

Case Report

Long-Term Agonist and Antagonist Therapy for Adolescent Opioid Dependence: A Description of Two Cases

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ABSTRACT

Adolescents constitute only a small percentage of treatment seekers in drug dependence treatment settings. Little research evidence is available for pharmacological treatment of adolescent opioid dependence and no prior case report is available from India. We discuss two adolescent patients with opioid (heroin) dependence visiting a tertiary care center who have been stabilized on agonist (sublingual buprenorphine-naloxone) and antagonist (oral naltrexone) respectively for a substantial period of time. A comprehensive management approach, including intensive psychosocial interventions and family involvement, was followed in addition to pharmacotherapies. More research is needed on the efficacy of pharmacological treatment in adolescent opioid users.

Key words: *Adolescents, buprenorphine, naltrexone, opioid dependence, treatment*

INTRODUCTION

Adolescents constitute only a small percentage of treatment seekers in drug dependence treatment settings (≤ 15 years: 0.4% and 16-20 years: 4.6%).^[1] Community surveys^[1,2] suggest that tobacco, alcohol and cannabis are prevalent substances of abuse among Indian adolescents, but opioid use is quite uncommon in this age group (about 1 in 1000). Heroin use was seen in 3.3% of drug-using adolescents in contact with Nehru Yuva Kendras (grass-root level voluntary organization for youth) across the country.^[1] Potentially serious complications, *e.g.* sexual risks, violence and other high

risk behaviors are associated with adolescent substance use, which may pose a significant public health issue.

The long-term pharmacotherapies for opioid dependence can be either in the form of an opioid agonist (*e.g.* buprenorphine) or antagonist (*e.g.* naltrexone) therapy. The use of pharmacotherapies, in conjunction with psychosocial support, is the mainstay of treatment of adult opioid users,^[3] but there is only a limited evidence base for their efficacy in adolescents with opioid dependence. Very few reports or studies are available till date on long-term buprenorphine maintenance for adolescent opioid users^[4-7] and only one study has described the use of naltrexone (antagonist) in adolescent opioid dependence.^[8]

Buprenorphine is a partial agonist at mu-opioid receptor, which is used in low to moderate doses to enable the patient to abstain from the use of illicit opioids and prevent craving or withdrawals. It is available as sublingual (2 mg/4 mg) tablets administered under supervision of staff usually on a daily basis in

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view of their abuse liability. A take-home combination of sublingual buprenorphine-naloxone (4:1) is available which is ineffective by intravenous route, thereby minimizing the risk of abuse. Naltrexone is an opioid receptor antagonist which blocks the effects of opioids and prevents the positive reinforcement associated with the use of opioids. It is available in India as an oral tablet (50 mg).^[3]

No prior study or case report from India has described the use of agonist maintenance or antagonist therapy for adolescent opioid users. We discuss two adolescent patients with opioid (heroin) dependence visiting National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi for treatment, who were stabilized on Buprenorphine and Naltrexone respectively for a substantial period of time.

CASE REPORTS

Case 1

Master A, 15 years old, studied up to 6th std and belonged to a middle socio-economic status joint family living in a small town in the state of Uttar Pradesh (300 km from centre). He presented to Adolescent clinic, NDDTC, AIIMS with parents for the first time in January 2009 with chief complaints of the regular use of tobacco (both smokeless and smoking) for 8 years, occasional cannabis (*ganja*) use for 3 years and regular heroin (*smack*) use for 3 years. Heroin, the primary drug of use, was initiated at the age of 12 years out of curiosity with some of his friends and later, continued for its pleasurable effects. There was evidence of tolerance, withdrawals and diminished control over the time and amount of heroin use. The usual daily dose was 2-3 *pudias* (worth Rs 100-150). As a result of drug use, he started having frequent discord with parents and siblings. He engaged in stealing and working as an accomplice of pick-pockets to sustain drug use. He spent many nights out of his house without informing his whereabouts and experienced a significant decline in physical health and social functioning. The heroin use continued uninterrupted for 3 years till he presented for treatment on parent's initiative. There was no family history of psychiatric illness or substance use disorders. The personal history suggested the presence of conduct symptoms (truancy, lying, stealing from home) since childhood prior to onset of drug use. The physical examination revealed no abnormality and motivation was poor. An ICD-10 diagnosis^[9] of opioid dependence, tobacco dependence and conduct disorder were made. The complete hemogram, blood sugar, liver and kidney function tests were within normal limits. HIV-Elisa test was non-reactive. Urine thin layer chromatography was morphine-positive, indicating recent heroin use.

Patient was hospitalized for management of withdrawals with gradually tapering the dose of low strength buprenorphine (0.4 mg S/L tab; 2 mg/day) and subsequently, initiated on Naltrexone (25 mg/day; dispensed from centre's pharmacy free of cost). Psychosocial interventions aimed at rapport-building, motivation enhancement and psycho education were offered. However, patient was lost to follow-up after discharge restarting the heroin use and spending time with drug-using peers. There were two more admissions in ensuing months (June 2009 and August 2009; about 2 weeks each) which were considered for the purpose of detoxification and reinstatement of Naltrexone in view of long distance of travel. The psychosocial intervention sessions were provided for patient (to identify high risk situations, relapse prevention, coping skills enhancement, vocational skill building). Efforts were also made to engage the family members more actively in treatment process (and address mother's overprotective behavior for patient and conflict between parents). However, after each of these admissions, there was no follow-up visit in OPD and patient resumed the drug use. However, after the 4th admission (2 weeks; October 2009) and subsequent discharge on naltrexone (25 mg/day), he followed up in out-patient clinic with parents as advised during the ward sessions. Patient continued with the fortnightly follow-up, compliant to medication and maintaining abstinence (as confirmed by parents and repeated urinalysis) for a period of 10 months (Oct 2009-Aug 2010). Throughout this duration, parents were actively involved in treatment process, supervising the compliance at home and participating in sessions. Patient would intermittently report disinclination to take naltrexone, due to occasional body aches, discomfort and "not feeling fit" (*protracted withdrawals*). Eventually, he refused to take naltrexone on his own, relapsed within a few days and was lost to follow up for nearly an year. He again presented to the out-patient clinic (in July 2011) with the current use of 3-4 *pudias* (small packets) *smack* on a daily basis. He was not doing any meaningful activity, mostly staying away of home even during nights and engaged in anti-social activities with drug-using peers. Plan for long term management was discussed with patient as well as both parents, during which patient reported disinclination to take naltrexone due to physical discomfort. After a re-assessment, patient was initiated and stabilized on agonist replacement regimen (buprenorphine-naloxone combination 4 mg/day), which was dispensed biweekly to either of parents.

Patient felt comfortable on above medication and completely abstained from street heroin (confirmed by negative results on urinalysis using thin layer

chromatography or rapid cassette tests), though occasional cannabis use continued. He would not go out with drug-using peers and started remaining at home, leading to improvement in his relationships with family. His father involved him in their small-scale manufacturing unit (packeted eatables/snacks) and patient fulfilled various responsibilities, including financial handlings with no complaints. Patient works for nearly 7-8 h in a day and spends time with family in evenings. Currently, patient is on the same dose of buprenorphine-naloxone (4 mg/day) for nearly 2 years (dispensed fortnightly to him/his parents), during which he visits the center every month for follow-up continuing till date.

Case 2

Master B, 17 years old, school drop-out after primary class, belonged to nuclear family of lower middle socioeconomic status residing in Delhi. Mother was the chief informant. Patient had a history of regular tobacco and occasional cannabis (*ganja*) use since 10 years of age, regular inhalant use (*correction fluid*-1 bottle/day) since 11 years of age and heroin use since 16 years of age. At the time of presentation, heroin was the primary drug of use for nearly a year, with a usual dose of 1-2 *pudias* (small packets; worth Rs 50-100) per day. There was significant dysfunction in all the major domains of functioning and patient never tried to abstain (except for 2-3 forced admissions in unauthorized privately run centers lasting few weeks). In the psychiatric history, at the age of 17 years, patient had a moderate depressive episode lasting 2 weeks and in the ensuing 6 months, there were further four depressive episodes (each lasting 10-20 days) and two hypo-manic episodes (3-5 days each), all of which had no apparent precipitating factor and remitted spontaneously. Patient was using tobacco and heroin during this period, but no temporal relationship was observed with drug use. There was a childhood history suggestive of hyperactivity/impulsivity and inattentiveness since 5-6 years of age leading to poor academic performance and subsequent drop-out from school. No treatment was sought and symptoms improved after early adolescence. In addition, there is also a history of conduct symptoms prior to onset of drug use (truancy, lying to parents, initiating quarrels, physical fights, throwing stones and kicking small animals, running away from home). No family history of psychiatric illness or substance use disorders was reported. No abnormality was found on physical examination. Motivation was poor at the time of initial visit.

Patient fulfilled the ICD-10 diagnostic criteria^[9] for tobacco dependence, opioid dependence and bipolar affective disorder-not otherwise specified, and a

lifetime diagnosis of volatile solvent dependence and hyperkinetic conduct disorder. The complete hemogram and biochemistry tests were within normal limits. HIV ELISA was non-reactive, while urinalysis was positive for morphine.

Psychosocial treatment sessions focused on enhancing motivation and providing psycho education on various aspects of substance use and psychiatric disorders. After a detailed assessment, by the third out-patient visit, the patient was started on Tab naltrexone (50 mg/day) and Tab valproate (1 gm/day).

Patient continued in regular follow up on the above medication for a period of 1 year and 4 months. The compliance was supervised by mother and he began assisting his father in tailoring in the initial few months. Later, he started working on his own, earning Rs 300 per day. There were no further mood episodes during this period and patient was largely abstinent from illicit substances, confirmed by repeated cassette tests. The occasional use of cannabis, however, persisted along with a few behavioral problems. The psychosocial intervention sessions were delivered at each follow-up and some of the patient's conflicts with parents were taken up during the sessions.

DISCUSSION

These case descriptions add to the limited literature on long term pharmacological treatment of adolescent patients with opioid dependence.

Both the adolescent patients had some common clinical features, *e.g.* school drop-outs, presence of psychiatric risk factors, very early-onset of first substance use (7 and 10 years respectively), use of multiple substances, progression from licit to illicit substance, significant dysfunction in various domains and poor motivation at baseline. These are in accordance to the existing literature on the adolescent-onset substance use disorders.^[10,11] After initiation of pharmacological treatment in conjunction with psychosocial intervention sessions, both the patients could be retained in long term follow-up (Patient A: 2 years; Patient B: 1.3 years), were abstinent from heroin and engaged in meaningful work.

The use of buprenorphine maintenance is quite uncommon among adolescent patients and very few studies have evaluated its efficacy in this age group, which is summarized here.^[4-7] A multi-site study of opioid-dependent youth (of which 12 were adolescents) examined buprenorphine-naloxone treatment *vs.* standard detoxification, and found significantly better outcomes in drug use and other

measures at the end of 12 weeks. However, the adolescent sub-sample in this study was deemed to be inadequate for a separate analysis.^[4] A file review from an Australian treatment setting compared first treatment episode of adolescents on buprenorphine ($n = 25$) versus methadone ($n = 20$), and found that treatment retention was higher in methadone compared to buprenorphine (mean: 354 days vs. 58 days) in adolescents.^[5] Another US study reported positive experiences of few adolescent patients on buprenorphine in a substance abuse treatment program that also focused on adolescent development.^[6] Finally, a Cochrane review of various databases (1966-2008) for randomized or controlled trials for effectiveness of *any* maintenance agent in adolescents, found only two trials (only one of which involved buprenorphine). The Cochrane review was inconclusive and meta-analysis could not be carried out with two heterogeneous trials.^[7]

There is often a general policy of dispensing agonist medication only to adult patients due to concerns about starting youth on treatment that is often long-term and reluctance to bring young patients into daily contact with adult patients with extensive addiction histories and antisocial behaviors. However, a small percentage of adolescents with early-onset of opioid dependence may experience severe dysfunction, engage in high risk and anti-social behaviors and show a poor motivation to quit. Harm reduction approach using an agonist medication may be considered for such adolescent patients.^[12,13] It has been recommended elsewhere too that agonist maintenance may be considered for adolescents who have opioid dependence, age is at least 16 years or above, opioid use ≥ 1 year and two documented failed attempts.^[14]

So far, only one study is available for naltrexone use in adolescent opioid dependence.^[8] In this preliminary non-controlled, extended-release naltrexone was found to be safe and efficacious in a sample of 16 adolescents and young adults (mean age: 18.5 years). Of total, 10 were retained in treatment for at least 4 months and 9 had a good outcome. In addition, few studies and case reports have evaluated the overall safety of naltrexone for adolescents with alcohol use disorders (sample age: 16-18 years; dose 50 mg/day).^[15-17] No significant adverse effects were noted other than nausea. In both the patients discussed above, naltrexone was initiated after a discussion with patient, parents and a review of existing literature. Naltrexone was tolerated well at the dose of 50 mg/day, with no significant adverse effects. Compared to patient A, Patient B had a shorter duration of heroin use and consequently, did not experience any protracted withdrawals, craving or need for an agonist. Abstinence

from opioids was maintained for a significant period while on naltrexone.

It is to be noted that adolescent opioid users frequently have a number of other problems, *e.g.* the use of drugs by peers, poor family support, living in a locality with easy availability of drugs and underlying psychiatric morbidity, some of which were present in one or both patients. Failure to address those issues will reduce the chance of successful treatment and increase the risk of relapse.^[18] The comorbid bipolar disorder was managed with a mood stabilizer in patient B, with no recurrence during follow-up period. A good family support was present in both cases, which played a crucial role in ensuring compliance to medication and other treatment aspects. For example, the take-home doses of buprenorphine-naloxone were dispensed free of cost as a policy, but family members had to travel several hours by train to reach center on a fortnightly basis, thereby investing time and other resources over these years. In Indian context, the active involvement of family in various aspects of treatment process contributes immensely toward improved functioning of the patient. Some drug using adolescents may not have a family or family support, but wherever available, their participation should be actively sought at all treatment steps.

To conclude, the case report adds to the limited literature on efficacy of pharmacotherapies for adolescent opioid use. However, there is a need to conduct systematically planned studies on the adolescent opioid use treatment.

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