Review

Update on the biological treatment of aggression

J. Volavka[1]
L. Citrome[2]
D. Huertas[3]

[1] New York University
Nathan S. Kline Institute for Psychiatric Research
USA

[2] Clinical Research and Evaluation Facility
New York University
Nathan S. Kline Institute for Psychiatric Research
USA

[3] University of Alcalá
Madrid (Spain)
Guadalajara University Hospital
Department of Psychiatry
Guadalajara (Spain)

This review is focused on aggressive behavior in adult patients with major mental disorders. Aggression, agitation, and hostility are defined. The roles of intramuscular forms of ziprasidone and olanzapine in the treatment of acute agitation and aggression are discussed. We review general considerations pertaining to persistent aggression in inpatients and outpatients, including comorbidity of major mental disorders with substance use disorders and personality disorders. The role of clozapine as an antiaggressive agent is well-established, particularly in inpatients. Evidence also exists for the efficacy of risperidone, olanzapine, quetiapine, and aripiprazole. Anticonvulsants and lithium are widely used with the intent to control aggression, but their efficacy lacks strong evidential support. Benzodiazepines have a role in controlling acute agitation, but their long-term use for persistent aggression is not recommended. There is evidence for antiaggressive effects of SSRIs and hormonal agents with antiandrogenic properties. Beta-adrenergic blockers and electroconvulstive treatment are rarely used in clinical practice to control aggression, but they may be effective. The heterogeneity of aggressive behavior is a challenge for developing rational treatments. Emerging genetic findings hold a promise of future treatments of aggressive behavior developed on the basis of individual patients' genotypes.

Key words:
Aggression. Violence. Biological Treatment. Hormonal Treatment.

Actas Esp Psiquiatr 2006;34(2):123-135

Actualización del tratamiento biológico de la agresión

Esta revisión está centrada en el comportamiento agresivo que presentan los pacientes adultos que sufren trastornos mentales severos. Se definen los comportamientos de agresión, agitación y hostilidad. Se exponen las indicaciones de las formulaciones intramusculares de ziprasidona y olanzapina en el tratamiento de la agitación y la agresión agudas. Se efectúa una revisión general del comportamiento agresivo persistente en los pacientes hospitalizados y ambulatorios, incluyendo la comorbilidad de los trastornos mentales graves con los trastornos relacionados con sustancias y con los trastornos de la personalidad. La función de clozapina como agente antiagresivo queda bien establecida, especialmente en los pacientes hospitalizados. También se presenta evidencia de la eficacia de risperidona, olanzapina, quetiapina y aripiprazol. Los antiepilépticos y el litio se utilizan con frecuencia para controlar la agresión, pero su eficacia no está fundamentada en pruebas sólidas. Las benzodiazepinas tienen cierta utilidad en el control de la agitación aguda, pero no se recomienda su administración a largo plazo en cuadros de agresión persistente. Hay pruebas que demuestran los efectos antiagresivos de los inhibidores selectivos de la recaptación de serotonina y de diversos agentes hormonales con acción antiandrogénica. Los bloqueadores betaadrenérgicos y el tratamiento electroconvulsivo no se suelen utilizar en la práctica clínica para el control de la agresión, aunque pueden ser abordajes terapéuticos eficaces. La heterogeneidad del comportamiento agresivo representa una dificultad para el desarrollo de tratamientos con eficacia razonable. Los nuevos hallazgos genéticos son prometedores respecto a la posibilidad de desarrollar tratamientos futuros frente al comportamiento agresivo en función del genotipo individual de cada paciente.

Palabras clave:
Agresión. Violencia. Tratamiento biológico. Tratamiento hormonal.

INTRODUCTION

Aggression is all around us, and historical record indicates that it has always been that way. Most of the aggressive behavior in today's world is committed by people who have

Correspondence:
David Huertas
Servicio de Psiquiatría
Hospital Universitario de Guadalajara
Donantes de Sangre, s/n
19002 Guadalajara (Spain)
E-mail: davhuertas@inicia.es

no diagnosable mental disorder and are motivated by factors such as ideology, revenge, greed, or jealousy. Biological psychiatry should not be expected to offer insights into train bombings, kidnappings, or «honor killings». There is, however, a fraction of aggressive events (eg, murders) that is attributable to major mental disorders. The size of that fraction varies among different societies and across different points in time[1]. In most current Western societies that fraction is probably not greater than 10 %. It is this fraction that biological psychiatry can address.

The literature on the treatment of aggression has been reviewed extensively over the past several years[1-5]. Basic features of these reviews are included here in order to introduce the topics. However, the overview presented here is focusing primarily on the more recent findings and on problems addressed by the present and future research.

Before reviewing the literature, we need to define the basic concepts used therein. The term agitation primarily denotes excessive motor or verbal activity. Other components of agitation may include overwhelming fear or anxiety, irritability, assaultiveness, poor impulse control, impaired judgment, decreased sleep, rapid fluctuation of symptoms over time, and personal distress.

Aggression is defined as overt behavior involving intent to deliver noxious stimulation or to behave destructively. The term is used to describe behavior in human and non-human species. Humans demonstrate three main subtypes of outwards aggression: verbal aggression, physical aggression against other people, and physical aggression against objects. *Violence* denotes physical aggression against other people and thus can be seen as a subtype of aggression. The term tends to be used by popular press and in the criminal justice system. *Hostility* is ill-defined in the psychiatric literature. Hostility may include agitation, aggression, irritability, suspicion, and uncooperativeness. Thus, the term may connote merely an attitude, but also a physical expression of that attitude. When hostility is used when describing results from a rating scale such as the Positive and Negative Syndrome Rating Scale (PANNS)[6], the definition includes verbal and physical behavior. The PANSS definition for the hostility item reads: «Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse and assaultiveness.» Ratings range from 1 («hostility absent») to 7 («extreme hostility that includes marked anger resulting in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others»)[6].

TREATMENT OF ACUTE AGITATION AND AGGRESSION

Intramuscular administration of a medication typically results in a higher maximum plasma concentration in a shorter period of time than oral administration. These pharmacokinetic properties result in an earlier onset of action and this advantage is highly desirable in acutely agitated and aggressive patients.

Up until recently the choices of intramuscular agents for these behavioral emergencies have been limited. In the United States, haloperidol 5 mg i.m. plus lorazepam 2 mg i.m. has been the typical emergency treatment. The release of intramuscular formulations of ziprasidone and olanzapine represents a major advance in the treatment of acute agitation and aggression. These atypical antipsychotics have a much lower propensity to cause extra-pyramidal symptoms (EPS) such as acute dystonia compared with haloperidol. Risk of iatrogenic akathisia (common with haloperidol) is also diminished, which is very important since this condition causes irritability and worsens agitation. These new formulations of atypical antipsychotics also provide the opportunity for a seamless transition to oral dosing of the same agent, obviating the need to switch from i.m. haloperidol to an atypical antipsychotic which is usually the drug of choice for long-term oral treatment.

Ziprasidone

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every 4 hours. The practice of co-administration of oral and intramuscular ziprasidone is not recommended.

Results from two studies in healthy volunteers indicated that absorption of i.m.ziprasidone was rapid (T_{max} < 1 hour). The mean i.m. elimination t(1/2) was short (approximately 2.5 hours). The mean bioavailability for the 5-mg i.m. ziprasidone dose was approximately 100 %[7].

In a 6-week, flexibly dosed study, patients with schizophrenia or schizoaffective disorder were randomized to ziprasidone (i.m. up to 3 days, then oral 40-80 mg, b.i.d.) or haloperidol (i.m. up to 3 days, then oral 5-20 mg/day)[8]. At the end of i.m. treatment, patients receiving ziprasidone (n = 427) showed significantly improved Brief Psychiatric Rating Scale Total (BPRS total) scores compared with those receiving haloperidol (n = 138). Haloperidol-treated patients exhibited significantly greater increases in extrapyramidal symptoms and akathisia at end of i.m. treatment[8]. Another naturalistic study showed that ziprasidone 20 mg i.m. reduced agitation in emergency room patients including those intoxicated by alcohol or other substances[9]. The onset of action was as early as 15 minutes after the injection.

The magnitude of QTc increases with IM ziprasidone is comparable to that described for oral ziprasidone. At the

time when ziprasidone was launched, the QT increase was a matter of some concern. However, subsequent clinical experience suggests that the cardiac risk is not as serious as originally suspected[10].

Olanzapine

The efficacy of intramuscular olanzapine in controlling agitation in patients with schizophrenia or bipolar mania disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. Maximal daily recommended dose is 30 mg (given in 3 injections 2-4 hours apart); orthostatic hypotension may occur.

Olanzapine i.m. results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes (compared with approximately 6 hours after an oral dose). Based upon pharmacokinetic studies, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine.

Clinical trials demonstrated efficacy of olanzapine in reducing acute agitation in patients with schizophrenia and schizoaffective disorder[11-15]. Onset of efficacy of intramuscular olanzapine (10 mg) is rapid, occurring as early as 15 minutes, and superior to intramuscular haloperidol (7.5 mg) among patients with schizophrenia[11]. An analogous study with bipolar mania revealed similar findings with onset of efficacy seen as early as 30 minutes, with superiority to intramuscular lorazepam (2 mg)[15]. Intramuscular olanzapine exhibited less extrapyramidal side effects compared with intramuscular haloperidol. No adverse event was significantly more frequent for intramuscular olanzapine than intramuscular haloperidol or intramuscular lorazepam. A critical review of the studies of i.m. olanzapine has been published[16].

Oral olanzapine has also been used in the treatment of agitation using a loading-dose strategy in a double-blind multi-center study whereby patients with schizophrenia, schizoaffective, schizophreniform disorder, or bipolar I disorder were randomized to receive either a minimum of 20 mg/day (up to 40 mg on days 1 and 2, and up to 30 mg on days 3 and 4) or 10 mg/day (with lorazepam as needed)[17]. Although improvement on measures of excitement occurred in both groups, higher olanzapine dosing was significantly more effective, and this difference was first significant at the 24-hour rating. No statistically significant differences between groups existed in treatment-emergent adverse events or potentially clinically significant laboratory abnormalities. Although the difference did not reach statistical significance, the patients in the high dose group were twice as likely to experience headache and dizziness.

PERSISTENT AGGRESSION: GENERAL CONSIDERATIONS

Aggression in inpatients

Once the acute episode of agitation is appropriately managed, most patients calm down and their aggressive behavior stops. However, there is a subset of patients whose aggressive behavior will continue. In an early study, it was found that 5 % of the patients in a long-term psychiatric hospital were responsible for more than 50 % of aggressive incidents[18]. Treating these persistently aggressive patients is a major challenge.

One of the reasons for the difficulty is that although aggressive behavior is generally acknowledged to be heterogeneous in its origins, very little is known about those heterogeneous underlying mechanisms in psychiatric patients. Intuitively, clinicians recognize that the patient who assaults someone because voices told him to do so (command hallucinations) will not have the same underlying mechanism of aggression as another patient who hits someone in revenge because of a disagreement about a borrowed cigarette. Unplanned, impulsive outbursts of aggression against staff members who ask the patients to do something appear to represent another underlying mechanism.

Guided by such intuitive understanding, we attempted to formally classify physical assaults among psychiatric inpatients[19]. We hypothesized that psychosis, disordered impulse control, and psychopathy contribute to assaults. We used a semistructured interview to elicit reasons for assaults from assailants and their victims on an inpatient research ward. Video monitoring provided supplemental information. We found that approximately 20 percent of the assaults in this sample were directly related to positive psychotic symptoms. Factor analysis revealed two psychosis-related factors, one related to positive psychotic symptoms and the other to psychotic confusion and disorganization, as well as a third factor that differentiated impulsive from psychopathic assaults. Since the publication of this study,[19], we have replicated its results in a different sample (Nolan et al., 2005, in preparation).

This information could be useful in the selection of rational antiaggressive treatment strategies. It is possible to hypothesize that psychotic assaultive behavior may respond to better antipsychotic treatment, that impulsive aggression could improve with adjunctive mood stabilizers, and that aggression in schizophrenia patients stemming from comorbid psychopathy would not be particularly responsive to psychopharmacological treatment. No formal research attempting to test this hypothesis has been published.

Psychopathy as defined by Hare and his colleagues[20,21] is prevalent among persistently aggressive patients diagnosed with schizophrenia or schizoaffective disorder[22]. It is becoming clear that aggressive behavior in patients with

comorbid psychopathy requires a considerable amount of non-pharmacological treatment. Standard psychiatric treatment programs have limited success in reducing recidivistic aggressive and criminal behavior in patients with persistent mental illness. A specialized, cognitive behavioral treatment program has been developed for such a population[23]. This is a long-term inpatient program; preliminary data suggest that it may reduce the rate of recidivism after discharge[24].

Aggression in outpatients

Community setting is more complex than the structured environment of an inpatient ward. There are two factors that substantially elevate the risk of aggressive behavior of discharged psychiatric patients in the community: substance use and non-adherence to antipsychotic treatment. The combination of medication non-adherence and substance abuse predicts serious aggressive acts. Patients with both alcohol and drug abuse appear to be at a particular risk for aggressive behavior[25]. The evidence for the elevated risk in major mental disorders comorbid with alcohol abuse is overwhelming[26-28]. It has even been reported that the discharged patients with major mental disorders are not at an elevated risk for aggressive behavior unless they use alcohol or drugs[29]. The report has been criticized on methodological grounds[30], and birth cohort studies have firmly established that the risk for aggressive behavior in schizophrenia is elevated even without comorbid substance use disorders[31,32]. Nevertheless, it is very clear that reducing aggression risk among persons with major mental disorders requires an integration of mental health and substance abuse treatment as well as a systematic approach to improving adherence to antipsychotic treatment.

BIOLOGICAL TREATMENT OF PERSISTENT AGGRESSION

Ideally, one would like to have tests that would identify the cause or causes of aggressive behavior in each mentally ill individual, and then tailor the treatment to the specific case. One of the potential avenues towards that ultimate goal was outlined above[19]. However, such tests are not yet available and the treatment of persistent aggression is therefore difficult to individualize. In general, medications should be targeted to the underlying diagnosis. However, persistently aggressive patients tend to have multiple psychiatric disorders; in fact, the risk of aggressive behavior increases with the number of psychiatric diagnoses for which patients meet diagnostic criteria[33]. Furthermore, persistent aggression appears to be associated with treatment resistance in schizophrenia[34]. Accordingly, monotherapy fails to relieve aggressive behavior in many cases.

Thus, in summary, the treatment of persistent aggressive behavior in patients with major mental disorders presents a difficult challenge. It is difficult to predict its efficacy in individual patients, Nevertheless, the pharmacological treatments outlined below may be useful for a variety of diagnoses, including schizophrenia, bipolar disorder, and dementia.

Atypical antipsychotics

In addition to their use in patients with schizophrenia, schizoaffective disorder, and bipolar disorder, atypical antipsychotics have also been used to manage aggression and behavioral dyscontrol among patients with dementia and among adolescents.

Clozapine

Early uncontrolled studies indicated reduction in the number of violent incidents and/or a decrease in the use of seclusion or restraint among inpatients after they began clozapine treatment; these studies are reviewed elsewhere[1-3]. Additional uncontrolled studies indicating antiaggressive efficacy of clozapine in adults, adolescents and children have been published[35,36]. The reductions of hostility[37] and aggression[38] after clozapine treatment were selective in the sense that they were (statistically) independent of the general antipsychotic effects of clozapine.

These uncontrolled studies suggested efficacy of clozapine in the management of persistent aggressive behavior. A randomized double-blind clinical trial[39] supported this conclusion. In that trial, hostility was assessed using the PANSS scale (see above), and overt physical aggression was recorded using the Overt Aggression Scale[40,41]. This 14-week study compared the specific anti-hostility effects and antiaggressive effects of clozapine, olanzapine, risperidone, and haloperidol in 157 inpatients with schizophrenia or schizoaffective disorder. Clozapine had significantly greater anti-hostility effect than haloperidol or risperidone[42]. This effect on hostility was specific: it was independent of antipsychotic effect on delusional thinking, formal thought disorder, or hallucinations, and independent of sedation. Additional analyses of data from this study using the Overt Aggression Scale[43] demonstrated that patients exhibiting overt aggression showed less overall improvement of psychopathology, but that antipsychotic efficacy of clozapine was greatest in aggressive patients, whereas the opposite was true for risperidone and olanzapine. A key finding was that a therapeutic dose of clozapine was necessary to achieve in order to achieve superior effects on the likelihood and the severity of overt aggression. Since it can take many days to titrate clozapine to a therapeutic dose, it is important not to terminate a clozapine trial prematurely[43].

New data from a 12-week randomized clinical trial comparing clozapine, olanzapine, and haloperidol among 101 pa-

tients with schizophrenia specifically selected because of prior aggressive behavior demonstrated the superiority of clozapine over both olanzapine and haloperidol in reducing the frequency and severity of both physical and verbal assaults[44]. This anti-aggressive effect was independent of any effect on psychotic symptoms.

However, there is at least one large study that does not support clozapine's superiority as antiaggressive agent. The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study compares the effectiveness of antipsychotic treatments in practice setting using a non-interventional, observational study design. The presence or absence of verbal or physical hostility/aggression was assessed retrospectively for the period of 6 months before enrollment, and prospectively in the period of 6 months after enrollment. At baseline, patients in five monotherapy treatment groups (combined n = 3135) were prescribed one of the treatments: clozapine, olanzapine, quetiapine, risperidone, or haloperidol. Hostile/aggressive behavior was reduced after enrollment. As monotherapy, both olanzapine and risperidone were superior to haloperidol and clozapine in reducing aggression. The relative lack of effectiveness of clozapine is surprising; it may be specific to this study population[45].

Risperidone

In a post-hoc analysis of a randomized, double-blind trial using schizophrenia patients, risperidone demonstrated a selective effect on hostility that was superior to haloperidol[46]. Several uncontrolled studies of antiaggressive effects of risperidone in schizophrenia showed mixed results. The antiaggressive effectiveness of risperidone in the IC-SOHO study was mentioned above[45]

Risperidone in low doses shows promise in the control of aggressive behavior in dementia[47-49] and in boys with oppositional disorder or conduct disorder[50].

Olanzapine

As mentioned above, olanzapine showed a superior antiaggressive effectiveness in comparison with clozapine and haloperidol in the IC-SOHO study[45]. In that study, olanzapine and risperidone appeared to have very similar antiaggressive effects.

However, in another observational study[51], olanzapine showed antiaggressive effects that risperidone lacked. This study prospectively examined the effectiveness of olanzapine versus risperidone in reducing aggressive behavior in 124 patients with schizophrenia in the community. The patients were followed for 3 years in with interviews at 6-month intervals to assess aggressive behavior. The study found that remaining on olanzapine for 1 year or more significantly lowered aggression, but no significant antiaggressive effect was found for subjects remaining on risperidone for 1 year or more. Thus, long-term treatment with olanzapine confers some advantage over risperidone in reducing aggression. Treatment compliance mediated the association between olanzapine treatment and reduced aggressive behavior[51].

Quetiapine

Quetiapine was superior to placebo in the measures of aggression and hostility as determined by a post-hoc analysis of a phase III randomized clinical registration trial[52]. This is supported by a case report describing a dramatic response to quetiapine monotherapy in a persistently aggressive patient with schizoaffective disorder who had failed to respond to numerous other medications[53]. It is possible that doses above the recommended range may have superior antiaggressive properties. A clinical trial testing the efficacy and safety of quetiapine 600 mg/day vs 1200 mg/day is in progress at the Nathan Kline Institute.

Aripiprazole

Several double-blind, randomized studies comparing the efficacy of aripiprazole with placebo and with haloperidol used PANSS ratings, and the PANSS «hostility« item was available for post-hoc analyses. The analyses showed significant superiority of aripiprazole in comparison with placebo, and no significant differences between aripiprazole and haloperidol[54]. Since aripiprazole showed a better safety profile than haloperidol in the same studies[55], aripiprazole appears to be the preferred medication to control hostility.

Anticonvulsants and lithium

Mood stabilizers such as lithium and anticonvulsants are used in almost 50 % inpatients (including those with schizophrenia) in New York State psychiatric facilities[56] and in approximately 30 % inpatients in a British psychiatric hospital[57]. Impulsive aggressive behavior is a principal intended target of these adjunctive treatments[1,57]. Expert consensus guidelines suggesting the use of adjunctive mood stabilizers in patients with schizophrenia with agitation, excitement, aggression, or violence[58], but the supporting evidence for this indication is based largely on uncontrolled studies and case reports. A recent small double-blind placebo-controlled study suggested antiaggressive effects of valproate and carbamazepine[59].

Valproate

The most commonly used mood stabilizer is valproate[56]. There are few controlled trials studying the antiaggressive

effects of adjunctive valproate. A recent experiment compared the effects of antipsychotic monotherapy (olanzapine or risperidone) with that of combination treatment with divalproex sodium among patients with schizophrenia experiencing an acute psychotic episode[60]. Inpatients with schizophrenia (n = 249) were randomly assigned to receive olanzapine plus placebo, olanzapine plus divalproex, risperidone plus placebo, or risperidone plus divalproex in a double-blind, 28-day trial. The hostility item of the PANSS was the principal outcome measure. Covariates included the PANSS items reflecting positive symptoms of schizophrenia. Combination therapy had a significantly greater antihostility effect at days 3 and 7 than monotherapy. This result was not seen beyond the first week of treatment. The effect on hostility appeared to be statistically independent of antipsychotic effect on other positive PANSS items reflecting delusional thinking, a formal thought disorder, or hallucinations. Thus, divalproex sodium may be useful as an adjunctive agent in specifically reducing hostility in the first week of treatment with risperidone or olanzapine among patients with schizophrenia experiencing an acute psychotic episode[60]. In a recent study, 52 outpatients with DSM-IV borderline personality disorder were randomly assigned to receive divalproex (n = 20) or placebo (n = 32), double-blind, for 12 weeks[61]. Trait impulsivity symptoms were determined by using the Barratt Impulsiveness Scale, and state aggression symptoms were determined by using the Overt Aggression Scale. Divalproex was superior to placebo in reducing impulsive aggression. Divalproex-treated patients responded better than placebo-treated patients among those with higher baseline trait impulsivity symptoms and state aggression symptoms[61].

Carbamazepine

The utilization rate of carbamazepine as an adjunctive treatment in schizophrenia has been decreasing, perhaps because alternatives such as valproate are easier to manage because carbamazepine induces its own metabolism. The evidence for its antipsychotic efficacy is not persuasive[62]. Nonetheless, an expert consensus statement recommended carbamazepine as a second line adjunctive treatment for the management of persistent aggressive behavior in psychotic patients[58]. A recent double-blind study indicated beneficial effects of carbamazepine in seven patients with impulsive aggression[59]. Other evidence for efficacy comes from older small trials or case reports. In these studies, plasma levels of concomitant antipsychotics were generally not assayed, leaving open the possibility for undetected pharmacokinetic interactions.

Lamotrigine

A report of a double-blind placebo-controlled crossover trial of adjunctive lamotrigine in treatment refractory patients who failed clozapine monotherapy (n = 34) demonstrated improvement in the positive symptoms of schizophrenia[63]. This report raised hopes for potential antiaggressive effects of lamotrigine.

However, a recently completed large multicenter trial using schizophrenia patients has not replicated Tiihonen´s results (report in preparation). A small randomized placebo-controlled double-blind clinical trial has shown that lamotrigine reduced anger in women with borderline personality disorder[64].

Lithium

Lithium may reduce manic symptoms, including aggressive behavior, in bipolar or schizoaffective disorder. An expert consensus statement recommends lithium as a second line adjunctive treatment of persistent aggressive behavior in psychotic patients[58]. A recent double-blind study demonstrated antiaggressive effects of lithium in manic adolescents[65]. There is very limited evidence supporting the antiaggressive efficacy of lithium in patients who are not manic.

OTHER TREATMENTS

Benzodiazepines

The experts participating in the Consensus Survey[68] disagreed with each other regarding the long-term use of benzodiazepines as adjunctive antiaggressive treatment in psychotic patients. Such long-term use can elicit physiological tolerance. Abrupt discontinuation of a benzodiazepine (for example, by missing scheduled doses) may elicit withdrawal symptoms that can lead to aggressive behavior. There is little evidence supporting the safety and efficacy of long-term benzodiazepine use to control aggression. On the contrary, a double-blind placebo-controlled trial of adjunctive clonazepam in 13 schizophrenic patients receiving antipsychotics showed no additional therapeutic benefit and four patients developed aggressive behavior during the course of clonazepam treatment[66].

Antidepressants

Central serotoninergic dysfunction is involved in the pathogenesis of impulsive aggression. Although the link between such dysfunction and aggressive behavior has not been confirmed in all populations studied, the evidence for this is quite persuasive[1]. Selective serotonin re-uptake inhibitors (SSRI) are therefore candidate treatments of impulsive aggressive behavior. Citalopram, an SSRI, was tested for antiaggressive effects in 15 chronically violent hospitalized schizophrenic patients[67]. This was a double-blind, placebo-controlled, crossover study that lasted 48 weeks (24 weeks

on active citalopram (20-60 mg/day), 24 weeks on citalopram placebo). Citalopram was added to the concurrent antipsychotic treatment. The frequency of aggressive incidents decreased during the active citalopram treatment. This result is consistent with the reduction of aggressive behavior in an open-label study of citalopram in patients diagnosed with a DSM-IV cluster B personality disorder or intermittent explosive disorder[68]. Several older studies of fluoxetine in patients with schizophrenia or personality disorders suggested antiaggressive effects. Thus, antidepressants may have a role in decreasing aggressive behavior in patients with varying diagnoses.

Reports in the lay press have indicated that anti-depressants may play a role in *causing* aggression. Fluoxetine has been blamed for inducing homicidal behavior and has been used as a legal defense and as a plaintiff's argument in seeking damages in a variety of court cases. The existing scientific literature does not support this link. However, recent evidence appears to support a link between SSRIs and suicidality in children and adolescents. In the United States, the Food and Drug Administration has issued a strong warning about this adverse effect; a similar warning was issued by Canadian authorities[69]. The use of several antidepressants in children and adolescents was banned in the United Kingdom.

Beta-adrenergic blockers

General overreactivity to the environment, specifically irritability, is mediated through noradrenergic mechanisms. Beta-adrenergic blocking agents are therefore candidate treatments for irritable aggression. Propranolol and nadolol are the most extensively studied beta-adrenergic blockers in the context of managing persistent irritable and aggressive behavior, particularly in brain injured patients. This research started in the 1970s[70], flourished through the 1980s[71], and some limited work continued in the 1990s[72]. Side effects such as hypotension and bradycardia, as well as the wide availability of atypical antipsychotics, have limited clinical use of beta blockers in the treatment of aggression.

Hormonal treatment

Investigation in animals and humans has revealed an association between androgens and aggression[73-79]. In our species, androgens modulate sexual and aggressive behavior. They do not cause direct behavioral reactions, but increase the probablility of response to specific stimuli[77]. Hormonal influence on aggression appears to be stronger in lower animal evolutive levels. In primates and humans, sociocultural factors significatily interact with biological factors to regulate behavior[1,80,81].

Androgenic modulation of human aggression appears to be strongly related to genotype expression[82]. Sensitivity to aggressivogenic properties of testosterone and its metabolites is variable in different cerebral regions and between individuals, being determined by the density and affinity of androgenic receptors in the cytoplasma of each neural population, which in his turn depends on the genomic decoding program for synthesizing such receptorial proteins. Thus, environmental modulation of aggression could be explained by postnatal genomic changes in response to life events and previous confrontation experiences[73,83-85].

Several studies have found in humans a significant relationship between elevated plasma, saliva and cerebrospinal fluid levels of testosterone and aggression, both in males[76,86-96] and females[97,98]. Also in children, a positive correlation between high salivary levels of testosterone and aggression during free play social behavior has been found[99].

Other investigations have examined the effect of exogenous androgens on aggression. Reinish[100] found in a cohort of children exposed to synthetic androgens during the prenatal period that after birth both females and males showed a clear predisposition to violence. Van Goozen et al.[101] studied the effect of cross-sex hormones on psychological parameters in a group of transsexuals. The administration of androgens to females was clearly associated with an increase in aggression proneness and a decrease in verbal fluency tasks, while deprivation of androgens in males exerted the opposite effect. Different researchers have confirmed a positive association between the administration of high doses of testosterone[102,103] OR anabolizers[104-107] and predisposition to extreme violence, including homicide.

Some emerging hypoyhesis propose the so-called *testosterone-serotonin link*[108,109]. According to these authors, androgenic neuromodulators tend to inhibit the serotonergic control over aggression in the prefrontal brain.

Antiandrogens have been mainly used in psychiatry to control hypersexual or paraphilic aggression[110,-116]. However, few studies have been published testing these compounds in non-sexual aggression or in specific psychiatric disorders, like OCD[117,118], bulimia nervosa[119] or Tourette´s syndrome[120].

Hormonal agents with antiandrogenic action modify the cytoplasmatic androgenic receptors affinity and block their regulatory effect on the cellular genomic expression[121]. They may also reduce the synthesis and liberation of gonadotrophins (FSH, LH) and decrease the production of testosterone and 5-α-dihydrotestosterone[122].

In 1978, Itil sustained that existing evidence for an antiaggressive effect of cyproterone acetate (CPA) in sexual violence could be extended to the general treatment of pathological aggression[123]. A number of investigations support this hypothesis, and show promise in the control of agressi-

ve behavior with antiandrogens[124-129]. Case reports on the specific antiaggressive action on cyproterone in mental retardation and psychosis have been published by Thibaut et al, using doses of 200-300 mg per day[74,130].

Orengo et al.[131] found that physical aggression in elderly men with dementia showed a strong positive correlation with elevated free testosterone in plasma, while estrogen levels showed significant negative correlations with measures of aggression. According to their findings, the authors recommend the use of antiandrogens (CPA, leuprolide acetate) in these patients, highlighting their superior tolerance in comparison to antipsychotics, that should be reserved to control aggression secondary to paranoid symptoms. Other studies have confirmed decreased aggression in patients with dementia under treatment with antiandrogens[132,133] or estrogens[134-137].

Along 1993-98, our group conducted a pilot, randomized, triple-blind, head-to-head, parallel-group clinical trial, to examine the effectiveness and safety of cyproterone against haloperidol in the treatment of aggression associated with Alzheimer's dementia[5]. Cyproterone proved to be significantly more effective and better tolerated than haloperidol as a specific antiaggressive treatment in this population (report in preparation).

The use of hormonal agents to control aggression is limited by their potential side effects. Estrogenic compounds produce feminization in males, and may cause liver abnormalities and increased risk of endometrium carcinoma with sustained administration. Several case reports suggest hepatotoxicity of cyproterone acetate[138-140] and liver genotoxicity[141,142], especially when administered in high doses or combined with estrogens[143]. Nonetheless, the association has not been conclusive. Systematic reviews of the clinical experience with CPA have not found significant evidence of liver damage or mutagenic effect[113,144-148]. Luteinizing hormone-releasing hormone (LHRH) agonists, like leuprolide, may produce hot flushes secondary to acute elevations in plasma testosterone at the beginning of treatment.

Electroconvulsive therapy (ECT)

Although ECT is used largely as a treatment for mood disorders, adjunctive ECT may be helpful in patients with persistent aggressive behavior. An open trial of ECT in combination with risperidone in males with schizophrenia and aggression resulted in a reduction in aggressive behavior for nine of the ten patients[149]. The improvement was sustained for at least 6 months.

CHALLENGES FOR FUTURE RESEARCH

It is clear and generally acknowledged that aggressive behavior is heterogeneous in its genesis. The heterogeneity is rarely studied in the context of antiaggressive treatment. In typical studies, the aggressive incidents are considered as a unitary phenomenon, and the treatment efficacy analyses assume that there are no subgroups of incidents or of disorders that could differ in their response to treatment. We made an initial effort to classify incidents[19], but so far we have not been able to use this classification in the context of a treatment trial. This is one of the challenges for future research.

Pharmacogenetics has the potential for developing individualized rational treatments of aggression. Polymorphism of the catechol O-methyltransferase (COMT) gene (specifically, the MET allele) appears to be associated with aggression in various psychiatric populations[150,153], and similar evidence is emerging for the serotonin transporter gene[153] and monoamine oxidase (MAO) gene[154].

The application of these developing pharmacogenetic findings to future research in the treatment of aggression is the next challenge to the field. Looking back at the original data on propranolol and aggression published in the 1980s, one is struck by the type of variation of the treatment response: some patients responded very well, but others showed no effect at all. Is it possible that this type of variability was due, for example, to the COMT polymorphism? Could it be that the responders were those whose COMT enzymatic activity was low (due to the presence of a MET allele that confers low activity), and who therefore benefited most from the beta-adrenergic block? Similar questions can be asked by future experiments. Some of these issues were discussed in more detail elsewhere[155,156].

Similar to other areas of psychiatry, the future lies in tailoring antiaggressive treatments to fit individual patients' genetic equipment, disease state, and personality. We hope that better understanding of neurobiological and psychological mechanisms regulating aggressive behavior in individuals will lead to the replacement of the currently employed trial-and-error treatment paradigm by a more effective, individual data-driven approach.

Future research should also confirm specific antiaggressive effect of antiandrogens, and open the road to the synthesis of new non-feminizing compounds with improved tolerance.

REFERENCES

1. Volavka J. Neurobiology of Violence, 2.nd ed. Washington: American Psychiatric Publishing, Inc., 2002.
2. Citrome L, Nolan KA, Volavka J. Science-based treatment of aggression and agitation in the science, treatment and prevention of antisocial behaviors: evidence-based practice. In: Fishbein D, Kingston NJ, editores. Civic Research Institute, Inc., 2004.

3. Citrome L, Volavka J. Treatment of violent behavior in psychiatry. In: Tasman A, Kay J, Lieberman JA, editores. Chichester: John Wiley & Sons, Ltd, 2003.
4. Volavka J. The neurobiology of violence: an update. J Neuropsychiatry Clin Neurosci 1999;11:307-14.
5. Huertas D, López-Ibor Aliño JJ, Crespo Hervás MD. Neurobiología de la agresividad humana. Barcelona: Ars Medica, 2005.
6. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.
7. Miceli JJ, Wilner KD, Swan SK, Tensfeldt TG. Pharmacokinetics, safety and tolerability of intramuscular ziprasidone in healthy volunteers. J Clin Pharmacol 2005;45:620-30.
8. Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl) 2005;178:514-23.
9. Preval H, Klotz SG, Southard R, Francis A. Rapid-acting IM ziprasidone in a psychiatric emergency service: a naturalistic study. Gen Hosp Psychiatry 2005;27:140-4.
10. Levy WO, Robichaux-Keene NR, Nunez C. No significant QTc interval changes with high-dose ziprasidone: a case series. J Psychiatr Pract 2004;10:227-32.
11. Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry 2001;158:1149-51.
12. Wright P, Meehan K, Birkett M, Lindborg SR, Taylor CC, Morris P, et al. A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. Clin Ther 2003;25:1420-8.
13. Wright P, Lindborg SR, Birkett M, Meehan K, Jones B, Alaka K, et al. Intramuscular olanzapine and intramuscular haloperidol in acute schizophrenia: antipsychotic efficacy and extrapyramidal safety during the first 24 hours of treatment. Can J Psychiatry 2003;48:716-21.
14. Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry 2002;59:441-8.
15. Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. J Clin Psychopharmacol 2001; 21:389-97.
16. Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. Cochrane Database Syst Rev 2005;CD003729.
17. Baker RW, Kinon BJ, Maguire GA, Liu H, Hill AL. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. J Clin Psychopharmacol 2003;23:342-8.
18. Convit A, Isay D, Otis D, Volavka J. Characteristics of repeatedly assaultive psychiatric inpatients. Hosp Community Psychiatry 1990;41:1112-5.
19. Nolan KA, Czobor P, Roy BB, Platt MM, Shope CB, Citrome LL, Volavka J. Characteristics of assaultive behavior among psychiatric inpatients. Psychiatr Serv 2003;54:1012-6.
20. Hare RD. Psychopathy and antisocial personality disorder: a case of diagnostic confusion. Psychiatric Times 1996; p. 39-40.
21. Hart SD, Hare RD, Forth AE. Psychopathy as a risk marker for violence: development and validation of a screening version of the revised psychopathy checklist in violence and mental disorder. In: Monahan J, Steadman HJ, editores. Developments in risk assessment. Chicago: The University of Chicago Press, 1994.
22. Nolan KA, Volavka J, Mohr P, Czobor P. Psychopathy and violent behavior among patients with schizophrenia or schizoaffective disorder. Psychiatric Services 1999;50:787-92.
23. Yates K, Kunz M, Czobor P, Rabinowitz S, Lindenmayer JP, Volavka J. A cognitive, behaviorally based program for patients with persistent mental illness and a history of aggression, crime or both: structure and correlates of completers of the program. J Am Acad Psychiatry Law 2005;33:214-22.
24. Kunz M, Yates KF, Czobor P, Rabinowitz S, Lindenmayer JP, Volavka J. Course of patients with histories of aggression and crime after discharge from a cognitive-behavioral program. Psychiatr Serv 2004;55:654-9.
25. Swartz MS, Swanson JW, Hiday VA, Borum R, Wagner R, Burns BJ. Taking the wrong drugs: the role of substance abuse and medication noncompliance in violence among severely mentally ill individuals. Soc Psychiatry Psychiatr Epidemiol 1998;33 (Suppl. 1):S75-80.
26. Lindqvist P, Allebeck P. Schizophrenia and assaultive behaviour: the role of alcohol and drug abuse. Acta Psychiatr Scand 1990;82:191-5.
27. Swanson JW. Mental disorder, substance abuse, and community violence: an epidemiological approach in violence and mental disorder. In: Monahan J, Steadman HJ, editores. Developments in risk assessment. Chicago: The University of Chicago Press, 1994.
28. Eronen M, Angermeyer MC, Schulze B. The psychiatric epidemiology of violent behaviour. Soc Psychiatry Psychiatr Epidemiol 1998;33(Suppl. 1):S13-23.
29. Steadman HJ, Mulvey EP, Monahan J, Robbins PC, Appelbaum PS, Grisso T, et al. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. Arch Gen Psychiatry 1998;55:393-401.
30. Czobor P, Volavka J. Violence in mentally ill: questions remain (Letter). Arch Gen Psychiatry 1999;56:193.
31. Arseneault L, Moffitt TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort: results from the Dunedin Sudy. Arch Gen Psychiatry 2000;57:979-86.
32. Brennan PA, Mednick SA, Hodgins S. Major mental disorders and criminal violence in a Danish birth cohort. Arch Gen Psychiatry 2000;57:494-500.
33. Swanson JW, Holzer CE, Ganju VK, Jono RT. Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area surveys. Hosp Community Psychiatry 1990;41:761-70.
34. Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. Schizophr Bull 1997;23:663-74.

35. Kraus JE, Sheitman BB. Clozapine reduces violent behavior in heterogeneous diagnostic groups. J Neuropsychiatry Clin Neurosci 2005;17:36-44.
36. Kranzler H, Roofeh D, Gerbino-Rosen G, Dombrowski C, McMeniman M, DeThomas C, et al. Clozapine: its impact on aggressive behavior among children and adolescents with schizophrenia. J Am Acad.Child Adolesc.Psychiatry 2005; 44:55-63.
37. Volavka J, Zito JM, Vitrai J, Czobor P. Clozapine effects on hostility and aggression in schizophrenia. J Clin Psychopharmacol 1993;13:287-9.
38. Buckley P, Bartell J, Donenwirth K, Lee S, Torigoe F, Schulz SC. Violence and schizophrenia: clozapine as a specific antiaggressive agent. Bull Am Acad Psychiatry Law 1995;23:607-11.
39. Volavka J, Czobor P, Sheitman B, Lindenmayer J-P, Citrome L, McEvoy J, et al. Clozapine, olanzapine, risperidone, and haloperidol in treatment-resistant patients with schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159:255-62.
40. Silver JM, Yudofsky SC. The overt aggression scale: overview and guiding principles. J Neuropsychiatry Clin Neurosci 1991;3:S22-9.
41. Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The overt aggression scale for the objective rating of verbal and physical aggression. Am J Psychiatry 1986;143:35-9.
42. Citrome L, Volavka J, Czobor P, Sheitman B, Lindenmayer J-P, McEvoy J, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility in treatment-resistant patients with schizophrenia and schizoaffective disorder. Psychiatric Serv 2001;52:1510-4.
43. Volavka J, Czobor P, Nolan K, Sheitman B, Lindenmayer JP, Citrome L, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacol 2004; 24:225-8.
44. Krakowski MI, Czobor P, Citrome LL, Tremeau F, Roy BB, Kline L. Clozapine, olanzapine, and haloperidol treatment of violent patients with schizophrenia. Proceedings of the 158th Annual Meeting of the American Psychiatric Association, Atlanta, Georgia, May 21-26, 2005, 89. 2005.
45. Bitter I, Czobor P, Dossenbach M, Volavka J. Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO). Eur Psychiatry 2005;20:403-8.
46. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15:243-9.
47. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134-43.
48. De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 2005;107-497-508.
49. Arriola E, Ignacio DJ, Antonio BJ, Gallego R. Open-label, observational study of the effects of risperidone on the behavioral and psychological symptoms of dementia and caregiver stress in the community setting. Am J Geriatr Pharmacother 2005;3:8-16.
50. Leblanc JC, Binder CE, Armenteros JL, Aman MG, Wang JS, Hew H, et al. Risperidone reduces aggression in boys with a disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled randomized trials. Int Clin Psychopharmacol 2005;20:275-83.
51. Swanson JW, Swartz MS, Elbogen EB, Van Dorn RA. Reducing violence risk in persons with schizophrenia: olanzapine versus risperidone. J Clin Psychiatry 2004;65:1666-73.
52. Chengappa KN, Goldstein JM, Greenwood M, John V, Levine J. A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. Clin Ther 2003;25:530-41.
53. Citrome L, Krakowski M, Greenberg WM, Andrade E, Volavka J. Antiaggressive effect of quetiapine in a patient with schizoaffective disorder. J Clin Psychiatry 2001;62:901.
54. Volavka J, Czobor P, Citrome L, McQuade RD, Carson WH, Kostic D, et al. Efficacy of aripiprazole against hostility in schizophrenia and schizoaffective disorder. J Clin Psychiatry 2006.
55. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003;61:123-36.
56. Citrome L, Jaffe A, Levine J. Datapoints-mood stabilizers: utilization trends in patients diagnosed with schizophrenia 1994-2001. Psychiatric Serv 2002;53:1212.
57. Haw C, Stubbs J. A survey of the off-label use of mood stabilizers in a large psychiatric hospital. J Psychopharmacol 2005; 19:402-7.
58. Kane JM, Leucht S, Carpenter D, Docherty JP. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. J Clin Psychiatry 2003;64(Suppl. 12):1-100.
59. Stanford MS, Helfritz LE, Conklin SM, Villemarette-Pittman NR, Greve KW, Adams D, et al. A comparison of anticonvulsants in the treatment of impulsive aggression. Exp Clin Psychopharmacol 2005;13:72-7.
60. Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. Psychiatr Serv 2004;55:290-4.
61. Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. Am J Psychiatry 2005;162:621-4.
62. Leucht S, McGrath J, White P, Kissling W. Carbamazepine augmentation for schizophrenia: how good is the evidence? J Clin Psychiatry 2002;63:218-24.
63. Tiihonen J, Hallikainen T, Ryynanen OP, Repo-Tiihonen E, Kotilainen I, Eronen M, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. Biol Psychiatry 2003; 54:1241-8.
64. Tritt K, Nickel C, Lahmann C, Leiberich PK, Rother WK, Loew TH, Nickel MK. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. J Psychopharmacol 2005;19:287-91.
65. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM. Lithium treatment of acute mania in adolescents: a placebo-

controlled discontinuation study. J Am Acad Child Adolesc Psychiatry 2004; 43:984-93.
66. Karson CN, Weinberger DR, Bigelow L, Wyatt RJ. Clonazepam treatment of chronic schizophrenia: negative results in a double-blind, placebo-controlled trial. Am J Psychiatry 1982; 139:1627-8.
67. Vartiainen H, Tiihonen J, Putkonen A, Koponen H, Virkkunen M, Hakola P, et al. Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. Acta Psychiatr Scand 1995;91:348-51.
68. Reist C, Nakamura K, Sagart E, Sokolski KN, Fujimoto KA. Impulsive aggressive behavior: open-label treatment with citalopram. J Clin Psychiatry 2003;64:81-5.
69. Kondro W. UK bans, Health Canada warns about antidepressants. CMAJ 2004;171:23.
70. Elliott FA. Propranolol for the control of belligerent behavior following acute brain damage. Ann Neurol 1977;1:489-91.
71. Yudofsky S, Williams D, Gorman J. Propranolol in the treatment of rage and violent behavior in patients with chronic brain syndrome. Am J Psychiatry 1981;138:218-20.
72. Silver JM, Yudofsky SC, Slater JA, Gold RK, Stryer BLK, Williams DT, et al. Propranolol treatment of chronically hospitalized aggressive patients. J Neuropsychiatry Clin Neurosci 1999; 11:328-35.
73. Mazur A, Lamb TH. Testosterone, status and mood in human males. Horm Behav 1980;14:236-46.
74. Thibaut F, Colonna L. Cyproterone acetate in the treatment of aggression. Am J Psychiatry 1992;149:3.
75. Rubinow DR, Schmidt PJ. Androgens, brain and behavior. Am J Psychiatry 1996;153:974-83.
76. Rasanen P, Hakko H, Visuri S, Paanila J, Kapanen P, Suomela T, et al. Serum testosterone levels, mental disorders and criminal behavior. Acta Psychiatr Scand 1999;99:348-52.
77. Christiansen K. Behavioural effects of androgen in men and women. J Endocrinol 2001;170:39-48.
78. Orengo CA, Kunik ME, Molinari V, Wristers K, Yudofsky SC. Do testosterone levels relate to aggression in elderly men with dementia? J Neuropsychiatry Clin Neurosci 2002;14:161-6.
79. Swann AC. Neuroreceptor mechanisms of aggression and its treatment. J Clin Psychiatry 2003;64(Suppl. 4):26-35.
80. Bandura A. Aggression: a social learning analysis. New Jersey: Prentice-Hall International, 1973.
81. Montagu A. La naturaleza de la agresividad humana. Madrid: Alianza Universidad, 1978.
82. Simon NG, McKenna SE, Lu SF, Cologer-Clifford A. Development and expression of hormonal systems regulating aggression. Ann N Y Acad Sci 1996;794:8-17.
83. McCaul KD, Gladue BA, Joppa M. Winning, losing, mood and testosterone. Horm Behav 1992;26:486-504.
84. Mazur A, Booth A. Testosterone and dominance in men. Behav Brain Sci 1998;21:353-63.
85. Zitzmann M, Nieschlag E. Testosterone levels in healthy men and the relation to behavioural and physical characteristics: facts and constructs. Eur J Endocrinol 2001;144:183-97.
86. Persky H, Smith KD, Basu GK. Relation of psychologic measures of aggression and hostility to testosterone production in man. Psychosom Med 1971;33:265-77.
87. Kreuz LE, Rose RM. Assessment of aggressive behavior and plasma testosterone in a young criminal population. Psychosom Med 1972;34:321-31.
88. Ehrenkranz J, Bliss E, Sheard MH. Plasma testosterone: correlation with aggressive behavior and social dominance in man. Psycosom Med 1974;36:469-75.
89. Olweus D, Mattsson A, Schalling D, Low H. Circulating testosterone levels and aggression in adolescent males: a causal analysis. Psychosom Med 1988;50:261-72.
90. Dabbs JM Jr, Jurkovic GJ, Frady RL. Salivary testosterone and cortisol among late adolescent male offenders. J Abnorm Child Psychol 1991;19:469-78.
91. Christiansen K, Winkler EM. Hormonal, anthropometrical and behavioral correlates of physical aggression in pKung San men of Namibia. Aggress Behav 1992;18:271-80.
92. Gerra G, Zaimovic A, Giucastro G, Folli F, Maestri D, Tessoni A, et al. Neurotransmitter-hormonal responses to psychological stress in peripubertal subjects: relationship to aggressive behavior. Life Sci 1998;62:617-25.
93. Salvador A, Simon V, Suay F, Llorens L. Testosterone and cortisol responses to competitive fighting in human males: a pilot study. Aggressive Behavior 1987;13:9-13.
94. George DT, Umhau JC, Phillips MJ, Emmela D, Ragan PW, Shoaf SE, et al. Serotonin, testosterone and alcohol in the etiology of domestic violence. Psychiatry Res 2001;104:27-37.
95. Lindberg N, Tani P, Appelberg B, Naukkarinen H, Rimon R, Porkka-Heiskanen T, et al. Human impulsive aggression: a sleep research perspective. J Psychiatr Res 2003;37:313-24.
96. Maras A, Laucht M, Lewicka S, Haack D, Malisova L, Schmidt MH. Role of androgens in externalizing behavior problems in adolescents. Z Kinder Jugendpsychiatr Psychother 2003;31:7-15.
97. Dabbs JM Jr, Hargrove MF. Age, testosterone, and behavior among female prison inmates. Psychosom Med 1997;59: 477-80.
98. Grant VJ, France JT. Dominance and testosterone in women. Biol Psychol 2001;58:41-7.
99. Sanchez-Martin JR, Fano E, Ahedo L, Cardas J, Brain PF, Azpiroz A. Relating testosterone levels and free play social behavior in male and female preschool children. Psychoneuroendocrinology 2000;25:773-83.
100. Reinish J. Prenatal exposure to synthetic progestins increases potencial for aggression in humans. Science 1981;211:1171-3.
101. Van Goozen SH, Cohen-Kettenis PT, Gooren LJG, Frijda NH, Van de Poll NE. Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology 1995;20:343-63.
102. Kouri EM, Lukas SE, Pope HG Jr, Oliva PS. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. Drug Alcohol Dependence 1995;40:73-9.
103. Pope HG, Kouri EM, Hudson JI. Effects of supraphysiolologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. Arch Gen Psychiatry 2000; 57: 133-40.
104. Pope HG Jr, Katz DL. Homicide and near-homicide by anabolic steroid users. J Clin Psychiatry 1990;51:28-31.
105. Corrigan B. Anabolic steroids and the mind. Med J Aust 1996; 165:222-6.

106. Midgley SJ, Heather N, Davies JB. Levels of aggression among a group of anabolic-androgenic steroid users. Med Sci Law 2001;41:309-14.
107. Thiblin I, Parlklo T. Anabolic androgenic steroids and violence. Acta Psychiatr Scand 2002;(Suppl 412):125-8.
108. Birger M, Swartz M, Cohen D, Alesh Y, Grishpan C, Kotelr M. Aggression: the testosterone-serotonin link. Isr Med Assoc J 2003;5:653-8.
109. Mong JA, Pfaff DW. Hormonal and genetic influences underlying arousal as it drives sex and aggression in animal and human brains. Neurobiol Aging 2003;24 (Suppl. 1):S83-8.
110. Laschet U, Laschet L, Fetzner HR, Glaesel HU, Mall G, Naab M. Results in the treatment of hyper-or abnormal sexuality of men with antiandrogens. Acta Endocrinológica 1967;119 (Suppl.):54.
111. Jeffcoate WJ, Matthews RW, Edwards CR, Field LH, Besser GM. The effect of cyproterone acetate on serum testosterone, LH, FSH and prolactin in male sexual offenders. Clin Endocrinol 1980;13:189-95.
112. Cooper AJ. Progestogens in the treatment of male sex offenders: a review. Can J Psychiatry 1986;31:73-9.
113. Neumann F, Kalmus J. Cyproterone acetate in the treatment of sexual disorders: pharmacological base and clinical experience. Exp Clin Endocrinol 1991;98:71-80.
114. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. Arch Sex Behav 2001;30:409-22.
115. Briken P, Nika E, Berner W. Treatment of paraphilia with luteinizing hormone-releasing hormone agonists. J Sex Marital Ther 2001;27:45-55.
116. Czerny JP, Briken P, Berner W. Antihormonal treatment of paraphilic patients in German forensic psychiatric clinics. Eur Psychiatry 2002;17:104-6.
117. Casas M, Álvarez E, Duro P, García-Ribera C, Udina C, Velat A, et al. Antiandrogenic treatment of obsessive-compulsive neurosis. Acta Psychiatr Scand 1986; 3:221-2.
118. Eriksson T. Antiandrogenic treatment for obsessive-compulsive disorder. Am J Psychiatry 2000;157:483.
119. Ruiz ME, Rodado J, Salorio P, Pagan G, Barcia D. Tratamiento con antiandrógenos de la bulimia nerviosa. Estudio preliminar. Ann Psiquiatría 1997;13:192-9.
120. Izmir M, Dursun SM. Cyproterone acetate treatment of Tourette's syndrome. Can J Psychiatry 1999;44:710-1.
121. Jänne OA, Bardin CW. Androgen and antiandrogen receptor binding. Ann Rev Physiol 1984;46:107-18.
122. Neri RO. Antiandrogens. Adv Sex Horm Res 1976;2:233-62.
123. Itil TM. Pharmacological treatment of syndromes of aggressivity. Quad Criminol Clin 1978;20:155-74.
124. Cooper AJ, Ismail AA, Phanjoo AL, Love DL. Antiandrogen (cyproterone acetate) therapy in deviant hypersexuality. Br J Psychiatry 1972;120:59-63.
125. Blumer D, Migeon C. Hormone and hormonal agents in the treatment of aggression. J Nerv Ment Dis 1975;160: 127-37.
126. Arnold SE. Estrogen for refractory aggression after traumatic brain injury. Am J Psychiatry 1993;150:1564-5.
127. Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behavior in traumatic brain injury. Brain Inj 1998;12:703-7.
128. Hier DB, Ahluwalie S, Melyn M, Hoganson GE Jr. Estrogens control aggressive behavior in some patients with Sanfilippo syndrome. Neurol Res 1999;21:611-2.
129. Wolf SS. Violent behavior and traumatic brain injury. Trauma 2001;43:337-26.
130. Thibaut F, Kuhn JM, Colonna L. A possible antiaggressive effect of cyproterone acetate. Br J Psychiatry 1991;159:298-9.
131. Orengo CA, Kunik ME, Ghusn H, Yudofsky SC. Correlation of testosterone with aggression in demented elderly men. J Nerv Ment Dis 1997;185:349-51.
132. Amadeo M. Antiandrogen treatment of aggressivity in men suffering from dementia. J Geriatr Psychiatry Neurol 1996;9: 142-5.
133. Flynn BL. Pharmacologic management of Alzheimer disease. Part I: hormonal and emerging investigational drug therapies. Ann Pharmacother 1999;33:178-87.
134. Kyomen HH, Nobel KW, Wei JY. The use of estrogen to decrease aggressive physical behavior in elderly men with dementia. JAGS 1991;39:1110-2.
135. Kyomen HH, Hennen J, Gottlieb GL, Wei JY. Estrogen therapy and noncognitive psychiatric signs and symptoms in elderly patients with dementia. Am J Psychiatry 2002;159:1225-7.
136. Kay P, Yurkow J, Forman L, Chopra A, Cavalieri T. Transdermal estradiol in the management of aggressive behaviors in male patients with dementia. Clin Gerontol 1995;15:54-8.
137. Shelton PS, Brooks VG. Estrogen for dementia-related aggression in elderly men. Ann Pharmacother 1999;33:808-12.
138. Hassler P, Duchene R. Hepatotoxicity of cyproterone acetate. Rev Med Interne 1992;13:245.
139. Murphy BJ, Collins BJ. Severe hepatitis and liver failure induced by cyproterone acetate. Aust N Z J Med 1996;26:724.
140. Giordano N, Nardi P, Santacroce C, Geraci S, Gennari C. Acute hepatitis induced by cyproterone acetate. Ann Pharmacother 2001;35:1053-5.
141. Ohri SK, Gaer JAR, Keane PF. Hepatocellular carcinoma and treatment with cyproterone acetate. Br J Psychiatry 1991;67: 213-21.
142. Watanabe S, Yamasaki S, Tanae A, Hibi I, Honna T. Three cases of hepatocellular carcinoma among cyproterone users. Lancet 1994;344:1567-8.
143. Rüdiger T, Beckmann J, Queiber W. Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinylestradiol. Lancet 1995;345:452-3.
144. Kaiser E, Gruner HS. Liver structure and function during long-term treatment with cyproterone acetate. Arch Gynecol 1987; 240:217-23.
145. Lewis S. Warning on cyproterone. Lancet 1995;345:247.
146. Rabe T, Feldmann K, Heinemann L, Runnebaum B. Cyproterone acetate: is it hepato or genotoxic? Drug Saf 1996;14:25-38.
147. Regidor PA, Speer K, Regidor M, Schindler EM. Long-term side-effects following cyproterone acetate containing therapy in gynecology. Zentralbl Gynakol 2000;122:268-73.
148. Kasper P. Cyproterone acetate: a genotoxic carcinogen? Pharmacol Toxicol 2001;88:223-31.
149. Hirose S, Ashby CR Jr, Mills MJ. Effectiveness of ECT combined with risperidone against aggression in schizophrenia. J ECT 2001;17:22-6.

150. Volavka J, Kennedy JL, Ni X, Czobor P, Nolan K, Sheitman B, et al. COMT158 polymorphism and hostility. Am J Med Genet 2004;127B:28-9.
151. Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T, Lachman HM. Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. Am J Med Genet 2003;120B:29-34.
152. Lachman HM, Nolan KA, Mohr P, Saito T, Volavka J. Association between catechol O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. Am J Psychiatry 1998;155:835-7.
153. Han DH, Park DB, Na C, Kee BS, Lee YS. Association of aggressive behavior in Korean male schizophrenic patients with polymorphisms in the serotonin transporter promoter and catecholamine-O-methyltransferase genes. Psychiatry Res 2004; 129:29-37.
154. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. Science 2002;297:851-4.
155. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 2004;29:1943-61.
156. Volavka J, Bilder R, Nolan K. Catecholamines and aggression: the role of COMT and MAO polymorphisms. Ann N Y Acad Sci 2004;1036:393-8.