

[g] group value calculated from reported individual values and figure, two studies combined.