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CHARLES BEASLEY

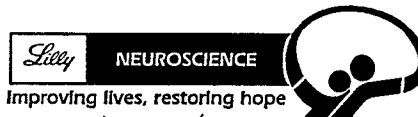
resistance: 'clinical superiority';
eg: park, akathisia, dystonia

D₃, 5-HT₃, 5HT_{2C}

protection: 'Extremely ^{high} ^{potency}
not ^{to} ^{be} ^{used} ⁱⁿ ^{patients}

schiz & related

P. 2,



- Dose related changes in
BPRS?

D - dopaminergic ↑ - ^{add} no clinical
manifestation

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C

benefits appear to be maintained for treatment periods of up to 1 year, as shown by analysis of the extension phase of several trials demonstrating decreased probability of hospitalisation over this period.

Olanzapine was associated with significantly fewer adverse movement disorders (e.g. akathisia, dystonia, hypertonia, EPS) than haloperidol but a higher frequency of weight gain, dry mouth and increased appetite. There have been no reports of agranulocytosis (as occurs with clozapine) or any other haemotoxicity attributed to olanzapine; however, levels of hepatic transaminases have risen transiently in some patients.

D

Although the antipsychotic activity of olanzapine has been well demonstrated, its efficacy in refractory schizophrenia and its place relative to other atypical antipsychotics remain to be determined. Nevertheless, if the long term tolerability profile of olanzapine is confirmed, the drug should provide a valuable therapeutic alternative in the management of schizophrenia.

Pharmacodynamic Properties

2

Olanzapine is a thienobenzodiazepine derivative with affinity for a number of neurotransmitter receptors. Olanzapine has significant *in vitro* inhibitory activity at dopamine D₁, D₂, D₄, serotonin 5-HT_{2A}, 5-HT_{2C}, histamine H₁, α₁-adrenergic and muscarinic receptors. The mixed-receptor activity of olanzapine is similar to that of clozapine. The *in vitro* binding affinity of olanzapine, like that of clozapine, is greater at 5-HT₂ receptors than dopamine D₂ receptors.

3

In electrophysiological studies, olanzapine produced a differential effect on nigrostriatal and mesolimbic systems within the CNS, which may be predictive of a low potential for the induction of extrapyramidal side effects (EPS).

4

Olanzapine is active in many animal behavioural models predictive of antipsychotic activity. Olanzapine also inhibited a number of dopamine and serotonin agonist-induced behaviours *in vivo*, confirming *in vitro* evidence of its receptor affinity profile. In animal models considered predictive of the potential to induce EPS, most studies indicate that olanzapine has less propensity than classical antipsychotics to induce EPS.

In patients with schizophrenia, olanzapine produced a dose-dependent increase in prolactin levels. However, the effect appears to be transient and smaller than that produced by haloperidol.

Pharmacokinetic Properties

6

As shown in healthy volunteers, maximum plasma olanzapine concentrations (C_{max}) after single oral doses (2.5 to 12.2mg) are reached within about 5 hours. Values for C_{max} and area under the plasma concentration-time curve are proportional to the dose. The volume of distribution of olanzapine has ranged from 10.3 to 18.4 L/kg.

7

Olanzapine is extensively metabolised: at least 10 different metabolites, which appear to be inactive, have been identified. The elimination half-life (t_{1/2β}) of olanzapine ranged from 27 to 38.6 hours in young healthy individuals. Elderly and female volunteers have shown a decreased total body clearance and a prolonged t_{1/2β}.

Although the metabolism of olanzapine is mediated by cytochrome P450 enzymes, there appears to be little potential for olanzapine to interact with other drugs metabolised by these enzymes.

Therapeutic Efficacy

Olanzapine is more effective than placebo and at least as effective as haloperidol, as shown in a number of large, randomised, double-blind trials in patients with schizophrenia. Reductions in Brief Psychiatric Rating Scale (BPRS) total scores tended to be dose dependent. Mean reductions in BPRS total scores ranged

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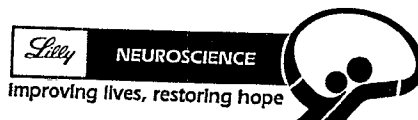
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~~high doses~~

~~psychosis~~ & psychopathology

Tolerability: D/C rates
for ADIC

Low dose not effective



- Tolerability

DC Rates less than Placebo

- ~~Dose~~
no titration

Range 5-20mg/day

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9

from 16 to 39% for patients receiving olanzapine 2.5 to 17.5 mg/day, 5 to 8% for placebo and were about 30% in those receiving haloperidol 10 to 20 mg/day. Significant differences between olanzapine ≥ 7.5 mg/day and placebo were evident within 1 to 2 weeks.

Olanzapine is effective in treating both the positive and negative symptoms of schizophrenia and appears to produce greater improvements than haloperidol in the latter. In 2 comparisons, olanzapine was associated with significantly greater reductions than placebo in the BPRS-positive subscale (23 to 33% vs 0% and 12%) and the BPRS-negative subscale (20 to 41% vs 3% and 6%). In some, but not all, assessments of subscales for negative symptoms, olanzapine in high dosages (>7.5 mg/day) was more effective than haloperidol 5 to 20 mg/day, as measured by the BPRS-negative subscale. The largest trial demonstrated a significant difference between the 2 drugs as shown by the PANSS-negative scale. According to a path analysis, olanzapine appears to exert a direct influence on primary rather than secondary negative symptoms.

10

Pooled data from the extension phases of randomised, controlled trials revealed that olanzapine 2.5 to 20 mg/day for up to 1 year was associated with a higher probability of maintaining response (defined as the absence of hospitalisation for psychosis) than either placebo or haloperidol (5 to 20mg). This suggests that the efficacy of olanzapine is maintained over this treatment period.

Tolerability

In placebo-controlled trials, the only adverse events occurring more often with olanzapine than with placebo were somnolence (12 to 39%), constipation (6 to 15%) and weight gain (0 to 12%). When compared with haloperidol, olanzapine was associated with significantly fewer adverse movement disorders, tremor, nervousness and salivation but a higher frequency of weight gain, dry mouth and increased appetite.

12

Olanzapine demonstrated little potential for the induction of EPS, as measured by rating scales assessing parkinsonism, akathisia and dystonia. Olanzapine produced either no effect on, or small improvements in, rating scale scores and was associated with significantly lower scores than haloperidol.

13

Treatment with olanzapine causes elevations in levels of hepatic enzymes; however, the increases appear to be transient and no clinical evidence of hepatotoxicity has been documented. No significant effect on haematological parameters (e.g. agranulocytosis) has been reported.

Dosage and Administration

In clinical trials, olanzapine 2.5 to 20 mg/day administered as a single daily dose was effective in the treatment of patients with schizophrenia. Although data from a small number of healthy volunteers suggest that total body clearance and $t_{1/2\beta}$ may be increased in elderly and female patients, it is unclear whether these groups require dosage adjustments.

1 **FIGURE 1** Olanzapine is a thienobenzodiazepine derivative which displays some structural and pharmacological similarities to the 'atypical' antipsychotic clozapine (fig. 1). In contrast to classical antipsychotics (e.g. phenothiazine, butyrophenones, thioxanthenes), olanzapine has

only modest affinity for dopamine D_2 -receptors but has affinity for a wide range of other receptors. 2 Traditionally, it was believed that antipsychotic activity was dependent on dopamine D_2 receptor blockade and was inseparable from the ability to produce extrapyramidal side effects (EPS).^[1] How-

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CL2 = 5HT₁
nicotinic

"Respondents" treated
SPECT

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ever, the introduction of new, atypical agents with different pharmacological profiles (e.g. clozapine, risperidone) but significant antipsychotic activity and a low propensity for EPS has led to new research into the molecular pathophysiology of schizophrenia.

1. Pharmacodynamic Properties

1.1 Neurotransmitter Receptor Binding

- 3 **TABLE I** *In vitro* radioligand binding studies in animals have demonstrated that olanzapine has affinity for numerous neurotransmitter receptors (table I). The drug has significant affinity for dopamine D₁, D₂, D₄, serotonin 5-HT_{2A}, 5-HT_{2C}, histamine H₁, α_1 -adrenergic and muscarinic (particularly M₁) receptors [inhibition constants (K_i) \leq 31 nmol/L]. A similar receptor binding profile has been demonstrated in human neuronal tissue.^[2]
- 4 The receptor binding profile of olanzapine contrasts with that of haloperidol, which has a high affinity for dopamine receptors but little activity at serotonergic and muscarinic receptors. The mixed receptor activity of olanzapine resembles that of clozapine, except that clozapine shows higher affinity for α_2 -adrenergic receptors. The ratio of activity between 5-HT_{2A} and dopamine D₂ receptors is somewhat lower with olanzapine than with clozapine; however, olanzapine is still more than twice as active at 5-HT_{2A} receptors as at dopamine D₂ receptors *in vitro*. By comparison, haloperidol was 78-fold more active at dopamine D₂ receptors than at 5-HT_{2A} receptors. The 5-HT_{2A}/dopamine D₂ receptor activity ratio has been suggested to be predictive of an atypical antipsychotic profile.^[2]
- 5 Olanzapine also demonstrated a relatively high affinity for the recently cloned 5-HT₆ receptor^[3] (found in high concentrations in the striatum)^[4] but not the 5-HT₇ receptor^[3] (located in the hypothalamus and limbic areas).^[4] Olanzapine has little affinity for γ -aminobutyric acid_A (GABA_A), benzodiazepine and β -adrenergic receptors.^[2]
- 6 The *in vivo* occupancy of striatal dopamine D₂ receptors in patients with schizophrenia treated with olanzapine was measured by single photon emission tomography.^[5] Striatal dopamine D₂ re-

Table I. Inhibition constants (K_i) for olanzapine (OLZ), clozapine (CLZ) and haloperidol (HAL)^[2]

Receptor type	Tissue	K _i (nmol/L)		
		OLZ	CLZ	HAL
Dopamine				
D ₁	Rat striatum	31	85	25
D ₂	Rat striatum	11	125	1
D ₄	COS-7 cells	27	9,21	5
Serotonin (5-HT)				
5-HT _{1A}	Rat cortex	>1000	770	7930
5-HT _{1B}	Rat cortex	1355	1200	>10 000
5-HT _{1D}	Bovine striatum	800	980	6950
5-HT _{2A}	Rat cortex	4	12	78
5-HT _{2C}	Human cortex, bovine choroid plexus	11	8	3085
5-HT ₃	Rat cortex	57	69	>1000
Muscarinic				
M ₁	Rat cortex	1.9	1.9	1475
M ₂	Rat heart	18	10	1200
M ₃	Rat salivary gland	25	14	1600
M ₄	Rat striatum	13	18	>10 000
Adrenergic				
α_1	Rat whole brain	19	7	46
α_2	Rat whole brain	230	8	360
Histaminergic				
H ₁	Rat whole brain	7	6	3630

ceptor occupancy with olanzapine was similar to that previously reported in a clozapine group and significantly less than in those receiving typical antipsychotics or risperidone.^[5] This effect may be indicative of a lower potential for inducing EPS.

1.2 Effects on Central Dopaminergic Systems

- 7 The nigrostriatal system (designated A9) is believed to mediate EPS, while activation of the mesolimbic system (A10) is thought to be associated with antipsychotic activity. Electrophysiological studies have demonstrated that short term ad-

ministration of classical antipsychotics affects central dopamine systems by increasing the number of spontaneously active cells in both the nigrostriatal and mesolimbic systems.^[6] However, long term administration of classical antipsychotics inhibits the firing of both A9 and A10 neurons by facilitating the development of a persistent depolarised state. In contrast, long term administration with atypical antipsychotics inhibits the firing of neurons from the mesolimbic system but not the nigrostriatal system.^[4]

8 Administration of a single 10 or 20 mg/kg subcutaneous dose of olanzapine to rats increased the number of spontaneously active A10, but not A9, dopamine cells.^[7] Long term administration of olanzapine decreased the number of spontaneously active A10, but not A9, dopamine cells.^[7,8] In addition, olanzapine was more potent in inhibiting the *d*-amphetamine-induced reduction in firing of A9 than of A10 dopamine cells.^[9] These effects are similar to those produced by clozapine.

1.3 Effects on Dopamine Metabolism

9 In an *ex vivo* study, administration of olanzapine 0.3 to 30 mg/kg intraperitoneally was associated with a dose-dependent increase in the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum and nucleus accumbens of rats.^[10] However, olanzapine had no effect on striatal or nucleus accumbens concentrations of dopamine, 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite) or noradrenaline (norepinephrine). In rats pretreated with γ -butyrolactone (a dopamine antagonist) and NSD1015 [a dihydroxyphenylalanine decarboxylase (DOPA) inhibitor], treatment with olanzapine antagonised the pergolide-induced decrease in striatal DOPA.^[10] This suggests that olanzapine blocks terminal and somatodendritic autoreceptors on dopaminergic neurons.

1.4 Animal Models of Behaviour

10 **TABLE II** Olanzapine is active in a large number of animal behavioural models (table II). The mod-

Table II. Behavioural effects altered by olanzapine in animal models of psychosis

Agonist-induced behaviours inhibited by olanzapine

Dopamine-mediated

Apomorphine-induced (dopamine agonist) climbing in mice and rats^[11,12]

RU 24213-induced (dopamine D₂ agonist) locomotion and sniffing in rats^[13]

A 68930-induced (dopamine D₁ agonist) grooming and chewing in rats^[13]

Amphetamine-induced hyperactivity in rats^[14]

Restored amphetamine-disrupted latent inhibition in rats^[15]

N-methyl-D-aspartate (NMDA)-mediated

Phencyclidine-induced (NMDA agonist) social withdrawal in rats^[11] and deficits in prepulse inhibition in rats^[16]

Dizocilpine-induced (NMDA agonist) locomotion and falling in rats^[11]

Mediated by other neurotransmitters

Oxotremorine-induced (muscarinic agonist) tremor in mice^[12]

5-hydroxytryptophan-induced (serotonin agonist) head twitches in mice^[12]

Other behavioural effects

Inhibition of avoidance responding in rats^[12]

Inhibition of lapping behaviour in rats^[17]

Increased rate of punished responding in pigeons and rats^[18-20]

els are predictive of antipsychotic activity and/or demonstrate *in vivo* receptor binding. Generally, the results confirm *in vitro* evidence (section 1.1) of receptor affinity. Olanzapine inhibited dopamine agonist-induced behaviours such as apomorphine-induced climbing,^[11,12] RU 24213-induced locomotion and sniffing^[13] and A68930-induced grooming and chewing^[13] in rodents. Olanzapine produced dose-dependent decreases inhibition of avoidance behaviour and apomorphine-induced climbing, which were virtually abolished at an olanzapine dosage of 10 mg/kg in rats.^[12]

11 However, olanzapine inhibited 5-hydroxytryptophan-induced head twitches in mice at doses much lower than those required to inhibit apomorphine-induced climbing, verifying that olanzapine is a more active inhibitor of 5-HT₂ receptors than of dopamine D₁/D₂ receptors.^[12] Olanzapine also inhibited the induction of tremor by oxotremorine, a muscarinic agonist.^[12]

12 In the paw test, an increase in hindlimb reaction time is predictive of antipsychotic efficacy,

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no, no impairment in
spatial memory. This
is the Janssen water
maze test results; just
slower than dpa

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whereas an increase in forelimb reaction time suggests potential to induce EPS.^[21] In rats treated with olanzapine, the dose required to enhance forelimb reaction time was 20-fold greater than that which enhanced hindlimb reaction time, indicating a similarity for olanzapine with atypical antipsychotics. In contrast, haloperidol enhanced forelimb and hindlimb reaction times at the same dose,^[21] a result typical of classical antipsychotics.

- 13 Moreover, in common with the atypical antipsychotics risperidone and sertindole, olanzapine dose-dependently inhibited dopamine-induced locomotor activity in the olfactory tubercle but had no effect on ergotamine-induced locomotor activity in the nucleus accumbens.^[21]
- 14 Increases in punished responding are considered predictive of antianxiety activity and may predict efficacy in treating the negative symptoms of schizophrenia.^[18] In rats and pigeons, olanzapine significantly increased punished responding, although the effect was smaller than that produced by the benzodiazepine chlordiazepoxide.^[18,20] Olanzapine caused impairment of spatial memory in rats.^[22]
- 15 Olanzapine induced catalepsy in rodents in a dose-dependent fashion, whereas clozapine demonstrated no cataleptogenic effect.^[11,12,14] In 2 studies,^[11,12] the olanzapine doses required to induce catalepsy were 8- and 42-fold greater than those required to induce antipsychotic activity, as measured by inhibition of apomorphine-induced climbing and avoidance responding. The ED₅₀ ratio for olanzapine was similar to that for the atypical drug risperidone, but was markedly larger than those for haloperidol and chlorpromazine (fig. 2).^{FIGURE 2} These collective results may indicate a low propensity for olanzapine to induce EPS. In contrast, another study reported that the doses required to induce catalepsy were similar to those required to antagonise amphetamine-induced hypermotility.^[14] The propensity for development of EPS in patients with schizophrenia treated with olanzapine is discussed in section 4.2.

1.5 Neuroendocrine Effects

- 16 Unlike classical antipsychotics, olanzapine appears to have minimal effect on prolactin levels. Olanzapine produced a dose-dependent increase in prolactin levels; however, the effect was small and transient.^[23,24] After 6 weeks of treatment, mean prolactin levels in patients receiving olanzapine 2.5 to 17.5 mg/day were similar to those in the placebo group and were significantly less than in those given haloperidol.^[23] Similarly, in a long term extension trial, the percentage of patients with prolactin levels exceeding the upper limit of normal at any time ranged from 22 to 46% in patients receiving olanzapine 2.5 to 17.5 mg/day. By comparison, 77% of patients given haloperidol 10 to 20 mg/day had elevated prolactin levels at some point during therapy.^[25] The differences between the drugs were significant, except in those receiving the highest olanzapine dose (12.5 to 17.5 mg/day).
- 17 Olanzapine inhibited the elevation of corticosterone levels in rats induced by quizapine (a 5-HT₂ receptor agonist) and, to a lesser extent, by pergolide (a dopamine D₂ receptor agonist).^[26] This supports receptor binding data indicating that olanzapine is a more potent blocker of 5-HT₂ receptors than of dopamine D₂ receptors.

2. Pharmacokinetic Properties

- 18 A few small studies investigating the pharmacokinetic properties of olanzapine in healthy volunteers have been published, mainly as abstracts.^[27-29] Table III summarises the pharmacokinetics of the drug after single oral doses.^{TABLE 3} Data in patients with schizophrenia or hepatic disease are lacking.

2.1 Absorption and Distribution

- 19 In 24 healthy volunteers receiving single doses of olanzapine 2.5, 5, 7.5 or 10mg, the maximum plasma concentrations (C_{max}) and areas under the plasma concentration-time curves (AUC) were proportional to the dose (values not specified).^[28] After administration of a single oral 12.2mg dose to 6 healthy volunteers, mean C_{max} was 11 µg/L and occurred 4.9 hours after the dose (t_{max}).^[27]

Table III. Pharmacokinetic properties of olanzapine in healthy volunteers after a single oral dose^[27,28]

Parameter	Value
C _{max} (µg/L)	11 ^a
AUC (µg/L·h)	227 ^a
t _{max} (h)	4.9 ^a
V (L/kg)	10.3-18.4 (young) 16.0-17.2 (elderly)
CL (L/h)	19-21.3 (young) 14.7-19.3 (elderly)
t _{1/2β} (h)	27-38.6 (young) 48.8-54.9 (elderly)
Urinary excretion ^b (%)	52
Faecal excretion ^b (%)	23

a After a single 12.2mg dose.

b Percentage of radioactive olanzapine dose administered.

Abbreviations: AUC = area under the plasma drug concentration-time curve; CL = total body clearance; C_{max} = maximum plasma concentration; t_{max} = time to C_{max}; t_{1/2β} = elimination half-life; V = volume of distribution.

Olanzapine appears to be widely distributed in tissues, as evidenced by a large volume of distribution (V) [10.3 to 18.4 L/kg].^[28]

2.2 Metabolism and Elimination

- 20 Olanzapine is extensively metabolised after oral administration. More than 85% of the radioactivity in plasma was attributable to compounds other than the radiolabelled parent drug.^[30] At least 10 metabolites have been identified. The 3 primary metabolic pathways are *N*-glucuronidation, allylic hydroxylation and *N*-oxidation and *N*-demethylation.^[30] The major metabolite in the urine and faeces of healthy volunteers was olanzapine-*N*-glucuronide.^[27] Other metabolites detected in the urine included olanzapine-*N*-oxide and *N*-desmethyl olanzapine.^[27] These metabolites appear to be inactive.
- 21 The elimination half-life (t_{1/2β}) of olanzapine ranged from 27 to 38.6 hours in young healthy volunteers (table III).

2.3 Effect of Age, Sex and Smoking on Pharmacokinetic Parameters

- 22 The t_{1/2β} of olanzapine appears to be prolonged in the elderly. In one study,^[28] the t_{1/2β} was signifi-

cantly longer (48.8 to 54.9 hours) in 16 healthy volunteers aged >65 years than in 8 individuals aged 20 to 41 years (29 to 38.6 hours). Female volunteers had a significantly longer t_{1/2β} (38.6 to 54.9 hours) than their male counterparts (29 to 48.8 hours).

- 23 In a population pharmacokinetic study^[29] involving 34 healthy volunteers (24 of whom were investigated by Bergstrom et al.^[28]), V and total body clearance (CL) were estimated to be 994L and 21.4 L/h, respectively.^[29] CL was 98% higher in volunteers who smoked but was decreased in the elderly (by 31%) and in women (30%). These results require confirmation in larger clinical trials before recommendations to adjust the dosage in these subgroups can be made.

2.4 Pharmacokinetic Drug Interactions

- 24 An *in vitro* study using human liver tissue demonstrated that the cytochrome P450 isozymes CYP1A2 and CYP2D6 are responsible for formation of the oxidative metabolites of olanzapine.^[31] The ability of olanzapine to inhibit metabolism mediated by CYP3A, CYP2D6, CYP2C9 and CYP2C19 was evaluated *in vitro*.^[32] The percent inhibition of each of these isozymes by olanzapine in a concentration assumed to be in the therapeutic range (0.2 µmol/L) was calculated to be <0.3%, suggesting that there is little potential for olanzapine to interact with drugs metabolised by these enzymes.
- 25 Coadministration of single (10mg) or multiple doses (10 mg/day for 8 days) of olanzapine to healthy male volunteers receiving a single dose of lithium 32.4 mmol/L had no significant effect on serum lithium concentrations.^[33] Moreover, olanzapine pharmacokinetic parameters were within the expected range.

3. Therapeutic Efficacy in Schizophrenia

- 26 Schizophrenia comprises a wide range of clinical symptoms which can generally be divided into positive and negative types.^[34] Negative symptoms can be subclassified as primary (those produced by the underlying pathology) or secondary

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Can doses in Table II
be expressed as
 5 ± 2.5 for 2.5-7.5
 10 ± 2.5 for 7.5-12.5
 15 ± 2.5 for 12.5-17.5

yes
BIO cell or 23 SAMS, not PAMS
using OT

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BPRS 18

general schizophrenic

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Table IV. Summary of 6-week, double-blind, randomised, multicentre trials comparing olanzapine (OLZ) with placebo (PLA) or haloperidol (HAL) in the treatment of patients with schizophrenia (DSM-III-R)

Reference	Dosage (mg/day)	No. of evaluable patients	Baseline BPRS score	Results (% decrease from baseline)				
				BPRS total	BPRS (positive)	BPRS (negative)	CGI-S	PANSS (negative)
Beasley et al. ^[25]	OLZ 1	51	39.6	5.0	6.7	4.4	(+)-2	0
	OLZ 10	49	37.4	20.6*	22.5*	19.7	12.2*	10.6*
	PLA	49	36.8	0.5	0	3.0	2	(+)-4.2
Beasley et al. ^[23]	OLZ 2.5-7.5	64	41.2	16.3	20.6	21.1*	8.2	18.1 ^b
	OLZ 7.5-12.5	63	42.8	29.4***	32**	20.1	19.6**	14.6 ^b
	OLZ 12.5-17.5	66	42.6	35.7***	33.3**	40.5***	20.0**	30.9***†† ^b
	HAL 10-20	68	41.8	30.9**	35.1*	28.3	18.4**	15.4 ^b
	PLA	66	39.7	7.8	11.5	5.7	6.1	4.3 ^b
Tran et al. ^{[25]^b}	OLZ 1	88	39.5	26.5			15.3	17.2
	OLZ 2.5-7.5	87	40.1	33.4			18.9	18.8
	OLZ 7.5-12.5	86	40.4	34.2			23.5	20.7
	OLZ 12.5-17.5	89	42.3	38.8			27.3 [†]	23.7
	HAL 10-20	81	41.2	30.1			20.8	17.2
Tran et al. ^{[24]^b}	OLZ 5-20	1099	33.06 ^c	32.9†† ^c				13.2 ^c ††
	HAL 5-20	514	34.29 ^c	23.1 ^c				9.6 ^c

a Scale used was the Scale for the Assessment of Negative Symptoms (SANS) composite score (sum of individual items)

b Abstract.

c Calculated using data obtained from graph.

Abbreviations and symbols: BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity of Illness score; PANSS = Positive and Negative Syndrome Scale; * p < 0.05, ** p < 0.01, *** p < 0.001 vs placebo; † p < 0.05 vs OLZ 1mg; †† p < 0.05 vs HAL.

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These represent a % change
amel
Beasley et al
Ref 23 used
the SANS
not PANSS

(related to positive symptoms or caused by medications).

27 Numerous rating scales are used to measure the efficacy of antipsychotic drugs in patients with positive and negative symptoms of schizophrenia. Symptomatic improvement is the major outcome criterion of treatment. Evaluation of any antipsychotic drug is hindered to some extent by the lack of objective measures and the relatively subjective nature of standard rating scales.

28 The Brief Psychiatric Rating Scale (BPRS), which consists of 16 symptom constructs, was the primary scale used to assess treatment effects with olanzapine. BPRS total score reflects the overall severity of symptoms, while the BPRS-positive and BPRS-negative subscales measure subsets of symptoms. Other rating scales used in clinical trials of olanzapine include the Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS) and the Clin-

ical Global Impression-Severity of Illness (CGI-S) scale.

3.1 Short Term Efficacy

29 ~~TABLE~~ Several large, double-blind, randomised, multicentre trials have compared the efficacy of olanzapine with that of placebo or haloperidol (table IV). Participants met DSM-III-R criteria for general schizophrenia. Most patients presented with an acute exacerbation of chronic, mixed disease and about half were diagnosed with the paranoid subtype. A minimum score of 18^[24] or 24^[2,25,35] on the BPRS total score was required for study entry; however, the mean BPRS total score at baseline was ≥ 38 in several studies, indicating relatively severe psychopathology. About 25% of patients in 1 trial^[35] had previously received clozapine. To eliminate placebo responders, a single-blind placebo washout phase of 4 to 7 days was generally initiated prior to starting the 6-week ac-

P.9

Lilly NEUROSCIENCE
Improving lives, restoring hope



~~31~~ Dose response effect was seen

(35)

2nd line -
can we delete?
mid ± 19

?

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tive treatment phase. Most protocols allowed a long term continuation phase.

- 30 Mean change from baseline (last response carried forward) was used to compare illness severity changes for the treatment groups. Responders were defined as patients with a decrease of $\geq 40\%$ from baseline in BPRS total score or a BPRS total score of ≤ 18 at endpoint in patients completing at least 6 visits (≥ 3 weeks).

3.1.1 Dose-Ranging Studies

- 31 An initial noncomparative 4-week trial in 10 patients with schizophrenia indicated efficacy for olanzapine in dosages ranging from 5 to 30 mg/day.^[36] A Japanese noncomparative trial^[37] found dosages of 2.5 to 15mg to be effective in 58% of 158 patients (no further data available). Dosages of 1 to 17.5 mg/day have been evaluated in controlled trials (table IV). In general, a dose-response effect was seen, with efficacy increasing over a dosage range of 2.5 to 17.5 mg/day. The lowest dosage of olanzapine assessed (1 mg/day) was no more effective than placebo.^[35]
- 32 Two studies^[23,25] compared low (2.5 to 7.5 mg/day), medium (7.5 to 12.5 mg/day) and high (12.5 to 17.5 mg/day) dosages of olanzapine. Although no statistically significant differences in efficacy were evident between the 3 dosage ranges, there was a distinct trend toward increasing efficacy with increasing dose. Mean decreases in BPRS total scores were 16% and 33% in the low-dose group, 29% and 34% in the medium-dose group and 36% and 39% in the high-dose group.
- 33 The dose-response effect was not so obvious in negative and positive symptom subscales and in the CGI-S. Mean declines in the BPRS-positive subscale were, respectively, 21%, 32% and 33% in the low-, medium- and high-dose groups, while the corresponding values for the BPRS-negative subscale were, respectively, 21%, 20% and 41%.^[23]

3.1.2 Comparisons with Placebo

- 34 Olanzapine at dosages >7.5 mg/day is superior to placebo. Treatment with olanzapine 2.5 to 17.5 mg/day reduced BPRS total scores by 16 to 36%, versus 0.5% and 8% for placebo in 2 trials.^[23,35] Pairwise comparisons between the olanzapine and

placebo groups showed statistically significant differences, except in those receiving low-dose olanzapine (2.5 to 7.5 mg/day) [table IV]. Olanzapine 2.5 to 17.5 mg/day also produced greater reductions in CGI-S (8 to 20%) than placebo (2% and 6%).^[23,35] Again, except for the low-dose group, pairwise comparisons favoured olanzapine.

- 35 Treatment with olanzapine 10 mg/day was associated with a significantly greater response rate (28%) than placebo (10%; $p = 0.03$) in one trial.^[35] In another,^[23] response rates did not differ between olanzapine 2.5 to 17.5 mg/day (58 to 67%) and placebo (59%), probably because of the high placebo response rate.
- 36 Olanzapine produced greater reductions than placebo in both the positive and negative subscales of the BPRS. Decreases of 23 to 33% (vs 0% and 12% for placebo) in the BPRS-positive subscale (measuring conceptual disorganisation, suspiciousness, hallucinatory behaviour, unusual thought content) and 20 to 41% (vs 3% and 6%) in the BPRS-negative subscale (measuring emotional withdrawal, motor retardation and blunted affect) were recorded.^[23,35] Some, but not all, of the differences in pairwise comparisons with placebo were statistically significant in favour of olanzapine (table IV). Additionally, olanzapine ≥ 10 mg/day produced a significantly greater reduction than placebo in the PANSS-negative subscale^[35] and the SANS^[23] scale.

- 37 Olanzapine has a relatively rapid onset of effect. Significant differences between olanzapine and placebo groups were seen within 1 to 2 weeks in BPRS total scores, 1 to 3 weeks for positive subscales (BPRS or PANSS) and 1 week for negative subscales (BPRS or PANSS).^[23,35]

3.1.3 Comparisons with Haloperidol

- 38 At present, several studies comparing olanzapine with haloperidol, including the largest trial, have yet to be fully published. Nonetheless, available data indicate that olanzapine is at least as effective as haloperidol and appears to have greater efficacy in certain populations, particularly those with negative symptoms (table IV). In patients with baseline BPRS total scores ≥ 40 , mean im-

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provements were similar between patients given olanzapine 2.5 to 17.5 mg/day (range 16 to 39%) and those receiving haloperidol 10 to 20 mg/day (about 30%).^[23,25]

39 However, in the largest multicentre, international trial, conducted in patients with lower baseline BPRS total scores (≈ 34), decreases in mean BPRS total scores were significantly larger with olanzapine 5 to 20 mg/day ($n = 1099$) than with haloperidol 5 to 20 mg/day ($n = 514$) [33 vs 23%, $p \leq 0.05$]. The study population included patients with schizophrenia (83.1%), schizophreniform disorder (1.9%) or schizoaffective disorder (15%), who had a baseline BPRS ≥ 18 .^[24] A greater proportion of the olanzapine group (66.4%) than the haloperidol group (46.8%) completed the initial 6-week treatment phase. Significantly more haloperidol than olanzapine recipients discontinued treatment because of adverse events (7.3 vs 4.5%), lack of efficacy (32.1 vs 20.7%) and personal decision (7.4 vs 3.6%).

40 In a separate analysis of this trial, olanzapine was associated with significant improvements in depressive symptomatology in patients with comorbid mood disturbances.^[38] In those ($n = 661$) with depression of at least moderate severity [defined as a score of ≥ 16 on the Montgomery Åsberg Depression Rating Scale (MADRS)], reductions in MADRS total score from baseline were greater in the olanzapine (48%) than the haloperidol group (37%).^[38]

41 Olanzapine has notable effects on negative symptoms. Olanzapine 12.5 to 17.5 mg/day produced significantly greater reductions in the BPRS-negative subscale (41%) than placebo (6%).^[23] In the 2 smaller studies, there was a trend toward greater improvement in negative symptoms with olanzapine than with haloperidol, although differences were not consistently statistically significant.^[23,25] Olanzapine in the highest dosage of 12.5 to 17.5 mg caused significant reductions in PANSS-negative scores in 1 trial^[23] but not the other.^[25] In contrast, treatment with olanzapine in the largest study was associated with significantly greater reductions than haloperidol in negative

symptoms, as measured by the PANSS-negative (table IV) and BPRS-negative subscales.^[24]

42 As assessed by a path analysis, the effect of olanzapine on negative symptoms was deemed to be related to a direct effect on primary negative symptoms.^[39] This model assessed the probable contribution of negative symptom improvement through improvements in positive symptoms, a direct effect on primary negative symptoms, improvement in depressive symptoms or improvements in EPS. According to this analysis, olanzapine produced a significantly greater direct effect on primary negative symptoms than haloperidol ($p = 0.01$). The effect of haloperidol on negative symptoms was primarily indirect via a reduction in positive symptoms.^[39]

3.2 Long Term Efficacy

43 Three of the randomised, controlled trials^[23-25] described above included a double-blind extension phase to assess the efficacy of olanzapine as maintenance therapy of schizophrenia, defined as the absence of hospitalisation for psychosis. Treatment was continued for up to 52 weeks. Data from these trials were combined and used to compare olanzapine 2.5 to 20 mg/day with haloperidol 5 to 20 mg/day, placebo and olanzapine 1 mg/day (placebo surrogate).^[40] In this abstract report, olanzapine 2.5 to 20 mg/day was associated with a significantly higher probability of maintaining response than either placebo, haloperidol or olanzapine 1 mg/day (fig. 3).^{FIGURE 3}

4. Tolerability

4.1 General Adverse Event Profile

44 In placebo-controlled trials,^[23,35] the most common adverse events (reported in $>10\%$ of patients) during olanzapine therapy were somnolence, agitation, asthenia, nervousness, hostility and paranoid reaction. It is possible that these psychomotor slowing and activating events are related to the underlying psychopathology rather than to a pharmacological effect of olanzapine.^[23] Other adverse events included headache, dizziness, insomnia,

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- constipation, anxiety, dry mouth and increases in levels of hepatic transaminases (section 4.3).^[23,35]
- 45 The only adverse events documented more frequently with olanzapine than with placebo (only some of the pairwise comparisons were statistically significant) were somnolence (12 to 39%), constipation (6 to 15%) and weight gain (0 to 12%).^[23] Anticholinergic adverse events such as constipation and dry mouth increased in a dose-dependent fashion, reflecting the drug's affinity for cholinergic receptors (section 1.1). However, the incidence of these effects was relatively low (<15%), even in the high-dose olanzapine group.^[23,35]
- 46 Compared with haloperidol, olanzapine was associated with significantly fewer adverse movement disorders such as akathisia, dystonia and hypertonia as well as EPS (section 4.2).^[23-25] Haloperidol also produced significantly more tremor, nervousness and salivation than olanzapine in at least one comparative trial.^[24,25] In contrast, olanzapine was associated with a significantly higher frequency of weight gain, dry mouth and increased appetite.^[23,24]

4.2 Extrapyramidal Symptom Rating Scales

- 47 ~~FIGURE~~ Olanzapine generally either had no effect on, or produced significant decreases in, baseline scores (indicating improvement in symptoms) for rating scales assessing parkinsonism (Simpson-Angus), akathisia (Barnes Akathisia Rating Global Score) or dyskinesia [Abnormal Involuntary Movement Scale (AIMS)] (fig. 4).^[23,25,35] Olanzapine was superior to placebo in reducing the Barnes Akathisia Rating Global Score in one trial.^[23] When compared with haloperidol, olanzapine produced significantly lower scores in the Simpson-Angus scale,^[23-25] the Barnes Akathisia Rating Global Score^[23-25] and the AIMS score.^[24]

4.3 Effects on Laboratory Values

- 48 Treatment with olanzapine produces transient elevations in levels of hepatic transaminases [alanine aminotransferase (ALT) and aspartate amino-

- transferase (AST)] as well as γ -glutamyl transferase.^[23-25,35] Increases tended to be dose-dependent: 9.2% of patients receiving olanzapine 12.5 to 17.5 mg/day showed ALT values above the upper limit of normal at trial endpoint in one study.^[23] Changes in hepatic transaminases are more frequent with olanzapine than with haloperidol, as shown in the largest trial (increased ALT in 7.9 vs 1.1% of patients).^[24] No clinical symptoms or other evidence of hepatotoxicity have been reported.
- 49 The atypical antipsychotic clozapine causes agranulocytosis in about 1% of patients.^[41] As yet, there have been no reports of granulocytopenia during olanzapine therapy. In addition, no significant differences were evident between olanzapine- and placebo-treated patients in mean haematological parameters after 6 weeks of treatment.^[23,35] No haemotoxicity was reported in the largest study;^[24] no further details are available from the abstract.

5. Dosage and Administration

- 50 Although the optimal dosage of olanzapine in the treatment of schizophrenia has not been determined, dosages ranging from 2.5 to 20 mg/day were demonstrated to be effective in clinical trials. There was no statistically significant difference in efficacy between these dosages; however, there was a trend towards increased efficacy in patients receiving higher dosages. Because of its long $t_{1/2\beta}$, olanzapine can be administered as a single daily dose. In clinical trials which used variable dosages, upward adjustments in dosage were allowed at 3- to 4-day intervals for the first 2 visits as clinically indicated, and at weekly intervals thereafter. There is insufficient information at present to determine whether prolonged clearance and $t_{1/2\beta}$ seen in a few elderly and female healthy volunteers will necessitate dosage adjustment in these subgroups of patients.

6. Place of Olanzapine in the Management of Schizophrenia

- 51 Schizophrenia is a severe chronic mental disorder characterised by a heterogeneous array of unusual internal experiences, socially inappropriate

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behaviours and reduced participation in ordinary social and occupational activities.^[42] Symptoms of schizophrenia can be divided into 2 categories: positive (florid) symptoms such as hallucinations, delusions, conceptual disorganisation, agitation and paranoia, which occur during acute episodes; and negative (residual) symptoms, including blunted affect, emotional and social withdrawal, apathy and anhedonia.^[34,42] Negative symptoms can be classified as primary or secondary.

- 52 Classical antipsychotics are highly effective treatments for the positive symptoms associated with acute episodes and in preventing relapse; however, these agents have a number of disadvantages. Dosages required to relieve psychotic symptoms are similar to those causing adverse effects such as EPS.^[43] Another disadvantage is that they are less effective against negative than positive symptoms, particularly primary negative symptoms. In addition, approximately 30% of patients with acute exacerbations have no, or only partial, response to classical antipsychotics.^[43] Therefore, when developing new antipsychotic drugs, the goals are to widen the therapeutic ratio between efficacy and adverse effects and to broaden the therapeutic profile to include efficacy against negative symptoms and refractory disease.
- 53 'Atypical' antipsychotic agents were developed in an attempt to achieve these goals. Although there is no uniform definition of the term atypical, it most commonly refers to an agent that produces a lower incidence of EPS than classical antipsychotics in dosages providing equivalent therapeutic efficacy.^[44] Clozapine was the first of the atypical agents developed. This agent met many of the above objectives, in that it possesses little EPS potential while demonstrating efficacy against negative symptoms and refractory schizophrenia. Although the introduction of clozapine represented a breakthrough in the treatment of schizophrenia, the drug is generally limited to use as a second-line agent because it causes agranulocytosis in approximately 1% of patients.^[41] Therefore, the need remains for additional well-tolerated atypical antipsychotic agents.

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54 Olanzapine is an atypical antipsychotic agent with a structural and pharmacological profile similar to that for clozapine. Like clozapine, olanzapine shows affinity for, and inhibits activity at, a variety of receptors. In contrast, the primary pharmacological property of classical antipsychotics such as haloperidol is inhibition at dopamine D₂ receptors. Although olanzapine and clozapine also bind to dopamine D₂ receptors, they have a higher affinity for 5-HT_{2A} receptors than for dopamine D₂ receptors. It has been suggested that an increased 5-HT_{2A}/dopamine D₂ receptor affinity ratio may protect against the development of EPS.^[2] However, it remains to be determined whether the similar pharmacological profiles of olanzapine and clozapine will translate into similar clinical benefits, as the 2 drugs have not yet been compared in clinical trials.

55 In patients with schizophrenia, olanzapine ameliorates symptoms and appears to have a favourable tolerability profile. Olanzapine did not alter, or improved, extrapyramidal event rating scales. In theory, reductions in the incidence of EPS have the potential to increase patient compliance. This is an important aspect of disease management, because noncompliance is a major cause of relapse in patients with schizophrenia.^[45] Indeed, one study reported that olanzapine was associated with a decreased likelihood of rehospitalisation because of psychosis, compared with haloperidol. Reduced EPS potential is also likely to improve patients' quality of life; so far, specific quality-of-life measures have not been validated for antipsychotic agents.^[34]

56 As yet, there have been no reports of agranulocytosis with olanzapine. However, olanzapine does produce dose-dependent elevations in levels of hepatic transaminases. Although these increases appear to be transient, and there have been no reports of hepatotoxicity with the drug, additional long term experience is required to determine whether this effect is clinically important.

57 The effect of classical antipsychotics on the negative symptoms of schizophrenia is not well defined. Negative symptoms accompanying productive symptoms (secondary negative symptoms) do

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improve after treatment with classical antipsychotics; however, it is not clear whether these agents are effective in treating primary negative symptoms.^[46] After short term treatment (≤ 6 weeks), olanzapine demonstrated efficacy in reducing negative symptoms, as measured by the BPRS-negative and PANSS-negative subscales, and was superior to haloperidol in the largest investigation. In addition, a path analysis model suggested a direct effect for olanzapine, but not for haloperidol, on primary negative symptoms. Future studies should seek to determine whether effects on negative symptoms differ between olanzapine and other atypical agents.

58 One of the most important therapeutic niches of clozapine is in the treatment of patients with refractory schizophrenia. At present, it is not known whether olanzapine is beneficial in such patients.

59 In summary, olanzapine is a new, atypical antipsychotic agent which has demonstrated significant efficacy in the treatment of schizophrenia, combined with a low propensity for producing EPS. Although further clinical experience is required to confirm its long term tolerability profile and to compare its effects with those of other atypical agents, olanzapine is expected to find a place as a valuable alternative to classical antipsychotics.

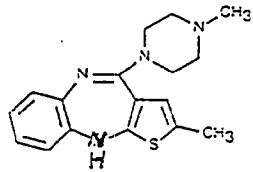
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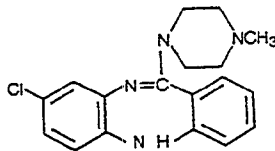
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olanzapine



clozapine

Fig. 1. Structural formulae of olanzapine and clozapine.

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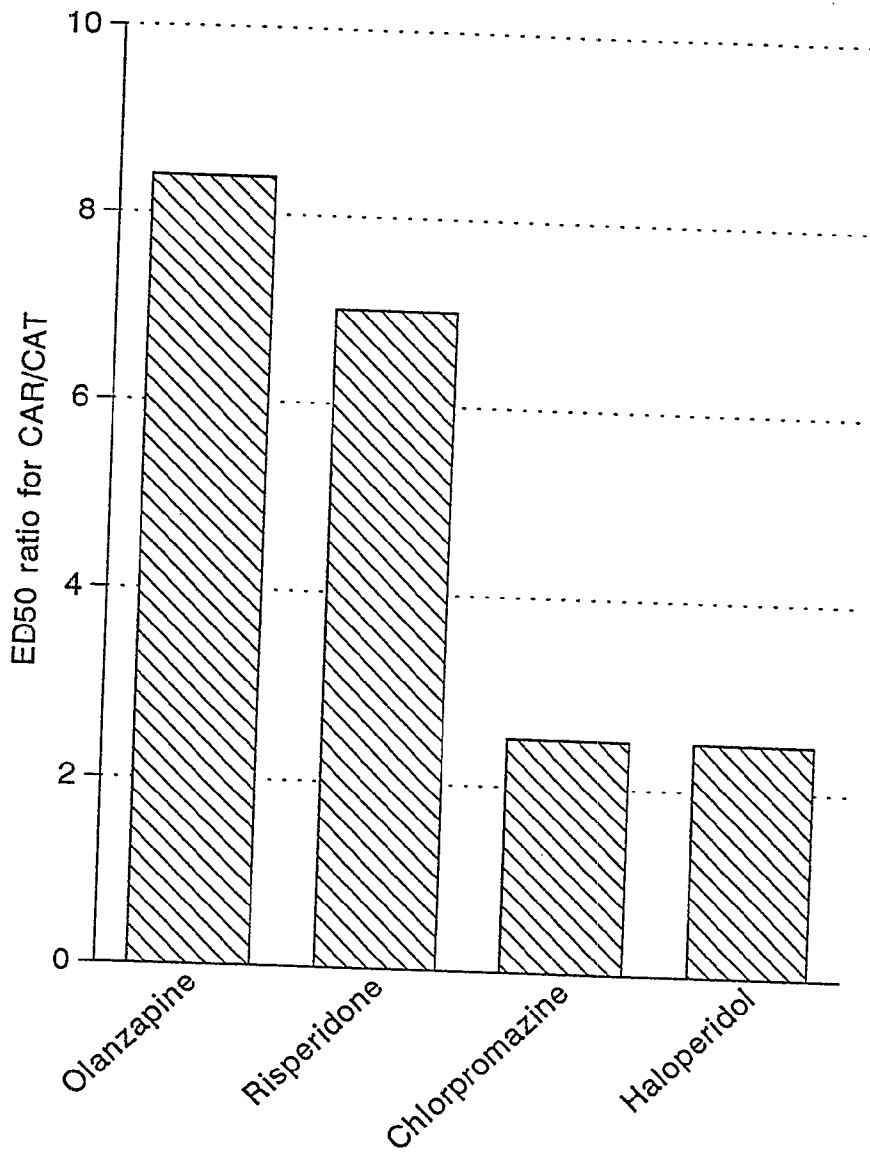


Fig. 2. Extrapyramidal effect potential of olanzapine. The ratio of the dose (ED_{50} values) of antipsychotic required to inhibit the conditioned avoidance response (CAR) over the dose required to induce catalepsy (CAT) in rats.^[12]

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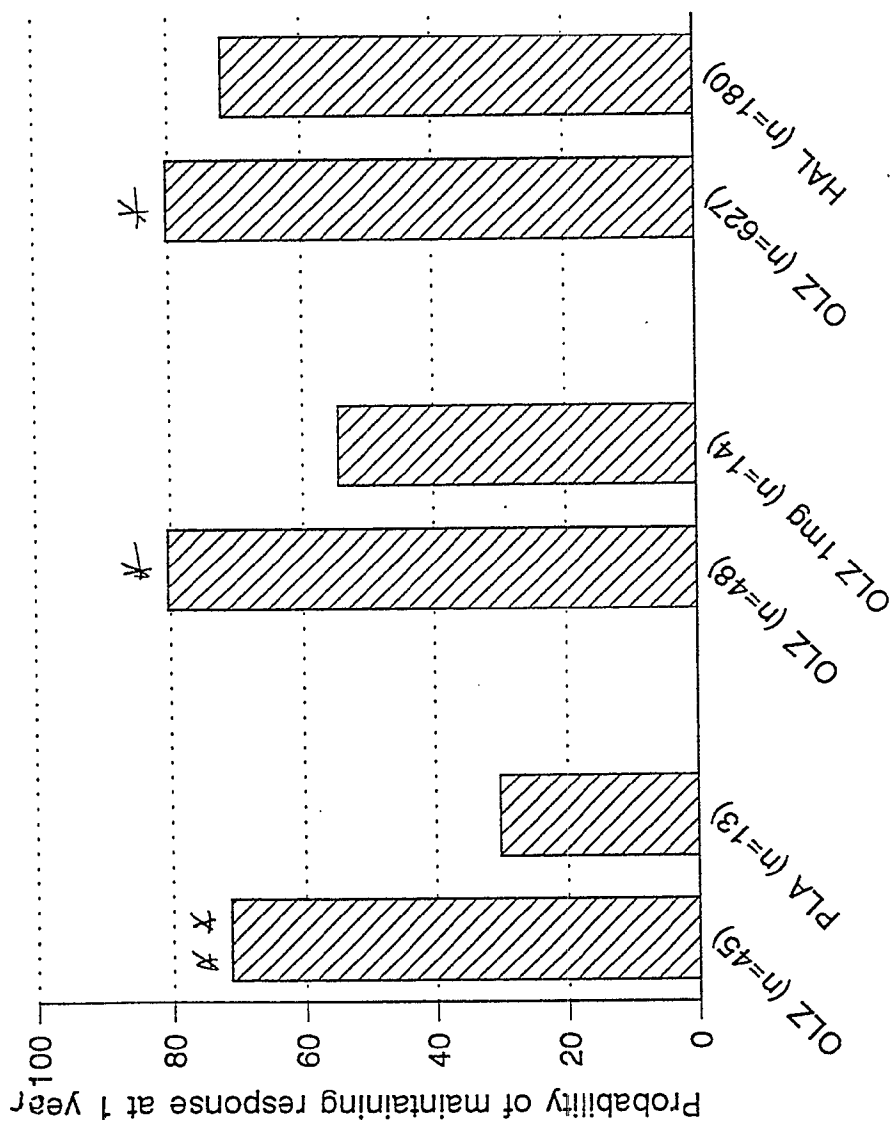


Fig. 3. Long term efficacy of olanzapine. Percentage of patients receiving olanzapine 2.5 to 17.5 mg/day (OLZ), placebo (PLA) or haloperidol 5 to 20 mg/day (HAL) who maintained efficacy after 1 year of therapy (defined as the absence of hospitalisation for psychosis).^[40]
 * p < 0.05, ** p < 0.01.

- ☐ Placebo
- ▨ OLZ-L
- ▩ OLZ-M
- ▧ OLZ-H
- ▤ Haloperidol

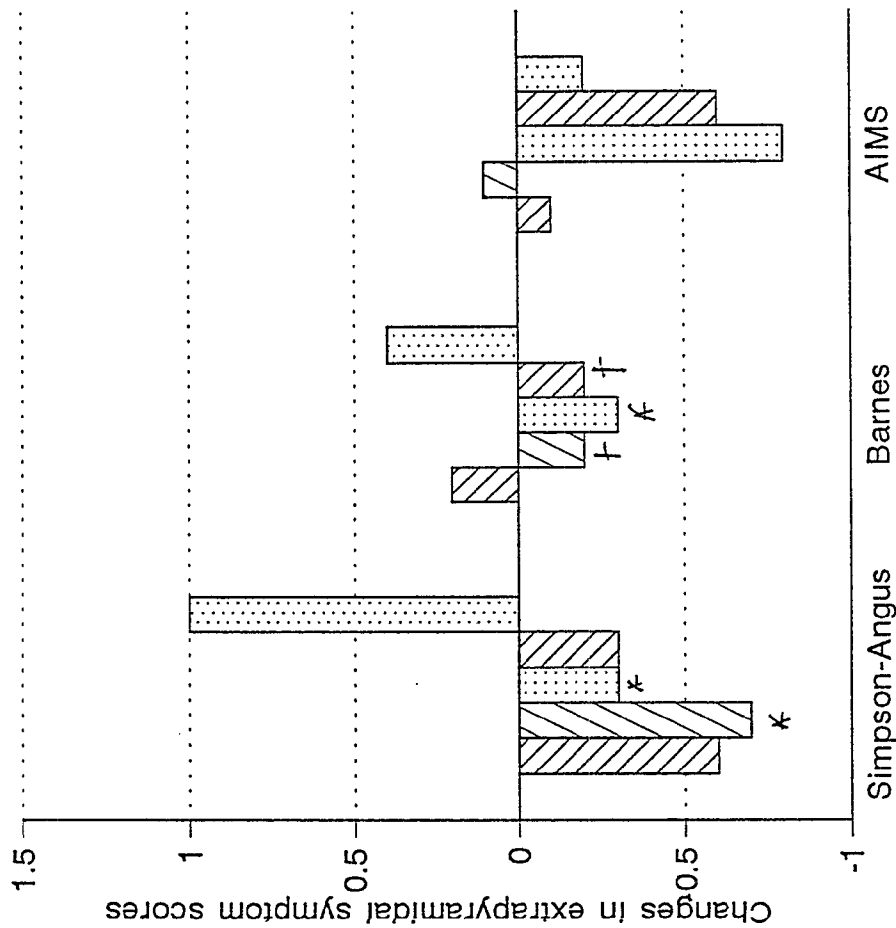


Fig. 4. Extrapyramidal effects of olanzapine versus placebo and haloperidol. Endpoint change (last observation carried forward) in extrapyramidal symptom scores in patients with schizophrenia receiving placebo (n = 64), olanzapine 2.5 to 7.5 mg/day (OLZ-L, n = 63), olanzapine 7.5 to 12.5 mg/day (OLZ-M, n = 63), olanzapine 12.5 to 17.5 mg/day (OLZ-H, n = 65) or haloperidol 10 to 20 mg/day (n = 68). ⁽²³⁾ AIMS = Assessment of Involuntary Movement Scale; Barnes = Barnes Akathisia Scale; Simpson-Angus = Simpson-Angus Scale; * p < 0.05 vs haloperidol; † p < 0.05 vs placebo.

Date: 6/17/96 3:28:39 PM
From: HALLSTEDT PHILIP A
Subject: Neuroscience GBU's Market Assessment of Olanzipine in Alzheimer's Disease
To: See Below

Winston Satterlee asked for a summary of the market potential of Olanzipine in Alzheimer's Disease. Key points driving the GBU's interest in the market include:

- 1) Alzheimer's Disease Demographics: 20-40% of Alzheimer's patients have psychotic symptoms that are detrimental to patient management. A safe, effective drug for problem behaviors could impact 1-3 million patients.
- 2) \$200M in sales: It appears that 20-30% of Respiradone's sales are in the Alzheimer's market segment. Alzheimer's caregivers are in need of an antipsychotic that is SAFE in the elderly without the EPS issues with Haldol. QD dosing would be a plus. Preliminary incremental Olanzipine sales in Alzheimer's Disease are \$200M in peak sales....perhaps higher depending on the product's profile.
- 3) Competitive Marketplace: Respiradone is building a beachhead in the elderly market. A key issue in this market segment is SAFETY which study "O" provides to the market (addresses safety of an anticholinergic in demented patients). Lilly needs some hints of efficacy in Alzheimer's patients now as Zyprexa is launching this Fall. (Note: Lilly may have more elderly demented patients in "O" than the total number of patients in open label studies with Respiradone to date)
- 4) Supports Behavioral Component of Alzheimer's Disease: A key component of Xanomeline's success is developing the paradigm of Alzheimer's as a disease with cognitive AND behavioral components. Zyprexa would provide a product NOW to begin actively positioning problem behaviors in the marketplace.

Again, the Neuroscience GBU will support any effort to quickly evaluate the existing information and bring positive news to the marketplace. Please let us know how we can provide additional assistance.

Phil Hallstedt

To: STEPHEN REAMS
To: WINSTON SATTERLEE
To: PATRICK BURNS
To: JOHN LUCAS
To: KELLY EADS
To: ALVIN RAMPEY
CC: GARY TOLLEFSON
CC: ANGELA SMITH
CC: HERVE DE CIDRAC
CC: GORDON COUTTS
CC: DENISE DICKSON
CC: LARRY ALTSTIEL

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