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Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibilityadd_3015 1669..1676 Marc J. Fishman1,2, Erin L. Winstanley3,4, Erin Curran1,2, Shannon Garrett2 & Geetha Subramaniam1,2 Johns Hopkins University School of Medicine, Depar tment of Psychiatry and Behavioral Sciences, MD, USA,1 Mountain Manor Treatment Center, MD, USA,2 University of Cincinnati College of Medicine, Depar tment of Psychiatry, OH, USA3 and Lindner Center of HOPE, OH, USA4

ABSTRACT Background Opioid dependence is an increasing problem among adolescents and young adults, but in contrast to the standard in the adult population, adoption of pharmacotherapies has been slow. Extended-release naltrexone (XRNTX) is a promising treatment that has been receiving increasing interest for adult opioid dependence. Clinical chart abstractions were performed on a convenience sample of 16 serial adolescent and young adult cases (mean age 18.5 years) treated for opioid dependence with XR-NTX who attended at least one out-patient clinical follow-up visit. Case descriptions Of these 16 cases, 10 of 16 (63%) were retained in treatment for at least 4 months and nine of 16 (56%) had a 'good' outcome defined as having substantially decreased opioid use, improvement in at least one psychosocial domain and no new problems due to substance use. Conclusions These descriptive results suggest that XR-NTX in the treatment of adolescents and young adults with opioid dependence is well tolerated over a period of 4 months and feasible in a community-based treatment setting, and associated with good outcomes in a preliminary, small noncontrolled case-series. This probably reflects an overall trend towards greater adoption of medication treatments for this population. Keywords Adolescents, extended-release naltrexone, naltrexone, opioid dependence, medication assisted treatment, pharmacotherapy, young adults. Correspondence to: Marc J. Fishman, Mountain Manor Treatment Center, 3800 Frederick Road, Baltimore, MD 21229, USA. E-mail: mjfishman@comcast.net Submitted 29 November 2009; initial review completed 5 February 2010; final version accepted 3 March 2010 INTRODUCTION Opioid use among adolescents has risen dramatically in the past decade. Past-year heroin use among 12th graders in the decade from 1995–2005 averaged 1%, while past-year non-medical use of prescription opioids nearly doubled from 4.7% to 9% during the same period. Non-medical use of prescription opiates is now the second most frequently used illicit drug among 12–17- year-olds, following marijuana [1,2,3]. Correspondingly, treatment admissions for opioid use disorders increased 196% between 1995 and 2005 [4]. Despite advances in adolescent substance abuse treatments and research over the past decade [5], there is relatively little documentation of treatment outcomes among the high-severity subpopulation of adolescent and young adult opioid users. Opioid-using adolescents have very high rates of relapse and treatment dropout in outpatient treatment [6] and greater severity and worse postresidential treatment outcomes compared to their nonopioid-using

counterparts [7]. The effectiveness of maintenance pharmacotherapy for opioid dependence in adults is well documented, and has become the treatment standard of care. Four medications are approved by the Food and Drug Administration (FDA) for the treatment of opioid dependence in adults—the pure agonist methadone, the pure antagonist naltrexone, the partial agonist buprenorphine and a buprenorphine/naloxone combination. However, there is very little information about the use and effectiveness of pharmacotherapies for opioid dependence in adolescents and young adults. CASE REPORT doi:10.1111/j.1360-0443.2010.03015.x © 2010 The Authors. Journal compilation © 2010 Society for the Study of Addiction Addiction, 105, 1669–1676 Methadone is not readily available to adolescents [8]. Its use is limited to highly regulated specialty clinics, where criteria for admission are relatively restrictive, adolescents are often not accepted and most importantly the treatment programming does not address the developmentally specific treatment needs of youth. Another barrier has been stigma associated with agonist treatments and lack of acceptability. There may be a sense that impressionable youth do not belong in methadone clinics among 'chronic' adult patients, or that adolescents are 'too young' for this strategy and should be encouraged to pursue the intrinsically more valued 'drug-free' approaches. Buprenorphine may have some pharmacological advantages over methadone, and will probably have better acceptability as it can be delivered in a broader variety of clinical settings, such as physician offices and adolescent treatment programs. In a multi-site trial of adolescents and young adults (mean age = 19.2 years), patients randomized to 12 weeks of buprenorphine maintenance had increased retention and decreased opioid positive urines compared to those who received 2 weeks of buprenorphine detoxification only [9]. However, because buprenorphine is a partial agonist, it continues to share some of the stigma of the pure agonists and resistance by some to its adoption as a maintenance therapy for adolescents. Oral naltrexone has been in use to treat opioid addiction in the United States since 1984. It acts as a pure competitive antagonist at the mu receptor. Despite the efficacy of oral naltrexone (NTX) for treating opioid dependence in controlled research trials, clinical experience has been disappointing because of poor medication adherence [10]. The exceptions have been in highly motivated populations and/or in situations of enhanced supervision and monitoring to increase medication compliance [11,12]. Two notable studies with oral naltrexone among young adults in Russia showed success, perhaps aided by parental medication supervision [13,14]. More recently, the development of extended-release formulations of naltrexone (XR-NTX), which is injected monthly, represents an advance because of the increased ease of medication adherence. Over the past several years there has been considerable interest in and evidence supporting the use of XR-NTX for the treatment of adult opioid-addicted populations, including a two-site randomized, double-blind placebo-controlled trial, which demonstrated significantly increased treatment retention and decreased opioid and other substance positive urines at 60-day follow-up, in a dose-related fashion [15]. Naltrexone implants have been used in Australia, and have been shown recently to be effective for 3 months in reducing relapse to regular heroin use in adults, compared to oral naltrexone [16]. An extended-release naltrexone preparation, Vivitrol®, was approved in the United States in 2006 for alcohol dependence, and is used in 'off-label' clinical practice for opioid dependence. Our group has been using this formulation of XR-NTX to treat opioid dependence in adolescents and young adults concurrently with cognitive behavioral therapy (CBT). We used a retrospective, open-label case-series to assess acceptability, feasibility, preliminary outcomes and to report initial clinical impressions associated with XR-NTX treatment in a specialty opioid dependence track within an adolescent and young adult drug treatment program. Treatment setting The treatment was conducted at Mountain Manor

Treatment Center (MMTC), a community-based adolescent substance abuse treatment program in Baltimore MD, which provides both residential and out-patient levels of care. The adolescent residential program is described elsewhere [7,17], and notably includes medical/nursing staff. The out-patient program includes a partial hospital program (PHP), an intensive out-patient program (IOP) and a mental health clinic for concurrent treatment of comorbid psychiatric disorders. A specialized opioid dependence out-patient track was developed in September 2007 and consists of one to two group counseling sessions per week, one individual counseling session per week using manual-based motivational enhancement therapy (MET)/CBT content and physician visits, typically beginning weekly then tapering to monthly. Typical treatment for patients with opioid dependence includes residential detoxification using a 7-day buprenorphine taper followed by a variable length of additional residential treatment, step-down to the outpatient PHP, and then the out-patient specialty opioid program. The length of stay at the residential and PHP levels of care are determined by clinical necessity and managed-care insurance limitations. The mean duration of residential treatment for this sample was 21 days (range 11–52). All patients undergoing residential opioid detoxification were offered a range of alternative treatments, including XR-NTX, maintenance buprenorphine, oral naltrexone and counseling treatment without medication support. Selection was based on patient and parent preference, and the clinical recommendation of a physician (M.F. or G.S.). Other factors influencing participation and choice of medication included ability to follow-up in our out-patient clinic based on geographical distance of residence from the facility and previous experience (including success or failure, compliance problems or diversion) with a particular medication (usually 1670 Marc J. Fishman et al. © 2010 The Authors. Journal compilation © 2010 Society for the Study of Addiction Addiction, 105, 1669–1676 buprenorphine, which is more broadly available). Reasons reported for declining XR-NTX included: rejection of any medication treatment, preference for buprenorphine, aversion to injection, lack of insurance medication coverage (expense of medication) and lack of insurance coverage for sufficient residential length of stay to initiate treatment. Many patients were also treated with medications for comorbid psychiatric conditions. Patients who elect XR-NTX are continued in residential treatment for long enough to ensure 7 days of lead-in abstinence from all opioids (including buprenorphine). Naltrexone induction is begun with oral naltrexone to establish tolerability using gradually titrated dosing over several days. We administer the first dose of XR-NTX 380 mg intramuscularly (i.m.) prior to residential discharge. Patients are then referred to out-patient continuing care, including monthly XR-NTX injections administered by nursing staff. Participants This is a convenience sample of the first 16 serial cases at MMTC started on XR-NTX for opioid dependence, between January 2007 and March 2008, with the treatment described here continuing to August 2008. Candidates for XR-NTX were identified during a residential treatment episode at MMTC, with the exception of one patient who received out-patient detoxification. Three patients were excluded because they never returned for any out-patient follow-up after receiving a single dose of XR-NTX during residential treatment. The 16 patients described are those who attended at least one out-patient treatment session after receiving XR-NTX. During that period of January 2007–March 2008, 59 opioiddependent patients received residential treatment, 37 received out-patient treatment, and of those 16 received XR-NTX, four oral NTX, nine buprenorphine/naloxone and 12 no medications. Chart abstraction Data and case summaries were abstracted from clinical charts in August 2008, with identifiable personal information removed. Clinicians were asked to rate retrospectively good treatment outcomes during the 4 months following initiation of out-patient treatment. Good

treatment outcomes were defined as: (i) a substantial reduction in opioid use (defined as either continued abstinence from opioids or discrete lapses once per week or less frequently) based on the combination of self-report and urine testing, (ii) no new drug-related problems (e.g. arrest or school expulsion) based on clinician judgement as ascertained through progress notes and consensus case reviews among counselors and physicians and (iii) improvement in at least one major domain of psychosocial functioning (e.g. school, work, legal status or family) determined as in criterion (ii). Patients who were lost to follow-up were considered putatively as relapsed. The study was approved by the Institutional Review Board (IRB) of the Johns Hopkins University. IRB approval specifying waiver of patient consent was granted. CASE DESCRIPTIONS Among the 19 patients who received at least a single dose of XR-NTX, 16 returned for at least one out-patient follow-up session and were included in this case-series. Overall, the sample is representative of the opioiddependent patients presenting for care at MMTC. Average age was 18.5 years (range 16–20), eight of 16 (50%) were female and 15 of 16 (94%) Caucasian. Twelve of 16 used heroin, 12 of 16 used prescription opioids and eight of 16 used both. Eleven of 16 were injection users. Outcomes for the 16 patients are summarized in Table 1. Two patients dropped out after only one outpatient follow-up session, and 10 (63%) were retained in treatment for 4 months. The mean number of doses of XR-NTX received during the 4 months after initiation was 2.5 (median 3), with 12 (75%) receiving at least two doses. Seven patients continued XR-NTX beyond 4 months, and the mean number of total doses at the time of data abstraction was 3.4 (median 3; range 1–8). Seven were in active ongoing treatment at the time of data abstraction. Eleven (69%) patients were abstinent or had substantial reductions in opioid use and nine (56%) met the criteria for a ‘good’ outcome at 4 months. There were no reports of overdoses. CONCLUSIONS In a case-series of our first 16 adolescent and young adult patients treated with XR-NTX, treatment retention and clinical outcomes were encouraging. Not surprisingly, treatment engagement was linked to treatment success. Two patients dropped out after attending only one outpatient session and relapsed. Of the 14 patients who attended at least two out-patient visits, 12 received at least two doses of XR-NTX, 10 were retained in treatment for 4 months and nine had a ‘good’ outcome. Treatment with XR-NTX was well tolerated and accepted by patients. While many patients reported initial transient local injection site soreness, it usually subsided within a few days. Only one patient discontinued due to side effects and this was due to severe recurrent injection site discomfort. Some of the patients and parents in this self-selected group seemed to have a sense that it was a more definitive or stronger treatment compared to buprenorphine, and some were specifically averse to an agonist. Enthusiasm for the treatment was especially XR-NTX for adolescent opioid treatment 1671 Addiction, 105, 1669–1676 Table 1 Summary of XR-NTX cases. Case # Age Sex Opioid Type Injection use Retention at 4 months # doses @ 4 months Abstinent from opioids or only minor lapses through 4 months ‘Good’ outcome @ 4 months Reason stopped XR-NTX Total doses received as of abstraction Notes (duration of XR-NX treatment; total duration of treatment) 1 19 F H Y Y 3 Y Y Pregnancy 3 Did well for 3 months on XR-NTX, and for an additional 5 months after discontinued due to pregnancy, but then relapsed and dropped out when left half-way house (5 monthsa; 8 monthsb) 2 20 F H, P Y N 1 N N Unexplained dropout 1 Dropped out after one visit (1 weeka; 1 weekb) 3 17 F H, P Y Y 5 Y Y Persistent injection site pain 8 Did well until stopped XR-NTX at 8 months, switched to oral NTX, then immediately relapsed (8 monthsa; 8 monthsb) 5 17 F H. P Y Y 3 Y Y Unexplained ‘personal decision’ 5 Relapsed 6 weeks after missed injection, returned 3 months later for residential detox and restarted XR-NTX for two doses,

relapsed after missed injection, switched to buprenorphine, then dropped out (5 monthsa; 6 monthsb) 6 20 M H, P Y Y 4 Y Y Scheduled surgery 8 Erratic course during 1 year of buprenorphine Rx, with complications of osteosarcoma. Switched to XR-NTX after requiring third residential detox. Did well for 8 months until medication discontinued for surgery due to cancer metastasis, then dropped out, then returned (8 monthsa ; 26 monthsb ongoing) 7 16 M H Y Y 3 Y N Scheduled surgery 6 Relapsed while on XR-NTX, but improved after third in-patient admission, switched to oral NTX because of surgery. Now opioid-free 4 months later, but using cocaine and MJ sporadically (6 monthsa; 10 monthsb ongoing) 10 20 M H Y N 1 N N Unexplained dropout 1 Dropped out after one out-patient visit (1 weeka; 1 weekb) 12 17 M P N Y 3 Y Y Wanted to get high 7 Did well for 7 months until relapsed in the context of suicidal depression following break-up with girlfriend. Attempted out-patient detox but failed, then re-started XR-NTX after residential detox, now abstinent again 1 month (8 monthsa; 10 monthsb ongoing) 13 17 M P N Y 3 Y Y Cost of Rx, and wanted to 'do it on my own' 3 Relapsed 2 months after stopping XR-NTX, readmitted for residential detox 1 month later, then started oral NTX because of lower cost. Now abstinent additional 3 months (3 monthsa; 8 monthsb ongoing) 1672 Marc J. Fishman et al. © 2010 The Authors. Journal compilation © 2010 Society for the Study of Addiction Addiction, 105, 1669–1676 14 18 F H, P Y Y 4 Y Y Decreased parental monitoring 5 Erratic compliance with oral NTX then did well after switched to XR-NTX. Stopped XR-NTX after 5 months but remained abstinent for 2 more months until prescribed opioid analgesics in ER following car accident, then relapsed to heroin (5 monthsa; 13 monthsb ongoing) 15 18 M H, P Y N 1 Y N Unexplained dropout 1 Failed several-month course oral NTX, then induced onto XR-NTX as an out-patient, dropped out after first dose. Reappeared 3 months later, failed out-patient buprenorphine induction, admitted to residential detox. Transferred to long-term residential program where medication support not allowed, then dropped out after several weeks and lost to follow-up (1 montha; 5 monthsb) 16 19 M P N N 3 Y Y Unexplained dropout 3 Unexplained dropout after 3 months, then reappeared 3 months later still abstinent but struggling with mood disorder symptoms (3 monthsa; 6 monthsb ongoing) 17 18 F H Y Y 2 Y Y Cost of Rx, and wanted to 'do it on my own' 2 Failed 3-month course of methadone, switched to XR-NTX during residential treatment episode. Switched to oral NTX after two doses, then stopped after 2 more months, although remains on Rx for mood disorder. Now abstinent an additional 6 months (2 monthsa; 12 monthsb ongoing) 18 16 F H, P N Y 4 Y Y Advice from NA sponsor, not 'real recovery' 5 Dropped out of treatment while abstinent and doing well because clinic too far (1.5-hour travel each way), lost to follow-up (5 monthsa; 5 monthsb) 19 17 F P N N 2 N N Cost 2 Switched to oral NTX after 2 doses, did well for an additional month then lost to follow-up. (2 monthsa; 3 monthsb) 20 18 M H, P N N 1 N N GI discomfort 1 Did well 2 months then dropped out of treatment, lost to follow-up (1 montha; 2 monthsb) H: heroin; P: prescription opioids; aduration of out-patient treatment while on extended-release naltrexone (XR-NTX); btotal cumulative duration of out-patient treatment, with or without XR-NTX, excluding interruptions; ongoing: continued to be retained in out-patient treatment at the time of data abstraction. GI: gastrointestinal. XR-NTX for adolescent opioid treatment 1673 © 2010 The Authors. Journal compilation © 2010 Society for the Study of Addiction Addiction , 105, 1669–1676 strong among patients' parents, who embraced the concept of blockade, the relief of a month's protection and the anticipation (although perhaps unrealistic) of control. It is important to note that the development of a specialty track for opioid dependence has been an important feature of the treatment. Although the center had not been collecting systematic retention data previously, it has been the overwhelming sense of the

treatment staff that patient engagement and retention is improved dramatically. The adoption of medication support as the new standard of care for opioid dependence at the treatment center was a paradigm shift, and entailed a gradual change within the counseling treatment culture that occurred with training and direct clinical experience. While initially there had been considerable skepticism among counselors about medications used as a replacement for counseling, over time their comments emphasized the apparent utility of medications in increasing retention and making patients more available for counseling than ever before. The reported blockade duration of XR-NTX is 30 days [18]; however, some patients were able to overcome the blockade towards the end of the month and it was fairly common for patients to test the blockade. In general, patients who reported using opioids while on XR-NTR experienced no or minimal subjective effects of intoxication or euphoria. This often had the therapeutic benefit of provoking a devaluation of the street drugs. One patient (case 3) had precipitated withdrawal when she received a dose of XR-NTX 2 days after using oxycodone (as reported in greater detail elsewhere) [19]. Another patient (case 7) claimed to have relapsed to frequent heroin use within a month of receiving a dose of XR-NTX, then after an episode of residential detoxification was restarted on medication. Some have speculated whether XR-NTX blockade might put adolescents at risk of overdose by attempting to overcome the blockade by use of very large amounts of opioids. Although, as a competitive antagonist, naltrexone's blockade can be overcome, this effect is gradual and stepwise both with respect to the time from naltrexone administration and the dose of opioid used without precipitous reversal [20], as has been shown in human laboratory settings [18], and clinically, as anesthesiologists have accumulated experience with opioid analgesia in naltrexone-treated patients. There is also no naltrexoneinduced hypersensitivity of the opioid receptor in humans [20]. The loss of tolerance with the risk of overdose on previously tolerated opioid doses after discontinuation of naltrexone is not different from the risk for patients detoxified without maintenance medications. This is included in our informed consent and should be part of the patient education for all patients in any opioid treatment modality [21]. The safety of XR-NTX in youth is also supported by a small case-series in Australia reporting a decrease in the number of overdose events following implant NTX treatment compared to pretreatment baseline for the same patients [22]. The typical course of these patients was one of shifting status, moving in and out of treatment, in and out of remission and lapse/relapse. As opposed to the more traditional approach of discrete time-limited treatment episodes, our longer-term medically managed maintenance approach seemed to facilitate retention or return to treatment after lapse/relapse. In a number of cases, although XR-NTX was not sustained, it seemed to provide a bridge to further successful treatment. For the most part, patients who remained on medication or returned to medication did well. Patients who relapsed did so primarily after missing a dose of XR-NTX, either inadvertently or more often intentionally, or following treatment dropout. The benefits of sustained protection against the temptations of non-compliance and relapse were appreciated by many of the patients. This contrasts with our clinical experience with buprenorphine and oral naltrexone, in which patients periodically stop their medications at any time throughout the month and within a few days are able to obtain the full intoxicating, reinforcing effects of street opioids. Our experience in general with each of the pharmacotherapies for opioid dependence is that medication adherence is paramount, and while monthly, extended-release dosing is by no means foolproof, it does seem to provide an advantage in this regard. Practical implementation issues included: the need for on-site physician and nursing staff; the need for billing and utilization management infrastructure to support out-patient medical services and medication prescription; and integration of the

medication component into the existing psychosocial treatment infrastructure, which required the cross-training of and support from the counselors to monitor and encourage compliance with the dosing schedules. Insurance coverage issues were prominent, as XR-NTX is a relatively new medication that has nonformulary status for many payors. For patients who did not have insurance that covered the medication cost was a major barrier, and this frequently influenced choice of medication. It is noteworthy that some parents were willing to pay cash for the medication despite its high cost ($800–900 per month), and expressed the sentiment that they had already expended considerable resources for what seemed like less effective interventions. We continued to find that despite some general ongoing resistance to medications for drug treatment, XR-NTX was better received as a maintenance medication compared to alternatives. For example, many local 1674 Marc J. Fishman et al. © 2010 The Authors. Journal compilation © 2010 Society for the Study of Addiction Addiction, 105, 1669–1676 half-way houses will not accept our patients because of their prohibitions against buprenorphine maintenance therapy. Nevertheless, some stigma against maintenance medications persists even for this pure antagonist, and this unfortunately remains a barrier for broader adoption. For example, one patient discontinued medication then dropped out of treatment after 5 months of abstinence on XR-NTX when her NA sponsor told she could not take a key tag at a Narcotics Anonymous (NA) meeting as a traditional token of sobriety because she was not 'really clean'. The limitations of this study include the retrospective case-series design without comparison group, lack of standard instrumentation and lack of objective outcome measures, such as systematic urine results. For adolescents and young adults with opioid dependence, XR-NTX medication treatment is feasible and can be implemented practically as a standard treatment in a community treatment program. The patients and their families seem to accept treatment with XR-NTX, and parents may even prefer it to other medications for opioid dependence because of their sense of longer-lasting protection. XR-NTX and other pharmacotherapies are integrated easily with counseling as part of a comprehensive treatment approach. Medication compliance is key to success and parental involvement may be an important ingredient in enhancing compliance. Treatment with XR-NTX appears to be a promising treatment for adolescent and young adult opioid dependence that may improve outcomes based on this limited sample. Declarations of interest Dr Fishman, the Medical Director of the Mountain Manor Treatment Center (MMTC) where patients were enrolled in the study described in this paper, is a faculty member of the Johns Hopkins University, and is a beneficiary of the trust which owns MMTC. Dr Fishman serves on the governing board of the trust and the Board of Directors of MMTC. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies. Acknowledgements A limited portion of this manuscript was presented as part of the NIDA sponsored symposium 'The Opioid Dependent Adolescent/Young Adult' at the American Academy of Child and Adolescent Psychiatry Annual Meeting in Toronto CA on 10/31/08. References 1. Johnston L. D., O'Malley P. M., Bachman J. G., Schulenberg J. E. Monitoring the Future National Survey Results on Drug Use, 1975–2005: Volume I, Secondary School Students (NIH Publication no. 06-5883). Bethesda, MD: National Institute on Drug Abuse; 2006. 2. Substance Abuse and Mental Health Services Administration (SAMHSA) Office of Applied Studies (OAS). The NSDUH Report: Patterns and Trends in Nonmedical Prescription Pain Reliever Use: 2002 to 2005. Rockville, MD: SAMHSA OAS; 2007. 3. Substance Abuse and Mental Health Services Administration. Results from the 2006 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-32, DHHS Publication no. SMA 07-4293). Rockville, MD: Substance Abuse

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