Atomoxetine for the Treatment of ADHD in Incarcerated Adolescents

Sarah Jillani, MD, Prina Patel, MD, Robert Trestman, MD, PhD, and Jayesh Kamath, MD, PhD

Effective interventions for adolescents with attention deficit/hyperactivity disorder (ADHD) in the correctional setting may improve care during incarceration, decrease risk of substance relapse, and reduce recidivism after release from the correctional setting of these individuals. The present report delineates the epidemiology of adolescent ADHD in the correctional setting and its association with substance use disorders and comorbid psychiatric illnesses. Evidence suggests that adolescents with ADHD have a higher risk of arrest and incarceration during adulthood. The present report examines evidence related to efficacy of atomoxetine, a nonstimulant medication for the treatment of adolescent ADHD, and presents data from a case series evaluating the effectiveness of atomoxetine for the treatment of adolescent ADHD in the Connecticut correctional setting. The results from the case series suggest that atomoxetine is effective for the treatment of adolescent ADHD in the context of significant past substance use. In summary, adolescents with ADHD have an elevated risk of incarceration and developing substance use disorders. The present review and pilot case series suggest that atomoxetine is an effective treatment for adolescents with ADHD in the correctional setting.

J Am Acad Psychiatry Law 44:158–63, 2016

Epidemiological studies of incarcerated adolescents report high prevalence rates (males 16.6%, females 21.4%) of attention-deficit hyperactivity disorder (ADHD).[1] Effective interventions for ADHD in the correctional setting may translate into improved behavioral management of these individuals during incarceration and may lead to better social integration, decreased risk of substance misuse, and reincarceration. Childhood ADHD is associated with an earlier age of onset of disruptive behavior and a higher risk of arrest and incarceration during adolescence and early adulthood.[2] Prospective follow-up studies of children with ADHD have emphasized the connection between ADHD, conduct problems, substance misuse, and delinquency.[3] In the present report, we review evidence related to adolescent ADHD, its association with substance misuse, psychiatric comorbidities, and the potential role of atomoxetine in treating ADHD in this population. We also describe a case series investigation of the effectiveness of atomoxetine in treating adolescent ADHD in a correctional setting.

Dr. Jillani is a Child and Adolescent Psychiatry Fellow, Yale Child Study Center, Yale University, New Haven, CT. Dr. Patel is a Pediatric Resident Physician, Winthrop University Hospital, Mineola, NY. Dr. Trestman is Professor of Medicine, Psychiatry, and Nursing, University of Connecticut School of Medicine, and Executive Director, UConn Health Correctional Managed Health Care, Farmington, CT. Dr. Kamath is Associate Professor, Department of Psychiatry, University of Connecticut Health Center, Farmington, CT. Address correspondence to: Jayesh Kamath, MD, PhD, Department of Psychiatry, 10 Talcott Notch Road, East Lobby, 3rd Floor, Farmington, CT 06030. E-mail: jkamath@uchc.edu.

Disclosure: The case series described in the article was supported by an investigator-initiated grant from Eli Lilly and Company, Indianapolis, IN.

Literature Search

For this nonexhaustive review, articles pertaining to child and adolescent ADHD in the correctional setting were retrieved from several search engines: Psych info, PubMed, Medline, and Google Scholar. Key search words included: (1) ADHD, Adolescents, and Prison; (2) ADHD, Adolescents, and Substance Use Disorders; and (3) Atomoxetine, ADHD, and Substance Use Disorders.

Adolescents With ADHD in the Correctional Setting

Epidemiological studies of incarcerated adolescents report high prevalence rates of ADHD for both genders.[1,4,5] The reported rates vary widely (11–45%) depending on whether the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,

Text Revision (DSM IV-TR)[6] criteria or the International Statistical Classification of Diseases and Related Health Problems 10 (ICD 10) criteria are used.[1,5,7] The prevalence is higher when subsyndromal ADHD is included.[7] These prevalence rates are 5 to 15 times greater than the 3 to 10 percent prevalence of child and adolescent ADHD found in the community.[8]

Research has revealed a strong association between childhood ADHD and delinquency in adulthood. Children with ADHD are at increased risk for both juvenile and adult criminality.[9] A study conducted in a large ($n = 2,713$) sample of Finnish boys identified hyperactivity as an important predictor of criminality in late adolescence.[10] Studies prospectively observing children with and without ADHD into adolescence and adulthood demonstrated significantly higher rates of criminal convictions compared with age-matched control subjects without ADHD.[3,11,12] Dalsgaard and colleagues[11] documented that children with ADHD are about 5 times more likely to have any conviction and 12 times more likely to be convicted for a violent crime than are peers without ADHD in the general population. The same study demonstrated that girls with ADHD are also at increased risk of criminal convictions compared with age-matched control subjects.

It is well-established that conduct disorder (CD) and oppositional defiant disorder (ODD) are highly comorbid with childhood ADHD and are significant predictors of antisocial behavior in adolescence and of criminality in both adolescence and adulthood. Evidence suggests that from 30 to 60 percent of children with ADHD also meet criteria for comorbid CD or ODD.[13,14] Studies have shown that hyperactive children with comorbid CD are at higher risk for later criminality compared with their peers without CD.[9,11,12] Research suggests that comorbid ADHD and CD are related to several biological and environmental risk factors, such as neurocognitive impairment, high rates of parental psychopathology, poor social functioning, and comorbid psychiatric disorders, especially substance use disorders.[15,16] These risk factors may also contribute to delinquency and incarceration during adolescence and adulthood. Evidence suggests that ADHD increases the risk of development of antisocial and substance use disorders in adolescence, which, in turn, increases the risk of criminal behavior.[3,16]

Comorbid Substance Use Disorders in Adolescents With ADHD

Substance use disorders (SUDs) are often intertwined with ADHD.[17,18] Longitudinal studies of children with ADHD have consistently demonstrated early substance use in adolescence and an overall higher risk of development of an SUD in adulthood compared with children without ADHD.[19] A meta-analytic review of the prospective association of childhood ADHD and substance use found that, compared with control subjects without ADHD, children with ADHD are 2.5 times more likely to develop an SUD overall; 2 times more likely to have an alcohol use disorder, 1.5 times more likely to develop a cannabis use disorder, 3 times more likely to report a nicotine use disorder, and 2 times more likely to meet criteria for cocaine abuse or dependence.[20] Studies have suggested that the risk that a child with ADHD will have an SUD is partially mediated by childhood and adolescent conduct disorder.[21,22] Evidence has also suggested that the combined (hyperactive and inattentive) subtype of ADHD is associated with more severe SUD and higher rates of comorbid conduct disorder.[23]

The presence of ADHD may affect the course of adolescent substance abuse in several ways, including increased likelihood of an earlier age of onset, longer duration of SUD, and progression from alcohol abuse to another drug use disorder.[19] It is also important to note that treatment may have targeted each comorbid illness specifically. Findings in studies have suggested that ADHD treatment in patients with comorbid SUD improves overall treatment outcomes and outcomes for ADHD with limited or no efficacy in the treatment of comorbid addictive disorders.[24]

Atomoxetine for the Treatment of Adolescent ADHD in Correctional Settings

Psychostimulant medications (such as methylphenidates and amphetamines) have been approved by the U.S. Federal Drug Administration (FDA) for the treatment of ADHD in both child/adolescent and adult patient populations (Table 1). These medications are highly effective in the treatment of core symptoms of ADHD and may reduce the risk of subsequent development of SUDs when used at an earlier age.[25] Their effectiveness in patients with coexisting ADHD-SUD remains controversial.[26] There are also concerns about the cardiovascular and

Table 1 Stimulants and Nonstimulants for the Treatment of ADHD

I. Stimulants: methylphenidates and amphetamines
MOA: blockade of dopamine transporters with additional effects of norepinephrine transporter blockade, dampening action of enzyme monoamine oxidase and enhanced release of dopamine in synaptic space
SE: appetite loss, abdominal pain, headaches, sleep disturbances, and cardiovascular and neuropsychiatric side effects
II. Nonstimulants
A. α2-Adrenoreceptor agonists (e.g., guanfacine and clonidine)
MOA: stimulation of the presynaptic and postsynaptic α2-adrenergic receptors that control the release of norepinephrine and the rate of cell firing
SE: drowsiness, dizziness, irritability, headache, abdominal pain, and cardiovascular side effects (bradycardia, hypotension, and QTc prolongation)
B. Atomoxetine
MOA: norepinephrine reuptake inhibition
SE: sedation, fatigue, nausea, vomiting, reduced appetite, headaches, and irritability

MOA, mechanism of action; SE, side effect.

neuropsychiatric effects of these medications in patients with active comorbid SUD caused by the known cardiovascular and neuropsychiatric effects of certain illicit substances, such as cocaine.[27] Use of psychostimulants is highly restricted in correctional settings because of their potential for abuse, misuse, and diversion.[24,28]

Another class of agents, the α2-adrenoreceptor agonists, have shown efficacy in the treatment of ADHD in children and adolescents. Several studies have demonstrated the efficacy of the immediate-release formulations of the α2 agonists clonidine and guanfacine for the treatment of ADHD in children and adolescents (reviewed in Ref. 29). These agents are not approved by the FDA for the treatment of ADHD, but are frequently used off label for this purpose. Extended-release formulations of clonidine and guanfacine have been approved by the FDA for the treatment of ADHD in children and adolescents. These agents are alternatives to psychostimulants in the correctional setting because of their limited potential for abuse. However, their use is restricted by possible cardiovascular side effects (Table 1).[29,30] These cardiovascular side effects include hypotension, bradycardia, and QTc prolongation.[29,30] Similar to psychostimulants, cardiovascular side effects with these agents may be especially problematic in the context of pre-existing cardiovascular damage subsequent to illicit substance use (e.g., cocaine). To date, studies have evaluated the effectiveness of α2-agonist agents in the correctional setting.

Atomoxetine, another nonstimulant medication, may offer an important alternative in patients with comorbid ADHD-SUD in the correctional setting because they have no abuse potential and are limited in cardiovascular risks.[26,31] Atomoxetine is a potent and selective norepinephrine reuptake inhibitor and norepinephrine transporter (NET) inhibitor.[32] It is approved by the FDA for the treatment of ADHD in children, adolescents, and adults.[32,33] Its safety and tolerability in the treatment of adolescent ADHD is well established.[33] The most common side effects reported in child and adolescent clinical trials include nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence.[32,33] Other less frequent side effects reported in clinical trials include headaches, increased blood pressure, dizziness, and risk of liver injury.[32,33] Selective NET inhibition of atomoxetine has been associated with its efficacy in the treatment of ADHD.[34] Evidence has suggested that the efficacy of atomoxetine is due to increases in norepinephrine and dopamine in the prefrontal cortex as result of selective NET inhibition.[34,35] The abuse potential of psychostimulants has been associated with increases of dopamine (primarily) and norepinephrine in the nucleus accumbens (NA).[36] Atomoxetine does not cause increases in dopamine or norepinephrine in the NA, as very few norepinephrine transporter inhibitors are located there.[35] It has been posited that atomoxetine can be an effective treatment for patients with ADHD with comorbid SUD and that it may have a positive impact on ADHD as well as SUD symptomatology in these patients.[37]

Atomoxetine may offer an important option for the safe and effective treatment of ADHD in incarcerated adolescents, with or without comorbid SUD. To our knowledge, no studies have been conducted to investigate the effectiveness of atomoxetine in the treatment of adolescent ADHD in the correctional setting.

Case Series of Atomoxetine for ADHD in Incarcerated Youths

An open-label case series was conducted in a youth facility in the Connecticut Department of Correction (CDOC). The purpose of this series was to investigate the effectiveness of atomoxetine for the treatment of adolescent ADHD in the correctional environment. The study protocol and procedures were approved by the Institutional Review Board of

the University of Connecticut Health Center and the Research Advisory Committee of the CDOC.

Design

Study participants were male inmates aged 16–20 years with a current diagnosis of ADHD without any other predominant psychiatric or medical comorbidity and without substance abuse or dependence within the past three months. Participants with primary psychotic disorders (e.g., schizophrenia, bipolar disorder) were excluded from participation. Patients with certain depression and anxiety disorders (e.g., major depressive disorder, panic disorder) were excluded if the diagnoses were primary and dominated the clinical presentation. Patients with certain comorbid psychiatric symptoms or disorders (e.g., comorbid depression or anxiety symptoms) were allowed to participate in the study if ADHD was the primary diagnosis and these symptoms or disorders were secondary to ADHD or comorbid with ADHD. The diagnosis of ADHD and its impact on function was confirmed with the administration of the ADHD Clinician Diagnostic Scale (ACDS) in conjunction with a comprehensive clinical interview.[6]

Methods

The participants were treated weekly by a research clinician over a 10-week period. The dosage of atomoxetine was incrementally titrated from 40 mg/day to a target dosage of 80 mg/day over a one-week period. The outcome measures administered by independent research assistants included the ADHD Investigator Symptoms Rating Scale (AISRS),[39] the Hamilton Rating Scale for Depression (HAM-D),[40] the Hamilton Anxiety Rating Scale (HAM-A),[41] and Short Form Health Survey (SF-36).[42]

Results

We enrolled five inmates in this naturalistic case series. All participants reported significant past substance abuse or dependency. Four inmates completed the study. One inmate withdrew at eight weeks because of persistent headaches. All who completed the study were able to tolerate the target 80-mg/day dosage of atomoxetine. The baseline AISRS scores ranged from 27 to 41. The change in the AISRS scores from baseline to the last follow-up visit showed an 80 to 90 percent improvement in ADHD symptoms (Fig. 1), and the change in HAM-A scores showed an improvement in anxiety symptoms (Fig. 2).

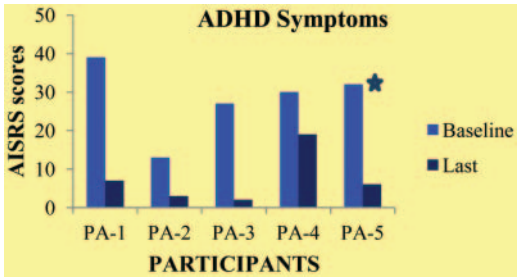

Figure 1. Change in ADHD symptoms before and after treatment with atomoxetine. PA, participant. Star: participant 5 (PA-5) withdrew at week 8 (of 10) because of persistent headaches.

Discussion and Conclusions

A qualitative, nonexhaustive review of literature suggests a high prevalence of ADHD in incarcerated adolescents with significant comorbidities, such as conduct disorders and SUDs. Psychostimulants are effective in the treatment of core symptoms of ADHD, but their use is restricted in correctional settings because of the high prevalence of comorbid substance use disorders and concerns about abuse, misuse, and diversion. The use of α2-adrenoreceptor agonists is also limited by concerns about cardiovascular side effects. Atomoxetine, a selective NET inhibitor, provides an important alternative for the treatment of adolescent ADHD with comorbid SUD in the correctional setting. The case series conducted in the CDOC suggests that atomoxetine would be effective for the treatment of adolescent ADHD in inmates. Atomoxetine was effective for ADHD symptoms in the context of significant past substance

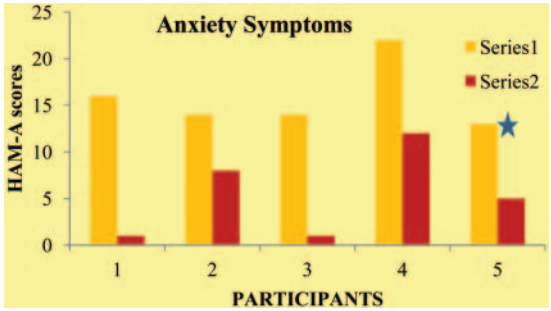

Figure 2. Change in anxiety symptoms before and after treatment with atomoxetine. PA: Participant. Star: participant 5 (PA-5) withdrew at week 8 (of 10) because of persistent headaches.

misuse. Atomoxetine also treated comorbid anxiety symptomatology in the participants. It showed a favorable safety and tolerability profile. Limitations of this case series include the small sample size, open-label status, and uncontrolled design. This pilot case series is a step toward larger, controlled studies to investigate the effectiveness of atomoxetine for the treatment of adolescent ADHD in correctional settings.

Acknowledgments

The authors thank the Connecticut Department of Correction (CDOC) for their support and the CDOC facility custody staff and Correctional Managed Health Care staff who made the implementation of this project possible.

References

1. Teplin LA, Abram KM, McClelland GM, *et al*: Psychiatric disorders in youth in juvenile detention. Arch Gen Psychiatry 59: 1133–43, 2002
2. Cahill BS, Coolidge FL, Segal DL, *et al*: Prevalence of ADHD and its subtypes in male and female adult prison inmates. Behav Sci & L 30:154–66, 2012
3. Mannuzza S, Klein RG, Moulton JL, *et al*: Lifetime criminality among boys with attention deficit hyperactivity disorder: a prospective follow-up study into adulthood using official arrest records. Psychiatry Res 160:237–46, 2008
4. Fazel S, Doll H, Langstrom N: Mental disorders among adolescents in juvenile detention and correctional facilities: a systematic review and meta-regression analysis of 25 surveys. J Am Acad Child Adolesc Psychiatry 47:1010–19, 2008
5. Rösler M, Retz W, Retz-Junginger P, *et al*: Prevalence of attention deficit-/hyperactivity disorder (ADHD) and comorbid disorders in young male prison inmates. Eur Arch Psychiatry Clin Neurosci 254:365–71, 2004
6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000
7. Gaïffas A, Galéra C, Mandon V, *et al*: Attention-deficit/hyperactivity disorder in young French male prisoners. J Forensic Sci 59:1016–9, 2014
8. Spencer TJ, Biederman J, Mick E: Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol 32:631–42, 2007
9. Satterfield JH, Schell A: A prospective study of hyperactive boys with conduct problems and normal boys: adolescent and adult criminality. J Am Acad Child Adolesc Psychiatry 36:1726–35, 1997
10. Sourander A, Elonheimo H, Niemela S, *et al*: Childhood predictors of male criminality: a prospective population-based follow-up study from age 8 to late adolescence. J Am Acad Child Adolesc Psychiatry 45:578–86, 2006
11. Dalsgaard S, Mortensen PB, Frydenberg M, *et al*: Long-term criminal outcome of children with attention deficit hyperactivity disorder. Crim Behav Ment Health 23:86–98, 2013
12. Mordre M, Groholt B, Kjelsberg E, *et al*: The impact of ADHD and conduct disorder in childhood on adult delinquency: a 30 years follow-up study using official crime records. BMC Psychiatry 11:57, 2011
13. Biederman J: Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 57:1215–20, 2005
14. Connor DF, Steeber J, McBurnett K: A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. J Dev Behav Pediatr 31:427–40, 2010
15. Von Polier GG, Vloet TD, Herpertz-Dahlmann B: ADHD and delinquency: a developmental perspective. Behav Sci & L 30:121–39, 2012
16. Knecht C, de Alvaro R, Martinez-Raga J, *et al*: Attention-deficit hyperactivity disorder (ADHD), substance use disorders, and criminality: a difficult problem with complex solutions. Int J Adolesc Med Health 27:163–75, 2015
17. Zulauf CA, Sprich SE, Safren SA, *et al*: The complicated relationship between attention deficit/hyperactivity disorder and substance use disorders. Curr Psychiatry Rep 16:436, 2014
18. Gudjonsson GH, Sigurdsson JF, Sigfusdottir ID, *et al*: An epidemiological study of ADHD symptoms among young persons and the relationship with cigarette smoking, alcohol consumption and illicit drug use. J Child Psychol Psychiatry 53:304–12, 2012
19. Charach A, Yeung E, Climans T, *et al*: Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. J Am Acad Child Adolesc Psychiatry 50:9–21, 2011
20. Lee SS, Humphreys KL, Flory K, *et al*: Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev 31:328–41, 2011
21. Wilens TE, Martelon M, Joshi G, *et al*: Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. J Am Acad Child Adolesc Psychiatry 50:543–53, 2011
22. Brook DW, Brook JS, Zhang C, *et al*: Association between attention-deficit/hyperactivity disorder in adolescence and substance use disorders in adulthood. Arch Pediatr Adolesc Med 164: 930–4, 2010
23. Tamm L, Adinoff B, Nakonezny PA, *et al*: Attention-deficit/hyperactivity disorder subtypes in adolescents with comorbid substance-use disorder. Am J Drug Alcohol Abuse 38:93–100, 2012
24. Klassen LJ, Bilkey TS, Katzman MA, *et al*: Comorbid attention deficit/hyperactivity disorder and substance use disorder: treatment considerations. Curr Drug Abuse Rev 5:190–8, 2012
25. Biederman J, Wilens T, Mick E, *et al*: Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics 104:e20, 1999
26. Clemow DB, Walker DJ: The potential for misuse and abuse of medications in ADHD: a review. Postgrad Med 6:64–81, 2014
27. Jordan CJ, Harvey RC, Baskin BB, *et al*: Cocaine-seeking behavior in a genetic model of attention-deficit/hyperactivity disorder following adolescent methylphenidate or atomoxetine treatments. Drug Alcohol Depend 140:24–32, 2014
28. Appelbaum KL: Assessment and treatment of correctional inmates with ADHD. Am J Psychiatry 165:1520–4, 2008
29. Hirota T, Schwartz S, Correll CU: Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. J Am Acad Child Adolesc Psychiatry 53:153–73, 2014
30. Sallee F, Connor DF, Newcorn JH: A review of the rationale and clinical utilization of α2-adrenoceptor agonists for the treatment of attention-deficit/hyperactivity and related disorders. J Child Adolesc Psychopharmacol 23:308–19, 2013
31. Appelbaum KL: Attention deficit hyperactivity disorder in prison: a treatment protocol. J Am Acad Psychiatry Law 37:45–9, 2009
32. Prince JB: Pharmacotherapy of attention-deficit hyperactivity disorder in children and adolescents; update on new stimulant preparations, atomoxetine, and novel treatments. Child Adolesc Psychiatr Clin N Am 15:13–50, 2006

33. Donnelly C, Bangs M, Trzepacz P, *et al*: Safety and tolerability of atomoxetine over 3 to 4 years in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 48:176–85, 2009
34. Ding YS, Naganawa M, Gallezot JD *et al*: Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: implications on treatment of depression and ADHD. Neuroimage 86:164–71, 2014
35. Swanson CJ, Perry KW, Koch-Krueger S, *et al*: Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. Neuropharmacology 50:755–60, 2006
36. Schmeichel BE, Berridge CW: Neurocircuitry underlying the preferential sensitivity of prefrontal catecholamines to low-dose psychostimulants. Neuropsychopharmacology 38:1078–84, 2013
37. Wilens TE, Adler L A, Tanaka Y, *et al*: Correlates of alcohol use in adults with ADHD and comorbid alcohol use disorders: exploratory analysis of a placebo-controlled trial of atomoxetine. Curr Med Res Opin 27:2309–20, 2011
38. Adler LA, Newcorn JH: Administering and evaluating the results of the adult ADHD Self-Report Scale (ASRS) in adolescents. J Clin Psychiatry 72:e20, 2011
39. Spencer TJ, Adler LA, Meihua Q, *et al*: Validation of the adult ADHD investigator symptom rating scale (AISRS). J Atten Disord 14:57–68, 2010
40. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatr 23:56–62, 1960
41. Hamilton M: The assessment of anxiety states by rating. Br J Med Psychol 32:50–5, 1959
42. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. Med Care 30:473–83, 1992