

Current Status of Buprenorphine/ Naloxone Maintenance Treatment in Istanbul Turkey

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Abstract

Although the rate of opioid abuse in Turkey is lower than that in North America and Europe, opioid abuse is an increasing public health problem in Turkey. This is because of both the use of heroin and the increasing number of individuals dependent on prescription opioids. Opioid maintenance treatment (OMT) for opioid dependence is effective in reducing mortality, HIV transmission, crime, and other drug use. Buprenorphine (BUP) maintenance is effective in treating opioid dependence, but problems with the misuse and diversion of BUP might limit its acceptability and dissemination. Abstinence oriented symptomatic treatment was the most commonly offered treatment option in Turkey until the end of 2009. Agonist treatments, including methadone, a single form of buprenorphine or a combined form of buprenorphine and naloxone (BN) were not available. Starting in April 2010, BN was approved for opioid dependence treatment as a detoxification or maintenance treatment by the Turkish Ministry of Health. However, the prescription of BN was restricted to hospitals that included a state-approved specialized clinic for the treatment of substance dependency. In Istanbul, with a population exceeding 13 million inhabitants, only 2 centers provide a BN maintenance treatment program. At the beginning of 2010, the Alcohol and Drug Research Treatment and Training Centre (AMATEM) in Istanbul started providing BN, but only to patients who were hospitalized. At the beginning of 2011, AMATEM published a guideline and extended the implementation of BN OMT to make it available on an outpatient basis. During this time, studies were conducted to evaluate BN OMT.

Keywords: Opioid maintenance treatment • Buprenorphine • Harm reduction • Istanbul • Diversion • Impulsivity

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Although the rate of opioid abuse in Turkey is lower than that in North America and Europe (United Nations Office on Drugs and Crime, 2012), opioid abuse is an increasing public health problem in Turkey. This is because of both the use of heroin and the increasing number of individuals dependent on prescription opioids (European Monitoring Centre for Drugs and Drug Addiction, 2010; Substance Abuse and Mental Health Services Administration, 2010). Illicit use of opioids has been associated with considerable societal costs, including increased rates of emergency department visits, drug overdoses, criminal activity, lost work days, and general medical and psychiatric consequences (Becker et al., 2008; Clausen, Waal, Thoresen, & Gossop, 2009; Shah, Lathrop, Reichard, & Landen, 2008; Wisniewski, Purdy, & Blondell, 2008). As observed in North America and Europe (European Monitoring Centre for Drugs and Drug Addiction, 2010), treatment admissions for opioid abuse and dependence in Turkey have increased dramatically in recent years.

Buprenorphine is a partial opioid agonist of the mu receptor, with antagonistic properties at the kappa receptor (Strain, 2006). To prevent buprenorphine abuse, buprenorphine is typically packaged with naloxone (buprenorphine/naloxone: BN, Suboxone[®]), which yields no effect when administered sublingually but exerts antagonist properties when injected (Helm, Trescot, Colson, Sehgal, & Silverman, 2008; Strain, 2006). Opioid maintenance treatment (OMT) for opioid dependence, such as BN, is effective in reducing mortality, HIV transmission, crime, and other drug use (Connock, 2007; Mattick, Kimber, Breen, & Davoli, 2008). BN has also been shown to be a safe and effective treatment of opioid dependence in non-specialized, outpatient, office-based settings (Fiellin et al., 2006; Fudala & Bridge, 2003; Stein, Cioe, & Friedmann, 2005).

Abstinence oriented symptomatic treatment was the most commonly offered treatment option in Turkey until the end of 2009. Agonist treatments, including methadone, a single form of buprenorphine or a combined form of BN were not available. Starting in early 2010, BN combination was approved for opioid dependence treatment, as a detoxification or a maintenance treatment, by the Turkish Ministry of Health (T.C. Sağlık Bakanlığı İlaç ve Eczacılık Genel Müdürlüğü, 2009). This approval acted to increase the number of patients with opioid dependence receiving treatment. The number of prescriptions for BN has increased steadily since its approval, and BN has been associated

with bringing new users into treatment. The prescription of BN was, however, restricted to hospitals that included a state-approved specialized clinic for treatment of substance dependency. Consistent with this, physician adoption has been primarily among addiction specialists who make up all the prescribers in Turkey. After its' approval, the Alcohol and Drug Research Treatment and Training Center (AMATEM) in Istanbul began administering BN OMT only to the patients who were hospitalized. In Istanbul, with a population exceeding 13 million inhabitants, only 2 centers provide a BN maintenance treatment (BMT) program. Thus, due to limited resources, there is a long waiting list to get into these maintenance programs. At the beginning of 2011 AMATEM has written a guideline (Evren et al., 2012) and started implementation of BN maintenance treatment also as an outpatient basis.

The central problem in the treatment of heroin dependency is the high rate of relapse to drug use after periods of forced or self-imposed abstinence (Bossert, Ghitza, Lu, Epstein, & Shaham, 2005). Retention in OMT has been associated with improved outcomes in adults (Armstrong, Kermode, Sharma, Langkham, & Crofts, 2010; Mintzer et al., 2007; Zhang, Friedman, & Gerstein, 2003), and discontinuation with relapse (Kakko, Svanborg, Kreek, & Heilig, 2003), overdose death (Davoli et al., 1993), and worse HIV treatment outcomes (Roux et al., 2009). Retention rates for BN maintenance treatment at 6 months ranged from 35% to 59% (Fiellin et al., 2006; Kakko et al., 2007; Stein et al., 2005), and 38% retention was reported in one study that followed patients for 2 years (Fiellin et al., 2008). Another study found that the overall retention rate was 56.9% (64.7% of their months were opioid-negative) for 1 year, with about half of the dropouts occurring in the first month (Soeffing, Martin, Fingerhood, Jasinski, & Rastegar, 2009). Pinto et al. (2010) reported that among 134 opioid dependent patients, 61.2% were retained in treatment at 3 months and 42.5% were retained in treatment at 6 months. Finally, in a recent study, Schwarz, Zelenev, Bruce, and Altice (2012) reported that over one third (37.2%) of subjects discontinued BN maintenance treatment within the first month following induction, while 25% of subjects stayed in treatment for at least 43 months (Schwarz et al., 2012).

There are few studies of OMT outcome that consider what factors might be associated with treatment dropout or what might be done to improve it. The

pre-treatment characteristics that are most consistently associated with poorer outcomes among heroin dependent patients in BN maintenance treatment include; male gender, lack of employment, younger age at the onset of opioid use, more continuous and longer opioid use, use of heroin rather than other opioids as the primary drug, higher levels of psychiatric symptoms, lower levels of general function, poorer psychosocial function and more severe legal problems (Stein et al., 2005; Marsch et al., 2005; Pani, Maremmani, Pirastu, Tagliamont, & Gessa, 2000; Petry & Bickel, 1999, 2000; Resnick, Resnick, & Galanter, 1991; Schottenfeld, Pakes, & Kosten, 1998; Soyka, Zingg, Koller, & Kuefner, 2008; Sullivan et al., 2010). However, depression was associated with treatment retention in two studies (Gerra et al. 2004; Marsch et al., 2005). During treatment, predictors of negative outcome in heroin dependents included lower doses, greater severity of withdrawal, side effects, more positive urine tests for opioids and other drugs, opioid positive drug screens at week 1, and fewer addiction counseling sessions (Connock et al., 2007; Leonardi, Hanna, Laurenzi, Fagetti, & I.D.A.C. Group, 2008; Stein et al., 2005; Soyka et al., 2008).

Treatment in AMATEM Istanbul

The decision for whether treatment will be outpatient or inpatient mainly depends on the AMATEM guideline (Evren et al., 20012). According to this guideline, patients that have a diagnosis of opioid dependence for at least two years, abuse depressants such as alcohol or benzodiazepines, use polysubstances and have dropped-out of outpatient OMT twice in a year are prescribed BN maintenance treatment as inpatients.

The induction and stabilization phase ends after one to two weeks. Baseline interviews with the patients were done before initiation of BN treatment. Both outpatients and inpatients (after being discharged from the hospital) were advised to participate in the Outpatient Treatment Program (OTP) once a week for at least one year, and were obligated to come to the outpatient treatment unit every month to for prescription of BN. BN prescription dose range was between 2 to 24 mg per day, with most patients receiving 8 to 12 mg per day.

Predictors of Outcome within 6 Month Follow-up among Heroin Dependent Patients undergoing Buprenorphine/Naloxone Maintenance Treatment

The aim of the first phase of the present study was to evaluate the 6 month outcome predictors among heroin dependent patients undergoing BN maintenance treatment, the only agent used for maintenance treatment in Turkey (Evren, Karabulut et al., 2014). A total of 392 heroin dependent patients consecutively admitted to the clinic ($n = 106, 27.04\%$) or enrolled as outpatients for BN maintenance treatment ($n = 286, 72.96\%$) were included in the study. Patients were investigated with the Bakirkoy Opioid Withdrawal Scale (BOWS), the Substance Craving Scale (SCS), the Drug Use Disorders Identification Test (DUDIT), the Drug Abuse Screening Test (DAST-10) and the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) at baseline evaluation. Among 392 heroin dependent patients, 287 (73.21%) were considered as relapsed to substance use or dropout from treatment, whereas 105 (26.79%) were considered as compliant to the BN maintenance treatment. Rates of a first degree relative with substance abuse, probation and history of a suicide attempt were higher in the relapsed/dropout group (RDG). Other than these characteristics, sociodemographic variables did not differ between these two groups. Mean scores of BOWS and SCS were higher in the RDG than the maintenance group in the first month, whereas DUDIT, DAST-10, SOCRATES scores and mean dose of BN did not differ between groups. Severity of craving predicted a negative outcome after sixth months of maintenance, together with probation and history of suicide attempt. Among items of SCS, "severity of craving" predicted a negative outcome. When the type of treatment was included in these regression analyses as an independent variable, outpatient treatment predicted a negative outcome, together with probation and history of suicide attempt (Evren, Karabulut et al., 2014).

In bivariate analyses, patients that relapsed to substance use or those considered as a drop-out from treatment had (a) higher rates of substance abuse among first degree relatives, (b) status of being under probation, (c) history of a suicide attempt, (d) higher severity of withdrawal, and (e) craving. In regression analysis, craving was associated with a negative outcome (relapse/dropout) together with probation and history of a suicide attempt. When type of the

treatment (inpatient/outpatient) was also evaluated as an independent variable, outpatient treatment predicted a negative outcome instead of craving, together with probation and history of a suicide attempt. This suggests that although the severity of craving was an important risk factor for treatment drop-out, two weeks of supervised treatment with additional educational programming in the stabilization phase might promote continuation of maintenance treatment in these patients. Finally, probation and history of a suicide attempt were two risk factors for a negative outcome, independent of both craving and the type of treatment (Evren, Karabulut et al., 2014).

Since the dose of BN did not differ between the RDG and those retained in maintenance treatment, the present study suggests that those with high withdrawal symptoms or craving, particularly those with a high severity of craving, might need a higher dose of BN. Probation and history of a suicide attempt were associated with a high risk of negative outcome, particularly among those in outpatient treatment. Thus, more observed (supervised) use of BN in the first two weeks, which is more available during inpatient treatment, might improve outcome in outpatient maintenance treatment (Evren, Karabulut et al., 2014).

At minimum, the findings of this study might suggest that clinics should review dosing and monitoring methods. Re-assessment of treatment efficacy through a possible dosage increase or combination with supportive psychosocial therapies could potentially increase adherence to BN maintenance treatment (Dreifuss et al., 2013; Roux, Carrieri et al., 2008).

Illicit Use and Diversion of Buprenorphine/Naloxone among Patients in Buprenorphine/Naloxone Maintenance Treatment in Istanbul, Turkey

OMT for opioid dependence is effective in reducing mortality, HIV transmission, crime, and other drug use (Martin & Finlayson, 2012). Buprenorphine (BUP) maintenance is effective in treating opioid dependence, but problems with the misuse and diversion of BUP might limit its acceptability and dissemination (Bell, 2012). Thus, the BN combination tablet was developed to reduce potential problems with misuse and diversion (Carrieri et al., 2006; Chiang & Hawks, 2003; Mammen & Bell, 2009; Mendelson & Jones, 2003). Two

qualitative, ethnographic studies based on interviews with people who abused opioids in Baltimore and throughout New England suggest that avoidance of withdrawal symptoms is the primary motivation for the use of diverted BUP (Gwin Mitchell et al., 2009; Monte, Mandell, Wilford, Tennyson, & Boyer, 2009). Previous studies exploring factors related to BUP injection have shown that the perception of inadequate BUP dosage prescription can influence BUP injection (Carrieri et al., 2003; Vidal-Trecañ, Varescon, Nabet, & Boissonnas, 2003), as well as the severity of drug dependence and suicide ideation or attempts, even in HIV-infected injection drug users (IDUs) receiving BUP treatment (Carrieri et al., 2003). The prevalence of recent diversion was over 10 times higher among those receiving supervised BUP compared with methadone (MET), with 23.8% of BUP-maintained participants reporting that they had diverted their dose in the preceding 12 months in Australia (Winstock, Lea, & Sheridan, 2008). In France, individuals perceiving their prescribed dosage as inadequate and dissatisfied with BUP treatment were at higher risk of sniffing (Roux, Villes, Bry et al., 2008) and injection (Roux, Villes, Blanche et al., 2008). Previous studies demonstrated that the illicit use of BUP is associated with attempted self-treatment rather than an attempt to “misuse” it (Roux, Villes, Blanche et al., 2008; Schuman-Olivier et al., 2010). Consistent with these data, in a previous study the percentage of BUP diversion was reported to be 46.5% (9.6% daily and 50.6% sporadically) within a 6-month follow-up, and the inability to access BUP treatment was reported as the main predictor (AOR: 7.31). As a result of the findings, the authors suggested that improving—rather than limiting—access to good quality, affordable BUP treatment might be an effective public health strategy to mitigate the illicit use of BUP (Lofwall & Havens, 2012). Seven published studies have documented the diversion and/or injection of BN (Alho, Sinclair, Vuori, & Holopainen, 2007; Bruce, Govindasamy, Sylla, Kamarulzaman, & Altice, 2009; Degenhardt et al., 2009; Larance et al., 2011; Monte et al., 2009; Robinson, Dukes, Robinson, Cooke, & Mahoney, 1993; Vicknasingam, Mazlan, Schottenfeld, & Chawarski, 2010). Three of these studies found BN to have a lower street value than BPN in the period immediately following the medication’s introduction (Alho et al., 2007; Degenhardt et al., 2009; Robinson et al., 1993), although it is not clear whether this has been sustained over time. Other studies found that the street price of BN increased over time to a price that was equivalent to

BUP (Bruce et al., 2009; Larance et al., 2011). Although 80% of drug users that tried injecting BN had a bad experience in Finland (Alho et al., 2007), a number of studies suggest that, while BN might have lower abuse liability than BUP, the inclusion of naloxone might not completely eliminate its potential misuse (Harris et al., 2000; Mendelson & Jones, 2003; Robinson et al., 1993). A Malaysian study found that the introduction of BN did not reduce injection-related risk behaviors among participants that had previously injected BUP, and even if withdrawal symptoms were reported, they did not result in a decrease in the self-administered BN dose (Bruce et al., 2009). A two-wave survey of BUP among IDUs was conducted shortly before BUP withdrawal from the Malaysian market ($n = 276$), and then again six months after BN was introduced ($n = 204$). The results suggest that the introduction of BN and withdrawal of BUP might have helped to reduce, but did not eliminate, the problems experienced with diversion and abuse in Kuala Lumpur, Malaysia (Vicknasingam et al., 2010). In 2009, while BN was less commonly and less frequently injected than BUP, both sublingual medications were diverted more than liquid MET (Larance et al., 2011).

Besides noting the measures taken in Turkey against the BN combination to suppress the misuse of therapeutic opiates, a detailed study on the illicit use of BN has become a priority. The aim of phase 2 of the present study was, in fact, to evaluate the extent of the illicit use and diversion of BN by patients in BN maintenance treatment (BMT) (Evren, Bozkurt et al., 2014). In this study 281 heroin-dependent patients were included. These patients had consecutively attended the Alcohol and Drug Research treatment and Training Center (AMATEM) polyclinic as BMT outpatients, and had reached the end of the stabilization phase at least 2 weeks after induction. Of these 281 heroin-dependent subjects in BMT, 110 (39.1%) were considered as belonging to the group that had used illicit (i.e., unprescribed) BN. This group had higher current doses, a higher use of BN before treatment, a shorter period of BN treatment and a lower frequency of remission of drug use. There was no difference between the two groups in estimates of dose adequacy, receiving education for BN use, having a legal problem and/or probation, using different routes for BN other than the sublingual route of administration, or giving away BN doses. In the group that used illicit BN, percentages of both the more frequent / higher dose use of BN and the less frequent / lower dose use of BN were higher than the

group that did not use illicit BN. Also the group that used illicit BN reported higher frequency for the use of other substances during BMT. Most of the patients that used illicit BN had done this before their monitored use of BN, and had used it to relieve withdrawal symptoms. This suggests that the main difficulty for those seeking illicit BN in Istanbul is how to access treatment (Evren, Bozkurt et al., 2014).

Motor Impulsivity Discriminated Relapsed Male Heroin Dependents from those who were still in Buprenorphine Maintenance Treatment at the 12-Month Follow-up

Impulsivity has been shown to be related to risk taking, lack of planning, and quick decision-making (Eysenck & Eysenck, 1977). Definitions of impulsivity suggest that such behaviors tend to be committed without forethought or conscious judgment, and are characterized by acting on the spur of the moment, an inability to focus on a specific task, and a lack of adequate planning (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001; Patton, Stanford, & Barratt, 1995). Some authors include temperamental traits, such as sensation seeking and risk taking, in their definition of impulsivity (Eysenck & Eysenck, 1977). There is accumulating evidence, from preclinical laboratory animal and clinical studies, indicating that impulsive behavior might be causally linked to several distinct processes in drug addiction, including its onset, maintenance, related problems and relapse into drug use (Bjork, Hommer, Grant, & Danube, 2004; Brady, Myrick, & McElroy, 1998; Kisa, Yildirim, & Goka, 2005; Pattij & De Vries, 2013; Vitaro, Ferland, Jacques, & Ladouceur, 1998). Impulsivity has also been found to be a high-risk factor in early substance use, and to be related to the severity of drug abuse and treatment retention (Patkar et al., 2004; Tarter et al., 2003). In a review by Acton (2003), it was argued that impulsivity is a temperamental risk factor for substance use. It has been suggested that impulsivity might be a fundamental mechanism both in the onset of excessive substance use (Lane, Cherek, Rhoades, Pietras, & Tcheremissine, 2003) and in relapse into substance use (Miller, 1991). Impulsivity might also serve to moderate the relationship between substance use behavior and substance-use outcomes, such as substance use-related problems (Simons, 2003; Simons & Carey, 2002). High relative comorbidity is observed between alcohol use

disorders and Axis I and Axis II psychiatric disorders found within the impulse control spectrum; i.e., antisocial personality disorder (Wills, Sandy, & Yaeger, 2002). Impulsivity might also serve to moderate the relationship between substance-use behavior and substance-use outcomes, such as substance use-related problems (Simons, 2003; Simons & Carey, 2002). Moreover, previous evidence suggests impulsivity as a mediator of the genetic basis of SUD (Ducci & Goldman, 2008). The existing literature suggests that impulsivity might be a multidimensional construct, and individual differences might exist across the different dimensions of impulsiveness, which might be related to different patterns and severities of substance use (Verheul & van den Brink, 2000). Impulsivity might interfere with the outpatient or inpatient treatment of substance dependence (Murray et al., 2003).

The aim of the third phase of the present study was to evaluate whether impulsivity was able to discriminate relapsed male heroin dependents from those who were still in buprenorphine maintenance treatment at 12-month follow-up, while checking the effects of depression, and state and trait anxieties (Evren, Yilmaz et al., 2014). Of 78 consecutively admitted male heroin dependents, 52 were examined during a face-to-face interview 12 months after discharge from hospital. Patients were investigated by applying the Barratt Impulsiveness Scale, version 11 (BIS-11), Beck Depression Inventory (BDI) and State and Trait Anxiety Inventory (STAI) at the end of 12 months. Of 52 heroin-dependent inpatients, 23 (44.2%) were considered as having relapsed into heroin use during the previous twelve months, whereas 29 (55.8%) were still in the maintenance treatment. Demographic variables did not differ between the two groups. Mean scores on the impulsivity subscales (motor, attentional and non-planning) and total BIS-11 were higher in the relapsed group than in the maintenance group at follow-up. So too, depression and anxiety scores were higher in the relapsed group. Impulsivity, particularly motor impulsiveness, discriminated the relapsed group from the maintenance group, together with a state of anxiety. Although motor impulsiveness was able to discriminate the relapsed group from the maintenance group, together with anxiety, this cross-sectional study did not evaluate the causal relationship. Despite these limitations, these results suggest that motor impulsiveness and anxiety might be the areas to focus on in the treatment of relapsed heroin dependents (Evren, Yilmaz et al., 2014).

Conclusion

Conclusions are as follows: (a) Addiction is a disease spanning a lifetime. (b) Remission and relapse are natural. (c) Treatment should always include a psychosocial program, such as grief counseling, therapeutic individual counseling, outpatient groups, inpatient therapy, rehabilitation programs, self-help groups. (d) Patient-specific strategies should be planned. (e) The target should be to determine the appropriate model (full sobriety-harm reduction), according to the patient's needs and opportunities. (f) Supervision of the program is important in maintenance treatment with BN. (g) There must be an information network between treatment centers that apply maintenance treatment, which might decrease both evaluation time and abuse risk of the drug. (h) Treatment centers that have maintenance treatment programs must reconsider their programs according to results of the treatment.

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