Neurobiology and Treatment of Aggression

A Translational Approach

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Definitions

- Aggression
- Violence
- Agitation
- Hostility
- Impulsivity

- The World Health Organization defines violence as the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm,

  maldevelopment, or deprivation
- It divides violence into 3 broad categories:

  self-directed, interpersonal, and collective

Psychiatric disorders and aggression in the printed media

- 39% of all articles covering topics of psychiatric disorders focused on dangerousness and criminal activities
- A vast majority of these articles presented mentally ill individuals as perpetrators, 71.8%
- Persons with psychotic disorders were most frequently presented as perpetrators (50.0%)
- Self-directed aggression behavior was reported 5.1% articles mentioning completed suicide, (7.2%) with attempted suicide, and in 2.1% articles selfharm was addressed

- homicide was associated mostly with psychotic (5.1%) and affective disorders (3.5%),
- cases of physical assault were most frequently mentioned in articles dealing with subjects with psychotic (4.0%), and organic disorders (N = 4, 1.1%).
- schizophrenia was most frequently mentioned in the context of homicide (40% of the articles).
- suicides and suicide attempts were most frequently reported in the context of affective disorders, depression and bipolar disorder poses the highest risk for suicide
- subjects with bipolar affective disorder and substance abuse comorbidity are reported to commit more violent crimes than the general population

Aggression and Violence

in Schizophrenia

- psychopathological symptoms such as delusions or hallucinations
- comorbid substance use
- social deterioration
- neurobiological mechanisms
- cognitive deficits
- structural abnormalities

Magnetic Resonance Imaging Studies

- Structural abnormalities repeatedly have been shown in violent and aggressive schizophrenia patients
- Reduced whole-brain and hippocampus volumes
- Indications of disturbed connectivity between the orbitofrontal cortex and the amygdala,
- Impulsiveness correlated negatively with reduced orbitofrontal gray
- The propensity for repetitive violence appeared to be associated with reduced volumes of both the orbitofrontal gray matter and the hippocampus.

- Larger volumes of the right orbitofrontal cortex were associated with worse neuropsychological performance
- Schizophrenia patients with violence were found to have reduced gray matter volumes
- Significant disturbances were found in the cerebellum, which may be of relevance for input from ventrolateral prefrontal cortex and parietal regions

Positron Emission Tomography/Single-Photon Computed Tomography Studies

- Patients with a history of one act of violence showed reduced absorption of radioactively labeled glucose in the inferior, anterior, and temporal cortex of both hemispheres
- Patients with a history of multiple acts of violence showed decreased FDG absorption in the anterior inferior, and temporal cortex of the left hemisphere
- Under neuropsychological stress (Wisconsin Card Sorting test), prefrontal function was significantly reduced in the violent patients

Functional MRI

- The group of violent schizophrenia patients showed a bilateral activation deficit in the frontal cortex and precuneus when compared with the healthy controls and deficits in the area of the right inferior parietal region when compared with the nonviolent schizophrenia patients
- Frontal (bilateral) and right-sided inferior parietal activity was negatively associated with the degree of violent behavior, whereby the right parietal region showed the strongest association, so that possible disturbances in executive functions may be part of the explanation for violence in schizophrenia patients

Other parameters that may induce Violence and Aggression in Schizophrenia

- Clinical symptoms („Command hallucinations'' may lead to aggressive behavior, although the risk may be small. Positive symptoms of schizophrenia, such as delusions and hallucinations.
- ''Neurocognitive impairments''
- Acute pharmacological effects of alcohol and certain drugs
- Substance use disorders (also associated with treatment nonadherence)
- historical (past violence, juvenile detention, physical abuse, and parental arrest record and perceived threats)

- Dispositional (age, sex, and income)
- Contextual factors
  (recent divorce, unemployment, and victimization)
- Confusion, impulsiveness, or psychopathic features
- Nonadherence
- Stress

Aggression and Violence in Borderline Personality Disorder(BPD)

Impulsiveness and Impulsive aggression

- Impulsivity is a multifaceted construct that can include concepts as varied as sensation seeking, lack of planning, lack of persistence, inability to delay gratification, insensitivity to delayed consequences, alteration in the perception of time, urgency, and risk taking
- Most major theories of impulsivity include dimensions of motor impulsivity (the inability to delay or inhibit a proponent motor response) and cognitive impulsivity (impulsive decision making such as the inability to shift sets or delay gratification despite negative or less than optimal consequences)

- Behavioral measures of both motor impulsivity (e.g., the Immediate Memory Task in which you have to inhibit a prepotent motor response) as well as cognitive impulsivity (e.g., the Passive Avoidance Task in which subjects have to discriminate numbers associated with monetary reward from those associated with monetary loss) are shown to discriminate between impulsive and nonimpulsive groups

- Borderline Personality Disorder as a Prototype of Emotion Dysregulation
- Disinhibited anger, which often leads to aggressive behavior
- Model of altered prefrontal–amygdala connectivity provides a model for the primary symptom in BPD, disinhibition of emotion
- This reciprocal interaction predicts that if cortical control of the thalamoamygdala pathway is reduced, emotional responses will be dysregulated

- Response to serotonergic challenge, specifically impulsive-aggressive BPD patients demonstrate decreased metabolism in anterior cingulate
- Impulsive aggression has been shown to respond the treatment with SSRIs
- IED-BPD have hypometabolism widely across the frontal lobe compared to healthy men, healthy women and women with BPD
- An early study of amygdala volume in BPD showed that total amygdala volume tended to be reduced in female BPD subjects compared to controls showed that BPD patients had greater cerebral blood flow signal in the amygdala bilaterally during unpleasant pictures compared with neutral pictures than healthy controls

Aggression and Violence in Major Depression and Bipolar Disorder

Transforming Clinical Trials

- **Suicide risk in depression and bipolar disorder: Do impulsiveness-aggressiveness and pharmacotherapy predict suicidal intent**

- Nearly one million lives are lost each year to suicide, and between 3%–5% of adults make at least one suicide attempt at some point in their life
- More than two-thirds of suicide completers and suicide attempters have (mostly untreated) major depressive episodes at the time of the suicidal act
- Major affective disorders (MAD), that is, unipolar major depressive disorder (MDD) and bipolar disorder type I and type II (BPD-I, BPD-II) patients are highly vulnerable to suicidal behavior. It is estimated that individuals with BPD are 30 times more likely to attempt suicide than those with no psychiatric disorder

- Short-term risk factors for suicidal behavior such as suicidal ideation and recent suicide attempt, the major precursors and the most powerful predictors of attempted and completed suicide
- Impulsivity/aggression has been reported to be related to suicidal behavior in several studies

In bipolar disorder, impulsivity has components that are dependent on not only the

- “state” (manic or depressive episode)
- “trait”(continued pattern)
- impulse control disorders and bipolar disorders have some features in common, such as risk seeking, sensation seeking, and seeking pleasurable activities
- The patients were euthymic at the time the questionnaires were completed and bipolar II patients had statistically significant higher scores on the Barratt scale

- Sensation seeking and aggressiveness that should be taken into account when studying the correlation between bipolar disorders and impulsivity.
- Sensation seeking scale: There are situations linked to impulsivity, such as sensation seeking, novelty seeking, and boredom susceptibility

- Barratt scale, impulsivity is noted to increase interepisodically in bipolar disorder, independent of manic episodes
- Biological factors: there are differences between patients who are impulsive-aggressive and those who are not
- Increased impulsivity would be associated with the prodrome of maniform states
- Depressive episodes are also associated with impulsivity especially if suicidal behaviour is present

- The scale most frequently used for evaluating aggressiveness is the Buss-Durkee Hostility Inventory
- Bipolar II patients score high on the violence subscale of the Buss-Durkee Hostility Inventory in the euthymic phase
- Patients whose predominant polarity was depressive had higher global scores on the Buss-Durkee Hostility Inventory as well as on the irritability subscale and the distrust subscale

Neuroanatomy of Aggression

- Prefrontal cortex (PFC)
- Orbital frontal cortex (OFC)
- Amygdala: basolateral complex (BLC) and the dorsal amygdala nucleus of the Central Nucleus (CN)

Neurobiology

of Aggressive Behavior

A Translational Approach

A translational approach, spanning basic and clinical science, may offer a superior tool and scientific framework for examining the treatment of aggression

Serotonin and Aggression

- A link between aggression and 5-HT was hypothesized was issued by Bourgault in 1963.
- In general, low levels of 5-HT appear to be associated with aggressive behavior, although the relationship might be more complex than previously believed
- Rats injected with p-chloro-N-methylamphetamine, which depletes 5-HT, exhibited an increased fighting frequency accompanied by a whole-brain decrease in 5-HT levels
- Depressed patients who had low levels of 5-HIAA in the CSF were more likely to attempt suicide and to use violent means to do so than those who had high levels of 5-HIAA.
- It has been hypothesized that the link between aggression and low 5-HIAA is specific to impulsive behavior

- Experimental evidence suggests that modulating the serotonergic system by administering selective serotonin reuptake inhibitors such as paroxetine and fluoxetine, which increase postsynaptic availability of 5-HTby blocking reuptake, can attenuate aggression
- Atypical antipsychotics, many of which act as antagonists on 5-HT2A receptors, have antiaggressive effects. These data suggest that the 5-HT2A receptor plays a major role in the neurobiology of aggression, as confirmed by preclinical studies in animal models.
- In addition, using positron emission tomography and the selective 5-HT2A receptor antagonist radioligand [11C]MDL100907, orbitofrontal 5-HT2A receptor availability has been demonstrated to be greater in patients with current physical aggression compared with patients without current physical aggression and healthy control subjects, confirming that this receptor is implicated in impulsive aggression

Dopamine and Aggression

- First indexed article regarding this issue was published by Karczmar and Scudder in 1967.
- aggression was highly correlated with changes in hypothalamic DA levels, and D2 receptors were the DA receptor subtype mediating the behavioral changes.
- Increases in tyrosine hydroxylase and DA transporter mRNA levels have been found in ventral tegmental area of winner male mice compared with losers and controls when they experienced repeated agonistic confrontations in animal models
- At mesolimbic level, electrophysiological in vivo recordings in freely moving rats demonstrated that an increase in dopaminergic activity takes place during a highly aversive condition such as defeat stress

- A rise in DA levels was also reported in nucleus accumbens during and after a single aggressive episode and when aggression was enhanced by alcohol administration
- Cerebrospinal fluid levels of homovanillic acid, a DA metabolite,are lower in impulsively aggressive violent offenders with antisocial personality disorder than in non - impulsively aggressive offenders with paranoid or passive-aggressive personality disorder
- Dopamine antagonists, particularly typical antipsychotics such as haloperidol, have been used effectively for decades to treat aggression in psychotic patients

GABA and Aggression

- The first evidence of a relationship between the GABAergic system and aggressive behavior was reported by Brody et al. in 1969, several years after the first studies on aggression

- The role of GABA receptors in aggression may appear counterintuitive and paradoxical. Indeed, in clinical practice, benzodiazepines, which are positive allosteric modulators of GABA-A receptors, are clinically used to ‘‘calm’’ people with impulsivity and violent behavior, but in other cases, they can also exert proaggressive effects

- In acute and emergency situations, because of their antianxiety and soporific-hypnotic properties, benzodiazepines can be used as antiaggressive agents

- The sedative and antiaggressive properties of benzodiazepine seem to be linked to their agonistic effect on the GABA-A/Alpha1 subunit. Benzodiazepines alter aggressive behavior in a biphasic manner, with low doses increasing attacks and threats and high doses decreasing these behaviors

- Pharmacotherapies using anticonvulsants, which indirectly activate GABAergic transmission through GABA synthetic enzymes, are commonly used to treat aggressive patients. Examples include valproate, phenytoin, and carbamazepine These drugs may attenuate impulsive aggressive acts specifically.
- In one study, for example, phenytoin significantly reduced the number and severity of aggressive acts in a group of impulsively aggressive prison inmates, but not in a group of non-impulsively aggressive inmates
- In male mice that GABA-B receptors modulate serotonergic neural activity in the dorsal raphe nucleus and, in particular, that the presynaptic GABA-B receptors on non-5-HT neurons are responsible for the escalation of aggressive behavior.

Glutamate and Aggression

- Of the various glutamate receptors, NMDA receptors appear to be the most promising targets for pharmacological intervention in treating aggression, although emerging evidence suggests that other receptors, including both ionotropic and metabotropic receptors, may play a role in aggression.

- It has been reported that several NMDA channel blockers and antagonists (PCP, MK-801, memantine, DCPPene) inhibit displays of aggression, but only at doses that also produce ataxia, suggesting that NMDA channel blockade does not selectively affect aggression

- GPI-5232, an inhibitor of the enzyme N-acetylated-alpha-linked acidic dipeptidase, which is responsible for converting N-acetylaspartylglutamate to N-acetylaspartate and glutamate, dose-dependently lowers aggressiveness in highly aggressive, individually housed mice.119 However, these results are not specific to NMDA receptors, and there is also evidence that other glutamate receptors are involved in aggression. For example, JNJ16259685, a selective antagonist of mGlu1 receptors, extinguishes or attenuates aggression at several doses

- Three 6-month randomized studies reported that treatment with memantine, a low-potency noncompetitive NMDA antagonist, resulted in significantly more participants experiencing improvement in the agitation/aggression symptom cluster than treatment with placebo

- Recently, it has also been demonstrated that antiaggressive drugs such as valproate and topiramate act on NMDA and AMPA receptors

Norepinephrine and Aggression

- Noradrenergic system may play a ‘‘permissive’’ role in aggressive behavior, helping to determine whether an individual elects to fight or flee in response to a challenge
- In one experiment, highly aggressive male mice were intraventricularly treated with 6-hydroxy-DA to destroy noradrenergic terminals in the brain, following which there was a significant inverse correlation between NE depletion and fighting.123 Similarly, rats given an intraventricular injection of 6-hydroxydopa, which reduces brain NE, but not DA, are more aggressive than controls
- Pharmacological interventions targeting the noradrenergic system have also been shown to modify aggressive behavior. For example, maprotiline, an NE reuptake inhibitor, stimulates aggression during dyadic social interactions in male mice

- The effects of noradrenergic manipulations on aggression

may be partly due to actions on alpha-2-receptors. For example, desipramine, an NE reuptake blocker, increases isolation-induced aggression in mice in a dose-dependent manner. The alpha2-receptor blocker yohimbine, but not the alpha1-receptor blocker prazosin, dose dependently counters this desipramine-induced enhancement in aggression. Treatment with clonidine, an alpha2-receptor agonist, also blocks the desipramine-induced enhancement of isolation-induced aggression

- Activation of the adrenergic autoreceptor decreases the

firing activity and release of NE at the postsynaptic level

- In addition, alpha2C-knockout mice attack faster than

wild-type mice, whereas tissue-specific overexpression of alpha-2-C receptors results in an increased latency to attack

- Treatment with noradrenergic blockers, including propranolol, appears to attenuate levels of aggressive behavior
- Propranolol, which blocks postsynaptic beta-adrenergic receptors, effectively controlled belligerence in all cases
- Pindolol, which blocks beta- adrenergic receptors as well as 5-HT1A receptors, has also been shown to decrease aggressive incidents when augmenting antipsychotic treatment in schizophrenic inpatients
- In line with animal research, the alpha-2-receptor agonist clonidine has been extensively used in the treatment of agitated and aggressive patients

Site of action of

antiaggressive drugs

- Drugs for aggression can indeed act at the presynaptic and postsynaptic level
- For example, Alpha-2 agonists and antagonists act at the level of the somatodendritic noradrenergic neurons of the locus coeruleus
- 5-HT1A partial agonists and antagonists act at the level ofthe serotonergic neurons of the dorsal raphe, and D2 agonists and antagonists act at the level of the dopaminergic neurons of the ventral tegmental area
- The final action of these presynaptic drugs is to enhance monoaminergic transmission at the postsynaptic level

- The most important areas involved in the control of aggression are the PFC, in particular the orbitoprefrontal cortex and the anterior cingulate cortex, as well as the amygdala, hypothalamus , hippocampus, septal nuclei, and periaqueductal gray of the midbrain
- The PFC represents the area not only where the main neurotransmitters implicated in aggression are released (5-HT, DA, NE, and glutamate), but also it is the area where the main receptors are located (ie,5-HT1A, 5-HT2A, NMDA, AMPA, D1, and D2)
- In addition, several drugs clinically used in the treatment of aggressive behavior produce specific neurochemical effects in the PFC, including clozapine, olanzapine, and quetiapine
- Valproate, for example, not only does act at the level of GABA, NMDA, and non-NMDA glutamatergic receptors in the PFC, but is also a histone deacetylase inhibitor and facilitates chromatin remodeling in the PFC when it is associated with clozapine or sulpiride, mediating the epigenetic down-regulation of reelin and GAD67 expression detected in cortical GABAergic interneurons of schizophrenic patients

The Psychopharmacology of Aggressive Behavior:
A Translational Approach
Clinical Studies Using Atypical Antipsychotics, Anticonvulsants, and Lithium

Antipsychotics

Aripiprazole

- A quinolinone derivative, is a unique atypical antipsychotic
- Partial agonist at the D2 and 5-HT1A receptors
- 5-HT2A antagonist, a 5-HT2C partial agonist, a 5-HT2B inverse agonist, a 5-HT6 weak antagonist, and a 5-HT7 weak partial agonist
- Modest affinity for the alpha-1 and H1 receptors and does not bind to muscarinic receptors

- Regions of the amygdala that facilitate defensive rage include the basal complex, which projects to the periaqueductal gray and uses excitatory amino acids as a neurotransmitter, and the medial nucleus, which projects to the medial hypothalamus and uses substance P as a neurotransmitter

- The electrical stimulation of the certain specific amygdaloid nuclei (ie, the lateral or the anteromedial group) may lead to control the behavior of highly aggressive, treatment-refractory individuals

- The major metabolite of aripiprazole is a pure dopamine D2 receptor antagonist.
- Recently, it has been reported that aripiprazole interacts with the N-methyl-D-aspartate (NMDA) system by reversing MK-801Y induced prepulse inhibition deficits through regulation of the mitogen-activated protein kinases pathway, a downstream signal transduction system that is common to both the dopaminergic and the NMDA systems.

- These diverse effects on neurotransmission suggest several possible mechanisms through which aripiprazole therapy might modulate aggression.
- For example, the dense population of 5-HT1A and 5-HT2A receptors in the prefrontal cortex may partly account for aripiprazole's antiaggressive properties because 5-HT1A activation in the prefrontal cortex produces inhibitory effects and 5-HT2A activation produces excitatory effects

Clozapine

- Dibenzodiazepine derivative
- Exhibits a much stronger affinity for 5-HT2 receptors than it does for D2 receptors
- It also binds with higher affinity to D4 receptors than it does to D2 receptors
- It binds with high affinity to the M1-M5, >1, H1, H3,5-HT2A, 5-HT2C, 5-HT3, 5-HT6, and 5-HT7 receptors.
- Affinity for the F-aminobutyric acid (GABA), sigma,NMDA, D3, and neuropeptide receptors, as well as the alpha-2- and A-adrenoreceptors

- Clozapine differentially modulates cholinergic transmission through the M4 receptors depending on the tissue, increases expression of several immediate-early genes in different brain areas such as the prefrontal cortex, alters GABAA levels and phosphorylation via the protein kinase C pathway, and enhances frontal NMDA receptor density in chronically treated rodents reared in isolation
- Clozapine further improves aggressive behavior over time, and progressive positive effects of clozapine can indeed be observed even 6 to 12 months after initiating treatment

Olanzapine

- Thienobenzodiazepine derivative, is a bioisostere of clozapine that possesses potent antagonist properties toward 5-HT2A, D2, >1, and H1 receptors
- It also acts as a low-affinity antagonist on D1 receptors.
- Olanzapine exhibits a lower D2 occupancy than clozapine, with values similar to those of typical antipsychotic drugs
- It also has a high affinity for all muscarinic receptors, particularly the M1 and M4 receptors, although it is unclear whether it acts as an agonist or antagonist on the muscarinic system because in vivo and in vitro studies have produced conflicting results

- Evidence also suggests that olanzapine acts directly on the GABAergic system by influencing the total density of GABA-A receptors in the prefrontal cortex, as well as indirectly by activating the neurosteroid system

- Because serotonergic, dopaminergic, adrenergic, and GABAergic mechanisms are posited to play a role in aggression, olanzapine's antiaggressive effects may be related to one or more of these nurotransmitter systems
- More recently, it has been shown that olanzapine induces the expression of retinoic acid and trophic factor signaling genes in the prefrontal cortex. Because the prefrontal cortex is implicated in the control of aggressive behavior, it may be worthwhile to investigate these mechanisms in the context of aggression

Quetiapine

- Dibenzothiazepine derivative with 5-HT2A and D2 antagonist properties and one of the lowest D2 affinities among the atypical antipsychotics.
- Moreover, it acts as a very high-affinity antagonist to alpha-1-adrenoreceptors compared with other atypical antipsychotics and also acts at H1 receptors and alpha-2-adrenoreceptors.
- Remarkably, quetiapine also exerts partial agonist activity at 5-HT1A receptors,and this property, along with its antagonist action at 5-HT2A receptors, is believed to be the neurobiological mechanism accounting for quetiapine's antidepressant properties.

- Its serotonergic, dopaminergic, and adrenergic effects may partly account for quetiapine's antiaggressive effects because all 3 neurotransmitter systems are implicated in aggression.
- A recent study suggests that quetiapine might modify gene expression, an effect that could also be responsible for its antipsychotic or antiaggressive effects. In this experiment, chronically stressed rats treated with quetiapine exhibited modified gene expression in the prefrontal cortex, an area implicated in aggression.

Risperidone

- Benzisoxazole derivative, is an atypical antipsychotic agent that acts mainly as a 5-HT2A antagonist because its binding affinity for 5-HT2A receptors is 20 times higher than that for D2 receptors
- Its potency as a dopaminergic antagonist is comparable to that of the typical antipsychotic haloperidol
- Risperidone is metabolized by cytochrome P4502D6 and 3A4 to 9-hydroxyrisperidone, known also as paliperidone
- Paliperidone largely retains risperidone's antipsychotic effects and has recently been approved by the Food and Drug Administration for the treatment of schizophrenia
- In additiont o its actions on the serotonergic and dopaminergic systems,
- Risperidone also exhibits nanomolar affinity for the alpha-1 and alpha-adrenergic receptors and the H1 receptor

Ziprasidone

- 3-benzisothiazolylpiperazine derivative
- Very high affinity for 5-HT2A and D2 receptors, with a high 5-HT2A/D2 affinity antagonist ratio
- Ziprasidone also rapidly blocks the D3 and D4 receptors but expresses very low affinity for the D1 receptor.
- It is likely that this receptor profile is at least partly responsible for ziprasidone's antiaggressive properties because its effects on aggression are similar to those of other atypical antipsychotic compounds
- Its actions on serotonergic receptors are somewhat unique; it acts as an agonist to the 5-HT1A receptor, but is a 5-HT1D, 5-HT2A, and 5-HT2C antagonist, and a low-potency alpha-1 and H1 antagonist, and does not seem to bind to the alpha2-adrenoreceptor
- Elevated affinity for the serotonin, dopamine, and noradrenergic transporters, although the nature of its effects on these transporters in vivo is still poorly understood

Amisulpride

- Benzamide derivative
- Highly selective D2 and D3 receptor antagonist properties. Its affinity for D3 is slightly higher than for D2
- Unlike other antipsychotics, it does not bind to other dopamine receptor subtypes nor alpha-adrenergic,H1, or cholinergic receptors
- At low doses, amisulpride acts primarily by blocking the presynaptic dopamine receptor, while its actions at postsynaptic receptors only occur at high doses

- These dose-dependent effects must be considered when evaluating amisulpride's mechanism of action on aggressive behavior
- Low doses of amisulpride block D2 and D3 autoreceptors, producing an increase in dopamine firing activity and release, which elicits an antidepressive effect; at higher doses, amisulpride also blocks postsynaptic receptors, producing antipsychotic and antiaggressive effects.
- More recently, it was reported that amisulpride acts as a potent antagonist at the 5-HT7A and 5-HT2B receptors. It was demonstrated that the drug's antidepressant properties derived from its action on 5-HT7A receptors; whether these mechanisms play a role in aggressive behavior remains to be elucidated.

Anticonvulsants

Topiramate

- Sulfamate-substituted monosaccharide, related to fructose
- Positive modulatory effect on the activity of GABA at GABAA receptors and a negative modulatory effect on the activity of glutamate at kainate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Remarkably, these electrophysiological and pharmacological properties belong even to valproate , a drug used for several years in the treatment of aggression.
- These pharmacological characteristics may account for topiramate's efficacy as a treatment for aggression in psychiatric patients.

Valproate

- Valproic acid (2-propylpentanoic acid)
- Increases GABAergic activity by inhibiting the enzymes responsible for its metabolism, such as succinate semialdehydedehydrogenase, GABA transaminase, and alpha-ketoglutarate dehydrogenase
- Antagonizes glutamatergic neurotransmission by blocking the excitatory responses of NMDA, AMPA, and kainate receptors at the prefrontal cortex
- Modulates Voltage-gated Na+ channels,and evidence also suggests an effect on the regulation of the Akt/GSK-3 signaling pathway
- These properties could explain its effect in aggression treatment

Lamotrigine

- Phenyltriazine derivative
- Its antiaggressive effects may be due to its action on several different neurotransmitter systems
- Lamotrigine acts by blocking voltage-gated Na+ channels and A-type K+ channels as well as by inhibiting excitatory postsynaptic currents via voltage-gated sodium and calcium channelblockade
- It also acts on excitatory neurotransmitters, especially the glutamatergic system, by inhibiting overexcited neuronal activities without significantly altering basal rates. Other reports suggest lamotrigine attenuates neuronal excitability on presynaptic sites, inhibits the postsynaptic AMPA receptor, and reduces glutamate release

- Lamotrigine's activity on the GABAergic remains poorly understood, and current results are somewhat contradictory; for example, one report suggests that lamotrigine acts presynaptically to enhance GABA release, whereas another study demonstrated that it attenuates GABA release

- A regulation of GSK-3 signaling pathway by lamotrigine has been also reported

Gabapentin

- 1-[Aminomethyl]cyclohexaneacetic acid) is derivate of GABA
- Modulates GABA transporter function (GAT1), increases GABA levels by inhibiting GABA-transaminase, and directly acts on GABA-B receptors
- Gabapentin is not a direct ligand to either the GABAA or the GABAB receptor or is it converted to GABA
- Gabapentin acts also at the levels of NMDA autoreceptors and affects the glutamate release
- These combined effects of gabapentin on both GABA and glutamate may account for its antiaggressive effect
- Moreover, gabapentin acts on the alpha-2C subunit of L-type voltage regulated calcium channels, which might also play a role in its antiaggressive properties

Lithium

- Monovalent cation belonging to the group of alkali metals, has been used in psychiatry for more than 60 years in the treatment of bipolar disorders
- It has been largely demonstrated that lithium reduces suicidality even more than antidepressants and decreases the recurrences of depressive and manic episodes in bipolar patients.
- Remarkably, the first translational studies in the psychopharmacology of aggression were carried out by M. Sheard in the early seventies.
- After publishing evidence that lithium enhances the metabolism of serotonin and prolongs the latency to defensive reactions to foot shock in
- A rat model, he carried out the first clinical single blind trial in 12 male aggressive prisoners. Using an on-off trial (lithium weeks 1-4, placebo weeks 4-8, and lithium weeks 8Y12), he noticed that the episodes of anger disappeared during the treatment with lithium (0.6-1.2 mEq/L).

- The mechanism of action in decreasing aggression has been not yet clarified. Electrophysiological studies report that lithium does not change the presynaptic electrical activity of serotonin neurons located in the dorsal raphe nuclei but enhances the effect of the electrical activation of the ascending 5-HT pathways on the firing activity of hyppocampal pyramidal neurons, thus potentiating the postsynaptic effect of 5-HT in CA3 hippocampus.
- However, it is reported that lithium interacts with neurotransmitters such as glutamate; in particular, chronic lithium treatment protects neurons in the central nervous system against excitotoxicity by inhibiting NMDA receptor-mediated calcium influx.
- Acts on D2 receptors and ion channels,
- Upregulates neurotrophins such as brain-derived neurotrophic factor, nerve growth factor, and neurotrophin-3
- Lithium is also a synthase kinase 3 (GSK-3) inhibitor that, together with valproate, presents synergistic neuroprotective effects
- Causes changes in the levels of several genes in rat frontal cortex a brain area also involved in the control of aggression

Clinical Trials for the treatment of Aggression

Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine*

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- Acute agitation, represented by a state of motor restlessness and accompanying mental tension, is a serious medical problem that can present in a number of psychiatric diso
- Characterised by symptoms that include pacing, hand wringing, fist clenching, pressured speech, yelling and threatening other people, agitation may escalate and necessitate physical restraint or seclusion to protect the individual, care providers and others in the immediate environment
- Rapid, effective, and safe intervention that does not produce excessive sedation is important in returning the agitated person to a less aroused and less potentially dangerous state, thereby facilitating further assessment of the individual and their treatment options.
- Antipsychotic drugs administered with or without supplemental benzodiazepines are the current standard of care in the acute treatment of agitation
- Speed of onset is one of the most important factors in choosing a route of medication administration. Intravenous administration of antipsychotic drugs affords a rapid onset of action, it is often impractical unless intravenous access is already established

- intramuscular administrations are more commonly used, but these routes can entail a notably delayed onset of action. For example, controlled studies of intramuscular antipsychotics demonstrate a statistically significant difference from placebo in agitation from 15 to 60 min.12–15 During such a delay, symptoms can escalate. Intramuscular administration is often resisted by individuals, further increasing the risk of escalating symptoms.
- there is a clear need for novel anti-agitation treatments that are rapid in onset, well tolerated, easy to administer and accepted by individuals and staff.
- Staccato system (product also known as AZ–004), a proprietary, breath-actuated delivery system that delivers loxapine with intravenous-like pharmacokinetics
- inhaled loxapine was well tolerated and, in participants with schizophrenia, had dose-related anti-agitation effects without evidence of excessive sedation.

Methodology

- At screening, agitation was evaluated by the Positive and Negative Syndrome Scale–Excited Component (PANSS–EC).
- Individuals were eligible if they had a total score of >14 (out of 35) and a score 54 (out of 7) on at least one of the five items.
- Key exclusion criteria were agitation primarily because of acute intoxication; a urine drug screen positive for psychostimulants; a history of drug or alcohol dependence in the previous 2 months; a serious risk of suicide; use of benzodiazepines or other hypnotics or oral or short-acting intramuscular antipsychotic drugs in the 4 h before study treatment; use of injectable depot antipsychotics within a one-dose interval before study treatment;

Study drug

- Inhaled loxapine was delivered by the Staccato system, a singledose, single-use, hand-held drug-device combination
- The rapid absorption of the drug provides peak plasma levels in the systemic circulation with a median Tmax (25, 75 percentiles) of 2 min after administration of the product

Assessments

- Baseline assessments, which were conducted in the 30 min before study treatment, were the PANSS–EC scale, the Clinical Global Impression–Severity scale (CGI–S, a pre-treatment assessment of agitation), the Agitation–Calmness Evaluation Scale (ACES, a scale developed Eli Lilly and Company) and vital signs measurements.
- After randomisation, dose one was administered and the 24 h evaluation period began. If necessary, a maximum of three doses of the study drug were allowed during that 24 h period: if agitation did not subside sufficiently after dose one or it recurred, dose two could be given 42 h after dose one (after completion of
- the 2 h assessments); if necessary, dose three could be given 54h after dose two.

Efficacy measures

- the PANSS–EC scale and the CGI–Improvement (CGI–I) scale.31 The PANSS–EC scale measures the following five symptoms associated with agitation: poor impulse control, tension, hostility, uncooperativeness and excitement. Each symptom is rated on a scale of one (absent) to seven (extreme) and scores are summed. Therefore, total scores can range from 5 (all symptoms absent) to 35 (all symptoms extreme).
- Participants were evaluated with the PANSS–EC scale at 10, 20, 30 and 45 min and 1, 1.5, 2, 4 and 24 h after dose one. The CGI–I scale was used to assess the change from baseline agitation. Scores range from one (very much improved) to seven (very much worse).Participants were evaluated using the CGI–I scale at 2 h after dose one.
- The primary end-point was the change from baseline in the PANSS–EC score 2 h after dose one of inhaled loxapine compared with the change from baseline after inhaled placebo. The key secondary efficacy end-point was the absolute CGI–I score 2 h after dose one of inhaled loxapine compared with inhaled placebo.

Safety and Tolerability

- Sedation was assessed using the ACES, which rates the participant on an agitated–calm–sleeping continuum. Scores range from one (marked agitation) to nine (unarousable), with a score of four indicating 'normal'. Participants were evaluated using the ACES at 2 h after dose one.

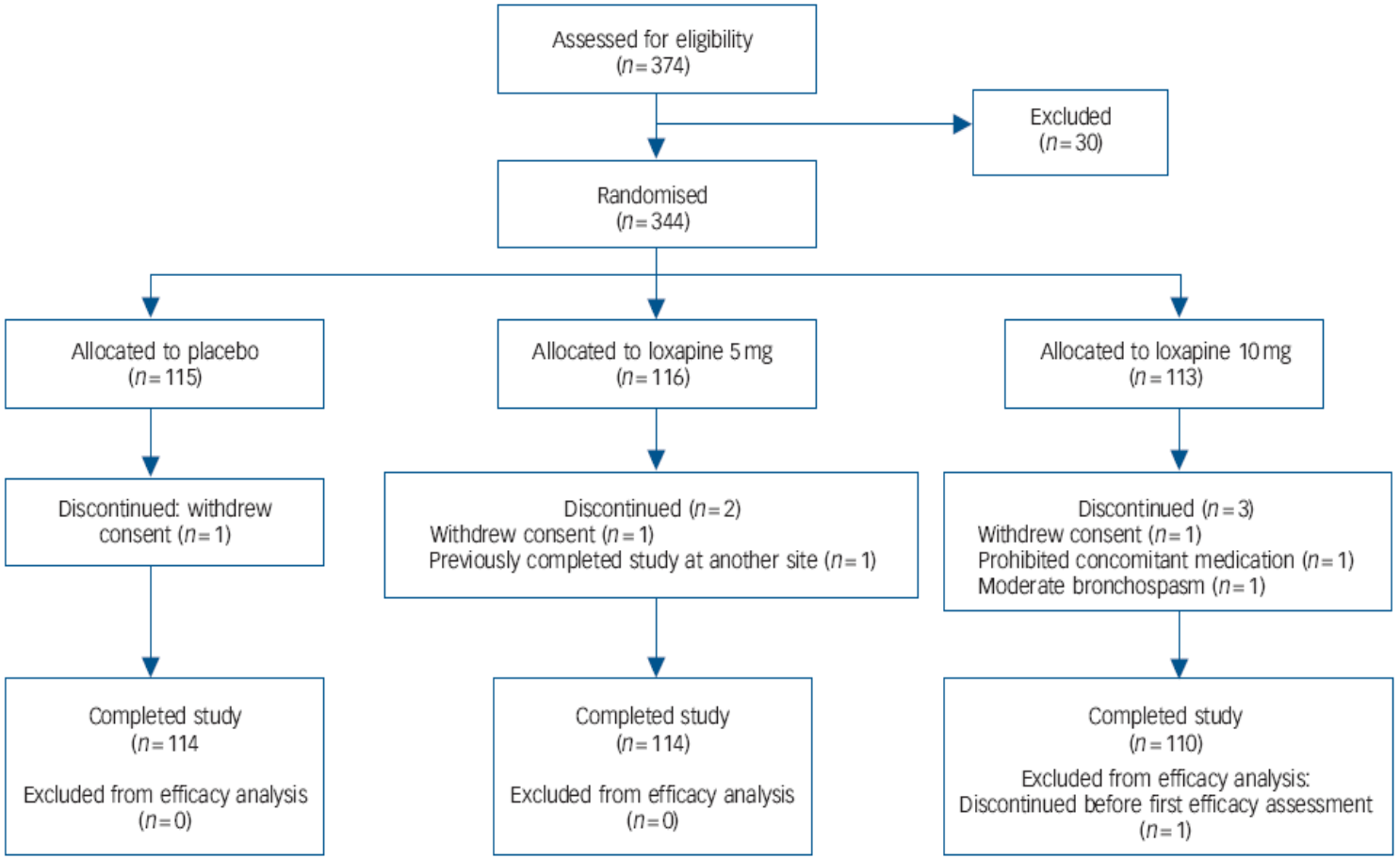

Fig. 2 Study flow chart.

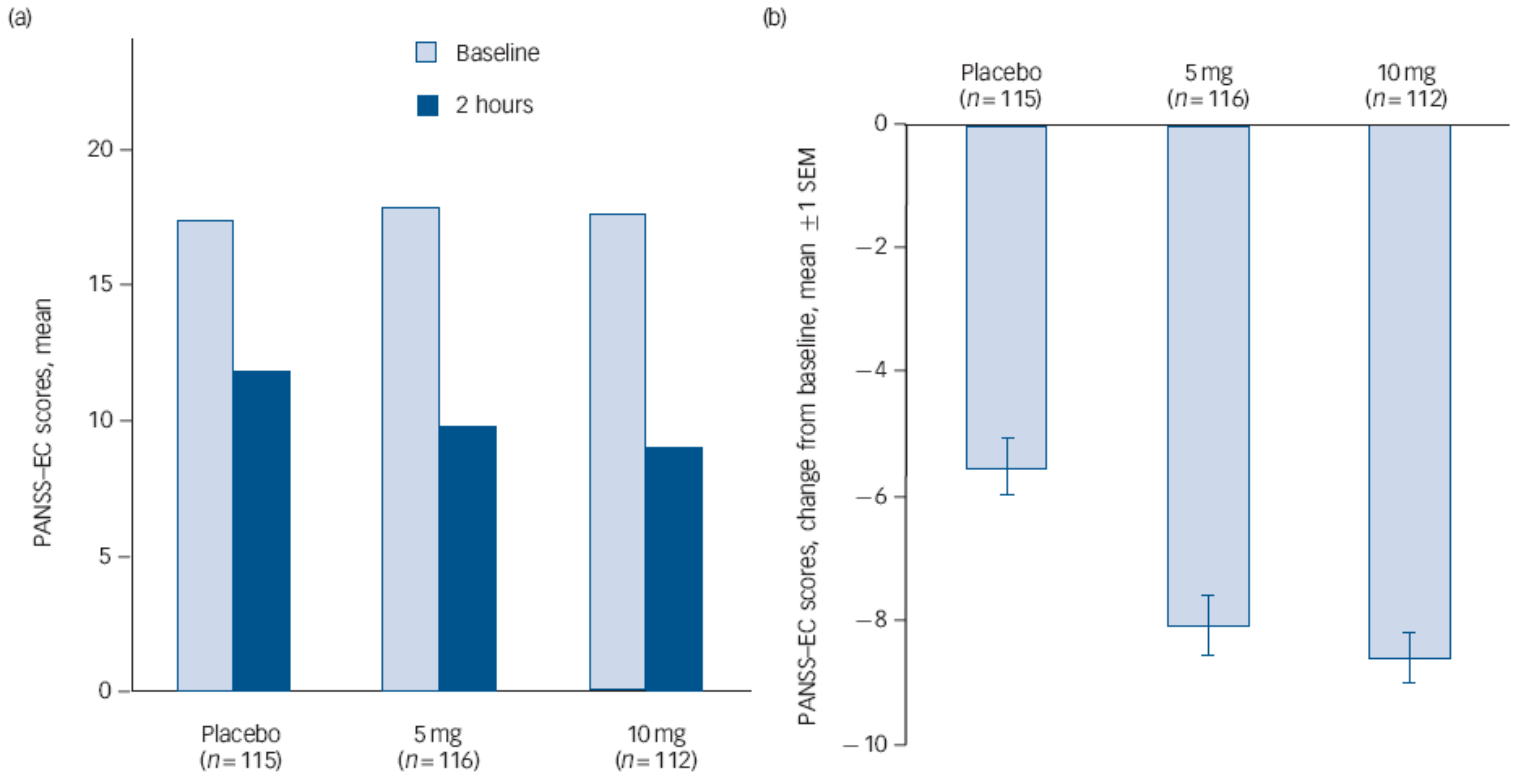

Fig. 3 Positive and Negative Syndrome Scale–Excited Component (PANSS–EC) scores in intention-to-treat population.

(a) PANSS–EC at baseline and 2 h assessment. (b) Primary end-point – change in PANSS–EC from baseline to 2 h assessment: highly statistically significant decreases in PANSS–EC score in 5 and 10 mg groups compared with placebo. SEM, standard error of the mean.

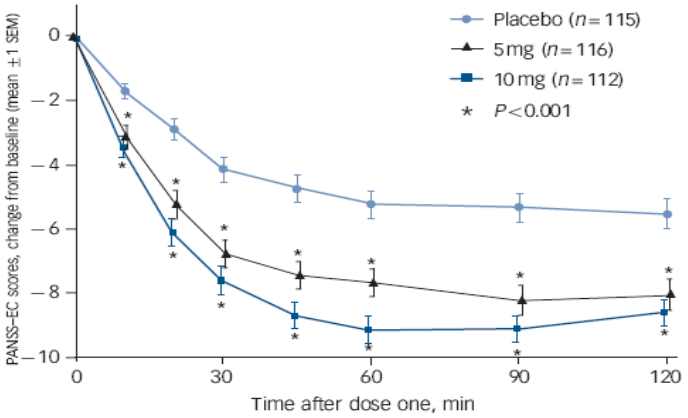

Fig. 4 Positive and Negative Syndrome Scale–Excited Component (PANSS–EC) time-course analysis up to 2 h.

Inhaled loxapine was rapidly effective, with highly statistically significant active–placebo differences 10 min after dose one, the earliest assessment time and significant differences at all subsequent assessments (intention-to-treat population). The testing of the 10 mg dose was planned and the 5 mg dose testing was *post hoc*.

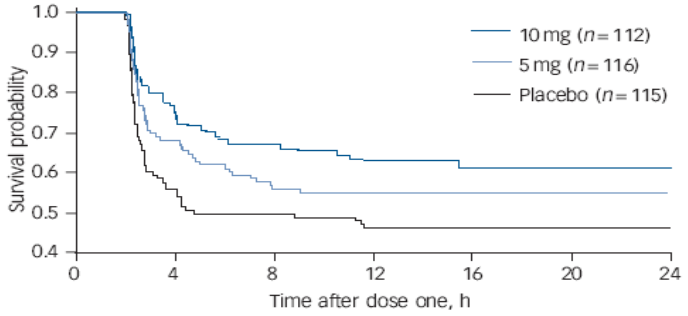

Fig. 5 Survival analysis of time to administration of dose two of study drug (as needed dose).

Participants taking the placebo took dose two significantly sooner than those taking loxapine (Kaplan–Meier overall comparison). In pair-wise comparisons 10 mg/placebo was statistically significant, whereas 5 mg/placebo was not. Lorazepam rescue medication was received by 6, 7 and 18 participants in the 10 mg, 5 mg and placebo groups respectively.

Side effects

- Inhaled loxapine was well tolerated. The percentage of participants who had at least one adverse event was similar in the placebo and loxapine groups (placebo group: 44/115; 5mg group: 40/116; 10 mg group: 43/113), and most events were judged to be of mild or moderate severity and resolved without intervention.
- The most common adverse events in participants receiving inhaled loxapine were sedation, dysgeusia and dizziness. Wheezing or bronchospasm was reported in three participants treated with inhaled loxapine: one participant receiving the 10 mg dose had moderate bronchospasm that resolved with use of an inhaled bronchodilator (albuterol, two puffs by metered-dose inhaler) and led to withdrawal from the study; two participants receiving the 5mg dose had mild wheezing that resolved without treatment. Only one participant reported cough (10 mg group), which was judged to be mild and possibly treatment related and it resolved without intervention.

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Elderly Patients with Dementia-Related Symptoms of Severe Agitation and Aggression: Consensus Statement on Treatment Options, Clinical Trials Methodology, and Policy

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Trial recommendations

- Pharmaceutical manufacturers of antipsychotic drugs should be encouraged to collaborate with research leaders to review the data from the 17 trials to see if the rating instruments used were sensitive to change in agitation
- Pilot studies are needed to test newly proposed methods for assessment. These should not be used as the basis for power calculations for larger trials as sampling errors for the effect size from these small trials are often unreasonably large. Instead, these should be used to check the feasibility of sampling, measurement, treatment delivery, and outcome assessment proposals.
- Participation in trials should be offered to those most likely to benefit from pharmacologic therapy and for whom there is minimal reason to expect serious side effects. Although it is not always feasible, a nonpharmacologic intervention should be attempted before enrolling a patient in a clinical trial. This may be facilitated by encouraging a standardized nonpharmacologic intervention for all patients at all sites.The intervention should be long enough to identify patients who respond to nonpharmacologic intervention and not so long as to make it difficult for patients with more severe symptom levels to be enrolled in the trial

- Patients enrolled in clinical trials should have severe and persistent or recurrent symptoms of agitation and/or aggression that are unresponsive to nonpharmacologic interventions. Enrollment should follow a central eligibility process to verify that the patient meets enrollment criteria. By establishing these entry criteria, early dropouts will be reduced.
- The trajectory of response is superior to an endpoint analysis as a measure of treatment efficacy. This requires a repeated measures design and contrasting the course of the response to drug or placebo over time. This design not only increases power to detect treatment effects, it facilitates intention to treat analysis and uses a measure more sensitive to change than any endpoint or change score using the same instrument
- A meaningful effect size should be pre-specified prior to trial initiation. This should be the area under the curve (AUC), which equals the probability that a patient in the treatment group has a response clinically preferable to one in the control group. With AUC one can incorporate consideration of multiple benefits and multiple harms into one clinically interpretable index.

- Multivariate analysis of effectiveness expressed as the numbers needed to treat (NNT) analyses may be the most readily interpretable type of data for clinicians, but further assessment with this approach is recommended
- Since deaths from atypical antipsychotics involved cardiovascular and infectious causes, it is prudent to monitor the medical status of patients very closely during clinical trials and for the protocol to explicitly state criteria for termination of a subject's participation in the study.
- Sedation may contribute to adverse events as well as treatment success and should be measured in clinical trials for agitation and aggression.
- Additional scientifically sound, adequately powered studies designed to assess the effectiveness of nonpharmacologic interventions should be initiated. The clinical trial methodology for essential multi-site trials remains to be established. Initial support should be provided by governmental agencies (e.g. NIH) and private sources. Pharmaceutical companies should pay increased attention to the appropriate combination/integration of pharmacologic and nonpharmacologic interventions insafety and efficacy studies of the treatment of agitation and aggression in patients with dementia.

- Consensus could not be reached on the question of on-going non-pharmacological treatments across all treatment arms over the course of medication trials in this population of patients with dementia and serious symptoms of agitation and/or aggression. Some conference participants did not recommend that on-going standardized non-pharmacologic treatment should be continued over the course of the trial in all treatment arms because of the absence of more definitive data on the efficacy of non-pharmacologic interventions,. These participants felt that ongoing standardized non-pharmacologic treatment continued over the course of the trial in all treatment arms, may well confound pharmacologic effects. They also argued that if standardized non-pharmacologic intervention is necessary in the interest of patient and/or caregiver welfare, then these clinical trials need to be clearly identified as studies of combined pharmacological and non-pharmacological treatment with bothmodalities clearly specified
- To advance drug trials in elderly individuals with dementia, better definitions of acute and chronic agitation and/or aggression are needed. The definition should provide specific diagnostic criteria for a syndrome of agitation and aggression associated with dementia.

- Reliable and valid rating scales are necessary to quantify the severity of agitation and aggression and changes with treatment in registration trials. Other worthy outcomes that may be secondary or primary in clinical trials include quality of life, mobility, drowsiness, mood, and independence in addition to emotional stability. A specific level of severity may be required for trial enrollment. Repeated measurement analyses are essential. Selection of scales will vary by trial, population, venue, and proposed analytic strategy. Commonly used scales for agitation and aggression include the CMAI and NPI, including family or nursing home versions. Measurement accuracy can be improved by the use of standardized raters, better training of raters and observers, and advances in measurement methods. In some cases, technological advances may augment clinical measures, e.g., actigraph recording of activities levels. Variability is characteristic of the phenomenon being measured (agitation and/or aggression) and must be anticipated in trials.
- Stratifying the sample for severity of agitation and aggression may insure an adequate number of more severely agitated patients, but stratification is to be avoided unless there is prior evidence that a baseline variable moderates treatment response

- Many classes of drugs may reduce agitation and may warrant testing in clinical trials, including antipsychotics, selective serotonin reuptake inhibitors, mood stabilizers, anxiolytics, cholinesterase inhibitors, memantine, and analgesics, as well as novel pharmacologic agents.
- Biological markers for drug response and adverse event susceptibility should be sought in clinical trials in order to determine if response (or failure) can be predicted and to determine whether side effect patterns can also be predicted.
- Time to emergence of behavioral events is an important measure of treatment success in trials of both symptomatic and disease-modifying agents for neurodegenerative disorders.
- Most studies in this population will require a Data and Safety Monitoring Board (DSMB), not only for review of adverse events and serious adverse events, but also to evaluate the research protocol and monitor fidelity to the clinical trial design and to help investigators deal with unexpected problems that often arise in large randomized placebo controlled trials.


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