15 Appendices

Appendix 1 Evidence on efficacy

Table 1.1: Multicentre, double-blind, randomised control trials of olanzapine

Author/date	Trial	Comparison	Dose	Entry criteria/patient group	Patient numbers
C M Beasley et al *Psychopharmacology* 1996[30]	HGAP	olanzapine fixed dose v olanzapine low fixed dose and placebo Crossover to open label olanzapine if no response at 3 weeks or after completion of acute phase	Ola 10mg/day Ola 1mg/day *5 to 20mg/day after crossover*	DSM-III-R diagnosis of schizophrenia BPRS >=24 CGI-Severity score of >=4 30% chronic disease, large proportion refractory and previously treated with clozapine	152, 12 sites
C M Beasley et al *Neuropsychopharmacology* 1996[31]	HGAD	olanzapine fixed dose ranges versus haloperidol fixed dose range and placebo	Ola 5mg/day Ola 10mg/day Ola15mg/day (All + or - 2.5mg/day) Hal 15mg/day + or -5mg/day Placebo	DSM-III-R diagnosis of schizophrenia with acute exacerbation BPRS >=24 CGI-Severity score of >=4	335 patients, 22 sites
CM Beasley et al, European Neuropsychopharmacology 1997[34]	E003	olanzapine fixed dose ranges versus olanzapine low fixed dose and haloperidol fixed dose range	Ola 1mg/day Ola 5mg/day - Ola 10 mg/day - Ola 15mg/day - + or - 5mg/day Hal 15mg/day + or -5mg/day	DSM-III-R diagnosis of schizophrenia with acute exacerbation BPRS >=24 CGI-Severity score of >=4	431 patients, 50 sites
Tollefson GD et al, *American Journal of Psychiatry* 1996 [33]	HGAJ	olanzapine versus haloperidol	Ola 5 to 20mg/day, Hal 5 to 20mg/day, Starting dose 5mg/day.	DSM-III-R diagnosis of schizophrenia (83%) or schizophreniform disorder (2%) or schizoaffective disorder, bipolar or depressive type.(15%) BPRS >=18 (98%) or inability to tolerate current therapy (unless haloperidol) (2%)	1996 patients, 174 sites

Table 1.1 ***(continued)***

Outcome measures	**Results:** ***mean change from baseline to endpoint,***	**Response rates**	**Other indications of quality/other comments**	**Duration**
BPRS, total, +ve, -ve PANSS, total, +ve, -ve CGI-Severity Repsonse: >=40% reduction BPRS or final BPRS<=18	Ola 10mg/day,:BPRS total: -7.7[a] BPRS -ve: -2.9$_a$ PANSS total: -12.3[a] PANSS +ve: -4.0[a] PANSS -ve: -2.8[a] CGI-Severity: -0.6[a]	Response: Placebo 10% Ola 1mg/day 12% Ola 10mg/day 28%[a]	Off conventional neuroleptic for 2 days, off depot for one dosing period. 4-9 day single blind placebo lead in - placebo responders discontinued.	6-week acute phase
BPRS, total, +ve, -ve SANS, composite and summary CGI-Severity Response: >=40% reduction BPRS or final BPRS<=18	Ola 5mg/day,:[a] BPRS -ve: --1.6[a] SANS composite: -8.7[a] SANS summary: -2.5[a] Ola 10mg/day:[a] BPRS total: -12.6 [a] BPRS +ve: -4.5 [a] CGI-Severity: -1.0[a] Ola 15mg/day:[a] BPRS total: -15.2 [a] BPRS +ve: -4.6 [a] BPRS -ve: -3.0 [a] SANS composite: -13.5 [a,b] SANS summary: -4.1 [a,b] CGI-Severity: -1.0[a] Hal 15mg/day::[a] BPRS total: -12.9 [a] BPRS +ve: -4.6 [a] CGI-Severity: -0.9[a]	Response: Placebo 59% Ola 5mg/day 58% Ola 10mg/day 64% Ola 15mg/day 67% Hal 15mg/day 62% (ns, but based on completing visit 7)	4-7 day single blind placebo lead in - placebo responders discontinued.	6-week acute phase extension phase (min. 46 weeks)
BPRS, total BPRS +ve BPRS -ve SANS, composite and summary CGI-Severity Response: >=40% reduction BPRS or final BPRS<=18	Ola 5mg/day: BPRS +ve: -4.5[c] Ola 15mg/day: BPRS +ve: -5.3 [c] PANSS +ve: -8.2 [c] CGI-Severity: -1.5 [c]	Response: Ola 1mg/day 42% Ola 5 mg/day 47% Ola 10mg/day 52% Ola 15mg/day 58%[c] Hal 15mg/day 48%	Placebo lead in - placebo responders discontinued	6-week acute phase extension phase (min. 46 weeks)
BPRS, total BPRS +ve BPRS -ve PANSS, total, +ve and -ve CGI-Severity MADRS QLS Response: >=40% reduction BPRS	Ola mean change: BPRS total: -10.9 BPRS -ve: -2.0 PANSS -ve: -4.5 CGI-Severity: -1.0 MADRS: -6.0 Hal mean change: BPRS total: -7.9 BPRS -ve: -1.3 PANSS -ve: -3.2 CGI-Severity: -0.7 MADRS: -3.1 Sig. Improvement in Ola v Hal patients	Response: Ola 52% Hal 34% Sig. Improvement in Ola v Hal patients	Haloperidol arm statistically significant higher baseline mean scores on BPRS (34.1 versus 33.1) and PANSS (90.1 versus 92.1) - unlikely to have had clinical importance. Olanzapine median dose 15 mg/day.	6-week acute phase extension phase for up to 46 weeks. Open label olanzapine available for non-responders.

[a] Better than placebo, p< .05 or smaller; [b] better than haloperidol 15mg/day, p< .05 or smaller; [c] better than olanzapine 1mg/day, p< .05 or smaller

Notes: 1. Only statistically significant results given above.

2. Large standard deviations were attached to changes in mean scores, reflecting variability in individual responses.

Table 1.2: Symptom severity rating scales used in olanzapine clinical trials

	Number of items	Scoring (total score)	Parameters measured
Brief Psychiatric Rating Scale (BPRS)	18	1 (symptom not present) to 7 (symptom extremely severe); 1 subtracted from each item to make a 0 to 6 score	Overall psychiatric symptomatology; subscales measure specific positive symptoms and specific negative symptoms
Positive and Negative Symptom Scale	30	1 (symptom not present) to 7 (symptom extremely severe)	Overall symptomatology; subscales measure specific positive symptoms and specific negative symptoms
Scale for the Assessment of Negative Symptoms (SANS)	24	0 (none) to 5 (severe)	Negative symptoms associated with schizophrenia
Clinical Global Impression - Severity (CGI-Severity)	1	1 (normal, not at all ill) to 7 (among the most extremely ill)	Severity of psychiatric illness
Montgomery-Asberg Depression Rating Scale (MADRS)	10	0 to 6	Severity of depressive mood symptoms

Further details of the trial findings are given below, including details of the clinical rating scales used.

Adverse events

Extrapyramidal symptoms

In the HGAP trial[30] the endpoint change in EPS (Simpson-Angus, Barnes and AIMS scales) in olanzapine treated patients was not significantly different from placebo. In the HGAD trial[31] parkinsonianism (Simpson Angus scores) and akathisia (Barnes scores) improved with respect to baseline in olanzapine treated patients, but worsened in haloperidol treated patients. There were no significant differences in improvement in dyskinesias (AIMS scores). In the HGAJ[33] trial 19.2% of olanzapine treated patients experienced any extrapyramidal adverse event, compared with 45.2% in the haloperidol group. There were significantly fewer cases of dystonic and parkinsonian events and fewer cases of akathisia. Parkinsonianism (Simpson-Angus scale) showed a 1 point improvement in olanzapine treated patients compared with a 1 point worsening in haloperidol treated patients, a statistically significant difference which was also seen in the Barnes Akathisia Scale. 17.1% of olanzapine treated patients had at least one dose of the allowed anticholinergic drug compared with 47.7% in the haloperidol group. The evidence indicates that olanzapine has a better EPS side effects profile than haloperidol in the doses used in the trial (dose range for HGAJ: 10 to 20mg/day, dose range for HGAJ 5mg/day to 20mg/day), with improved discontinuation rates because of such events (5% of all olanzapine treated patients compared with 8% of haloperidol treated patients).

Other adverse events

Weight gain 20% of olanzapine patients gained 7% or more of their body weight from baseline, a statistically significant difference from placebo or haloperidol.
Prolactin concentration Although prolactin concentrations in olanzapine treated

patients in the acute phase of the HGAD trial were more elevated than in placebo, they were lower than in haloperidol treated patients.
Sedation Somnolence was reported by 26% of trial patients receiving olanzapine compared with 15% on placebo[30, 31, 32, 33, 37].

Negative symptoms

In the two higher quality trials out of the three where olanzapine was compared to haloperidol, olanzapine has been shown to be superior to haloperidol in respect to mean change in rating scales for negative symptoms in short term treatment (HGAD[31], using SANS, HGAJ[33] using PANSS negative).
A caution should be sounded about the ability of the trials to evaluate olanzapine's role in treatment of the deficit domain of schizophrenia which is defined by primary trait negative symptoms. Rating scales measure all negative symptoms, regardless of origin. Such symptoms can arise from the psychotic component (highly aroused, but withdrawn patient), from side effects of medication (parkinsonian symptoms and sedation) and from depression, as well as from the deficit component of schizophrenia. Improvements in negative symptoms may result from reduction in psychosis, reduction in side effects and reduction in depression, as well from an improvement in primary negative trait symptoms[5].

Tollefson and Sanger[40] attempt to address these difficulties with respect to the HGAD trial data through the use of path analysis to explore direct and indirect therapeutic effects on negative symptoms. The direct effect of therapy on negative symptoms was that which remained after allowing for the changes in positive, depressive and extrapyramidal symptoms, and it is suggested that this direct effect measures the change in primary negative symptoms. In this trial both low (5mg/day) and high (15mg/day) dose olanzapine were associated with mean change in SANS summary score significantly better than placebo and high dose olanzapine was significantly superior to haloperidol. In the path analysis the direct therapeutic effect of high-dose olanzapine on negative symptoms relative to placebo accounted for 55% of the olanzapine advantage. Control of positive symptoms accounted for 43%. 84% of the high-dose olanzapine advantage compared with haloperidol in controlling negative symptoms was a direct effect on negative symptoms and 13% resulted from improvement in extrapyramidal side effects.

In addition, subgroup analyses were carried out on groups of patients with negative symptom defined in two ways, using baseline SANS score and in a validated model derived from BPRS. Only 46 patients were common to the two subgroups. In the SANS defined group, high dose olanzapine was superior to haloperidol and placebo with regard change in total SANS score. In the BPRS-based subgroup, haloperidol and high dose olanzapine were both superior to placebo for mean change in total SANS score.

This analysis does suggest, then, that olanzapine has some efficacy in the treatment of the deficit syndrome. The evidence available, however, is limited and a rider should be added that, in HGAD, 5mg/day of olanzapine and 15mg/day olanzapine were associated with significant reductions in negative symptoms but that 10mg/day were not, and a dose response relationship might have been expected if olanzapine did have an effect.

The change over baseline in the SANS summary score was -4.1 for high dose olanzapine, -2.0 for haloperidol and -0.6 for placebo (HGAD) over a 25 point scale. The clinical significance for individual patients of a change in mean score of this magnitude compared with the change achieved with haloperidol is unclear.

Appendix 2

Index of health-related quality of life (IHQL)
Rachel Rosser, Michaela Cottee, Rosalind Rabin, Caroline Selai[45]

The IHQL provides a broad and sensitive measure of social, psychological and physical functioning, and is designed to be applicable across all diagnostic groups. Using this instrument, it is possible to derive an assessment of health status on a single unidimensional scale.

The IHQL is derived from the original two-dimensional Rosser Index based on the dimensions of disability and distress. In this scale, distress is separated into physical and emotional components, to give three dimensions (disability, physical distress and emotional distress).

Valuations for the 175 composite health states were obtained using standard gamble for states of 1 year duration. No assessment has yet been made of the test-retest reliability of the scaling method, the stability of ratings over time, or the consensus of the values obtained from different sample groups.

3 - Dimensional Classification

Disability

D1 No physical disability; perfectly mobile and physically active; able to perform all self-care and role functions.
D2 Slight social disability, e.g. having a slight cold. No limitations with physical ability, self-care or mobility, but some role functions slightly impaired by social disability.
D3 Slight physical disability. Able to get round house and community, but unable to perform heavy physical tasks. Role functions slightly limited by physical disability. Able to perform all self-care activities.
D4 Able to get round house and do lighter physical work. Some difficulty in getting community due to weakness or other physical limitations. Can perform all self-care activities. Ability to perform role functions limited.
D5 Difficulty in getting around house, can only go out with assistance. Major physical limitations, e.g. can only do light work. Can perform most self-care activities, but need help getting in and out of the bath. Limited ability to perform role functions.
D6 Confined to a chair, therefore can only get out with assistance. Can only do the lightest of tasks, e.g. switch on the TV. Can feed self, but needs help with all other health care activities. Very limited ability to perform role functions.
D7 Confined to bed. Needs help with all self-care activities. Minimal ability to perform role functions.
D8 Unconscious.

Discomfort (Physical)

P1 No pain.
P2 Slight pain: (a) occasionally, (b) frequently, (c) almost all the time.
P3 Moderate pain: (a) occasionally, (b) frequently, (c) almost all the time.
P4 Severe pain: (a) occasionally, (b) frequently, (c) almost all the time.
P5 Agonising pain: (a) occasionally, (b) frequently, (c) almost all the time.

Distress (Emotional)

E1 No distress: very happy and relaxed almost all of the time.
E2 Slight distress: happy and relaxed most of the time, but anxious and depressed some of the time.
E3 Moderate distress: anxious and depressed most of the time, but happy and relaxed some of the time.
E4 Severe distress: very anxious and depressed almost all of the time.
E5 Extremely depressed: actively suicidal.

Composite state valuations (0-1 scale of values)

		E1	E2	E3	E4	E5
P1	D1	1.000	0.970	0.894	0.791	0.643
	D2	0.990	0.960	0.884	0.781	0.632
	D3	0.971	0.940	0.864	0.762	0.614
	D4	0.946	0.917	0.840	0.738	0.590
	D5	0.917	0.887	0.811	0.710	0.561
	D6	0.885	0.855	0.780	0.678	0.530
	D7	0.838	0.804	0.729	0.628	0.481
P2	D1	0.944	0.915	0.838	0.736	0.588
	D2	0.934	0.904	0.828	0.726	0.578
	D3	0.915	0.885	0.810	0.708	0.559
	D4	0.891	0.861	0.785	0.684	0.537
	D5	0.861	0.831	0.756	0.654	0.508
	D6	0.829	0.799	0.724	0.623	0.477
	D7	0.779	0.750	0.675	0.574	0.427
P3	D1	0.867	0.837	0.761	0.660	0.513
	D2	0.857	0.827	0.751	0.650	0.503
	D3	0.837	0.808	0.732	0.631	0.485
	D4	0.814	0.784	0.709	0.608	0.461
	D5	0.785	0.755	0.680	0.579	0.433
	D6	0.753	0.723	0.648	0.548	0.402
	D7	0.702	0.674	0.598	0.498	0.353
P4	D1	0.714	0.685	0.610	0.510	0.365
	D2	0.703	0.675	0.599	0.499	0.354
	D3	0.685	0.656	0.581	0.481	0.337
	D4	0.661	0.632	0.557	0.458	0.313
	D5	0.632	0.604	0.528	0.429	0.285
	D6	0.601	0.572	0.497	0.399	0.254
	D7	0.551	0.522	0.449	0.350	0.207
P5	D1	0.468	0.439	0.365	0.267	0.125
	D2	0.457	0.428	0.355	0.257	0.114
	D3	0.439	0.410	0.337	0.239	0.097
	D4	0.416	0.387	0.314	0.216	0.074
	D5	0.387	0.358	0.285	0.188	0.047
	D6	0.356	0.327	0.255	0.159	0.017
	D7	0.308	0.279	0.207	0.111	-0.03

Appendix 3

Details of the quality of life analysis

Patient pathways and transition probabilities

The decision tree in Figure 3.1 shows the medication associated with treatment packages, as well as for a hypothetical case in which patients receive no neuroleptic therapy. Patients not completing or responding to their initial therapy are assumed to switch to alternative therapy with a conventional neuroleptic (haloperidol or fluphenazine) with the same probability of response as that achieved by haloperidol in the HGAJ trial[33] except where olanzapine is considered as a second choice therapy following haloperidol. Transition probabilities are shown in Table 3.1. It was assumed that non-responders to second choice therapies would switch to therapy with a further conventional neuroleptic cost neutral with haloperidol. Further options for treatment resistant patients are not considered, nor is the use of risperidone or clozapine.

It is assumed that a 40% or more improvement in the BPRS score (the outcome in the HGAJ trial) produces a sufficient improvement to have a worthwhile effect on patients' quality of life. Other outcome data and dose are also taken from the HGAJ trial as this is by far the largest trial and the only one that allows a wide range of titrated doses. Responders in the model were calculated by incorporating the probability of completing the acute phase of the trial (that is on an intent to treat basis). It was assumed that lesser improvements in the BPRS will not change the quality of life of the patient, although they would have some effect on disease severity. Fluphenazine was assumed to perform similarly to haloperidol. No extra responses were allowed for after 6 weeks of treatment, and no responses were allowed with third choice therapies, although some lesser improvement might be expected. IHQL weightings were allocated to an acute episode schizophrenia, response to neuroleptics and relapse (Table 3.2).

Maintenance of response for oral neuroleptics was taken from the overview of extension phase of olanzapine trials[32] No information on censored patients is given and maintenance of response (olanzapine 80%, haloperidol 72%) may be overestimated. Relapse is defined as requirement for hospitalisation in an outpatient. Relapse rates for compliant depot treatment are assumed to be 24% in one year[1]. All of these relapse rates probably underestimate compliance and are therefore likely to be over-optimistic. Weiden[58] has estimated a monthly real world non-compliance rate after discharge of 7.6% and a monthly relapse rate for stabilised schizophrenic patients for who become non-compliant of 11%.

Placebo arms of control trials in default of better evidence provide an indication of the natural history of schizophrenia untreated by neuroleptics. There are several problems, most severe in more recent trials and any estimate will be overly-optimistic on the prognosis of untreated patients. Few schizophrenia patients are neuroleptically naïve; placebo arms often display inadequate washout; patients who deteriorate will drop out; trial patients are generally highly selected. Estimates have been taken from an early review of neuroleptic therapy[60] which, when considering clinical effectiveness, quotes the first NIMH-PSC Cooperative Study[61]. Earlier studies are likely to have fewer problems with patients switching from placebo to neuroleptic drugs and with

contamination by prior treatment. Following acute treatment with placebo, a quarter were considered very much improved (a "response" in terms of the analysis presented here) and one half were unchanged or worse. 65% of responders with no neuroleptic treatment in the maintenance phase are assumed to have relapsed by the end of the first year[1] Transition probabilities are given in Table 3.4.

A trial of a neuroleptic in acute treatment was modelled as lasting 6 weeks. The period between treatment initiation and switch to maintenance neuroleptics or to longer term inpatient care was 14 weeks (based on the mean duration of an acute episode taken from Shepherd[15]). Oral neuroleptics are assumed to continue at the same dose. Relapses are assumed to occur at a median time of six months, and response rates following relapse are the same as those following the initial episode.

If patient did not complete acute treatment then they switched to second choice neuroleptic. Switches to alternative treatment after failure to complete treatment or to respond are assumed to occur at six weeks after the start of treatment with the drug in question. Patients who switch drugs have same completion and response rates as other patients.

Figure 3.1 shows the decision trees for each of the treatment packages. Outcomes and transition probabilities are given in Table 3.1.

IQHL weightings

Table 3.2 gives the patient states incorporated into the model and the IHQL[45] values attached to each state. Alternative values are given for patients who might be assumed to experience EPS events are given, but, to keep the model relatively simple, EPS events have not been modelled. As the IHQL is weighted towards physical disability, Disability Weightings (DW) used in the "Global Burden of Disease" study are used in a sensitivity analysis (Table 3.2)[46].

Table 3.3 shows the time-weighted IHQL and DW weightings attached to each outcome, that is response, response then relapse, response to a second choice neuroleptic, response to a second choice neuroleptic then relapse and no response.

Table 3.1: Transition probabilities

For first choice treatment options:	**Completion of initial treatment**	**Response on completion of 6 weeks therapy**	**Response on second choice neuroleptic**	**Relapse after initial response**
No active treatment*	.59	.25	-	.65
Olanzapine	.67	.52	.47x.34=.16	.80
Olanzapine followed by depot	.67	.52	.47x.34=.16	.74
Haloperidol	.47	.34	.47x.34=.16	.72
Haloperidol followed by depot	.47	.34	.47x.34=.16	.74
Olanzapine as second choice treatment				
Haloperidol 1st choice, olanzapine 2nd choice:**	.47	.34	.67x.52=.35	
Haloperidol responders Olanzapine responders				.72 .80
Haloperidol 1st choice, olanzapine 2nd choice, depot maintenance**	.47	.34	.67x.52=.35	.74

* Hypothetical group; ** Sensitivity analyses see Footnote page 12

Table 3.2: IHQL index and disability weight for events with substantial impact on quality of life over one year

IHQL weightings:	**IHQL domains**				**Disability weighting**
	Disability	Discomfort	Distress	IHQL	
Need for acute treatment	D3	P1	E4	0.762	0.351
Response	D2	P1	E2	0.960	0.627
Relapse (includes hospitalization)	D3	P1	E4	0.762	0.351
EPS events					
In acute episode/relapse	D3	P3	E4	0.631	
After response	D3	P3	E2	0.808	

Figure 3.1: First choice acute treatment of schizophrenia: decision trees for treatment options over 1 year

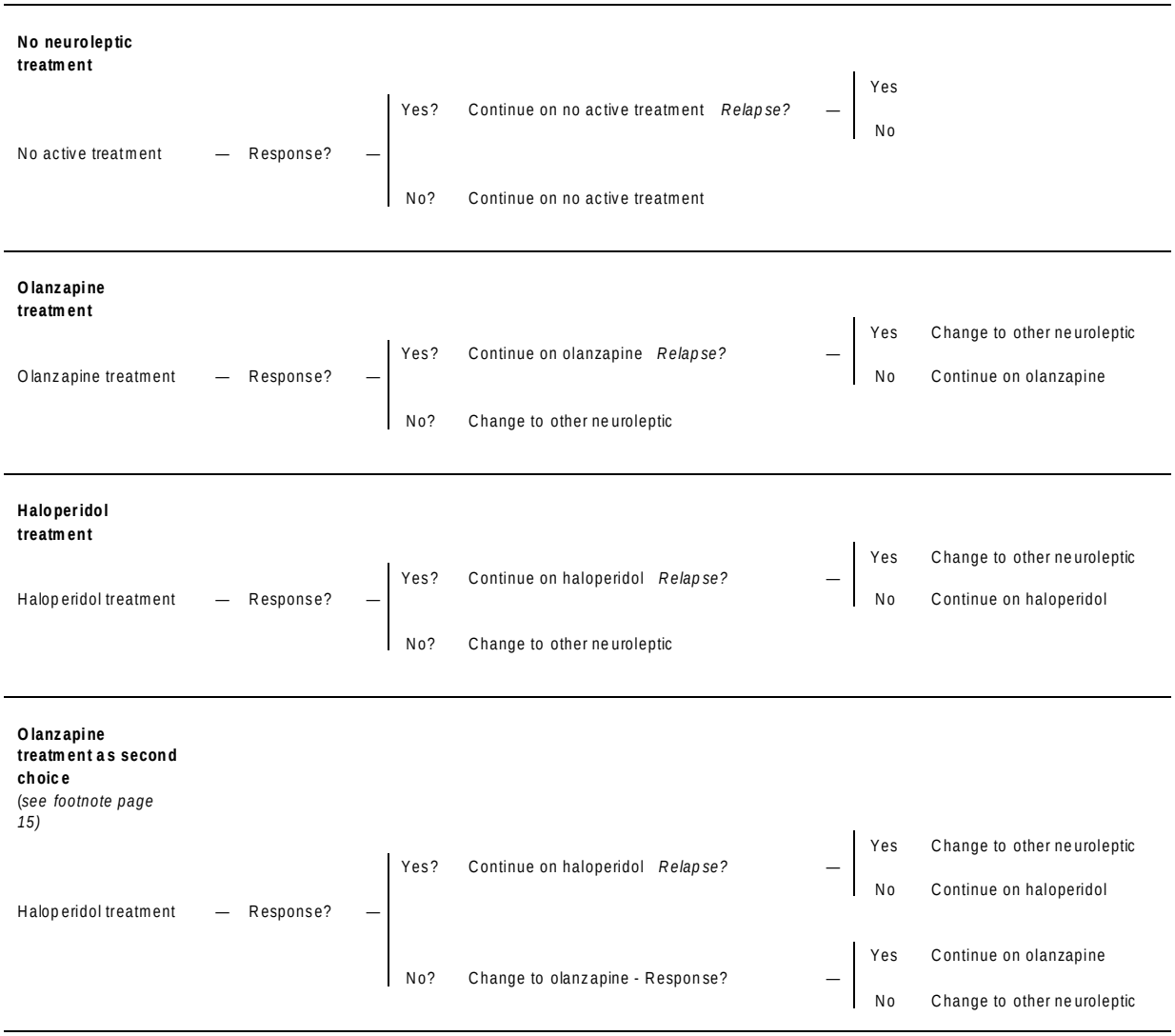

Table 3.3: IHQL index and Disability Weighting (DW) for outcomes over a one year period following acute treatment

	Week 1	Week 6	Week 10	Week 14	Week 34	Week 52	Over 1 year
Responds	0.762 (IHQL) 0.351 (DW) acute episode Week 1-6	0.960 (IHQL) 0.627 (DW) response Week 7-52					IHQL = 0.937 DW = 0.595
Responds then relapses	0.762 (IHQL) 0.351 (DW) acute episode Week 1-6	0.960 (IHQL) 0.627 (DW) acute episode Week 7-33			0.762 (IHQL) 0.351 (DW) relapse Week 34-52		IHQL = 0.865 DW = 0.494
No response	0.762 (IHQL) 0.351 (DW) acute episode Week 1-52						IHQL = 0.762 DW = 0.351
Responds on second choice neuroleptic	0.762 (IHQL) 0.351 (DW) acute episode Week 1-10		0.960 (IHQL) 0.627 (DW) acute episode Week 11-52				IHQL = 0.922 DW = 0.574
Responds on 2nd choice neuroleptic tghen relapses	0.762 (IHQL) 0.351 (DW) acute episode Week 1-10		0.96 (IHQL) 0.627 (DW) acute episode Week 11-33		0.762 (IHQL) 0.351 (DW) acute episode Week 34-52		IHQL = 0.850 DW = 0.473

Table 3.4: QALYs gained per patient over 1 year for range of treatment options

	Base case Number/ 1000	IHQL	IHQL x N
No active treatment			
Responds	162	0.937	151.8
Responds then relapses	88	0.865	76.1
No response	750	0.762	571.5
Total IHQL for 1000 patients over 1 year			799.4
IHQL per patient			0.8
Total DW for 1000 patients over 1 year			403.2
DW per patient			0.4
Olanzapine as first choice and maintenance			
Responds	279	0.937	261.5
Responds then relapses	70	0.865	60.5
No response	547	0.762	416.8
Responds on second choice neuroleptic	77	0.922	71.0
Responds on 2nd choice neuroleptic then relapses	27	0.850	22.9
Total IHQL for 1000 patients over 1 year			832.7
IHQL per patient			0.8
Total DW for 1000 patients over 1 year			449.6
DW per patient			0.5
Haloperiodol as first choice and maintenance			
Responds	115	0.937	107.8
Responds then relapses	45	0.865	38.9
No response	706	0.762	538.0
Responds on second choice neuroleptic	97	0.922	89.4
Responds on 2nd choice neuroleptic then relapses	38	0.850	32.3
Total IHQL for 1000 patients over 1 year			806.4
IHQL per patient			0.8
Total DW for 1000 patients over 1 year			412.2
DW per patient			0.4
Haloperidol first choice, olanzapine 2nd choice, oral maintenance *(sensitivity analysis)*			
Responds	115	0.937	107.8
Responds then relapses	45	0.865	38.9
No response	546	0.762	416.1
Responds on second choice neuroleptic	235	0.922	216.7
Responds on 2nd choice neuroleptic then relapses	59	0.850	50.1
Total IHQL for 1000 patients over 1 year			829.5
IHQL per patient			0.8
Total DW for 1000 patients over 1 year			445.1
DW per patient			0.4

Appendix 4

Details of cost analysis

(Figures have been rounded to nearest pound but calculations have been made in pounds and pence. Therefore, there may be some rounding errors.)

Table 4.1: Unit costs of schizophrenia treatment

	Unit cost
*Drugs**	
Olanzapine 10mg/day	£5.65
Haloperidol 15mg/day	£0.28
Fluphenazine 10mg/day	£0.18
Benztropine 0.33mg/day	£0.00
Benztropine 1.29mg/day	£0.02
*Other resources***	
Inpatient care short stay (day)	£128.00
Inpatient care long stay (day)	£106.00
Outpatient visits	£88.00
Day care	£34.00
Community psychiatric visits	£47.00
** from BNF March 1997*	
*** from Netton and Dennett[54]*	

Table 4.2: Resource use in one year for a prevalent group of patients

	Unit cost	*Group 1*		*Group 2*		*Group 3*		*Group 4a*		*Group 4b*	
		Single episode, average duration 22 weeks		*Episodes of major disorder lasting up to 1 year*		*Episodes for 1-2.5 years*		*Episodes more than 2.5 years*			
								Community care		*Hospital care*	
		Units	*Costs (£)*	*Units*	*Costs (£)*	*Units*	*Costs (£)*	*Units*	*Costs (£)*	*Units*	*Costs (£)*
Inpatient short stay (days)	£128	26	3,328	26	3,328	40	5,120	41	5,248	98	12,544
Inpatient long stay (days)	£106	0	0	0	0	0	0	0	0	267	28.302
Outpatient visits	£88	0.6	53	1.4	123	1.4	123	2.8	246	0	0
Day care	£34	4.7	160	11.1	377	16.8	571	20	680	59.5	2,023
Community support (visits)	£47	4.7	221	11.3	531	16.7	785	22.4	1,053	0	0
Total non-drug costs			3,762		4,360		6,599		7,227		42,869

Costs taken from Netton and Dennett[54], resource use from Davies and Drummond[27].

Table 4.3: Annual cost of a range of treatment options

a) No neuroleptic treatment

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Non-drug costs				
Responders: Group 1 annual costs	£3,761.50	1	96	£361,104
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	22	£95,215
Group 3 (14%) annual costs	6,599.30	1	7	£48,042
Group 4a (44%) annual costs	7,227.20	1	23	£165,358
No response: Group 4b	42,869.00	1	852	£36,524,388
Total non drug costs				£37,194,109
Total costs				£37,194,109
Costs per person				£37,194

b) Olanzapine as first choice treatment, haloperidol/depot second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Olanzapine responders, no relapse				
Olanzapine 15mg/day	£5.65	365	279	£575,331
Benztropine 0.33mg/day	£0.00	365	279	£492
2nd choice responders, no relapse				
Olanzapine 15mg/day	£5.65	28	77	£12,187
Benztropine 0.33mg/day	£0.00	28	77	£10
Haloperidol 10mg/day	£0.28	70	77	£1,531
Benztropine 1.29mg/day	£0.02	336	77	£484
Haloperidol decanoate 50mg/every 4 weeks	£4.35	10	77	£3,350
No response				
Olanzapine 15mg/day	£5.65	28	547	£86,530
Benztropine 0.33mg/day	£0.00	28	547	£74
Haloperidol 10mg/day or cost neutral	£0.28	336	547	£52,197
Benztropine 1.29mg/day	£0.02	336	547	£3,438
olanzapine responders, relapse				
Olanzapine 15mg/day	£5.65	231	70	£91,355
Benztropine 0.33mg/day	£0.00	231	70	£78
Haloperidol 10mg/day	£0.28	133	70	£2,644
Benztropine 1.29mg/day	£0.02	133	70	£174
2nd choice neuroleptic responders, relapse				
Olanzapine 15mg/day	£5.65	28	27	£4,271
Benztropine 0.33mg/day	£0.00	28	27	£4
Haloperidol 10mg/day	£0.28	70	27	£537
Benztropine 1.29mg/day	£0.02	336	27	£170
Haloperidol decanoate 50mg/every 4 weeks	£4.35	5	27	£587
Fluphenazine 10mg/day	£0.18	133	27	£636
Total drug costs				£836,073
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	356	£1,339,094
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	41	£177,614
Group 3 (14%) annual costs	6,599.30	1	14	£89,619
Group 4a (44%) annual costs	7,227.20	1	43	£308,457
No response				
Group 4b	42,869.00	1	547	£23,449,343
Total non drug costs				£25,364,127
Total costs				£26,200,199
Costs per person				£26,200

c) Olanzapine/depot as first choice treatment, haloperidol/depot second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Olanzapine responders, no relapse				
Olanzapine 15mg/day	£5.65	98	258	£142,846
Benztropine 0.33mg/day	£0.00	98	258	£122
Haloperidol decanoate 50mg/every 4 weeks	£4.35	10	258	£11,223
Benztropine 1.29mg/day	£0.02	266	258	£1,284
2nd choice responders, no relapse				
Olanzapine 15mg/day	£5.65	28	77	£12,181
Benztropine 0.33mg/day	£0.00	28	77	£10
Haloperidol 10mg/day	£0.28	70	77	£1,531
Benztropine 1.29mg/day	£0.02	336	77	£484
Haloperidol decanoate 50mg/every 4 weeks	£4.35	9	77	£3,015
No response				
Olanzapine 15mg/day	£5.65	28	547	£86,530
Benztropine 0.33mg/day	£0.00	28	547	£74
Haloperidol 10mg/day or cost neutral	£0.28	336	547	£52,197
Benztropine 1.29mg/day	£0.02	336	547	£3,438
Olanzapine responders, relapse				
Olanzapine 15mg/day	£5.65	231	91	£118,761
Benztropine 0.33mg/day	£0.00	231	91	£102
Haloperidol decanoate 50mg/every 4 weeks	£4.35	5	91	£1,979
Benztropine 1.29mg/day	£0.02	133	91	£226
2nd choice neuroleptic responders, relapse				
Olanzapine 15mg/day	£5.65	28	27	£4,271
Benztropine 0.33mg/day	£0.00	28	27	£4
Haloperidol 10mg/day	£0.28	70	27	£537
Benztropine 1.29mg/day	£0.02	336	27	£170
Haloperidol decanoate 50mg/every 4 weeks	£4.35	4	27	£470
Fluphenazine 10mg/day	£0.18	133	27	£636
Total drug costs				£442,089
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	335	£1,260,103
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	50	£216,067
Group 3 (14%) annual costs	6,599.30	1	17	£109,020
Group 4a (44%) annual costs	7,227.20	1	52	£375,236
No response				
Group 4b	42,869.00	1	547	£23,449,343
Total non drug costs				£25,409,769
Total costs				£25,851,857
Costs per person				£25,852

d) Haloperidol/oral as first choice treatment, fluphenazine/oral second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Haloperidol responders, no relapse				
Haloperidol 10mg/day	£0.28	365	115	£11,921
Benztropine 1.29mg/day	£0.02	365	115	£785
2nd choice responders, no relapse				
Haloperidol 10mg/day	£0.28	28	97	£771
Benztropine 1.29mg/day	£0.02	365	97	£662
Fluphenazine 10mg/day	£0.18	336	97	£5,769
No response				
Haloperidol 10mg/day	£0.28	28	706	£5,614
Benztropine 1.29mg/day	£0.02	365	706	£4,820
Fluphenazine 10mg/day or cost neutral	£0.18	336	706	£41,987
haloperidol responders, relapse				
Haloperidol 10mg/day	£0.28	231	45	£2,952
Benztropine 1.29mg/day	£0.02	365	45	£307
Fluphenazine 10mg/day	£0.18	133	45	£1,059
2nd choice neuroleptic responders, relapse				
Haloperidol 10mg/day	£0.28	28	38	£302
Benztropine 1.29mg/day	£0.02	365	38	£259
Fluphenazine 10mg/day	£0.18	70	38	£471
Total drug costs				£77,681
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	212	£797,438
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	34	£150,148
Group 3 (14%) annual costs	6,599.30	1	11	£75,760
Group 4a (44%) annual costs	7,227.20	1	36	£260,757
No response				
Group 4b	42,869.00	1	706	£30,265,514
Total non drug costs				£31,549,617
Total costs				£31,627,298
Costs per person				£31,627

e) Haloperidol/depot as first choice treatment, fluphenazine/depot second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Haloperidol responders, no relapse				
Haloperidol 10mg/day	£0.28	98	258	£7,181
Benztropine 1.29mg/day	£0.02	98	258	£473
Haloperidol decanoate 50mg/every 4 weeks	£4.35	10	258	£11,223
Benztropine 1.29mg/day	£0.02	266	258	£1,284
2nd choice responders, no relapse				
Haloperidol 10mg/day	£0.28	28	77	£612
Benztropine 1.29mg/day	£0.02	365	77	£526
Fluphenazine 10mg/day	£0.18	70	77	£954
Haloperidol decanoate 50mg/every 4 weeks	£4.35	9	77	£3,015
No response				
Haloperidol 10mg/day	£0.28	28	547	£4,350
Benztropine 1.29mg/day	£0.02	365	547	£3,735
Fluphenazine 10mg/day or cost neutral	£0.18	336	547	£32,531
haloperidol responders, relapse				
Haloperidol 10mg/day	£0.28	231	91	£5,970
Benztropine 1.29mg/day	£0.02	365	91	£621
Haloperidol decanoate 50mg/every 4 weeks	£4.35	5	91	£1,979
2nd choice neuroleptic responders, relapse				
Haloperidol 10mg/day	£0.28	28	27	£215
Benztropine 1.29mg/day	£0.02	365	27	£184
Fluphenazine 10mg/day	£0.18	203	27	£970
Haloperidol decanoate 50mg/every 4 weeks	£4.35	4	27	£470
Total drug costs				£76,292
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	218	£820,007
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	32	£140,993
Group 3 (14%) annual costs	6,599.30	1	11	£71,140
Group 4a (44%) annual costs	7,227.20	1	34	£244,858
No response				
Group 4b	42,869.00	1	706	£30,265,514
Total non drug costs				£31,542,512
Total costs				£31,618,804
Costs per person				£31,619

f) Haloperidol/oral as first choice treatment, olanzapine second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Haloperidol responders, no relapse				
Haloperidol 10mg/day	£0.28	365	115	£11,921
Benztropine 1.29mg/day	£0.02	365	115	£785
2nd choice responders, no relapse				
Haloperidol 10mg/day	£0.28	28	235	£1,869
Benztropine 1.29mg/day	£0.02	28	235	£123
Olanzapine 15mg/day	£5.65	336	235	£446,096
Benztropine 0.33mg/day	£0.00	336	235	£382
No response				
Haloperidol 10mg/day	£0.28	28	546	£4,342
Benztropine 1.29mg/day	£0.02	336	546	£3,436
Olanzapine 15mg/day	£5.65	42	546	£129,558
Benztropine 0.33mg/day	£0.00	42	546	£111
Fluphenazine 10mg/day or cost neutral	£0.18	294	546	£28,413
haloperidol responders, relapse				
Haloperidol 10mg/day	£0.28	231	45	£2,952
Benztropine 1.29mg/day	£0.02	322	45	£271
Olanzapine 15mg/day	£5.65	42	45	£10,678
Benztropine 0.33mg/day	£0.00	42	45	£9
Fluphenazine 10mg/day or cost neutral	£0.18	91	45	£725
2nd choice neuroleptic responders, relapse				
Haloperidol 10mg/day	£0.28	28	59	£469
Benztropine 1.29mg/day	£0.02	28	59	£31
Olanzapine 15mg/day	£5.65	70	59	£23,333
Benztropine 0.33mg/day	£0.00	336	59	£96
Fluphenazine 10mg/day	£0.18	133	59	£1,389
Total drug costs				£666,983
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	350	£1,316,525
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	44	£190,432
Group 3 (14%) annual costs	6,599.30	1	15	£96,086
Group 4a (44%) annual costs	7,227.20	1	46	£330,717
No response				
Group 4b	42,869.00	1	546	£23,406,474
Total non drug costs				£25,340,233
Total costs				£26,007,216
Costs per person				£26,007

g) Haloperidol/depot as first choice treatment, olanzapine/depot second choice

	Unit cost	*Units*	*Number*	*Cost over 1 year*
Drug costs				
Haloperidol responders, no relapse				
Haloperidol 10mg/day	£0.28	98	118	£3,284
Benztropine 1.29mg/day	£0.02	365	118	£806
Haloperidol decanoate 50mg/every 4 weeks	£4.35	10	118	£5,133
2nd choice responders, no relapse				
Haloperidol 10mg/day	£0.28	28	218	£1,733
Benztropine 1.29mg/day	£0.02	365	218	£1,488
Olanzapine 15mg/day	£5.65	70	218	£86,216
Benztropine 0.33mg/day	£0.00	70	218	£74
Haloperidol decanoate 50mg/every 4 weeks	£4.35	10	218	£9,483
No response				
Haloperidol 10mg/day	£0.28	28	546	£4,342
Benztropine 1.29mg/day	£0.02	322	546	£3,289
Olanzapine 15mg/day	£5.65	42	546	£129,558
Benztropine 0.33mg/day	£0.00	42	546	£111
Fluphenazine 10mg/day or cost neutral	£0.18	294	546	£28,413
haloperidol responders, relapse				
Haloperidol 10mg/day	£0.28	231	41	£2,690
Benztropine 1.29mg/day	£0.02	365	41	£280
Haloperidol decanoate 50mg/every 4 weeks	£4.35	5	41	£892
Fluphenazine 10mg/day or cost neutral	£0.18	133	41	£965
2nd choice neuroleptic responders, relapse				
Haloperidol 10mg/day	£0.28	28	76	£604
Benztropine 1.29mg/day	£0.02	294	76	£418
Olanzapine 15mg/day	£5.65	70	76	£30,056
Benztropine 0.33mg/day	£0.00	70	76	£26
Haloperidol decanoate 50mg/every 4 weeks	£4.35	4	76	£1,322
Fluphenazine 10mg/day or cost neutral	£0.18	133	76	£1,789
Total drug costs				£312,969
Non-drug costs				
Responders				
Group 1 annual costs	£3,761.50	1	336	£1,263,864
Responders who relapse				
Group 2 (42%) annual costs	4,359.70	1	50	£216,067
Group 3 (14%) annual costs	6,599.30	1	17	£109,020
Group 4a (44%) annual costs	7,227.20	1	52	£375,236
No response				
Group 4b	42,869.00	1	546	£23,406,474
Total non drug costs				£25,370,661
Total costs				£25,683,630
Costs per person				£25,684

Appendix 5

Olanzapine DEC report update

The olanzapine report was completed in March 1998. The bibliographic database searches were updated in July 1998. Relevant new literature found is described below.

Summary

Most publications of primary research since the completion of the DEC report have been further reports of the four pre-licensing trials confirming previously reported results on efficacy, maintenance of response and side effects profile in more detail.

A trial of olanzapine and chlorpromazine indicated that olanzapine was of very limited efficacy in treatment-resistant disease and no more effective than chlorpromazine.

A study of NHS prescribing of olanzapine and some economic analyses have also become available.

NHS prescribing

A study of prescribing for 202 patients in 15 NHS Trusts examined the prescribing of olanzapine as described in prescription charts in May 1997[1].

Those who had been prescribed olanzapine for less than six weeks were assumed to be in the titration phase of therapy, while those prescribed the drug for longer were assumed to be in the maintenance phase. The recommended starting and routine maintenance dose of olanzapine is 10 mg daily, but the mean dose for patients assumes to be on maintenance was 15 and the median dose was 15.8. The mean dose for patients in the first six week of therapy was 12.4 and the median dose was 10 mg daily. Thus, higher doses than recommended are prescribed. The median dose in the olanzapine trial which allowed titrated doses, however, was 15 mg daily, and this was the dose used in the economic analysis in the olanzapine DEC report.

Only 56% of those in the first six weeks of therapy and only 64% of those on maintenance were prescribed olanzapine as their sole antipsychotic drug. If benefits are to be gained from olanzapine's side effects profile, then olanzapine monotherapy is to be preferred. Some of the patients prescribed more than one antipsychotic may have had treatment-refractory disease. The role of olanzapine in refractory disease is unclear at present (see below).

Quality of life and efficacy

A further report of the double blind, fixed dose, olanzapine, placebo and haloperidol trial reported efficacy and quality of life after 24 weeks of therapy (that is, in the extension phase of the six week trial)[2]. Small sample sizes precluded analysis of quality of life data after this point. Quality of life was evaluated using the quality of life scale (QLS), a disease specific measure of schizophrenia deficit (enduring negative symptoms). The QLS was administered at baseline for all patients and at 12 and 24 weeks for responders to therapy.

There were significant changes in QLS score from baseline to week 24 for the medium and high dose olanzapine responder groups, but not for placebo or haloperidol responders. Only 17% of the haloperidol group, however, continued into the extension phase, so the sample size was small. Responders had better QLS scores at baseline, so the QLS may be predictive of patient response. Although these results suggest an improvement of quality of life in olanzapine responders, confirmation of this will need larger samples and follow-up of both responders and non-responders to treatment.

Maintenance treatment

Two further reports of the previously published three trials with maintenance extension phases have been published, but do not give any substantial new information. One of these compares standard dose olanzapine with ineffective dose olanzapine and placebo[3], the other compares olanzapine with haloperidol[4]. Their conclusions are in line with information already available and reported in the DEC report.

There were statistically significant differences in the chance of relapse in the trial when olanzapine was compared to placebo (29% compared to 70% at one year) and the trial where olanzapine at standard dose was compared to olanzapine at ineffective dose (13% compared to 36%). Only small numbers of patients were included, however (olanzapine 45, placebo 13 and standard dose olanzapine 48, ineffective dose 14), and there were high rates of discontinuation for reasons other than relapse.

Three trials compared olanzapine to haloperidol, and subjects were pooled. Only the largest trial (titrated dose) showed a statistically significant difference with a one year risk of relapse of 19% for olanzapine and 28% for haloperidol. The one year risk of relapse from the pooled data was 20% for olanzapine and 28% for haloperidol. 36% of the olanzapine patients and 39% of the haloperidol patients were discontinued from the study for reasons other than relapse (need to modify treatment, adverse events, non-compliance, patient's decision, loss to follow-up). This and other factors, including more frequent patient evaluation than in clinical practice, limits the generalisability of the study.

Anxious and depressive symptoms

A further report of one of the previously published trials considered the effect of olanzapine, placebo and haloperidol in fixed doses on anxious and depressive symptoms[5]. Medium and high dose olanzapine produced statistically significantly greater improvements in BPRS anxiety/depression factor than was seen with placebo. Path analysis suggested that part of this improvement was a direct effect on anxiety/depression.

Side effects

Extrapyramidal symptoms

A further analysis of the three trials comparing olanzapine with haloperidol considered extrapyramidal symptoms in three ways, through detection of adverse events, through rating scales and through use of anticholinergic medication[6].

The olanzapine group had a lowered incidence of any treatment emergent exprapyramidal event (18% olanzapine, 47% haloperidol, statistically significant). Olanzapine patients also scored better on rating scales and used significantly less anticholinergic medication for the control of extrapyramidal symptoms. The study confirms olanzapine's superior side effects profile relative to haloperidol.

Treatment emergent tardive dyskinesia

A report of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol in responders entered into the maintenance extension phases of three previously published trials has been published[7].

The analysis included 707 patients with 237 median days of exposure to olanzapine and 197 patients with 203 median days of exposure to haloperidol without historical or baseline evidence of tardive dyskinesia. Olanzapine patient AIMS (Abnormal Involuntary Movement Scale) scores significantly improves from baseline to endpoint, while haloperidol patient scores significantly worsened. 50 (7%) of the olanzapine group and 32 (16%) of the haloperidol group developed treatment emergent tardive dyskinesia symptoms at any visit, while 2% of the olanzapine group and 8% of the haloperidol group manifested tardive dyskinesia at the last study visit and 1% of the olanzapine group and 5% of the haloperidol group showed such symptoms on the last two study visits (all statistically significant differences).

These results are encouraging, but further long term comparative controlled studies are required.

Prolactin concentration

Raised levels of prolactin are commonly associated with typical neuroleptic medication, and are associated with galactorrhoea, amenorrhoea, reduced libido and a predisposition to osteoporosis. A further report of a previously published trial indicated that treatment emergent elevations of serum prolactin concentrations were transient and lower than those associated with haloperidol[8].

Treatment resistant disease

An open label study of olanzapine in a dose range of 15 to 25 mg daily for treatment refractory schizophrenia achieved responses (>=35% decrease in BPRS) in 9 (36%) of 25 patients[9]. Although this might be taken to suggest that olanzapine might have some value in the treatment of these patients, this has not been confirmed in a randomised control trial.

A good quality trial of olanzapine compared with chlorpromazine in treatment resistant schizophrenia, however, achieved only very modest improvements[10]. 103 treatment refractory patients were given a trial of haloperidol. 84 who did not respond and who agreed to continue were entered into a double blind trial of fixed dose olanzapine 25mg daily or chlorpromazine 1200g and benzotropine for eight weeks after a 1-2 week washout period. There were no significant differences in completion rates. Three olanzapine patients out of 42 (7%) responded and no chlorpromazine patients responded (non significant).

Comments on risperidone and olanzapine trial

The olanzapine risperidone trial has been criticised for using high risperidone dosages that do not correspond to current clinical practice, and for not adjusting for multiple comparisons in the statistical analysis, with the conclusion that the trial showed only equal efficacy for olanzapine and risperidone[11]. This was also the conclusion reported in the DEC report.

Economic analyses

The costs model comparing olanzapine and haloperidol discussed in the DEC report has now been published[12]. See the discussion in the DEC report.

The open label study of olanzapine in the treatment of refractory schizophrenia had a costs study attached[13]. Medical resource use was collected retrospectively for six months prior to treatment and at the end of six months of treatment. The analysis focused on direct medical costs which were higher in the six months before treatment, although the results did not reach statistical significance. The small size of the study and the lack of evidence that olanzapine is effective for treatment refractory patients limits the relevance of this study.

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