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Reduction of Aggressive Episodes After Repeated Transdermal Nicotine Administration in a Hospitalized Adolescent with Autism Spectrum Disorder

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Abstract

Aggression remains a major cause of morbidity in patients with autism spectrum disorder (ASD). Current pharmacotherapy for aggression is not always effective and is often associated with morbidity. Nicotinic acetylcholinergic neurotransmission may play a prominent role in ASD pathophysiology based on human and animal studies, and preclinical studies show nicotine administration can reduce aggression-related behaviors. Transdermal nicotine has been used to treat agitation in neuropsychiatric conditions with cholinergic dysfunction. Here we report the use of transdermal nicotine as an adjunctive medication to treat aggression in a hospitalized adolescent with ASD. Nicotine patch was recurrently well tolerated, and reduced the need for emergency medication and restraint. These findings suggest further study of transdermal nicotine for aggression comorbid with ASD is warranted.

Keywords

Autism spectrum disorder; Developmental disorder; Aggression; Irritability; Nicotine; Nicotine patch; Nicotinic acetylcholine receptor

Introduction

Aggression and irritability are major symptom dimensions in autism spectrum disorder (ASD), with some estimates of prevalence as high as 68 % (Kanne and Mazurek 2011) and greater prevalence in individuals with low-cognitive ability (Hartley et al. 2008). It is argued that the optimal management of these symptoms includes both behavioral and pharmacological interventions (McDougle et al. 2003), with the latter often constituting the only treatment option in settings where there is limited knowledge and capacity for implementing behavioral strategies. Atypical antipsychotics, especially risperidone and

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aripiprazole, are broadly considered to be the first-line pharmacological treatment for aggression in patients with ASD (Stigler and McDougle 2008); however, more recent work suggests that drug-refractory cases are more common than previously supposed, with almost 40 % of a sample of ASD individuals (n = 135) resistant to pharmacotherapy over a 3–5 year period (Adler et al. 2014). Furthermore, concerns about metabolic and other side effects remain significant, which leaves patients, physicians, and families in a difficult balancing act between limiting aggression and potential for iatrogenic harm. Further complicating the matter is evidence suggesting metabolic effects are even more significant in an ASD population (Hellings et al. 2001). The intersection of incomplete efficacy with significant morbidity of current pharmacotherapy underscores the need for a greater repertoire of pharmacological options, including development of treatments with greater specificity for neurobiological mechanisms underlying ASD.

The acetylcholinergic system comprises both muscarinic receptors and nicotinic acetylcholine receptors (nAChRs). Acetylcholine plays an important role in neuromodulation, influencing neurotransmitter systems important in many cognitive processes (Levin 2013; Picciotto et al. 2012). Human post-mortem (Kemper and Bauman 1998; Lee et al. 2002; Martin-Ruiz et al. 2004; Perry et al. 2001), epigenetic (Leblond et al. 2012; Mikhail et al. 2011), genetic (Leblond et al. 2012; Yasui et al. 2011), and animal model (Hoppman-Chaney et al. 2013; Karvat and Kimchi 2014; McTighe et al. 2013) studies of ASD have identified alterations in nAChR expression and acetylcholine levels, suggesting that impairment in nAChR function and signaling may play a role in the pathophysiology of ASD (reviewed in Deutsch et al. 2010). Pharmacotherapy targeting nAChRs, including the canonical nAChR agonist nicotine, may potentially be of value in ASD, as it is in other neuropsychiatric disorders with altered cholinergic signaling, including Alzheimer's disease (Carmel and Sheitman 2007; Rosin et al. 2001; White and Levin 1999), mild cognitive impairment (Newhouse et al. 2012; White and Levin 1999), and schizophrenia (Allen et al. 2011). Acute administration of nicotine reduces aggression in animal models, including rodents (Driscoll and Baettig 1981; Johnson et al. 2003; Rodgers 1979; Waldbillig 1980) and cats (Berntson et al. 1976). Given a mechanism of action independent of the current dopamine receptor agents typically used for aggression in ASD, we hypothesized that nicotine, delivered transdermally, may safely reduce aggression and irritability in people with ASD and comorbid aggression with incomplete symptom response despite both behavioral treatments and polypharmacy. The availability and relative safety of transdermal nicotine (TN) makes translating these laboratory and preclinical data into treatment a possibility. Here we report the repeated use of TN in an adolescent patient requiring hospitalization for persistent aggression despite high doses of antipsychotic and mood stabilizer medications. We found that TN was well tolerated and reduced the need for emergency medication and restraints during the hospitalization.

Case Report

JC was admitted to our hospital's adolescent inpatient unit for severe and worsening behavioral problems, including self-directed aggression (head banging and biting ultimately requiring antibiotic treatment for self-inflicted wounds and continuously re-opened old wounds in various stages of healing) and aggression toward others. These behaviors were in

the context of a diagnosis of non-verbal ASD, and the patient required support with each of his activities of daily living. The patient's behaviors had escalated in spite of an extensive medication regimen, multiple school and home behavioral interventions, and constant intervention by therapeutic staff. It was reported that the patient's behavior had also become less predictable, and his mother reported the patient had suddenly attacked her while he was eating breakfast, attempted to punch and strangle her suddenly while he was taking a bath, and violently attacked staff at school. She further explained that the aggression at school was sudden, accompanied by pacing and crying, and was so severe that more than five staff members were required to restrain him and keep him and others safe. He was also biting himself, and had deep forehead excoriations from violent scratching. Previous medication regimens included the use of haloperidol (which was discontinued due to extrapyramidal side-effects), lorazepam (which caused lip swelling) and risperidone (which led to the development of a rash).

These behaviors continued on admission to the inpatient unit where he was physically aggressive towards himself, peers, and staff members. On admission, the patient's oral medication regimen comprised chlorpromazine 50 mg three times daily, clonidine 0.2 mg nightly, guanfacine 1 mg twice daily, and hydroxyzine 50 mg twice daily. Guanfacine was discontinued, and clonidine was increased to 0.15 mg twice daily and 0.2 mg nightly. Behavioral interventions on the unit included 1:1 or 2:1 monitoring using consistent staff, and institution of a regular schedule. The patient continued to require as-needed chlorpromazine for agitation, at a dose of 50 mg, two or three times a day. As such, the standing chlorpromazine was increased to 50 mg and later 75 mg four times daily. Also during the first month of the patient's admission, divalproex sodium was initiated, and titrated up to a dose of 1500 mg nightly. Thus after 6 weeks of admission the patient's oral medication regimen consisted of clonidine 0.15 mg twice daily and 0.2 mg nightly, divalproex sodium 1500 mg nightly, and chlorpromazine 75 mg four times daily (see Table 1). Despite these behavioral and pharmacological treatments, the patient continued to have frequent behavioral outbursts, requiring physical holds on average two or three times a day, additional as-needed doses of chlorpromazine on average two times a day, and was placed in four-point restraints on three occasions over the following 4 weeks.

Informed consent was obtained from the patient's parents to use a 21 mg nicotine patch on an as-needed basis for agitation, irritability, or aggression. We confirmed that there was no smoking in the patient's household and no consistent second-hand smoke exposure. This dose of nicotine was chosen given the patient's body mass of 320 lbs, and the 21 mg dose was reported as effective for agitation in a case report of refractory aggression in severe dementia (Carmel and Sheitman 2007). Had we not had the benefit of 24-h observation as was afforded us on the in-patient unit, we would have used a lower dose patch (either 7 or 14 mg) to ensure tolerability. The patch was placed on the upper part of the patient's back, and secured with Tegaderm. It was generally not difficult for the patch to be placed and did not appear to be a source of distress for the patient. The first patch placement occurred during an episode when the patient started to become agitated. Given the numerous occurrences of agitation and consistent staffing, we were able to identify characteristic signs and symptoms of imminent agitation and aggression. Following this first placement, the patient did not escalate further, and physical restraint was avoided. The next day, when the

patient again became agitated, the patch was not utilized, and a physical restraint was required. Subsequently a protocol was instituted that the patch was applied when the patient showed early signs of agitation, and would subsequently be left on the skin for 5–7 h. The patient had a prolonged hospitalization, and the patch was used on several occasions over a period of 6 weeks. After initiation of the TN protocol, the patient required no further emergency medication administration and no further restraint application. By our observation, it appeared the patient's agitation frequently did not escalate to physical aggression, and in instances when he did become physically aggressive, the level of severity was reduced following TN treatment. On rare occasions the patch was applied after the patient had become markedly agitated, in which case the episode duration appeared to be shortened and the patient was able to regain behavioral control quickly. The patient did not attempt to remove the patch and showed no signs of local skin irritation. The use of the patch was steadily titrated down after 4 weeks of frequent use, and was discontinued prior to the patient's discharge, by which time his behavioral control was significantly improved and he required no further physical holds or restraints. The patient appeared to tolerate the discontinuation of the patch with no obvious physical symptoms of nicotine withdrawal, and no rebound of agitation following discontinuation. The patient's symptom course and treatments are summarized in Table 1.

Discussion

Here we report a case of a hospitalized adolescent patient with ASD treated with TN for the specific indication of aggression toward self and others. The patient was admitted due to aggression unmanageable outside of an inpatient unit, and showed improvement over the course of his hospitalization. The patient appeared to display reduced aggression after TN administration. This was evidenced by a significant reduction in the frequency of emergency chlorpromazine use, physical holds, and no further need for four-point restraints after treatment with TN was initiated (Table 1). While this case cannot establish the efficacy of nicotine in treating aggression associated with ASD, these findings, with no observed adverse effects as well as reduced need for restraints and antipsychotic medication, substantiate a need for further, more rigorous study.

The mechanism as to how nicotine might improve specific core or related symptoms of ASD in humans on a molecular or neural circuitry basis is not yet understood, especially when one considers the heterogeneity of non-syndromic cases of ASD. However, precedent exists for the use of TN to treat neuropsychiatric disorders whose pathophysiology incorporates cholinergic dysfunction, including to target aggression and irritability. Two case series report efficacy of TN for the treatment of aggression associated with severe dementia, without significant tolerability concerns using dosing between 7 and 21 mg nicotine patches (Carmel and Sheitman 2007; Rosin et al. 2001). Transdermal nicotine (21 mg) used as an adjunct to standard treatment was found by a double-blind, randomized trial to be efficacious in reducing agitation and aggression in patients with schizophrenia and nicotine dependence presenting to an emergency psychiatry setting (Allen et al. 2011). To our knowledge, there are no published reports of systematic use of nicotine, TN or otherwise, for the treatment of symptoms of ASD. However, other agents active at nAChRs or that alter cholinergic tone in the central nervous system have been reported. Mecamylamine, a non-

specific nAChR antagonist, was tested in a placebo-controlled pilot trial with children (4–12 years of age) with ASD (Arnold et al. 2012). Mecamylamine was well tolerated but no differences with placebo were found, although the authors note the parents of four individuals treated with mecamylamine spontaneously reported reduced irritability, and continued treatment with mecamylamine post-trial. A case report describing the treatment of a 9-year old boy with ASD using varenicline, a smoking cessation drug that is an α4β2 nAChR partial agonist, reported improvements in numerous domains (Arnold et al. 2013). These improvements were lost upon discontinuation of varenicline and returned upon its reinstitution. Animal models of ASD have supported the use of acetylcholine-based treatments with the goal of normalizing cholinergic misregulation. For instance, social deficits and cognitive rigidity in the BTBR mouse, a commonly used mouse model of ASD, were improved by administration of the acetylcholinesterase-inhibitor donepezil (Karvat and Kimchi 2014; McTighe et al. 2013), and donepezil has demonstrated encouraging, albeit inconclusive, results on core symptoms in humans with ASD (Buckley et al. 2011; Handen et al. 2011; Hardan and Handen 2002).

The safety and tolerability of TN in people with ASD has not been systematically studied. However, TN has been tested extensively in both smoking and non-smoking neurotypical adults, including use for extended periods of time and using dose-response paradigms (Srivastava et al. 1991). Use of TN is well tolerated by adult populations that may be increasingly vulnerable to adverse effects, including geriatric populations (Carmel and Sheitman 2007; Newhouse et al. 2012; Rosin et al. 2001; White and Levin 1999, 2004) and smokers with cardiovascular or pulmonary comorbidities (Murray et al. 1996; Joseph et al. 1996). Furthermore, previous studies of TN in non-smokers (Newhouse et al. 2012; Snaedal et al. (1996); White and Levin 1999, 2004) and smokers quitting tobacco (Hughes et al. 2004; West et al. 2000) show limited dependence potential, with dependence potential thought to vary proportionally with the speed of nicotine delivery (Hajek et al. 2007). Taken together, data from these previous reports suggest it is unlikely that TN used therapeutically in an ASD population would result in individuals becoming dependent on TN, undergoing significant nicotine withdrawal, or initiating an incontrovertibly harmful health behavior such as cigarette smoking. Future studies directed specifically at assessing the safety of TN and other nAChR in ASD individuals are necessary.

In the varenicline case report described above, the authors note that varenicline treatment was specifically requested by the boy's parents, having at some previous period learning of research demonstrating altered nAChRs in ASD samples (Arnold et al. 2013). This detail should not be overlooked. A simple web search reveals substantial interest in the use of nicotine to treat symptoms of ASD, with many parents resorting to this treatment despite the lack of systematic data on its safety or efficacy in ASD. This concerning finding heightens the need to further evaluate this treatment approach so that clinicians can provide more informed care to patients and families. The use of nicotine and other agents acting at nAChRs follows from preclinical data, and our case report demonstrates tolerability and efficacy in one adolescent severely affected by ASD and aggression. A logical progression will take the form of evaluating the tolerability and safety of TN in ASD subjects, and from there determining whether TN or other nAChR-active agents are effective for aggression or other symptomatology in ASD using expanded case series or open label studies.

Furthermore, it is important that research into new pharmacological interventions does not distract from the importance of further promoting existing, non-pharmacological, evidenced based strategies for management of these symptoms.

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References

Adler BA, Wink LK, Early M, Shaffer R, Minshawi N, McDougle CJ, Erickson CA. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: A chart review study. Autism: The International Journal of Research and Practice. 201410.1177/1362361314524641

Allen MH, Debanné M, Lazignac C, Adam E, Dickinson LM, Damsa C. Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: A double-blind, randomized, placebo-controlled study. The American Journal of Psychiatry. 2011; 168(4):395–399.10.1176/appi.ajp.2010.10040569 [PubMed: 21245085]

Arnold LE, Aman MG, Hollway J, Hurt E, Bates B, Li X, et al. Placebo-controlled pilot trial of mecamylamine for treatment of autism spectrum disorders. Journal of Child and Adolescent Psychopharmacology. 2012; 22(3):198–205.10.1089/cap.2011.0056 [PubMed: 22537359]

Arnold LE, Anand R, Aman M. Varencline in autistic disorder: Hypothesis and case report of single-patient crossover. Journal of Child and Adolescent Psychopharmacology. 201310.1089/cap.2012.0025

Berntson GG, Beattie MS, Walker JM. Effects of nicotinic and muscarinic compounds on biting attack in the cat. Pharmacology, Biochemistry and Behavior. 1976; 5(3):235–239.

Buckley AW, Sassower K, Rodriguez AJ, Jennison K, Wingert K, Buckley J, et al. An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. Journal of Child and Adolescent Psychopharmacology. 2011; 21:353–357.10.1089/cap.2010.0121 [PubMed: 21851192]

Carmel H, Sheitman BB. Adjunctive transdermal nicotine reduced behavioral agitation in severe dementia. The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry. 2007; 15(5):449.10.1097/01.JGP.0000235688.05709.e2 [PubMed: 17463196]

Deutsch SI, Urbano MR, Neumann SA, Burket JA, Katz E. Cholinergic abnormalities in autism: Is there a rationale for selective nicotinic agonist interventions? Clinical Neuropharmacology. 2010; 33(3):114–120.10.1097/WNF.0b013e3181d6f7ad [PubMed: 20190638]

Driscoll P, Baettig K. Selective inhibition by nicotine of shock-induced fighting in the rat. Pharmacology, Biochemistry and Behavior. 1981; 14(2):175–179.

Hajek P, McRobbie H, Gillison F. Dependence potential of nicotine replacement treatments: Effects of product type, patient characteristics, and cost to user. Preventive Medicine. 2007; 44:230–234.10.1016/j.ypmed.2006.10.005 [PubMed: 17207524]

Handen BL, Johnson CR, McAuliffe-Bellin S, Murray PJ, Hardan AY. Safety and efficacy of donepezil in children and adolescents with autism: Neuropsychological measures. Journal of Child and Adolescent Psychopharmacology. 2011; 21:43–50.10.1089/cap.2010.0024 [PubMed: 21309696]

Hardan AY, Handen BL. A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. Journal of Child and Adolescent Psychopharmacology. 2002; 12:237–241.10.1089/104454602760386923 [PubMed: 12427297]

Hartley S, Sikora D, McCoy R. Prevalence and risk factors of maladaptive behaviour in young children with Autistic Disorder. Journal of Intellectual Disability Research. 2008; 52(10):819–829.10.1111/j.1365-2788.2008.01065.x.Prevalence [PubMed: 18444989]

Hellings JA, Zarcone JR, Crandall K, Wallace D, Schroeder SR. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. Journal of Child and Adolescent Psychopharmacology. 2001; 11(3):229–238.10.1089/10445460152595559 [PubMed: 11642473]

Hoppman-Chaney N, Wain K, Seger PR, Superneau DW, Hodge JC. Identification of single gene deletions at 15q13.3: Further evidence that CHRNA7 causes the 15q13.3 microdeletion syndrome phenotype. Clinical Genetics. 2013; 83:345–351.10.1111/j.1399-0004.2012.01925.x [PubMed: 22775350]

Hughes JR, Pillitteri JL, Callas PW, Callahan R, Kenny M. Misuse of and dependence on over-the-counter nicotine gum in a volunteer sample. Nicotine and Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco. 2004; 6:79–84.10.1080/14622200310001656894 [PubMed: 14982691]

Johnson SK, Carlson KM, Lee J, Burr LE, Wagner GC. Effects of nicotine on target biting and resident-intruder attack. Life Sciences. 2003; 73(3):311–317. [PubMed: 12757838]

Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. The New England Journal of Medicine. 1996; 335:1792–1798.10.1056/NEJM199612123352402 [PubMed: 8943160]

Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: Prevalence and risk factors. Journal of Autism and Developmental Disorders. 2011; 41(7):926–937.10.1007/s10803-010-1118-4 [PubMed: 20960041]

Karvat G, Kimchi T. Acetylcholine elevation relieves cognitive rigidity and social deficiency in a mouse model of autism. Neuropsychopharmacology. 2014; 39:831–840.10.1038/npp.2013.274 [PubMed: 24096295]

Kemper TL, Bauman M. Neuropathology of infantile autism. Journal of Neuropathology and Experimental Neurology. 1998; 57:645–652.10.1097/00005072-199807000-00001 [PubMed: 9690668]

Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, et al. Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. PLoS Genetics. 2012; 8(2):e1002521.10.1371/journal.pgen.1002521 [PubMed: 22346768]

Lee M, Martin-Ruiz C, Graham A, Court J, Jaros E, Perry R, et al. Nicotinic receptor abnormalities in the cerebellar cortex in autism. Brain: A Journal of Neurology. 2002; 125(Pt 7):1483–1495. [PubMed: 12076999]

Levin ED. Complex relationships of nicotinic receptor actions and cognitive functions. Biochemical Pharmacology. 201310.1016/j.bcp.2013.07.021

Martin-Ruiz CM, Lee M, Perry RH, Baumann M, Court JA, Perry EK. Molecular analysis of nicotinic receptor expression in autism. Brain Research Molecular Brain Research. 2004; 123(1–2):81–90.10.1016/j.molbrainres.2004.01.003 [PubMed: 15046869]

McDougle CJ, Stigler KA, Posey DJ. Treatment of aggression in children and adolescents with autism and conduct disorder. Journal of Clinical Psychiatry. 2003; 64:16–25. [PubMed: 12672261]

McTighe SM, Neal SJ, Lin Q, Hughes ZA, Smith DG. The BTBR mouse model of autism spectrum disorders has learning and attentional impairments and alterations in acetylcholine and kynurenic acid in prefrontal cortex. PLoS ONE. 201310.1371/journal.pone.0062189

Mikhail FM, Lose EJ, Robin NH, Descartes MD, Rutledge KD, Rutledge SL, et al. Clinically relevant single gene or intragenic deletions encompassing critical neurodevelopmental genes in patients with developmental delay, mental retardation, and/or autism spectrum disorders. American Journal of Medical Genetics, Part A. 2011; 155:2386–2396.10.1002/ajmg.a.34177 [PubMed: 22031302]

Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Chest. 1996; 109:438–445.10.1378/chest.109.2.438 [PubMed: 8620719]

Newhouse P, Kellar K, Aisen P, White H, Wesnes K, Coderre E, et al. Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial. Neurology. 2012; 78:91–101.10.1212/WNL.0b013e31823efcbb [PubMed: 22232050]

Perry EK, Lee ML, Martin-Ruiz CM, Court JA, Volsen SG, Merrit J, et al. Cholinergic activity in autism: Abnormalities in the cerebral cortex and basal forebrain. The American Journal of Psychiatry. 2001; 158(7):1058–1066. [PubMed: 11431227]

Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: Cholinergic signaling shapes nervous system function and behavior. Neuron. 2012; 76(1):116–129.10.1016/j.neuron.2012.08.036 [PubMed: 23040810]

Rodgers RJ. Effects of nicotine, mecamylamine, and hexamethonium on shock-induced fighting, pain reactivity, and locomotor behaviour in rats. Psychopharmacology (Berl). 1979; 66(1):93–98. [PubMed: 120548]

Rosin RA, Levine MD, Peskind E. Transdermal nicotine for agitation in dementia. The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry. 2001; 9(4):443–444.10.1176/appi.ajgp.9.4.443 [PubMed: 11739072]

Srivastava ED, Russell MA, Feyerabend C, Masterson JG, Rhodes J. Sensitivity and tolerance to nicotine in smokers and nonsmokers. Psychopharmacology (Berl). 1991; 105:63–68.10.1007/BF02316865 [PubMed: 1745713]

Stigler KA, McDougle CJ. Pharmacotherapy of irritability in pervasive developmental disorders. Child and Adolescent Psychiatric Clinics of North America. 2008; 17(4):739–752.10.1016/j.chc.2008.06.002 [PubMed: 18775367]

Snaedal J, Johannesson T, Jonsson JE, Gylfadottir G. The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. Dementia (Basel, Switzerland). 1996; 7:47–52.

Waldbillig RJ. Suppressive effects of intraperitoneal and intraventricular injections of nicotine on muricide and shock-induced attack on conspecifics. Pharmacology, Biochemistry and Behavior. 1980; 12(4):619–623.

West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. Psychopharmacology (Berl). 2000; 149:198–202.10.1007/s002130000382 [PubMed: 10823399]

White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl). 1999; 143:158–165.10.1007/s002130050931 [PubMed: 10326778]

White HK, Levin ED. Chronic transdermal nicotine patch treatment effects on cognitive performance in age-associated memory impairment. Psychopharmacology (Berl). 2004; 171:465–471.10.1007/s00213-003-1614-8 [PubMed: 14534771]

Yasui DH, Scoles HA, Horike SI, Meguro-Horike M, Dunaway KW, Schroeder DI, Lasalle JM. 15q11.2-13.3 chromatin analysis reveals epigenetic regulation of CHRNA7 with deficiencies in Rett and autism brain. Human Molecular Genetics. 2011; 20(22):4311–4323.10.1093/hmg/ddr357 [PubMed: 21840925]

Table 1

Summary of behavioral changes and emergency medication and restraint requirement during hospitalization

Hospital week number	Medication change	Emergency medication	Four-point restraints	Physical holds
1	Discontinuation of guanfacine; clonidine optimized	CPZ 50 mg PRN two to three times per day	1	Three to four times per day
3	CPZ increased to 50 mg QID	CPZ 50 mg PRN twice to three times per day	1	Three to four times per day
4	CPZ increased to 75 mg QID; initiated divalproex sodium	CPZ 50 mg PRN twice to three times per day	1	Three to four times per day
5	Divalproex sodium dose increased	CPZ 50 mg PRN once or twice per day	0	Three to four times per day
6	Divalproex sodium at 1500 mg	CPZ 50 mg PRN once or twice per day	0	Two to three times per day
8	Initiation of 21 mg TN during periods of agitation	CPZ 50 mg PRN not used or once per day	0	Once or twice a day, never required after patch placement
9	TN used several times per week	None used	0	None
12	TN taper initiated	None used	0	None
14	TN used once or twice per week	None used	0	None
16	TN discontinued	None used	0	None

PRN, as needed; QID, four times daily; CPZ, chlorpromazine; TN, transdermal nicotine