The Safety and Effectiveness of High-Dose Propranolol as a Treatment for Challenging Behaviors in Individuals With Autism Spectrum Disorders

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Abstract:
Purpose/Background: Individuals with autism spectrum disorders present with social communication deficits and a rigid adherence to sameness. Along with these symptoms, many individuals also present with severe challenging behaviors that place themselves as well as their families and communities at risk for injury. For these individuals, new and effective treatments are acutely needed. Propranolol has been used worldwide for over 50 years. Its primary indication is for hypertension, but there is evidence that, at higher doses, propranolol inhibits rage and anger through its effects on the central nervous system. This effect has been demonstrated in a variety of neuropsychiatric disorders.

Methods/Procedures: Here, we present 46 retrospective analyses of clinical cases that were followed by a psychiatrist. Propranolol was prescribed as an add-on to the patients’ existing medications. The doses ranged from 120 to 960 mg per day (mean = 462 mg).

Findings/Results: Thirty-nine (85%) of 46 patients were found to be much improved or very much improved on the physician-rated Clinical Global Impression Improvement scale. There were few side effects noted, with only 2 subjects unable to tolerate the propranolol.

Implications/Conclusions: It appears that high-dose propranolol can be given safely with minimal adverse cardiovascular problems, provided that close clinical monitoring is maintained. A more rigorous clinical trial is needed to elucidate and verify its clinical utility, clinical practice parameters, and the effects of propranolol as a monotherapy versus as an add-on to the patient’s existing medication regimen.

Key Words: propranolol, autism, challenging behaviors

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T he autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopmental disorders with multiple etiologies, pathophysiologies, and behavioral presentations. This suggests that any unitary treatment for the disorder is unlikely. Rather, optimal management of the symptoms, especially the severe symptoms, would require combining components of effective behavioral and pharmacologic interventions into a multimodal package. Moreover, such a multimodal treatment package requires individualization based on the patient’s clinical symptoms and characteristics, such as age (due to increased body size and strength, some behavioral treatments become difficult or impossible), level and mode of communication, and social interest and awareness, with particular consideration for the behaviors that may impede daily life.

The core symptoms of ASD comprise social communication deficits and rigid adherence to routines and repetitive behaviors. Despite advances in early diagnosis and behavior intervention, there is no Food and Drug Administration (FDA)-approved medication specifically targeting these symptoms to date. Several pharmacological studies targeting the core symptoms of ASD have been conducted using oxytocin, with no significant change, whereas repeated transcranial magnetic stimulation (rTMS) had a moderate effect on social behavior, repetitive behaviors, and accuracy in executive function tasks.

In addition to social deficits and stereotyped behaviors, many individuals with ASD also present with comorbid behavioral symptoms, including tantrums, aggression, self-injury, hyperactivity, anxiety, and rapid changes in mood, among others. These symptoms, especially the most severe among them—aggression and self-injurious behaviors (SIB)—are often the chief complaint of parents and educators and at times far outweigh the core symptoms as problems. The prevalence of these symptoms in ASD cases varies according to the patient samples studied, however, with reports as high as 68%. Presently, the treatments for these symptoms continue to yield only partial benefits for many.

Two antipsychotic medications, risperidone and aripiprazole, are the only FDA-approved (in the United States) medications for the treatment of ASD, and more specifically, for the “irritability associated with ASD” (tantrums, aggression, and self-injury). Although they are very successful for some, their efficacy is far from optimal, with 1 study showing that 40% of the sampled individuals were resistant to all pharmacotherapy. Furthermore, these medications are associated with many adverse side effects, making their long-term use problematic. The need for improved treatments for these symptoms is acute.

Behavior-analytic interventions for challenging behaviors have been successfully used for many years. Behavior-analytic methods are based on cause–effect relationships, and the treatment is accomplished by altering the environmental component of the relationship. The success of applied behavior analysis has been well documented in the literature. In fact, failure to use individualized behavior intervention may lead to needless delays in implementing effective treatment procedures, countereffect outcomes from arbitrarily selected interventions, or unnecessary, sometimes aversive, procedures. Including the use of physical force, takedowns, and 4-point restraint.

Perhaps, the main barrier to using behavioral methods is the limitation caused by the inadequate number of behavior analysts with the knowledge and ability to implement function-based strategies, as well as the cost associated with intensive intervention. Even if the service delivery systems are optimal, there are limitations to using behavioral methods alone. In individuals who engage in SIB, 25% of the behaviors were found to be maintained by “automatic reinforcement.” In other words, the behavior was...
not in response to any demonstrable environmental variable. Instead, automatically reinforced, sensory-maintained behaviors are thought to be self-reinforcing, and therefore internal biologic mechanisms are likely to be driving the behavior. Because a challenging behavior may also serve multiple functions, the behavior may be facilitated, at least in part, by the biologic underpinnings of that individual, implying that combination of treatments would be synergistic (ie, potentiation) and, therefore, superior.

Broader public health issues also need to be considered. There are frequent emergency psychiatric hospitalizations in this population, with 10.8% of children with ASD having had a hospitalization, most commonly for SIB or aggression. Medicaid expenditures are 10 times higher for those diagnosed with ASD than for other children, and the difference is largely attributable to patient psychiatric care. As the children age, the expenditure for these behavioral challenges increases, and there is a concomitant decrease in the expenditure for other services which are more consistent with medical home aspirations and life skills. Therefore, a relatively substantial portion of the resources devoted to ASD goes to the management of those with severe symptoms at the expense of other less emergent but necessary goals.

In the literature, large, well-designed studies for the chronic and serious challenging behaviors associated with ASD are scarce (excluding the 2 abovementioned FDA-approved medications). However, there have been many anecdotal or small case series reports that show some promise. One of these strategies involves the beta-adrenergic blocking agent propranolol. Ratey et al25 reported a case series of 8 adults with violent or SIB. They described a "remarkable" effect on previously intractable aggressive behavior, which was consistent with similar findings for individuals with schizophrenia, brain damage, and severe intellectual disabilities, among others. In a recent review of the effect of beta-adrenergic blockers on the challenging behaviors of individuals with developmental disability, it was reported that many had positive outcomes, supporting the efficacy of this indication. However, it was noted that the overall quality of the research was poor, with no randomized controlled studies. In a review of studies on individuals with brain injury presenting with aggression, it was concluded that beta blockers have the best evidence for efficacy, but the lack of high-quality studies was also highlighted.

It is notable that propranolol has shown other benefits in ASD, including verbal problem solving, word fluency, facial scanning, and conversation reciprocity. Despite the urgent need for effective treatment for these debilitating symptoms and the anecdotal evidence of success propranolol has had for challenging behaviors across a range of diagnoses, it appears that it is not commonly used for individuals with ASD. In the United Kingdom, adrenergic blocking agents are rarely prescribed, with only 2% of patients with ASD receiving any type of beta blockers. In a study of pharmacologic treatments in Germany, no beta blockers were listed among the 25 most commonly prescribed medications for ASD. In systematic reviews of treatments for ASD, propranolol is either not mentioned or only briefly mentioned in the context of the paucity of high-quality studies demonstrating its efficacy. In light of the above, we report a retrospective case series of 46 individuals who had been diagnosed with ASD with high levels of aggression, SIB, and disruptive behaviors and were treated with high-dose propranolol. In each case, the patient had received prior treatment with at least 1 antipsychotic medication. In most cases, many medications had been tried, with either a lack of efficacy or only partial efficacy, calling for further treatment attempts. The majority of the patients (although not all) had received reasonably high-quality behavioral intervention before the introduction of propranolol.

**METHODS**

**Participants**

We report on a retrospective chart review of 46 cases, which were treated by 1 physician (first author) over approximately 10 years. The inclusion criteria for being reported in this series are: (1) a clinically based DSM-IV diagnosis of ASD; (2) a chief complaint to the psychiatrist of either aggression, SIB, or severely disruptive behaviors; (3) based on these challenging behaviors, the patient had a Clinical Global Impression Severity scale (CGI-S) score of 6 or 7; (4) a previous trial and failure with at least 1 antipsychotic medication (although the vast majority of cases had been tried on many psychotropic medications); and (5) clinical follow-up, which allowed for dose titration to optimize the dose (up to 960 mg per day) based on response to medication. Patients whose medication was terminated at the discretion of the treating physician or the consenting guardian due to adverse effects or lack of efficacy were included in the study.

Exclusion criteria included cases (1) which were lost to follow-up and (2) in which the medication was terminated due to withdrawal of parent or guardian's consent before achieving a therapeutic dose. Follow-up of at least 6 months was required unless terminated earlier by the physician. It is not known whether these patients were different in any way from those who remained in treatment.

**Medication Dosage**

Given that all patients included in the data analysis presented with serious challenging behaviors and each patient had been on medications previously with variable efficacy, propranolol was added while the patients remained on their existing medications. During the time on propranolol, if any benefit was noted, attempts were made to lower or discontinue other medications, although there was often a lack of incentive clinically to adjust a newly successful regimen. The propranolol was generally started at low doses (eg, 10 mg, three times per day) and titrated up. High doses were prescribed based on the literature indicating effectiveness at a dosage of 640 mg in alleviating challenging behaviors. As this was a clinical retrospective review, the titration was done variably based on the circumstances of the case. Propranolol was given in both immediate-release and extended-release forms depending on the clinical needs of the patient.

**Dependent Measure and Safety Precautions**

The cases were retrospectively reviewed. The treating psychiatrist met with the patient and his/her caregiver and obtained relevant clinical information regarding the frequency and intensity of the challenging behavior. The severity of the symptoms and the efficacy of the medication were quantitated using the Clinical Global Impression (CGI) scales. The CGI Severity (CGI-S) score was ascertained immediately before the first dose of propranolol and again at the time of the retrospective review (some continued in treatment up to the time of the review, while others were no longer in treatment), and it was based on the treating psychiatrist's response to the question, Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? by using the following 7-point scale: 0, not assessed; 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, among the most extremely ill patients.

Then, the CGI Improvement (CGI-I) scale was used to obtain the patient's global functioning based on observed and reported symptoms before and after medication administration on a similar
## TABLE 1. Summary of the Trial on Propranolol

| Case | Age/Sex | Dx DSM-5 | Concurrent Medications | Dose (mg) | CGI-I Score | Time on Prop | Challenging Behaviors | Comments |
|------|---------|---------|-------------------------|-----------|-------------|--------------|----------------------|----------|
| 1    | 11/M    | F84.0   | R, A, O, V, S, P        | 300       | 4           | 1 y          | Agg, SIB, Incontinence | No improvement on any meds, severe family issues |
| 2    | 18/M    | F84.0   | A, F, Li                | 320       | 1           | 5 y          | SIB, picking, Agg quick temper | Rare to 0 behaviors on Prop for 5 years |
| 3    | 10/M    | F84.0   | R, C                    | 300       | 2           | 2 y          | SIB – hangs, hits, and bites self, tantrums, Agg | On Prop +R much lower frequency and severity |
| 4    | 13/M    | F84.0   | R, Oxa, Lam, Lev, Foc, Dex, Gu | 120   | 1           | 3 y          | Agg | Blood pressure lowered, stopped Prop and relapsed, resumed Prop |
| 5    | 34/M    | F84.0   | A, Z, Lor, Car          | 640       | 2           | 1 y          | Compulsions—aggressions | Side effects on antipsychotics |
| 6    | 15/M    | F84.0   | A, Cpz, O, C, Alp, V    | 480       | 1           | 2 y          | Aggression (injuries) | O worked but broke thru, Prop +Alp now |
| 7    | 14/M    | F84.0   | R, Q, Mol, H, Oxa, Gu, E S, Lor, Car | 480   | 2           | 3 y          | Agg, (injuries) | Well on Prop, Lor, H, Car |
| 8    | 12/M    | Tri 15 F84.0 | V, Add, C, Mir, tra | 600 | 2 | 1 y | Agg, screaming, hyper, off task, SIB, sleep problems | On Prop + Mirt behaviors are at a low level |
| 9    | 12/F    | F84.0   | R, A, Gab, Top, Add, SSRIs | 480   | 4           | 2 y          | Anx skin pinch, hyper, moody | Prop worked but broke thru similar to other medicines |
| 10   | 15/F    | F84.0   | A, O, R, Oxa, Lam, Ver, Alp,Mir, C, Gu | 300 | 1 | <6 mo | Agg, anxiety perseverations | Best ever on Prop, bronchospasm dc’d |
| 11   | 15/F    | F84.0   | A, R, Z, F, Chl, Top, V, Oxa, Lor, Clo | 360 | 1 | 3 y | Agg, disrobing, sleep problems | Doing well on Prop, Oxa, V and R. Needs all |
| 12   | 16/M    | F84.0   | O, Gu, Li               | 400       | 2           | 2 y          | Agg, SIB, repetitive | Agg and SIB markedly reduced; repetitive behavior unchanged |
| 13   | 18/M    | F84.0   | Q, V, Lev               | 320       | 3           | 3 y          | Agg, SIB, crying, hyper, sensory sensitivities | Status varies with seizures |
| 14   | 12/M    | F84.0   | R, O                    | 240       | 1           | 2 y          | Agg, SIB, rituals | Agg, SIB eliminated, rituals = or worse |
| 15   | 13/M    | F84.0   | R, Q, Top, Oxa, Bac, Na, V, S, P, Clo, Bus | 960 | 2 | 3 y | Agg, SIB, tantrums. Mood liability, hyper | Doing well on Pro, Oxa, and Top. |
| 16   | 17/M    | F84.0   | R, P, Li                | 240       | 2           | 1 y          | Agg, headbutts, SIB hits head, hyper | Occasional Agg, parent refused further dose increase |
| 17   | 12/M    | F84.0   | R, Q, A, Met, Oxa, V    | 480       | 1           | 3 y          | Agg, bites, kicks, hyper, drops, whistles, attention seeking | Agg and SIB close to 0; still very hyperactive |
| 18   | 19/M    | F84.0   | O                       | 120       | 1           | 6 mo         | Agg, public masturbation. | Z effective for years, broke thru, on Prop 0 Agg |
| 19   | 16/F    | F84.0   | R, V, C                 | 300       | 2           | 6 mo         | Agg, hitting, slap, kick bite, repetitive, mood liability | Agg responded, mood and rigidity remain, recent seizures |
| 20   | 20/M    | F84.0   | R, Z, A, Lev, V, Tra, Hyd, Gu, Zol | 640 | 1 | 2 y | Agg, pinch, hit, headbutt, sleep problems | Agg = 0 on Prop gained 100 lbs on R |
| 21   | 11/M    | F84.0   | A, C, Gu, S             | 480       | 2           | 6 mo         | Agg, pinch kick hairpull, SIB, bites, hits head, severe rituals | Agg and SIB better, rituals ongoing |
| 22   | 15/M    | F84.0 FAS Q86.0 | R, V, Lev, F, C, Bac | 360 | 2 | 6 mo | SIB, hits head (hours) | Better, but parent refused increased dose |
| No. | Date | Age | Gender | Meds | Dose | Duration | History | Response | Comments |
|-----|------|-----|--------|------|------|----------|---------|----------|----------|
| 23  | 13/M | F84.0 | A, Z, V, Met, Tra, Zol, Tem | 600 | 2 | 4 y | Agg, digs nails, SIB, hits head and induced hemiparesis hyper, rep, sleep | On Pro, Z, Tem, Tra some cycling |
| 24  | 16/M | F84.0 | H, Z, V, Gu, Met | 600 | 2 | 3 y | Agg hits, suddenly spits hyper | Agg much better, laughs when he hits, indicating secondary reinforcement |
| 25  | 18/M | F84.0 | R, Gu | 480 | 1 | 3 y | Agg, bites SIB, sleep problems, screams | Agg 900 episodes per month on R, down to 0 on Prop |
| 26  | 13/M | F84.0 | R, O, H, A, V, Top, Li, Clo | 600 | 3 | 3 y on and off | Agg, headbut, SIB throws self on floor (IC bleed) impulsive | Agg, SIB down on Prop, seems to enjoy behaviors, very unfocused |
| 27  | 32/M | F84.0 | R, O, Gu, Car, Hyd | 720 | 4 | 6 mo | Agg attacks when redirected, SIB, hits self, tantrums | Prop eliminated Agg—mood declined |
| 28  | 14/M | F84.0 | A, Esc, F, Bup, Mir | 600 | 2 | 6 mo | Agg attacks, fights, kicks tantrums | Nothing successful Parents refuse polypharmacy so only used each med alone |
| 29  | 13/M | F84.0 | R, S, Oxa, Gu | 600 | 2 | 4 y | Agg, hits, kicks, headbutts, SIB head hang, hyper, tantrums | On R and Oxa with Prop |
| 30  | 11/M | F84.0 | A, S, Cit, Gu, C | 480 | 2 | 1 y | Agg, scratch, headbut, kick, rituals | Doing well on Pro, A and Gu |
| 31  | 19/M | F84.0 | R, Z, Q, F, S, P, Gu, C, Bus, Ari, Add, Top, Lam, Lev, Oxa, Sab, Vim | 480 | 1 | 1 y | Agg, scratches, pulls strangers hair, SIB hits head | Agg 36/month—0 Agg on pro |
| 32  | 17/M | F84.0 | R, V | 240 | 1 | 6 mo | Agg, SIB headbanging | On R, V and Prop, SIB ~0. prior 30 episodes per month |
| 33  | 15/M | F84.0 | R, O, Tra, Lor, Hyd | 720 | 2 | 2 y | Agg, hit teachers, strangers, + mom | Previously hospitalized twice, CGI 1 for 2 for years until recent slip, parents divorcing |
| 34  | 8/M  | F84.0 | A, Z, O, Gu | 180 | 1 | 6 mo | Agg, attacked young sibs | Did well but discontinued due to wheezing, also side effects on antipsychotics |
| 35  | 21/M | F84.0 | A, R, O | 640 | 2 | 6 mo | Agg, lashes out unpredictable, SIB, hits head, picks at self | Prop with O, Agg minimal, occasional SIB |
| 36  | 22/M | F84.0 | R, Nef, Alp | 640 | 2 | 2 y | Agg, punches, pulls strangers hair, SIB hits head | On Prop, Alp R, rare aggression, but breaks thru with stress |
| 37  | 10/M | F84.0 | Z, A, R, O, Q, F, Oxa, Lam, Lev, Bac | 640 | 2 | 9 y | Agg, hitting, hyper, perseveration, fears | On Prop, O, Lam, F, Bac, rare Agg and SIB |
| 38  | 16/M | F84.0 | Z, R, Clp, Thi, F, V, C, Gu, Lor, Tra | 480 | 4 | 6 mo | Agg, rages, SIB, crying insomnia | No benefit on Prop |
| 39  | 14/F | F84.0 | O, R, Lur, A, Q, S, Esc, Gu, Stim | 640 | 2 | 6 mo | Agg, scratches, hits, SIB, screams | Agg and SIB much better, still screams |
| 40  | 18/M | F84.0 | R, O | 360 | 1 | 10 y | SIB, hits head and deformed skull | On Prop + O doing very well |
| 41  | 21/F | F84.0 | A, Q, R, Oxa, Gab, Gu, Bus, Esc, C, Dia, Li, Lam | 480 | 2 | 6 y | Agg, pinches, SIB, hits, bites self, tantrums, screams | On Prop, A, Lac, S, Agg, and SIB much lower rates |
| 42  | 12/F | F84.0 | R, A, Li, C, S, Tra, Mir, D, Ese, Oxa | 360 | 2 | 1 y | Agg, haves in car, SIB, repetitive behavior, disrobing | SIB and Agg minor, still tantrums and repetitive |
| 43  | 13/M | F84.0 | R, A, H, O, Z, Q, Oxa, Top, V, Flu, Mir, Tra, Lor, Zol, Tem | 600 | 2 | 4 y | Agg, loses interest, sleep problems | Improves on antipsychotics, but side effects are problematic |
| 44  | 21/M | F84.0 | R, A, P | 600 | 2 | 10 y | Agg, SIB, sleep problems, crying, repetitive behaviors | Still cries and repetitive, Agg SIB rare |
| 45  | 32/F | F84.0 | R, Z, Q, H, Tra, Clo, V, Lor | 240 | 2 | 6 y | Agg, severe leads to frequent hospitalizations | Experienced bleeding and low blood pressure, so Prop D/C'd |
| 46  | 12/M | F84.0 | R, O, Z, A, V, Oxa, Li, Nan, C, F, Mir, Ato, Alp, Zol, Dia | 360 | 6 | 1 mo | Agg, SIB, hits self, screams | Worsened dramatically but d/c A at same time |

Agg = aggression; hyper = hyperactivity; prop = propranolol; FAS = fetal alcohol syndrome; Frag X = fragile X; M = male; F = female.
underwent echocardiographic assessment. All the patients had them underwent a baseline and follow-up EKG, and 20 of them were repeatedly uncooperative with the Holter monitor. All of the 45 patients received a 24-hour Holter monitor (the other 5 blocker therapy for severe challenging behaviors. Forty (88%) of theogist (E.F.) due to their taking moderate to high doses of beta cardiac abnormalities under the supervision of a pediatric cardiol- 2.0-point scale: 0, not assessed; 1, very much improved since the initiation of treatment; 2, much improved; 3, minimally improved; 7, very much worse; 6, much worse; 5, minimally worse; 6, much worse; 7, very much worse since the initiation of treatment. Adverse effects were also noted. Despite being a generally safe medication, the effects of high doses on children and those with developmental disabilities have not been sufficiently documented. We, therefore, conducted (in addition to standard medical care) an in-depth cardiology evaluation on 45 patients. This evaluation was done in the later part of the period under review. Therefore, although some of the cases overlap (ie, some patients had both behavioral and cardiology reviews), others with the cardiology workup were not part of the retrospective chart review. Thus, we have data on the cardiologic effects of high-dose propranolol on subjects with ASD, but we are not able to correlate the cardiologic effects with behavioral effects, as they were at least partially from distinct populations.

RESULTS

The behavioral results of this retrospective review are presented in Table 1. Thirty-nine (85%) of 46 patients were much improved or very much improved (CGI-I 1 or 2) in their challenging behaviors. Two (4%) of 46 were slightly improved (CGI-I 3), whereas 5 (11%) of 46 of the cases were not improved or worsened (CGI-I 4 or greater). Although not quantitated, there was little to no benefit in commonly reoccurring symptoms such as hyperactivity, repetitive behaviors, and mood.

The 46 patients included 8 females and 38 males. Ages ranged from 8 to 32 years (mean, 16 years). The propranolol dose ranged from 120 to 960 mg per day (mean, 462 mg). The duration on propranolol ranged from 1 month (1 patient who deteriorated on propranolol, although he discontinued an antipsychotic at the same time) to 10 years (mean = 2.6 years). The mean number of medications previously and/or currently being tried was 6.2 (the abbreviations for the medications in Table 1 can be found in Table 2).

Cardiology Results

As part of the clinical care, 45 patients were evaluated for any cardiac abnormalities under the supervision of a pediatric cardiologist (E.F.) due to their taking moderate to high doses of beta blocker therapy for severe challenging behaviors. Forty (88%) of the 45 patients received a 24-hour Holter monitor (the other 5 were repeatedly uncooperative with the Holter monitor). All of them underwent a baseline and follow-up EKG, and 20 of them underwent echocardiographic assessment. All the patients had frequent vital sign evaluation while receiving propranolol. The majority of these patients were also taking other psychotropic medications, as described above. A chart review and discussion with caretakers did not reveal evidence of any adverse cardiopulmonary symptoms or events except for 1 case in which lethargy and peripheral cyanosis occurred, though it is unclear if this was related to beta blocker therapy. There were no incidents of deleterious arrhythmias, adverse bradycardia, or hypotension, or any evidence of decreased cardiac output or cardiomyopathy based on clinical evaluation or diagnostic studies.

DISCUSSION

Challenging behaviors such as aggression, SIB, and severely disruptive behaviors demand attention from the clinical and research community serving those with ASD.9,23,40 Despite the existence of promising reports using propranolol for challenging behaviors for over 30 years, methodologically rigorous research has been scarce. This has resulted in propranolol and other beta blocking agents being marginal in the armamentarium of medications which could provide reduction in these symptoms. This retrospective chart review, although anecdotal, contributes to the literature by supporting the potential of propranolol for this indication. We make a new contribution by offering the largest body of case series evidence for the use of propranolol in conjunction with antipsychotics for individuals with ASD presenting with challenging behaviors. In addition, we provide long-term follow-ups of the patients (mean, 2.5 years) and document the extent of the cardiovascular effects of using high doses of propranolol in this high-need population. Therefore, it appears that moderate and high-dose beta blocker therapy can be given safely without adverse cardiovascular problems provided that close clinical monitoring is maintained.

Thirty-nine (85%) of 46 patients were rated as much improved or very much improved on the CGI-I. This improvement and efficacy is outstanding and would be superior to any medication currently used if this finding is confirmed with more rigorous clinical research methodologies. To validate and optimize its clinical use, many other questions need to be answered. The literature on the use of propranolol for challenging behaviors suffers from various limitations. Most previous studies were also case studies, although there have been 6 small double-blind and/or placebo-controlled studies.41 These studies, which targeted aggression, self-injury, and destructive behaviors, were done on many different psychiatric diagnoses, including intermittent explosive disorder (with and without known brain damage), conduct disorders, attention deficit disorder, schizophrenia, atypical psychosis, schizoaffective disorder, drug abuse, seizure disorder, borderline personality disorder, various
types of intellectual disabilities with various etiologic origins, and dementia.28,30,42 Some studies used mixed diagnostic populations. The studies were done on a wide range of ages, from children to geriatric populations, and over a wide range of intellectual abilities.

The symptoms being targeted—aggression, self-injury, and disruptive behaviors—may constitute a very heterogeneous group of problems. Carroll et al. subdivided aggression and found that in ASD, there were 5 different subtypes. They used the concept of “hot” and “cold” aggression. In “cold” aggression, the aggressive behavior is intended to achieve a desired outcome, and it occurs without anger or prior provocation. On the other hand, “hot” aggression occurs in response to a provocation and is often impulsive. It is possible that “cold” aggression types were underrepresented in our sample, as those cases were more successfully treated with function-based behavioral interventions and may not have received referrals for medication treatment. Therefore, it is likely that propranolol is more effective in treating “hot” aggression associated with autonomic and emotional dysregulation. Some of our few treatment failures had clear antecedents (precipitants) to their aggressive episodes and were likely aimed at a desired outcome and thus of the “cold” aggression variety.

**Limitations**

In the context of evidence-based medicine, randomized control-group trials are considered the gold standard. Given the economical and practical challenges of conducting a rigorous clinical trial with a vulnerable population such as those with ASD, observations made from a clinical series can also contribute to our current knowledge about treating refractory patients who do not fit into predetermined research selection criteria.

Here, the inclusion of only chronically refractory patients provides us with a relatively skewed but homogeneous group of patients with similar behavioral topography independent of their comorbid intellectual impairment or psychiatric diagnoses. This group remains understudied at least partially due to the difficulties in studying this population. In the current series, patients were all given the same intervention and standard of care, such as ongoing behavior interventions, frequency of follow-up appointments, and management of complications. Therefore, although case series are highly susceptible to extraneous variables, the findings from this case series provide another set of anecdotal evidence for the use of propranolol in patients with ASD presenting with challenging behaviors.

There are several inherent methodological limitations of a case series report such as this. First, the treating psychiatrist was not blinded, which may have influenced the retrospective scoring of the CGI, possibly contributing to the robustness of the findings and therefore the validity of the results. Second, apart from the treating psychiatrist's CGI scores, no other data were systematically collected. Therefore, no absolute risk or relative effect can be calculated from this case series. In addition, propranolol was prescribed as an add-on to the existing treatment regimen, without any control for psychotropic medications, making it difficult to attribute any behavioral changes solely to propranolol.

**Practice Parameters**

Based on the extant literature, it is challenging to derive practice parameters for the clinician. One very important parameter is dosing. The studies in the literature used various dosing strategies, and with the above described heterogeneity, it is not surprising that the effective doses reported were wide-ranging, from 60 mg per day to 1760 mg per day. Based on these reports which obtained benefit at very high doses, we elected to continue titrating the dose up until we obtained acceptable benefit (as determined by the treating physician and the consenting family or guardian) or side effects became apparent. In fact, side effects were rarely a problem at very high doses, raising the possibility that the cardiovascular effects might have hit a ceiling effect after the saturation of peripheral receptors. In this sample, we saw a few cases which responded to doses as low as 120 mg per day; however, the average final dose was 462 mg, with only a few cases responding well to doses lower than 300 mg per day. In our experience, there was often a clinical urgency to treat the symptoms, as the challenging behaviors often created danger to the patients themselves, their peers, and their caregivers. This led to an urgency to identify the therapeutic dose quickly. It is possible that with a slower titration and more time at each lower dose, we might have seen benefit at lower doses. In this report, the end-point dose was a clinical decision. We ended the titration when parents and staff were pleased enough with the behavioral improvement that they wanted to stop the titration. It is also possible that some patients might have further improved on higher doses.

In this case series, the propranolol was added to the patients' existing medications, so we are unable to observe how propranolol might influence these symptoms if it were to be used as the only pharmaceutical agent. Ethical considerations of doing research on violent and danger-inducing behaviors make taking the patient off of partially effective medications difficult, if not impossible. Attempts to lower or discontinue the antipsychotic medications after deriving the benefits of propranolol generally resulted in deterioration (although we did not document this systematically), which lends some support to the idea that propranolol by itself would not be as successful. Some previous studies did note the ability to reduce or stop other medications when on propranolol in some cases,42–44 while other studies found, as we did, that stopping or reducing the other medications resulted in a reemergence of symptoms.45

**Mechanism of Action**

Several possible mechanisms of action have been discussed in the literature; however, direct support for any of them is lacking.41 One proposed mechanism is the blockade of peripheral sympathetic activity, and this is supported by those studies which used nadolol and other less lipophilic agents, which are less likely to have central effects.46,47 In our sample, the clinical improvement seemed to come at high doses, which might suggest that peripheral mechanisms alone cannot explain the benefits noted, as central effects have been reported to increase with higher doses.48

Another hypothesis is that the benefits may be due to central effects. Beta adrenergic stimulation of the amygdala has been shown to enhance the fear mechanisms and may contribute to the persistence and severity of traumatic memories.49 There is preliminary evidence that the blockade of this adrenergic tone with a beta blocker can attenuate the symptoms of posttraumatic stress disorder (PTSD). Noradrenergic signaling is critical for memory consolidation and reconsolidation.50 Inhibition of beta adrenergic receptor activity during reconsolidation leads to memory disruption within both appetitive and aversive memory paradigms.51 This suggests that beta blockers can block the reconsolidation of emotionally charged memories (both positive and negative). In non-verbal or minimally verbal people, the association between memories and behavior is difficult to observe because challenging behaviors are often triggered by what appear to be relatively benign stimuli. Given that individuals with ASD are often in a hypersympathetic state and/or a central hyperadrenergic state,52–57 it is plausible that a PTSD-type reaction might be triggered by stimuli which are difficult for others to readily identify. Likewise, individuals with PTSD may be triggered by idiosyncratic stimuli, although in that case, the origin of these triggers can be self-reported. Functional connectivity scanning research58,59 suggests...
another central effect which may lead to a decrease in aggression and SIB. The addition of pranopanol has been shown to alter the connectivity of various circuits (some circuits increase in connectivity, while others decrease). The neuromodulatory function of the adrenergic system is central to the recruiting and coordination of various circuits.60 This flexibility of response may enable the individual to have a more appropriate coping mechanism for a stressor than resorting to an autonomic-driven fight or flight and then demonstrating the symptoms of aggression or SIB.

As previously noted, several of our successful cases deteriorated when antipsychotics were reduced. Antipsychotic medications have been shown to increase prepulse inhibition in patients, with atypical antipsychotics activating the locus coeruleus,61 where the majority of forebrain noradrenergic neurons originate. The locus coeruleus regulates attention, cognitive functioning, and the maintenance of high arousal and vigilance and has a prominent role in stress responses. It is possible that in at least some cases, when antipsychotics alone do not produce adequate relief of symptoms, it is because a central adrenergic hyperactivity is present and the beta blocker is necessary in addition to the antipsychotic to reduce adrenergic tone. Pranopanol is able to cross the blood–brain barrier fairly abundantly62 and exert effects in the central nervous system in addition to its peripheral activity. The mechanism of pranopanol has still not been established, further complicating the understanding of the mechanism by which higher doses work in this high-need population.

CONCLUSIONS

Pranopanol was the first successful beta blocker developed and now has been on the market for over 50 years.63 It is on the World Health Organization’s List of Essential Medicines, a list of the most important medications needed in a basic health system, reflecting its widespread use. Its safety concerns are well known and quite manageable. Due to a lack of rigorous research studies, the clinical use of pranopanol for challenging behaviors such as aggression, self-injury, and disruptive behaviors remains limited. Moreover, the heterogeneity of ASD further complicates the understanding of the pathophysiology of this disorder, and consequently, no single treatment can be effective for all patients with ASD. Therefore, stratifying patients based on their individual characteristics, such as the presence of comorbid intellectual disability and/or psychiatric diagnoses and the patients’ responses to intervention, would be essential for future investigations.

For those individuals with ASD and their families, the need for the medical community to ameliorate these challenging behaviors is acute. It is our hope that this retrospective review of 46 clinical cases will prompt the type of studies necessary to substantiate or invalidate pranopanol’s place in the armamentarium of medications for the treatment of severe challenging behaviors in people with ASD.

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