Author Query Form

Journal Title : Journal of Psychopharmacology (JOP)
Article Number : 408962

Dear Author/Editor,
Greetings, and thank you for publishing with SAGE. Your article has been copyedited and typeset, and we have a few queries for you. Please address these queries when you return your proof corrections. Thank you for your time and effort.

Please ensure that you have obtained and enclosed all necessary permissions for the reproduction of artistic works, (e.g. illustrations, photographs, charts, maps, other visual material, etc.) not owned by yourself, and ensure that the Contribution contains no unlawful statements and does not infringe any rights of others, and agree to indemnify the Publisher, SAGE Publications Ltd, against any claims in respect of the above warranties and that you agree that the Conditions of Publication form part of the Publishing Agreement.

Any colour figures have been incorporated for the on-line version only. Colour printing in the journal must be arranged with the Production Editor, please refer to the figure colour policy outlined in the e-mail.

Please assist us by clarifying the following queries:

1. Please confirm whether the conflict of interest statement is appropriate.
2. Kaufman et al., 2003 does not appear in the ref list, please supply reference (or should this citation be 2002?)
3. citations Miczek et al., 2005 in text amended to 2004 as per refs, is this correct
4. Puglisi-Allegra et al., 1991 amended to 1981 as per refs, is this correct
5. Gill (2009) amended to 2002 as per refs, is this correct
6. references Mattes JA (2005) and Mattes JA (2008) are not cited – please cite where appropriate or remove from the ref list
7. ref Gourley SL, Debold JF, Yin W, Cook J and Miczek KA (2005) is not cited – please cite where appropriate or remove from the ref list

1. The conflict of interest is correct.
2. should be Kaufman 2002.
3. Miczek et al., (2004) is correct.
4. Puglisi-Allegra et al., (1981) is correct.
5. Gill (2002) is correct.
6. please remove Mattes (2005) and Mattes (2008).
7. add this citation to page 1, column 2, line 6, ['benzodiazepines increase aggression']

Original Paper

Psychopharm

Journal of Psychopharmacology
0(0) 1–11

DOI: 10.1177/0269881111408962
jop.sagepub.com
SAGE

Chronic tiagabine administration and aggressive responding in individuals with a history of substance abuse and antisocial behavior

Joshua L Gowin[1], Charles E Green[2,3], Joseph L Alcorn[1], Alan C Swann[1,2], F Gerard Moeller[1,2] and Scott D Lane[1,2]

Abstract

Objectives: Anticonvulsants, notably those which modulate GABA activity, have shown efficacy in reducing aggressive behavior. Previously, we found dose-related decreases in human aggressive responding following acute tiagabine administration. Here, we examined the effects of chronic tiagabine over a 5-week period.

Methods: Twelve individuals at increased risk for aggressive and violent behavior (currently on parole/probation with personality and/or substance use disorders) were randomly assigned to placebo ($n = 6$) or an escalating dose sequence of placebo, 4 mg, 8 mg, 12 mg, placebo ($n = 6$). Data were analyzed using both frequentist and Bayesian mixed models, evaluating aggressive behavior as a function of time, dose condition, and their interaction.

Results: For aggressive responding, there was a significant interaction of drug condition and time. Aggression in the tiagabine condition decreased for each additional week in the study, while participants in the placebo condition failed to demonstrate similar change over time. For monetary-reinforced responding, no drug or drug by time interactions were observed, suggesting specificity of drug effects on aggression.

Conclusions: The small number of subjects limits the generality of the findings, and previous studies with tiagabine are limited to acute dosing and case report investigations. However, the present data provide an indication that tiagabine merits further examination as an agent for management of impulsive aggression.

Keywords

GABA, human aggression, PSAP, tiagabine

Introduction

Anticonvulsant drugs have frequently been employed for the management of human aggressive behavior. A number of these drugs, including valproate, phenytoin, and carbamazepine, have been shown to mitigate aggression (Barratt et al., 1997; Kim, 2002; Stanford et al., 2005, 2009). However, Hellings et al. (2005) did not find valproate to be significantly different from placebo in managing aggression in patients with developmental disabilities. Similarly, in a large-scale clinical trial of divalproex sodium, Hollander et al. (2003) did not find a significant reduction in impulsive aggression versus placebo, although greater response was noted in patients with cluster B personality disorders. To better understand the relationship between anticonvulsants and aggression, further analysis is required.

Many anticonvulsants target the γ-aminobutyric acid (GABA) neurotransmitter system, the primary inhibitory neurotransmitter in the central nervous system (CNS). Research has consistently demonstrated a relationship between aggressive behavior and GABA (Miczek et al., 2004). CNS and plasma GABA levels generally show an inverse relationship with aggressive behavior (Bjork et al., 2001; Earley and Leonard, 1977; although see Lee et al., 2009). Preclinical studies indicate that systemically increasing GABAergic transmission can inhibit aggressive behavior (Poshivalov, 1981; Puglisi-Allegra et al., 1981). While drugs that allosterically activate GABA-A receptors (e.g. benzodiazepines and alcohol) can paradoxically increase aggression (Saias and Gallarda, 2008; Miczek et al., 2003), many GABAergic drugs have proven effective at attenuating aggression (Barratt et al., 1997; De Almeida et al., 2005; Griffith, 1985; Miczek et al., 2004). Continued examination of GABA in the neurobiological regulation of aggression appears

[1]Program in Neuroscience, Graduate School of Biomedical Sciences, University of Texas Health Science Center, Houston, USA.
[2]Department of Psychiatry & Behavioral Sciences, School of Medicine, University of Texas Health Science Center, Houston, USA.
[3]Center for Clinical Research & Evidence Based Medicine, University of Texas Health Science Center, Houston, USA.

Corresponding author:
SD Lane, Department of Psychiatry & Behavioral Sciences, UTHSC-Houston, 1941 East Road, Houston, TX 77054, USA
Email: scott.d.lane@uth.tmc.edu

warranted (De Almeida et al., 2005; Huband et al., 2010; Khalifa et al., 2010; Siegel et al., 1999).

Although the research is less extensive, more recently developed anticonvulsants, ~~which modulate GABA,~~ such as tiagabine and topiramate, have been reported to reduce aggression in acute laboratory models and controlled trials. Tiagabine is an anticonvulsant that operates by inhibiting the re-uptake of GABA. A preclinical experiment in rats indicated that topiramate ~~both~~ caused an increased release of GABA and also increased the GABA-A receptor inhibitory response in the basolateral amygdala (Braga et al., 2009). Using a laboratory model of human aggression (the point-subtraction aggression paradigm (PSAP) Cherek et al., 1992), aggressive behavior was diminished following acute doses of tiagabine (Lieving et al., 2008) and topiramate (Lane et al., 2009). Based on State–Trait Anger Expression Inventory (Spielberger et al., 1983) scores, topiramate reduced aggression in a clinical trial of patients with Borderline Personality Disorder (Nickel, 2007; Nickel et al., 2005).

In a recent review of anticonvulsants for the management of impulsive aggression, Stanford et al. (2009) noted that while efficacy has been demonstrated in several compounds, additional studies are needed. Unfortunately, many anticonvulsants can produce undesirable side effects, including cognitive distortions, memory problems, and lack of tolerability to initial doses (Cramer et al., 2010; Guay, 2007; Huband et al., 2010). In addition, some may cause increases in irritability and aggression at lower doses or during initial exposure (Cherek et al., 2004; Guay, 2007; Lane et al., 2009). Thus, newer compounds featuring fewer unwanted cognitive and behavior effects are desirable (Huband et al., 2010; Khalifa et al., 2010). An open pilot study reported that tiagabine was both more effective than placebo at reducing alcohol dependence and was also well tolerated by patients, with only a minority reporting adverse events at the beginning of treatment (Paparrigopoulos et al., 2010).

Using a within-subject acute dosing design, we recently showed that tiagabine was effective in reducing human aggressive responding (Lieving et al., 2008). In the present report, we investigated tiagabine effects over a 5-week period using a chronic dosing design. Aggression was measured via the PSAP, which has the advantage of within-subject~~s~~ repeated measurement to assess change over time and~~/or~~ experimental condition, thus providing a useful measurement tool for chronic dosing designs.

In this project, we specifically selected individuals at risk for elevated rates of aggressive and violent behavior, a strategy we have employed previously (Cherek and Lane, 2001; Lane et al., 2009). Public health research has demonstrated that individuals with histories of criminal prosecution and incarceration (on parole/probation), Axis II personality disorders (e.g. antisocial, borderline), and substance use disorders (SUD) present increased risk for physically violent and/or aggressive behavior (Arseneault et al., 2000; Kessler et al., 2006; Rasmussen and Levander, 1996; Robins, 1993; Swanson et al., 1990). For example, those with antisocial personality disorder and SUD are 10–15 times more likely than healthy, matched controls to exhibit serious aggressive behavior (Arseneault et al., 2000; Steadman et al., 1998; Swanson et al., 1990). In addition, there is evidence that individuals with single nucleotide polymorphisms (SNPs) of the α2 subunit of the GABA-A receptor are at increased risk for developing alcohol use disorders, which suggests potential alterations of GABA function (Bierut et al., 2010; Edenberg and Foroud, 2006). GABA-A α2 SNPs also interact with childhood trauma, and the relationship is predictive of substance dependence for cocaine, heroin and alcohol dependence (Enoch et al., 2010). The role of GABA in aggression is well documented (Miczek et al., 2004)~~. Altered~~ GABA function could potentially mediate the relationship between SUDs and aggression.

Based on the anti-aggressive efficacy of anticonvulsants, our prior study of acute tiagabine effects on aggression, the utilization of a population at increased risk for aggression, and the demonstrated role of GABA in modulating aggressive behavior, we expected that chronic tiagabine administration would produce decreases in laboratory-measured aggression.

Methods

All experimental procedures were reviewed and approved by the Institutional Review Board for the University of Texas Health Science Center-Houston. Informed consent was obtained from all subjects prior to study participation.

Subjects

Potential volunteers ~~of~~ responded to advertisements for research studies seeking individuals on parole or probation, these advertisements were placed in freely distributed papers in the Houston area. Recruitment for individuals on parole or probation was sought because of the high incidence of antisocial and aggressive behavior associated with this population. Potential subjects underwent a physical exam in order to be screened for any exclusionary medical conditions (e.g. HIV, seizures, ~~asthma~~). Women were excluded if they were pregnant at the time of screening. Pregnancy tests were also conducted each day of testing to ensure no female subjects had become pregnant during the study. In addition, prior to study participation potential subjects were screened for any current or past psychiatric illness using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revised (DSM-IV TR) (SCID-P, First et al., 1996). Subjects were excluded for any Axis I disorder except for past substance dependence or abuse. The SCID-II Structured Clinical Interview for DSM-IV (First et al., 1997) was used to assess if the potential subject met for childhood Conduct Disorder (CD) by age 15, Antisocial Personality Disorder (ASPD), or Borderline Personality Disorder.

Twelve subjects completed the study (10 male). Six of the subjects met DSM-IV TR criteria for ASPD, two subjects met DSM-IV TR criteria only for childhood CD, and four subjects did not met DSM-IV TR criteria for either ASPD or CD. No subjects met criteria for Borderline Personality Disorder. Cognitive functioning was assessed via the Shipley Institute of Living Scale (Zachary, 1986), which assesses general intellectual aptitude through a 40-item vocabulary test and a 20-item abstract reasoning test. Normalized percentiles

Table 1. Baseline characteristics of subjects in both groups. Data show either the count (%) for dichotomous variables, or the mean (±SD) for continuous variables. The right-hand column shows the *p* value for statistical comparison between groups

Variable	Placebo ($n = 6$)	Tiagabine ($n = 6$)	Statistical Test*
Gender, Male	5(83.33)	5(83.33)	$p \leq 1.00$†
Ethnicity			$p \leq 1.00$†
African-American	5(83.33)	6 (100)	
Hispanic	1(16.67)	0(0)	
Education, HS	5(83.33)	6(100)	$p \leq 1.00$†
CD (Present)	4(66.67)	3(50.00)	$p \leq 1.00$†
ASPD (Present)	3(50.00)	3(50.00)	$p \leq 1.00$†
ADHD (Present)	0(0)	0(0)	NA‡
BD (Present)	0(0)	0(0)	NA‡
Smoker (Yes)	5(83.33)	4(66.67)	$p \leq 1.00$†
Parole/Probation			$p \leq 1.00$†
Parole	1(16.67)	3(50.00)	
Probation	2(33.33)	2(33.33)	
Age	32.00 (±5.02)	25.17 (3.82)	$p \leq 0.12$§
BPAQ	65.17 (±11.48)	67.00 (±26.71)	$p \leq 1.00$§
STAXI	95.67 (±8.14)	97.67 (±29.11)	$p \leq 0.56$§
LHA	21.60 (±10.92)	20.67 (±14.90)	$p \leq 1.00$§
EIVQ	25.83 (±9.47)	31.33 (±6.50)	$p \leq 0.56$§
BIS-11	55.67 (±11.48)	64.17 (±11.09)	$p \leq 0.56$§
ROAS	7.00 (±3.46)	4.83 (±4.07)	$p \leq 1.00$§
Cigarettes/Day	4.67 (±3.44)	4.33 (±4.59)	$p \leq 1.00$§
Shipley WAIS	105.83 (±5.11)	105.33 (±12.66)	$p \leq 1.00$§
Shipley WAIS-R	96.50 (±6.25)	94.67 (±14.38)	$p \leq 1.00$§

*Holm–Bonferroni Stepdown Method used to adjust for multiple comparisons.
CD, Conduct Disorder; ASPD, Anti-Social Personality Disorder; ADHD, Attention Deficit Hyperactivity Disorder; BD, Borderline Personality Disorder; BPAQ, Buss–Perry Aggression Questionnaire; STAXI, State–Trait Anger Expression Inventory; LHA, Lifetime History of Aggression Questionnaire; EIVQ, Eysenck Impulsivity Venturesomeness Questionnaire; BIS-11, Barratt Impulsiveness Scale; ROAS, Retrospective Overt Aggression Scale; WAIS, Wechsler Adult Intelligence Scale
† Fisher's Exact Test.
‡ No ADHD or BD detected in either sample.
§ Wilcoxon Two-Sample, Monte Carlo, Exact Test.

were obtained from both tests. All 12 subjects were within one standard deviation of the mean age-adjusted normative percentile, with a Wechsler Adult Intelligence Scale (WAIS) estimated mean score of 105.58 (range 93–129, see Table 1). Appendix A provides details regarding drug use history, parole/probation status, and past criminal offenses.

Expired breath samples and urine samples were collected from subjects on each day of participation prior to the first experimental session. The alcohol content of expired breath samples was measured using an Alcosensor III (Intoximeter, Model 3000, St. Louis, Missouri, USA). Urine samples were subjected to a complete drug screen analysis (marijuana, cocaine, opiates, amphetamine, methamphetamines, and benzodiazepines) using the Enzyme Multiple Immunoassay Technique – Drug Abuse Urine Assay (EMIT d.a.u. by SYLVA Corporation, Palo Alto, California, USA). Any subject with a positive blood alcohol level or urinalysis (UA) test was sent home and participation was rescheduled. Subjects were removed from the study if more than two positive tests of alcohol or drug use were recorded. Three subjects were removed for positive UA tests, two for marijuana and one for alcohol. To avoid potential interactions with tiagabine, subjects had to be free of illicit and prescription drugs during the study. All completed subjects had drug-free urine samples throughout the study. No subjects were taking any other prescription or over-the-counter medications, monitored by a morning questionnaire given to subjects each day of testing.

Apparatus

Subjects were seated in a 1.2 m × 1.8 m sound-attenuated testing chamber containing a video graph array (VGA) monitor and a 10 cm × 43 cm × 25 cm response panel. Three microswitch push buttons labeled 'A', 'B', and 'C' were mounted horizontally on the top of the response panel. The monitor and response panel were linked to a Pentium-based computer outside the testing chamber using a MedAssociates (Georgia, Vermont, USA) interface card and a customized hardware/software system. This computer interface controlled and recorded all experimental sessions.

Procedures

Aggressive, escape, and monetary-reinforced responding were measured using the PSAP (Cherek et al., 1992, 2003). The external validity of the PSAP has been established; individuals with a more extensive history of aggressive behavior respond more frequently than controls on the operationally defined aggressive response option (Cherek and Lane, 1999;

Moeller et al., 1998). During the experimental session, subjects chose between three response buttons labeled A, B, and C. Button A was associated with a monetary-reinforced response option; button B with an operationally defined aggressive response option, which ostensibly subtracted 15 cents from a fictitious other person paired with the subject; and button C with an escape response option that protected the subject′s counter from subtractions (attributed to the fictitious other person) for a variable period of time. Monetary subtractions from the subjects counter (e.g. 'provocations') occurred at random intervals between 6 and 120 s.

At the beginning of every experimental session the letters A, B, and C and counter of the subject's earnings appeared on the computer screen. A single response on any button (A, B, or C) disabled the other two response options and the letters of those options disappeared from the screen. When option A (monetary-reinforced) was chosen, 100 consecutive presses on button A (fixed ratio 100 schedule) would add 15 cents to the subject's counter. If option B (aggressive) or option C (escape) were chosen, then 10 consecutive responses (fixed ratio 10) produced a time period that was free of any provocations (i.e. a provocation-free interval, or PFI). The PFI lasted 125 s on average, with a range of 100–150 s. After a PFI ended, subtractions to the subject's counter were reinstated. If the subject responded on either option B (aggressive) or option C (escape), the number of provocations per session that would occur could be reduced, outwardly suggesting an effect ~~of~~ B and C responding on the 'other' person's subsequent behavior. After completing the response requirement for any of the selected button options, the selected letter disappeared from the computer screen for a period of 2 s. After the 2-s period, all three letters reappeared as a signal to the subject that all three response options were again available.

The presence of the fictitious other person and all PSAP contingencies (real and apparent) were established via instructions prior to the first PSAP test session (Cherek and Lane, 1999). Subjects were shown a diagram of the computer monitor and response panel, and were then read a set of scripted instructions. If the subject asked questions, portions of the script were repeated. At the end of every testing day (approximately 3:00 pm), subjects were given a brief questionnaire to assess the veracity of the instructional deception. Any subject reporting suspicion about the presence of another person would be excluded from the study at that point. In the current study, all subjects reported being paired with another person on every testing day.

Subjects participated 2–3 days a week (Mon–Fri) in six 25-min sessions for each day of testing. Experimental sessions occurred at 9:00 am, 10:00 am, 11:00 am, 12:00 pm, 1:30 pm, and 2:30 pm. Subjects arrived in the laboratory at approximately 8:00 am for each day of testing. A standardized lunch was provided at approximately 11:30 pm. Breath and urine samples were obtained immediately upon arrival. Between experimental sessions, all subjects waited in a common area containing a television and magazines.

During the consent process, all subjects were provided information about their potential earnings, breath alcohol testing, urine drug screening, psychiatric screening, and experimental procedures. At the end of each testing day, all subjects were evaluated for signs of impairment and completed a 22-item side effects questionnaire in which they answered Yes/No to each item. Subjects were then paid in cash the sum of all earnings across the six PSAP test sessions, plus bonuses of $10 for on-time attendance and $10 for clean BAL and UA samples. Side effect data are provided in Appendix B, which lists each of the 22 side effects and the total. Exact Poisson regression with false discovery rate (FDR) correction for multiple comparisons was used to analyze side effect counts over the 5-week course of the study. Subjects in the tiagabine group reported greater thirst, nervousness, and total side effects than the placebo group ($p < 0.003$ after FDR correction, see Appendix B for details).

Dosing design and capsule administration

Subjects participated for 6 weeks. After signing consent, subjects were randomly assigned to a placebo ($n = 6$, 5 male) or tiagabine ($n = 6$, 5 male) group. Consistent with our prior acute tiagabine dosing study (Lieving et al., 2008), and at the request of the local Institutional Review Board, an ascending dose sequence was selected for safety, with a focus on minimizing potential GABA-related side effects (e.g. drowsiness, cognitive or motor disruption). For chronic dosing in the treatment of seizures, it is recommended to use gradual dose escalation following the observation that optimally effective doses may also be in the range likely to produce side effects (Perucca, 2004). During the first week of participation, subjects responded under non-drug (i.e. baseline conditions) in order to stabilize responding on the PSAP, which is typically achieved within 1–2 days. In week 2, all subjects were administered placebo capsules BID. In weeks 3, 4, and 5, subjects were administered either placebo or 4 mg, 8 mg, and 12 mg tiagabine BID, respectively. All subjects received placebo capsules BID in week 6.

On each testing day, placebo or tiagabine capsules were administered at 9:00 a.m. All doses were encapsulated in #00 opaque blue capsules. Cornstarch was used to fill the remainder of the capsules. Placebo capsules contained only cornstarch. The bioavailability of tiagabine is 90%, with peak plasma levels reached approximately 1–2 h after oral administration. The elimination half-life ranges from 4–9 h. A second dose was self-administered by the subject at 6:00 p.m. On days when subjects were not scheduled to come to the laboratory, capsules were self-administered at home at 9:00 a.m. and 6:00 p.m. Research assistants blinded to the drug condition conducted the dose administration in the laboratory and administered take-home Medication Event Monitoring System (MEMS) bottles. Throughout the course of the study, neither the subject nor the research assistants were aware of the capsule contents. Compliance with the self-administration (at home) dosing protocol was monitored by placing capsules in MEMS bottles (AARDEX Ltd/APREX, Union City, CA, USA), which electronically recorded bottle opening times. Based on MEMS data, compliance with the at-home dosing protocol was generally high. Defined as a bottle opening within 90 min of the protocol times (9:00 a.m., 6:00 p.m.), mean compliance was 89.17% (±6.02, range 65–100%) for the placebo group, and 80.00% (±6.78, range 50–97%) for the tiagabine group. Compliance

rates were not significantly different across the groups, $t(10) = 1.01$, $p = 0.33$.

Questionnaires

At the end of the study, subjects completed six questionnaires related to aggression: (1) Buss–Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992), (2) State–Trait Anger Expression Inventory (STAXI) (Spielberger et al., 1983), (3) Lifetime History of Aggression Questionnaire (LHA) (Coccaro et al., 1997), (4) Eysenck Impulsivity Venturesomeness Questionnaire (~~IEVQ~~) (Eysenck et al., 1985), (5) Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995), and (6) Retrospective Overt Aggression Scale (ROAS) (Sorgi et al, 1991). Mean values are shown in Table 1. No significant differences were found between subjects who received tiagabine dose versus subjects who received placebo doses.

Data analyses

Parallel analytic approaches were used to evaluate performance in the monetary earning (button A) and aggressive responding (button B) conditions. Aggressive responding was measured as aggressive responses per provocation; a measure of ~~subjects'~~ reactivity to the provoking stimulus (monetary subtraction). Less than half of all subjects used the escape response option (button C), and those who did use it did so sporadically. Accordingly, escape responding was not analyzed. Preliminary repeated-measures ANOVA models across the six daily test sessions revealed no effect of session on either monetary earning or aggressive responding (F values < 2.0). Accordingly, data were averaged across the six daily test sessions for each week, yielding a mean weekly score for each participant.

Mixed models evaluated performance as a function of time (week), dose condition (placebo vs. tiagabine), and their interaction. Following recent recommendations (Wijeysundera et al., 2009) analyses employed both frequentist (using SAS v. 9.2; PROC GLIMMIX) and Bayesian (using MLWin v. 2.20) statistical approaches. Conventional frequentist analyses permit rejection of the null hypothesis but do not directly address the probability of various values for the alternative hypothesis. Bayesian statistical reasoning permits statements regarding the probability that a value, or some range of values, constitutes the governing parameter for the process under examination.

While frequentist methods treat the parameter as fixed and the data as random, Bayesian methods treat the data as fixed and the parameter value as random. Frequentist methods estimate the probability of the data (or data more extreme) given a parameter of some value. Bayesian methods estimate the probability of a parameter of some magnitude given the data. Summarizing the posterior distribution in terms of some measure of central tendency and an index of variability provides point and interval estimates which characterize the best estimate of the parameter value and the uncertainty for that estimate. All inferences are made on the basis of the posterior distribution. Due to its influence on the posterior distribution, the choice of prior distribution is critical. Prior distributions for level-one error variances take the form of a Gamma distribution; see Browne (2009) for mathematical details. Essentially, these prior distributions will yield similar values to traditional frequentist estimates; however, the information contained in the posterior distribution permits probabilistic statements regarding various alternative hypotheses.

Results

Given the small sample size, the degree to which randomization may have rendered comparable groups requires evaluation. If baseline characteristics were correlated with both group membership and performance measures, then the potential for confounding existed. Table 1 provides demographic and psychometric information for each group. Inspection of baseline characteristics failed to demonstrate any group differences after controlling for Type I Error due to multiple comparisons (see Table 1).

Frequentist analysis

Evaluation of the aggressive responding (B button responses per provocation) indicated a reliable interaction of drug condition and time ($F(1, 46) = 5.25$, $p \leq 0.027$). For participants in the tiagabine condition, aggressive responding decreased ($b = -2.33$ (95% Confidence Interval (CI) -3.46–-1.20)) for each additional week in the study. Participants in the placebo condition did not demonstrate change over time ($b = -0.47$ (95% CI -1.71–0.76)). Evaluation of monetary-reinforced responding (A button responses per second) did not demonstrate an interaction of condition by time ($F(1, 36) = 0.10, \leq 0.756$) or a main effect for condition ($F(1, 36) = 2.29, \leq 0.139$); however, both groups' rates increased over time ($F(1, 11) = 5.52$, $p \leq 0.039$; $b = 156.91$ (95% CI 9.98–303.85). Figure 1 depicts the model-estimated scores as a function of time, condition and the interaction of time and condition for each ~~experimental paradigm~~ (solid lines). Individual data points show group averages ($\pm$SEM) at each week.

Bayesian analysis

The posterior distribution of parameter values for the interaction term for aggressive responding is depicted in Figure 2 (lower panel). The parameter estimate for the interaction term is $b = -1.863$ (95% Credible Interval (CBI) -3.706–-0.025). Assuming that no effect is indicated by a parameter value of zero (see reference line), the posterior distribution indicates that the probability that an interaction occurred (i.e. an effect < 0) is 0.977. The posterior distribution also permits statements regarding effect sizes of varying magnitudes (shown in Table 2): the probabilities that the interaction parameter value is less than -0.5, -1.0, -1.5, and -2.0 are 0.928, 0.823, 0.652, 0.440, respectively. Among participants receiving tiagabine, aggressive responding decreased over time ($b = -2.332$ (95% CBI -3.329–-1.336)), while participants in the placebo condition failed to reliably demonstrate change over time ($b = -0.474$ (95% CBI -2.107–1.158)). Inspection of the posterior distribution of the simple effects of time within each drug condition indicates that the

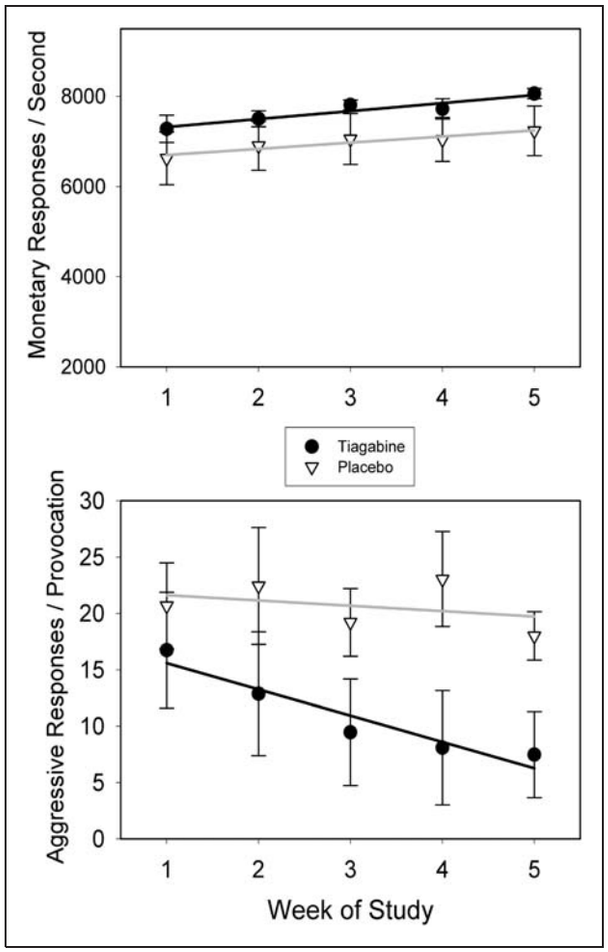

Figure 1. Solid lines represent model estimated scores as a function of time (week of the study), dose condition, (placebo or tiagabine) and the interaction of time and condition. Individual data points show group averages ($\pm$SEM) at each week; unfilled triangles = placebo; filled circles = tiagabine. Top and bottom panels show data for monetary and aggressive responding, respectively.

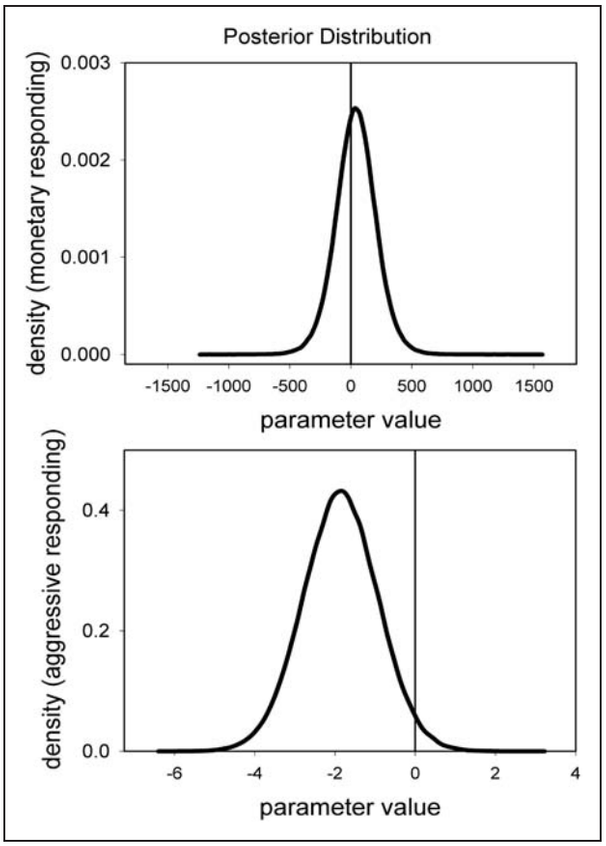

Figure 2. Density functions derived from the Bayesian analyses of monetary and aggressive responding. The posterior probability distribution of the parameter value for the time (week) by condition (dose) interaction term is shown in the upper panel for monetary-reinforced responding and in the lower panel for aggressive responding.

probabilities of slope parameters less than zero are ≥ 0.999 and 0.725 for tiagabine and placebo, respectively. Examining the probability that a larger parameter is governing the observed process indicates that, for tiagabine, the probability is 0.949 and that the slope is less than $b = -1.5$, compared with a probability of 0.101 for placebo. From these Bayesian arguments, it follows that there is a high probability of a linear decrease in aggression over time in the tiagabine condition and a contrastingly low probability in the placebo condition.

The posterior distribution of the parameter value for the interaction term for monetary-reinforced responding is depicted in Figure 2 (upper panel). The parameter estimate for the interaction term is $b = 41.323$, (95% CBI −293.966–376.446), which fails to show reliable difference from zero. Inspection of the posterior distribution indicates that the probabilities of $b = 0.0$, −0.5, −1.0, −1.5, and −2.0 are 0.396, 0.395, 0.394, 0.393 and 0.391, respectively. The clustering of these probabilities reflects the smaller variance in the posterior distribution for monetary responding versus aggressive responding (Figure 2). This is due to the overall response rate and allocation of behavior to the aggressive versus monetary earning response option inherent in the PSAP. Specifically, even the most aggressive individuals still allocate the majority of responding to the monetary earning option. Further inspection of the model indicated that there was reliable change over time for both conditions ($b = 156.967$, (95% CBI −0.570–314.464)). The probability of a slope greater than zero is 0.975, while the probabilities of a slopes as large as $b = 100$ and $b = 150$ are 0.775 and 0.538, respectively. This indicates that, across both groups, subjects responded faster on the monetary earning option (e.g. became more efficient at earning money) over the 5-week duration of the study, as depicted in the increasing slopes in Figure 1. Figure 2 shows the posterior distributions for the interaction terms (i.e. Drug Condition × Time). Table 2 provides the posterior probabilities for interaction effects of various magnitudes for both the monetary earning and aggressive response options.

The combination of frequentist and Bayesian analyses permits application of different definitions of probability in

Table 2. Posterior probabilities for interaction effects of various magnitudes in the monetary earning and aggressive response options

Parameter Value	Prob of Parameter Value	
	Time × Condition	
(Aggressive Responding)	Time × Condition	
(Monetary Earning)		
< 0.0	0.977	0.396
< -0.5	0.928	0.395
< -1.0	0.823	0.394
< -1.5	0.652	0.393
< -2.0	0.440	0.391

assessing uncertainty regarding the governing parameter(s) of some process. (For an accessible exposition on these different definitions see Gill (2002)). Presently, this facilitated the probabilistic evaluation of both the null and alternative hypotheses for change in aggressive and monetary-reinforced responding.

Discussion

In a subject population of parolees at increased risk for violence, tiagabine produced decreases in aggressive responding over 5 weeks corresponding to weekly increases in dose (4 mg, 8 mg, 12 mg). No changes over time were observed in the placebo group. Both groups showed similar increases in monetary responding over time, corresponding to an increase in efficiency on the PSAP and subsequently higher earnings per session. These differential changes between response classes (monetary vs. aggressive) and dose condition (placebo vs. tiagabine) suggest that tiagabine's effects were specific to aggressive behavior rather than to non-specific effects (e.g. sedation).

To our knowledge, these data represent the first placebo-controlled examination of tiagabine for aggressive behavior using a chronic, extended dosing regimen. The results are consistent with our previous study of acute tiagabine effects (Lieving et al., 2008) and two reported case studies using tiagabine for the management of aggression in highly agitated patients (Hoffman, 2005; Kaufman et al., 2002). Though limited, these data collectively suggest that tiagabine merits further examination as an anti-aggressive drug. In contrast to a previous study of acute topiramate effects on aggression (Lane et al., 2009), we observed no reports of adverse side effects with tiagabine BID over 3 weeks in the dose range 4–12 mg. Insofar as the PSAP can serve as a proxy for gauging real-world risk for aggressive behavior, the present data suggest that the efficacy of tiagabine in reducing aggression may be superior to topiramate, which~~, acute,~~ showed an inverted-U shaped dose-response function with increases at doses of 100 mg and 200 mg and modest decreases at 400 mg. However, differences in dosing design (acute vs. chronic) limit the interpretation of this comparison.

The data indicate that tiagabine significantly reduced aggressive responding. However, due to the restricted sample size, cautious interpretation of the results is warranted and generalizabilty to broader populations is unknown. Replication of tiagabine's effect on reducing aggressive responding in a larger sample is warranted.

Subjects received tiagabine in an ascending dose sequence, starting with a week of placebo and then escalating from 4 mg to 12 mg BID over 3 weeks and concluding with a week of placebo. This sequential design was chosen for subject safety and dose tolerance (Perucca, 2004), but order effects are possible. Specifically, while the placebo group served as a control for general decreases in aggression over time, it cannot be determined whether the apparent linear decrease over each week was a function of increased dose, or an interaction of time and accumulating exposure to the drug. As discussed in more detail below, the lack of recovery toward baseline in the return to placebo during final week further obscures these issues. In addition, we did not collect collateral behavioral, subjective, or biological measures over time, and thus cannot determine if tolerance or sensitivity played a role in the observed outcomes. Other possible designs and measures might control for this possibility in future studies. A crossover design that switched subject dose condition after 5 weeks, while time intensive, would feature the advantage of exposing subjects to each condition. A randomized counterbalanced dosing order, while susceptible to increased risk of side effects, carryover effects, and increases in behavioral variability across doses, would better control for possible dose by time interactions.

Our sample was limited to a specific population of individuals on parole/probation with SUDs and DSM-IV Axis II personality disorders such as ASPD. Individuals with a history of substance dependence show reduced white matter integrity in prefrontal brain regions known to subserve decision-making processes (Lane et al., 2010). In addition, individuals with SUDs and/or personality disorders are known to have both abnormalities in prefrontal/frontal lobe function and decision-making deficits (Miczek et al., 2007; New et al., 2007; Siever, 2008; Volkow et al., 1993). Altered prefrontal and frontal lobe function and ~~related~~ impaired decision-making processes may place such individuals at increased risk for committing acts of aggression. While the contribution of these factors to the present results is not clear, future work is likely to provide increased coherence through direct measurement of these variables and their relationship to drug effects on aggression. A more generalizable understanding of tiagabine's effects on human aggression will also require a larger, more diverse sample.

Subjects in the tiagabine group maintained lower levels of aggressive responding, even after active doses were terminated and both groups returned to placebo, i.e. they did not return to week 1 placebo levels of aggressive responding during the week 5 return to placebo. Given the short half-life (7–9 h) of tiagabine, the drug should have cleared the system by week 5. One possibility is that changes in behavioral patterns on the PSAP, established over the course of weeks, may not be reversible. We observed a similar pattern of behavior in a study of paroxetine (Cherek et al., 2002). That study employed an equivalent chronic dosing design, and similarly did not observe a reversal to initial levels of aggression during a 2-week return to placebo at the end of the study. Additional possibilities are that a drug may persist

longer in the brain than in plasma, or may produce persistent adaptive changes in the brain.

Anticonvulsants such as valproate, phenytoin and carbamazepine have been used extensively to treat impulsive aggression in clinical populations and are generally effective. However, the results are not unequivocal. Some studies with valproate (Hellings et al., 2005) and divalproex (Hollander et al., 2003) did not demonstrate any difference greater than placebo, although effects of divalproex were greater in more impulsive and aggressive subjects (Hollander et al., 2005). Tiagabine has not been studied as extensively as other anticonvulsants, but previous acute dosing data show potential efficacy (Lieving et al., 2008). Some anticonvulsants may produce undesirable side effects such as memory alteration and, paradoxically, irritability, at least at certain doses (Cramer et al., 2010; Huband et al., 2010; Lane et al., 2009). Newer anticonvulsants, including tiagabine, have a lower side effect profile and thus may be safer. Further, tiagabine presents little risk for dependence or abuse, which may make it a better option for some at-risk populations. The abuse liability profile of tiagabine is very low, as with other newer anticonvulsants (Malcolm, 2003). Importantly, it has been effectively used in clinical trials for the treatment of alcohol and cocaine dependence (González et al., 2007; Paparrigopoulos et al., 2010; Winhusen et al., 2007). The present results indicate that tiagabine reduced aggressive responding in a sample at high risk for aggression, suggesting that further investigation of the psychopharmacology of tiagabine in a larger, more diverse sample is warranted.

Funding

This work was funded by National Institutes of Health (NIDA) grants R01 DA 03166 (SDL) and K02 DA 00403 (FGM) and DA P50 009262 (FGM).

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

The authors would like to acknowledge the contributions of Koyun Chi, Nuvan Rathnayaka, Irshad Prasla, Laura Madden-Fuentes, Tara Watts, and Sarly Vasquez to this research project.

References

Arseneault L, Moffitt TE, Caspi A, Taylor PJ and Silva PA (2000) Mental disorders and violence in a total birth cohort: results from the Dunedin Study. *Arch Gen Psychiatry* 57: 979–986.

Barratt ES, Stanford MS, Felthous AR and Kent TA (1997) The Effects of phenytoin on impulsive and premeditated aggression: a controlled study. *J Clin Psychopharmacol* 17: 341–349.

Bierut LJ, Agrawal A, Bucholz KK, Doheny KF, Laurie C, Pugh E, Fisher S, et al. (2010) A genome-wide association study of alcohol dependence. *Proc Natl Acad Sci U S A* 107: 5082–5087.

Bjork JM, Moeller FG, Kramer GL, Kram M, Suris A, Rush AJ, et al. (2001) Plasma GABA levels correlate with aggressiveness in relatives of patients with unipolar depressive disorder. *Psychiatry Res* 101: 131–136.

Braga MF, Aroniadou-Anderjaska V, Li H and Rogawski MA (2009) Topiramate reduces excitability in the basolateral amygdala by selectively inhibiting GluK1 (GluR5) kainate receptors on interneurons and positively modulating GABAA receptors on principal neurons. *J Pharmacol Exp Ther* 330: 558–566.

Browne WJ (2009) *MCMC Estimation in MlwiN*. University of Bristol: Bristol, UK: Centre for Multilevel Modelling.

Buss AH and Perry M (1992) The Aggression Questionnaire. *J Pers Soc Psychology* 63: 452–459.

Cherek DR and Lane SD (1999) Laboratory and psychometric measurements of impulsivity among violent and nonviolent female parolees. *Biol Psychiatry* 46: 273–280.

Cherek DR and Lane SD (2001) Acute effects of d-fenfluramine on simultaneous measures of aggressive, escape and impulsive responses of adult males with and without a history of conduct disorder. *Psychopharmacology* 157: 221–227.

Cherek DR, Lane SD and Pietras CJ (2003) Laboratory Measures: Point Subtraction Aggression Paradigm (PSAP). In: Coccaro EF (ed.) *Aggression: Assessment and Treatment*. New York: Marcel Dekker.

Cherek DR, Lane SD, Pietras CJ and Steinberg JL (2002) Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. *Psychopharmacology (Berl)* 159: 266–274.

Cherek DR, Spiga R and Egli M (1992) Effects of response requirement and alcohol on human aggressive responding. *J Exp Anal Behav* 58: 577–587.

Cherek DR, Tcheremissine OV, Lane SD and Pietras CJ (2004) Acute effects of gabapentin on laboratory measures of aggressive and escape responses of adult parolees with and without a history of conduct disorder. *Psychopharmacology (Berl)* 171: 405–412.

Coccaro EF, Berman ME and Kavoussi RJ (1997) Assessment of life history aggression: development and psychometric characteristics. *Psychiatry Res* 73: 147–157.

Cramer JA, Mintzer S, Wheless J and Mattson RH (2010) Adverse effects of antiepileptic drugs: a brief overview of important issues. *Expert Rev Neurother* 10: 885–891.

De Almeida RM, Ferrari PF, Parmigiani S and Miczek KA (2005) Escalated aggressive behavior: dopamine, serotonin and GABA. *Eur J Pharmacol* 526: 51–64.

Earley CJ and Leonard BE (1977) The effect of testosterone and cyproterone acetate on the concentration of gamma-aminobutyric acid in brain areas of aggressive and non-aggressive mice. *Pharmacol Biochem Behav* 6: 409–413.

Edenberg HJ and Foroud T (2006) Review: The genetics of alcoholism: identifying specific genes through family studies. *Addict Biol* 11: 386–396.

Enoch MA, Hodgkinson CA, Yuan Q, Shen PH, Goldman D and Roy A (2010) The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. *Biol Psychiatry* 67: 20–27.

Eysenck HJ, Barrett P and Eysenck SB (1985) Indices of factor comparison for homologous and non-homologous personality scales in 24 different countries. *Pers Individ Dif* 6: 503–505.

First MB, Spitzer RL, Gibbon M and Williams JBW (1996) *Structured Clinical Interview for DSM-IV Axis I Disorders: Non patient edition (SCID-NP)*. New York: NY State Psychiatric Institute.

First MB, Spitzer RL, Gibbon M, Williams JBW and Benjamin LS (1997) *Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II)*. Washington, DC: American Psychiatric Press, Inc.

Gill J (2002) *Bayesian Methods: A Social and Behavioral Sciences Approach*. Boca Raton, FL: Chapman & Hall/CRC.

González G, Desai R, Sofuoglu M, Poling J, Oliveto A, Gonsai K, et al. (2007) Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine dependent methadone-treated patients. *Drug Alcohol Depend* 87: 1–9.

Gourley SL, Debold JF, Yin W, Cook J and Miczek KA (2005) Benzodiazepines and heightened aggressive behavior in rats: reduction by Gaba(A)/Alpha(1) receptor antagonists. *Psychopharmacology (Berl)* 178: 232–240.

Griffith JL (1985) Treatment of episodic behavioral disorders with rapidly absorbed benzodiazepines. *J Nerv Ment Dis* 173: 312–315.

Guay DR (2007) Newer antiepileptic drugs in the management of agitation/aggression in patients with dementia or developmental disability. *Consult Pharm* 22: 1004–1034.

Hellings JA, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese RM, et al. (2005) A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 15: 682–692.

Hoffman DA (2005) Tiagabine for rage, aggression, and anxiety. *J Neuropsychiatry Clin Neurosci* 17: 252.

Hollander ES, Swann AC, Coccaro EF, Jiang P and Smith TB (2005) Impact of trait impulsivity and state aggression on divalproex versus placebo in borderline personality disorder. *Am J Psychiatry* 162: 621–624.

Hollander E, Tracy KA, Swann AC, Coccaro EF, Mcelroy SL, Wozniak P, et al. (2003) Divalproex in the treatment of impulsive aggression: efficacy in Cluster B personality disorders. *Neuropsychopharmacology* 28: 1186–1197.

Huband N, Ferriter M, Nathan R and Jones H (2010) *Antiepileptics for aggression and associated impulsivity*. *Cochrane Database Syst Rev* 2: CD003499.

Kaufman KR, Kugler SL and Sachdeo RC (2002) Tiagabine in the management of postencephalitic epilepsy and impulse control. *Epilepsy Behav* 3: 190–194.

Kessler RC, Coccaro EF, Fava M, Jaeger S, Jin R and Walters E (2006) The prevalence and correlates of DSM-IV intermittent explosive disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 63: 669–678.

Khalifa N, Duggan C, Stoffers J, Huband N, Vollm BA, Ferriter M, et al. (2010) Pharmacological interventions for antisocial personality disorder. *Cochrane Database Syst Rev* 8: CD007667.

Kim E (2002) The use of newer anticonvulsants in neuropsychiatric disorders. *Curr Psychiatry Rep* 4: 331–337.

Lane SD, Gowin JL, Green CE, Steinberg JL, Moeller FG and Cherek DR (2009) Acute topiramate differentially affects human aggressive responding at low vs. moderate doses in subjects with histories of substance abuse and antisocial behavior. *Pharmacol Biochem Behav* 92: 357–362.

Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, et al. (2010) Diffusion tensor imaging and decision making in cocaine dependence. *PLoS One* 5: e11591.

Lee R, Petty F and Coccaro EF (2009) Cerebrospinal fluid GABA concentration: relationship with impulsivity and history of suicidal behavior, but not aggression, in human subjects. *J Psychiatr Res* 43: 353–359.

Lieving LM, Cherek DR, Lane SD, Tcheremissine OV and Nouvion SO (2008) Effects of acute tiagabine administration on aggressive responses of adult male parolees. *J Psychopharmacol* 22: 144–152.

Malcolm RJ (2003) GABA systems, benzodiazepines, and substance dependence. *J Clin Psychiatry* 64(Suppl 3): 36–40.

Mattes JA (2005) Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 25: 575–579.

Mattes JA (2008) Levetiracetam in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 69: 310–315.

Miczek KA, De Almeida RM, Kravitz EA, Rissman EF, de Boer SF and Raine A (2007) Neurobiology of escalated aggression and violence. *J Neurosci* 27: 11803–11806.

Miczek KA, Faccidomo S, De Almeida RM, Bannai M, Fish EW and Debold JF (2004) Escalated aggressive behavior: new pharmacotherapeutic approaches and opportunities. *Ann N Y Acad Sci* 1036: 336–355.

Miczek KA, Fish EW and De Bold JF (2003) Neurosteroids, GABAA receptors, and escalated aggressive behavior. *Horm Behav* 44: 242–257.

Moeller FG, Dougherty DM, Lane SD, Steinberg JL and Cherek DR (1998) Antisocial personality disorder and alcohol-induced aggression. *Alcohol Clin Exp Res* 22: 1898–1902.

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, et al. (2007) Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology* 32: 1629–1640.

Nickel MK (2007) Topiramate treatment of aggression in male borderline patients. *Aust N Z J Psychiatry* 41: 461–462.

Nickel MK, Nickel C, Kaplan P, Lahmann C, Muhlbacher M, Tritt K, et al. (2005) Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol Psychiatry* 57: 495–499.

Patton JH, Stanford MS and Barratt ES (1995) Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 51: 768–774.

Perucca E (2004) General Principles of Medical Treatment. In: Shorvon SD, Fish D, Perucca E and Dodson WE (eds) *The Treatment of Epilepsy*. *Vol. 2*, Malden, MA: Blackwell.

Paparrigopoulos T, Tzavellas E, Karaiskos D, Malitas P and Liappas I (2010) An open pilot study of tiagabine in alcohol dependence: tolerability and clinical effects. *J Psychopharmacol* 24: 1375–1380.

Poshivalov VP (1981) Pharmaco-ethological analysis of social behaviour of isolated mice. *Pharmacol Biochem Behav* 14(Suppl 1): 53–59.

Puglisi-Allegra S, Simler S, Kempf E and Mandel P (1981) Involvement of the GABAergic system on shock-induced aggressive behavior in two strains of mice. *Pharmacol Biochem Behav* 14(Suppl 1): 13–18.

Rasmussen K and Levander S (1996) Symptoms and personality characteristics of patients in a maximum security psychiatric unit. *Int J Law Psychiatry* 19: 27–37.

Robins LN (1993) Childhood Conduct Problems, Adult Psychopathology, and Crime. In: Hodgins S (ed.) *Mental Disorder and Crime*. Newbury Park, CA: Sage.

Saias T and Gallarda T (2008) [Paradoxical aggressive reactions to benzodiazepine use: a review]. *Encephale* 34: 330–336.

Siever LJ (2008) Neurobiology of aggression and violence. *Am J Psychiatry* 165: 429–442.

Siegel A, Roeling TA, Gregg TR and Kruk MR (1999) Neuropharmacology of brain-stimulation-evoked aggression. *Neurosci Biobehav Rev* 23: 359–389.

Sorgi P, Ratey JJ, Knoedler DW, Markert RJ and Reichman M (1991) Rating aggression in the clinical setting: a retrospective adaptation of the overt aggression scale. *J Neuropsychiatry Clin Neurosci* 3: S52–S56.

Spielberger CD, Jacobs G, Russell S, Crane RS, Butcher JN and Spielberger CD (1983) *Assessment of Anger: The State-Trait Anger Scale, Advances in Personality Assessment*. *Vol. 2*, Hillsdale, NJ: Erlbaum.

Stanford MS, Anderson NE, Lake SL and Baldridge RM (2009) Pharmacologic treatment of impulsive aggression with antiepileptic drugs. *Curr Treat Options Neurol* 11: 383–390.

Stanford MS, Helfritz LE, Conklin SM, Villemarette-Pittman NR, Greve KW, Adams D, et al. (2005) A comparison of anticonvulsants in the treatment of impulsive aggression. *Exp Clin Psychopharmacol* 13: 72–77.

Steadman HJ, Mulvey EP, Monahan J, Robbins PC, Appelbaum PS, Grisso T, et al. (1998) Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. *Arch Gen Psychiatry* 55: 393–401.

Swanson JW, Holzer CE, 3rd, Ganju VK and Jono RT (1990) Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area surveys. *Hosp Community Psychiatry* 41: 761–770.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, et al. (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* 14: 169–177.

Wijeysundera DN, Austin PC, Hux JE, Beattie WS and Laupacis A (2009) Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiology* 62: 13–21.

Winhusen T, Somoza E, Ciraulo DA, Harrer JM, Goldsmith RJ, Grabowski J, et al. (2007) A double-blind, placebo-controlled trial of tiagabine for the treatment of cocaine dependence. *Drug Alcohol Depend* 91: 141–148.

Zachary RA (1986) *Shipley Institute of Living Scale: Revised Manual*. Los Angeles: Western Psychological Services.

Appendix A

Drug use history (top) and criminal record with parole probation history (bottom)

Subject	Group	Drug	Past Abuse	Past Dependence	Heaviest Use; Duration
3146	PLC	Alcohol	Yes	No	3×/wk; 1 year
		Cocaine	No	No	2×/wk; 2 years
3148	PLC	Cannabis	Yes	Yes	4–5 joints/daily; 3 years
		Opiate: Codeine	Yes	Yes	1–3 cups/daily; 0.33 years
3165	PLC	Cannabis	Yes	Yes	3–6 ×/day; 1 year
	PLC	Hallucinogens: MDMA	Yes	Yes	1×/week; 7 months
3220	PLC	Stim: Methamphetamine	Yes	Yes	3–4×/wk; 1 year
		Cocaine	Yes	No	1×/mo; 2 years
3244	PLC	Alcohol	Yes	No	10 drinks; 2.5 years
		Cannabis	Yes	No	4 joints/daily; 1 year
6441	PLC	Alcohol	Yes	Yes	12 drinks/day; 2 year
		Cannabis	Yes	Yes	4–5 joints/day; 2 years
		Cocaine	Yes	Yes	2–3 grams/daily; 1 year
3164	TGB	Alcohol	Yes	Yes	4–6 drinks/day, 3-4 years
		Cannabis	Yes	Yes	10 joints/day; 1 year
3170	TGB	None	None	None	None
3173	TGB	Alcohol	No	No	
3215	TGB	Alcohol	Yes	Yes	6–7 drinks/day; 1 year
		Cannabis	Yes	Yes	8–10 joints/day; 1 year
3218	TGB	Alcohol	Yes	No	4–5 drinks/day; 0.5-1 year
		Benzodiazepine: Xanax	Yes	Yes	8–11 pills/day: 1.25 year
		Cannabis	Yes	No	4–5 joints/day; 5 years
		Opiate: Codeine	Yes	No	1–2×/mo; 2-3 months
3279	TGB	Alcohol	Yes	No	4 drinks/day; 1 year
		Benzodiazepine: Xanax	Yes	Yes	2 pills 2×/wk; 1 year
		Cannabis	Yes	Yes	4 joints/day; 1year

Subject	Group	Drug	Past Abuse	Past Dependence	Heaviest Use; Duration
Subject	Group	Parole/Prob	Current Offense		Past Offenses
3146	PLC	Probation	Fraud		
3148	PLC	No			
3165	PLC	Parole	Assault		
3220	PLC	Parole	Burglary		
3244	PLC	Parole	Assault		
6441	PLC	Probation	No		drug trafficking
3164	TGB	Probation	Probation violation		possess of controlled substance
3170	TGB	No			
3173	TGB	Parole	Assault		
3215	TGB	Parole	Burglary		
3218	TGB	Parole	Burglary		
3279	TGB	Parole	possess of controlled substance		posses of controlled substance; unauthorized use of motor vehicle; credit card fraud

Appendix B

Side effects profile for tiagabine and control subjects. For each question, the two values represent the number of subjects reporting 'Yes' to the side effect at least once, and the total number of 'Yes' reports, respectively. The last two columns show the 95% confidence interval and statistical outcome from exact Poisson regression (for each item) with false discovery rate (FDR) correction for multiple comparisons. *p*-values are reported only for items that were significant after FDR correction (<0.003).

Side Effect Item	Placebo	Tiagabine	95% CI	significance
Thirsty	2, 11	4, 40	0.61–2.06	< 0.0001
Frequent urination	2, 8	3, 11	-0.69–1.37	ns
Drowsiness	6, 29	5, 12	-1.66–-0.18	ns
Fine hand tremor	0, 0	3, 6	0.16–inf	ns
Nausea	0, 0	2, 4	-0.42–inf	ns
Diarrhea	1, 1	0, 0	inf–3.66	ns
Vomiting	1, 1	2, 6	-0.32–5.62	ns
Unsteadiness	1, 1	4, 7	-0.11–5.75	ns
Difficulty walking	0, 0	1, 1	-3.66–inf	ns
Muscle weakness	2, 3	3, 7	-0.63–2.64	ns
Dizziness	0, 0	2, 4	-0.42–inf	ns
Blurred vision	0, 0	1, 7	0.37–inf	ns
Skin rash	2, 2	0, 0	inf–1.67	ns
Swelling	0, 0	0, 0	ns	
Fever/Chills	0, 0	0, 0	ns	
Cramps	0, 0	1, 2	-1.67–inf	ns
Loss of appetite	1, 2	2, 14	0.47–4.15	ns
Indigestion/Stomach pain	1, 1	1, 1	-4.36–4.36	ns
Headache	2, 3	2, 2	-2.89–1.76	ns
Heart pounding	1, 1	4, 4	-0.93–5.28	ns
Difficulty sleeping	1, 2	1, 8	-0.22–3.65	ns
Nervous	0, 0	2, 20	1.60–inf	< 0.0001
Total	6, 65	6, 157	0.59–1.17	< 0.0001