In response to the critical need for adjunctive treatments for soldiers with refractory forms of mental injury — primarily posttraumatic stress disorder (PTSD) — the US military is developing complementary and alternative medicine (CAM) techniques, including animal-assisted intervention (AAI).\(^1,2\)

CAM modalities include therapies such as yoga, meditation, and creative art therapies, shown to have an effect on the mind’s capacity to regulate the brain and body’s response to social and environmental challenges by reducing stress and enhancing the immune function through the release of the neuropeptide oxytocin by the brain.

Olff et al\(^3\) suggest PTSD symptom treatment would be improved by increasing endogenous levels of oxytocin through optimizing of social support. Studies show that dogs can provide such an optimization of social support and that positive interactions with dogs may offer a safe, effective, and relatively inexpensive way to increase endogenous levels of oxytocin and other important anti-stress agents in humans.

**ROLE OF OXYTOCIN**

Oxytocin is a well-established modulator of a pro-social, anti-stress brain network with the potential to modulate symptoms of PTSD such as: anxiety, including fear response and hyperarousal; interpersonal difficulties/social isolation; physical pain; and sleep disturbances. Human oxytocin research has shown that oxytocin can increase our sense of trust, empathy, and optimism and even increase our response to hypnosis. In rodents, central administration of oxytocin enhanced acupuncture’s analgesic effects. Studies also suggest that oxytocin is a central mediator of the placebo effect.\(^4,7\)

Several studies show that friendly, social interaction with dogs increases blood and urine levels of oxytocin in humans.\(^8\) These human-dog, contact-induced effects gain particular significance in light of a recent brain imaging study which showed that peripheral increases in oxytocin correspond with concurrent activation of the oxytocin brain centers that control the human stress response.\(^13\)

Oxytocin neurons originate in the hypothalamus and connect to the major brain centers that control behavior and emotion. Oxytocin modulates the hypothalamic-pituitary-adrenal axis (HPA axis), the locus coeruleus, the central amygdala (CeA) and other arousal centers of the central nervous system to attenuate stress-induced neuroendocrine activity. Oxytocin receptor-expressing neural circuits in the CeA connect to the medial prefrontal cortex to suppress neurons that produce the freeze-
Oxytocin has also been shown to modulate the serotonin system and reduce levels of cytokines, adrenocorticotrophic hormone, and cortisol. All of these brain systems and neurochemical responses have shown to be functionally important in PTSD. With respect to pain and sleep disturbances, oxytocin has been shown to modulate pain in humans and has been shown to impact sleep patterns in animal studies. Oxytocin has also been shown to be a powerful antioxidant that can bolster the immune system and protect against sepsis. One dose of oxytocin given to war veterans with PTSD demonstrated decreased physiologic responding to provoked combat memories. Oxytocin in humans, has been shown to enhance the processing of positive social information compared to negative information, increase a sense of trust in others, reverse the effect of aversive conditioning of social stimuli, enhance the buffering effect of social support on stress responsiveness, and reduce the stress response in people with a history of early trauma.

This same pro-social/anti-stress response has also been observed in service members with PTSD who train service dogs. As we will demonstrate, shaping the behaviors of service dogs requires the focused nurturing social attention towards dogs that has been shown to naturally increase oxytocin blood levels in humans. There are many potential uses of animals in support for service members and veterans. The reminder of this article shows one program which has great promise. Others are covered in more detail in *Canine-Assisted Therapy in Military Medicine.*

**WARRIOR CANINE CONNECTION**

The Warrior Canine Connection (WCC) is a nonprofit organization, based in Brookeville, MD, that enlists “wounded warriors” with PTSD and traumatic brain injury (TBI) in the training of service dogs for fellow veterans as a therapeutic intervention. WCC currently has dogs in training at several military treatment facilities (Walter Reed National Military Medical Center, Fort Belvoir, and National Intrepid Center of Excellence) and the Palo Alto Veterans Administration (VA) Healthcare System.

Occupational therapists utilize some of these programs as therapeutic “work therapy” internships with the goal to facilitate a purposeful and meaningful occupational intervention that builds skill sets for functional independence. The program engages service members in a healing mission, instructing soldiers with PTSD and TBI on how to train service dogs for fellow veterans with physical and psychological injuries.

WCC’s training philosophy is based on positive methods of shaping behaviors and the premise that mastering the skills and patience required to train a service dog helps the WCC trainers regain control of their own emotions, focus their attention, and improve their social competence and overall sense of well-being. Since beginning this therapeutic intervention model, very promising responses to this program from both active-duty service members involved in the current conflicts, as well as veterans have been observed by clinical staff (see Sidebar).

The WCC training was developed by a social worker and service dog trainer, Rick Yount, MS, LSW, to address all three symptom clusters associated with PTSD: re-experiencing, avoidance/numbing, and increased arousal. The interventions in the program are targeted to remediate each category of these symptoms as follows.

**Re-experiencing**

Procedures used in training service dogs require the trainer to focus on the dog’s point of view of the present, in order to recognize the “teachable moments” when instruction will be most effectively processed and retained. The presence of the dog during a stressful situation or encounter changes the context of the arousal event and anchors the trainer in the present, reminding the service member or veteran that they are no longer in dangerous circumstances. If the patient/trainee does experience a trigger for symptoms, the presence of the dog can lower anxiety levels.

**Avoidance and Numbing**

Service dog training requires that the dog is exposed to a wide range of experiences in the community. This also creates opportunities for the soldier-trainer to re-integrate into civilian life. As part of the training, the service members are responsible for teaching the dogs that the world is a safe place. Through that process, the PTSD-affected soldiers must convince themselves of the same.

For example, the soldier-trainers are taught to praise and treat the dogs when they hear a car backfire or other startling events. Rather than turning inward to ruminate on their past trauma, they must get outside of their own heads to focus on the dogs and their mission to help another veteran.

Additionally, the dogs can help offer veterans who often isolate themselves from society, opportunities to experience positive interactions with members of the community. The training program requires soldiers who have likely “numbed” their feelings to instead demonstrate positive emotion, such
as praising the dogs to successfully teach them. Many program participants have reported that this use of positive emotion has significantly improved their family dynamics as their children respond to this positive “parenting” strategy.

In order to shape the behavior of a service dog, trainers with PTSD must also overcome their emotional and affective numbness in order to heighten their tone of voice, bodily movements, and capacity for patience so that they can deliver their commands with positive, assertive clarity of intention and confidence. In doing this, trainers soon discover they can earn their dog’s attention and best guide them to the correct response.

The dog’s success must then be rewarded with emotionally-based praise. The WCC training technique allows the trainers to experience rewarding positive emotional stimulation and social feedback. The basic daily needs of a service dog involve structured activities that also bring the trainer and dog into the kind of close nurturing contact that further creates a behavioral and psychological antidote to social avoidance.

Hyperarousal

WCC service dogs are bred to be responsive to human emotions and needs. Their sensitivity to and reflection of their trainer’s emotional state provides immediate and accurate measures of the trainer’s projected emotion. This also challenges the trainer to overcome his or her tendency for startle reactions so that he or she can relay a sense of leadership and positive feedback when their young dogs are faced with environmental challenges such as cars backfiring or being approached by strangers.

WCC service dogs are also bred to be affectionate and have a low-arousal temperament that puts their trainers “at ease.” With these dogs at their sides, trainers perceive greater relaxation and social competence and are able to shift out of their hyper-vigilant, defensive mode into a relaxed state that makes them ready and able to connect with others.

**Representative Cases in Animal-Assisted Therapy**

**Case 1**

A Marine injured by 13 separate improvised explosive device (IED) detonations during his multiple tours in Operation Iraqi Freedom and Operation Enduring Freedom had been in a PTSD treatment program for several weeks but was not responding despite a myriad of behavioral and pharmacological interventions.

He sat in the corner with his sunglasses on, occasionally twitching his head from side to side in a tic-like manner. His peers were hesitant to interact with him due to his body language and lack of response to their attempts to connect with him.

An 8-month-old golden retriever repeatedly nudged his arm, intent on making a new friend. Although the Marine rejected the dog’s first several attempts, the pup’s persistence paid off and soon was able to elicit a smile from the Marine. Noticing the emerging connection, the treatment staff asked the Marine if he would consider helping to train the dog to help a fellow veteran. His commitment to helping other warriors along with his interest in the dogs prompted him to participate in the service dog training program.

Within 2 days of working in the program, he began to smile and bond with the dog. His involvement led to his first positive interactions with staff and fellow veterans. Instead of leaving the PTSD program without successfully completing it, he was able to finish the entire program and process his trauma through the support of his dog, peers, and treatment team. Through training the service dog, the Marine learned to teach the dog to associate loud noises with praise and treats. To do this, he had to challenge his automatic thoughts about his own triggers in order to convince the dog that the world around him was a safe place.

**Case 2**

A young Marine Sergeant was referred to the WCC program as part of his treatment for PTSD and TBI. He endorsed difficulty sleeping, isolating, regulating his emotions, and parenting his 4-year-old daughter. The Marine reported a love for dogs and jumped at the chance to participate in WCC. He specifically focused on using his “praise voice” when marking and reinforcing desired behaviors, and while regulating his emotions when correcting unwelcome behaviors.

The Marine was offered an opportunity to keep the dog overnight after he developed a bond and sufficient skills to handle the dog. The next day, he reported a significant improvement in his quality of sleep. The dynamics between him and his daughter also showed improvement following the dog’s overnight stay.

The Marine was encouraged to use the same positive techniques of using praise...
and patience with his daughter. He reported that learning to train the service dog had a profound impact on his parenting style. Rather than focusing on his daughter’s mistakes, he began to look for opportunities to praise her and set her up for success. He now has his own service dog and is working with his local VA to develop a service dog program in his local area.

CONCLUSION
These cases demonstrate the effects of service dog training as a purpose-driven intervention have on the symptoms of PTSD and mild TBI and how such a program can facilitate psychological and social improvement, and functional independence. They also indicate that the focus, intention, and nurturing social contact involved in shaping the behavior of young service dogs may be acting as a potent agonist of neurophysiological systems known to be dysregulated in PTSD.

A number of studies now show that human-dog interactions, such as those used to train service dogs, naturally increase circulating oxytocin levels in people. Further research is required to establish the psychological and behavioral effectiveness of the service dog training model and to investigate the underlying physiological mechanisms that support the observed reductions of PTSD symptoms.

Identifying a potent, safe, natural method of stimulating the anti-stress/pro-social oxytocin brain network is very important since there is no US Food and Drug Administration-approved oxytocin drug available at this time. A stronger scientific understanding of cause and effects of therapy dog training will provide scientific, objective guidelines for the appropriate training for therapy animals and policies that regulate how and when therapy animals may be used to help service members and veterans.

REFERENCES
INDICATIONS AND USAGE
LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- LATUDA is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS
LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole).
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS
Cerebrovascular Adverse Reactions, Including Stroke: LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after antipsychotic drugs administered to the patient increase. However, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

Potential for Cognitive and Motor Impairment: In short-term, placebo-controlled trials, somnolence was reported in 17.0% (256/1508) of patients treated with LATUDA compared to 7.1% (50/708) of placebo patients, respectively. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS
Commonly Observed Adverse Reactions: (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Please see brief summary of prescribing information on adjacent pages, including Boxed Warning.


FOR MORE INFORMATION, PLEASE CALL 1-888-394-7377 OR VISIT www.LatudaHCP.com.
1. INDICATIONS AND USAGE
LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia [see Clinical Studies (14.1)].

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [seeDosage and Administration (2)].

4. CONTRAINDICATIONS
LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation.
- Angioedema has been observed with lurasidone [see Adverse Reactions (6.1)].
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) [see Drug Interactions (7.1)].
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin) [see Drug Interactions (7.1)].

5. WARNINGS AND PRECAUTIONS
5.1. Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2. Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions (5.1)].

5.3. Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinolyis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal symptoms and signs (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.4. Tardive Dyskinesia
Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase.

However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby possibly delay the manifestation of the syndrome.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness (that) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.5. Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients may require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 2: Change in Fasting Glucose

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=680</td>
<td>n=71</td>
<td>n=678</td>
<td>n=508</td>
<td>n=283</td>
<td>n=113</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.0</td>
<td>8.0</td>
<td>2.0</td>
<td>-1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts to ≥126 mg/dL

<table>
<thead>
<tr>
<th>Serum Glucose (≥126 mg/dL)</th>
<th>8.3% (52/628)</th>
<th>11.7% (76/650)</th>
<th>12.7% (77/604)</th>
<th>6.8% (32/475)</th>
<th>10.0% (26/256)</th>
<th>5.6% (6/108)</th>
</tr>
</thead>
</table>

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=353), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).
5.6. Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported by impairing gonadal steroidogenesis in both female and male patients.

Table 5: Median Change in Prolactin (ng/mL) from Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 40 mg</th>
<th>LATUDA 80 mg</th>
<th>LATUDA 160 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>-1.9</td>
<td>-1.1</td>
<td>-1.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>80 mg/day</td>
<td>-1.5</td>
<td>-1.9</td>
<td>-2.1</td>
<td>-0.7</td>
</tr>
<tr>
<td>160 mg/day</td>
<td>-1.7</td>
<td>-2.0</td>
<td>-2.5</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

Proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 1.5% for LATUDA-treated patients versus 0.2% for placebo-treated patients. The proportion of male patients with prolactin elevations ≥ 5×ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled, long-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 and -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 4. The mean weight gain was 0.43 kg for LATUDA-treated patients compared to 0.02 kg for placebo-treated patients. Changes in weight from baseline for olanzapine was 4.15 kg and for quetiapine extended-release was 2.09 kg in Studies 3 and 5 (see Clinical Studies (14.1), respectively. The proportion of patients with a >7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 4: Mean Change in Weight from Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 40 mg</th>
<th>LATUDA 80 mg</th>
<th>LATUDA 160 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>-0.2</td>
<td>0.1</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>80 mg/day</td>
<td>-0.1</td>
<td>0.2</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>160 mg/day</td>
<td>-0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

In the uncontrolled, long-term studies (primarily open-label extension studies), LATUDA was associated with a median change from baseline of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice (see Nonclinical Toxicology (13)). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.
5.13. Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.14. Use in Patients with Concomitant Illness
Clinical experience with LATUDA in patients with certain concomitant illnesses is limited [see Clinical Pharmacology (12.3)].

Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease [see Warnings and Precautions (5.8)].

6. ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:
• Use in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
• Cerebrovascular Adverse Reactions, Including Stroke [see Warnings and Precautions (5.2)]
• Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.3)]
• Tardive Dyskinesia [see Warnings and Precautions (5.4)]
• Hyperglycemia and Diabetes Mellitus [see Warnings and Precautions (5.5)]
• Hyperprolactinemia [see Warnings and Precautions (5.6)]
• Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.7)]
• Orthostatic Hypotension and Syncope [see Warnings and Precautions (5.8)]
• Seizures [see Warnings and Precautions (5.9)]
• Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.10)]
• Body Temperature Regulation [see Warnings and Precautions (5.11)]
• Suicide [see Warnings and Precautions (5.12)]
• Dysphagia [see Warnings and Precautions (5.13)]

6.1. Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from a clinical study database for LATUDA consisting of 2905 patients with schizophrenia exposed to one or more doses with a total experience of 985.3 patient-years. Of these patients, 1508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total of 769 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (N=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and Parkinsonism.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (86/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 6.

Table 6: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Dictionary-derived Term</th>
<th>Placebo (N=700)</th>
<th>LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Salivary Hypersalivation</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Parkinsonism</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Dyssomnia***</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

*Somnolence includes adverse event terms: hypersomnia, hypnagogic, sedation, and somnolence
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hyperkinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
***Dysphoria includes adverse event terms: dystonia, acrocute crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

Dose-Related Adverse Reactions
In pooled data from the short-term, placebo-controlled, fixed-dose studies, there were no dose-related adverse reactions (greater than 5% incidence) in patients treated with LATUDA across the 20 mg/day to 160 mg/day dose range. However, the frequency of akathisia increased with dose up to 120 mg/day (5.6% LATUDA 20 mg, 10.7% LATUDA 40 mg, 12.3% LATUDA 80 mg, 22.0% LATUDA 120 mg); akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo.

Extrapyramidal Symptoms
In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 7.

Table 7: Incidence of EPS Compared to Placebo

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=700)</th>
<th>LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(N=1508)</td>
</tr>
<tr>
<td>20 mg/day</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>40 mg/day</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>80 mg/day</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>120 mg/day</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>160 mg/day</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

All EPS events, akathisia and restlessness

Note: Figures rounded to the nearest integer

*Akathisia includes adverse event terms: dystonia, acrocute crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hyperkinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to normal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%) and the SAS (LATUDA, 5.0%; placebo, 2.3%).
Dystonia

**Class Effect:** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

**Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA**

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2905 patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 6 or those that appear at least 1/100 patients (frequent) (only those not already listed in the tabulated treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes prolonged abnormal contractions of dystonia is observed in males and younger age groups.

**Symptoms of Dystonia:**  
- Spasm of the neck muscles, sometimes prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue.

**Contraindications (4)**]  
LATUDA is contraindicated in patients with a history of hypersensitivity to any component of the product. LATUDA is also contraindicated in patients with a known history of abnormal ergot metabolism.

**Other Patient Factors**  
- Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis. (see Boxed Warning).

**8. USE IN SPECIFIC POPULATIONS**

### 8.1. Pregnancy

**Teratogenic Effects**

Pregnancy Category B

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Non-teratogenic Effects**

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypotonia, hypotension, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

**Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.**

**Animal Data**

No adverse developmental effects were seen in a study in which pregnant rats were given LATUDA during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day. This dose is approximately half of the MRHD based on body surface area.

**No teratogenic effects were seen in studies in which pregnant rats and rabbits were given LATUDA during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 160 mg/day based on body surface area.**

**8.3. Nursing Mothers**

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering risk of drug discontinuation to the mother.

**8.5. Geriatric Use**

Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 65), LATUDA concentrations (20 mg/day) were similar to those in younger subjects (see Clinical Pharmacology (12.3)). No dose adjustment is necessary in elderly patients (Figure 2).

**Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis.**

**8.6. Other Patient Factors**

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 5.
10. OVERDOSAGE

10.1. Human Experience

In premarketing clinical studies involving 2905 patients, accidental or intentional
overdose of LATUDA was identified in one patient who ingested an estimated
560 mg of LATUDA. This patient recovered without sequelae. This patient
resumed LATUDA treatment for an additional two months.

10.2. Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice.
There is no specific antidote to LATUDA, therefore, appropriate supportive
measures should be instituted and close medical supervision and monitoring
should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including
continuous electrocardiographic monitoring for possible arrhythmias. If
antiarrhythmic therapy is administered, disopyramide, procainamide, and
quinidine carry a theoretical hazard of additive QT-prolonging effects when
administered in patients with an acute overdose of LATUDA. Similarly, the alpha-
blocking properties of bretylium might be additive to those of LATUDA, resulting
in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate
measures. Epinephrine and dopamine should not be used, or other
sympathomimetics with beta-agonist activity, since beta stimulation may
worsen hypotension in the setting of LATUDA-induced alpha blockade. In
the event of severe extrapyramidal symptoms, anticholinergic medication should
be administered.

Gastric lavage (after intubation if patient is unconscious) and administration
of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and
neck following overdose may create a risk of aspiration with induced emesis.