INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2001; **16**: S33–S61.
DOI: 10.1002/gps.571

A current review of olanzapine's safety in the geriatric patient: from pre-clinical pharmacology to clinical data

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SUMMARY

Objective Olanzapine (OLZ) is unique among currently available antipsychotic medications in its antagonism of a range of receptor systems including dopamine, norepinephrine, serotonin, acetylcholine, and histamine. Olanzapine's mechanistic complexity provides a broad efficacy profile in patients with schizophrenia and acute, pure or mixed mania. Patients experience symptomatic relief of mania, anxiety, hallucinations, delusions, and agitation/aggression and reduced depressive, negative, and some cognitive symptoms. This paper will review the safety profile of OLZ, focusing on the elderly, where data are available.

Method Preclinical and clinical studies of OLZ are reviewed, with emphasis on its possible effects on the cholinergic system and the histamine H_1 receptor. Weight change and related metabolic considerations, cardiac and cardiovascular safety, and motor function during treatment with OLZ are also reviewed.

Results and Conclusion *In vitro* receptor characterization methods, when done using physiologically relevant conditions allow accurate prediction of the relatively low rate of anticholinergic-like adverse events, extrapyramidal symptoms, and cardiovascular adverse events during treatment with OLZ. Currently available clinical data suggest olanzapine is predictably safe in treating adult patients of any age with schizophrenia and acute bipolar mania, as well as in treatment of patients with some types of neurodegenerative disorders. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — olanzapine; receptors; geriatric; dementia; Alzheimer's dementia; schizophrenia; bipolar disorder; diabetes; safety

INTRODUCTION

Olanzapine (OLZ) is unique among the currently available psychotropic medicines in possessing two pharmacological characteristics at therapeutic dosages: (1) activity at multiple neurotransmitter receptor systems including dopamine, norepinephrine, serotonin, acetylcholine, and histamine and (2) activity that is solely antagonistic. OLZ has been termed a Multi-Acting-Receptor-Targeted-Antipsychotic (MARTA) (Tran *et al*., 2000). There have been extensive efforts focused on clarifying the molecular mechanisms underlying its efficacy in patients with schizophrenia and acute pure or mixed mania and its ability to suppress mania, anxiety, hallucinations, delusions, and agitation/aggression with concomitant reduction of depressive, negative, and some cognitive symptoms. Data examining the effects of OLZ in Alzheimer's disease (AD) (Street *et al*., 2000) suggest that it may also demonstrate a similar clinical profile in this neuropathologically distinct patient population. However, just as the mechanisms underlying OLZ's efficacy require clarification, a careful examination of its safety profile is necessary. Perhaps the most important safety concerns for the clinician are, first, predicting for any particular patient if a medicine is likely to prove to be unsafe before prescribing and, second, determining, after prescribing the medicine,

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Contract/grant sponsor: Eli Lilly and Company.

Received 27 September 2001
Accepted 4 October 2001

whether an unwanted change is truly related to the medicine or to a different, intercurrent illness or other factor(s), independent of the medicine. The task of clarifying these two clinical foci in the elderly is daunting at the individual patient level, in part because of considerable variation in tissue-specific physiologic responses associated with normal, age-related changes, tissue-specific disorders that increase in prevalence with age. The broadly prevalent practice of polypharmacy in the elderly is an additional complicating factor. In particular, polypharmacy may lead to unpredictable adverse events as multiple medications may have synergistic pharmacodynamic effects.

The clinical safety data presented here is focused at the population, rather than individual, level due to the lack of methods to directly predict adverse events. A focus at the population level allows for an estimation of the probability of an adverse event in patients treated with medication relative to a comparator control (untreated) group. We include clinical data derived from young patients as they are likely to reflect the nature and frequency of adverse events in physically healthy, elderly individuals. However, a significant limitation of focusing only on the young patient is that comparisons with a healthy elderly population may not be completely valid. For example, some events might increase in frequency while others decrease. Moreover, special populations may have focal impairment of an organ, such as the neurodegenerative changes of the brain in AD or cardiac output problems in congestive heart failure. Because of the gross derangement of tissue, for example, in AD or Parkinson's disease, adverse events may be revealed that are not considered potentially drug-related in different diagnostic categories of either elderly or younger patients. With these limitations in mind, we present data concerning OLZ's safety profile in elderly patients, while also reporting the available data on OLZ's safety characteristics in younger patients with schizophrenia and bipolar disorder.

There has been an extensive effort to apply preclinical methods in the prediction of the potential for adverse events. However, because the elderly population is diverse, with disparate, comorbid medical problems, it is particularly important to view preclinical data in the light of patient-specific factors. In consideration of this goal to review the safety profile of OLZ in elderly and younger patients, it is important to know the human biological systems with which OLZ directly interacts in a potentially meaningful way as well as those systems that OLZ does not significantly affect (shown in Table 1).

Table 1. Binding profile for olanzapine, data from Nova Screen

	% Inhibition at 1 μM
Neurotransmitter related receptors	
Adenosine, non-selective	4
GABA-B	− 21
Glutamate, AMPA	− 3
Glutamate, kainate	− 6
Glutamate, NMDA agonist	− 1
Glutamate, NMDA, glycine (strycinsen)	4
Glycine–strychnine sensitive	− 6
Histamine H_2	21
Opiate, delta1	16
Opiate, Kappa	− 7
Opiate, Mu	5
Purinergic, P2Y	7
Serotonin4	7
Sigma non-selective	4
Peptides	
Cholecystokinin A	18
Cholecystokinin B	4
Neurokinin1	3
Neurokinin2	− 24
Neuropeptide Y non-selective	8
Neurotensin	− 3
Uptake transporters	
Choline transporter	− 2
Dopamine transporter	8
GABA uptake	4
Ion channel receptors	
Calcium channel—L type	− 3
Calcium channel—N type	− 13
Chloride channel	12
Glutamate MK801 site	4
Glutamate, NMDA, PCP	− 10
K + channel—ATP sensitive	3
K + channel Ca activated. Voltage Insensitive	1
K + channel Ca activated Voltage Sensitive	2
Sodium site 2	
Prostaglandins	
Leukotriene D4, LTD4	7
Enzymes	
Acetylcholinesterase	− 5
Choline acetyltransferase	13
Monoamine Oxidase A, MAO-A	− 1
Monoamine Oxidase A, MAO-B	5

POTENTIAL CHOLINERGIC ACTIVITY OF OLZ

Acetylcholine is a primary neurotransmitter in the central nervous system where it appears to be involved in memory formation, consolidation, and retrieval, and movement. It is also a primary neurotransmitter in the autonomic nervous system where it is principally involved in life-sustaining activities such as the regulation of cardiac output and digestion. Cholinergic physiology and the effects of procholinergic and anticholinergic medicines have been a

Table 2. Principal locations and potential effects of antagonism of hM^{1-5} receptors

Receptor	Location	Effects of agonists	Effects of antagonists
hM_1	Central: greatest in hippocampus	Improve cognition	Worsen cognitive function
	Peripheral: sympathetic ganglia	Increase bronchial constriction, gastric acid secretion, heart rate and blood pressure	
hM_2	On presynaptic neurons: function as autoreceptors	Decrease acetylcholine release	Increase acetylcholine release
	Central: greatest in nucleus basalis		
	Peripheral: heart and smooth muscle	Bradycardia, inhibit relaxation of smooth muscle	Increased heart rate
hM_3	Central: very low densities, greatest in frontal, temporal, and parietal cortex	Unknown	Unknown
	Peripheral: exocrine glands	Salivation, lacrimation, sweating	Dry mouth, eyes and skin;
	Low concentrations in smooth muscle	Intestinal and urinary bladder contractions	Aggravation of glaucoma Constipation and urinary bladder atony (urinary retention)
hM_4	Mostly central, not well characterized	Role in dopaminergic function?	Role in dopaminergic function?
hM_5	Mostly central, not well characterized	Role in dopaminergic function?	Role in dopaminergic function?

primary area of research related to aging. Cholinergic therapy holds promise for the treatment of psychosis, cognitive decline, and dementias, although potential for parasympathetic adverse events must be carefully managed, especially in the elderly.

Based on published *in vitro* receptor binding data (Bymaster *et al*., 1996), OLZ was initially expected to be associated with a high frequency of adverse events potentially attributable to 'anticholinergic' activity. As is evident from a review of Table 2, if OLZ possessed significant anticholinergic activity, one would expect to see increased frequencies of certain adverse events. However, repeatedly in several studies, anticholinergic adverse events (blurred vision, dry mouth, constipation, and urinary retention) were observed at lower rates than expected.

The lower than anticipated rate of anticholinergic adverse events suggests that the method of determining the *in vitro* occupancy of anticholinergic receptor for OLZ was not optimal, *in vitro* binding/activities observed simply do not reflect what occurs *in vivo*, or OLZ's unique, complex receptor pharmacology as a MARTA contributes to the discrepancy between *in vitro*-based assumptions and the actual adverse events observed in patients (i.e. its actions at multiple receptors may result in procholinergic effects offsetting direct cholinergic antagonism).

The *in vitro* binding affinities to the neuronal nicotinic and human muscarinic (M) receptors as well as several other receptors for OLZ and six other medicines: clozapine (CLZ), quetiapine (QUET), risperidone (RIS), ziprasidone (ZIP), chlorpromazine (CPZ), and haloperidol (HAL) are presented in Table 3. As none of these antipsychotics, including OLZ, has any direct receptor interactions with neuronal nicotinic receptors (see Table 3), our discussion is restricted to the distribution and potentially clinically significant effects of these medications at human muscarinic receptors. Assays were performed in artificial cerebrospinal fluid-like media with broken, washed membranes from frozen cells. Assays used the scintillation proximity assay (SPA) method. As illustrated by the data in Table 3, it is expected that at the human muscarinic-1 (hM_1) receptor, the rank order of antagonism would be CLZ $>>$ QUET $\geqslant$ OLZ and that other medicines would have no potentially clinically significantly activity. OLZ is unique in possessing greater hM_2 antagonism than hM antagonism. This difference in affinity may be clinically relevant as the M_1 and M_2 receptors have significantly different neuroanatomical distribution and opposing functional effects *in vivo*. The typical distribution of muscarinic receptors in humans (hM_{1-5}) has recently been reviewed (Kennedy *et al.*, 1998) and is briefly discussed below. The principal locations and potential effects of agonism and antagonism of the hM_{1-5} receptors are summarized in Table 2.

In the CNS, hM_1 receptors are found in order of descending density in the postsynaptic elements of the hippocampus $>$ temporal cortex $>$ frontal cortex $>$ parietal cortex $>$ occipital cortex $=$ putamen $>$ nucleus basalis (Flynn *et al*., 1995). They are thought

Table 3. Individual antipsychotic medication receptor binding affinity ratios (receptor K_i (nM) for hX = human or rX = rat receptors) for h5HT$_{2A,2C}$, hM$_{(1-5)}$, rN, hH1, rα_1, and rα_2 Binding affinities at each receptor are presented in parentheses. The ratio of X/hD$_{2L}$ is presented outside parentheses. Binding affinities $\geqslant$ 10,000 indicate no appreciable binding at that receptor*

Compound (hD$_{2L}$ binding affinity)	h5HT$_{2A}$/hD$_{2L}$	h5HT$_{2C}$/hD$_{2L}$	hM$_1$/hD$_{2L}$	hM$_2$/hD$_{2L}$	hM$_3$/hD$_{2L}$	hM$_4$/hD$_{2L}$	hM$_5$/hD$_{2L}$	rN/ hD$_{2L}$	rα_1/hD$_{2L}$	rα_2/hD$_{2L}$	hH$_1$/hD$_{2L}$
Olanzapine (31)	(3) 0.10	(30) 0.97	(280) 9.03	(215) 6.94	(310) 10.00	(320) 10.32	(259) 8.35	($>10^4$) 300	(26.2) 0.85	(306) 9.87	(0.65) 0.02
Clozapine (190)	(6) 0.03	(39) 0.21	(280) 1.47	(440) 2.32	(403) 2.12	(625) 3.29)	(120) 0.63	($>10^4$) >300	(2.52) 0.01	(20.4) 0.11	(0.23) 0.001
Quetiapine (310)	(303) 0.98	(4232) 13.65	(2410) 7.77	(2830) 9.13	(29,780) 96.06	(4140) 13.35	(7710) 24.87	(>100) >30	(9.30) 0.03	(>3000) >10	(2.2).007
Risperidone (5.9)	(1) 0.17	(99) 16.78	($>10^4$) >1700	14,000) 2373	($>10^4$) >1700	($>10^4$) >1700	($>10^4$) >1700	(>100) >30	(2.51) 0.43	(13.5) 2.29	(27) 4.58
Ziprasidone (4.6)	(4) 0.87	(3) 0.65	($>10^4$) >2000	($>10^4$) >2000	($>10^4$) >2000	($>10^4$) >2000	($>10^4$) >2000	(>100) >30	(6.9) 1.50	(119) 25.87	(15) 3.26
Chlorpromazine (3.2)	(8) 2.50	(97) 30.31	(890) 278.1	(1025) 320.3	(930) 290.6	(1405) 439.1	(435) 135.9	($>10^4$) >300	(.365) 0.11	(535) 167.2	(ND)
Haloperidol (2.2)	(203) 92.27	(7531) 3423	($>10^4$) >5000	(8900) 4645	($>10^4$) >5000	($>10^4$) >5000	($>10^4$) >5000	($>10^4$) >300	(12.2) 5.55	(>3000) >1000	(790) 359.1

*, ND not done.
(x) → Binding affinity (higher number indicates medication binds less readily to the receptor).
x.xx → Ratio of binding affinities of the receptor of interest divided by hD$_{2L}$.

to have a significant role in cognition, and antagonism may worsen cognitive function (Avery *et al*., 1997; Fisher *et al*., 2000; Cummings *et al*., in press). In the periphery, hM_1 receptors are found principally in association with sympathetic postganglionic neurons and agonism is thought to mediate vagal-induced bronchial constriction, gastric acid secretion, and increases in heart rate and blood pressure. The CNS hM_2 receptors are found predominately presynaptically, where they function as classical autoreceptors (i.e. agonism decreases acetylcholine release) but are thought to be present on some postsynaptic neurons, where their function is not clear. In the human CNS, M_2 density is nucleus basalis > occipital cortex > hippocampus > frontal cortex = temporal cortex = parietal cortex > putamen (Flynn *et al*., 1995). In the periphery, hM_2 receptors are found in very high concentrations in the heart, where stimulation may produce bradycardia (Mutschler *et al*., 1995) and in smooth muscle such as in the intestine and bladder, where activation may indirectly inhibit relaxation (Ehlert and Thomas, 1995). hM_3 receptors are found at very low densities in the CNS and may have limited effects there (Ehlert and Thomas, 1995). Their CNS density is reported to be frontal cortex = temporal cortex = parietal cortex > occipital cortex > hippocampus > nucleus basalis > > putamen (Flynn *et al*., 1995). hM_3 receptors are thought to be much more important in the periphery than in the CNS. Peripheral hM_3 receptors are found in very high concentrations in exocrine glands, where stimulation may produce salivation, lacrimation, and sweating and, conversely, blockade might be expected to produce dry mouth, dry eyes and dry skin. hM_3 receptors are found in moderate concentrations in ocular ciliary muscle and peripheral smooth muscle, where stimulation may produce increased ocular fluid outflow, contraction of intestinal smooth muscle and urinary bladder contractions and blockade may produce acute exacerbation of glaucoma, constipation and urinary bladder atony (Pang *et al*., 1994; Ehlert and Thomas, 1995; Mutschler *et al*., 1995; Erickson and Schroeder, 2000). hM_4 receptors are predominately localized to the basal ganglia and cerebral cortex with the highest concentrations observed in neostriatum, olfactory tubercle and islands of Callej, suggesting an important role in extrapyramidal function (Levey, 1993; Yasuda *et al*., 1993). Although controversial, the hM_5 receptor is believed to be unique among muscarinic receptors in its restricted expression to CNS, with highest concentrations found in cortex, substantia nigra, and ventral tegmentum. A role in dopamine regulation has been proposed (Eglen and Nahorski, 2000).

Initial *in vitro* receptor binding studies, conducted under *nonphysiologic* conditions utilizing receptors attached to broken cell membranes in hypotonic medium, indicated that OLZ and CLZ have high receptor affinity for muscarinic receptors M_1–M_5 (Bymaster *et al*., 1996). This affinity was significantly lower when binding was performed in whole, living cells, in an artificial [ionic and pH normal] cerebrospinal fluid medium (aCSF) (Bymaster and Falcone, 2000) rather than saline, whereas the affinity of atropine and amytriptyline were not appreciably decreased. This suggests that the OLZ binding reported in the originally published *in vitro,* radioligand binding study overestimated what occurs *in vivo*. OLZ is apparently very sensitive to the microenvironment in which it is studied (Bymaster and Falcone, 2000). Under *physiological* conditions similar to those expected to occur in the CNS, OLZ appears to undergo substantial weakening of its binding affinity to most of the hM receptors. This effect of experimental conditions on muscarinic receptor affinity for OLZ and CLZ is summarized in Table 4. Note that the revised receptor binding reported in Table 4 is somewhat different than that in Table 2 because of differences in technique. Assays reported in Table 3, as mentioned above, were from broken, washed

Table 4. Original and revised muscarinic receptor binding affinity of olanzapine, clozapine, atropine, and risperidone (receptor Ki, nM)

Compound/Receptor		M1	M2	M3	M4	M5
Olanzapine	Original*	2.5	18	13	10	6
	Revised**	73 ± 14	96 ± 24	132 ± 30	32 ± 6	48 ± 10
Clozapine	Original*	1.4	10	7	6	5
	Revised**	31 ± 9	204 ± 33	109 ± 22	27 ± 3	26 ± 18
Atropine	Original*	0.2	1.5	0.2	0.1	0.6
	Revised**	1.1 ± 0.3	0.9 ± 0.1	0.8 ± 0.1	0.3 ± 0.02	0.5 ± 0.2
Risperidone	Original*			> 5000		

*Data from: (^{3}H) QNB binding to rat cortex membranes in hypnotic (nonphysiological) media. Ref: Bymaster *et al.* 1996.
**Data from (^{3}H) NMS binding to clonal human muscarinic receptor subtypes in physiological media. Ref: Bymaster *et al*. (2000).

membranes from frozen CHO cells using the scintillation proximity assay method. In contrast, the revised method in Table 4 used whole, living CHO cells. Receptors with bound radioactivity were separated from buffer and unbound radioactivity with vacuum filtration through glass fiber filters. Both used artificial cerebrospinal fluid and measured 3H-N-methylscopolamine binding. Generally, although binding affinities differ somewhat by technique, relative affinity and rank order of medications are similar between the two assays.

To test the validity of *in vitro* receptor pharmacological methods to predict *in vivo* experiences in patients requires examination of relevant data from human studies. Clinical data include two studies comparing anticholinergic-like adverse events during treatment with OLZ versus RIS and CLZ, respectively, in patients age 18–65 with schizophrenia (Chengappa *et al.*, 1999; Kennedy *et al.*, 2000). These studies evaluated peripheral activity, in a posthoc analysis of spontaneously reported adverse events (Kennedy *et al.*, 2000) and by directed enquiry into anticholinergic-like events (Chengappa *et al.*, 1999). For OLZ-treated patients, four key anticholinergic-like events (blurred vision, dry mouth, constipation, and urinary difficulties) occurred at relatively low rates compared to anticipated rates based upon characterized *in vitro* pharmacology. These results further support a conclusion that the original *in vitro* binding data showing high affinity of OLZ to muscarinic receptors inaccurately reflects *in vivo* anticholinergic-like adverse events. Instead, data from these studies indicate that the rate of anticholinergic-like adverse events observed in patients is comparable or lower than that temporally associated with other antipsychotic medications such as RIS. Because RIS has very low *in vitro* (Table 2) or reported *in vivo* direct interaction with cholinergic receptors, the observation of anticholinergic-like events with RIS calls into question the specificity of the relationship between these events and direct cholinergic receptor antagonism.

Further clinical evidence suggesting a lack of potent anticholinergic effects during OLZ treatment is presented by Purdon *et al.* (2000), who examined centrally-mediated cognitive changes in patients treated with OLZ, RIS, and HAL early in their schizophrenia illness course. In this small, prospective study, within group analysis of the mean change from baseline found that during treatment with OLZ, there were statistically improved cognitive functioning in six of seven measures, in three of seven measures with RIS, and in two of seven measures with HAL. Patients treated with OLZ showed statistically superior cognitive functioning on two of seven measures compared to RIS and HAL treated patients. Neither of these comparators was superior to OLZ on any measure. Of particular note, measures of new learning, considered especially sensitive to the adverse effects of anticholinergic medication (Kennedy *et al.*, 1998), actually improved during OLZ therapy.

A summary of the data, which is included in the US Food and Drug Administration (FDA) approved prescribing information, related to four anticholinergic type events (blurred vision, dry mouth, constipation, micturition disturbances) for five medicines [RIS, QUET, OLZ, Nefazodone (Serzone®), Certirizine (CERT, Zyrtec®)] (Table 5) suggests that these events reflect a broader range of interacting effects on neurotransmission and are not well predicted by simple *in vitro* estimates of muscarinic antagonism. The variety of the possible mechanisms of these clinically observed events has been previously noted (Bein, 1977). For example, recent research indicates that constipation is mechanistically and clinically attributable to 5-HT antagonism (Briejer *et al.*, 1995a,b; Borman and Burleigh, 1996; Nagakura *et al.*, 1996; Graf and Sarna, 1997), while other

Table 5. Anticholinergic-like adverse events during treatment with nefazodone, olanzapine, risperidone, quetiapine, and certirizine. Data are based upon data reviewed by the FDA and published in the manufacturers' Physician's Desk Reference (2001), not upon head to head, placebo-controlled comparative trials. Therefore, this table may not reflect the adverse events during treatment with each drug relative to placebo

	Nefazodone	Olanzapine	Risperidone†	Quetiapine	Certirizine
Dry Mouth	2 × > placebo	2 × > placebo	2 × > placebo	2 × > placebo	2 × > placebo
Blurred vision	3 × > placebo	Infrequent*	2 × > placebo	Infrequent**	< 2%
Constipation	2 × > placebo	2 × > placebo	2 × > placebo	9% *vs* 5%	2%
Micturition disturbances.	2 × > placebo	Infrequent	2 × > placebo	Infrequent	< 2%

†post-US marketing information.
*15 ± 2.5 mg/day.
** > 75 mg/day.

events, such as dry mouth, may also be related completely or in part to activity at other receptors (Boyd *et al*., 1997; Sekine *et al*., 1999; Spencer *et al*., 1999; Zisook *et al*., 2000; Penttila *et al*., 2001; Schweitzer *et al*., 2001). The data for OLZ (Table 5) are most consistent with non-cholinergic receptor based mechanism(s) influencing the relatively infrequent occurrence of peripheral anticholinergic type events with OLZ therapy. For OLZ, as can be seen in Table 3, the hM_3/D_{2L} ratio is '10' (i.e. approximately tenfold greater affinity for D_2 versus hM_3). This large ratio suggests that, except at very high dosages, OLZ would not be anticipated to interact significantly with the hM_3 receptor, the muscarinic receptor that in large part regulates salivation. Therefore, an event such as dry mouth, which does occur at a relatively low rate with OLZ therapy, is unlikely to be mediated by antagonism of the hM_3 receptor. Events such as dry mouth and constipation may best be referred to as 'anticholinergic-like' as they seem unlikely to reflect direct cholinergic antagonism.

To fully evaluate anticholinergic as well as anticholinergic-like activity, it is necessary to examine a population known to be sensitive to adverse consequences of anticholinergic medicines. This could include patients with AD, as they have been experimentally demonstrated to be more sensitive to the adverse potential of a well-characterized anticholinergic medicine (scopolamine) compared to elderly normal controls (Sunderland *et al*., 1987). Two large, placebo-controlled, clinical trials (HGEU, Street *et al*. (2000) and HGAO, Satterlee *et al*. (1995) and Lane *et al*. (1998)) have evaluated OLZ's safety and efficacy for psychosis in patients with AD in nursing home and outpatient settings. The total pooled sample of randomized, AD patients by therapy group were Placebo ($n = 139$), OLZ [1–8 mg/day; mean modal dose 2.4 mg/day] ($n = 189$), OLZ [5 mg/day] ($n = 56$), OLZ [10 mg/day] ($n = 50$), and OLZ [15 mg/day] ($n = 54$). Across dementia trials in the pooled mean modal dose range of 1–15 mg OLZ, adverse events observed more often with OLZ than placebo included somnolence (dose dependent above 10 mg/day) and changes in gait (discussed below). Compared to placebo, in none of the OLZ dose cohorts in HGEU did patients experience statistically significantly greater peripheral anticholinergic events (blurred vision, dry mouth, constipation, urinary retention), or cognitive impairment. In fact, a focused enquiry into any central and peripheral anticholinergic-like events in study HGEU found no single event was more common for any OLZ dose cohort compared to placebo. Only patients treated with 15 mg OLZ experienced significantly greater anticholinergic-like peripheral events than placebo when all peripheral events were summed (see Table 6). Somnolence (discussed below) was the only event that increased dose dependently in this population with OLZ administration and this was most evident in the dose transition from 10 to 15 mg.

Table 6. Potential central and peripheral treatment—emergent anticholinergic-like events in patients with Alzheimer's disease (HGEU).[2] No event at any dose was significantly different from placebo.

COSTART Term	Placebo ($n = 47$)	Olanzapine 5 mg ($n = 56$)	Olanzapine 10 mg ($n = 50$)	Olanzapine 15 mg ($n = 53$)
Central	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Agitation	4 (8.5)	5 (8.9)	6 (12.0)	6 (11.0)
Confusion	2 (4.3)	2 (3.6)	5 (10.0)	3 (5.7)
Delirium	0 (0)	0 (0)	1 (2.0)	0 (0)
Delusions	3 (6.4)	1 (1.8)	3 (6.0)	0 (0)
Dyskinesia	0 (0)	1 (1.8)	0 (0)	0 (0)
Fever	1 (2.1)	5 (8.9)	7 (14.0)	7 (13.0)
Hallucinations	2 (4.3)	4 (7.1)	2 (4.0)	3 (5.7)
Thinking Abnormal	0 (0)	3 (5.4)	4 (8.0)	0 (0)
Twitching	0 (0)	0 (0)	0 (0)	1 (1.9)
Peripheral				
Amblyopia	0 (0)	1 (1.8)	0 (0)	0 (0)
Constipation	2 (4.3)	2 (3.6)	3 (6.0)	4 (7.5)
Dry Mouth	1 (2.1)	3 (5.4)	1 (2.0)	0 (0)
Dry Skin	0 (0)	0 (0)	0 (0)	1 (1.9)
Fecal Impaction	1 (2.1)	1 (1.8)	1 (2.0)	2 (3.8)
Intestinal Obstruction	0 (0)	0 (0)	1 (2.0)	0 (0)
Tachycardia	0 (0)	2 (3.6)	1 (2.0)	1 (1.9)
Urinary Retention	0 (0)	0 (0)	1 (2.0)	1 (1.9)
Vasodilation	0 (0)	0 (0)	1 (2.0)	0 (0)

Finally, as reported separately in this supplement (Kennedy *et al*., 2001), a subanalysis of the HGEU nursing home study (Street *et al.*, 2000) suggests that the occurrence of presumed, centrally-mediated adverse events, such as hallucinations or delusions, was not significantly greater in AD patients treated with OLZ compared to placebo. These observations are also not expected of a medication with significant anticholinergic effects.

However, excess sedation, confusion, hallucinations, and delirium have been reported in elderly patients during treatment with OLZ and other atypical antipsychotics (RIS, CLZ, QUET) (Pitner *et al*., 1995; Byerly *et al*., 1995; Lee and Robertson, 1997; Stanilland *et al*., 1997; Ravona-Springer *et al*., 1998; Young *et al*., 1998; Fernandez *et al*., 1999; Doig *et al*., 2000; Sim *et al*., 2000). Such reports stand in counterpoint to the suggested cognition benefit in young patients with schizophrenia as well as that which possibly occurs in elderly AD patients with psychosis and agitation. That such adverse events also have been reported at variable rates during treatment with all atypical antipsychotic medications suggests a potentially significant role for H_1 antagonism. However, the lack of any public report of the activity of a highly specific H_1 antagonist with predictable CNS activity limits the ability to conclude that H_1 receptor antagonism is principally responsible. It is known that the H_1 receptor has a CNS distribution that is primarily cortical with a variable density distribution in several brain regions (Nath *et al*., 1988; Cacabelos *et al*., 1989; Klemm, 1989; Higuchi *et al*., 2000; Allison and Casey, 2001). Clinical evidence in support of these adverse events being attributable to hH_1 antagonism is seen in the effects of the widely prescribed, specific hH_1 antagonist certirizine (US tradename Zyrtec®). Certirizine (CERT) has predictable (i.e. commonly reported) dry mouth, somnolence and infrequent ($< 2\%$) adverse events including confusion and increased appetite, amongst many others (Nath *et al*., 1988; Cacabelos *et al*., 1989; Klem, 1989; Higuchi *et al*., 2000). The rank order of human H_1 (hH_1)/hD_2 ratios, as presented in Table 3, is CLZ $(0.001) = $ QUET $(0.007) > > $ OLZ $(0.02) > > $ ZIP $(3.3) = $ RIS $(4.6) > > >$ HAL (359). All of the examined atypical medications have an hH_1/hD_{2L} ratio suggestive of potential hH_1-related clinical activity within each medication's therapeutic dose range. However, the relative frequency of adverse events that may be related to H_1 antagonism, such as weight gain, does not correspond in a simple and predictable fashion to these ratios (Allison and Casey, 2001). Among many potential reasons for the apparent lack of a predictive relationship between the ratio of binding to hH_1/D_{2L} is the large variation in circulating drug concentrations across individuals receiving the same oral dose of a medication. For example, the plasma level variation for OLZ is modest (Callaghan *et al*., 1999), while for RIS plasma level variation is very large (DeVane, 1995). This may explain partly why it is difficult to predict the potential for treatment-emergent adverse events such as EPS and confusion during treatment with some medications, even at very low doses. Also, there are large differences between medications in their lipophilicity. This chemical characteristic influences the relationship between blood and brain concentrations of medications such that for medications with very high lipophilicity compared to those with lower lipophilicity, the brain concentrations would be expected to be higher. For these reasons, the significance of the apparent hH_1/D_{2L} numerical ratio differences between OLZ, RIS, and ZIP is unclear. These differences, for example, would suggest that less weight gain would be expected in RIS-treated patients than in ZIP-treated patients, and it appears, based upon review of data from non-head to head trials (Physicians Desk Reference, 2001), that this is not the case. Therefore, given very large variations in blood concentrations across patients from the same, fixed oral dose, it can be hypothesized that the capacity of atypical antipsychotic medications to block the hH_1 receptor, even at very low doses, may play a role in sedation, confusion, and in patients with neurodegeneration, possibly, hallucinations and, potentially, delirium. As a final consideration of the complexity surrounding the assignment of causality to any particular receptor effect alone for adverse events commonly considered to be due to anticholinergic activity, somnolence, which may be attributable primarily to atypical antipsychotic antagonism of the H_1 receptor in the cortex (Hill *et al*., 1978), theoretically, may also arise independently of hH_1 antagonism through the class-related effect of increasing brain dopamine concentrations. It is well understood that some agonists that mimic dopamine effects at the D_1 receptor commonly produce sedation. Therefore, increased stimulation of the D_1 receptor should be evaluated as a potential contributor to the sedation observed in some patients with AD during treatment with OLZ and the other atypical antipsychotics. It is noteworthy, however, that while somnolence was noted to occur in 25 and 26% of the 5 and 10 mg/day OLZ patients, respectively, in the HGEU study of patients with Alzheimer's Disease and psychosis (Street *et al*., 2000) this adverse event was not a

dominant factor in the causes of discontinuation in these treatment groups. In fact, the overall group-related discontinuation rates in that study were numerically higher on placebo than in the 5 mg OLZ group, very similar for placebo and OLZ 10 mg/day, but significantly lower on placebo than in the 15 mg OLZ group in this study of, on average, severely demented AD patients with psychosis. This suggests that, when somnolence was present in patients treated with 5 and 10 mg OLZ per day, it was only infrequently more than mild in intensity.

In summary, in the currently available dose range of 2.5–20 mg/day (where the daily dose will most often be lower than 15 mg for treatment of psychosis occurring in AD, but the dose may be 20 mg for some elderly patients with schizophrenia) OLZ is well tolerated from the perspective of peripheral and central nervous system cholinergic activity.

The clinical data discussed above on central and peripheral adverse events are consistent with the revised preclinical observation that OLZ possesses moderate to weak hM receptor affinity, as presented in Tables 2 and 4. OLZ appears *in vitro* to differ from other antipsychotic medications in having greater hM_2 than hM_1 receptor antagonist activity. The *in vitro*-characterized data concerning potential cholinergic system activity *in vivo* in humans suggests that, for agents such as OLZ, examination of human muscarinic receptor binding affinity, under approximate physiological conditions, is predictive of their effects in clinical populations. The ability to predict differences between medications based upon *in vitro*-characterized histaminic receptor activity is unclear.

EXPLORING THE MECHANISTIC RELATIONSHIP OF WEIGHT CHANGE WITH ATYPICAL ANTIPSYCHOTICS AND THE ASSOCIATION OF WEIGHT GAIN WITH DYSREGULATION OF BLOOD GLUCOSE AND CHOLESTEROL LEVELS

The mechanism(s) underlying weight gain during treatment with psychotropic medications is unclear. Antagonism of several receptors (e.g. histaminergic, serotonergic) has been suggested to influence weight in humans. It is likely that the important but very small percentage of patients who experience very large weight gain do so because of the involvement of multiple biopsychosocial factors, where individual sensitivity to a biological mechanism is contributing to their differential response. From a mechanistic perspective, as discussed above, antagonism of the H_1 receptor is a common feature of the atypical antipsychotics for which treatment-emergent weight gain has been reported. However as discussed above, the relative amount of treatment-emergent weight gain does not correspond well to hH_1/D_{2L} ratios. In addition to the physicochemical and pharmacokinetic differences discussed above, a further potential explanation for this disparity is that binding to hH_1 receptors is only part of the explanation for weight gain and, likely more than one mechanism is involved. In this regard, recent interest has focused on the role of serotonin $5HT_{2C}$ receptor antagonism in weight gain. Mice with genetic 'knockout' of $5HT_{2C}$ receptors demonstrate increased food intake, increased body weight and adipose tissue and reduced sensitivity to the appetite suppressing effects of non-specific serotonin agonists compared to wild-type mice (Tecott *et al*., 1995). However, counter to the theory that $5HT_{2C}$ antagonism has a prominent role in weight regulation is the observation that both ZIP and CLZ are potent $5HT_{2C}$ antagonists (Table 3), yet relatively low mean weight gain has been reported during ZIP treatment, in contrast to patients treated with CLZ (Allison *et al*., 1999). It may be that the effects of hH_1 antagonism when potent, are more important than potent $h5HT_{2C}$ blockade and that the effects of potent $5HT_{2C}$ blockade only become apparent in the presence of less potent hH_1 antagonism.

Weight gain more commonly affects younger patients rather than the elderly. In clinical studies of schizophrenia and related disorders, patients, aged 18–65, had a statistically significantly greater increase in weight during treatment with OLZ compared to placebo or HAL (Dewey and O'Suilleabhain, 2000; Basson *et al*., 2001; Kinon *et al.*, 2001). In acute treatment (6 weeks), OLZ treated patients gained significantly more weight than HAL treated patients, but no significant differences occurred between OLZ and RIS treated patients (Basson *et al*., 2001) (see Figure 1). However, after 28 weeks of treatment, OLZ treated patients gained significantly more weight than RIS treated patients (4.1 kg *vs* 2.3 kg) (Tran *et al*., 1997). Conley and Mahmoud (2001) found significantly greater weight gain in OLZ treated patients compared to RIS treated patients after 8 weeks. In long-term treatment (between 39 weeks and 3 years), OLZ treated patients (mean duration of treatment: 2.5 years) gained a mean of 6.26 kg (13.8 lb) compared to 0.69 kg (1.5 lb) for HAL treated patients (mean duration of treatment: 1.2 years) (Kinon *et al*., 2001). Within relatively young, schizophrenia afflicted patients treated with OLZ for up to three years, weight gain was inversely related to entry baseline body mass index, correlated with greater

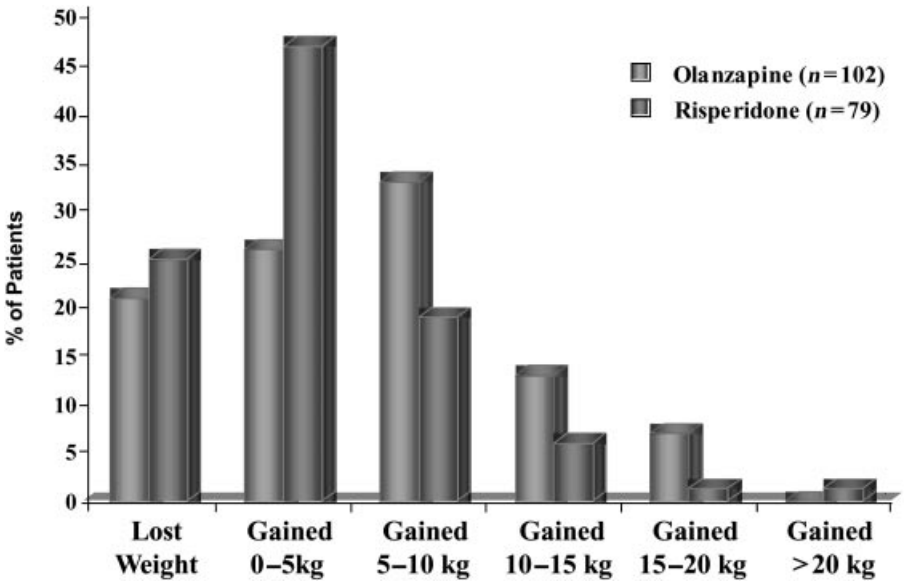

Figure 1. Weight change in patients treated with olanzapine versus risperidone at 28 weeks. Data from Jones *et al*., 2001

efficacy, began early in treatment, and plateaued after about 39 weeks of treatment (Dewey and O'Suilleabhain, 2000; Basson *et al*., 2001; Kinon *et al*., 2001).

In the elderly patient with dementia, weight loss is the more relevant concern (Henderson, 1990). The prevalence of undernutrition in community-dwelling elderly people is reportedly 5–12% (Henderson, 1990; Elander and Hermeren, 1995; McCormack, 1997). In nursing home patients, the prevalence ranges from 20–54% (Friedman, 1991; Thomas *et al*., 1991; Keller, 1993; Morley and Kraenzle, 1994; Gants, 1997; Jimenez-Jimenez *et al*., 1998; Silver *et al*., 1998; Fernandez *et al*., 2000; Manson *et al*., 2000). It is important to note that aging per se is associated with physiological anorexia. Unintentional loss of $\geqslant 5\%$ of their body weight in 30 days or 10% of their body weight in 180 days occurs in 10% of nursing home residents (Blaum *et al*., 1995). For example, in very healthy elderly individuals as well as the general elderly population there is an established decline in food intake and energy expenditure (Cohen, 2000). Roberts *et al*. (1996) found that when elderly individuals decrease their food intake, they appear to reset their 'appetostat' and then find it difficult to increase food intake appropriately after weight loss.

Some evidence exists that elderly patients with AD may not experience the same degree of weight gain during OLZ treatment as younger patients with schizophrenia. In the 8 week outpatient study HGAO (Satterlee *et al*., 1995; Lane *et al*., 1998), at a mean modal dose of 2.4 mg/day, OLZ patients had modest, but statistically significant weight increases compared to placebo. In the six week, HGEU study (Street *et al*., 2000), OLZ—treated, AD patients with psychosis gained a mean 0.8 kg compared to a mean loss of 0.19 kg for the placebo group. These data suggest that some AD patients will gain weight, which is often a desirable outcome; however, this is not a robust or predictable outcome.

Glucose dysregulation

An important clinical concern is whether weight gain during treatment with psychotropic medications may predispose patients toward or exacerbate other medical conditions such as diabetes or heart disease. The criteria for defining the presence of elevated blood glucose and the threshold for defining the presence of diabetes has been a recent focus of research by the World Health Organization (Lim *et al*., 2000; Metcalf and Scragg, 2000) and the American Diabetes Association (ADA) (ADA, 2000). Current ADA guidelines indicate fasting glucose $\geqslant 126$ mg/dL or 2 hour post-prandial glucose $\geqslant 200$ mg/dL support a diagnosis of diabetes mellitus and elevation of random plasma glucose > 160 mg/dL is a clinical indication for further workup for diabetes.

From an epidemiological perspective, obesity is one of many risk factors for diabetes. There is an

established association between being overweight and increased risk for type 2 diabetes (non-insulin dependent diabetes mellitus) (Kannel, 2000) [odds ratio for women $\geqslant 75\%$ above their ideal body weight compared to women $< 10\%$ above their ideal body weight is 7.2 (Morris *et al*., 1989)]. It is also clear from epidemiological studies that diabetics have an increased risk of cardiovascular disease, excess mortality from cardiovascular disease, and worse outcomes after myocardial infarctions. Abnormal glucose tolerance is associated with over 200 times excess risk accumulated over many decades for cardiovascular disease (Bonora *et al*., 2000; Van Rossum *et al*., 2000). In the new National Cholesterol Education Program (NCEP) guidelines (NCEP, 2001), diabetes is considered as a coronary heart disease (CHD) equivalent because the future risk of a cardiovascular disease event in a diabetic individual is similar to an individual who has already had a myocardial infarction. However, this should not be interpreted to imply the presence of a 1:1 causal relationship for such undesirable outcomes. In fact, impaired glucose tolerance is only one of many risk factors for cardiac disease and, when present, it does not always result in a worsened cardiac status.

In the general US adult population, the prevalence of diagnosed diabetes was 5.1% (Harris *et al*., 1998). More recent data suggest that the prevalence of undiagnosed diabetes is approximately 2.7%, and the prevalence of impaired glucose tolerance (previously called borderline diabetes) is 6.9% (Harris *et al*., 1998; Mokdad *et al*., 2000; Bednar *et al*., 2001). In contrast, the prevalence of diabetes in the overall US schizophrenia population has been estimated to be 2 to 4 times greater than in reference populations (Keskiner *et al*., 1973; McKee *et al*., 1986; Mukherjee, 1995), as high as 24.5% (Mukherjee, 1995) and a series of reports, several antedating the introduction of antipsychotic drugs (Lorenz, 1922; Braceland *et al*., 1945; Freeman, 1946), document higher than anticipated prevalence of diabetes in schizophrenia.

What then are the clinical implications arising from the preceding? To date, the available data suggest the interpretation that predisposition, such as family history or other less certain factors, may be the most important risk predictor for diabetes. Also, new onset diabetes will be observed in patients treated with any antipsychotic medication and, therefore, attention to this health issue, intended to allow its recognition and optimal treatment, is a good standard of medical practice. Many of the health risks associated with diabetes exist when diabetes is undiagnosed, diagnosed but not treated, and treated in such a fashion that it remains poorly controlled.

The differential etiology of type 2 diabetes, impaired glucose tolerance, and/or impaired fasting glucose is very lengthy (National Diabetes Data Group, 1995) including obesity and weight gain, dyslipidemia, lack of exercise, and hypertension (ADA, 2000; Rewers and Hamman, 1995; Ford *et al*., 1997). Secondary causes include conditions such as pancreatic insufficiency due to alcohol abuse, chronic pancreatitis of multiple potential etiologies, hemochromatosis, malignancies of the pancreas, and endocrine disorders (see reviews by ADA Screening for Type 2 Diabetes (ADA, 2000), Foss *et al*. (1995); Rewers and Hamman (1995); Cowie and Eberhardt (1996); and Ford *et al*. (1997)). Type 2 diabetes, impaired glucose tolerance, and/or impaired fasting glucose are associated with intrinsic factors such as family history, ethnicity, previous history of glucose intolerance, and advancing age (> 45 years) (Harris *et al*., 1998), as individuals decrease their activity levels and lose lean body mass and gain fat stores. Because of the many conditions associated with type 2 diabetes, impaired glucose tolerance, and/or impaired fasting glucose, it is important to be mindful when assessing their etiology in populations particularly vulnerable to such conditions.

Insulin resistance and other metabolic abnormalities are characteristic but not pathognomonic or pre-determinant features of type 2 diabetes (Harris, 1995; Mayfield, 1998). Epidemiological data from the US have suggested that the incidence of type 2 diabetes increases with age, with an almost two-fold increase past age forty-nine (Bednar *et al*., 2001). Other epidemiological data from Europe, North America, and other continents suggest that, in geriatric patients in the community and long-term residential supervised care, impaired glucose tolerance, as well as frank diabetes, often are unrecognized by the patient, family, and medical community (Spooner *et al*., 2000; Teuscher *et al*., 2001). Therefore, given such high background rates and high rates of unrecognized impaired glucose tolerance, it is difficult to evaluate the effects of medications when cases of glucose dysregulation are seen in temporal association with their administration. As has been discussed elsewhere (Gait *et al*., 2001; Altman *et al*., 2001), a primary reason for placebo-controlled, randomized medication trials is the need to assess the safety of new medications. Although such trials are typically focused on efficacy, if they are large enough and the adverse event of interest frequent enough, they may also reveal a causal relationship to a previously

expected or unexpected adverse event of the medication. However, clinical trials have limitations. Even those with relatively large sample sizes may still not have the ability to uncover relatively rare events. A stronger tool may be the use of epidemiological studies. A recent, retrospective cohort study determined the risk of developing diabetes mellitus during antipsychotic treatment, using prescription claim data from AdvancePCS (300 million prescription claims per year were processed for over 50 million members across the US) (Cavazzoni *et al*., 2001). Patients who were managed by a single antipsychotic (19,782 patients on conventional and 38,969 patients on atypical antipsychotic medications) were examined using new prescription claims for anti-diabetic agents. In this large database, results indicated an increased risk of developing diabetes compared to the general AdvancePCS patient population for patients treated with either conventional or atypical antipsychotics. The risk of diabetes was fairly comparable for all antipsychotic cohorts studied.

The mechanisms underlying type 2 diabetes have been examined for many years. Type 2 diabetes involves a defect in insulin secretion and insulin resistance. The relative contribution varies across individuals, influenced by factors such as weight, obesity, and ethnic background. Nevertheless, it remains uncertain what role, if any, antipsychotics have in the high rates of diabetes in the mentally ill population. It has been suggested that drugs may have a direct effect to decrease insulin secretion or cause insulin resistance directly, and that there are weight related effects of drugs on metabolic parameters including glucose and lipids. In light of the preceding, it is noteworthy that many case studies have reported at least a temporal association between impaired glucose tolerance and psychiatric medications including the phenothiazines (Thonnard-Neumann, 1968), HAL (Mukherjee *et al*., 1989), loxapine (Tollefson and Lesar, 1983), and QUET (Sobel, *et al*., 1999), RIS (Melamed *et al*., 1998; Croakin *et al*., 2000), CLZ (Lamberti *et al*., 1992; Koval *et al*., 1994; Kostakoglu *et al*., 1996; Popli *et al*., 1997; Mir and Taylor, 2001), and OLZ (Lamberti *et al*., 1992; Wirshing *et al*., 1998; Lindenmayer and Patel, 1999; Rigalleau *et al*., 2000; Mir and Taylor, 2001). Reports also suggest an association between antipsychotic medications and diabetes (Lamberti *et al*., 1992; Leadbetter *et al*., 1992) and cardiovascular disease (Koval *et al*., 1994; Popli *et al*., 1997). However, on closer inspection, most of these case studies include patients with other risk factors, and the associations are based upon relatively short-term observations with small sample sizes. Additional analyses were performed to better characterize diabetes risk in OLZ-treated patients.

Across controlled schizophrenia trials with active comparators (Allison *et al*., 2001) (OLZ *vs* HAL: $N = 2599$, OLZ *vs* placebo: $N = 366$, and OLZ *vs* RIS: $N = 339$), mean random plasma glucose increased during OLZ treatment from 0.8–4.6 mg/dL. While the mean increase in glucose during OLZ treatment was significantly less than that observed with CLZ (13.2 mg/dL), it was not significantly different than observed with RIS (2.6 mg/dL), and was significantly greater than observed with HAL (0.2 mg/dL). In this population analysis, after accounting for the mean increases, plasma glucose levels remained well within the clinically normal range. Because the clinical significance of small changes in mean random glucose are not always apparent, a second analysis (Allison *et al*., 2001; Allison and Casey, 2001) examined the likelihood of a patient experiencing a glucose value exceeding any of four potentially important random glucose thresholds: 126, 140, 160, and 200 mg/dL. The likelihood of reaching any of these thresholds did not significantly differ between OLZ, HAL or RIS treated patients. OLZ treated patients were less likely than CLZ treated patients to reach the 126 or 140 mg/dL thresholds. Across comparisons, few patients reached the 160 and 200 mg/dL thresholds, thereby decreasing the power to detect such differences (Beasley *et al*., 2000). In a separate subanalysis of the overall 2500 patient database which examined 573 patients with schizophrenia who took OLZ (5–20 mg) for between 39 weeks and 3 years, it has been demonstrated (Kinon *et al*., 2001) that median serum glucose at endpoint was not statistically different between treatment groups and was not significantly associated with weight change at endpoint ($p = 0.096$). In this analysis, 79% of patients that demonstrated any degree of hyperglycemia (random glucose $\geqslant 126$ mg/dL) did not demonstrate significant weight gain. Further, 95% of patients who gained weight demonstrated normal glycemic control. Limitations of these studies include their moderate durations and the post hoc nature of the analyses. However, these data do support the view that factors other than weight gain have a substantial role in altering blood glucose concentrations.

Reports from newly available clinical agents will continue to provide an opportunity to clarify the mechanisms of drug action which contribute to the development of glucose dysregulation. One such example is ZIP, which has been marketed as having an advantage over other available agents in demon-

strating a lesser potential to be associated with weight gain. While little data concerning ZIP's effects in the elderly are currently available, the public release of a head-to-head study of ZIP versus OLZ in patients with schizophrenia is of interest despite being conducted in patients who were not elderly. A recent, Pfizer-sponsored, prospective, 6-week long study (Glick *et al*., 2001) found no differences in fasting blood glucose in patients with schizophrenia treated with ZIP ($n = 136$) or OLZ ($n = 133$). Median fasting plasma glucose increased by 1μg/dL in both the ZIP and OLZ groups. Weight, fasting insulin, and insulin resistance (as measured by HOMA IR: [insulin × glucose]/22.5) increased significantly within OLZ—but not within ZIP-treated patients. However, there was no significant between-group difference. The within group effects potentially reflect the lower mean weight gain during treatment with ZIP (Keck *et al*., 1998; Daniel *et al*., 1999; Simpson *et al*., 2001), perhaps due in part to the nausea commonly observed (Keck *et al*., 1998; Daniel *et al*., 1999). These data do provide support for the view that modest weight gain or weight loss present for short periods of time across a population of patients, does not allow prediction of the effects of such weight change on insulin-related activity.

Given the many factors that can destabilize glucose, the lack of a 1:1 correspondence between weight change and hyperglycemia or diabetes, and the high rate of diabetes among individuals with schizophrenia, definitive conclusions regarding the relationship between OLZ and impaired glucose tolerance cannot be drawn at this time.

Finally, data on glucose regulation in the elderly is very limited. Based on the limited epidemiological data, there is no suggestion of difference in young *vs* old patients treated with OLZ.

Cholesterol and triglycerides

As would be expected of any class of medications being closely examined for potential unwanted effects on glucose metabolism, there are some anecdotal reports of cholesterol increasing during OLZ treatment (e.g. Fryburg *et al*., 2001); however, other authors do not confirm this association (Osser *et al*., 1999; Kinon *et al*., 2001). In fact, the largest and longest study involving 573 patients (Kinon *et al*., 2001) (discussed above) median cholesterol in patients observed for a median of 2.5 years was essentially unchanged. The overall prevalence of cholesterol > 240 mg/dL after OLZ was 23.8%, which is similar to the general US population rate of approximately 20% (Ernst *et al*., 1997). Obesity is a risk factor for hypercholesterolemia. In this post-hoc analysis, median nonfasting cholesterol increased from 205.0 to 205.7 mg/dL. A correlation between median serum cholesterol and weight gain ($p < 0.001$) was found among OLZ treated patients (Kinon *et al*., 2001). The incidence of cholesterol ⩾ 240 mg/dL at endpoint was significantly more likely in participants gaining > 10 kg compared to those gaining ⩽ 10 kg (24.3% *vs* 11.6%; $p < 0.01$).

With respect to the elderly patient, hypercholesterolemia is very prevalent in the general population (Guize *et al*., 1998; Gardner *et al*., 2000; Hall and Luepker, 2000). In the National Health and Nutrition Survey (NHANES III), 39% of 65 to 74 year old respondents and 32% of respondents ⩾ 75 years old had cholesterol levels ⩾ 6.20 mM/L (240mg/dL) (Sempos *et al*., 1993). Within the limited OLZ database of elderly patients, the pattern of cholesterol changes appears to be the same as that seen in the younger patient population.

Given the association of obesity of any etiology and elevated cholesterol levels, it is a good standard of medical practice to assess and, if necessary, treat elevated cholesterol levels in patients with substantial, persistent weight gain. It is also important to note recent changes in the US guidelines for which individuals should receive prophylactic care for high cholesterol (NCEP, 2001). Because of the guideline changes, more patients will fall into categories requiring intervention.

Fewer data are available on triglycerides. Available reports include several retrospective case series of individuals with some elevation during OLZ treatment (Sheitman *et al*., 1999; Melkersson *et al*., 2000), one cross-sectional study ($n = 44$) (Bouchard *et al*., 2001) indicating OLZ treated patients had significantly higher plasma triglyceride concentrations than RIS treated patients, a prospective trial ($n = 25$), reporting a median increase of 60 mg/dL after 12 weeks on a mean dose of 13.8 mg/day OLZ (Osser *et al*., 1999), and a head to head trial of OLZ *vs* ZIP (Glick *et al*., 2001), reporting significant increases in insulin, insulin resistance, and weight during OLZ treatment. Increased appetite has been commonly reported during OLZ treatment.

There are many causes of elevated triglycerides including insulin resistance, diabetes, obesity and weight gain, high carbohydrate diet, physical inactivity, smoking, alcohol, genetic dyslipidemias, and renal failure. Triglyceride concentration appears more sensitive to diet (and therefore, increased appetite) than is serum cholesterol (Ros, 2000). There is also

very large intra and interindividual variability in triglyceride levels. Therefore, it is plausible that over an extended period of time increases in average triglyceride levels may occur in any patient who experiences weight gain in whole or in part as a result of increased appetite during treatment with a psychotropic medication. However, more study is needed in young and elderly patients during treatment with OLZ and other antipsychotic medicines to clarify whether hypertriglyceridemia occurs more often with OLZ than other antipsychotics or more often than would be expected simply as a result of the background prevalence associated with obesity of any etiology.

MANAGEMENT OF WEIGHT GAIN IN PATIENTS

Obesity in the elderly is a prevalent problem, independent of psychotropic medication use (Lin *et al*., 1999). For the patient of any age who becomes obese during treatment with psychotropic medication, pharmacological interventions for weight gain are second line interventions that follow assessment, counseling and behavioral education. This reflects the reality that currently available, potentially helpful, pharmacological interventions are limited because many currently available agents, including sympathomimetics and amphetamines, may interfere with the actions of the psychotropic medication. Also, the available evidence from controlled behavioral intervention trials suggests that behavioral interventions can influence some patients to alter behaviors so that reductions in weight and other associated factors occur (Wirshing *et al*., 1999; Nguyen, 2001). Finally, preclinical, *in vivo*, studies may predict the efficacy of adjunct pharmacological therapies in the clinic, but the lack of well-controlled, clinical treatment trials in psychiatric patients who have become overweight during treatment with psychotropic medication leaves unclear the consequences of applying them clinically. One example of a preclinical finding is that sibutramine, a serotonergic and norepinephrine reuptake inhibitor approved for weight loss in obese patients, when examined in combination with a moderate carbohydrate, low fat diet, significantly reduced weight gain in female Sprague-Dawley rats treated with OLZ. Amantadine and mazindol also decreased weight gain but to a lesser extent than sibutramine (Leander and Gleason, 2001).

Clinical pharmacologic strategies attempting to address weight increases can be divided into two broad approaches: prevention or minimization of weight gain before it has become excessive and induction of weight loss in individuals who have already developed excess weight gain. With respect to the prevention/inhibition of excess weight gain, the use of H_2 antagonists for weight loss has been reported in the peer reviewed literature (Stoa-Birketvedt *et al*., 1998; Sacchetti *et al*., 2000). H_2 antagonists are very widely prescribed for their class-related indications: treatment of ulcers, hypersecretory states, gastroesophageal reflux disease, and erosive esophagitis. Recently their potential role in minimization of weight gain has begun to be evaluated. Sacchetti *et al*. (2000) reported that the H_2 antagonist nizatidine (150 mg bid) given for 4 weeks to a young patient with schizophrenia being treated with OLZ produced a 5% weight loss. The weight loss was maintained during a 2-month follow-up period. Interim results from a recent, placebo-controlled, randomized, double-blind study of nizatidine to prevent weight gain (Breier *et al*., 2001) in OLZ treated patients indicated that significantly less weight gain occurred after a minimum of 3 weeks of treatment with nizatidine (300 mg bid), compared to placebo ($p < 0.02$). In this study, which used a last observation carried forward (LOCF) analysis approach, weight gain at week 16 was 12.1 lbs for OLZ treated patients on placebo, 9.7 lbs. for OLZ treated patients on nizatidine 150 mg bid, and 6.1 lbs. for OLZ treated patients on nizatidine 300 mg bid. The mechanism underlying this apparent effect of H_2 blockade in dose-dependently suppressing early weight gain is currently unknown. It is also unclear in whom this early weight suppressing effects during nizatidine treatment will occur and whether the effect will be maintained.

With respect to induction of weight loss in patients who have already gained excessive weight, some data suggest that amantadine (Correa *et al*., 1987; Floris *et al*., 2001), topiramate (Gordon and Price, 1999; Dursun, 2001) and metformin (Cottingham, 2000) may be developed as safe and effective means of weight loss. It therefore appears that weight gain from antipsychotic therapy may be managed pharmacologically. Prospective studies are clearly needed to identify the most effective therapies for weight management in patients with excessive weight gain and also to determine how to match patients to the prevention strategy most effective for them.

CLINICALLY CHARACTERIZED CARDIOVASCULAR FUNCTION INCLUDING CHANGES IN BLOOD PRESSURE, HEART RATE, AND EFFECTS ON QTc INTERVAL

The human aging process carries with it an ever increasing risk of cardiovascular disorders. For

example, the estimated prevalence of hypotension in the elderly is between 5 to 33% (Alli *et al*., 1992; Verhaeverbeke and Mets, 1997) , cardiac arrhythmias may be equally as common (Tresch, 2001), and heart failure may be present in over 10% of patients age 65 or greater (McGowan *et al*., 2000). Coronary artery disease is the leading cause of death in the US and accounts for approximately 500,000 deaths per year (Centers for Disease Control and Prevention, 2001; Mortality Weekly Report, 2001). Recent studies suggest that coronary calcification, often present as a subclinical event, is strongly associated with male gender and age (Ledru *et al*., 2001) and is associated with frailty (Newman *et al*., 2001). In light of this, it is not surprising that a prevalent clinical concern in assisting the elderly patient is that many commonly used medications may further impair already compromised cardiovascular functioning.

A common clinical concern is the potential for psychotropic medications to induce hypotension (Mets, 1995). Blood pressure is maintained by the ongoing dynamic relationship between vascular resistance and cardiac output. With normal, healthy aging, there is an age-related attenuation in the hemodynamic reflex to orthostatic stress. This is manifested in the elderly patient, in part, as a blunting of reflex tachycardia, which is partially compensated for by a lesser decline in cardiac stroke volume compared to young patients. Typically, systemic venous vascular resistance is not changed with age (Wing *et al*., 1997). However, drugs may alter vascular resistance and increase the propensity for episodic hypotension, perhaps most evidently when the patient changes posture, e.g. standing from a recumbent position. One receptor understood to have a significant role in the regulation of venous vascular resistance is the alpha-1-adrenergic receptor (Garcia-Sainz *et al*., 1999). Antagonism of this receptor may contribute to the emergence of hypotension, urinary incontinence, and peripheral edema. As delineated in Table 3, most antipsychotic medications antagonize this receptor and so induce venous relaxation. The rank order of $r\alpha 1/hD_{2L}$ is $CLZ = QUET > > RIS \geqslant OLZ > ZIP > HAL > > > CPZ$. These *in vitro* data suggest that the risk of $\alpha 1$-antagonism-associated hypotension should be substantially less for patients treated with OLZ compared to CLZ or QUET and less for OLZ than RIS. However, there are several subtypes of the $\alpha 1$ receptor with considerable tissue specific differences in their distribution and data in Table 3 are based on rat $\alpha 1$ receptors only. Examination of the various subtypes using human receptors may produce different results. Consistent with the $\alpha 1$-adrenergic data in Table 3, during clinical trials of over 3,400 largely young patients with schizophrenia, comparing OLZ to either placebo or HAL, there were few clinically significant changes in blood pressure (Beasley *et al*., 1997). However, head-to-head trials in young patients with schizophrenia, of RIS *vs* CLZ, (Azorin *et al*., 2001) OLZ *vs* RIS and OLZ *vs* CLZ (Tran *et al*., 1997; Conley and Mahmoud, 2001; Tollefson *et al*., 2001) have not supported the prediction of *in vitro* data that RIS or OLZ would have a substantially smaller risk of orthostatic hypotension than CLZ. With respect to the elderly population with AD, data from studies HGEU and HGAO found no indication that elevated or hypotensive blood pressure were statistically different than seen in the placebo comparator groups (Satterlee *et al*., 1995; Lane *et al*., 1998; Street *et al*., 2000).

The risk for OLZ to be associated with hypotension was increased with concurrent, acute use of a benzodiazepine (Physicians Desk Reference, 2001). Benzodiazepines during acute co-therapy or alcohol can potentiate the risk for a hypotensive episode. This presumably reflects, in part, the acute effects of benzodiazepines on relaxing muscles, which otherwise provide biomechanical support to veins, assisting blood return to the heart.

Another source of concern is that many medications, including some antipsychotic drugs, are reported to have an intrinsic ability to prolong the cardiac QT interval. QT interval is a measure of the electrophysiological changes from the beginning of cardiac depolarization of the ventricles (QRS complex) through cardiac repolarization of the ventricles (T waves) (see Figure 2). The electrical pattern from the end of the QRS complex to the end of the T wave (referred to as the JT interval) embedded in the electrocardiogram reflects the activity of ions exchanging across the cardiac (myocyte) cell membrane through ion channels. The QT interval is primarily contributed to by repolarization (the JT interval). The QT interval is considered important because it represents the repolarization phase of the cardiac cell cycle and prolongation of the QT interval reflects a slowing of the repolarization of the ventricular myocardium. Derangement during the repolarization phases may lead to arrhythmia and even sudden death in association with ventricular tachyarrhythmia, or torsade de pointe. While several ion channels involved in repolarization have been identified, those which have been of most interest from the standpoint of torsade de pointe are those involved in potassium conductance because reduction in potassium conductance is associated with QT prolongation (Bednar *et al*., 2001).

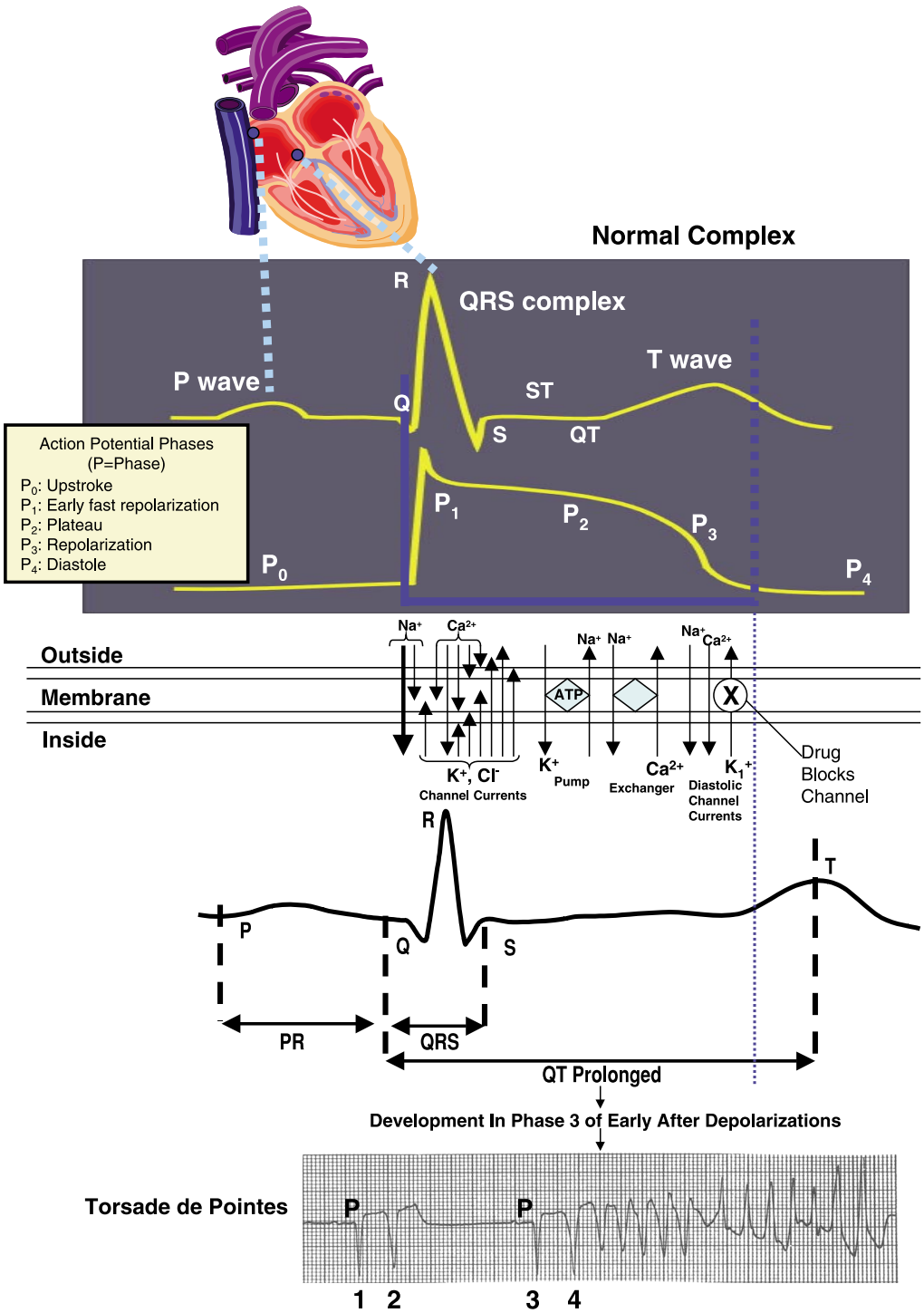

Figure 2. Electrocardiographic Cycle. Phase 1: I_{tb} channels. Phase 2: Near equal ion flow of potassium outward through delayed rectifying potassium channels (I_{Kr}, I_{Ksus}, I_{Kur}) and flow of calcium inward through L-type channels. Phase 3: Increasing conductance of potassium through the rapid delayed rectifying potassium channel (I_{Kr}) and inward rectifying channel (I_{Kl}). Rapid terminal repolarization is prolonged in hERG during this phase. Drugs prolonging QTc alter ion channels involved in Phase 2 and/or Phase 3

The four potassium channels responsible for repolarization of the myocardium, which have been a focus of QT research interest, include the transient outward potassium channel (I_{to}); sustained current potassium channel (I_{sus}); inwardly rectifying potassium channel (I_{kl}), and the rapid component of the delayed rectifier potassium channel (I_{kr}). I_{kr} is most commonly linked to drug-induced QT prolongation. A gene mutation in the human ether-a-go-go related gene (HERG) produces a protein that underlies the I_{kr}, and is associated with hereditary long QT syndrome (Bednar *et al*., 2001).

In the clinical setting, the measured length of the QT interval is dependent upon the heart rate. The QT interval shortens with increasing heart rate. Thus, a corrected QT interval (QTc) should be used to make evaluations independent of this effect. The correction is typically made by applying the Bazett formula [QTc = QT interval/RR interval$^{1/2}$]) (Bazett, 1920). The Bazett formula is the common algorithmic calculation found in most physician's office electronic electrocardiographic machines. An alternate method of correcting for heart rate effects on the QT interval is the Fridericia formula (Fridericia, 1920) [QTc = QT interval/RR interval$^{1/3}$]. This method is not widely known outside of cardiology and, because it is not a standard formula incorporated into office-based ECG machines, physicians must compute it by hand. A published review of the OLZ clinical trial database (discussed below) revealed few electrocardiographic changes other than a slight, but statistically significant, increase in sinus rate (Beasley *et al*., 1997). The magnitude of this heart rate increase during OLZ treatment was not considered clinically significant and results in a corresponding decrease in the absolute QT interval after correction.

As discussed above, prolongation of the electrocardiogram's QTc interval can be a warning sign for ventricular arrhythmias or sudden death (Moss, 1993). Generally, a QTc interval greater than 450 msec for males and 470 msec for females is of potential concern and an interval greater than 500 msec indicates increased potential risk for ventricular arrhythmias or sudden death (Morganroth *et al*., 1991; Garson, 1993). Medications that prolong QTc interval commonly act in a dose-related fashion. However, at any particular time, especially if attention is not paid to the timing of an ECG in relation to expected peak plasma drug concentration, it is possible that a person experiencing intermittent QTc prolongation would not evidence this on an ECG. Therefore, ongoing, periodic monitoring of patients being treated with these medications may suggest incorrectly that no conduction problem is present.

An *in vitro* approach to characterizing the risk of a medication to prolong the QTc *in vivo* is to examine the medication's effects on cardiac muscle ion channel electrophysiology. Crumb *et al*. (1999) examined the potential for eight antipsychotics to block HERG channels, thought to be important in QTc prolongation, and found that over the therapeutic range, OLZ, RIS, and pimozide produced less than 10–15% blockade. However, thioridazine (THIO), HAL, and CLZ produced up to 50% reductions in HERG current within the therapeutic range. SERT and ZIP blocked HERG current at concentrations as low as 1 nM (20% and 10% reduction, respectively. These *in vitro* data suggest that, in the expected therapeutic free plasma drug concentration (i.e. nonprotein bound), OLZ should not manifest any systematic ability to prolong the QTc. In support of the *in vitro* data reported by Crumb *et al*. (1999) as having predictive *in vivo* relevance, a comparative study of cardiac conduction in young, healthy male patients with schizophrenia during treatment with several antipsychotic medicines is instructive. In this Pfizer supported open-label, parallel group, safety study ($n = 183$), schizophrenia patients received ZIP, RIS, OLZ, QUET, THIO, or HAL (Pfizer Pharmaceuticals, 2000). QT interval was measured at baseline, during steady state medication treatment, and during concomitant treatment with an inhibitor of the cytochrome P450 system. Mean change in QTc intervals, applying Bazett's correction, was lowest on HAL (4.7 msec) and OLZ (6.8 msec) and highest on THIO (35.6 msec) and ZIP (20.3 msec). Using Fridericia's correction, mean change was lowest during treatment with OLZ (1.1 msec) and RIS (3.0 msec) and again highest during treatment with THIO (29.6 msec) and ZIP (15.5 msec). Categorical analyses, using Bazett's formula, revealed that patients treated with OLZ had the lowest percentage of treatment-emergent QTc intervals above 450 msec and 500 msec thresholds (4% and 0%, respectively) and of QTc increases of 60 msec or greater (4%). No OLZ patient developed a 75 msec or greater increase in QTc (see Figure 3). Concomitant administration of fluvoxamine (which inhibits primary hepatic pathway for OLZ metabolism, CYP1A2) indicated that, despite the expected elevation in plasma concentrations, QTc intervals for OLZ-treated patients did not increase significantly during metabolic inhibition compared to steady state. The absence of QTc changes when circulating drug concentrations are increased by the inhibition of the hepatic P450 enzymes which metabolize OLZ provides strong clinical evidence for the absence of any dose relationship between OLZ blood levels and

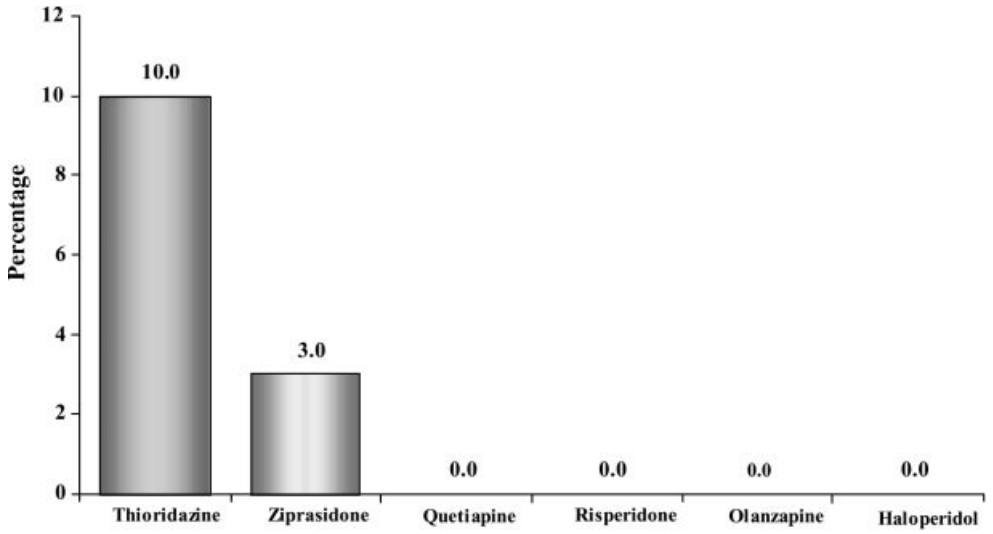

Figure 3. Percentage of participants with QTc change $\geqslant$ 75 msec at steady state. Data from Pfizer, Inc. (2000)

change in QTc, as predicted by the preclinical studies of Crumb *et al*. (1999).

Data from OLZ controlled trials and other literature also provide evidence supportive of the *in vitro* study results. An analysis of the OLZ clinical safety database found no evidence of a consistent, significant, positive dose dependent relationship with QTc prolongation (Czekella *et al.*, 2001). Safety data from 1342 patients with schizophrenia aged 18–86 years showed that OLZ at therapeutic doses did not have a clinically significant effect on cardiac repolarization (Czekella *et al.*, 2001). Therefore, data from the *in vitro* cardiac channel study by Crumb *et al*. (1999), the laboratory study of ECG by Pfizer, and the cumulative OLZ clinical trial database all suggest that OLZ does not have a clinically significant effect on QTc. In the clinical trials of OLZ in patients with AD (HGEU, HGAO), there was no indication of systematic changes in heart rate or electrocardiogram features which were statistically different than placebo effects. A Medline search of the literature through September, 2000 found no case reports of OLZ in temporal association with a fatal cardiac event, sudden death, or electrocardiograph changes. In contrast, several antipsychotics, including QUET, RIS, CLZ, CPZ, HAL, THIO, and pimozide, have been temporally associated with arrhythmia's (Ochiai *et al.*, 1990; Paoloni *et al.*, 1992; Jackson *et al.*, 1997; Lawrence and Nasraway, 1997; Ravin and Levenson, 1997; Sharma *et al.*, 1998; Czekella *et al.*, 2001).

As noted above, the elderly carry an ever-increasing risk for cardiovascular disorders, some readily apparent on clinical assessment and, particularly for subclinical pathology, some not apparent. Epidemiological research has identified some of the clinical risk factors for QTc prolongation. Many of the identified risk factors for QTc prolongation are heavily present in the geriatric population. These include being elderly, being female, having pre-existing cardiac disease, having factors which can lower circulating potassium concentrations including diuretic use, and using multiple medications concurrently which prolong the QTc (Bednar *et al.*, 2001). The dementia population carries many of these risk factors and warrants specific attention because of their frequent inability to accurately report past medical history and current medication use.

Because of (1) the adverse potential for drug–drug interactions attributable to saturation of hepatic P450 pathways, which as demonstrated in the Pfizer sponsored study, may result in very much higher circulating blood concentrations of medications such that, in some individuals, even low oral dosages might produce very high blood levels of medication; (2) the proposed mechanism(s) by which ion channel blockade produces QTc prolongation; and (3) the very prevalent concurrent use by the elderly of multiple medicines, each prolonging (even modestly) the QTc individually and in combination, they may have additive or synergistic effects, the geriatric physician must be vigilant about assessing the risk:benefit ratio associated with polypharmacy. By increasing free, unbound drug levels or by synergistic drug–drug interactions with cardiac ion channels, polypharmacy

can increase the potential for cumulative saturation/blockade of cardiac ion channels with the resultant, significantly increased potential for sudden death in the elderly due to an undetected, intermittent ventricular tachyarrhythmia and progression to torsade de pointes.

EXTRAPYRAMIDAL SYMPTOMS: ACUTE DYSTONIA, RESIDUAL EXTRAPYRAMIDAL EVENTS, PARKINSONISM, GAIT DISTURBANCE, TARDIVE DYSKINESIA AND NEUROLEPTIC MALIGNANT SYNDROME

The presence or relative absence of antipsychotic medicine-evoked extrapyramidal symptoms (EPS) including dystonia, Parkinson's disease (PD), akathisia, tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS) has been proposed to be the primary differentiating attribute in characterizing antipsychotic medications as 'typical' or 'atypical.' (Glazer, 2000; Stanniland and Taylor, 2000; The mechanisms which underlie the various forms of EPS also differ. For example, akathisia appears to be attributable to increased norepinephrine tone (Adler *et al.*, 1989), and support for this is seen in the preferential use of beta blockers to reduce it. OLZ and RIS significantly increase brain norepinephrine (Bymaster *et al.*, 1999; Nasif *et al.*, 2000) and both are associated with greater akathesia than placebo. PD is associated with diminished postsynaptic dopaminergic tone. It increases in prevalence with age and Parkinsonism, as well as TD, also increases with typical antipsychotic use and age. Compared to haloperidol, the $5HT_{2A}$ atypical medications have reduced risk for PD. Therefore, the atypical antipsychotics may have a particularly important role in reducing the unwanted occurrence of such EPS phenomena in the elderly. The necessary and sufficient conditions for a favorable EPS profile remain uncertain. A ratio of higher $5HT_{2A}$ receptor blockade than D_2 receptor blockade has been proposed and confirmed by the emergence of atypical antipsychotics that were designed specifically with these chemical characteristics. However, this hypothesis has been tested in the clinic for a relatively short time and very long-term studies will be necessary to know whether this binding profile simply reduces the annual occurrence of events such as TD or whether this does diminish the total cumulative risk. This is among the reasons that all antipsychotics prescribed in the US still contain a warning about the risk for TD in their physician prescribing information sheets. Other non-$5HT_{2A}$ preclinical models have also been proposed to predict a lowered risk for EPS. One such model is whether the medication binds tightly or loosely to the D_2 receptor, with looser binding expected to predict lower risk for EPS (Seeman and Trallerico, 1999; Kapur and Seeman, 2001). Tightly-bound medications include HAL, RIS, and ZIP, moderately-bound include OLZ, and loosely-bound include CLZ and QUET (Kapur and Seeman, 2001). Another model predicts that medication selective for effects on dopamine neuronal activity in the A10 rather than the A9 brain area will have a favorable EPS profile (Chiodo and Bunney, 1983). In this regard, CLZ and OLZ are A10-selective (Chiodo and Bunney, 1983; Skarsteldt, 1995; Stockton and Rasmussen, 1996), while HAL and RIS are not (Chiodo and Bunney, 1983; Skarsteldt, 1995). Examination of the emergence of EPS in dose ranging studies of different clinical populations can provide guidance on which of these mechanisms alone or in combination is responsible for EPS differences between the older and newer antipsychotic agents.

In preclinical, behavioral pharmacology studies using a rat model, the OLZ dose required to increase hindlimb reaction time (predictive of antipsychotic activity) was significantly lower (20X) than the dose required to increase forelimb reaction time (predictive of EPS) (Cools *et al.*, 1995). The ratio of the dose required to interfere with conditioned avoidance compared to that inducing catalepsy (8X) also suggests OLZ has a favorable EPS profile (Moore *et al.*, 1997). Finally, studies in HAL-sensitized cebus monkeys indicated the estimated OLZ dose to predictably induce EPS in humans is 100–200 mg, or approximately 10–20 times the recommended daily dosage for clinical use (Eli Lilly and Co, data on file).

Analyses of treatment-emergent events during acute phase studies (6 weeks) of OLZ treated patients aged 18 or older at study entry revealed no significant differences in dystonic, PD, dyskinetic, or residual events compared to placebo. With the exception of 'residual events,' all EPS occurred significantly less often with OLZ compared to HAL (Tollefson *et al.*, 1997b). On the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970), OLZ treated patients experienced no significant change from baseline scores compared to placebo; however, HAL treated patients had significantly greater change from baseline SAS scores compared to OLZ treated patients. OLZ treated patients had significantly greater decreases in Barnes Akathesia Scale scores (BAS) (Barnes, 1989) compared to placebo or HAL treated patients. This pattern was also seen in an analysis of schizophrenia patients aged 60 or older treated in a

double blind fashion with either HAL or OLZ (Maguire *et al*., 2001). Thus, by several preclinical methods as well as by examination in the clinic, OLZ has a favorable profile with respect to acute EPS in patients with schizophrenia. This has also been reported for patients with bipolar mania (Tohen *et al.*, 2000) and dementia (Street *et al.*, 2000).

Perhaps the most challenging population is patients with PD and concomitant dopaminergic drug-induced psychosis. Several external investigator-initiated, Lilly-funded reports of OLZ in this patient group suggest that response to OLZ treatment at doses of 2.5–15 mg/day is much less predictable than in other patients (Wolters *et al.*, 1996; Molho and Factor, 1999; Goetz *et al.*, 2000). Potential explanations for the observed differences between these PD studies are that the design, OLZ titration/dopaminomimetic dose optimization, and OLZ doses were quite different in each study. In the study most closely mirroring clinical practice where dopaminomimetic therapy was adjusted to optimize patient response and the time allowed for adjusting both OLZ and dopaminomimetic doses was lengthy (Wolters *et al.*, 1996), OLZ improved psychotic symptoms without consistently increasing EPS in patients with PD. Clearly, some PD patients respond very well to OLZ, while others do not. The use of high OLZ doses (2.5–15 mg) may also have contributed to an undesirable benefit/risk outcome in published studies. In support of this view, for CLZ, the typical dose ratio for schizophrenia compared to PD is approximately 400 mg/25 mg. Similarly, while only open label studies have been reported to date, QUET has been suggested to be very helpful in this population at doses of 25 mg or greater. Typically, a minimum effective anti-schizophrenia dose of QUET is about 400 mg/day. Therefore, it is reasonable to conjecture that OLZ doses in these studies may have been too high. An alternate possible explanation is based on the pharmacodynamic effects of OLZ in the brain of the patient with PD. Patients with PD demonstrate very significantly diminished presynaptic dopamine release. OLZ binds moderately tightly to D_2 receptors *in vitro* as it produces D_2 blockade. Because patients with PD may have relatively well preserved presynaptic cholinergic neurons and OLZ has been shown in preclinical functional studies to enhance acetylcholine release, this degree of moderate binding to the D_2 receptor could theoretically produce EPS in such patients. The possible relationship between OLZ and the altered cholinergic-dopaminergic system balance in PD may prove to be particularly relevant in light of the earlier discussion of OLZ's likely absence of central anticholinergic activity at lower therapeutic dosages, a property that differentiates OLZ from both CLZ and QUET. EPS apparently does not occur very commonly in OLZ-treated AD patients with baseline EPS or in patients with Lewy Body Dementia (Cummings *et al.*, in press). This post hoc analysis examined 29 patients with dementia with Lewy bodies and psychosis in a 6 week study. Patients were randomized to 0, 5, 10, and 15 mg OLZ groups ($n = 5$–10 per group). By definition, all patients had at least minimally apparent clinical EPS at baseline. No significant exacerbation of symptoms was seen and mean SAS scores decreased slightly in each group (0.14–1.6 points in the OLZ treated patients). Finally, symptoms suggestive of anticholinergic toxicity did not differ among groups. The differences in response of this population, compared to young patients with PD, may be an example of pharmacokonosology and reflect the differences in dopamine release and cholinergic system pathology of AD, Lewy Body Dementia, and PD (Perry *et al.*, 1994). To date, very low dose CLZ (6.25–25 mg/day), despite its required weekly blood draws to monitor for treatment-emergent agranulocytosis, remains the first line treatment for this vexing clinical problem (based upon published placebo controlled trials, Friedman and Factor, 2000).

Gait disturbance

Compared to younger patients, the elderly are both more prone to fall and more vulnerable to the medical sequelae of falling (Koutsavlis and Wolfson, 2000) and this is particularly true in the elderly dementia patient (Bueno-Cavanillas *et al.*, 2000). Such events can arise from multiple causes, including cardiovascular system related syncope, gait disturbance related to the effects of sedation on the conscious elements of gait, and gait abnormalities attributable to medication associated EPS (Nickens, 1985; Campbell, 1991; Bueno-Cavanillas *et al.*, 2000). It is noteworthy that gait disturbance is an inherent clinical feature of the dementias and increases in prevalence in association with dementia severity (Ala and Frey, 1995; Lopez *et al.*, 1997).

In the recently published HGEU study (Street *et al.*, 2000) which examined 206 AD patients who were primarily experiencing very severe dementia, 28 of 206 patients across treatment groups experienced treatment-emergent adverse events related to gait. In this study, gait change occurring at any time was reported by patients or caregivers as a treatment-emergent change when they presented for a scheduled

Table 7. Olanzapine in Alzheimer's disease: Simpson–Angus Scale assessment of 24 patients with treatment—emergent abnormal gait. A total of 28 patients reported treatment—emergent abnormal gait, of those, 24 patients had been assessed with the Simpson–Angus Scale-Street *et al*. (2000).

	Worsened, baseline to endpoint (*n*)	No change, baseline to endpoint (*n*)	Improved, baseline to endpoint (*n*)
Placebo ($n=1$)	1	0	0
5 mg OLZ ($n=9$)	1	5	3
10 mg OLZ ($n=7$)	1	6	0
15 mg OLZ ($n=7$)	4	3	0
Total ($n=24$)	7	14	3

study visit. When gait change was reported, study investigators objectively evaluated the patient's gait as a component of the overall visit required safety assessment. As discussed below, this formally characterized any change present by using the gait item of the SAS. Reports of abnormal gait were significantly greater than placebo (one patient [2.1%]) for patients in the 5 mg (11 patients [19.6%]; $p=0.006$) and 15 mg (9 patients [17%]; $p=0.018$) OLZ groups; however, the 10 mg group (7 [14.0%]; $p=0.06$) was not significantly different from placebo.

A full understanding of the observation of abnormal gait in the Street *et al.* (2000) study is impossible because gait abnormality was not a prestratified variable included in the randomization plan. Therefore, there is no assurance that there was a balanced case distribution before randomization. This methodological limitation leaves unclear if any differences were due to drug effect or were simply a result of the randomization of patients at greater risk to active medication compared to placebo. Further, replication may not occur in a subsequent study. However, to attempt to further clarify the meaning of abnormal gait, a post hoc analysis of these events was undertaken. At each visit, the investigator was required to complete a full Simpson–Angus Scale (SAS) concurrently to evaluating the patient for Parkinsonian signs. The SAS contains an item noted as 'gait.' Patients were instructed to walk about, swinging their arms, and the clinician noted their general posture. The operationalized description of patients' 'gait' ranged from 0 = normal to 4 = stooped, shuffling gait with propulsion and retropulsion. In the HGEU study, 24 of the 28 patients with the adverse event 'abnormal gait' had at least baseline and endpoint SAS 'gait' item scores present for analysis (Table 7). Of these 24 patients, 17 demonstrated either no change (14 patients; OLZ 5 mg: 5/24; 10 mg: 6/24; 15 mg: 3/24) or an improvement (three patients; OLZ 5 mg: 3/24) at endpoint compared with baseline. Seven patients were identified as worsened (placebo: 1/24; OLZ 5 mg: 1/24; 10 mg: 1/24; 15 mg: 4/24). The placebo treated and one OLZ 15 mg treated patient had scores of zero, or normal, at baseline and endpoint scores of 2 and 1, respectively. The other five patients with worsened endpoint scores began the study with scores ranging from 1 to 3.

A further analysis of gait outcome (classified as no change, improved, or worsened) of the overall patient sample revealed no statistically significant differences between any OLZ treatment group (5, 10, or 15 mg) or the total OLZ-treated population ($n=134$) compared with placebo ($n=37$). In summary, one patient each on placebo, 5 mg OLZ, and 10 mg OLZ, and four patients on 15 mg OLZ experienced worsened gait. In contrast, three patients on 5 mg OLZ and one patient on 15 mg OLZ improved in gait. Overall, the reported statistically significant change in gait for the 5 mg OLZ group reflected improvement, not worsening. The overall change in gait in the 15 mg OLZ group reflected a worsening (four patients worsened). A further secondary analysis of this study population, which examined the small number of patients who had some degree of EPS at randomization in the absence of any documented history of previous neuroleptic use, found no worsening of gait at any OLZ dose (Cummings *et al.*, in press).

Tardive dyskinesia

TD is prototypically characterized by abnormal, involuntary hyperkinetic movements during or shortly after stopping pharmacotherapy with an antipsychotic medication. TD due to antipsychotic medications is particularly strongly associated with the older typical agents, and their use in young patients has been associated with a 5% cumulative annual incidence of treatment-emergent TD (Glazer, 2000). The specific mechanism(s) which give rise to this potentially life-threatening problem remain unclear but do appear

to involve D_2 blockade as well as other receptor-based interactions such as the absence of $5HT_{2A}$ antagonism. In the elderly, the cumulative annual incidence of TD is 20–25% (Jeste, 2000).

Several risk factors for TD have been identified, including duration of exposure (but not dose), female gender, advanced age, mood impairment, and pre-existing brain damage (Jeste *et al.*, 1998). While the risk factors clearly include many patients who are elderly, that young patients also commonly demonstrate TD in the first year of treatment with the same medications which may cause TD at a very high rate in the elderly suggest that the rates of TD in younger patients treated with OLZ may be particularly predictive of what might be expected to occur in the elderly.

Using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) and the cross-sectional research diagnosis criteria for TD suggested by Schooler and Kane (1982), incidence of treatment-emergent TD was examined in acute and long-term (1 year or longer) OLZ clinical trials of patients with schizophrenia. Tollefson *et al.* (1997a,b) examined 707 OLZ treated and 197 HAL-treated patients with 237 and 203 median days of medication exposure, respectively. With chronic treatment, patients receiving HAL had a significantly higher incidence (4.6%) of treatment-emergent TD than OLZ-treated patients (1.0%). Beasley *et al.* (1999) examined 1192 OLZ-treated and 522 HAL-treated patients, who had been treated for up to 2.5 years. Excluding cases occurring during the first 6 weeks of treatment because they may have represented withdrawal dyskinesias, the estimated 1-year risk for developing TD was 0.52% for the OLZ group and 7.45% for the HAL group ($p < 0.002$).

Because young patients with bipolar disorder may be more susceptible to TD and EPS than those with schizophrenia (Mukherjee *et al.*, 1986), they may be a better group to examine the predictive risk of TD in the elderly population (Waddington and Yousset, 1988; Hunt and Silverstone,1988; Frye *et al.*, 1998). Further evidence suggesting the increased risk of patients with bipolar disorder to develop TD is seen in the reports of bipolar patients developing EPS and TD during treatment with non-neuroleptic mood stabilizers (Lazarus, 1994; Ghadirian *et al.*, 1996). A suggested predictive risk factor for TD in bipolar disorder is the presence of extrapyramidal symptoms (Muscettola *et al.*, 1999). The risk for newly treated elderly bipolar patients to develop TD is unknown. Based on generalization from the younger population, it would not be surprising if elderly, bipolar patients demonstrate a similar increased risk in comparison to the risk in other functional neuropsychiatric disorders. Despite the unclear, possibly increased, risk of TD in bipolar patients and recommendations for limiting their exposure to typical antipsychotics, these medications are used extensively for acute management of mania and maintenance treatment. Recently, OLZ received approval in the US for the treatment of acute mania associated with bipolar disorder.

This approval was obtained from the FDA upon review of two acute studies. These two studies with OLZ, a 3-week trial (Tohen *et al.*, 1999) and a 4-week trial (Tohen *et al.*, 2000) indicated OLZ was superior to placebo in treating acute mania and demonstrated OLZ was comparable to placebo on EPS ratings. No cases of treatment-emergent TD occurred in the acute phase nor in a one year, open-label extension phase of 113 patients (Sanger *et al.*, 2001). These studies included a very small number of patients aged 50–72 years old ($n = 47$), and OLZ appeared to have a similar risk profile in this group as in the younger cohort (Beyer *et al.*, 2001). Regarding safety of TD in high risk populations, such as elderly females with dementia, to date, in short term studies of 6–8 weeks, OLZ appears to have a safety profile similar to that seen in patients with schizophrenia aged 60 or greater ($n = 83$) (Maguire *et al.*, 2001) and bipolar patients age 50–72 (Beyer *et al.*, 2001). However, longer-term studies in the elderly are required to characterize the long term risk for OLZ treatment associated TD. Such studies are currently underway in the US.

Neuroleptic malignant syndrome

NMS is a rare, potentially life-threatening disorder characterized by hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (e.g. irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additionally, patients may have elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Diagnosis is difficult because the clinician must rule out medical illnesses, such as pneumonia and systemic infections, and untreated or inadequately treated EPS. Perhaps because of its fortunate rarity, the pathophysiology of NMS is very poorly understood. Many centrally-acting medications have been implicated in NMS (Pelonero *et al.*, 1998). In the US, all medications with established antipsychotic activity, including OLZ, are required by the FDA to carry a warning for risk of this potentially fatal disorder.

The temporal association between OLZ and NMS appears to be very rare. A causal relationship has not been established. Pre-marketing clinical trial experience indicated one case of NMS in an OLZ

treated patient; however, the patient had had multiple confounding factors that could have contributed to the disorder, making a determination of causation impossible (Maguire *et al*,. 2001). An examination of the spontaneous safety database for OLZ during the first two years of marketing indicated NMS was very rarely reported to Eli Lilly and Company ($< 0.01\%$). Finally, there are several case reports in the literature regarding OLZ and its possible relationship to NMS (e.g. Johnson and Bruxner, 1998; Marcus *et al*., 1999; Jarventausta *et al*., 2000). These case reports, however, have not been controlled for the presence of risk factors, concomitant medications, or pre-existing illnesses.

CONCLUSIONS

Pharmacological receptor characterization methods, when conducted using human receptors under physiologically meaningful conditions, can help predict the frequency of certain adverse events during treatment with a medication. Muscarinic receptor binding to human receptors under physiologic conditions does predict the relatively low rate of anticholinergic-like adverse events during OLZ treatment. Dopamine receptor binding data for OLZ including the published data on it possessing moderately loose binding to the D_2 receptor and moderately potent 5-HT_{2A} antagonism does appear to account for OLZ's favorable EPS profile across several different population with the exception of PD patients with dopaminetic medication induced psychosis. It is also apparent that the binding ratio of rα1-adrenergic/D_{2L} is consistent with the low incidence of clinically significant hypotension observed during OLZ treatment across the several populations studied to date. However, it does not appear that the examination of H_1 receptor antagonism allows prediction of otherwise expectable substantial differences in rates or severity of possibly hH_1 related adverse events during treatment with the differing atypical antipsychotics.

Preclinical functional characterization of the various antipsychotic medications using valid systems, such as examination of the electrophysiology of cardiac myocytes' response or differences in the A10 to A9 effects of the differing atypical antipsychotic medications, can be useful in predicting their safety profiles. For example, in terms of QTc prolongation, patients receiving ZIP appear to experience a greater magnitude of change from baseline to endpoint than do patients treated with OLZ. However, because human physiology is subject to individual variation, preclinical evaluations do not fully assure that any rare adverse event will not be seen during the clinical use of any medication, including OLZ. The occurrence of a rare adverse event should not lead the clinician to prematurely attribute causation to the medicine, but rather the clinician should maintain an open, differential diagnostic list of potential causes of the event. With OLZ, the data suggest that it is safe in patients with schizophrenia and bipolar mania, and in elderly patients with these same illnesses, as well as dementia. However, the database of controlled exposures of elderly patients including those with dementia, to any antipsychotic drug including OLZ, is so small, and the diversity of comorbid medical problems so immense, the clinician should remain vigilant concerning the potential for antipsychotic medications to produce adverse events in clinical populations at a higher rate than we report to occur in the selected, relatively healthy populations who participated in controlled studies.

ACKNOWLEDGEMENT

This work was sponsored by Eli Lilly and Company.

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