REVIEW ARTICLE

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Tolerability of Atypical Antipsychotics

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Abstract

Atypical antipsychotics are expected to be better tolerated than older antipsychotics because of their lower propensity to cause certain adverse effects. All atypical drugs have been shown to cause fewer acute extrapyramidal symptoms (EPS) than a standard typical agent (usually haloperidol) and some (clozapine, sertindole and quetiapine) appear to cause these effects no more often than placebo. In the longer term, clozapine, olanzapine and (less robustly) other atypical antipsychotics are thought to cause less tardive dyskinesia than typical antipsychotics. Problems caused by hyperprolactinaemia occur less often with some atypical antipsychotics than with typical drugs although risperidone and amisulpride appear to have no advantages in this respect.

Other adverse effects may occur as frequently with some atypical antipsychotics as with some typical drugs. Clozapine, risperidone and quetiapine are known to cause postural hypotension; clozapine, olanzapine and quetiapine are clearly sedative; and anticholinergic effects are commonly seen with clozapine, and, much less frequently, with olanzapine. Some adverse effects are more frequent with atypical drugs. Idiosyncratic effects seem particularly troublesome with clozapine and, to a lesser extent, sertindole, olanzapine and zotepine. Bodyweight gain is probably more problematic with atypical antipsychotics than with typical drugs.

Overall tolerability, as judged by withdrawals from therapy, is not clearly proven to be better with atypical drugs, although some individual trials do indicate an advantage with atypical agents. Differences in tolerability between individual atypical antipsychotics have not been clearly shown.

The tolerability profile of atypical drugs certainly benefits from a lower incidence of acute EPS effects, along with less certain or less uniform benefits in symptomatic hyperprolactinaemia or tardive dyskinesia. Other, perhaps more trivial, adverse effects militate against their good tolerability, and effects such as bodyweight gain may severely reduce tolerability. Without clear advantages in tolerability in patient groups used in trials, drug choice in regard to adverse effects should continue to be on a patient to patient basis.

1. What is Tolerability?

The word 'tolerate' is defined as 'to find or treat as endurable' or 'to be unharmed by'. Drug tolerability by implication includes the likelihood of adverse effects caused by a drug, and whether or not these effects are distressing to the patient. When comparing the tolerabilities of drug therapies for schizophrenia, most clinicians think first of their propensity to cause extrapyramidal symptoms (EPS). However, patients responding to a survey by Day et al.[1] rated other adverse effects, particularly menstrual problems, bodyweight gain and tiredness, as more distressing than EPS. Thus, it is important to consider the full range of ways in which antipsychotics (neuroleptics) give rise to poor tolerability. This review compares data on the tolerabilities of the newer atypical antipsychotics, namely clozapine, risperidone, sertindole, olanzapine, quetiapine, amisulpride, ziprasidone and zotepine. All papers were published in full in peer-reviewed journals and were retrieved from a Medline search conducted in August 1998 using the search terms '(drug name)' and 'adverse effects'. Reference sections of each paper were scrutinised for further relevant articles. We also searched our own files for other sources of data such as conference posters or abstracts.

2. Withdrawals from Clinical Trials

There may be many reasons why patients withdraw from clinical trials, for example, lack of response to medication, violation of the trial protocol, noncompliance with medication or intolerable adverse effects. The proportion of patients who withdraw because of adverse effects may be used as an indirect indication of the endurability or tolerability of the drug treatment.

Data on the withdrawal rates from studies involving atypical antipsychotics are presented in table I. Full statistical analyses were rarely presented for comparisons of atypical and typical antipsychotics such as haloperidol, chlorpromazine and zuclopenthixol, making it difficult to compare their overall tolerabilities. In the few trials that did report the results of statistical analyses, olanzapine was significantly better tolerated than haloperidol,[18] and amisulpride recipients had a significantly lower withdrawal rate than flupenthixol recipients.[24] Loo et al.[23] stated that amisulpride was better tolerated than placebo, but the statistical significance was not given. When olanzapine and risperidone were compared head-to-head, withdrawal rates due to adverse effects were equivalent, although they were slightly lower with olanzapine.[15,16]

Although many trials are presented in table I, it is inappropriate to compare them because they were invariably conducted under different conditions and there may be a number of confounding variables. In addition, most of the trials were only conducted over 4 to 8 weeks, whereas most patients with schizophrenia will take antipsychotics for many years or for the rest of their lives. It could be argued that most withdrawals occur during the first 6 to 8 weeks of treatment. On the other hand, longer term trials involving clozapine (26 to 52 weeks)[4,5,7] produced withdrawal rates due to adverse events of 12 to 13% compared with around 6% in a 6-week study.[2] This suggests that patients may be more likely to accept some adverse effects if they know that drug therapy will be withdrawn within a few weeks. Therefore, until more realistic

Table I. Rates of withdrawal from clinical trials

Reference	Study duration (wk)	Daily drug dosage (mean or range; mg/day)	No. of patients	Percentage of withdrawals because of adverse events
Kane et al.[2]	6	Clozapine ≤900	126	6[a]
		Chlorpromazine ≤1800	142	
Naber & Hippius[3]	NR	Clozapine 304	503	7
Clozapine Study Group[4]	26	Clozapine 450–500	54	13
Lieberman et al.[5]	52	Clozapine 25–900	84	12
Klieser et al.[6]	4	Risperidone 4	20	5.0
		Risperidone 8	19	10.5
		Clozapine 400	20	20.0
Rosenheck et al.[7]	52	Clozapine 552	205	12.9
		Haloperidol 28	218	12.2
Hong et al.[8]	12	Clozapine 543	21	9.5
		Chlorpromazine 1163	19	10.5
Blin et al.[9]	4	Risperidone 7.4	21	0
		Haloperidol 7.6	20	0
		Levomepromazine 100	21	9.5
Chouinard et al.[10]	8	Placebo	22	4.5
		Risperidone 2	24	4.2
		Risperidone 6	22	4.5
		Risperidone 10	22	4.5
		Risperidone 16	24	0.0
		Haloperidol 20	21	4.8
Huttunen et al.[11]	6	Risperidone 8 (2–20)	48	20.8
		Zuclopenthixol 38 (10–100)	50	30.0
Claus et al.[12]	12	Risperidone 12.0	21	0.0
		Haloperidol 10.3	21	4.8
Peuskens et al.[13]	8	Risperidone 1	229	7.9
		Risperidone 4	227	6.6
		Risperidone 8	230	7.4
		Risperidone 12	226	9.7
		Risperidone 16	224	13.8
		Haloperidol 10	226	10.2
Zimbroff et al.[14]	8	Placebo	73	1.4
		Sertindole 12–24	216	5.6
		Haloperidol 4–16	208	9.1
Tran et al.[15]	28	Olanzapine 17.2	172	9.9
		Risperidone 7.2	167	10.2
Conley et al.[16]	8	Risperidone 2–6	202	10.9
		Olanzapine 5–20	205	8.3
Beasley et al.[17]	6	Placebo	68	10.3
		Olanzapine 6.6	65	7.7
		Olanzapine 11.6	64	1.6
		Olanzapine 16.3	69	5.8
		Haloperidol 16.4	69	8.7
Tollefson et al.[18]	6	Olanzapine 11.8	1336	4.5
		Haloperidol 13.2	660	7.3[*]
Borison et al.[19]	6	Quetiapine 307 (58–526)	54	6
		Placebo	55	4
Small et al.[20]	6	Quetiapine 360 (50–566)	96	7.3
		Quetiapine 209 (50–267)	94	7.4
		Placebo	96	3.1
Peuskens & Link[21]	6	Quetiapine 407	101	4
		Chlorpromazine 384	100	9

Continued on next page

Table I. Contd

Reference	Study duration (wk)	Daily drug dosage (mean or range; mg/day)	No. of patients	Percentage of withdrawals because of adverse events
Arvanitis et al.[22]	6	Placebo	51	4
		Quetiapine 75–600	204	0
		Quetiapine 750	54	2
		Haloperidol 12	52	8
Loo et al.[23]	26	Amisulpride 100	69	1.4
		Placebo	72	6.9
Freeman[24]	6	Amisulpride 1000	70	6
		Flupenthixol 25	62	18**
Puech et al.[25]	4	Amisulpride 100	61	0
		Amisulpride 400	64	5
		Amisulpride 800	65	3
		Amisulpride 1200	65	5
		Haloperidol 16	64	16
Daniel et al.[26]	6	Ziprasidone 80 or 160	702	4.1
		Placebo	273	2.1
Goff et al.[27]	4	Ziprasidone 4	19	5.3
		Ziprasidone 10	17	0
		Ziprasidone 40	17	0
		Ziprasidone 160	20	5.0
		Haloperidol 15	17	5.9
Keck Jr et al.[28]	4	Placebo	48	0
		Ziprasidone 40	44	2
		Ziprasidone 120	47	9
Barnas et al.[29]	7	Zotepine 94.4	15	0
		Haloperidol 4.2	15	40
Petit et al.[30]	8	Zotepine 300	63	15.9
		Haloperidol 20	63	11.1

a Overall rate for both groups (rates equivalent between groups).

NR = not reported; * $p < 0.01$ *vs* olanzapine; ** $p < 0.05$ *vs* amisulpride.

longer term data on withdrawal rates are available, the frequency and severity of various groups of adverse effects should be considered as more reliable indicators of antipsychotic tolerability.

3. Anticholinergic Adverse Effects

This section uses the data presented in table II to evaluate anticholinergic effects of the atypical antipsychotics, such as constipation, dry mouth, blurred vision, urinary retention, possible cognitive impairment and confusion.[36] Some authorities would include *in vitro* binding studies in the assessment of anticholinergic effects of drugs. However, these can be misleading because, for example, most ligand binding studies merely indicate that a substance binds to a receptor, and not whether it is an agonist or antagonist. As a more specific example, olanzapine is reported as having few anticholinergic adverse effects, despite a high *in vitro* ability to bind to muscarinic receptors.[37]

The first marketed atypical antipsychotic, clozapine, caused rates of constipation that were equivalent to those with both chlorpromazine (with concomitant benzatropine)[2] and haloperidol.[31] Compared with haloperidol, risperidone also caused similar rates of anticholinergic effects.[13,32] In 1 trial, anticholinergic effects with olanzapine increased with dose, and constipation at higher doses was worse than with haloperidol.[17] However, Tollefson et al.[18] found that olanzapine produced fewer anticholinergic effects, apart for dry mouth, than haloperidol ($p < 0.05$), although it might be assumed that this difference resulted from the significantly greater use of benzatropine to treat EPS in the haloperidol group ($p < 0.001$). In a comparison with risperidone, olanzapine produced significantly less blurred vision.[15] Again, anticholin-

Table II. Data on anticholinergic effects of atypical antipsychotics

Reference (study duration)	Daily drug dosage (mean or range; mg/day) [no. of patients]	Anticholinergic effects (% of patients)			
		constipation	dry mouth	blurred vision	micturition difficulties
Kane et al.[2] (6wk)	Clozapine ≤900 [126]	16	5		
	Chlorpromazine ≤1800 [142]	12	20*		
Breier et al.[31] (10wk)	Clozapine 410.5	16	11		
	Haloperidol 24.8	25	65[a]		
Hong et al.[8] (12wk)	Clozapine 543		9.5		
	Chlorpromazine 1163		36.9		
Claus et al.[12] (12wk)	Risperidone 12.0 [21]	19.0	41.3	42.9	
	Haloperidol 10.3 [21]	14.3	28.6	14.3	
Peuskens et al.[13] (8wk)	Risperidone 1–16	13.7–15.4[a]	10.1–16.5[b]	8.8–17[b]	
	Haloperidol 10	15.6	13.8	17.3	
Marder & Meibach[32] (8wk)	Risperidone 10–16	1.5–6.3			
	Haloperidol 20	1.5			
	Placebo	0			
Blin et al.[9] (4wk)	Risperidone 7.4 [21]	9.5 45.0 4.8	33.3 50.0 42.9		
	Haloperidol 7.6 [20]				
	Levomepromazine 100 [21]				
Sramek et al.[33] (1.5y)	Sertindole ≤24 [16]		62.5		
Tran et al.[15] (28wk)	Olanzapine 17.2			9.6	
	Risperidone 7.2			20.6*	
Conley et al.[16] (8wk)	Olanzapine 5–20		20.0		
	Risperidone 2–6		8.4		
Beasley et al.[17] (6wk)	Olanzapine 5–15	6.2–14.5**	3.1–13.0		
	Haloperidol 15	5.8**	4.3		
	Placebo	0	4.4		
Tollefson et al.[18] (6wk)	Olanzapine 13.2		22.2	10.6	3.6
	Haloperidol 11.8		16.2***	15.1***	6.1***
Borison et al.[19] (6wk)	Quetiapine 307	11	17		
	Placebo	7	5		
Small et al.[20] (6wk)	Quetiapine 360	11	6		
	Quetiapine 209	6	4		
	Placebo	3	1		
Peuskens & Link[21] (6wk)	Quetiapine 407	2	8		
	Chlorpromazine 384	8	6		
Arvanitis et al.[22] (6wk)	Quetiapine 300–600	2–12			
	Haloperidol 12	6			
	Placebo	6			
Speller et al.[34] (1y)	Amisulpride 100–800	10	21	14	7
	Haloperidol 3–20	19	39	19	6
Gunn et al.[35] (4wk)	Ziprasidone 40 [116], 80 [48]	6–12			
	Haloperidol 15 [17]	6			
	Placebo [98]	3			
Keck Jr et al.[28] (4wk)	Ziprasidone 40 [44], 120 [47]	7, 11			
	Placebo [48]	4			
Barnas et al.[29] (7wk)	Zotepine 94.4 [15]		0		
	Haloperidol 4.2 [15]		13.3		
Petit et al.[30] (8wk)	Zotepine 300 [63]	7.9	7.9		
	Haloperidol 20 [63]	3.2	3.2		

a Results for risperidone 1 to 8mg.

b Results for risperidone 4 to 16mg.

***** $p < 0.007$ *vs* comparator; ****** = $p = 0.021$ (comparison between all groups); ******* $p < 0.05$ *vs* olanzapine.

Table III. Data on the effects of atypical antipsychotics on prolactin levels and sexual function

Reference	Study duration	Daily drug dosage (mean or range; mg/day)	No. of patients	Results (% of pts) [p value] and comments
Klieser et al.[6]	4wk	Risperidone 4 Risperidone 8 Clozapine 400	20 19 20	No clinically significant changes in laboratory values
Blin et al.[9]	4wk	Risperidone 7.4 Haloperidol 7.6 Levomepromazine 100	21 20 21	Effects on sexual life: risperidone (4.8), haloperidol (0), levomepromazine (9.5)
Chouinard et al.[10]	8wk	Risperidone 2–16 Haloperidol 20 Placebo	92 21 22	No changes in laboratory values
Claus et al.[12]	12wk	Risperidone 12 Haloperidol 10	21 21	No meaningful conclusions able to be made
Marder & Meibach[32]	8wk	Risperidone 2–16 Haloperidol 20 Placebo	256 66 66	Dysmenorrhoea: 1 of 4 pts taking risperidone 10 mg/day. No clinically significant changes in laboratory values
Peuskens et al.[13]	8wk	Risperidone 1–16 Haloperidol 10	1136 226	Amenorrhoea: risperidone 4–16 mg/day (5.3–13.1), haloperidol (10.5)
Crawford et al.[38]	52wk	Olanzapine 5–15 Haloperidol 15 Placebo	170 (men) 62 (men) 62 (men)	Fewer prolactin ↑ with olanzapine than haloperidol, results significant at weeks 2 and 6 ($p < 0.05$)
Tran et al.[15]	28wk	Olanzapine 17.2 Risperidone 7.2	167 16	↑ prolactin with olanzapine (51.2), risperidone (94.4) [$p < 0.001$]
Conley et al.[16]	8wk	Olanzapine 5–20 Risperidone 2–6	205 202	Nonpuerperal lactation/discharge: risperidone (1.5), olanzapine (0.5%) Gynaecomastia = risperidone (0.5), olanzapine (0.5) No correlation between prolactin levels and adverse events
Beasley et al.[17]	6wk	Olanzapine 6.6–16. Haloperidol 15 Placebo	198 69 68	Prolactin levels ↑ with haloperidol *vs* other groups [$p < 0.001$]
Tollefson et al.[18]	6wk	Olanzapine 13.2 Haloperidol 11.8	1336 660	Smaller ↑ in prolactin levels with olanzapine [$p < 0.001$]
Borison et al.[19]	6wk	Quetiapine 307 Placebo	54 55	Prolactin levels ↓ in both groups
Small et al.[20]	6wk	Quetiapine 360 Quetiapine 209 Placebo	96 94 96	Prolactin levels ↓ in all groups
Peuskens & Link[21]	6wk	Quetiapine 407 Chlorpromazine 384	101 100	Prolactin levels ↓ slightly with chlorpromazine, markedly with quetiapine [$p < 0.0001$ *vs* baseline at wk 42]
Arvanitis et al.[22]	6wk	Quetiapine 75–750 Haloperidol 12 Placebo	258 52 51	Prolactin levels ↑ with haloperidol *vs* placebo [$p = 0.008$]. Final prolactin levels: haloperidol = 28.8 ng/mol; placebo = 14.7 ng/mol
Loo et al.[23]	26wk	Amisulpride 100 Placebo	69 (23 women) 72	Amenorrhoea: amisulpride (17.4); frequency with placebo NR
Freeman[24] (study 3)	6wk	Amisulpride 1000 Flupenthixol 25	34 24	Galactorrhoea: amisulpride (11.8), flupenthixol (12.5) Breast enlargement: amisulpride (5.9), flupenthixol (8.3)
Gunn et al.[35]	Various (pooled data)	Ziprasidone 40–160 Haloperidol 15 Placebo	231 17 98	Prolactin levels ↑ with ziprasidone transient and smaller *vs* haloperidol
Goff et al.[27]	4wk	Ziprasidone 4–160 Haloperidol 15	73 17	Prolactin levels significantly ↑ with haloperidol

NR = not reported; **pts** = patients; ↑ = increased; ↓ = decreased .

ergic medication was used more frequently to treat EPS in the risperidone group ($p = 0.001$).

Unfortunately, statistical parameters were not presented in other trials involving atypical antipsychotics. Nevertheless, in 1 direct comparison, risperidone caused dry mouth in 8.4% of patients, whereas the rate in olanzapine-treated patients was 20.0%.[16] Low dose amisulpride also caused dry mouth in a considerably lower proportion of patients than haloperidol (21 *vs* 39%).[34]

From these data, anticholinergic effects with most atypical antipsychotics appear to be no worse than those with haloperidol. However, tolerability may be slightly improved with olanzapine or amisulpride. Clinical observations suggest that tolerability may be worse with clozapine but that tolerance to anticholinergic effects often develops.

4. Serum Prolactin Levels

Increased prolactin levels may be asymptomatic, but can be linked to breast swelling, galactorrhoea, menstrual cycle irregularities and sexual dysfunction.[36,37] Data relating to prolactin changes with the atypical antipsychotics are presented in table III. In some of the studies, prolactin levels were not reported, so indirect markers such as the frequency of sexual adverse effects have been evaluated. However, these results must be interpreted with caution, since prolactin level elevation may not be the only way in which antipsychotics affect sexual function.[37]

Although clozapine has been widely reported as causing no increase in serum prolactin levels, only 1 of the trials reviewed mentioned that there were no clinically significant changes in laboratory parameters.[6] In contrast, olanzapine was reported as causing significantly less prolactin elevation than haloperidol[17,18,38] or risperidone.[15] In a trial only reported in poster form, olanzapine caused fewer potentially prolactin-related adverse events than risperidone, although no statistical parameters were presented.[16] Prolactin levels with quetiapine were not significantly different from placebo,[19,20] and were markedly reduced compared with chlorpromazine.[21] As women are probably more susceptible to prolactin level elevations, some of these results could be explained by the fact that the percentage of women differed between the groups. However, although 2 of the trials discussed in this section did not comment on this,[15,18] the demographic data presented in the other papers showed no significant differences between treatment groups. The other atypical antipsychotics may have been better tolerated than typical antipsychotics, but the available evidence was either lacking or not supported by statistical analysis.

In patients in whom prolactin elevations are associated with symptoms, olanzapine or quetiapine are likely to be better tolerated than conventional antipsychotics or risperidone. In clinical practice, clozapine and sertindole appear to cause fewer prolactin elevations than conventional antipsychotics. However, this in itself may not be sufficient justification to initiate clozapine. No data could be found relating to prolactin levels with zotepine.

5. Hypotension/Dizziness

Another aspect of the tolerability of atypical antipsychotics is their propensity to cause hypotension. We have evaluated this using the data presented in table IV.

From the available data, it can be seen that clozapine caused less hypotension than chlorpromazine, but the proportion of patients reporting dizziness was not significantly different.[2] Evidence on the effects of risperidone on hypotension or dizziness is conflicting, with some trials showing much higher incidences than others.[9,10,12,13,32] The discrepancies may be partially explained by variations in titration rates. For example, Blin et al.[9] started risperidone at 4 mg/day, whereas Marder and Meibach[32] titrated dosages from 2 mg/day. Hypotensive effects also appeared to be common with sertindole (based on the incidence of dizziness in patients taking the drug).[33] Compared with haloperidol, the incidences of hypotension with olanzapine[17,18] and zotepine[30] were similar, whereas amisulpride[34] produced lower rates of dizziness than haloperidol (statistical significance not given). Quetiapine may cause less

Table IV. Data on hypotension or dizziness caused by atypical antipsychotics

Reference	Study duration	Daily drug dosage (mean or range; mg/day) [no. of patients]	Patients (pts) [%]	
			hypotension[a]	dizziness
Kane et al.[2]	6wk	Clozapine ≤900 [126] Chlorpromazine ≤1800 [142]	13 38*	14 16
Clozapine Study Group[4]	26wk	Clozapine (450–500mg) [54]	6	41
Breier et al.[31]	10wk	Clozapine 410.5 [19] Haloperidol 24.8 [20]		37 20
Lieberman et al.[5]	52wk	Clozapine 411 (acute) [12] Clozapine 459 (continuation) [57]		50 3.5
Klieser et al.[6]	4wk	Risperidone 4 [20] Risperidone 8 [19] Clozapine 400 [20]		15 17 20
Hong et al.[8]	12wk	Clozapine 543 [21] Chlorpromazine 1163 [19]	4.8 0	
Olesen et al.[39]	Various	Clozapine 350 (228–425) [30]	16.7	
Blin et al.[9]	4wk	Risperidone 7.4 [21] Haloperidol 7.6 [20] Levomepromazine 100 [21]		28.6 25 71.4[b]
Chouinard et al.[10]	8wk	Risperidone 2–16 [92] Haloperidol 20 [21] Placebo [22]	1 pt receiving risperidone 16 mg/day; 1 pt receiving risperidone 6 mg/day; no hypotension with placebo or haloperidol	1 pt receiving risperidone 10 mg/day; no dizziness with placebo or haloperidol
Marder & Meibach[32]	8wk	Risperidone 2–16 [256] Haloperidol 20 [66] Placebo [66]		1.5–10.9** 0 0
Claus et al.[12]	12wk	Risperidone 12 [21] Haloperidol 10.3 [21]		38 23.8
Peuskens et al.[13]	8wk	Risperidone 1–16 [1136] Haloperidol 10 [225]		15–30.4 23.1
Sramek et al.[33]	1.5y	Sertindole ≤24 [16]		50
Tran et al.[15]	28wk	Olanzapine 17.2 [167] Risperidone 7.2 [16]	ns	
Conley et al.[16]	8wk	Olanzapine 5–20 [205] Risperidone 2–6 [202]		12.2 11.9
Beasley et al.[17]	6wk	Olanzapine 5–15 [198] Haloperidol 15 [69] Placebo [68]		7.7–17.4 7.2 2.9
Tollefson et al.[18]	6wk	Olanzapine 13.2 Haloperidol 11.8	ns	
Borison et al.[19]	6wk	Quetiapine 307 (58–526) [54] Placebo [55]	9 0	
Small et al.[20]	6wk	Quetiapine 209 or 360 [190] Placebo [96]		11 1
Peuskens & Link[21]	6wk	Quetiapine 407 [101] Chlorpromazine 384 [100]	5 18	
Arvanitis et al.[22]	6wk	Quetiapine 75–750 [258] Haloperidol 12 [52] Placebo [51]	4–14 2 8	
Speller et al.[34]	1y	Amisulpride 100–800 [29] Haloperidol 3–20 [31]		10 19
Tandon et al.[40]	Various	Ziprasidone 80–160 [702] Placebo [273]	1.3 0.4	8 6
Keck Jr et al.[28]	4wk	Ziprasidone 40 or 120 [91] Placebo [48]		5 or 2 2
Petit et al.[30]	8wk	Zotepine 300 Haloperidol 20	ns	

a Includes orthostatic hypotension.

b Orthostatic symptoms.

ns = no significant differences between treatment groups; ***** $p < 0.001$ *vs* clozapine; ****** $p < 0.05$ for risperidone 6 and 16mg *vs* placebo.

hypotension than chlorpromazine,[21] while hypotension with ziprasidone[40] was not significantly worse than with placebo.

Orthostatic hypotension may be linked to α-adrenergic blockade.[36,37] Hypotensive effects are particularly undesirable in the elderly, because they may lead to falls and fractures. They may be managed by adjusting the dose more carefully. Clinical observations indicate that tolerance often develops, so changes in medication are not always necessary.

6. Bodyweight Gain

Bodyweight gain is an important adverse event because it is thought to increase the risk of hypertension, is associated with cardiovascular morbidity and is socially unacceptable to patients. Bodyweight gain is one of the most readily measured parameters in medicine; precise measurements can be made by any personnel.

The data regarding bodyweight changes with the atypical antipsychotics are presented in table V. It would appear that all atypical antipsychotics cause bodyweight gain to some extent and these gains can be substantial. Clozapine appears to be associated with the highest proportion of patients with bodyweight gain, and this continues into the second and third years of treatment.[41] Although it is thought that most bodyweight is gained during the first year of treatment, this cannot be confirmed for atypical antipsychotics other than clozapine until clinical trials or naturalistic observations lasting several years have been completed. Studies on clozapine and olanzapine suggest that patients with lower initial body bodyweight are at greatest risk of gaining bodyweight, but that those who are overweight at baseline still end up being the most overweight.[18,41] However, when body mass index (BMI) was measured rather than bodyweight, patients with medium BMI gained more weight with olanzapine than those with low or high BMI.[16] Although statistical parameters were not calculated, bodyweight gain was observed with the atypical antipsychotics quetiapine[19-21,44] and amisulpride.[23] Zotepine, on the other hand, did cause significantly more bodyweight gain than haloperidol over 8 weeks.[30] There is some evidence that bodyweight gain with ziprasidone may be equivalent to that with placebo,[40,44] but more data are needed.

Dietary adjustments and exercise are indicated, but may not be effective, for the prevention of bodyweight gain with antipsychotics.[45] However, patients can be encouraged by the fact that in some of the trials, some patients did eventually lose bodyweight.[5,8,23]

7. Effects on Sleep and Alertness

It is well known that sedation is a common adverse effect of CNS active drugs, including conventional antipsychotics.[36] Low potency antipsychotics such as chlorpromazine tend to be more sedating than high potency drugs such as haloperidol. Initially, sedation may be useful in a patient who has lost sleep because of psychotic experiences. However, long term sedation can be distressing if it prevents patients from carrying out their daily tasks. It is of particular importance if a patient is operating dangerous machinery or driving.

Data on the sedative/alerting effects of the atypical antipsychotics are shown in table VI. These data would suggest, somewhat surprisingly, that clozapine is no more sedating than haloperidol[31] or chlorpromazine,[2,8] but significantly more sedating than risperidone.[47] However, it should be noted that the doses of haloperidol and chlorpromazine used were rather high.[31] By contrast, risperidone caused more dreams and nightmares than olanzapine,[15,16] although there was no difference between the rates of insomnia with risperidone and haloperidol.[32] The comparisons between olanzapine and haloperidol are conflicting, suggesting that olanzapine can cause both increased drowsiness and sleep disturbance compared with haloperidol.[17,18] The effects on sleep of quetiapine were not significantly different from chlorpromazine,[21] while low dose amisulpride was comparable to placebo.[23] Although no statistical parameters were presented for ziprasidone or

Table V. Data relating to bodyweight changes with atypical antipsychotics

Reference	Study duration	Daily drug dosage (mean or range; mg/day)	Mean change in bodyweight (kg) from baseline or comments	Proportion of pts with bodyweight increase (↑) or decrease (↓) from baseline[a]
Umbricht et al.[41]	≤ 90mo	Clozapine 500–600	At week 12 +6.4 ± 5.6	Over 12wk: 12% ↑[b] At 1y: 60% ↑[c] At 2y: 6% ↑[d] At 3y: 8% ↑[d]
Lieberman et al.[5]	52wk	Clozapine 411 (acute) Clozapine 458 (continuation)		33.3% ↑; 16.6% ↓ 10.5% ↑; 1.7% ↓
Hong et al.[8]	12wk	Clozapine 543 Chlorpromazine 1163		21.1% ↑[c]; 5.9% ↓[c] 42.1% ↑[c]; 10.5% ↓[c]
Frankenburg et al.[42]	37–39mo	Clozapine 328–348	BMI increased[e*]	
Peuskens et al.[13]	8wk	Risperidone 1–16 Haloperidol 10	+0.3–1.6	
Marder & Meibach[32]	8wk	Risperidone 2–16 Haloperidol 20 Placebo	Gain significantly dose related ($p < 0.05$)	
Lee et al.[43]	1.5y	Sertindole 20–24	+4–14[f]	
Zimbroff et al.[14]	8wk	Sertindole 12–24 Haloperidol 8	+2.2–3.3	
Tran et al.[15]	28wk	Olanzapine 17.2 Risperidone 7.2	+4.1 +2.3[**]	
Conley et al.[16]	8wk	Olanzapine 5–20 Risperidone 2–6	+3.4[g] +1.6[g]	29% ↑ 14% ↑[c**]
Beasley et al.[17]	6wk	Olanzapine 5 Olanzapine 10 Olanzapine 15 Haloperidol 15 Placebo		12.3% ↑[†] 7.8% ↑[††] 0 2.9% ↑ 0
Tollefson et al.[18]	6wk	Olanzapine 13.2 Haloperidol 11.8	+1.88 +0.02	
Borison et al.[19]	6wk	Quetiapine 307 Placebo	+5.5 +0.5	25% ↑ 4% ↑[c]
Small et al.[20]	6wk	Quetiapine 360 Quetiapine 209 Placebo		25% ↑ 16% ↑ 5% ↑[c]
Peuskens & Link[21]	6wk	Quetiapine 407 Chlorpromazine 384	+1.8 +1.3	27% ↑[c] 18% ↑[c]
Arvanitis et al.[22]	6wk	Quetiapine 75–150 Haloperidol 12 Placebo	+0.9 to +2.9 +0.3 –0.8	
Loo et al.[23]	26wk	Amisulpride 100 Placebo	+8.7% (+1.4) –6.9% (–0.8)	
Tandon et al.[40]	Various	Ziprasidone 80–160 Placebo		9.8% ↑ 4% ↑[c]
Allison et al.[44]	Various	Various[h]	Placebo > molindone> ziprasidone > fluphenazine > haloperidol > risperidone > chlorpromazine > sertindole > thioridazine > olanzapine > clozapine (+4.5) at 10wk	
Keck Jr et al.[28]	4wk	Ziprasidone 40 Ziprasidone 120 Placebo	ns ns	

Table V. Contd

Reference	Study duration	Daily drug dosage (mean or range; mg/day)	Mean change in bodyweight (kg) from baseline or comments	Proportion of pts with bodyweight increase (↑) or decrease (↓) from baseline[a]
Petit et al.[30]	8wk	Zotepine 300 Haloperidol 20	+2.32 –0.81	

a Unless indicated, bodyweight gain was not defined.

b Pts gaining ≥20% of ideal bodyweight.

c Incidence of >5% bodyweight gain or clinically significant gain.

d Incidence of ≥40% bodyweight gain.

e $p \leq 0.001$ *vs* baseline.

f Reported by 4 of 10 patients.

g Results estimated from graph.

h Dose range was not given but the author stated that the doses were standardised.

BMI = body mass index; **ns** = no significant changes in bodyweight; **pts** = patients; **>** indicates a significantly better profile with first than second agent; ↓ indicates that symptoms reduced; ↑ indicates that symptoms increased; ***** $p \leq 0.001$ *vs* baseline; ****** $p < 0.05$ *vs* comparator; † $p < 0.05$ *vs* placebo and haloperidol; †† $p = 0.050$ *vs* placebo.

zotepine, the data suggest that they produced similar rates of insomnia to haloperidol.

Overall, the atypical antipsychotics vary in their ability to cause sedation or sleep disturbance compared with conventional antipsychotics. Of the atypical antipsychotics, clozapine was the most sedating and risperidone, ziprasidone and zotepine were associated with the most sleep disturbance. However, one problem in interpreting the data is that most authors present rates of sedation or insomnia, with no indication of severity. Therefore, it is difficult to provide a conclusive appraisal of the data.

8. Extrapyramidal Symptoms

It is well known that older antipsychotics cause the range of motor effects that comprise EPS.[36] These effects are thought to be linked to dopamine D_2 and serotonin 5-HT_2 receptor occupancies.[51] With the advent of the atypical antipsychotics, it became clear that EPS are not inextricably linked to antipsychotic efficacy.

The evidence regarding EPS with atypical antipsychotics is presented in table VII. It is difficult to compare the trials for reasons outlined in the section on withdrawals and because different rating scales were used. Some trials measured the maximum change in EPS whereas others measured the change in EPS at end-point and still more trials presented the proportion of patients reporting EPS rather than using a rating scale. Nevertheless, the effects of olanzapine,[17] quetiapine,[19,20] sertindole[14] and risperidone[32] (at <10 mg/day) on EPS were equivalent to placebo. Active comparisons showed that clozapine[2,8] produced significantly fewer EPS than chlorpromazine, whereas quetiapine showed no significant difference.[21] In other studies, clozapine produced fewer EPS than risperidone,[52] which in turn produced fewer EPS than haloperidol.[10,13,53,59] Other atypical antipsychotics which produced less severe EPS than haloperidol include sertindole,[14] olanzapine[17,18] and amisulpride.[24,25] However, it must be noted that it is not difficult for an antipsychotic to cause fewer EPS than a high potency drug such as haloperidol. Some studies suggested that EPS with risperidone[13,53] and with amisulpride[24,25] may increase with dose. Although statistical parameters were not presented, the incidence of EPS with ziprasidone appeared to be 6%,[35,51] whereas the incidence with zotepine ranged from 8[30] to 13%.[29]

As a group, atypical antipsychotics cause fewer EPS than typical antipsychotics, although risperidone, amisulpride and zotepine produce moderate EPS at higher doses. There should be reduced requirements for concomitant anticholinergic medication.

Table VI. Data on the effects of atypical antipsychptics on sedation and sleep

Reference [study duration]	Daily drug dosage (mean or range; mg/day) [patient no.]	Incidence (%)	
		Sedative effects[a]	Sleep disturbance/insomnia
Kane et al.[2] [6wk]	Clozapine ≤900 [126] Chlorpromazine ≤1800 [142]	21 13	
Naber & Hippius[3] [NR]	Clozapine 304 [503]	17	
Clozapine Study Group[4] [26wk]	Clozapine 450–500 [54]	46	
Breier et al.[31] [10wk]	Clozapine 410.5 [19] Haloperidol 24.8 [19]	37 37	
Gerlach & Peacock[46] [48wk]	Clozapine 400 [100] Control [100]	4 4	
Lieberman et al.[5] [52wk]	Clozapine 411 (acute) [12] Clozapine 458 (continuation) [57]	66.6 24.5	0.0 1.7
Daniel et al.[47] [6wk]	Clozapine 375 [20][b] Risperidone 6.1 [20][b]	Patients more likely to experience sleepiness while receiving clozapine ($p < 0.0001$)	Patients more likely to experience insomnia while receiving risperidone ($p < 0.002$)
Klieser et al.[6] [4wk]	Clozapine 400 [20] Risperidone 4, 8 [39]	15 5-20	
Hong et al.[8] [12wk]	Clozapine 543 [21] Chlorpromazine 1163 [19]	23.8 21.1	
Hinze-Selch et al.[48] [2wk]	Clozapine titration doses	No. of awakenings: baseline = 18.3 ±11.2; 2 wk = 2 ± 5.5 ($p < 0.01$)	NR
Grohmann et al.[49] [45 day]	Clozapine 188 [959]	31	
Claus et al.[12] [12wk]	Risperidone 12.0 [21] Haloperidol 10.3 [21]	51.7-71.4 61.9-66.7	
Chouinard et al.[10] [8wk]	Risperidone 2–16 [92] Haloperidol 20 [21] Placebo [22]		54.5-58.3 66.7 36.4
Peuskens et al.[13] [8wk]	Risperidone 1–16 [1136] Haloperidol 10 [226]	23.5-47.8 39.6	
Marder & Meibach[32] [8wk]	Risperidone 2–16 [256] Haloperidol 20 [66] Placebo [66]	3.1-9.4[*] 4.5 0	9.4-15.9 12.1 9.1
Blin et al.[9] [4wk]	Risperidone 7.4 [21] Haloperidol 7.6 [20] Levomepromazine 100 [21]	42.9 55.0 33.3	19.0 30.0 4.8
Lee et al.[11] [1.5y]	Sertindole 20–24 [10]	30	50
Zimbroff et al.[14] [8wk]	Sertindole 12–24 [216] Haloperidol 4–16 [208] Placebo [73]	9-21 7-21 19	
Tran et al.[15] [28wk]	Olanzapine 17.2 [167] Risperidone 7.2 [165]		11.4 19.4[c**]
Conley et al.[16] [8wk]	Risperidone 2–6 [202] Olanzapine 5–20 [205]	30.7 29.8	20.3 14.6
Beasley et al.[17] [6wk]	Olanzapine 5–15 [198] Haloperidol 15 [69] Placebo [68]	20-39.1 34.8 16.2 ($p = 0.013$)	
Tollefson et al.[18] [6wk]	Olanzapine 13.2 [1306] Haloperidol 11.8 [636]	26.0 31.3[**]	13-22.9 17.3-30.328.8[d**]
Borison et al.[19] [6wk]	Quetiapine 307 [54] Placebo [55]	39 7	15 15
Small et al.[20] [6wk]	Quetiapine 360 [96] Quetiapine 209 [94] Placebo [96]	25 19 15	10 13
Peuskens & Link[21] [6wk]	Quetiapine 407 [101] Chlorpromazine 384 [100]	14 16	10 16

Table VI. Contd

Reference [study duration]	Daily drug dosage (mean or range; mg/day) [patient no.]	Incidence (%)	
		Sedative effects[a]	Sleep disturbance/insomnia
Arvanitis et al.[22] [6wk]	Quetiapine 75–750 [258]	6-11	4-6
	Haloperidol 12 [52]	6	12
	Placebo [51]	8	10
Loo et al.[23] [6mo]	Amisulpride 100 [69]		11.6
	Placebo [72]		11.1
Speller et al.[34] [1y]	Amisulpride 100–800 [29]	41	3
	Haloperidol 3–20 [31]	23	16
Freeman[24] (study 2) [6wk]	Amisulpride 800 [94]	1	6
	Haloperidol 20 [94]	5	10
Gunn et al.[35] [4wk]	Ziprasidone 40–160 [231]	4-15	0-10
	Haloperidol 15 [17]	12	0
	Placebo [98]	0	10
Davis & Markham[50] [4–6wk]	Ziprasidone 80–160 [702]	14	
	Placebo [273]	7	
Keck Jr et al.[28] [4wk]	Ziprasidone 40, 120 [89]	7-9	0-2
	Placebo [48]	8	4
Petit et al.[30] [6wk]	Zotepine 300 [63]		14.3
	Haloperidol 20 [63]		11.1

a Includes drowsiness, sedation, sleepiness and fatigue.

b Crossover comparison study.

c Patients with dreams/nightmares.

d Patients with either of the following: difficulty falling asleep, interrupted sleep, shortened sleep, increased dreams and nightmares.

NR = not reported; * $p < 0.05$ *vs* placebo for risperidone 16mg; ** $p < 0.05$ *vs* comparator.

9. Tardive Dyskinesia

Around 20% of patients receiving extended treatment with conventional antipsychotics will be found to have tardive dyskinesia at any time and the probability per year of developing tardive dyskinesia is about 5%.[37] Older patients are at increased risk for tardive dyskinesia even with short term antipsychotic treatment.[60] The syndrome is characterised by abnormal involuntary orofacial movements such as tongue protrusion or increased rates of eye blinking, and persists despite antipsychotic withdrawal.

The data on tardive dyskinesia with atypical antipsychotics are presented in table VII. One of the remarkable properties of clozapine is its ability to treat pre-existing tardive dyskinesia.[56,57,61,62] Risperidone allowed the emergence of tardive dyskinesia in only 0.3% of 1156 patients treated for 1 year,[54] while tardive dyskinesia symptoms improved with sertindole 20mg compared with placebo.[14] In the study by Tollefson et al.,[63] the prevalence of tardive dyskinesia at the final 2 AIMS assessments was 1.0% for olanzapine compared with 4.6% for haloperidol. This trial was long, and discounted withdrawal tardive dyskinesia. However, most other trials were conducted over only 4 to 8 weeks. This is not long enough to demonstrate the effects of a drug on tardive dyskinesia. Moreover, any exacerbations of tardive dyskinesia that occur during a short term clinical trial may have been caused by the withdrawal of the previous antipsychotic.

There is a small quantity of evidence to suggest that olanzapine, and possibly risperidone, may be useful treatment options in patients at risk for tardive dyskinesia, and indeed one author has used olanzapine to successfully treat tardive dyskinesia.[64] The emergence of tardive dyskinesia may even justify the introduction of clozapine at an earlier than normal stage of treatment.

10. Other Important Adverse Reactions

As clinical experience with the atypical antipsychotics has grown, there have been increasing

Table VII. Data for atypical antipsychotics on extrapyramidal symptoms (EPS) and effects on tardive dyskinesia

Reference [study duration]	Daily drug dosage (mean or range; mg/day)	Scale used to assess EPS/tardive dyskinesia	Results (> indicates that the first drug has a better profile than the second drug: differences are significant where indicated)	
			EPS	Tardive dyskinesia
Kane et al.[2] [6wk]	Clozapine ≤900 Chlorpromazine ≤1800	SAS, AIMS	Clozapine > chlorpromazine	Clozapine ≡ chlorpromazine
Clozapine Study Group[4] [26wk]	Clozapine 450–500	SAS	Clozapine > baseline[a] (baseline > clozapine for salivation)	
Breier et al.[31] [10wk]	Clozapine 410.5 Haloperidol 24.8	SAS, Maryland Psychiatric Research Center Involuntary Movement Scale	Clozapine > haloperidol	ns
Lieberman et al.[5] [52wk]	Clozapine 411 (acute) Clozapine 458 (maintenance)	SAS, SDS	Clozapine > baseline[b]	Clozapine > baseline[b]
Klieser et al.[6] [4wk]	Clozapine 400 Risperidone 4, 8	SAS	ns	
Hong et al.[8] [12wk]	Clozapine 543 Chlorpromazine 1163		Clozapine > baseline[c] for tremor*	Clozapine ≡ chlorpromazine for improvement in symptoms; clozapine > chlorpromazine for deterioration in symptoms
Miller et al.[52] [13wk]	Clozapine 425.6 Risperidone 4.7 Typical antipsychotics	BARS, SAS	Clozapine > risperidone > typical antipsychotics ($p < 0.05$ for clozapine *vs* risperidone and clozapine *vs* typical antipsychotics)	
Simpson & Lindenmayer[53] [8wk]	Risperidone 2–16 Haloperidol 20 Placebo	ESRS	Risperidone ≡ placebo > haloperidol**	
Blin et al.[9] [4wk]	Risperidone 7.4 Haloperidol 7.6 Levomepromazine 100	ESRS	Levomepromazine > risperidone > haloperidol ($p < 0.05$ for haloperidol *vs* levomepromazine)	
Chouinard et al.[10] [8wk]	Risperidone 2–16 Haloperidol 20 Placebo	ESRS	Placebo > risperidone 10 and haloperidol for parkinsonism* All risperidone doses > less dyskinesia than placebo and haloperidol*	
Lindström et al.[54] [2y]	Risperidone 8–9.4	ESRS	Risperidone > baseline*	
Huttunen et al.[11] [6wk]	Risperidone 8 Zuclopenthixol 38	ESRS, CGI	Risperidone > zuclopenthixol*	ns
Claus et al.[12] [12wk]	Risperidone 12 Haloperidol 10.3	ESRS	Dyskinesia decreased with haloperidol *vs* baseline*	
Marder & Meibach[32] [8wk]	Risperidone 2–16 Haloperidol 20 Placebo	ESRS, CGI	Risperidone ≡ placebo > haloperidol*	ns
Peuskens et al.[13] [8wk]	Risperidone 1–16 Haloperidol 10	ESRS	Risperidone > haloperidol for parkinsonism and dystonia*	

Table VII. Contd

Reference [study duration]	Daily drug dosage (mean or range; mg/day)	Scale used to assess EPS/tardive dyskinesia	Results (> indicates that the first drug has a better profile than the second drug: differences are significant where indicated)	
			EPS	Tardive dyskinesia
Zimbroff et al.[14] [8wk]	Sertindole 12–24 Haloperidol–16 Placebo	SAS, BARS, AIMS	Sertindole & placebo > haloperidol	Sertindole 20 & placebo > haloperidol
Tran et al.[15] [28wk]	Olanzapine 17.2 Risperidone 7.2	SAS, BARS, AIMS	Olanzapine > risperidone for parkinsonism or akathisia*	Olanzapine > risperidone
Conley et al.[16] [8wk]	Olanzapine 5–20 Risperidone 2–6	ESRS	Olanzapine & risperidone > baseline[d]	
Beasley et al.[17] [6wk]	Olanzapine 6.6–16.3 Haloperidol 15 Placebo	SAS, BARS, AIMS	Olanzapine & placebo > haloperidol*	Medium dose (11.6 ± 1.5 mg/day) olanzapine > baseline[e*]
Tollefson et al.[18] [6wk]	Olanzapine 13.2 Haloperidol 11.8	SAS, BARS, AIMS	Olanzapine > haloperidol*	Olanzapine > haloperidol
Small et al.[20] [6wk]	Quetiapine 360 Quetiapine209 Placebo	SAS, BARS, AIMS	ns	ns
Peuskens & Link[21] [6wk]	Quetiapine407 Chlorpromazine 384	SAS	ns	ns
Arvanitis et al.[22] [6wk]	Quetiapine 75–750 Haloperidol 12 Placebo	SAS	Quetiapine and placebo > haloperidol	ns
Speller et al.[34] [1y]	Amisulpride 100–800 Haloperidol 3–20	BARS	ns	ns
Freeman[24] (study 1) [4wk]	Amisulpride 100–1200 Haloperidol 16	SAS, AIMS	Amisulpride 100 > amisulpride 1200	ns
Freeman[24] (study 2) [6wk]	Amisulpride 800 Haloperidol 20	SAS	Amisulpride > haloperidol ($p < 0.05$ between for amisulpiride *vs* haloperidol)	ns
Freeman[24] (study 3) [6wk]	Amisulpride 1000 Flupenthixol 25	SAS, BARS	Amisulpride > flupenthixol	Amisulpride > flupenthixol
Puech et al.[25] [4wk]	Amisulpride 100–1200 Haloperidol 16	SAS	Amisulpride 100 > amisulpride 1200 & haloperidol	
Boyer et al.[55] [6wk]	Amisulpride 100, 300 Placebo	ESRS	ns	
Gunn et al.[35] [4wk]	Ziprasidone 40–160 Haloperidol 15 Placebo		ns	
Goff et al.[27] [4wk]	Ziprasidone 4–160 Haloperidol 15	SAS, BARS, AIMS	ns	ns
Keck et al.[28] [4wk]	Ziprasidone 40, 120 Placebo	SAS, BARS, AIMS	ns	ns
Barnas et al.[29] [7wk]	Zotepine 94.4 Haloperidol 4.2		Zotepine > haloperidol	
Tamminga et al.[56] [1y]	Clozapine 293.8 Haloperidol 28.5	Maryland Psychiatric Research Center Involuntary Movement Scale		

Continued on next page

Table VII. Contd

Reference [study duration]	Daily drug dosage (mean or range; mg/day)	Scale used to assess EPS/tardive dyskinesia	Results (> indicates that the first drug has a better profile than the second drug: differences are significant where indicated)	
			EPS	Tardive dyskinesia
Rosenheck et al.[7] [1y]	Clozapine 552 Haloperidol 28	AIMS		Clozapine > haloperidol
Spivak et al.[57] [18wk]	Clozapine 46.2–213.1	AIMS		Clozapine > baseline[f] ($p < 0.0001$)
Brecher et al.[58] [1y]	Risperidone 3.5–10.0			Incidence 0.3%
Petit et al.[30] [8wk]	Zotepine 300 Haloperidol 20	AIMS	Haloperidol > zotepine	ns

a Prior to baseline all patients completed a 4week washout.

b Prior to baseline all patients completed a 2–4week washout.

c All patients had received haloperidol 60 mg/day for a trial period of up to 6 weeks at baseline.

d Prior to baseline all patients completed a 1 week washout period.

e Patients were required to have discontinued oral antipsychotics a minimum of 2 days before baseline and to have discontinued depot antipsychotics a minimum of 6 weeks before baseline.

f All patients had a 2 week washout prior to baseline.

AIMS = abnormal voluntary movement scale; **BARS** = Barnes Akathisia Scale; **CGI** = Clinical Global Impressions Scale; **ESRS** = Extrapyramidal Symptoms Rating Scale; **ns** = not significant; **SAS** = Simpson Angus Scale; **SDS** = Self-Rating Depression Scale; ***** $p \leq 0.05$ *vs* comparator; ****** $p < 0.001$ for risperidone *vs* haloperidol and haloperidol *vs* placebo.

numbers of case reports of other important adverse reactions. For example, clozapine may have caused enuresis,[65,66] hypersalivation,[67] EEG alterations,[68] cellulitis, eosinophilia, pleural effusion,[69] hepatotoxicity,[70] diabetes mellitus,[71] necrotising colitis,[72] and cardiomyopathy.[73] Case reports of adverse reactions with other atypical antipsychotics include a fatal cardiac event and enuresis with risperidone,[74,75] and priapism, acute dystonia and severe akathisia with olanzapine.[76-78] Although clozapine appears to be the most toxic drug, the number of adverse reaction reports may simply reflect greater clinical experience with the older drug.

Care must be exercised when comparing these data because some important reactions are largely only noticed during postmarketing surveillance of case reports. However, events that have been documented during clinical trials of atypical antipsychotics include agranulocytosis and hypersalivation with clozapine,[2-8,79] QTc prolongation with sertindole,[14] raised hepatic enzymes levels and priapism with olanzapine,[17,18,76] rash and subclinical hypothyroidism with quetiapine[19-21] and raised hepatic enzymes and hypo-uricaemia with zotepine.[29,30] The blood monitoring requirements for clozapine are well known. Sertindole was withdrawn from the market towards the end of 1998 because of concerns over its cardiac effects.

Although neuroleptic malignant syndrome is perhaps assumed to be a less frequent occurrence with the atypical than with typical antipsychotics, the syndrome has been reported, particularly with clozapine[80-82] and risperidone.[83,84] Because of the dramatic prognosis of this syndrome, clinicians should be vigilant for signs such as hyperthermia, fluctuating consciousness and muscular rigidity.

11. Compliance

As with many long term conditions, compliance rates with drug therapy among patients with schizophrenia are probably around 50%.[85] One of the factors affecting compliance is 'medication affinity', which is defined as feeling subjectively better on treatment rather than feeling pressured to comply.[86] Noncompliance may therefore be an indicator that the adverse effects of a medicine are subjectively worse than the improvements perceived by the patient.

Although it is good practice for compliance to be measured during clinical trials, very few authors present the results of measures such as tablet counts so it is inappropriate to comment on them. Some show withdrawal rates due to noncompliance, which can be used as an indirect marker. However, some only record withdrawal rates due to lack of cooperation or withdrawn consent, which may or may not include noncompliance with medication.

Compliance rates in clinical trials are always higher than in clinical practice because of the regular contact with health professionals and checks on compliance that patients receive as part of the trial protocol. Nevertheless, compliance rates seem to be equivalent between the atypical antipsychotics.[3,5,7,14,15,18,27] This is despite factors that might be expected to decrease compliance rates such as blood monitoring with clozapine, ECG monitoring with sertindole and dose titration with clozapine, risperidone, sertindole, quetiapine and amisulpride. Interestingly, in 1 study, patients' and relatives' views of clozapine were actually more positive than those of nurses.[86]

12. Conclusion

The drawing of any firm conclusions about the relative tolerability of atypical antipsychotics is impeded by 2 factors. First, the data available are generally short term, poorly controlled and poorly evaluated. Secondly, individual differences between atypical antipsychotics (differences which have also only been superficially evaluated) mean that broad statements about the relative tolerability of atypical and typical drugs are not appropriate.

It is clear that some atypical antipsychotics cause EPS relatively less often than typical drugs and sometimes no more frequently than with placebo. Clozapine and olanzapine and perhaps others may cause tardive dyskinesia less often than typical drugs, and hyperprolactinaemia is relatively less severe with all atypical antipsychotics except risperidone and amisulpride. Nevertheless, anticholinergic, sedative and hypotensive effects do occur with atypical antipsychotics to a varied extent according to the individual drug and bodyweight gain seems common with all atypical antipsychotics. Moreover, idiosyncratic adverse effects have been observed and, as with all new drugs, new adverse effects can be expected to transpire. With these observations in mind, it is not surprising that no clear benefit in overall tolerability (judged by withdrawals from therapy) can be discerned and nor can clear advantages in compliance yet be seen.

Thus, judged only by withdrawal rates from short term clinical trials, atypical antipsychotics do not show clear superiority over typical antipsychotics. Nevertheless, the observed reduction in serious adverse effects such as hyperprolactinaemia, tardive dyskinesia and EPS do form a strong case for atypical antipsychotics to be used as first line agents. Individual differences between drugs also allow clinicians to choose the most appropriate drug for each patient. Moreover, to prescribe typical drugs is perhaps, based on comparative data presented here, knowingly to do harm when a suitable alternative is available. Given these observations, atypical antipsychotics can be recommended as first line agents based on their tolerability alone.

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