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Effects of Opioid Pharmacotherapy on Psychomotor and Cognitive Performance: A Review of Human Laboratory Studies of Methadone and Buprenorphine

Miriam Z. Mintzer

Summary

Opioid pharmacotherapy can provide the stability necessary to initiate lifestyle changes, obtain steady employment and function in society. Thus, a critical question is the extent to which pharmacotherapy is associated with impairment in psychomotor and cognitive performance that might affect functioning. In this article, I review human laboratory studies of the effects of the most common opioid pharmacotherapies, methadone and buprenorphine, on psychomotor and cognitive performance (both observational group comparison and experimental drug administration studies) and the effects of withdrawal from opioid pharmacotherapy on performance. I then outline some recommendations for further study in this area.

Key Words: Opioid Pharmacotherapy - Cognitive Performance - Methadone - Buprenorphine

The most widespread single intervention for opioid dependence is pharmacological treatment (primarily opioid substitution pharmacotherapy) (1). An important benefit of pharmacotherapy is that it can provide the stability necessary to initiate lifestyle changes, obtain steady employment and function in society. Thus, a critical question is the extent to which pharmacotherapy is associated with impairment in psychomotor and cognitive performance that might affect functioning. In this article, I review the literature on the effects of the most common opioid pharmacotherapies, methadone and buprenorphine, on psychomotor and cognitive performance. Methadone, a long-acting...
mu opioid agonist that is well absorbed orally, has been used as a pharmacotherapy for opioid dependence since the mid-1960’s (2). Buprenorphine, a mu opioid partial agonist and kappa antagonist, is currently used as an analgesic and as a treatment for opioid dependence (3). As a treatment for opioid dependence, buprenorphine was first approved in France in 1995 and is currently approved in 44 countries worldwide (Dr. Rolley E. Johnson, Reckitt Benckiser, personal communication, June, 2006). Buprenorphine is approved for sublingual administration alone (Subutex) and in combination with the opioid antagonist naloxone (Suboxone; as a treatment for opioid dependence, United States, Australia and New Zealand). The buprenorphine/naloxone sublingual combination product was designed to minimize intravenous abuse of buprenorphine by dependent opioid abusers. Because naloxone has poor sublingual bioavailability (4), use of buprenorphine/naloxone tablets by the therapeutic sublingual route produces a predominantly buprenorphine effect; however, when the tablets are dissolved and injected by a dependent opioid abuser, naloxone precipitates a withdrawal syndrome (5-8).

After reviewing human laboratory studies of the effects of opioid pharmacotherapy on performance (both observational group comparison and experimental drug administration studies) and the effects of withdrawal from opioid pharmacotherapy on performance, I outline some recommendations for further study in this area.

Effects of opioid pharmacotherapy on performance: Group comparison studies

This section reviews group comparison studies that examined performance (using standardized neuropsychological batteries or other measures of cognitive and/or psychomotor performance) in methadone-maintenance patients (MMP) or buprenorphine-maintenance patients (BMP) relative to various control groups.

MMP/BMP vs. non-drug abusing controls. A number of studies have examined the performance of MMP or BMP relative to non-drug abusing controls (i.e., individuals with no known history of drug abuse). Rothenberg et al. (10) compared 12 MMP who reported having had little or no drug use (other than methadone) for at least one month prior to testing (confirmed via urinalysis), to 12 non-drug abusing controls in a similar age range. Relative to controls, MMP were unimpaired on a continuous performance test (measuring sustained attention) and actually exhibited shorter reaction times on a simple visual reaction time (RT) task. While these results provide no evidence for impairment in MMP, interpretation is somewhat limited by the absence of information about matching of the two groups on variables that might affect performance (e.g., years of education, IQ) and the limited range of measures. Grevert et al. (11) tested the memory performance of 30 MMP (and 31 patients being maintained on LAAM) at three separate timepoints: prior to beginning pharmacotherapy, and following one and three months of pharmacotherapy. A control group of 26 non-drug abusers who were matched to individual MMP participants with respect to age, gender, education, ethnicity, and employment status were tested at similar intervals. There were no significant differences among groups at any of the three timepoints and no differences
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within either pharmacotherapy group at the later timepoints relative to pre-treatment performance.

Using a standardized neuropsychological battery, Darke et al. \(^{(12)}\) examined the performance of 30 MMP relative to 30 non-drug abusers matched with respect to age, gender, and years of education. The battery included measures of premorbid intelligence, psychomotor performance, information processing, attention, short-term memory, long-term memory, and problem solving. While the groups did not differ with respect to premorbid intelligence, MMP performed significantly worse than controls on all other measures. The wide range of impaired functions is striking. However, conclusions based on this study are limited for the following reasons. First, a urine drug screen was not performed prior to neuropsychological testing. A larger proportion of MMP than controls in the study reported current use of a variety of drugs, including benzodiazepines which have well-documented performance-impairing effects \(^{(13)}\); thus, it is difficult to differentiate effects of opioid use from other acute drug effects. Second, there was an exceptionally high prevalence of reported head injury in the MMP group (67% compared to only 20% for controls), which may also have contributed to impaired performance in MMP. Third, testing was conducted prior to daily methadone dosing, raising the possibility that some MMP may have been in early withdrawal during testing.

Using a standardized battery developed by the Austrian Road Safety Board to assess driving-related skills (Act & React Test System), Specka et al. \(^{(14)}\) examined the performance of 54 MMP relative to 54 non-drug abusers matched with respect to age, gender, and years of education. An important strength of the study is the relatively large sample size. MMP were impaired relative to controls on a tachistoscopic perception task, a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns, and a task requiring the capacity to integrate information under high-pressure conditions. On a choice reaction time task, MMP were faster than controls but produced more errors. On two tasks requiring visual tracking, MMP were more accurate but slower. Although a urine drug screen was performed prior to performance testing, MMP with a positive drug screen (38 out of 54 MMP) were not excluded, again making it difficult to differentiate effects of opioid use from other acute drug effects. It is important to note, however, that analyses comparing MMP with positive drug screens versus negative drug screens at the time of performance testing revealed no significant differences in performance.

In a study conducted in our laboratory \(^{(15)}\), we examined the performance of 18 MMP relative to 21 non-drug abusers matched with respect to gender, race, age, years of education, current employment status, current reading level, and estimated IQ score. Recent drug abstinence was verified by urinalysis. MMP exhibited impairment relative to controls in psychomotor speed (as assessed by the Digit Symbol Substitution test: DSST, and computerized trail-making tests), working memory (as assessed by the two-back task, which requires participants to temporarily maintain in memory and continuously update the identity and order of the two previous letters in a sequence of
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letters presented consecutively on the screen), decision making [as assessed by a computerized version of the gambling task (16-18), which requires the evaluation of long-term consequences of current decisions], and metamemory (awareness and knowledge of one’s own memory). Results also suggested possible impairment in inhibitory mechanisms (Stroop color-word task), although the effect was not statistically significant. MMP did not exhibit impairment in time estimation, conceptual flexibility or episodic memory. Like the Darke et al. (12) study, these results provide evidence for impairment in a wide range of functions.

A few recent studies have specifically examined decision-making in opioid-pharmacotherapy patients. Rotheram-Fuller et al. (19) examined performance on a version of Bechara’s gambling task as well as the Wisconsin Card Sorting Task (WCST; a measure of conceptual thinking and flexibility) of four groups, matched with respect to age, gender, and estimated IQ score: Methadone-maintained tobacco smokers (N = 9) and non-smokers (N = 9), and control (non-drug abusing) smokers (N = 9) and non-smokers (N = 10). While there were no significant differences among groups in WCST performance, methadone-maintained smokers (but not non-smokers) were significantly impaired on the gambling task relative to both control groups. An analysis comparing the two MMP groups indicated that the smokers were also significantly impaired relative to the non-smokers. These results are consistent with Mintzer and Stitzer’s (15) findings with the gambling task, but additionally suggest that tobacco smoking may be a risk factor for decision-making impairment in MMP. Interestingly, the differences among groups disappeared when participants performed the gambling task a second time after being informed of the optimal strategy for performing the task. This pattern suggests that the impairment in smoking MMP is related to deficient strategy learning rather than to continued use of sub-optimal decision-making strategies despite awareness of consequences. Although MMP were encouraged to abstain from other drug use throughout the study, participants who reported drug use were not excluded, again making it difficult to differentiate effects of opioid use from other acute drug effects.

Madden et al. (20) and Petry, Bickel, & Arnett (21) examined decision-making in BMP. Using the delay-discounting task, Madden et al. (20) compared the rate of temporal discounting of monetary rewards in 18 BMP to that of 38 non-drug abusing controls matched with respect to age, gender, education, and estimated IQ. BMP discounted the subjective value of hypothetical delayed monetary rewards significantly more (reflecting greater impulsivity) than did controls. Petry et al. (21) compared the performance of 34 BMP to that of 59 non-drug abusing controls matched with respect to age, gender, education and estimated IQ on a version of Bechara’s gambling task and on the Future Perspective Task (FTP) in which participants are asked to make predictions about the timing and ordering of future events. BMP were less likely than controls to predict events far into the future and to systematically organize events in the future on the FTP (suggesting a shortened time horizon) and were impaired relative to controls on the gambling task [consistent with the Mintzer & Stitzer (15) and Rotheram-Fuller et al. (19) studies described above]. No information is provided about the current drug use of
the BMP and no urine drug screens are reported prior to testing in these studies, again making it difficult to differentiate effects of opioid use from other acute drug effects.

MMP/BMP vs. abstinent opioid abusers. In the studies reviewed above, MMP/BMP were compared to non-drug abusing controls only, making it difficult to differentiate the effects of current opioid pharmacotherapy treatment from the effects of a history of long-term opioid abuse. This section reviews studies that included abstinent opioid abusers (i.e., individuals with a history of long-term opioid abuse, but with no current use) as controls.

Using a broad range of measures, Gritz et al. (22) examined the performance of 10 MMP relative to a control group of 10 former opioid abusers residing in an abstinence colony. The groups did not differ significantly with respect to level of education. Recent drug abstinence was verified in both groups via urinalysis. MMP were impaired relative to controls on measures of perception, story memory (assessed via recall), and memory for difficult pairs of words, but unimpaired on immediate digit span, story memory (assessed via recognition), object recognition memory, memory for easy pairs of words, and the DSST. Robinson and Moskowitz found that MMP were unimpaired, relative to abstinent opioid abusers in a similar age range, on tracking (23), divided attention, and visual search tasks (24), but that the rate of processing of tachistoscopically-presented information was reduced in the MMP (24). Recent drug abstinence was verified in both groups via urinalysis. Gordon and Appel found that MMP were unimpaired relative to control groups of abstinent opioid abusers and non-drug abusing controls on the DSST (25) and the continuous performance task (26), and exhibited comparable or shorter reaction times relative to controls on visual reaction time tasks (27). Recent drug abstinence was verified via urinalysis.

Davis et al. (28) examined performance on a neuropsychological battery (which included measures of attention, spatial and verbal learning, immediate and delayed spatial and verbal recall, verbal fluency, and conceptual flexibility) of 15 MMP relative to 16 abstinent opioid abusers enrolled in drug-free treatment programs and 14 non-drug abusing controls (pain management patients). The MMP and abstinent opioid abusers did not differ significantly in terms of age or estimated IQ score, and had similar histories of drug abuse. MMP were significantly impaired relative to abstinent opioid abusers on the verbal fluency task (a measure of semantic memory), and the overall incidence of impaired performance (defined as a score of two or more standard deviations below published norms on two or more neuropsychological measures) in the abstinent opioid abusers (31%) fell between that in the MMP (60%; highest incidence of impairment) and that in the non-drug abusing controls (7%; lowest incidence of impairment). The incidence of impairment was significantly different in the MMP vs. control groups, but no other paired comparisons were significant. Although the incidence of impairment in the abstinent opioid abuser group was not significantly different from that in the MMP group, the pattern of results suggests that current methadone maintenance may be associated with additional impairment over and above that associated with long-term opioid abuse. It should be noted that no information is provided about the current
drug use of the MMP and no drug urine screens are reported prior to testing, making it difficult to differentiate effects of methadone from other acute drug effects.

In our laboratory (29), we compared performance of a control group of 21 currently abstinent, formerly dependent opioid abusers retrospectively to our earlier groups (MMP and non-drug abusing controls; 15; cf. MMP/BMP vs. non-drug abusing controls, above) on the same battery of performance measures. Consistent with the Davis et al. (28) study, performance of the abstinent opioid abusers fell between that of the MMP and non-drug abusing controls on most measures, although MMP were only significantly impaired relative to the abstinent opioid abusers on one measure (conceptual flexibility). While conclusions based on retrospective comparisons are inherently limited, it is important to note that the MMP and abstinent opioid abusers did not differ significantly with respect to gender, race, mean age, years of education, current reading level or estimated IQ, and had similar histories of drug abuse.

Verdejo et al. (30) examined the performance of 18 MMP relative to 23 abstinent opioid abusers on a neuropsychological battery that included semantic and phonological fluency, working memory, Stroop color-word, measures of processing speed, visuo-spatial attention, cognitive flexibility, response inhibition, and analogical reasoning, and the WCST. The groups were matched with respect to age, education, pre-morbid IQ, and employment status. Recent drug abstinence was verified by urinalysis. Relative to abstinent opioid abusers, MMP exhibited slower performance on tests of processing speed, visuo-spatial attention, and cognitive flexibility, as well as reduced accuracy on tests of working memory and analogical reasoning.

In a recent study, Prosser et al. (31) examined the performance of 29 MMP relative to 27 abstinent opioid abusers and 29 non-drug abusers matched with respect to gender. Recent drug abstinence was verified by urinalysis. After differences between groups in level of education and age were statistically controlled, MMP exhibited impairment relative to non-drug abusing controls on the WAIS-R Vocabulary Test (an estimate of general IQ) and on the Benton Visual Retention Test (BVRT; a test of visual memory and visual construction), but not on the Controlled Oral Word Association test (COWA; a test of verbal fluency). Interestingly, MMP did not exhibit impairment relative to abstinent opioid abusers on any measure and actually performed significantly better than the abstinent abusers on the Benton Visual Retention Test.

MMP vs. BMP. A few studies have compared the performance of MMP and BMP. As a partial agonist, buprenorphine may produce less performance impairment than methadone. Soyka et al. (32) retrospectively compared the performance of 28 BMP to that of 13 MMP who had been previously tested on the same standardized battery developed by the Austrian Road Safety Board to assess driving-related skills (Act & React Test System; ART-90). MMP exhibited significant impairment relative to BMP on a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns, a task requiring the capacity to integrate information under high-pressure conditions, and a choice reaction time task. Although these results support the hypothesis of less performance impairment with buprenorphine
than methadone, conclusions are limited due to the absence of controlled procedures and matching of patients in the two groups.

Schindler et al. (33) also used a version of the Act & React Test System (ART 2020) to examine the performance of 15 MMP and 15 BMP. Each maintenance group participant was matched with a group of non-drug abusing controls (n = 3-56; the median performance score for the control group was then compared to that of the matched maintenance group participant) with respect to age, gender, and score on a measure of intelligence. The controls were selected from a sample of people who had previously completed the ART 2020 battery. The combined MMP and BMP group exhibited significantly longer mean reaction and decision times relative to controls on a task in which participants are required to respond as quickly as possible to specific stimuli appearing in a video sequence of a city drive from the driver’s perspective. In addition, the percentage of incorrect responses was significantly higher in the combined MMP and BMP group relative to controls on a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns. However, the overall number of responses and the number of correct responses were also significantly higher in the combined groups, making this result somewhat difficult to interpret. There were no significant differences between the combined group and the controls on the other four tasks of the ART 2020 battery.

Analyses comparing each pharmacotherapy group separately to controls revealed that the MMP group exhibited the same pattern of impairment relative to controls as described above in the combined group, whereas the BMP group exhibited significant differences relative to controls only on the 7-min pattern-comparison task (increases in percentage of incorrect responses only). The authors suggest that MMP (and BMP to a lesser degree) may sacrifice accuracy for speed. Although these results support the hypothesis of less performance impairment with buprenorphine than methadone, conclusions are limited for the following reasons. First, the MMP and BMP groups were not directly compared because they were not matched. Second, conclusions regarding differences between MMP and BMP are complicated by the fact that testing began 22 hours after last medication dosing; given the half-life differences between methadone and buprenorphine, it is more likely that MMP than BMP may have started to experience opioid withdrawal symptoms during the test battery, making it difficult to differentiate drug effects from early drug withdrawal effects. Third, although a urine drug screen was performed prior to performance testing, participants with positive drug screens for other drugs were not excluded, making it difficult to differentiate effects of opioid use from other acute drug effects. In fact, MMP/BMP with positive drug screens at the time of neuropsychological testing exhibited greater impairment relative to controls than those with negative drug screens.

In a well-designed study, Pirastu et al. (34) directly compared 30 MMP and 18 BMP, matched with respect to gender, age, and level of education. Consistent with the hypothesis of less impairment with buprenorphine, MMP were significantly impaired relative to BMP on Bechara’s gambling task. Both MMP and BMP were impaired relative to
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non-drug abusing controls on WAIS-R full-scale IQ and the Benton Visual Retention Test, and there were no differences between MMP and BMP on these measures or on the WCST.

Summary. The results of group comparisons of MMP/BMP to non-drug abusers or abstinent opioid abusers are inconsistent, with some studies showing impairment in a wide range of functions and some providing no evidence for impairment. However, two conclusions that are supported by several different studies may be drawn. First, opioid pharmacotherapy patients appear to exhibit impairment in processing information when performing at high speeds. Given Schindler et al.’s (33) suggestion that MMP (and BMP to a lesser degree) may sacrifice accuracy for speed, this conclusion is not inconsistent with reports of shorter RTs for MMP in some RT tasks (10,27). Second, opioid pharmacotherapy patients appear to exhibit impairment in decision-making tasks. The results of a few studies that compared MMP and BMP provide some support for the hypothesis of less impairment with buprenorphine than methadone, although conclusions are limited due to methodological issues and further research is needed.

It is important to note that although group comparison studies can provide valuable, clinically relevant information about performance impairment, the conclusions that can be drawn are limited due to difficulties in differentiating impairments attributable to acute opioid pharmacotherapy dosing, chronic opioid pharmacotherapy dosing, poly-drug abuse, and other confounding factors (e.g., differences in personality, brain dysfunction, environment). Furthermore, group comparison studies do not enable differentiation of impairments that are a consequence of opioid abuse versus impairments that predated the opioid abuse. In the case of the observed decision-making deficits, it is possible that the impairment may have predated the opioid abuse and in fact even played a role in its development, rather than being a consequence of the abuse. The next section reviews experimental studies involving performance testing following administration of additional acute doses of methadone to MMP or additional acute doses of methadone or buprenorphine to dependent opioid abusers being maintained experimentally on methadone or buprenorphine respectively, and experimental studies involving performance testing following chronic administration of methadone or buprenorphine to dependent opioid abusers.

Effects of opioid pharmacotherapy on performance: Drug administration studies

Rothenberg et al. (10) found that an additional dose of up to 10 mg had no effect on simple visual RT or sustained attention in 12 MMP being maintained on 20-70 mg methadone/day. Using a battery of tasks that included finger tapping, simple visual RT, the DSST, digit cancellation (measuring sustained attention), and immediate and delayed prose recall, Curran and colleagues examined the effects of increasing MMP’s daily dose. They found that increasing patients’ usual dose by 33% did not affect performance in 18 MMP being maintained on 20-80 mg methadone/day (35) (mean daily dose:
44 mg; N = 18). However, administering the full daily dose on a single occasion to 20 MMP accustomed to receiving 50% of their dose at each of two occasions during the day significantly impaired delayed recall of prose in a task that has been shown to be a good predictor of everyday memory performance (mean daily dose: 33 mg, range: 10-50 mg; N = 20). Acute methadone (15-60 mg) did not impair DSST or short-term memory performance in 13 dependent opioid abusers being maintained on 30 or 60 mg methadone/day (37). Likewise, acute buprenorphine (4-16 mg intramuscular) did not impair DSST or short-term memory performance in 8 dependent opioid abusers being maintained on 8 mg sublingual buprenorphine/day (38).

Results of an early study in which 15 non-dependent opioid abusers were given doses of up to 400 mg methadone/day for a period ranging from 28 to 186 days show that following chronic methadone administration, participants performed arithmetic and coordination tests at similar rates of speed as at baseline, but with substantially more errors, and that participants’ mean IQ (measured by the Otis intelligence test) decreased by 7 points relative to baseline (39). Although this is the only published experimental study to provide information about chronic dosing effects of methadone at such high doses, results must be interpreted cautiously due to lack of statistical analysis and controlled procedures (e.g., daily dose, duration of treatment were not consistent across participants).

A study in our laboratory (40) evaluated the chronic dose-effects of buprenorphine/naloxone (8/2, 16/4, 32/8 mg, sublingual tablets) in dependent opioid abusers on performance of a broad range of psychomotor and cognitive tasks, following a period of 7-10 days of repeated dosing at each dose, in a double-blind, within-subject, crossover design. Results indicated only one significant effect: Impairment in episodic memory performance for 32/8 relative to 8/2 and 16/4 mg buprenorphine/naloxone. The absence of impairment on most measures, and the finding of impairment in episodic memory only at the highest dose (32/8 mg; doses of 4-24 mg buprenorphine are recommended for opioid pharmacotherapy) support the hypothesis of limited impairment with buprenorphine. However, these null effects should be interpreted cautiously due to the absence of a placebo condition or control group.

Lenne et al. (41) used an independent groups design to test dependent opioid abusers randomly assigned to three months of daily dosing of methadone (n = 10; mean daily dose: 48 mg) or buprenorphine (n =11; mean daily dose: 14.4 mg) on simulated driving, and found no performance differences between the methadone and buprenorphine groups. In addition, neither pharmacotherapy group performed significantly worse than a group of non-drug abusing age-matched controls. While these results support the hypothesis of limited impairment with buprenorphine, conclusions are limited by the lack of impairment in the methadone group (possibly due to the low methadone doses).

Soyka et al. (42) tested dependent opioid abusers randomly assigned to daily dosing of either methadone (N = 24) or buprenorphine (N = 22) on the Act & React Test System (ART-90) after 8-10 weeks of treatment. There were no significant differences
between the groups with respect to age, gender, level of education, or duration of opioid dependence. On a task in which the participant is instructed to press a button when a particular tone and light signal appear, participants in the methadone group produced significantly more false positive errors than those in the buprenorphine group. Although this finding provides some support for the hypothesis of less impairment with buprenorphine, it should be noted that there were no significant differences between the groups on any other measure of this large battery. In addition, the authors note that 85% of the patients were using cannabis, benzodiazepines or opioids at the time of testing but do not indicate whether the percentage differed between groups, making the results difficult to interpret.

**Effects of opioid pharmacotherapy withdrawal on performance**

Two studies have examined effects of withdrawal on performance in MMP\(^{(43, 44)}\). To our knowledge, no performance studies of withdrawal have been conducted in BMP. Using a within-subject design, Kelley et al.\(^{(43)}\) examined the performance of 30 MMP (mean daily methadone dose: 63 mg, range: 20-120; mean duration of methadone maintenance treatment: 240 days, range: 28-874) tested 1 hr vs. 25 hr (short-term abstinence) after daily methadone dosing. The battery included measures of auditory threshold, distance perception, reaction time, time perception, digit span, and attention span. The only measure that showed an effect of time of testing was distance perception, and interpretation of the direction of the effect is ambiguous. Using an independent groups design, Lyvers and Yakimoff\(^{(44)}\) compared performance on the WCST of a group of MMP tested 90 min after daily methadone dosing (N = 21; peak methadone effect) and a group tested 24 hr after daily methadone dosing (N = 18; short-term abstinence). For both groups, participants had to be stabilized on at least 25 mg daily methadone (mean = 66.9) for at least one month prior to testing. MMP with excessive alcohol consumption, recent use of drugs other than methadone, or a history of treatment for alcohol or non-opioid drug-related problems were excluded from participation. MMP tested 24 hr after methadone dosing exhibited significantly higher rates of perseverative responses and errors (considered measures of impaired frontal lobe functioning) relative to MMP tested 90 min after methadone dosing. There were no differences in rates of non-perseverative errors.

Withdrawal effects on performance have also been examined using opioid antagonists to precipitate withdrawal in dependent opioid abusers being maintained on methadone. The opioid antagonist naloxone administered 20 hr or more after methadone dosing in opioid abusers maintained on daily methadone has been shown to precipitate symptoms of withdrawal as assessed by standard objective and subjective scales, but not to impair performance as assessed by the DSST\(^{(7, 45-49)}\), immediate digit recall\(^{(7, 45-49)}\), the Maddox Wing test\(^{(50)}\), the Stroop test, or the digit span test\(^{(51)}\).
Recommendations for further study

Use of controlled longitudinal designs. To better understand the effects of opioid pharmacotherapies on performance, there is a need for studies that test performance in dependent opioid abusers prior to beginning opioid pharmacotherapy and at multiple timepoints during the course of opioid pharmacotherapy treatment. To our knowledge, the only study that used a longitudinal design in opioid pharmacotherapy patients was an early study that only tested memory performance (11).

Studies of high-dose methadone. The original methadone dose recommendation made by Dole and colleagues (52) was 80-120 mg/day (with some patients requiring higher doses), and the superior efficacy of doses ≥ 80 mg relative to lower doses was supported by subsequent clinical research (53, 54; cf 55). In the 1980’s, there were attempts to reduce methadone doses in many clinics, such that a survey conducted in 1988 found that the average maintenance dose was 50 mg/day or less at 68% of U.S. methadone maintenance treatment clinics (56). Although the issue of optimal methadone dosing is still controversial (57-61), recently there has been a trend towards using increasingly higher maintenance doses. An informal national survey found that the average daily methadone dose in U.S. clinics increased from 45 mg in 1988 to 56.6 mg in 1993 to 69.4 mg in 1998 (62). This trend is supported by recent clinical data suggesting that some patients require doses considerably higher than the 100 mg “glass ceiling” common in the 1980’s (higher than 200 mg/day, and as high as 1100 mg/day in some cases; (63-65). Increasingly higher doses may also be needed due to higher dependence levels resulting from increased purity of street heroin (66). Given that patients being maintained on high methadone doses would be expected to be most vulnerable to performance impairment, information about the effects of methadone at high doses is now needed. Yet, with the exception of the Isbell et al. (39) study that examined effects of doses as high as 400 mg, most studies of methadone have examined low to moderate doses, and none has examined multiple doses to provide information about performance dose-effect functions.

Dose-transition studies. Opioid pharmacotherapy patients are likely to be at increased risk for performance impairment following dose escalation. Yet, to our knowledge, there are little or no data on the effects of specific methadone or buprenorphine dose increases on performance in MMP or BMP (cf. Effects of opioid pharmacotherapy on performance: Drug administration studies). Results of the few studies that have been conducted in MMP suggest that acute increases of up to 33% of the daily maintenance dose do not impair performance, whereas increases of 100% of the daily dose may impair performance (35, 36). There is a need for studies in which the effects of specific opioid pharmacotherapy dose increases and decreases on performance are examined. Data from such studies may aid clinicians in making decisions about opioid pharmacotherapy dosing schedules, particularly in patients with additional risk factors for impairment.

Interaction studies of opioid pharmacotherapy with alcohol and benzodiazepines. Polydrug abuse is common in dependent opioid abusers. Clinical surveys indicate that
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Rates of alcohol and benzodiazepine abuse are particularly high in MMP (67-70). Relative to other MMP, patients who abuse benzodiazepines and/or alcohol exhibit a more severe profile of symptoms including greater psychopathology, more HIV risk-taking behavior, poorer health and social functioning, and a greater mortality risk (67, 71-75). For both alcohol and benzodiazepines, patients commonly report using the drugs to “boost” the effects of their daily methadone (69, 76, 77). These clinical observations are supported by evidence that experimental administration of the benzodiazepine diazepam potentiates the subjective and physiological (e.g., pupil constriction) effects of methadone and decreases methadone self-administration in MMP (78, 79).

Given that alcohol and benzodiazepines are both known to profoundly impair performance after acute administration (67, 80), potentiation of performance-impairing effects of opioid pharmacotherapies could have serious consequences. In fact, results of an epidemiological study of suspected drug-impaired drivers indicated that all methadone-positive samples were also positive for an additional drug, raising concerns about possible functional performance impairment associated with methadone/drug combinations (81). To our knowledge, only one laboratory study has examined interactive effects of alcohol on performance in MMP and BMP (41), and only one has examined interactive effects of a benzodiazepine (82). As noted earlier, Lenne et al. (41) reported that opioid abusers receiving daily chronic dosing of methadone or buprenorphine were unimpaired on simulated driving relative to controls. Although acute alcohol dosing impaired simulated driving in all three groups, it did not differentially affect performance of the pharmacotherapy groups relative to controls. While these results do not provide support for the hypothesis of additive interactions between methadone/buprenorphine and alcohol, conclusions are limited by the lack of impairment in the pharmacotherapy groups in the absence of alcohol and the relatively low alcohol dose (at or below .05% blood alcohol). Linnoila and colleagues (83, 84) demonstrated that another opioid, codeine, potentiated the performance-impairing effects of alcohol on simulated driving, supporting the hypothesis of additive interactions between opioids and alcohol. Lintzeris et al. (82) examined the effects of acute doses of the benzodiazepine diazepam (10 and 20 mg, placebo) in 8 MMP (mean daily dose: 55 mg) and 8 BMP (mean daily dose: 10.5 mg). Diazepam produced significant impairment relative to placebo on cancellation time, reaction time, and DSST performance in the MMP but only on cancellation time in the BMP. While these results suggest that interactive effects with benzodiazepines may be greater for MMP, conclusions are limited because the two groups were not directly compared to each other due to the small sample size.

Comparison of effects of opioid pharmacotherapy versus alcohol and other drugs. A critical issue is the extent to which opioid pharmacotherapy may be associated with functional impairment in a patient’s natural environment. One way to address the issue of functional impairment is to estimate the degree of expected impairment in the environment by directly comparing the performance deficits to those produced by other drugs that have already been established as producing clinically significant impairment. The World Health Organization has recommended that alcohol (which
has a well-established association with traffic accidents and driving impairment) be used as a reference drug against which to compare other drugs with respect to performance impairment (85). Likewise, the International Council on Alcohol, Drugs and Traffic Safety has proposed that categories of drug-induced driving-related impairment be defined in reference to specific blood alcohol levels, and researchers have recommended that alcohol be included as an active drug control when evaluating effects of drugs on driving (86). This approach of using alcohol as a reference drug for assessing performance impairment has been employed by researchers to estimate the impairment associated with opioid analgesics and other drugs used as anesthetics during ambulatory surgical procedures (87,88). However, to our knowledge, it has not been applied to pharmacotherapies for opioid dependence. Some investigators have also argued for the usefulness of establishing a hierarchy of performance impairment in which drugs are ranked relative to each other with respect to their performance-impairing effects (89,90). Such a hierarchy was attempted with alcohol, benzodiazepines, antihistamines, caffeine, and nicotine, but opioids were not included (89).

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Introduction

Methadone is a synthetic opiate used for the treatment of heroin abuse and pain. Methadone was first synthesized in 1939 as a long acting narcotic in Germany and patented in 1941, but was never widely manufactured or prescribed since German scientists were unable to develop a safe protocol for its use. It was brought to the U.S. Public Health Hospital, in Lexington, Kentucky after World War II as one of the spoils of war. Methadone was found to be an analgesic and effective medication to withdraw

Key Words: Methadone Maintenance - Heroin Addiction
Treatment - Integrated Model- Dual Diagnosis
addicts from heroin. Subsequently, it was used for both purposes—withdrawal and pain treatment. In the 1960s, at The Rockefeller University under the direction of Dole and Nyswander, methadone’s properties as a maintenance medication were discovered, and a clinical protocol for methadone maintenance was developed (1).

The benefits and safety of methadone maintenance in the treatment of heroin addiction have been supported over the last 30 years by numerous research studies (2, 3, 4, 5, 6, 7). As a result, methadone treatment programs have been established in most of the United States, including Puerto Rico and the Virgin Islands.

However, with the spread of serious infectious diseases among heroin/opiate abusers, the declining funding for social services and the prevalence of mental illness among the addicted population (8), the present urban methadone treatment programs are considered to be full-scale medical and human services agencies trying to address all the medical and psychosocial problems presented by the patient population (9).

This paper will describe the treatment services provided at the Vincent P. Dole Research and Treatment Institute for Opiate Dependence (The Institute), a methadone program in New York City, which could serve as a guide for the development of patient-centered services to opiate dependent individuals.

The Institute’s treatment services are founded on a biopsychosocial conceptual model, which integrates the delivery of treatment services to patients through interdisciplinary collaboration. The biopsychosocial model is based on a system framework which encompasses the interaction of biological, psychological and social factors in the evaluation of the individual for clinical interventions. Furthermore, it incorporates a social learning or behavioral approach to treatment interventions (10).

Treatment of opiate addiction through methadone maintenance requires of our patients a commitment to abstain from illicit drugs and to work intensively with the staff on issues that will promote a healthy lifestyle. Attention must be paid not only to patients’ physiological problems, but also to their psychological personality make-ups as well as their ability to function as productive social beings.

Central to the Institute’s mission is the continuous search for excellence of clinical pathways that meet the treatment needs of each of our patients and empower them to assume positive control of their lives. Similarly, the Institute’s philosophy is based on a set of individual but interrelated principles and assumptions which constitute the essence of wisdom that guides clinical strategies and interventions. The tenets underlining our treatment philosophy are based on the following:

- Addiction is a disease with physiological, psychological and social ramifications.
- Although a methadone patient is solely responsible for his/her recovery, he/she cannot achieve recovery alone. Self-motivation is the impetus of recovery which requires the strength and support of others.
- Methadone maintenance controls the craving and withdrawal from opiates, but the total recovery is a one-day-at-a-time lifelong process. A methadone patient can change the course and quality of his/her life by changing how
he/she behaves in the world; by learning behaviors that are responsible; and by gaining self-respect and self-worth.

- Recovery is enhanced by the empowerment of the individual – free of illicit drugs, independent, productive, prepared vocationally and educationally for career or employment commensurate with skills and interest level. Empowerment is a process of continuous growth and change throughout the patient’s lifetime.

Although addiction to opiates/heroin is a metabolic disease, the methadone patients might exhibit behavior symptomatic of a past or present dysfunctional family system; of repressed or blocked painful, traumatic experiences, and lastly, symptomatic of feelings of isolation, alienation, powerlessness and hopelessness. Hence, treatment relies on the capacity of recovering methadone patients to take their rightful and responsible roles as individuals and caring parents, spouses and members of the community at large. Therefore, we believe that the longer the treatment, the more comprehensive the treatment, the greater the chances will be for rehabilitation.

History

The Vincent P. Dole Research and Treatment Institute for Opiate Disorders (the “Institute”) of the Weill Cornell Medical College and the New York Presbyterian Hospital consists of two methadone clinics that provide treatment to a population of about 300 patients. The clinics originated in 1969-72 in the wake of the heroin epidemic of the 1960’s. The two clinics serve distinct populations: one is the Adolescent Development Program that specializes in the treatment of adolescents and younger adults and the other is the Adult Services Clinic that treats older adults whose average age is 45.

The Adolescent Development Program (ADP) was established by Drs. Marie Nyswander and Vincent P. Dole in 1969 at the Rockefeller University. In 1971 the program was moved to the Cornell Medical College Department of Public Health and Pediatrics under the leadership of Drs. Robert Millman and Elizabeth Khuri. It is the only nonresidential outpatient day program in the United States that offers methadone maintenance to qualifying adolescents who are opiate addicted as well as young adults. The program specializes in providing comprehensive treatment services to two distinct populations: youth and young adults with psychiatric disorders.

The Adult Services Clinic (ASC) was established in 1972. From its inception the program has been a source of hope and a treatment choice for older, chronic opiate addicted individuals who could not control their addiction through drug-free treatment. The patients are from all walks of life: many are gainfully employed; others are engaged in vocational training or pursuing academic goals; some are homemakers; and, others are suffering from chronic medical and psychiatric debilitating illnesses.

On September 2001, with the assistance of Dr. Herman Joseph from the New York State Office of Alcoholism and Substance Abuse Services, the clinic expanded its services in response to the need for moving on to a higher level of care those patients
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who are psychosocially rehabilitated. A physician/pharmacy-based unit was created, under the sponsorship of the New York State Office of Alcoholism and Substance Abuse Services, U. S. Center for Substance Abuse Treatment and the Department of Public Health of the Cornell Medical College. Patients who are fully rehabilitated and meet a specific treatment criterion are transferred to the new unit where they see a physician once a month and pick up their medication at a neighborhood pharmacy without observed ingestion by pharmacy staff.

The Institute participates in the Weill Medical College/New York Presbyterian Hospital’s Community Health Fairs which provides opportunities to further educate the community at large about addiction and the Clinics’ services. In addition, it sponsors an annual art show featuring paintings, drawings, photography and poetry contributed by staff and patients, to which community residents and merchants are invited.

Academic and Research Mission

As part of the Weill Cornell Medical College academic mission, the Institute provides education on addiction medicine and is a practicum for medical students and fellows, graduate social work interns and nursing students. Furthermore, the Institute has established research collaboration with other departments of the College and Hospital as well as with other institutions, such as the Rockefeller University.

Direct Care Staff

The direct care staff of the Institute’s clinics is composed of six psychiatric social workers, two substance abuse counselors, three psychiatrists, two internists, two registered nurses and two licensed practical nurses.

Treatment Services

As previously mentioned, we believe that recovery is enhanced by the empowerment of the individual patient. We define empowerment as a process of continuous growth and change throughout the patient’s lifetime. Therefore our treatment services focus on a holistic, individualized approach to habilitation/rehabilitation of the patient.

The treatment interventions are outlined with the patient during the first 30 days following admission after a thorough intake assessment is performed. The intake assessment includes the following: history of substance abuse; medical and psychiatric history; as well as a history of psychosocial development and functioning (employment, legal, domestic violence, education, family and support system, spirituality). In addition, a special needs assessment is done to elicit the treatment needs of our female patients. The intake assessment is used as the basis for the initial treatment plan, after a thorough discussion with and approval by the patient and the interdisciplinary team. The plan is reviewed periodically during the course of the patient’s treatment.
During the admission process a physical examination, which includes PPD test, chest X-rays for HIV+ and PPD+ patients, as well as HIV (voluntary) is performed. In addition, the admission screenings include blood testing for HCV, HAV and HBV antibodies and antigen, liver function test (ALT/AST) and sexually transmitted diseases. Laboratory results are reviewed and discussed with patients by the physician. Patients who are negative for HBV and HAV are given immunizations of either HBV or HAV/ HBV combination for a series of 3 doses to be given in 6 months. All patients are also counseled and provided health education, prevention focusing on sexually transmitted diseases and Hepatitis C, and wellness. Furthermore, an EKG is performed on all patients since some patients in methadone treatment programs may have conditions or behaviors, including abuse of cardiotoxic substances, cardiovascular disease, electrolyte imbalances, or are on prescribed medications that may foster cardiac repolarization disturbances that are associated with increased risk for arrhythmia (11).

Most of our patients are either dually or multiply diagnosed. Some of the diagnostic categories are reported in table 1.

The services offered are as follows:

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Disorders</td>
<td>56%</td>
</tr>
<tr>
<td>HIV+</td>
<td>12%</td>
</tr>
<tr>
<td>HCV+</td>
<td>64%</td>
</tr>
<tr>
<td>Asthma</td>
<td>10%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12%</td>
</tr>
<tr>
<td>Cardiovascular problems</td>
<td>27%</td>
</tr>
</tbody>
</table>

**Substance Abuse - methadone/buprenorphine**

Immediately after admission the patient receives the first dosage of methadone. Dosages are individualized and determined by the patient’s history of opiate use and medical status. For example, a Hepatitis C+ patient with a liver condition might necessitate a specific dosage of methadone to be taken two times per day in order to avoid withdrawal symptoms. Initially, the patients are medicated in the clinics’ setting on a daily basis six times per week, and take home a dosage for Sundays. As the patient progresses in treatment, take home medications are increased up to a month of take home dosages after three years in treatment.

The clinic also offers buprenorphine to a selected number of patients through the individual licenses of some of the clinics’ physicians. Patients on buprenorphine are inducted in the clinic, and a prescription for a week supply of medication is provided. The Institute has arranged with the same pharmacy that dispenses the methadone to the pharmacy-based methadone patients to do the same with the buprenorphine. Similar
to the methadone maintained patient, a prescription for monthly medication can be
provided when indicated by the patient’s progress in treatment.

Both during the initial phase and during the course of treatment the clinical staff
monitors the patient’s stabilization, providing individual and group counseling which
includes relapse prevention interventions. Important as well, is the patient’s participa-
tion in outside-based methadone anonymous groups. Furthermore, on going collection
of urine specimen and, when indicated, blood analyses are conducted to ensure stabi-

dization and appropriate dosing. In cases in which a patient has to give a supervised
urine specimen, the patient is asked to empty their pockets and to leave packages or
pocketbooks outside the urine collection room. At no time, is the staff in the room with
the patient nor are patients observed through two way mirrors or cameras.

Medical Treatment

The clinics serve as the primary care setting for most of the patients. Internists are
available to provide the necessary health care, either through preventive interventions
or through follow-up of acute and chronic conditions. In addition, the clinics have a
close relationship with the other Hospital’s Specialty Clinic for an integrated patient-
centered health care. Some of the services provided at the clinics are:

1. Annual physical examinations that, depending upon the age and medical his-
tory of the patient, include: urine and blood analysis; PPD or anergy panel
and chest X-ray when indicated; EKG if indicated; prostate screening, bone
density for male and female patients over the age of 40, mammogram, and
colonoscopy, testing for Hepatitis A, B, when indicated;

2. HIV testing and medical follow-up for patients who are positive. Psychoedu-
cational interventions as well as support therapy groups, focusing on treatment
adherence and prevention of risky behaviors.

3. Hepatitis C testing and follow-up. Upon determination of reactive HCV virus,
the patient is referred to the Hospital’s Hepatitis C Clinic. A week prior to ap-
pointment, the patient is given a Health Assessment Form (a tool to measure
fatigue scale and medical history). Peak and trough methadone level is also
obtained to determine how fast the liver metabolizes the methadone which
may require an increase in dose. Once the patient is seen at the Hepatitis Clinic
and medications are started, ongoing appointments with the clinics’ internists
and the psychiatrists are scheduled in order to closely monitor adherence.
Important as well is the provision of health education focusing on prevention
of risky behaviors.

4. Smoking Cessation. This medical service consists of administration of the
Pulmonary Function Test, medication assisted treatment through the pre-
scription of nicotine patches as well as provision of individual and/or group
counseling using cognitive behavioral techniques.

5. Follow-up of patients with hypertension, diabetes and/or asthma, which in-
cludes health education.

6. All along, the medical services provided at the clinic included bone density
testing for female patients. However, in 2003 bone density testing for male patients, age 40+ was initiated. Of the first group of 70 patients tested, 39 were positive for either osteopenia or osteoporosis, which prompted the medical director to initiate treatment for those patients. The prevalence of low bone density in methadone maintained patients was recently discussed in an article in the Addiction Treatment Forum (12). The article summarizes a study of bone density conducted by researchers at the Boston University School of Medicine with a sample of 92 patients enrolled in a methadone maintenance treatment program. The study showed below normal bone density in 83% of the sample, with 35% showing osteoporosis and 48% showing signs of osteopenia. Although the authors include the male gender as a significant predictor of low bone density, they do not indicate the specific number of males and females included in the study nor the age group.

7. Pain management services coordinated with the Hospital’s Pain Management Clinic. All patients are assessed for pain during the intake admission and periodically as needed. If the patient has a chronic condition he/she might be referred to the Hospital’s Pain Clinic or provided follow up by the clinics’ physicians. Pain medication prescribed by the Pain Management Clinic and the medical director of the Institute are documented in the patients’ methadone treatment records. We are therefore aware of all aspects of the patients’ treatment and medications prescribed, and, when indicated methadone dosages can be adjusted.

8. Gender-specific services for female patients. On-site gynecological services are provided through pap smears analysis once a year, or as needed. This service was instituted due to the fact that female patients were not following up with the annual referrals to the Hospital Gyn Clinic, due to feeling uncomfortable with disclosing their drug addiction history and status as methadone patients. The female patients who are 35+ years are referred for mammographies and bone density testing. Women’s group, family planning and parenting classes are also provided.

9. Annual influenza vaccinations and pneumococcal and tetanus vaccines, when indicated.

**Psychiatric Services**

It has been established that opioid addicted individuals in methadone treatment programs have higher rates of co-morbid psychiatric and substance abuse disorders (13, 14). Receiving appropriate treatment for their co-morbid disorders has been difficult for these patients, particularly due to the fact that historically, both the mental health and the substance abuse treatment systems have developed well defined disease specific categories for the delivery of treatment services. This perceived bias is for the most part in the direction of treatment of primarily single rather than dual diagnosis symptomatology. In addressing this problem, we have developed an integrated approach to the delivery of treatment services to our psychiatric and substance abuse dually
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diagnosed patients.

During the intake phase a thorough mental health status assessment is performed by the social worker to determine whether the patient requires immediate psychiatric intervention. If the patient is not in need of immediate psychiatric care, an appointment is scheduled with one of the clinics’ psychiatrists for an evaluation. During the evaluation, the psychiatrist diagnoses the patient and, if needed, provides the patient with the required psychotropic medications and follow-up plan, which includes monitoring of psychotropic medications’ interaction with the methadone. The evaluation also includes the assessment of the patient’s possible use of other illegal substances as well as “street purchased pills” and the purpose that they serve to the patient’s mental health illness (“self-medication”). We need to mention that a very important aspect of the treatment of the mentally-ill patients in our clinics is the ongoing psychotherapy (individual and group) provided by the psychiatric social workers.

In case a patient requires in-patient hospitalization, he/she is admitted to the Hospital’s Psychiatric Department with follow-up by the psychiatrists and social workers while they are hospitalized. However, it is worthwhile mentioning that although 56% of our patients have an AXIS I diagnosis (other than opioid addiction) less than 2% have been hospitalized for psychiatric reasons within the last 5 years. In addition, because of appropriate prescribing of psychiatric medication, there has been no evidence of oversedation in the patients caused by the use of illicitly obtained sedatives, which is a problem often seen in methadone treatment programs that do not provide psychiatric services.

Other Psychosocial Services

The provision of concrete services to some of our patients is also a significant aspect of The Institute’s treatment milieu. In terms of social rehabilitation, the clinic population can be described as follows: 45% fully employed or full time homemakers, 6% homeless, 8% physical or mentally disabled, 41% unemployed.

The Institute has developed collaborative efforts with community agencies to provide services to patients in need of housing, vocational/educational training and social welfare entitlements. In addition, graduate social work students from various universities and colleges provide vocational/educational assessments and preparation for high school equivalency diploma as well as concrete psychosocial services and case management. It needs to be mentioned that outreach to the families of patients is a consistent effort on the part of the staff in order to educate them about methadone treatment and to facilitate reintegration of the patient to the family system.

In summary, being cognizant of the biopsychosocial problems facing opiate/heroin addicts and the struggles and stigma often faced by methadone maintained patients when seeking services elsewhere, we have successfully developed comprehensive treatment services that involve an interdisciplinary approach, collaboration with other community agencies and graduate schools of social work. This approach has enabled the clinics to be a “one-stop shopping” setting that facilitates a seamless delivery of services that ensures a patient-centered treatment environment.
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Opioid Substitution with Methadone and Buprenorphine:
Sexual Dysfunction as a Side Effect of Therapy

Randall T. Brown and Megan Zueldorff

Summary

Opioid substitution is the most widespread and well-researched treatment modality for opioid dependence. Methadone and buprenorphine are currently the most commonly used pharmacotherapeutic agents. Sexual dysfunction has been reported as an adverse effect of opioids including methadone and buprenorphine. The current article describes proposed mechanisms for sexual dysfunction as an adverse effect of methadone and buprenorphine, summarizes research conducted on subjects on these agents, and explores appropriate evaluation and intervention in the management of the types of sexual dysfunction most commonly encountered during opioid substitution treatment (libido, erectile, and orgasm dysfunction).

Key Words: Opioid Replacement Therapy - Methadone - Buprenorphine - Sexual Dysfunction

Opioid substitution treatment (OST) is the most common and most effective modality for the treatment of opioid dependence. Currently, in Europe, over 460,000 individuals (18) and, in the U.S., over 241,000(32) receive opioid substitution in the form of methadone or buprenorphine. Of individuals receiving methadone or buprenorphine for opioid dependence, 99% in the U.S. (31) and 91% in Europe (18) receive methadone.

Sexual dysfunction is a commonly reported side effect of opioid medications, and has been investigated in samples receiving OST, primarily methadone maintained males. Common complaints related to sexual function, and potentially to sex hormone levels,
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among those on OST include decline in libido, orgasm dysfunction (delayed orgasm or inability to achieve orgasm), and menstrual irregularity (primarily oligomenorrhea and amenorrhea)\(^{16,17}\). Disorders of detumescence, or resolution, have not been associated with opioids or OST.

Consideration of sexual dysfunction as a medication side effect is important, because, besides creating difficulty in intimate relationships, it has the potential to lead to decreased compliance with therapy and to interfere with the known benefits of OST. While the impact of sexual dysfunction upon treatment compliance has not been studied in OST-receiving samples, sexual dysfunction has been shown to interfere with therapeutic compliance among subjects with depression, \(^{22}\) HIV, \(^{37}\) and hypertension \(^{31}\).

Reproductive physiology

**Male**

The normal secretion of male sex hormones (i.e. androgens) is mediated by pituitary hormones, primarily FSH, which is regulated by inputs from the hypothalamus (gonadotropin releasing hormone = GnRH) and gonadal tissue (inhibin). This feedback pathway is illustrated diagrammatically in Figure 1.

GnRH exhibits wide diurnal fluctuations in serum concentration. GnRH, in turn, regulates the secretion by the pituitary of FSH in men, which, in turn, stimulates the production of sperm and testosterone (by Leydig cells) in the testes. Only the portion of testosterone which is free in serum (as opposed to that portion which is protein-
bound) is physiologically active. Inhibin, secreted by Sertoli cells in the testes, provides negative feedback to both the pituitary and the hypothalamus to further regulate this feedback system in the male.

Achievement of normal arousal, erection, and ejaculation also depends upon intact neurological and vascular function. Parasympathetic stimulation of nitric oxide (endothelial-derived relaxation factor) secretion results in relaxation of corporeal smooth muscle and erection. Ejaculation is controlled via sympathetic input. Sympathetic input then results in stimulation of alpha-1 and alpha-2 adrenergic receptors in the corpora cavernosum and, hence, detumescence.

Testosterone plays an important role in sexual functioning for males. Lower-than-normal serum testosterone may manifest as reduced libido and erectile dysfunction. With prolonged depression of serum testosterone, seminal emission may be inhibited, as well. Hypogonadal men who undergo testosterone replacement demonstrate increases in sexual interest and erectile function \(^4\).

Sexual dysfunction among men on OST appears to be related to lower-than-normal serum levels of testosterone \(^10,13,24,25\). The association between opioids and low serum testosterone levels may occur through a variety of mechanisms. Opioids have been shown to suppress normal pituitary secretion of FSH and LH, which, in turn, would interfere with normal testosterone and sperm production by the testes. More proximal interruption of normal endocrine function may occur through alteration of the normal pulsatile secretion of GnRH by opioids, which would also interfere with normal activity of LH and FSH. Interference with the usual dopaminergic mediation of prolactin secretion, leading to elevated prolactin levels, and, in turn, decreased testosterone production may also cause sexual dysfunction in men on OST. Opioids may also act directly upon testicular tissue to suppress normal testosterone production \(^14\).

**Female**

Research regarding sexual dysfunction among females on OST is more scant. Sexual dysfunction among women on OST appears to be primarily related to interference with the normal cyclic production of LH and FSH, possibly due to elevated production of prolactin. This process interferes both with hormones necessary for maintenance of a normal menstrual cycle (estrogen, progesterone) and for normal libido (androgens). Interference with these sex hormones is thought to lead to the common signs and symptoms of sexual dysfunction and hormonal dysregulation among women on OST: depressed libido and oligomenorrhea or amenorrhea.

While it is clear that impaired androgen production is closely and directly associated with sexual dysfunction in males, the relationship within females is more complicated and less clear. The normal mid-cycle rise in serum androgens in women has not been strongly related to sex drive \(^4\). Transdermal replacement of lower-than-normal serum androgens in female subjects, however, has been shown to result in improvements in mood and libido \(^3,7\). Additionally, women with normal levels of serum testosterone, when given testosterone supplementation, have demonstrated an increased sexual response \(^38\).
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Methadone: Specific study findings

Studies have demonstrated higher rates of sexual dysfunction in methadone-maintained populations than in the general population (9, 20, 23, 27, 28, 35, 36). Estimates of prevalence, however, vary significantly: 30-100% (14, 17, 20). Additionally, the prevalence of specific types of sexual dysfunction (libido, erectile, and orgasm dysfunction) has not been examined in detail.

Early studies did not consistently demonstrate a dose-response relationship between methadone and sexual dysfunction or between methadone dose and serum hormone levels. In 1974, Cushman and colleagues failed to find a main relationship between a one-time methadone dose and serum levels of LH, FSH, prolactin, or testosterone in 8 male volunteers. Stable long-term doses of methadone were likewise not found to have an effect on serum LH, FSH, prolactin, or testosterone in these subjects (12). Early work also indicated that, if LH and FSH levels were affected by methadone, that the effect was likely mild and transient (6, 12). In an interview study of 50 men enrolled in a methadone maintenance program, sexual dysfunction was highly prevalent in the group (33%), but no relationship was found between sexual dysfunction and demographics, methadone dose, or substance use history (20).

Several studies provided conflicting results, however, indicating that methadone influenced sex hormone levels. Willenbring et al demonstrated a maximally stimulated level of prolactin in 15 men (average daily dose of 52.7 mg of methadone, average duration of maintenance 18 months), providing evidence for interference by prolactin as a potential pathway leading to depressed testosterone and, hence, to sexual dysfunction in men on methadone maintenance (39). Cicero et al in their 1975 study found multiple sexual effects in 29 methadone-maintained male subjects. Ejaculate volume and seminal and prostatic secretions were found to be 50% of those in 43 narcotic-free controls. Serum testosterone levels were, on average, 43% of control subjects'. The mean daily methadone dose in this study population was 67 mg. (9) Cicero replicated similar findings in a male rat model. Serum levels of LH were undetectable in rats receiving methadone or morphine. This lead to the hypothesis that methadone may act to reduce serum testosterone levels via interference with pituitary or hypothalamic regulatory hormones.

In one of the first studies to examine particular types of sexual dysfunction in a methadone maintained sample, Teusch et al found men maintained on methadone to report reduced libido and orgasm dysfunction more frequently than controls (36). Similar to earlier studies, however, the severity of dysfunction and methadone dose were unrelated. In more recent work, Brown et al also demonstrated a link between methadone dose and orgasm dysfunction among 92 men maintained on an average of 100 mg methadone daily (8). Surprisingly, serum testosterone and prolactin levels were not found to be, on average, outside the normal range in spite of the relatively high daily methadone dose compared to previous study samples. Elevated prolactin was, however, the most common endocrinologic abnormality in the sample.

Spring et al provided some of the earliest evidence demonstrating a relationship
between sexual dysfunction and methadone dose \(^{(35)}\). Their study used a validated instrument to examine sexual dysfunction in 25 men maintained on methadone for an average of 2 months. They found that men experiencing significant sexual dysfunction were more likely to be on higher doses of methadone. However, this was a cross-sectional study, and men with sexual dysfunction also endorsed a greater number of psychological symptoms, an important potential confounder for an effect by higher methadone dose.

Mendelson et al conducted a prospective study of the effect of acetylmethadol administration on serum testosterone levels in 13 men with opioid dependence which yielded significant results. A statistically and biologically significant decrease in serum testosterone was found 7-9 hours after acetylmethadol administration. Testosterone levels attained normal levels 48 hours after drug administration\(^{(24)}\). Mendelson also conducted some of the earliest work demonstrating a relationship between methadone dose and serum testosterone concentration\(^{(25)}\). When the sample (n =38) was dichotomized into groups receiving lower dose (10-60 mg) and higher dose (80-150 mg) methadone, the men receiving higher daily doses of methadone were found to be more likely to have abnormally low serum testosterone. As further evidence of an inverse relationship between methadone dose and serum testosterone levels in this study, reductions in methadone dose were associated with recovery of testosterone levels. Mendelson et al found similar results in a sample of 10 men administered heroin in a controlled setting for 7 days and then detoxified using methadone at a starting dose of 35 mg.\(^{(26)}\). Again, abnormally low serum testosterone levels found during and after the period of heroin administration were found to recover to baseline after methadone detoxification.

Literature regarding sexual dysfunction in female subjects on OST is scant. One study indicated that 50% of women switching from heroin to methadone experienced improvement in sexual function\(^{(1)}\). Methadone was shown to depress serum testosterone levels in female subjects in one study \(^{(11)}\). This depression of testosterone in women was also associated with increases in serum prolactin\(^{(34)}\).

Nearly 50% of women experience menstrual irregularity while on methadone maintenance. The effect appears to be dose-related, and appears to decline over time, with the potential for resumption of normal menses without alteration of methadone dosing\(^{(33)}\).

**Buprenorphine: Specific study findings**

Buprenorphine is a partial mu agonist with a high receptor affinity and, like full mu agonists, has been shown to be efficacious in the treatment of opioid dependence. Studies comparing buprenorphine to the more commonly used methadone have found that rates of success in treatment are similar and that buprenorphine may result in fewer adverse effects. However, only one study to date has examined the prevalence of sexual dysfunction in particular among patients treated with buprenorphine.

In 2005, Bliesener and colleagues examined 17 male patients maintained on
buprenorphine and 37 male patients maintained on methadone\(^5\). Patients self-reported effects on libido and potency, and total and free testosterone, LH, FSH, estradiol, and prolactin were assayed. Blood samples from 51 male volunteers were used as a control group for the hormone analyses.

Twenty-three percent of patients in the buprenorphine group reported a decrease in libido, as compared to 83% in the methadone group. Twelve percent reported reduced potency, as compared to 72% in the methadone group. Other forms of sexual dysfunction, such as orgasm dysfunction, were not examined in this study.

The Bliesener study also found that patients treated with buprenorphine had significantly higher mean levels of total (5.1 ± 1.2 ng/mL) and free (17.1 ± 4.8 pg/mL) testosterone than did patients treated with methadone (2.8 ± 1.2 ng/mL and 7.8 ± 2.9 pg/mL, respectively), and that in fact mean total testosterone levels of those patients being treated with buprenorphine did not significantly differ from levels in the healthy control group sample (4.9 ± 1.3 ng/mL). Mean levels of prolactin were significantly higher in the methadone group (8.7 ± 8.3 ng/mL) than in the buprenorphine group (5.0 ± 2.0 ng/mL), though all groups were in the normal range. There were no other significant differences found in the hormonal analysis.

In an examination of BDI scores collected in the same study, mean scores of the opioid therapy groups were not found to differ significantly from one another. This lack of difference, as well as a lack of significant difference in age, medical status, length of addiction concurrent medications, or frequency of illicit opioid use led the authors to conclude that it was most likely the treatment drug rather than other variables that contributed to the differences between therapy groups in hormone levels and reports of sexual dysfunction.

**Implications for evaluation and treatment**

**Libido dysfunction**

Low serum testosterone due to opioid effects on the hypothalamic-pituitary-gonadal axis may explain libidinal depression. However, because psychological factors are common causes of depression of sex drive, and because psychiatric comorbidity is so prevalent in the substance dependent population, mental and emotional health should be investigated in addition to hormonal assays. Conditions of potential importance include mood disorders, psychosis, situational stressors, gender identity issues, and age-related psychological issues.

Medications other than OST should also be reviewed, as these are also common causes of a depressed sex drive. Common offenders include antihypertensives and psychotropic agents.

Should other etiologies be ruled out, given the associations in the literature between methadone dose and serum testosterone level, reasonable therapeutic approaches may include replacement (parenteral or transdermal) of abnormally low testosterone or a reduction in daily methadone dose. In an open-label study, methadone-maintained men
Erectile dysfunction

Erectile dysfunction (ED) more commonly has an organic or iatrogenic etiology. A variety of systemic illnesses are associated with ED. These include chronic liver disease, renal failure, arteriosclerotic cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and malignancy. Spinal trauma and genitourinary surgery are of potential etiologic importance in ED, as well (21). Though more rare, congenital and other anatomic genitourinary anomalies (e.g. Peyronie’s Disease, phimosis, post-traumatic aneurysm) should be considered.

Medications commonly associated with ED include antihypertensives, psychotropic agents, and medications with anticholinergic effects. Smoking (19) is strongly associated with ED. The relative risk for ED increases by 1.31 for every 10 pack-years of smoking (29).

Though organic factors commonly cause ED, mental and emotional health issues may be significant contributors, as well. Depressive symptoms have been most strongly associated with ED, with 90% of men with severe depression reporting ED in one study (2). Association with anxiety disorders has also been reported (32).

Summary

OST, primarily methadone, appears to be associated with alteration of serum levels of hormones related to normal sexual function. In males, opioids may act via: (1) interference with the normal production of hypothalamic and pituitary regulatory hormones (LH, FSH, GnRH), (2) elevation of serum prolactin, (3) direct action on the testes to suppress testosterone production. While elimination of other common medical and psychiatric etiologies for sexual dysfunction is warranted, replacement of abnormally low serum testosterone may effectively treat libido or erectile dysfunction, and potentially delayed orgasm or anorgasmia. Replacement of abnormally low androgens in women on OST may also improve libido as well as mood. Abnormalities in the menstrual cycle are thought to be transient and may not require alteration of OST dosing. Patients with refractory sexual dysfunction and a stable course in terms of their opioid use disorder may respond to reduction in the dose of their OST agent, with methadone likely being of greater significance here than buprenorphine.

In light of the paucity of studies in the area of sexual dysfunction as an adverse effect of buprenorphine, more research is needed, utilizing larger patient populations and examining more thoroughly specific types of dysfunction in both male and female populations.
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Paxil (Paroxetine)  in Complex Therapy in Heroin Addicts

Maya Rokhlina, Tatiana Kitkina and Georgi Gubanov

Summary

The efficiency of Paroxetine was studied in 27 males with heroin addiction (average age: 26.2 years, average disease duration: 3.4 years) undergoing detoxification. After 3-4 days of paroxetine (initial dose 20 mg/day, maximum dose 40 mg/day) the first improvement of affective symptoms were noticed. By the 14th day of treatment, affective discomfort had been arrested in most cases. On the whole paroxetine can be considered an effective medicine for contrasting affective discomfort of heroin addicts in the post-withdrawal stage, as long as agonist compounds are not available.

Key Words: Heroin Addiction- Affective Disorders - Antidepressants – Paroxetine

Introduction

Affective symptoms are frequent and prominent among other psychopathological symptoms in patients with heroin addiction. Extensive research proved that affective disorders are present to a variable extent at every stage of the disease: dysphoria and irritability are featured in chronic heroin intoxication and amplify during withdrawal, parallel to the somatic and vegetative symptoms. By the time acute

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Symptoms of the withdrawal have faded (days), affective symptoms will loom in the foreground. In almost all cases low mood is accompanied by irritation, asthenia, general displeasure, dissatisfaction with treatment, proneness to aggressive and violent behavior, often in a psychopathic, unpredictable mode. During heroin-free periods, weakness, flabbiness and fatigability may prevail over properly depressive symptoms, while patients complain for low mood, lack of motivation and irritability accompanied by an attraction towards drugs. Emotional unsteadiness, enhanced sensibility and vulnerability are as well featured, patients becoming quite sensitive to even the smallest emotional discomfort and prone to distress for low levels of effort. Such a syndrome is known to be specifically responsive to opiate agonists, while it is expected to worsen under naltrexone treatment\(^{(15)}\). In Russia, methadone is not widely available for maintenance treatment of heroin addicts, so that the intervention upon drug addiction is limited to the intervention upon secondary symptoms. As for affective symptoms, antidepressants may be resorted to as means of discomfort reduction, hopefully retaining patients in treatment and contrasting their affective distress until methadone and buprenorphine patients are eventually available. In particular, selective serotonin reuptake inhibitors are safer and easier to manage. Moreover, some common biological grounds have been described. In man, the exhaustion of vein muscle produced by repeated inoculations of 5-hydroxytryptamine (5-HT) is antagonized by naloxone. During opiate withdrawal, the loss of vein sensitivity to 5-HT is observed together with the acute stress of opiate metabolism \(^{(3, 24)}\). The same phenomenon is documented for migraine sufferers during and between headache attacks \(^{(24)}\). Naltrexone is also effective in suppressing 5-HT-induced platelet aggregation \(^{(5)}\). Therefore, at least to some extent, 5-HT and opioid metabolism seem to be directly related. The impairment of 5-HT-metabolism is present in detoxified heroin addicts, regardless of psychiatric axis I or II comorbidity \(^{(6)}\). On clinical grounds, SSRIs are known to increase the likelihood of retention in naltrexone-based programs \(^{(7, 9, 12, 14, 25)}\). Lastly, buspirone was effective in reducing symptoms of opiate discontinuation in a double blind setting \(^{(21)}\). On the other hand, SSRI do not seem to be effective in preventing relapsing behaviour in non-abstinent, methadone maintained heroin addicts, and does not produce any significant improvement in depressive symptoms in these patients \(^{(2)}\).

Paroxetine \(^{(4, 10, 16, 17)}\) is one of the most specific inhibitors of serotonin reuptake, and the most potent. Its action on muscarin, and \(\alpha\) and \(\beta\) adrenoreceptors is not significant. Paroxetine’s half-life is between 16 and 21 hours, which allows once-a-day prescription, and has no active metabolites. Meals do not influence absorption of the medicine.

We reasonably expected that, in the absence of any specific agonist treatment, paroxetine may provide with some improvement of endogenous opioid function, or at least replace for failing opioid-mediated functions through the enhancement of 5HT metabolism. Such a property may be hypothesized for temporarily abstinent heroin addicts who have recently undergone detoxification, rather than in active users.
Methods

This study comprised 27 males with DSM-IV TR-rated heroin addiction were consecutively admitted for treatment at the Unit for Clinical Research on Drug Addictions at the National Scientific Centre for Drug Addiction of the Ministry of Health of the Russian Federation, during the period from February to December 2003. Patients with other known concomitant psychiatric disorders were excluded from the study. Patients were aged 19-34 years (average: 26.2 years). The disease lasted between 8 months and 10 years (the average disease duration: 3.4 years). Patients underwent the traditional detoxification schedule (Clonidine, Tramal, Tiopridal, Diazepam) followed by two weeks of paroxetine alone.

Patients were assessed at treatment entrance by a special rating scale including the most widespread symptoms of affective disorders typical of heroin addiction (see table 1). Each sign was registered according to a 0-3 grading scale (0 = absent; 1= mild or moderate; 2 = marked). Subsequently, each patient’s conditions were assessed on a daily basis during inpatient treatment, twice a week in the out-patient setting.

Paroxetine was prescribed from the 4th-8th day of inpatient treatment, after the extinction of the acute withdrawal syndrome was achieved. For all patients, the initial dose was 20 mg per day. Dosages could be increased on a clinical basis.

Results and comment

Retention was complete for the 27 patients enrolled, and all appointments scheduled on an outpatient basis were attended. Maximum administered dose was 40 mg per day. Increased dosages were administered to those patients, who showed symptoms of greater severity. In no case was paroxetine discontinued due to side effects or intolerance.

Improvement of symptomatology is reported in table 1. The first signs of improvement in the patients’ conditions were noticed as early as on the 3rd-4th day of paroxetine treatment. At the start of treatment the great majority of patients (n=21; 77.8%) reported marked depressed mood and melancholy, but by the 4th-7th day these symptoms were weakly or moderately expressed in a significant number of patients (n = 18; 89.9%). By the 14th day of treatment depressed mood was marked in 3 patients (11.1%) only, 12 (44.4%) had moderately depressed mood, and 12 (44.4%) showed no melancholy or depressed mood.

Some patients (n = 23; 85.2 %) had experienced a sense of guilt and aimlessness. By the 7th day of treatment only a few patients (n =10; 37%) alleged this symptom, which was absent by the 14th day of treatment in the great majority of patients (n = 24; 88.9 %).

Even more apparent changes were noticed in the analysis of symptoms such as anxiety and dysphoria. By the 4th day of treatment, anxiety was absent in 9 patients (33.3%), by the 7th in 12 patients (44,4%), and by the 14th in the great majority of patients (n=24; 88,9%). Disphoria and irritability showed the same trend: by the 14th day both anxiety and dysphoria had extinguished in the vast majority of patients (n=24; 88,9%).
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The great majority of patients claimed enhanced fatigability (n=22; 81.5%); some of them noticed weakness (n=12; 44.4%). Fewer patients claimed apathy and indifference (n=10; 37%). During the course of treatment fatigability significantly decreased: by the 14th day of treatment it was marked in 3 patients only (11.1%). By the 14th day of treatment 15 patients claimed slight weakness (55.6%), and 12 (44.4%) denied it.
Table 1: Efficacy of Paroxetine on affective symptomatology in heroin addicts

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As for apathy and indifference, it was absent in 18 patients (66.7%) by the 14th day of treatment. In a few patients (3 subjects: 11.1%) depressed mood was accompanied by slow psychomotor reactions, which disappeared by the end of treatment. Restlessness, alleged by 3 subjects (11.1%), also disappeared or was weak by the 14th day of treatment. A majority of patients (n= 19; 70.4%) showed low interest in activities of any kind. By the end of treatment 15 of them (55.6%) had become more active and
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interested. A significant number of patients (18 subjects: 66.7%) complained for the absence of sex drive at the beginning of treatment. This symptom proved to be the least curable, consistently with paroxetine side-effects profile: it could only be improved by the 7th day; by the 14th day it was absent in 12 patients (44.4%), but persisted in 6 patients (22.2%). At the beginning, most of the patients (n=21; 77.8%) showed marked or moderate concentration or attention impairment. By the 14th day of treatment with Paroxetine the concentration of attention had been restored in 2/3 of patients (66.7%). The analysis of symptoms such as slow mental processes revealed the same trend. By the 14th day of treatment these disorders were absent. On the whole, the improvement observed was consistent with known paroxetine antidepressant properties on non addicted depressed and anxious patients. The latency of improvement was shorter than expected, which is usually between two and four weeks. In some of the patients remission was gradual, while in others (n =3; 11%), despite eventual improvement, it appeared to be unsteady. Among unsteady responders (n=2; 7.4%) patients experienced a relapse into narcotic use and a subsequent exacerbation of affective symptoms. In these cases the prescription of paroxetine was prolonged until the elimination of affective disorders was complete, by 3-4 months.

Results were consistent with previous observations about the possibility to improve affective state in detoxified heroin addicts (1,13).

Conclusions

Paroxetine provided short-term relief of symptoms of affective discomfort in opiate addicts recently detoxified from heroin, who could not receive opiate agonist compounds due to legal limitations. Improvement was rapid and noticeable by two weeks for all symptoms typical of the post-detoxification state, with special regard to aimlessness, dysphoria, anxiety, apathy and lack of motivational drive.

In the absence of any agonist treatment option for the control of addictive symptoms and relapsing behavior, paroxetine may be useful to contrast post-withdrawal affective discomfort, between and across relapses.

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Use of Sodium Gamma-Hydroxybutyrate (GHB) in Alcoholic Heroin Addicts and Polydrug-Abusers

Icro Maremmani¹,²,³, and Matteo Pacini¹,³

Summary

Sodium gamma-hydroxybutyrate (GHB) in one of the most effective options available for the treatment of hard-core alcoholism in maintenance programmes that aim to achieve relapse prevention and rehabilitation. Polysubstance abuse and multiple addiction have become quite common in alcoholic youths and former heroin addicts receiving inadequate or no specific treatment. In approaching these categories, GHB is usually neglected, on the basis of the idea that its abuse potential must be amplified in abuse-prone individuals. However, the normalizing effects of anticraving treatment on the behaviour of heroin addicts may make GHB a suitable remedy for the heroin-alcohol polyabuse picture. The same cannot be said of cocaine abusers, due to the lack of anticraving treatments possessing major, reliable effectiveness. After reviewing the data in the literature on the use of GHB in alcoholics and other kinds of abusers, we describe 13 cases of alcohol-abusing heroin addicts, in which GHB proved to possess some effectiveness, even if there were major limitations regarding compliance and completeness of response.

Key Words: GHB, Polyabuse, Abuse Liability, Alcohol-Abusing, Heroin Addicts, Methadone, Buprenorphine.

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Use of GHB in alcohol dependence

Safety and efficacy

Sodium gamma-hydroxybutyrate (GHB) is a natural compound which can be found as a metabolite in human nervous tissues; it binds to specific receptorial sites in the brain. It exerts its action by modulating other systems too, or by affecting multiple-ligand receptorial sites. At different dose levels, GHB’s effects may be primarily anaesthetic or euphoric. At lower dosages it increases dopamine release, which is consistent with its documented anticraving properties, and its valuable impact on abuse liability and on the psychotic symptoms produced by overdosing. The onset of its effects is rapid; its half-life is so short as to require dose-refraction at least into thirds during the course of the day in therapeutic regimens, or using greater refraction (with fractions at intervals as short as three hours, corresponding to 8 fractions a day) – a procedure which results in more stable effects.

After failing to show antipsychotic properties in schizophrenic patients in two preliminary evaluations, GHB proved effective against alcohol withdrawal and alcohol addiction. In these therapeutic settings, GHB was safe and well tolerated. As for the treatment of alcohol withdrawal, it is preferable to other agents because of its shorter half-life, which allows repeated administration free of the risks of late overdosing by accumulation. Its binding rate to plasma proteins is negligible, it is eliminated almost completely without producing metabolites, and it does not affect the liver metabolic system.

In the meantime, reports about its abuse, its use as a date rape drug, and its recreational use outside therapeutic settings raised major concerns about the spread of GHB treatment. Hence, most of its therapeutic potential has been neglected in the attempt to avoid misuse. The outcome is that GHB, despite being one of the few effective drugs for the treatment of alcoholism, is rarely resorted to, and then mainly through inclusion in short-term schedules.

GHB has proved to be superior to placebo, benzodiazepines and clomethiazole in the management of alcohol withdrawal. When compared to flunitrazepam, GHB showed it was more effective against autonomic symptoms (lower rate of adjunct clonidine administration), though less effective against psychotic symptoms related to the transient increase of dopaminergic transmission (higher rate of adjunct haloperidol administration). GHB is as effective as diazepam over the whole range of alcohol withdrawal, and it allows a quicker resolution of psychic symptoms.

Research has proved that GHB is effective in reducing alcohol use by addicted subjects during periods of variable length (3-12 months). On methodological grounds, the effectiveness of GHB may be questioned, because of the absence of randomized controlled trials. However, due to the lack of widely available, mainly effective medications for the average alcoholic, the behavioural effects of GHB must necessarily be compared to the spontaneous course of alcoholism when left untreated. Moreover, participants in GHB studies were selected either on the basis of documented resistance.
to other available treatments or on the grounds of a severe grade of alcoholism.

In a multicentre study on 179 patients, complete response (sobriety) was achieved in 78% of the sample, the relapse rate being as high as 69.3% within a 6 month follow-up, and 78.6% in a 12 month follow-up after treatment discontinuation (3). In a 12-month study on treatment-resistant alcoholics, the retention rate was as high as 60%, with a 10% rate of complete response and a further 15% rate of partial response (comprising a reduction in drinking amounts and/or frequency). Interestingly, partial response was not associated with a worse outcome with respect to complete response. The possibility of achieving a complete response seems to be related to lower baseline consumption amounts.

Responsiveness to GHB seems to vary through time: in two separate studies, Addolorato and colleagues (3,4) reported a momentous response rate of 78.1% at 6 months and of 67.8% among two-month survivors. In the 12-month study by Maremmani and colleagues, complete response was less frequent, and less likely in the long-term, though it must be noted that the subjects enrolled in this inquiry were all resistant to other treatments. Moreover these authors regard retention in treatment (60%) as a parameter of effectiveness on addictive behaviour, though clearly not on consumption levels. Lastly, these authors have proved that equivalent results can be achieved with more severely ill subjects, regardless of sobriety, in terms of psychosocial adjustment and improvement (33). The short-term retention rate with GHB is higher: in the study by Maremmani and colleagues, none patients had dropped out by the end of the first month (33), while Addolorato and colleagues report a survival rate above two thirds at two months and of about two thirds at three months, in two separate samples (3). The reduction recorded in the retention rate in moving from the shorter to the longer term should not be interpreted as a tendency for GHB to lose its apparent effectiveness; in reality, the long–term values simply yield a more realistic picture in reflecting GHB’s therapeutic impact on a chronic relapsing disease such as alcoholism.

As is true of the general stereotype of addiction, in alcoholism too withdrawal and short-term compliance are quite likely to be accomplished for a variety of reasons; they represent non-specific behavioural features which can be observed during the early phase of treatment without possessing any therapeutic meaning. The longer the length of observation, the easier it becomes to recognize a behavioural change or a gradually changing trend induced by ongoing treatment, so allowing discrimination from a transient phase of apparent remission.

Given its short half-life, GHB should be administered in refracted or repeated doses. Repeated dosing is needed in the management of withdrawal, to maintain symptoms suppression through time by the replacement of eliminated GHB with further oral amounts. In maintenance regimens, dosages are refracted: in this case, repeated dosing is meant to provide the brain with a tonic, stable, stimulation. The difference is that higher single doses produce stronger but quickly fading effects, which are phasic in nature, while lower doses that are administered more frequently, but with equal cumulative daily amounts, have a weaker but steadier effect, with a narrow concentration gap
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and a lower liability to abuse. On clinical grounds, a six-fraction schedule turned out to allow a higher retention rate than less frequent administrations of equal cumulative amounts (30). In another study (4) the transition from a three- to a five-fraction schedule (with equal daily doses of 50 mg/day) appeared to permit a major improvement in treatment response; of 37 patients retained at two months with partial response, over two thirds achieved and maintained sobriety during the following two months, after being shifted to the five-fraction schedule. Despite the large size of the sample (n= 154), no definitive statement can be made as to whether that improvement can be attributed to the change in schedule or to an increase in the short-term response to GHB through time for partial responders.

In conclusion, on one hand it is advisable to increase the refraction ratio rather than increasing single dosages. On the other, it is not yet possible to achieve stable high levels of GHB in the blood by using high rates of refraction, that is, high levels of GHB tonic stimulation. A slow-release form of GHB would overcome this problem by allowing the use of GHB to produce slow-acting, long-lasting effects along a dose-response curve, as happens in the case of methadone. In this case, it would be possible to increase dosages up to the level required to neutralize severe alcohol craving.

Withdrawal and abuse liability

As might be expected, prolonged GHB administration leads to the development of tolerance, and heightens susceptibility to abrupt discontinuation in the form of rebound symptoms of variable severity. The reasons for such variability, though, are still unclear. In the short term, for instance, it is quite unlikely that one will develop withdrawal from GHB, even after taking it as a substitution treatment for alcohol withdrawal (17); as far as the medium to long term is concerned, no cases of GHB withdrawal were reported in a group of narcoleptic patients to whom it had been administered at doses of 3 to 9 g/day (51). It therefore seems that GHB withdrawal is more typical of subjects taking high GHB dosages outside any therapeutic setting, as a recreational drug, or when patients abuse prescribed GHB (8,12,20,39,46). Moreover, it may be that withdrawal develops accidentally in subjects who abruptly discontinue prescribed GHB without seeking medical advice: it is, however, improbable that alcoholics who take GHB for therapeutic purposes, when dropping out of programmes or showing unresponsiveness to GHB, will fail to react by increasing alcohol consumption, so avoiding any rebound. Apart from this, subjects compliant with therapeutic protocols will have their GHB gradually tapered, so no withdrawal can be expected.

GHB withdrawal does stick to the general model of depressant withdrawal (8,12). It is characterized by a very quick onset (1 to 3 hours after latest dose), an escalation to a delirium state which develops more rapidly than with other depressants, and a gradual extinction in times similar to those encountered with alcohol or short-acting withdrawal from benzodiazepine. Psychic symptoms are more prominent than somatic ones (49). Diazepam treatment is quite effective (2,3).

GHB is traded illegally as a recreational drug with pleasurable narcotic and euphoric effects. In particular, it is employed as a sex-enhancing drug, and in some cases it is
administered to unsuspecting victims in order to make them prone to sexual intercourse and induce retrograde amnesia (a feature of date rape drugs), as happens with other substances, such as flunitrazepam.

In a laboratory setting, GHB has euphoric effects at dosages of 30 mg/kg but not at 15 mg/kg (45). In a clinical sample of alcoholics receiving 50 mg/kg /die three times a day, abuse occurred in 10% of patients over a six-month exposure period (3). A trend towards abuse may develop in the long term, and be forerun by a period of balance. It is advisable to keep single doses low, so that the subject does not become conscious of the effects of GHB, because if he or she does, this usually acts as a predictor of subsequent abuse due to positive reinforcement. GHB abuse should be defined with reference to how subjects handle their GHB; some subjects, for instance, report taking GHB in order to avoid resorting to alcohol, and may ask for increasing dosages in order to achieve better control of their alcohol craving. Such patients are not GHB abusers, nor are those who keep on drinking alcohol although they are taking GHB. GHB abusers are those who run out of prescribed GHB due to a self-determined increase in dosages, and usually take larger dosages less often than prescribed (for example, taking their whole daily dose in one single administration), because this reveals a specific craving for GHB. An overdose of GHB, below the coma level, may induce sedation, simple confusion or psychotic confusion (delirium) (24, 40). Chronic abusers are expected to develop intoxication symptoms similar to those induced by alcohol or benzodiazepines (16).

Treatment of alcoholic heroin addicts

GHB and heroin abuse

GHB has proved to be effective in blocking opiate withdrawal in subjects tolerant to heroin or methadone (17, 19): the onset of action is rapid and the effects of GHB can be maintained by repeated administration.

During the period of observation, subjects stopped using opiates, as proved by negative urinalyses and negative naloxone challenges at the end of treatment (17, 19). The mechanism of interaction between GHB and the opioid system is unclear, but it does not seem to be directly mediated by opioidergic receptors (13, 45). In a small sample of heroin addicts rendered tolerant to stable methadone doses, single doses of GHB caused no toxic effects (45).

On these grounds, GHB has been used, in short-term or even rapid detoxification programmes, in subjects tolerant to heroin, for whom methadone or buprenorphine would have been more reasonable therapeutic options. Episodes of malpractice have happened too, GHB being employed to favour the accomplishment of medically supervised detoxification from therapeutic methadone. The liability of GHB to abuse, when it is administered as an anticraving agent to populations of methadone-maintained heroin addicts, has not yet been measured. If slow-release GHB became available, research in this field would be more viable and the use of GHB would become safer.
GHB in the treatment of alcoholic heroin addicts

GHB may be effective in treating alcoholic heroin addicts because of its opioid agonist action, and there are no scientific foundations for regarding alcohol-abusing heroin addicts as unfit for this kind of treatment. The concurrent use of GHB and methadone is feasible and safe \(^{(32, 35)}\). However, unlike methadone, GHB induces craving in certain patients; moreover, addicts in general are a population at risk, with a high incidence of impulsive and reckless subjects, so that it might be imprudent to expose addicted patients to a potential drug of abuse such as GHB. In any case, it should be remembered that, on behavioural grounds, heroin addicts successfully maintained on methadone can be viewed as radically different from untreated heroin addicts. Treatment responders do, in fact, display normalized behaviour, not only as far as opiate use is concerned, but also in terms of impulsiveness associated with ongoing abuse of other substances: the behavioural stereotype of methadone-maintained subjects does not include proneness to substance abuse.

In alcoholics with high levels of impulsiveness, habitual binge-drinking is incompatible with GHB prescription, due to the risk of toxic synergy. By contrast, in heroin-using heroin addicts or alcohol-abusing methadone-maintained subjects, binge drinking is less likely; methadone treatment, even when ineffective in preventing or treating alcohol abuse, may modify the drinking pattern, and bring binge drinking to extinction. Paradoxically, some precautions, which are needed for pure alcoholics, may be inappropriate for heroin-addicted alcoholics.

Table 1 displays data on GHB treatment administered to heroin alcoholics at the Vincent P. Dole Dual Diagnosis Team of the Department of Psychiatry of the University of Pisa.

It should be borne in mind that the following precautions should be taken when exposing methadone-maintained heroin addicts to GHB:

- administration to be supervised by a significant one;
- controlled availability of the drug, so as to prevent overdosing;
- the use of lower single doses, given that heroin addicts are able to discriminate GHB when it is administered at higher single doses \(^{(45)}\);
- assessment of subjective effects, in line with the rule according to which a stable, peakless effect is associated with a low likelihood of abuse;
- GHB to be started separately from methadone, only after tolerance to opiates has become high or stable, and the patient has recently been abstinent from heroin;
- methadone treatment is preliminary to GHB treatment; only subjects who have stopped using heroin should be started on GHB.

GHB use in polyabuse patterns

GHB is one of the few effective agents against chronic alcohol craving \(^{(3, 4, 30, 33)}\). It may be employed as maintenance therapy, and does allow the achievement of satisfactory
levels of social adjustment in formerly impaired alcoholics, even when sobriety is not attained. Its mechanism of action seems to comprise pro-dopaminergic and gabaergic properties (29, 48, 50). Due to its pro-dopaminergic action, GHB may turn out to be helpful both to polydrug abusers and polyaddicts, who are becoming increasingly frequent in the population of treatment-seeking alcoholics.

On the other hand, polyabusers, due to their high level of impulsiveness, are not sufficiently reliable to be admitted to a structured treatment programme, both on decisional and behavioural grounds. Despite this limitation, one reasonable strategy is to target cravings one by one, starting with the most destabilizing substance and/or the most effective treatment regimen, and setting up a “Chinese box” sequence. After putting up shutters against the first source of destabilization, a second treatment regimen may be added, so that the second treatment may count on a greater level of baseline compliance. The effectiveness of some agents, even when hampered by a low level of compliance, may still be a usable resource.

In the literature it is still controversial whether GHB can be used for subjects who have abused or are abusing other substances apart from alcohol, with special reference to narcotics. On the other hand, alcohol is seldom the only abused substance in young drinkers, and polysubstance dependence is far from rare.

Polyabusers may resort to alcohol secondarily, without being addicted to it, in order to handle intoxication from their substance of choice by enhancing its pleasurable effects or producing a pleasurable mixture. However, secondary abuse may turn into actual addiction, regardless of which substance was abused first; some alcohol polyabusers may thus end up as alcoholics or polyaddicts. The selection of polyabusing subjects for GHB treatment should account for differential diagnosis between alcohol abuse and addiction, rather than the chronological sequence of abuse. Also, the criteria for exclusion should include some behavioural trends or mental states which imply poor compliance and impulsiveness.

<table>
<thead>
<tr>
<th></th>
<th>Dosages (mg/daily)</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
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<td>Methadone (stabilization)</td>
<td></td>
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<td>150</td>
<td>380</td>
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<tr>
<td>GHB</td>
<td></td>
<td>1750</td>
<td>4725</td>
<td>5250</td>
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<tr>
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<td>5</td>
<td>9</td>
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<td>Trimipramine</td>
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Maremmani et al, Heroin Addict Rel Clin Probl, 2003 (Revised)
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Cocaine
As long as cocaine consumption is out of control, and unless craving has been kept under control for some time, cocaine abusers should be regarded as unsuitable for GHB prescription. In fact, polyabuse pictures often feature cocaine as the main cause of global impulsiveness and unreliability, and no treatment option has proved of major efficacy against cocaine abuse in terms of compliance and the suppression of craving.

Heroin and Morphine (fast-acting opiates)
It must, however, be added that GHB use is conceivable in an alcoholic heroin addict, once satisfactory behavioural stability has been achieved by means of agonist treatment.

In subjects who are given stable dosages of an opiate agonist, the addition of GHB does not produce unfavourable reactions (45). In the Vincent P. Dole Dual Diagnosis Team Methadone Maintenance Treatment Programme, a group of stabilized patients on an average methadone dose of 150 mg/day (range 60-380 mg/day), reduced alcohol consumption after being started on GHB at an average dosage of 4.725 g/day (range 1.75-5.25 g/day) (32, 35).

In heroin addicts, alcohol dependence can develop before heroin addiction or together with it (7, 11, 28, 37); alternatively, it may mark a later-stage transition from a more expensive, illegal drug to a cheaper, legal one, across a common opioidergic bridge. Some heroin addicts, incorrectly treated in short-term or agonist-free programmes, may resort to alcohol in order to stay detached from a heroin environment. Lastly, treatment with ineffective methadone dosages (known as ‘undermedication’) favours alcohol consumption and abuse during the programme (31, 34, 36, 42). Eventually, some heroin addicts belonging to the previous categories will end up becoming actual alcoholics through a secondary form of alcohol abuse. Others may stay detached from alcohol, avoiding addiction at all stages, simply through the (re)introduction or dose-adjustment of agonist treatment (6, 28, 37, 38). In other words, GHB may be administered to heroin addicts whose alcohol abuse fails to respond to effective dosages of methadone during a maintenance programme.

GHB may be administered to heroin addicts, regardless of whether alcoholism is primary or secondary to heroin addiction in a chronological sense, after ascertaining that alcohol abuse is not an indirect expression of an unbalanced craving for opiates (masked heroinism). It would be useful to compare a maintenance regime at blocking dosages (100 mg/day) to a combined regimen of methadone and GHB, in order to clarify the interconnection between cravings for heroin and alcohol in this particular population of alcohol abusers.

Moreover, GHB may be used to treat recently detoxified heroin addicts who have recently experienced an intensifying craving for alcohol, so as to prevent its evolution towards secondary alcohol abuse.

Lastly, GHB may be resorted to in the case of abstinent heroin addicts who do not clearly need agonist treatment to be restored, but show an increasing trend towards drink.
Benzodiazepines

Concurrent alcohol and benzodiazepine abuse may develop in two ways: benzodiazepines may either act as a replacement for alcohol episodically or cyclically, or be combined with it after specific craving drives, which signify an autonomously developed benzodiazepine addiction. Independent benzodiazepine addiction should be challenged with induction and stabilization with clonazepam at blocking dosages.

In the programme run by the Vincent P. Dole Dual Diagnosis Team, a subgroup of alcoholic heroin addicts was successfully treated with a combination of clonazepam (average dose 5 mg/day, range 5-9 mg/day) and GHB (average dose 4.725 g/day, range 1.75-5.25 g/day). As to the possible synergic effect of benzodiazepines and GHB, the induction of GABA-A tolerance by higher clonazepam dosages allows patients a higher level of safety, since it provides protection against intermittent GABA-A stimulation with abused depressants.

Principles for the safe and effective use of GHB

GHB’s metabolic profile is the main limitation to the feasibility of maintenance treatment. In fact, its short half-life requires a certain level of compliance for effective dosages to be reached and maintained by regular self-administration. Addicts usually show poor compliance; in the specific case of heroin addicts, this problem can be partly overcome by tying the patient to the treatment setting through his or her acquired tolerance to agonist medications. On the other hand, a long-acting formulation of GHB would be unsafe in the early phase of treatment, due to potentially unfavourable interactions with alcohol, just as in the case of long-acting disulfiram. On one hand, the short latency of action of GHB is useful in the rapid buffering of alcohol withdrawal, but, on the other, it functions as the basis for GHB’s abuse liability, together with its pro-dopaminergic action.

In order to minimize the risk of abuse, one must choose subjects for whom GHB treatment looms as feasible, and, secondly, select those at low risk of abuse behaviours. Whenever possible, GHB should be handed over to a third person (a significant one), whose duty is supervise its administration at prescribed doses and at regular intervals. Subjects should not handle large amounts of GHB, especially when self-administering it; limited supplies should be made available at regular intervals. It is advisable to divide daily dosages, right from the start, into four to six small fractions, so as to assess a patient’s compliance and avoid the narcotic effects that would be elicited by large single doses.

Apart from justified concerns about side-effects and possible interactions with other abused substances, the aim of this strategy is to avoid GHB being discriminated by the brain as a source of euphoria. In particular, subjects who have already experienced opiate-induced euphoria are likely to discriminate GHB when it is administered at higher single doses, even when the cumulative daily amounts of exposure are equal.

Once treatment has started, the persistence of drinking behaviours – though these
will probably occur at lower levels – is not a reason for terminating treatment. In fact, this kind of benefit constitutes a partial response to GHB (reduction in drinking frequency and/or amounts) and it resembles the outcome that constitutes a complete response (sobriety) \(^{(33)}\).

Alcohol use during GHB treatment cannot be regarded as GHB misuse, just as heroin use during methadone treatment cannot be classified as methadone misuse. Subjects taking lower GHB doses may try to achieve greater control over their craving by increasing their GHB doses autonomously. These behaviours should not be mistaken for GHB abuse, either; GHB abuse consists of the consumption of higher GHB doses in order to elicit euphoric effects.

GHB may be combined with other effective treatments for alcohol abuse. After some time disulfiram can be added to a GHB regime, in order to proceed step by step towards complete sobriety after partial control over drinking has been achieved. In psychotic subjects, who are sensitive to GHB’s dopaminergic effects, this combination is potentially harmful. A GHB-naltrexone combination is theoretically feasible, since doses of GHB do not seem to act directly via opioid receptors \(^{(13, 45)}\).

**Case reports**

Cases 1-8 have been described by Maremmani and Pacini \(^{(34)}\) and cases 9-13 by Lamanna and Maremmani \(^{(25)}\).

**Case 1**

G.C: male, 34 years, married, with a 6-year-old daughter. He works as a salesman for a wine factory; his work requires him to travel frequently and he lives with his family in a small town. His family of origin belongs to an intermediate-income class with an average cultural level; both of his parents have white-collar jobs. His only brother is an alcoholic who keeps sober for long periods of time (the latest period lasted two years), has repeatedly tried disulfiram treatment, but relapsed after discontinuing the self-administration of the drug more than once, reaching levels of intoxication which required hospitalization.

The patient applied for cocaine abuse treatment. Information gathered by the clinical interview led to a diagnosis of alcohol addiction, opiate addiction and cocaine addiction. He first tried alcohol at the age of 14, he first abused it at 16, and started drinking regularly at 18 (six 33 cl beers and 6 high-grade alcoholic drinks). Regular consumption proceeded for the following 16 years with two intervals of sobriety, one within a therapeutic community for heroin addicts, the other determined in a spontaneous way because of alcohol-related health concerns. On two occasions the patient went into a drink-induced coma, and on two other occasions he had car accidents while driving under the influence of drink; he suffered several minor traumas due to alcoholic intoxication. The patient first tried heroin at the age of 23 and became a regular user.
within the following two years. At the age of 27 he spent some time in a therapeutic community, but he relapsed into alcohol abuse shortly after being discharged; he was soon drinking as much as before, and after two months relapsed into heroin abuse, too. Binge-drinking became very frequent (over three times a week). Approximately one year before entering our programme the patient suffered from acute alcoholic hepatitis; on that occasion he was also diagnosed as HCV-infected: as a reaction, the patient stopped using alcohol and minimized heroin use by resorting to cocaine, but soon become addicted to that. At the time of our first evaluation, he has been addicted to cocaine for 6 months, to opiates for 180 months and to alcohol for 292 months. He had never undergone specific treatment programmes for any of his addictions.

He was initially started on buprenorphine combined with a dopaminergic drug (ropinirole 0.75 g/day) in order to overcome cocaine craving, within a clinical trial. Opiate and cocaine use dwindled to extinction. After 4 months, the patient increased his drinking and dropped out of the programme, soon to relapse into heroin and cocaine use as well. Accompanied by his family, he applied for re-entry into treatment and was started back on the same regimen, adding GHB at a 2.625 g/day dose. Although control over cocaine and opiate abuse was satisfactory, compliance with treatment was limited to buprenorphine (8 mg/day); the patient discontinued ropinirole after a few weeks, and stopped taking GHB on a regular basis, with two periods of total discontinuation. Alcohol abuse increase every time GHB was discontinued. After buprenorphine dosage was stepped up to 12 mg/day, alcohol abuse evolved according to a different pattern, free from binge-drinking episodes. At that point the patient began working and had a good relationship with his significant ones.

After two years of treatment, a depressive episode set in, followed by a hypomanic phase, during which the patient intensified his drinking habits and experienced a bout of opiate craving. Buprenorphine was autonomously discontinued for one week in order to allow heroin use, but the patient promptly applied for treatment; in line with medical advice, he was transferred to a methadone programme, receiving 60 mg/day in the induction period. During the first two weeks, as he was still hypomanic, he continued his use of opiates and turned dysphoric as soon as an opioid blockade was established, but soon after reaching a dose of 100 mg/day, his craving was extinguished and his mood normalized. Meanwhile, GHB was reintroduced (this was the third attempt), this time under his wife’s supervision, at 2.625 g/day. To date, the patient has taken GHB regularly for eight weeks, with a stable reduction of drinking amounts. Symptoms of muscular contractions and speech during sleep were reported, but were probably due to the antidepressant the patient had started taking on his own initiative (citalopram), and stopped after it was discontinued. EEG and NMR were negative, as well as general blood tests. No symptoms of alcohol withdrawal were recorded. Opiate use is again almost down to zero (with only two episodes in the last two weeks). Cocaine use was not ongoing this time, and did not restart; the patient is currently taking 0.50 mg/day of ropinirole.
Case 2

LM: female, 40 years old, divorced. She used to run a little shop together with her sister but got into debt and went bankrupt. Lately, she has found a job as a clerk. Her family belongs to the working class. Her twin sister is a heroin addict, but was successfully treated in a methadone maintenance programme at an average dose (100 mg/day). Her former husband is a habitual drinker.

The patient first tried heroin while staying abroad, at the age of 23, during a hypomanic phase. She started using heroin regularly after two weeks and continued for some months, but she eventually stopped after her return to Italy. Meanwhile, she had started drinking occasionally, and some episodes of intoxication occurred; in the next few years, she kept on drinking without any regular pattern. Four years ago, while facing financial and family problems, she reported an intensification of alcohol use, and started drinking regularly, beginning early each morning. Moreover, her use of heroin resumed, and she started using illegal methadone at a 10 mg daily dose, on a regular basis, since it was cheaper than heroin and lasted longer, bringing stable mood elation, talkativeness, increased physical energy, and an optimistic attitude. These effects are identical with those reported by her sister when using heroin. Alcohol use has increased up to the present, with frequent episodes of intoxication, along with benzodiazepine polyabuse. One episode of coma and a car accident due to depressant intoxication have been reported. The patient applied for alcohol abuse treatment, following her sister’s advice. She was diagnosed as suffering from Bipolar II disorder, against the background of a cyclothymic temperament, and a histrionic-borderline personality mode. She was started on GHB, but was not compliant (she skipped doses, and missed taking GHB for whole days). After eight weeks, symptoms of depressant intoxication were still significant and episodes of intoxication still occurred. At this time she was hospitalized for coma due to acute jugular thrombosis, whose origin is still unknown. After discharge she kept on drinking, with severe symptoms of intoxication, and was soon hospitalized in a psychiatric ward. Although her urinalyses revealed recent consumption of alcohol, benzodiazepines and methadone, and her blood tests revealed high levels of benzodiazepines, the patient vehemently denied taking anything but alcohol, and kept up her denials even when confronted with the evidence of drug blisters found in her bag. Some days later, she admitted using these substances, but still minimized the amounts. Two weeks after discharge, she still had poor insight, claiming she had drastically improved her control over alcohol craving, but agreed to enter a methadone maintenance programme. Dosage was increased up to 30 mg/day and combined with gabapentin at a dose of 1200 mg/day. She refused to try GHB again, claiming she was intolerant to it. Methadone was further increased to 100 mg/day and was effective in suppressing benzodiazepine use and binge-drinking. Alcohol consumption remained stable, with at most five high-grade drinks a day. A depressive episode occurred six months later during treatment and was challenged by fluoxetine, but she got over it within 10 days after fluoxetine initiation. The patient tapered her methadone to 60 mg/day against medical advice and increased her drinking; she then accepted the introduction
of GHB as an alternative to increasing methadone again. When taking GHB 3.5 g/day she did not display symptoms of intolerance or alcohol withdrawal. Alcohol use fell to two drinks a day within a week and remained stable over the following eight weeks. The patient has kept working since, but she is still in conflict with family members over her personality features. Her somatic condition is currently of some concern; it comprises hardening of the hepatic portal venous system, a duodenal tumour with an unspecified grade of malignancy, and anaemia due to iron deficiency.

Case 3

BN: female, 35 years old. She is married with a 12-year-old daughter, who is being fostered by her mother’s parents, as ordered in a trial sentence. She used to work in her family’s factory, but was unable to continue, due to her addictive disease. Her husband is a heroin addict, and they live together in a small town. The socioeconomic status of both families of origin is good. Alcohol does not run in her family at all. The patient applied for treatment together with her husband; they had been referred to the centre by both their families in order to achieve detoxification from heroin. Alcohol intoxication was evident in both, and more severe for her; she denies serious drinking habits, and only admits to taking one drink a day. She first used heroin at the age of 20, and became a regular user at 26, always snorting it. Some months before our evaluation, husband and wife travelled to Switzerland on their own, in order to attempt self-managed detoxification from heroin, and came back two months later. Although they stayed heroin-free, he had resorted to heavy alcohol use, and she had intensified her drinking habits in such a way as to become chronically intoxicated. The patient reported first using alcohol at 20 years, when she became a regular drinker, increasing her consumption to about 7 drinks a day by 26. She never stopped drinking while using heroin, and, after detoxification from heroin, reached a daily intake of 14 drinks. She had never undergone any treatment for either addictive disorder. Methadone was started and increased up to 70 mg/day, more gradually than on average in order to reduce the risk of a combined overdose in the period when the patient’s tolerance of opiates was still low. Afterwards, she was induced into GHB treatment at a 3.5 g. At this first attempt, compliance was poor; she discontinued GHB after three weeks, only to restart a week later, though not on a regular basis. Opiate use was over, while alcohol abuse persisted, and increased during the GHB-free week. After psychoeducational sessions, the patient agreed to try GHB again, reducing alcohol use to 3 drinks a day. In the meantime, she was able to go back to work, which had not happened, despite a stable heroin-free condition, in the previous six months of treatment. Later on, she autonomously discontinued GHB and relapsed into heavier alcohol use, which required further psychoeducational work. Her insight has always been poor, but was to some extent improved by regular psychoeducational sessions. In reporting the recent course of her drinking, she was eager to minimize. She denied that she has ever drunk large amounts, and claimed that she is currently drinking “definitely less” than before, but gave no details, and concluded
that her drinking habits are no different from anyone else’s.

**Case 4**

L.M.: male, 37 years old, married to the woman described in case 3. He is the younger of two brothers; he used to work in his family’s factory as a departmental director, but stopped because of drug-related problems. His family belongs to an upper socioeconomic class. No case of alcohol abuse has been reported among relatives. He started using heroin at 18 years old (two years before his wife-to-be, to whom she was already engaged at the time), and became a regular user at 27 (one year later than his wife), always snorting it. Alcohol use was insignificant before their attempt to achieve detoxification from heroin, some months before our evaluation. He was started on methadone and stabilized at 70 mg/day within 12 weeks (see case 3). Due to persistent daily alcohol use, GHB was added at a dose of 3.5 g. The patient took GHB regularly for the first two months and became detached from alcohol quite rapidly, discontinuing alcohol altogether some time later. He has so far experienced no relapse into heroin or alcohol use. No GHB withdrawal symptoms have been reported.

**Case 5**

D.G., female, 39 years old, a widow. She was born the second of four siblings, studied as an interpreter in foreign languages and used to work in that capacity until drug-related problems caused interference. She has lived in various different towns, moving in response to the requirements of her job. She is now living with her family of origin, due to financial difficulties. Her mother suffers from an obsessive-compulsive disorder, her father is an alcoholic and her sister a heroin addict.

She first used heroin at the age of 15; she became addicted during the first year of use and started injecting it. At the age of 18 she spent a period in a therapeutic community, relapsing after discharge. In the following months, she was hospitalized in order to undergo detoxification and short-term naltrexone administration. None of this treatment, despite high expectations, ever provided a stable resolution of the disease. She first enrolled in a methadone maintenance programme in 1992, and stopped using heroin for a year. She eventually negotiated programme termination with her case managers, and became heroin-free and highly functional for three years, but eventually relapsed into heroin use and applied for treatment in the same programme, with satisfactory results. Treatment again achieved results thanks to methadone tapering, but after a time opiate use was resumed, becoming regular again after three years, when the patient applied for treatment for the third time; on this occasion the benefit was complete and rapidly accomplished.

Alcohol use began quite early (when she was 13 years old), and became regular while heroin use was still occasional (at 15). The patient’s alcohol consumption pattern has been regular, and does not show a single period of sobriety, the highest amounts recorded
being 1.5 litres of beer a day, without binge-drinking episodes. In 1997, when she was about to relapse into heroin use, she was hospitalized due to acute liver failure caused by alcohol intoxication combined with chronic HCV infection. She stayed abstinent for two months after discharge, while she was following a methadone maintenance treatment programme at a 40 mg/day dose and taking GHB at 3.5 g. Treatment with GHB was tapered on medical advice (which seems to have been unreasonable, considering her clinical therapeutic history); she remained abstinent from heroin during methadone treatment, but relapsed heavily into alcohol use.

Case 6

R.S.: male, 44 years old, an only son, never married; he lives with his family in a town, and finds temporary employment as a blue-collar worker. His family belongs to the working class. He first tried alcohol when he was 18, and became a regular drinker at 25. Amounts are usually as high as one bottle of wine a day, but he might drink twice or three times as much during weekends, and he drinks excessively during evenings and nights with friends. He had been drinking for ten years without periods of sobriety, and following a stable pattern, when he started on heroin at the age of 33. Heroin addiction took less than a year to set in, and a year later he applied for short-term methadone treatment, which was followed by an immediate relapse. During an outpatient treatment programme he rapidly stopped heroin use, at a dosage of only 60 mg/day (far below the average of our sample), but alcohol use persisted, even if with lower amounts and fewer binge episodes. In that period the patient’s condition improved. GHB was introduced after two years of successful methadone maintenance; at that point the patient accepted the proposal that his alcoholism should be treated in a specific way. At a GHB dose of 3.5 g/day, alcohol showed a fall of 20% at two weeks, and of 50% at four weeks. Compliance with regular GHB treatment was targeted during repeated brief psychoeducational sessions, which were started at the patient’s request after he had stopped GHB for one week and immediately relapsed into heavy drinking. The reintroduction of GHB was effective, and alcohol consumption has stayed as low as 30% of baseline and 15% of the lifetime maximum.

Case 7

M.G.: female, 36 years; her only son lives with her former partner. She is homeless and trades sex for hospitality and drugs. She started using substance in her late adolescence as a polyabuser (cocaine, alcohol, heroin and depressants), and was admitted to emergency departments several times when suffering from intoxication or withdrawal from depressants. She was once hospitalized in a psychiatric ward in order to stop her abuse practices, and was started on methadone, up to a 130 mg/day stabilization dosage. Abuse was minimized until 1995, when a team of case managers convinced the patient she should stop taking methadone in order to be regarded as a reliable mother
and be allowed to have a stable relationship with her son. She was advised to enter a therapeutic community and have her methadone tapered there, where she could start meeting her son. After five months she left the community, leaving her son to the social workers, and relapsing into polyabuse. Her social situation radically deteriorated until the next treatment period, starting in 1999 (methadone maintenance at 150 mg/day). Regrettably, that second attempt failed to control alcohol abuse, so that rehabilitation was not as satisfactory as it had been the previous time. After three years, her dosage was as low as 40 mg/day, but alcohol abuse had not intensified with respect to the 150 mg/day phase, and the patient agreed to add GHB 3.5 g/day in order to be able to benefit from social facilities, since she had to meet the requirement of sobriety to receive support from Social Services. Drinking was minimized within one month, but her case managers paradoxically suggested she should discontinue GHB in order to complete her treatment, and she relapsed within a week, reaching previous levels of abuse. She is now receiving treatment for the third time at another centre, and has achieved a significant reduction in her alcohol craving, but her compliance is unstable and she swings between periods of light drinking when receiving GHB treatment and periods of heavy drinking after GHB discontinuation. Her psychosocial situation has not improved significantly, and she has continued to trade sex for a place to stay.

Case 8

A.D.: female, 22 years old, lives with her family (three brothers and her parents) in a small town. Her family is well off, and owns a little factory; her brother is a university student, while she found a blue-collar job after leaving high school. She applied for alcohol abuse treatment on her mother’s insistent advice. Symptoms of affective instability are relevant, although the patient shows a degree of concern about recurrent anxiety (panic attacks) and social phobia, which she has tried to counteract by alcohol use. She has used a variety of substances from the age of 18 (cannabis, alcohol, MDMA and amphetamines), including heroin, but she took heroin only over a three-month period, when she was 20. She decided to stop using heroin as soon as she experienced withdrawal symptoms, without needing any medication, but then switched to cocaine first, and alcohol later, showing a binge pattern. Binges used to take place twice a week with friends, but became a daily event in the last period before consultation. Initially, amounts of consumption were as high as 1.5 litres of beer and 10 high-grade drinks; later on, she started drinking a further 0.5 litres of beer before seeing friends, and regularly became drunk, with promiscuous sexual behaviour during the nights and multiple car accidents in the mornings. The patient also abused cocaine and prescribed benzodiazepines, though irregularly, while heroin use was sporadic (two episodes in 4 months). Cocaine was consumed at the end of alcohol binges, while benzodiazepines were resorted to in the mornings in order to control agoraphobia and allow her to reach her place of work. The patient was given a prescription of gabapentin (1600 mg/day), paroxetine 20 mg/day and GHB, up to 3.5 g/day. At two weeks she had managed to
reduce her drinking by 50%, with a lower frequency of binges; at eight weeks, alcohol use had fallen to 10% of its earlier levels, and no binges had occurred recently. Blood tests were normal. On two occasions, however, the patient took low doses of benzodiazepines in the morning, stealing them from her mother’s closet, after being denied a medical prescription. After four month’s abstinence from alcohol and benzodiazepines, the patient suddenly took 12.25 g of GHB all at once in the morning, and was treated for CNS depressant intoxication; this was certainly the first episode of GHB abuse, since GHB had been always administered by her mother before she seized it that morning, and GHB is not easy to find on the Italian black market. The patient reported taking GHB on an impulse, without any precise expectation, but in a state of excitement about trying the effect, and definitely without any suicidal intention. GHB was not confirmed, and she was given a prescription of valproic acid and carbamazepine. Despite staying abstinent from alcoholics, the patient relapsed into daily heroin use by injection for two weeks; as a result, she was started on buprenorphine in combination with valproic acid only. After reaching 8 mg of buprenorphine, the patient has stayed abstinent from both alcohol and opiates for six months, and substance use has remained limited to cannabis, showing an irregular pattern.

Case 9

S.D.: 40 years old, male, never married, suffering from a Bipolar Disorder, type I. Metadone stabilization dosage was 210 mg/day and GHB was employed at 10.5 g/day. The patient was initially hospitalized in a Prison Hospital for mentally ill detainees, and was recognized as suffering from a severe psychiatric disturbance complicated by polydrug abuse. At the time of our first evaluation, he was receiving heavy doses of traditional benzodiazepines and neuroleptics, which did not influence his cravings and self-destructive impulsiveness.

Despite methadone maintenance at 210 mg/day, the patient’s craving for alcohol and sedatives stayed high: despite his refusal to increase methadone, GHB was combined with significant improvement. The patient became more accessible to dialogue, stopped self-destructive behaviours and showed less frequent and severe mood swings; this made possible the tapering of his neuroleptic medications, while maintaining his mood stabilizers and traditional psychotropic medications.

Case 10

C.C., 35 years, female, black, never married, suffering from bipolar disorder of type II and HIV+. In her history, alcohol use was primary with respect to heroin use, but she had become addicted to both substances. Methadone and GHB treatments were started together, maximum dosages being 60 mg/day of methadone and 7 g/day of GHB. and her condition improved radically, with the extinction both of craving and addictive behaviours. Moreover, the state of her infections was found to have improved, too,
and the course towards AIDS has been arrested so far.

**Case 11**

S.R.: 43 years old, male, married, suffering from Bipolar Disorder of type II. He had been in treatment with methadone for a long time at a 100 mg/day stabilization dosage, but had displayed alcohol abuse practices of increasing frequency and severity throughout the previous months, despite staying abstinent from opiates, as before. After the induction of GHB at 40 mg/day, satisfactory remission was achieved.

**Case 12**

S.N.: 39 years old, male, never married, suffering from Bipolar Disorder, type II, and Panic Disorder. He had a longstanding history of severe heroin addiction, which was brought to an end by methadone maintenance treatment at a maximum dosage of 160 mg/day. One year ago, the patient went through stressful life events, with a resumption of panic symptoms and generalized anxiety, which he tried to control by increasing his consumption of alcohol and benzodiazepines. Since the patient was reluctant to increase his methadone dosage, GHB was proposed and introduced up to a 5.25 g/day dosage. His consumption of alcohol and benzodiazepines fell drastically, and has so far stayed below the level of intoxication.

**Case 13**

N.G.: 42 years, male, living with his partner, suffering from Bipolar Disorder, type I, and HIV+. He had started methadone treatment after many years of heroin addiction, and had become stably heroin-free and rehabilitated at a dose of 80 mg/day. Periods of alcohol intoxication were, however, recurrent, and he had been hospitalized more than once with symptoms of liver failure. During the last hospitalization period, GHB was introduced at a 5.25 g/day dosage. Alcohol abuse has been under control ever since.

**Conclusions**

Sodium gamma-hydroxybutyrate (GHB) may be resorted to as means of alcohol abuse control even in polyabusers. Precautions must, however, be taken to counteract the higher level of impulsivity in such populations, because the substance polyabuse tends to raise GHB’s potential for abuse. GHB may be used in heroin addicts who have already been stabilized on methadone treatment, due to the anti-impulsive effect of methadone maintenance and the minimization of secondary alcohol and depressant abuse with adequate methadone dosages. Cocaine users should not be given prescriptions of GHB in an outpatient setting; cocaine craving should, in fact, be targeted first, so as to increase compliance up to the minimum required to allow adherence to a main-
tenance, fractioned-dose GHB programme. The availability of a slow-acting, longer half-life GHB would change its pharmacokinetic profile into one more suitable for the healing of craving-related brain pathways. Its abuse potential would be minimized as a result, and its use could then be extended to impulsive individuals, as happens with methadone or buprenorphine.

Bibliografia


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Heroin Addiction and Related Clinical Problems

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1:00 pm **Icro Maremmani** (Pisa, Italy, EU)
Predictors of response to treatment: Methadone vs Buprenorphine.

1:20 pm **Matteo Pacini** (Pisa, Italy, EU)
The patient's resistance to methadone treatment - the clinical and therapeutic aspects.

1:40 pm **Barbara Lovrecic** and Mercedes Lovrecic (Ljubljana, Slovenia, EU)
Infectious Diseases and Mortality in Slovenian Heroin Addicts

2:00 pm **Pier Paolo Pani** (Cagliari, Italy, EU)
Psychopathology and Methadone Maintenance: the state of the art

2:20 pm **Lev Blagov**, (Moscow, Russian Federation)
Opioid Dependence and its relationship with alcoholism in young Russian men

2:40 pm **Alexander Kantchelov** (Sofia, Bulgaria)
From harm reduction to methadone-assisted therapy. 12 years of Bulgarian experience

3:00 pm **Aud L Krook**, Dorthe Stokka, Bernt Heger and Egil Nygaard (Oslo, Norway)
Successful treatment of hepatitis C genotype 3a in Norwegian opioid dependants: a pilot study

3:20 pm **Gilberto Gerra**, A. Zaimovic, F. Brambilla, G. Friso, and C. Donnini (Parma and Milan, Italy, EU)
Gene variants at risk for substance use disorders: possible interactions with environmental factors.

3:40 pm Nina Ebner, Bernadette Winklbaur, Nina Kopf, Andjela Baewert, Kenneth Thau, **Gabriele Fischer** (Vienna, Austria, EU)
Opioid dependent pregnant women and pregnancy

4:00 pm **Nikolaj Kunøe**, Philipp Lobmaier & Helge Waal (Oslo, Norway)
Naltrexone implants to prevent relapse after inpatient treatment for opioid addiction: a randomised controlled trial.

4:20 pm **Andrej Kastelic** (Ljubljana, Slovenia, EU)
Medically Assisted Rehabilitation in Slovenian Prison

4:40 pm **Thomas Clausen** and Helge Waal (Oslo, Norway)
Patterns of mortality after opioid maintenance treatment
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