Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity

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Objective: Therapeutic approaches for benzodiazepine (BZD) dependence in patients in methadone maintenance treatment (MMT) have met with limited success.
Clonazepam detoxification (CDTX) and clonazepam maintenance treatment (CMT) were compared in an open, clinical naturalistic study on such patients.
Methods: Benzodiazepine dependent patients substituted their BZD of abuse for clonazepam and were then either detoxified (CDTX) or a maintenance dose was reached and maintained (CMT). Patients were considered as failing the trial if they either abused BZDs (CDTX group) or abused BZDs over the maintenance dose (CMT group). Treatment outcome was evaluated based upon self and staff reports over 1 year after beginning treatment. Axis I and II psychiatric diagnosis was assessed and methadone dosage and history of abuse was recorded.
Results: In the CDTX group, 9/33 (27.3%), were BZD-free after 2 months. In the CMT group, 26/33 (78.8%) refrained from abusing additional BZDs over the maintenance dose after 2 months. The same success rate remained over the entire year. Survival analysis showed CMT to be more successful than the CDTX. Axis I psychiatric comorbidity was found to be positively related to treatment success in the CMT group while axis II antisocial personality disorder was found to be negatively related to treatment success in that group. It had no impact in the CDTX group.
Conclusions: Maintenance strategy with clonazepam is a useful BZD treatment modality for BZD-dependent MMT patients with a long-term history of abuse and previous attempts at detoxification. Psychiatric comorbidity may have an important role in choosing the adequate treatment modality and influencing treatment outcome.
Key words: benzodiazepine abuse, benzodiazepine dependence, detoxification, methadone dosage, methadone maintenance, psychiatric comorbidity.

Australian and New Zealand Journal of Psychiatry 2003; 37:458–463

Benzodiazepine (BZD) dependence in the heroin-abusing population and in patients undergoing methadone maintenance treatment (MMT) has been found to be endemic worldwide, with lifetime prevalence ranging from 61–94% and current prevalence ranging from 10.5–70.4% of patients declaring the use of BZDs [1–4].

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Received 24 April 2002; revised 3 April 2003; accepted 14 April 2003.

In heroin addicts, it has been observed to exacerbate already dominant vocational, criminal, psychological and medical problems [5–7]. Limited research has been done on treatment modalities for BZD dependence and even less on BZD-dependence treatment in heroin addicts or MMT patients. Most investigations have centred on the tapered detoxification of BZD with [8] or without [9] substitution by a barbiturate (e.g. phenobarbitol) or a long-acting BZD (e.g. diazepam [10] or clonazepam [11–13]), and they reported essentially limited efficacy of these approaches [9,10]. Significantly, few study designs included any adequate follow-up after the completion of the detoxification process [8,10], and most lacked reliable and repeated measures to determine whether or not patients remained BZD free [14]. Furthermore most studies lacked a standardized approach to psychiatric diagnosis and did not investigate the influence of axis I and II diagnoses upon treatment outcomes.

In their report describing the limited efficacy of BZD detoxification and the dangers associated with it, Joughin *et al*. [9] suggested using a maintenance approach for long-term BZD-dependent individuals.

Prolonged use of BZD agents often raise objections of physicians due to the fear of tolerance and various side-effects. However, in the case of severely dependent BZD abusers with previous attempts at detoxification and a history of polydrug abuse, the rationale of a maintenance approach for BZD is sound. It is based partly upon the success of methadone maintenance as an ongoing pharmacotherapy for heroin dependence and the fact that there are many reports of patients maintained on BZDs for years with apparent benefit, with minimal development of tolerance or side-effects [15].

Clonazepam is a highly potent long-acting BZD. At the time of this study Clonazepam is not a street drug in Israel and none of our patients abuse it [1]. Three studies [11–13] showed it to be an effective agent for BZD substitution, enabling the gradual detoxification from alprazolam in patients with anxiety disorders. In the present open clinical study, we compared two pharmacological modalities, clonazepam detoxification (CDTX) and clonazepam maintenance (CMT), for treating long-term BZD dependence in MMT patients. Based upon a preliminary study we conducted earlier on clonazepam maintenance [16], we anticipated a better outcome for CMT over CDTX. We also studied the possible relationship between methadone dose, drug abuse history, psychiatric comorbidity (axis I and II) and treatment success in both protocols.

Method

Setting: Patients in an Israeli MMT clinic, situated within the campus of a major general hospital in the centre of Tel Aviv. The policy of the clinic is to use adequate doses of methadone pharmacotherapy (we have no legal upper-limit constraints), combined with a multidisciplinary approach (i.e. nurses, social workers, psychologists, psychiatrists and a generalist) participated in this study which was approved by the institutional ethics committee.

The Adelson Clinic for Drug Abuse Treatment and Research is a 200–220 patient clinic, giving patients daily methadone dosages. Take-home practices (except for Fridays and Saturdays when the clinic is closed) are flexibly given to patients based upon their not abusing any illegal drug, working status, general improvement in therapy and physical condition (whether a patient is fit to come daily to the clinic). The use of benzodiazepines limits strongly the number of take-homes that can be received. The general orientation of the clinic is non-punitive and has reaching-out practices. Each patient meets a nurse at the methadone (as well as other medication) dispensing point who checks upon the general well-being of the patient as well as for signs of sedation, intoxication and craving by having an 'informal' talk with him/her. The patient also receives weekly therapy sessions, and may ask for an appointment with any of the doctors present, which will be accommodated, based upon availability, either immediately or within a few days.

During a 3-year period, 80 patients were identified as currently abusing BZDs as well as having a DSM-IV defined long-term dependency (of at least 3 years) on large doses of BZDs, with multiple attempts at abstinence. The first diagnosis of BZD dependency was based upon self-report, staff report and twice weekly randomly taken and observed urine samples and confirmed by a psychiatrist interview using the DSM-IV SCID interview module for benzodiazepine dependence. Over 3 years, the clinic psychiatrist offered these patients a choice of two treatments for their BZD problem. Fourteen patients declined, while 66 patients agreed to receive treatment and were then given the choice of either clonazepam detoxification (CDTX) or clonazepam maintenance (CMT). The procedures for each treatment mode were explained in detail to the patients who gave written informed consent to participate in this study. They were told that they would be kept in treatment for BZD abuse until they decided it was too difficult and wished to stop or, if they preferred, they could switch to the alternative mode of treatment (with the psychiatrist's consent). They were also told that there would be no repercussions on their MMT should they decide to stop this treatment for BZD dependence.

During the 3-year study period, 33 patients formed the CDTX group and 33 patients comprised the CMT group. They were all started on a regimen of clonazepam 6 mg/daily for 2 weeks and then either underwent a gradual detoxification with an individual tapering schedule of approximately 6 weeks until no clonazepam was used (for the CDTX group), or a gradual tapering until an individual maintenance dose was achieved (for the CMT group). This maintenance dose was the lowest level at which the patient found the BZD dose to be adequate in terms of being free of symptoms of BZD craving or overdose. The process of adapting a maintenance dose was an ongoing one, and it could take a patient 4–8 weeks before reaching stabilization. Clonazepam was provided under supervision and ingested daily under supervision (except on Fridays and Saturdays).

The clinic's preference was a standard protocol of a fixed start of 6 mg clonazepam daily: this is slightly less than the average maximal daily dose taken by our patients but it was our impression that it would supply the BZD needs of the great majority of our patients.

The patients were asked to identify what were the various BZD pills ingested and the maximum daily use during the preceding month.

Maximum daily use of BZD was then calculated in equivalents of mg clonazepam.

Based upon twice-weekly random and observed urine tests a composite measure of the number of different additional drugs of abuse (ADA) in current use was recorded. This assessment included the concomitant use of alcohol, cocaine, amphetamines and cannabis but did not include the use of heroin, as we only wanted to assess the use of secondary drugs of abuse. The number of additional drugs used was summed.

The maximal daily methadone dose during the study period was recorded and a Hebrew adaptation of the Addiction Severity Index (ASI) was administered in order to assess severity of abuse [17].

Before entering either CMT or CDTX, patients were administered the SCID I and SCID II psychiatric interviews. The Structural Clinical Interviews for DSM-IV axis I provides information for making lifetime and current diagnoses for many conditions, including those common in substance use disorders such as mood disorders, anxiety disorders and psychotic disorders. The SCID II provides information for making axis II personality disorders diagnoses. Studies have shown good retest reliability [18,19]. Both interviews take about 1–2 h and have been administered either by a trained psychiatrist or psychologist. The statistical analysis as to the relationship between psychiatric comorbidity and treatment outcome was performed for the 2 months treatment period only.

This was an open study. If patients opted for another treatment mode, only the results of the first treatment mode until the time of crossover were taken into account. The decision to change was independent of treatment success. Failure in both modalities was defined by evidence of excessive BZD use above which has been permitted, which in our experience translates into two daily consecutive benzodiazepine abuses above the permitted dose. This assessment of treatment endpoint permits for patients who get 'off track' once in a while to get back to the program, and for those who continue to abuse BZDs to either change modality or stop BZD treatment altogether.

Assessment of BZD use was based upon daily self-reports, intensive daily staff observations by nurses, weekly observations by the patients' personal therapists, observations by the physician and their psychiatrist. A daily question was put by the nurses to the patients as they came to receive their methadone: 'Have you used any "Hypnodorms" [flunitrazepam], Valium or other benzodiazepines . . .' (for the CMT group was added '. . . other than those given to you by us') '. . . during the past week?' The same question was put by the therapist at their weekly session, as well as by the physician and/or psychiatrist when they met. As part of the routine, if a patient seems sleepy, slury or intoxicated he is immediately referred to the physician/psychiatrist that will question him as to the reasons for this. Referral can happen either by the nursing staff that distributes methadone or by any other staff member present in the waiting room. There is always staff in the waiting room doing outreaching.

None of the staff were blind to the treatment protocol, as all knew the patients who were part of the study. Whenever a patient declared, or was suspected, of having abused BZDs this was brought to the attention of the treating psychiatrist or physician who verified this. The observation of patients continued even if they were BZD-free. None of the patients in the BZD treatment program left (or was discharged) during that period.

Results

Group comparisons

The CDTX patients did not differ from the CMT patients in terms of gender, age, education or marital status. No difference could be observed in the maximum BZD dose of abuse during the month preceding assessment. All patients but one (65/66, 98.5%) abused flunitrazepam as the major agent of BZD abuse, while 42/66 (63.6%) patients also abused diazepam, 9/66 (13.6%) alprazolam, and 7/66 nitrazepam (10.6%) as their secondary BZD agent of abuse.

The groups were similar for years of heroin abuse, for years of BZD abuse, in the number of additional secondary drugs of abuse and in days of methadone treatment. The only difference between them among the examined parameters was that the CMT group had significantly higher maximal methadone doses than the CDTX group [CDTX = 112.31 (SD = 29.7), CMT = 133.48 (SD = 26.47), $t = -3.1$, $p < 0.004$].

Similary, no significant differences were found on the ASI addiction severity scales.

The mean BZD maintenance dose for the CMT group was 2.64 mg clonazepam (SD = 1.46, range 0.5–6: 1–2 mg, n = 16; 3–4 mg, n = 15; 5–6 mg, n = 2).

Using χ^2 analysis for each diagnosis as well as for categories of diagnoses, no differences were found in the prevalence of psychiatric comorbidity between the CMT and CDTX groups. Forty-two (63.6%) had at least one current disorder, 52 (78.8%) had at least one lifetime disorder. Twenty-five (37.9%) had a current mood disorder; 21 (31.8%) had a current anxiety disorder; 3 (4.5%) had schizophrenia, and 19 (28.8%) had a current drug-induced disorder. Forty-six (69.7%) were diagnosed with a personality disorder and 33 (50%) were found to have an antisocial personality disorder.

Clonazepam maintenance treatment versus clonazepam detoxification

Kaplan-Meier Survival Analysis procedure showed CMT to be significantly superior to CDTX (Breslow = 13.58; df = 1; p = 0.0002; Tarone-Ware = 13.26; df = 1; p = 0.0003). Failure and success rate for each modality over time is presented in Table 1.

No impact of dosage on survival rate was found independent of treatment modality (Cox survival regression analysis: Wald = 6.99; df = 1; Exp(B) = 0.36; p = 0.008; Dosage was removed from the equation with: Score= 0.000; df = 1; p = 0.983).

Within the CDTX group after 2 months, we did not find any differences in maximum methadone dosage between the success and failure groups (success group = 122.8 mg (SD = 36.3); failure group 108.9 mg (SD = 26.7); t = 1.2; df = 31; p = ns). The same comparison within the CMT group revealed significantly higher methadone dosages in the 'failure' group than in the 'success' group [success group = 130 mg (SD = 28.2); failure group 146.42 (SD = 12.8); $t = -2.23$, df = 22.66, $p < 0.04$].

Comparing the success and failure groups on psychiatric diagnosis, the success group was found to have more often an axis I current ($\chi^2 = 3.96$, $p = 0.047$) and lifetime ($\chi^2 = 8.46$, $p = 0.004$) diagnosis although no difference was found between the distinct axis I diagnostic categories. Also patients in the failure group received more often an

Table 1. Success and failure rates of clonazepam detoxification (CDTX) and maintenance (CMT) at 2, 4, 6, 8, 10 and 12 months

	2 months	4 months	6 months	8 months	10 months	12 months
CDTX	n = 33	n = 31	n = 30	n = 30	n = 29	n = 29
Success	9 (27.3%)	7 (22.6%)	5 (16.7%)	5 (16.7%)	4 (13.8%)	4 (13.8%)
Failure	24 (72.7%)	24 (77.4%)	25 (83.3%)	25 (83.3%)	25 (86.2%)	25 (86.2%)
CMT	n = 33	n = 33	n = 32	n = 29	n = 28	n = 26
Success	26 (78.8%)	25 (75.8%)	24 (75%)	20 (69%)	19 (65.5%)	17 (65.4%)
Failure	7 (22.2%)	8 (24.2%)	8 (25%)	9 (31%)	9 (34.5%)	9 (34.6%)

antisocial personality disorder (ASPD) diagnosis than those in the success group ($\chi^2 = 8.74$, $p = 0.003$). Studying the treatment groups separately we found that these results hold true in the CMT group (current axis I disorder: $\chi^2 = 8.74$, $p = 0.003$; lifetime axis I disorder: $\chi^2 = 12.2$, $p = 0.0001$; ASPD: $\chi^2 = 3.80$, $p = 0.05$) but not in the CDTX group.

In an attempt to explain the differences between the success and failure of the groups in relation to the maximal methadone dose, the following assessments were carried out: post hoc analysis of ASI scales; maximal methadone dose; the number of additional drugs of abuse (ADAs), and the maximum BZD use in clonazepam equivalents in the past month. Chi-square tests, t-tests and logistic regressions for continuous measures were used for analysis. A significant difference was found when comparing the maximum quantity of a clonazepam equivalent that had been abused within several months prior to the study. The post hoc analysis showed a strong trend of the 'failure' group within the CMT to have abused larger quantities of BZD (mean 'success' group = 6.34, SD = 3.7; mean failure 'group' = 9.64, SD = 4.2, logistic regression = 0.22, Wald = 3.38, df = 1, p = 0. 06), and a significantly larger number of different additional drugs of abuse (ADA mean for the 'success' group = 0.61, SD = 0.69; ADA mean for the 'failure' group = 1.42, SD = 1.27; logistic regression = 0.99, Wald = 3.9, df = 1, p = 0.04).

None of the patients left their methadone treatment during the periods taken into account for this study.

Discussion

In this open clinical study, we compared two pharmacological modalities, CDTX and CMT, for treating BZD dependence in MMT patients. Clonazepam was found to be effective in both modalities, but more so in the CMT modality. The CDTX success rate fell within the span of success rates in other studies using detoxification procedures for BZD abuse in heroin abusers, but our CMT procedure was found to be more effective. McDuff *et al*. [10] reported 12 out of 22 alprazolam-dependent MMT patients who completed detoxification. Rickels *et al*. [14] described 48 patients who successfully completed a BZD-tapering schedule out of 123 patients diagnosed with anxiety disorders. Ravi *et al*. [8] described 3/5 MMT patients who were successfully detoxified from alprazolam with phenobarbitol, but they had no or only minimal follow-up. Another study [9] in which the investigators used a very intensive inpatient BZD-tapered discontinuation procedure reported a 67% success rate at 6 months. Using clonazepam as a tapering agent for 37 patients treated with alprazolam for anxiety disorders, Patterson [12] reported a 100% success rate at 1 month follow-up. Those patients, however, were not undergoing MMT, they were not heroin addicts, nor was it clear that they were BZD-dependent; and the 1 month follow-up data were derived from only one meeting with the physician. In a study comparing very slowly tapered diazepam to tapered placebo, Cappell *et al*. [20] observed that 7/21 patients supplemented BZDs to the diazepam-tapering schedule compared to 16/19 who added BZDs to the placebo-tapering schedule. There is some possibility that close continuous monitoring and an adequate follow-up period would have resulted in poorer success rates in most of the studies cited above.

Although the patients in the current study chose their own treatment modality and were not randomly assigned to one of the groups, the CDTX and CMT groups did not differ on any abuse severity measure or in psychiatric diagnosis. There was a difference in maximal daily methadone dose, with patients in the CMT group having higher doses. It might be assumed that the higher methadone dose played a significant role in favour of a higher success rate being achieved by the CMT patients. However, comparisons within the CMT group showed that the 'failure' subgroup had significantly higher maximal methadone doses than the 'success' group, suggesting that higher methadone dosages were not responsible for success in the CMT group.

One of the limitations of this study is that our results were based upon self- and staff reports. Self-reports of drug use, however, have been found to be reliable and highly correlated with urine analysis testing [21], and we were very confident of our ability to assess extra BZD use due to the fact that patients in our clinic are under daily supervision by the nursing staff, have weekly

1 hour meetings with their therapists and meet regularly with the clinic physician and psychiatrist, and are constantly in interaction with the staff which has an outreach policy, both in the waiting room as well as making regular phone calls and home visits to patients. This makes it very difficult for long-term deception.

The positive relationship between axis I disorders and treatment success in the CMT group, might relate to the fact that these patients are very aware of their chronic ailment and of their need for treatment, and obviously the benefit they can receive from treatment. Studies have shown that psychiatric patients may gain more than non-psychiatric patients from psychotherapy [22]. These results may extend to other treatment modes which reduce psychological distress such as BZDs. Previous studies have shown that BZDs are often the drug of choice for those who attempt to self-medicate their psychological distress [1].

Alternatively, the negative relationship between axis II antisocial personality disorder with treatment outcome goes in line with other studies showing poor compliance for MMT treatment in these patients [23].

As for the possible relationship between maximal methadone dose and BZD treatment results, it appears that the more successful patients in the CDTX group were those who received a higher maximal methadone dose, and this remained the case over time. The finding that higher daily doses of methadone might also enable the patient to successfully detoxify from BZDs is supported by other studies showing similar effects of methadone dose on the treatment of cocaine abuse [24,25]. Within the CMT group, the 'failure' subgroup received higher maximal methadone doses than did the 'success' subgroup. These patients (the 'failure' subgroup) ingested comparatively more BZDs during the month prior to entering treatment, used a greater variety of drugs (alcohol, cocaine, amphetamines and cannabis) and needed higher BZD as well as methadone doses in addition to not being satisfied with the clonazepam dose they received. After reviewing our data, we are considering the possibility of attempting maintenance therapy with higher clonazepam doses for these patients.

The interpretation and generalization of our results need to take into account that our study population is comprised entirely of polydrug abusers with long-term heroin and BZD dependence and multiple attempts at BZD abstinence as well as a very high rate of patients with comorbid psychiatric disorders. Compared to an ongoing study in the present clinic [26,27] the percentage of patients with axis I or II diagnosis in the present study by far exceeds the prevalence of such a diagnosis in the overall clinic sample. Clearly, not all BZD-abusing patients should be treated with maintenance. It is possible that our conclusions are applicable for this specific group of high-risk patients who are chronic polysubstance abusers and who have axis I psychiatric disorders. Perhaps a small proportion of those patient will be able to withdraw successfully; the rest may be better off with maintenance.

Our results strengthen the need for psychiatrists to ensure adequate methadone dosing, a comprehensive treatment policy for axis I disorders and to have an adequate armementarium for the treatment of secondary drugs of abuse in MMT.

This was not a double-blind study and there was no placebo control group. The patients could choose one of two treatment modalities and then decide to switch them. These limitations notwithstanding, we found encouraging results in the use of clonazepam for the treatment of BZD dependence in both detoxification and maintenance treatments, but with a clear advantage for the maintenance mode.

Acknowledgement

We thank Esther Eshkol for her assistance.

References

1. Gelkopf M, Bleich A, Hayward R, Bodner G, Adelson M. Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1-year prospective study in an Israeli clinic. *Drug and Alcohol Dependence* 1999; 55:63–68.
2. Igushi MY, Handelsman L, Bickel W, Griffiths RR. Benzodiazepine and sedative use/abuse by methadone maintenance clients. *Drug and Alcohol Dependence* 1993; 32:257–266.
3. San L, Tato J, Torrens M, Castillo M, Farre M, Cami J. Flunitrazepam consumption among heroin addicts admitted for in patient detoxification. *Drug and Alcohol Dependence* 1993; 32:281–286.
4. Darke S, Hall W, Ross M, Wodak A. Benzodiazepine use and HIV risk-taking behavior among injecting drug users. *Drug and Alcohol Dependence* 1992; 31:31–36.
5. Bleich A, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M. Correlates of benzodiazepine abuse in methadone maintenance treatment patients: a 1-year prospective study in an Israeli clinic. *Addiction* 1999; 94:1533–1540.
6. Darke S. The use of benzodiazepines among injecting drug users. *Drug and Alcohol Review* 1994; 13:63–69.
7. Klee H, Faugier J, Hayes C, Boulton T, Morris J. AIDS-related risk behaviour, polydrug use and temazepam. *British Journal of Addiction* 1990; 85:1125–1132.
8. Ravi NV, Maany I, Burke WM, Dhopesh V, Woody G. Detoxification with phenobarbitol of alprazolam-dependent polysubstance abusers. *Journal of Substance Abuse Treatment* 1990; 7:55–58.
9. Joughin M, Tata P, Collins M, Hooper C, Falkowsky J. In-patient withdrawal from long-term benzodiazepine use. *British Journal of Addictions* 1991; 86:449–455.

10. McDuff DR, Schwartz R, Tommasello A, Tiegel S, Donovan T, Johnson JL. Outpatient benzodiazepine detoxification procedure for methadone patients. *Journal of Substance Abuse Treatment* 1993; 10:297–302.
11. Albeck JH. Withdrawal and detoxification from benzodiazepine dependence: a potential role for clonazepam. *Journal of Clinical Psychiatry* 1998; 48 (Suppl.):43–48.
12. Patterson JF. Alprazolam dependency: use of clonazepam for withdrawal. *South Medical Journal* 1998; 81:830–836.
13. Patterson JF. Withdrawal from alprazolam dependency using clonazepam: clinical observations. *Journal of Clinical Psychiatry* 1991; 51 (Suppl.):47–49.
14. Rickels K, Case WC, Schweizer E, Garcia-Espana F, Friedman R. Long-term benzodiazepine users 3 years after participation in a discontinuation program. *American Journal of Psychiatry* 1991; 148:757–761.
15. Klein D. *Diagnostic and drug treatment for psychiatry* 2nd ed. Baltimore: Williams & Wilkins, 1980.
16. Bleich A, Gelkopf M, Weizman T, Adelson M. Benzodiazepine abuse in a methadone maintenance treatment clinic in Israel: Characteristics and a pharmacotherapeutic approach. *Israel Journal of Psychiatry and Related Sciences* 2002; 39:104–113.
17. Cacciola J, Griffith J, McLellan TA. *ASI: Instruction Manual.* Washington, DC: Veterans Administration, 1983.
18. Perry JC. Problems and considerations in the valid assessment of personality disorders. *American Journal of Psychiatry* 1992; 149:1645–1653.
19. Williams JBW, Gibbon M, First MB, *et al.* The structured clinical interview for DSM-II-R (SCID), II. multisite test-retest reliability. *Archives of General Psychiatry* 1992; 49:630–636.
20. Cappell H, Busto U, Kay G, Naranjo CA, Sellers EM, Sanchez-Craig M. Drug deprivation and reinforcement by diazepam in a dependent population. *Psychopharmacology* 1987; 91:154–160.
21. Digustio E, Serer V, Bibby A, Batey RD. Concordance between urine analysis results and self-reported drug use by applicants for methadone maintenance in Australia. *Addiction Behaviors* 1996; 21:319–326.
22. Woody GE, McLellan T, Luborsky L, *et al.* Severity of psychiatric syptoms as a predictor of benefits from psychotherapy: The Veterans Administration-Penn study. *American Journal of Psychiatry* 1984; 141:1172–1177.
23. Alterman AI, Rutherford MJ, Cacciola JS, Woody GE. Response to methadone maintenance and counseling in antisocial patients with and without major depression. *Journal of Nervous and Mental Disease* 1996; 184:695–702.
24. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose–response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine* 1993; 119:23–27.
25. Tennant F, Shannon J. Cocaine abuse in methadone maintenance patients is associated with low serum methadone concentration. *Journal of Addiction Diseases* 1995; 14:67–74.
26. Bleich A, Gelkopf M. *Dual Diagnosis in a Methadone Maintenance Clinic in Tel Aviv* Report of the Anti-Drug Authority. Jerusalem 1998.
27. Bleich A, Gelkopf M, Weizman T, Melamed Y, Adelson M. The impact of psychiatric comorbidity on drug abuse treatment retention and infectious diseases. A one-year study of an Israeli methadone maintenance clinic, in press.