

DRUG BULLETIN

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CATIE and Typical Antipsychotics

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Introduction

Atypical antipsychotics have largely replaced typical antipsychotics in clinical practice due to their perceived superiority in efficacy and lower risk of neurological adverse effects, which is believed to result in improved compliance. In fact, many treatment algorithms recommend the use of atypical antipsychotics as the only first-line medication treatment option^{1,2,3}. However, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) has cast doubts over the superiority of atypical antipsychotics over the older, less expensive typical antipsychotics⁴. More recently, an independent British study of similar design has also had similar findings to that of CATIE⁵. This bulletin will review the results of CATIE and revisit the use of oral typical antipsychotics in clinical practice.

CATIE Background

CATIE was a landmark study funded by the National Institute of Mental Health in the United States of America and was published in the September 22, 2005, *New England Journal of Medicine*. One of the aims of CATIE phase 1 was to determine the long-term effectiveness and cost-effectiveness of the newer atypical antipsychotics, relative to typical antipsychotics across the spectrum of schizophrenic illness⁴. The other aim was to compare the atypical antipsychotics against each other⁴, however due to limitations of this bulletin, this will not be addressed. CATIE aimed to test the effectiveness of different antipsychotics under conditions that more accurately reflect actual clinical practice⁴. Phase 1 of CATIE randomised and double-blinded 1460 patients to receive oral olanzapine, risperidone, quetiapine, ziprasidone (an atypical antipsychotic not marketed in Australia) or perphenazine (a typical antipsychotic not marketed in Australia) over an 18-month period. Aripiprazole and amisulpride were not included in the study, as they were not available on

the United States market at the time of the study and clozapine was investigated in phase II of CATIE.

Significance of CATIE

CATIE was the largest, longest and most comprehensive independent trial ever conducted examining the treatment options for schizophrenia. Before CATIE, the relative effectiveness of typical and atypical antipsychotics had been incompletely addressed, with the exception of clozapine^{6,7}. Most previous studies of atypical antipsychotics were of short duration (4 to 8 weeks), focused on narrow outcomes, had strict inclusion/exclusion criteria and usually only had one comparator drug.

What CATIE Found

The primary endpoint of the CATIE study for determining overall effectiveness was treatment discontinuation for any cause. This measure was selected because it combined efficacy, safety, and tolerability and incorporated doctor and patient assessments⁴. Overall, 74% of patients in the study discontinued their medication before receiving the full 18 months of therapy, suggesting substantial limitations in the long-term clinical effectiveness of currently available antipsychotic drugs; the discontinuation rates in ascending order were: olanzapine (64%), risperidone (74%), perphenazine (75%), ziprasidone (79%) and quetiapine (82%)⁴. Contrary to expectations, perphenazine was as equally efficacious as the atypical antipsychotics except for olanzapine and was just as well tolerated⁴. In addition, there were no significant differences across the groups in the incidence of extrapyramidal side effects (EPSE), although significantly more perphenazine patients discontinued treatment due to extrapyramidal adverse effects (8 percent vs 2 to 4 percent, $P=0.002$)⁴. The advantage of olanzapine over perphenazine was moderate and needs to be weighed

against the burden of greater increases in weight gain and indices of lipid and glucose metabolism that were evident in the olanzapine group.

In the analysis of costs and quality-of-life factors associated with each of the five medications used in Phase 1 of the CATIE trial, researchers found that total monthly health costs, a figure that includes both average medication costs and inpatient and outpatient costs, were up to 30 percent lower for those taking the perphenazine than for those taking the atypical antipsychotics⁸. In addition, the researchers found no statistically significant difference in overall effectiveness between perphenazine and the atypical antipsychotics with regard to symptom relief and side effect burden⁸.

Applicability of Results and Limitations

The finding that perphenazine was as effective and well tolerated as most atypical antipsychotics has led to calls for typical antipsychotics to be used as a first-line treatment option, especially considering that perphenazine was also shown to be more cost-effective⁹. However, there are limitations to the CATIE trial that preclude this conclusion from being reached; these are discussed below. The results of CATIE actually suggest that it is necessary that several drugs are available, from which the appropriate treatment can be selected for the individual¹⁰.

Perphenazine as a Representative of Typical Antipsychotics

Most drug company sponsored trials of atypical antipsychotics have used haloperidol as a comparator drug. Haloperidol is well known for causing amongst the highest rates of EPSE of the typical antipsychotics, making it a difficult drug to tolerate. Utilizing haloperidol may bias results by making a comparator drug appear relatively tolerable, particularly when concomitant anticholinergic medication is disallowed¹⁰. Perphenazine was selected as the drug representative of the typical antipsychotics due to its intermediate risk of causing EPSE compared with other typical antipsychotics⁴. Although all typical antipsychotics are believed to be equally effective at therapeutic doses, they differ markedly in their adverse effect profiles. Hence, it is difficult to extrapolate the perphenazine results in CATIE to other typical antipsychotics. Table 1 compares the adverse effects of perphenazine to the oral typical antipsychotics that are marketed in Australia.

Patient Applicability

CATIE was intended to be representative of 'real-world' patients, however results may not be generalisable to the groups of patients that were excluded. Enrolees were aged between 18-64 years, recruited from a variety of mental health settings,

and had a diagnosis of schizophrenia with an average length of illness of 14.4 years. Patients that were excluded included those who were in a first episode of psychosis, those with treatment-resistant schizophrenia, and those with serious and unstable medical conditions. Patients with other co-morbidities, receiving concomitant medication or who had substance abuse were not excluded from the study.

Although first-episode patients were excluded, comparative studies have found little support for substantial differences in efficacy of atypical antipsychotics relative to typical antipsychotics in this group¹¹. Even so, it is important to consider that these patients may have a different susceptibility to developing EPSE compared to the chronic patients that were studied in CATIE¹².

The results of CATIE may not be applicable to elderly patients, especially considering that these patients may be more susceptible to developing EPSE including tardive dyskinesia as well as being more sensitive to other adverse effects¹³.

The findings of CATIE phase 1 are not applicable to treatment resistant patients; treatment resistant patients were studied in CATIE phase 2, however, typical antipsychotics were not included in this phase.

Long-term Adverse Effects

Tardive dyskinesia (TD), a later-onset EPSE characterised by involuntary choreoathetoid movements that are often irreversible, has been mostly associated with typical antipsychotics. Patients with a history of TD were excluded from being randomised to perphenazine due to ethical reasons⁴. Although this may have affected the results, as patients with TD may be more sensitive to developing EPSE, it is important to note that comparisons between the atypical antipsychotics and perphenazine excluded subjects with TD at baseline⁴. While there were no significant differences in TD incidence between the treatment groups, the trial may not have been long enough to measure TD and the majority of patients in the trial did not remain on study medication long enough for TD to occur¹⁴. The CATIE trial may not accurately portray the real and relative risks of developing TD with these medications. Aside from TD, CATIE may not adequately address differences in other long-term adverse effects that can develop years after treatment such as diabetes, weight gain or cardiovascular disease.

Dosing Issues

Since the publication of CATIE, there has been criticism regarding the doses used^{23,24}. Olanzapine was dosed comparatively higher (average dose 20.1mg), which may partially explain its improved effectiveness over the other antipsychotics²⁴.

Table 1 Typical Antipsychotics- Comparative Information^{10,15,16}

	Equivalent dose approximations (a)	Adult dose range (b)	Anticholinergic effects (c)	Sedation* (d)	Hypotension* (e)	EPSE* (f)	Relative risk of arrhythmia (g)	Metabolic syndrome* (h)	Prolactin Elevation* (i)	Relative seizure risk (j)	Sexual dysfunction* (k)	Comments
Low-potency typical antipsychotics												
Chlorpromazine (Aliphatic phenothiazine)	100mg	Ambulatory patients: 25-100 mg 3 times daily Maximum dose: 600-800mg daily	+++	+++	+++	++	high	+++	+++	high	+	Chlorpromazine is a well established but imperfect antipsychotic due to its multiple receptor affinities and resultant adverse effects ¹⁷ . The adverse effect of sedation can, in certain clinical situations, be a useful adjunct to any antipsychotic properties that chlorpromazine may have ¹⁷ . Other notable adverse effects of chlorpromazine include: photosensitivity, lens opacity, cholestatic jaundice and agranulocytosis ¹⁵ .
Pericyazine (Piperidine phenothiazine)	15mg	15-30mg daily in divided doses with largest dose given in the evening. For hospitalised patients, initial dosage is 25 to 75 mg/day orally, administered in divided doses. Maximum dose: 75mg daily	+++	+++	++	+	low	++	+++	high	++	Although pericyazine is a piperidine phenothiazine, it more closely resembles chlorpromazine in its actions and adverse effect profile. The primary advantages claimed for pericyazine over chlorpromazine are greater efficacy for aggressive-type symptomatology and a lower incidence of adverse effects ¹⁸ . However, neither of these advantages has been convincingly demonstrated, with the possible exception of a lower incidence of photosensitivity ¹⁸ .
Thioridazine (Piperidine phenothiazine)	100mg	Usual starting dose is 100mg 3 times daily. Usual daily dose range for ambulatory patients is 50-300mg daily and 100 to 600mg daily for hospitalised patients. Maximum dose: 800mg daily	+++	+++	++	+	high	+++	+++	high	+++	The adverse effect profile of thioridazine is similar to that of typical drugs overall, but with a lower overall level of extrapyramidal adverse events. Thioridazine may cause serious cardiac arrhythmias; ECG monitoring is necessary before commencing therapy and periodically during therapy. Because of this, thioridazine is a second-line drug for patients that have failed on two or more other antipsychotics ¹⁵ . PBS authority is required for thioridazine to be prescribed.
Intermediate-potency typical antipsychotics												
Zuclopenthixol (Thioxanthene)	12mg	Ambulatory patients: 20-40mg daily Hospitalised patients: 10-50mg daily Maximum dose: 75mg daily	+++	+++	+	+++	low	++	+++	low	+	Zuclopenthixol has an intermediate adverse effect profile compared to other typical antipsychotics. There is some suggestion that oral zuclopenthixol may have some clinical advantage, at least in the short term, over other older drugs in terms of global state ¹⁹ . Zuclopenthixol is not PBS listed.
Trifluoperazine (Piperidine phenothiazine)	5mg	Ambulatory patients: 1-2mg twice daily, maximum 6mg daily. Hospitalised patients: 2-5mg twice daily, can be increased to 15mg daily in divided doses after a week. Most patients will show optimum response on 15 to 20 mg daily, although a few will require more	+	+	+	+++	low	++	+++	low	+	The adverse effect profile of trifluoperazine seems similar to that of typical drugs overall, but in common with haloperidol, it may have a higher level of extrapyramidal adverse events ²⁰ . It has been claimed that trifluoperazine is effective at low doses for patients with schizophrenia but this does not appear to be based on good quality trial based evidence ²⁰ . Although not systematically studied, trifluoperazine may cause less weight gain than other antipsychotics ²⁰ .
Perphenazine (Piperidine phenothiazine)	10mg	Ambulatory patients: 4-8 mg 3 times a day Hospitalised patients: 8-16 mg 2-4 times a day; Maximum dose: 64 mg/day in divided doses	+	++	+	+++	low	++	+++	low	+	Perphenazine is an intermediate potency antipsychotic that was selected to represent the typical antipsychotics in the CATIE trial. Perphenazine is not marketed in Australia. There is less risk of sedation and orthostatic hypotension but greater risk of EPSE than with low potency antipsychotics. The average dose used in the CATIE trial was 20.8mg, which is considered a moderate dose. EPSE are more likely to occur at doses greater than 24mg daily ¹⁸ .
High-potency typical antipsychotics												
Haloperidol (Butyrophenone)	2mg	Ambulatory patients: 1-5mg daily Hospitalised patients: 5-15mg daily Maximum dose: 30mg daily	+	+	+	+++	high	++	+++	low	+	Haloperidol is more potent than many other typical antipsychotics and is more likely to cause EPSE. However, it lacks significant anticholinergic and antihistaminic properties. There is some evidence from short-term studies that lower doses of haloperidol are as effective as higher doses ²¹ . Doses above the 3-7.5 mg/day range are associated with increased risk of extrapyramidal adverse effects and probably should be avoided, especially given there is no clear evidence for added efficacy over doses of >0.25-1.5 mg/day ²¹ .
Pimozide (Diphenyl-butylpiperidine)	2mg	The initial recommended dose in chronic patients is 2 to 4 mg once daily. The daily dose may be increased in increments of 2 to 4 mg at intervals of not less than one week. The usual daily maintenance dose is from 2 to 12 mg (average 6 mg) Maximum dose: 20 mg	++	++	+	++	high	0	+++	low	0	Pimozide may be more likely than other typical drugs to cause parkinsonian tremor but appears less sedating than other drugs. Pimozide has a long half-life (55-150 hours) which means it can be given as infrequently as three times weekly in the maintenance phase; this may be useful for people whose compliance is poor but who refuse depot medication ²² . It has been claimed that pimozide is useful for delusional disorder; however, this is not based on trial derived evidence ²² . Relative high risk of dose-dependent QTc prolongation may limit its use; careful ECG monitoring is required ¹⁵ . Sudden death in patients taking daily doses of pimozide above 12 mg has been reported ¹⁵ .

*Frequency of adverse effects at therapeutic doses: +++ (>30% frequency), ++ (>10% frequency), + (>2% frequency), 0 (<2% frequency); this table outlines the frequency and not necessarily the severity of adverse effects.

(a) Comparative doses are approximations only and are based on D₂ affinities and pharmacokinetics. (b) Adult dose range only, refer to product information for recommended doses for elderly and paediatric patients. The lowest effective dose should be used; dose should be individualised to balance efficacy and tolerability of adverse effects. (c) Anticholinergic effects can mitigate EPSE, however other anticholinergic effects include dry mucous membranes, blurred vision, constipation and urinary retention. (d) Sedation occurs as a result of H₁ blockade. Sedation is dose-related and tolerance to this adverse effect can develop over time. (e) Orthostatic hypotension occurs as a result of alpha-1-adrenergic antagonism. Orthostatic hypotension may be more profound at the start of therapy, or with rapid dose escalation. (f) EPSEs are believed to occur when D₂ occupancy exceeds 78-80%. Use the lowest effective dose to prevent EPSE. Routine prophylactic treatment with anticholinergic drugs to prevent EPSE is not recommended, as not all patients will be affected. (g) See www.qdrugs.org for a list of drugs that have been reported to prolong the QTc interval and cause torsade de pointes. QTc prolongation occurs in a dose dependent manner. (h) Metabolic syndrome involves the triad of weight gain, insulin resistance and hyperlipidaemia. Of the typical antipsychotics, this syndrome is associated most with the phenothiazines. (i) Prolactin elevation is dose-dependent and it is thought to occur when D₂ occupancy exceeds 72%. Effects of elevated prolactin include: galactorrhoea, amenorrhoea, breast enlargement, sexual dysfunction and reduction in bone mineral density. (j) The low-potency antipsychotics are thought to cause fewer EEG changes than the high-potency antipsychotics. Chlorpromazine is thought to be the most epileptogenic of the typical antipsychotics. EEG changes occur in a dose-dependent manner. (k) Antipsychotic-induced hyperprolactinaemia is the most significant cause of sexual dysfunction. Anticholinergic effects can also cause disorders of arousal, drugs that block peripheral alpha₁ receptors can cause problems with ejaculation and erection in men and drugs that block both receptors can cause priapism. There are case reports of priapism with all phenothiazines, with most reports for thioridazine; there are other rare case reports of priapism for other antipsychotics as well.

The dose of perphenazine chosen for the study was low to minimize the potential for EPSE that may have biased previous comparisons of typical and atypical antipsychotics. Perphenazine was given at a mean dose of 20.8mg daily, with a maximum allowable dose of 32mg daily; this is significantly lower than the licensed maximum dose of 64mg daily¹⁸. It is not known if different doses would have produced a different set of results. However, the results from CATIE suggest that there may be a subset of patients for whom moderate doses of moderate-potency typical antipsychotics may be relatively efficacious and tolerable¹⁰.

Efficacy on Sub-Measures

Patients receiving perphenazine had similar scores on the positive symptom subscales on the Positive and Negative Symptom Scale (PANSS) to those receiving atypical antipsychotics, with the exception of olanzapine, which showed superiority over the other antipsychotics for reduction in positive symptoms, particularly in the early stages of therapy⁴. Contrary to expectations, perphenazine showed similar efficacy on the negative symptom subscale on PANSS compared with the atypical antipsychotics⁴. It has been suggested that this result may have occurred because of comparative rates of EPSE between perphenazine and the atypical antipsychotics¹⁴. Clinical effects of EPSE extend beyond motor effects and include: worsening of cognition, negative symptoms, depression, and increased risk of tardive dyskinesia^{15,24}. Hence, avoiding EPSE and

concomitant anticholinergic medication with the typical antipsychotics may be the key to realising 'atypical benefits'²⁴. Although broad efficacy measures appeared similar, it is unknown if there are differences between the typical and atypical antipsychotics in other efficacy outcome measures such as cognition, substance abuse or aggression; future CATIE publications will address such issues.

Conclusions

Many typical antipsychotics available overseas such as perphenazine, are not marketed in Australia. The typical antipsychotics available differ markedly in their adverse effect profiles; hence, caution is required when applying the results of CATIE to Australian patients. While typical antipsychotics are not currently advocated as first-line treatment for all patients, they should not be discounted as a potential therapeutic option for certain individuals. CATIE has shown that of the drugs studied, there is no antipsychotic that is clearly more effective and better tolerated than other antipsychotics. Choice of antipsychotic should be tailored to the individual taking into account efficacy, adverse effect profile and cost.

Erratum: In the Therapeutic Drug Monitoring article in the October 2006 Drug Bulletin it should be noted that elderly patients usually require lower doses of medication to achieve therapeutic plasma levels and that they may be more sensitive to adverse effects even when the drug level is in the therapeutic range.

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