

Sexual Dysfunction Associated with Methadone Maintenance: Treatment with Bromocryptine

Marc S. Shinderman and Sarz Maxwell

Summary

Sexual dysfunction, a side-effect of methadone maintenance treatment, may be caused by opioid-induced hyperprolactinemia; on this basis, a dopamine agonist could reverse the effect. We treated 34 (23 male; 11 female) patients with bromocryptine, 2.5-10mg/d. 65% of males and 36% of females reported a positive response. Responders and non-responders had a similar age (44 vs 40 yrs), time in MMT (45.5 mos), and use of serotonergic antidepressant therapy (21.1% vs 26.7%). Responders took higher doses of methadone (220.3 vs 165.6 mg/d), and were more likely to be taking bupropion or methylphenidate (42.1% vs 26.7%). Alternative therapies with other dopaminergic agonists are discussed.

Key Words: Methadone Maintenance; Sexual Dysfunction;
Psychiatric Comorbidity

Introduction

Sexual dysfunction is not an uncommon complaint among patients on methadone maintenance treatment (MMT) (12). Sexual side-effects of medication are seldom spontaneously reported (16, 17); the incidence is thus difficult to accurately determine. When sexual symptoms are attributed to MMT by the patient and are not satisfactorily addressed by the physician, adverse outcomes may result. Cocaine use, the reduction of methadone dosage, and the discontinuation of MMT are some strategies patients may use to attempt self-treatment of sexual dysfunction (SD).

Elevated prolactin levels have been reported in association with the chronic administration of opioid agonists (5, 8, 15, 18, 19, 20) by a mechanism involving the μ -

opiate receptor (9,13). Medical conditions associated with hyperprolactinemia (e.g. pituitary prolactinoma) commonly cause sexual dysfunction (4). Bromocryptine (BRC), which decreases prolactin by increasing dopaminergic tone (19), has been utilised in the treatment of pituitary adenomas (4). Decreasing prolactin levels in these BRC-treated patients are correlated with the normalisation of testosterone and other hormone levels, the resumption of menses, the reversal of erectile dysfunction, and the restoration of libido in both sexes (6).

Tagliamonte (personal communication, 1998) reported that 17 male MMT patients complaining of loss of libido and exhibiting high serum prolactin levels responded to BRC therapy with restoration of libido. We thus began to utilise BRC in the treatment of MMT patients suffering from SD. We report herein our clinical experiences with this modality.

Methods

Patients in methadone maintenance treatment were self-referred for a medical evaluation of sexual dysfunction associated with MMT. Patients were evaluated and treated by one of the authors. Patients were included in the study if they had been on MMT for at least six months, were stable on their methadone dose and ancillary medications, did not have a medical condition associated with organic SD (e.g. IDDM), and were willing to take a medication that was not FDA-approved for their complaint. The symptoms evaluated for the purpose of the study were, for males, erectile dysfunction (difficulty in achieving or maintaining an erection) and, for females, lack of libido. Response was measured by patients' reports of subjective alleviation of the target symptoms. Patients were followed with at least monthly physician visits. Data were collected by reviewing the clinical charts. Due to cost concerns, only 4 patients agreed to laboratory evaluation of serum prolactin levels.

Results

Thirty-four patients took bromocryptine; 23 were male and 11 female. The mean age was 41.1 years (range 29-59; 37.8 for females; 44.5 for males). Average time under methadone maintenance treatment was 45.5 months, and mean dose of methadone 196.2 mg/d. The overall response rate was 55.9%. 65% of males and 36% of females had a positive response to BCR therapy. The non-responders did not differ from responders with respect to age (40 vs 44 yrs), time on MMT (45.5 vs 45.5 months), or use of selective-serotonin-reuptake-inhibitor antidepressants (SSRIs) (26.7 vs 21.1%). Responders tended to be taking higher doses of methadone (220.3 mg./d) than non-responders (165.6 mg/d), and were more likely to be taking ancillary medications with dopaminergic activity (bupropion and methylphenidate) (42.1% vs 26.7%). 100% of non-responders discontinued BCR before 90 days of tx; most (73.3%) because of non-efficacy. Responders also had a high attrition rate; only 4 (21%) continued BCR up to 90 days. Reasons for discontinuation were sedation (10.6%) and cost (68.4%).

Table 1. Characteristics of patients under MM treated for sexual dysfunctions		
	Non-responders n=15	Responders n=19
Age	40.4 years	43.9 years
Time on in MMT	45.5 months	45.5 months
Methadone Dose	165.6 mg/d	220.3 mg/d
Ancillary meds.: Dopaminergic	26.7%	42.1%
Ancillary meds.: SSRI	26.7%	42.1%
D/C for SE of BCR	12.6%	10.5%

Discussion

The data from this clinical survey are preliminary, but we have formed some clinical conclusions based on examination of the trends. It is not surprising that more males than females had a positive response to BCR treatment; this is true in the treatment of SD of any aetiology (10). The tendency for responders to have a higher mean methadone dose than non-responders is somewhat puzzling until it is juxtaposed with the data regarding ancillary medications (Table 1). Responders had a higher methadone dose, and were no more likely to be taking SSRI antidepressants (which may cause SD), but were more likely to be taking ancillary medications with dopaminergic activity. These observations are in agreement with the findings that methadone causes sexual dysfunction via opioidergic stimulation of a dopamine-sensitive system, e.g. prolactin (9,18).

Only four patients had serum prolactin levels performed; the two with lower levels (16 and 21 ng/ml [reference range 0-18 ng/ml]) were non-responders, and the two with higher prolactin levels (22 and 44 ng/ml) responded to bromocryptine treatment. These data are insufficient to allow an attribution of even clinical significance, but the trend continues to agree with the science. It is this consistent agreement with the established scientific findings previously referenced that lends credence to the observations made in this uncontrolled series of cases.

Clinically, however, bromocryptine seems to be a poor treatment, mainly for practical (financial) reasons. There was an acceptably low rate of discontinuation ascribed to side-effects (10.5% of responders; 12.6% of non-responders), and the side effects reported (sedation and nausea) are not difficult to manage clinically. However, an unacceptably high proportion of responders (68.4%) discontinued the medication because of cost. This finding relates to the effectiveness of a medication – a parameter that takes into account not only efficacy but general acceptability of the treatment. Bromocryptine seems to be efficacious, but not effective, in the treatment of methadone-

induced sexual dysfunction.

These clinical findings are encouraging, however, as bromocryptine is certainly not the only dopaminergic agonist available in our pharmacopoeia. We are having good early responses to two of the dopaminergic medications we commonly use in psychiatric treatment of opiate-dependent patients: bupropion and methylphenidate. Patients in the "responder" bromocryptine treatment group were more likely to be taking these medications; response may have been partly due to the action of these ancillary medications. Bupropion is an effective antidepressant, and its dopaminergic profile has been associated with decreased cravings for cocaine (1). In the United States it also has an FDA-approved indication for treatment of nicotine dependence. The hypothesised mechanism of action is, again, dopaminergic alleviation of cravings (14). The use of such an agent could thus have a triple effect: reversing sexual dysfunction, treating depression, and alleviating cravings for other drugs of abuse. Surely the use of bupropion deserves further investigation.

The use of methylphenidate in patients with addiction disease is controversial, but the controversy is based on a misunderstanding of the nature of addictive disorders. The common lay perception of addiction is: The problem with addicts is that they use drugs, therefore the solution to addiction is to remove the drug(s). However, addiction is not a behavioural choice but an Axis I disorder caused by a chemical imbalance in the brain, and judicious pharmacotherapy is usually the most effective treatment for Axis I disorders. Pharmacotherapy is particularly crucial in the treatment of addicts with additional Axis I disorders. There has been interest recently in the high incidence of Attention Deficit Hyperactivity Disorder, Adult Type (ADHD-A) in patients with addictive disorders (3). In the United States, treatment of choice for ADHD, in adults or children, in addicts or non-addicts, is stimulants (11). In patients who have ADHD-A and sexual dysfunction associated with methadone treatment, stimulants may be doubly effective: Treatment of the ADHD-A and alleviation of the sexual dysfunction.

Thus, careful evaluation for psychiatric comorbidity is crucial in choosing the proper pharmacological agent for a patient complaining of sexual dysfunction in association with MMT. A diagnosis of depression would indicate bupropion; that of ADHD-A would indicate methylphenidate as a first line of treatment. Concomitant cocaine abuse would tend to contraindicate the use of stimulants, unless the patient also has ADHD-A, in which case stimulant therapy is indicated (11). A patient with bipolar disorder should be treated prophylactically with mood stabilisers, and monitored carefully.

Another avenue for further investigation is treatment of the weight gain associated with opiate substitution therapy. This effect is also probably related to hyperprolactinemia (7). This side-effect can be severe – 30 to 50 pounds in three to six months is not unusual. It is very distressing to patients, and very difficult to manage. This side-effect does not seem to respond to non-pharmacological treatment (e.g. diet and exercise), and it commonly occurs in patients who have never been overweight before methadone maintenance treatment. We hypothesise that this side-effect may lead patients to abuse

of illicit stimulants (e.g. cocaine), undertreatment (trying to minimise the side-effect by decreasing the dose), and discontinuation of opiate substitution therapy. Because of the association of this weight gain with opioid-induced hyperprolactinemia, this effect may respond to dopaminergic treatment (7). This theory has been advanced for the treatment of weight gain induced by antipsychotic medications (2).

It is arguably true that we are observing greater frequency and severity of methadone side-effects because we tend to treat patients with higher doses than some practitioners. This is possible, as the mean dose for patients in this study (196.2 mg/d) is significantly higher than the average methadone dose for the clinic as a whole (119 mg/d) and very much higher than the average dose in some other clinics. However, this argument is tautological. Most side-effects of most medications are dose-related; this is not an argument for insufficient doses. Naturally patients will have fewer side-effects when treated with homeopathic doses. This is not an indication to withhold efficacious doses. With methadone, as with any other medication, the management of side-effects is preferable to the discontinuation of therapy.

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