Rational pharmacotherapy in early psychosis*

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Background An increased focus in research specific to first-episode schizophrenia has provided a rapidly growing body of evidence that can be directly translated to clinical practice.

Aims To provide clinical recommendations specific to effective pharmacotherapy of first-episode schizophrenia.

Method Evidence from clinical trials focused on the first-episode population is combined with data from other areas of investigation.

Results In first-episode psychosis, when to initiate treatment is not always clear, being intimately linked to challenges regarding early detection and diagnosis. There may be differences in antipsychotic dosing, patterns of response and sensitivity to side-effects. Adherence appears to be even more problematic at this stage.

Conclusions Clinicians currently treating early psychosis have considerably more information to guide their decision-making. However, the speed at which the field is growing is a reminder to treat this knowledge as a work in progress.

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It is unlikely that there would have been a call for a paper of this sort even a decade ago. Over the course of many years antipsychotic treatment had come to be viewed as phase-specific, with distinctions really confined to issues of acute *v.* maintenance treatment. The notion that treatment of psychosis was stage-dependent, that it varied as a function of where an individual was in the course of the illness, was not viewed as particularly relevant.

Within the last decade, however, stage of illness has received considerably more attention, a shift based on evidence arising from opposite ends of the treatment continuum. By the early 1990s clozapine had been reintroduced for clinical use in a number of countries, with accumulating evidence that it was superior even to other second-generation antipsychotics in refractory psychosis (Remington & Kapur, 2000). Meanwhile, there was a growing body of evidence that individuals in the early stages of psychosis might also be distinguishable in terms of treatment, both in terms of response and side-effects (Lieberman *et al*, 1993, 1996).

Taken together, the evidence suggested that the pharmacotherapy of psychotic illnesses, such as schizophrenia, needed to consider stage of illness. Decision-making regarding individuals in the initial stages of psychosis is not the same as for those who have experienced multiple episodes, i.e. those in the 'chronic' phase of the illness who frequently appear 'partially responsive'. There is, in addition, this sub-population of individuals who, even in the face of ongoing treatment with various antipsychotics, show a suboptimal response, a group that is defined by the 'refractory' form of their illness.

Before proceeding further, it is worth noting that the term 'psychosis' is being used generically here. This is, at least in part, related to the focus of the article, i.e. early psychosis. At this particular point in treatment it is often impossible to make a clear diagnosis; however, based on existing knowledge in using antipsychotics, initially the same principles apply. In contrast, over the longer-term course of illness use of antipsychotics may vary as a function of diagnosis.

It also needs to be noted at the outset that the terms 'typical' and 'atypical' are used here as a means of distinguishing between the older and newer antipsychotics. Readers will be most familiar with such a distinction, but there is reason to challenge this choice of terms and even the underlying concept. With clinical experience, it is apparent that such a clear-cut dichotomy does not exist, particularly as new antipsychotics enter the market and we expand our measures of outcome (Remington, 2003). There is, in fact, already ample evidence that the newer agents are not equal on the various domains, making it impossible to distinguish two distinct classes (Waddington & O'Callaghan, 1997).

This article addresses a number of questions thought to be relevant to antipsychotic use in early psychosis: when to intervene, what antipsychotic; what dose; and, for how long. Previous articles published by the author and discussing this topic form the basis for the overview (Remington *et al*, 1998, 2000, 2001*a*). Recommendations are premised on the notion that we are dealing with a chronic psychotic illness, such as schizophrenia, where antipsychotic treatment represents the cornerstone of effective treatment programmes.

METHOD

When should antipsychotic therapy be introduced?

Evidence from several lines of investigation suggests that early, effective interventions improve outcome. For example, diminishing the duration of untreated psychosis (DUP) has been associated with better outcome (Loebel *et al*, 1992; Scully *et al*, 1997; Wyatt *et al*, 1997; McGorry *et al*, 2001). Similarly, it has been shown that with each episode of psychosis, at least in the early stages, it takes longer to establish response and the degree of response diminishes (Lieberman *et al*, 1996). These types of findings provide support for the hypothesis that psychosis may represent some sort of 'toxic' process that incurs progressive damage in its untreated state (Wyatt, 1995).

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Conceptually, this line of thinking fits with the notion that schizophrenia represents a neurodevelopmental, and possibly neuroprogressive, disorder (Censits *et al*, 1997; Lieberman, 1999; Finlay, 2001; Weinberger, 2002). Effective interventions as early as possible should, at least in theory, carry the potential of delaying, arresting, or even possibly reversing various deficits that can be seen as early as the first identified episode.

The idea that early intervention improves outcome has spawned 'first-episode' programmes worldwide and amongst their goals has been the identification of cases as soon as possible. That this is a worthy and achievable objective gains support from evidence that in actual practice DUP can be as much as a year or longer, and we now have data to suggest that these types of programmes can effectively reduce this interval (Haas & Sweeney, 1992; Hafner & an der Heiden, 1997). For example, the combined Norwegian/USA programme reported a dramatic reduction in DUP, from 118 to 20 weeks, with a focused programme that included a public education component (Pelosi & Birchwood, 2003).

Clearly there is the opportunity for earlier intervention based on the length of time psychotic symptoms go untreated. But is it possible to intervene even earlier? There is now a growing interest in the prodrome of schizophrenia, a stage lasting on average 5 years before the onset of frank psychotic symptoms (Hafner & an der Heiden, 1997). Its presentation highlights other symptom domains, for example, affective (depression), cognitive (decreased attention, concentration), deficit (amotivation, social withdrawal), but like later stages of the illness is characterised by a functional decline. It is appealing to imagine that an effective intervention strategy, here too, might favourably alter outcome. Pharmacological intervention with antipsychotics immediately comes to mind, given that use of these medications is integral to the longer-term management of schizophrenia. Moreover, there has been evidence with the newer antipsychotics that their benefits may be seen along these other symptom dimensions, in addition to psychotic symptoms *per se* (Waddington & O'Callaghan, 1997; Buckley, 1999).

The benefit of antipsychotic treatment initiated during the prodromal phase remains unclear, if for no other reason than lack of data. Several uncontrolled reports have supported the symptomatic benefits of antipsychotic therapy (Cannon *et al*, 2002; Cornblatt *et al*, 2002), although in one of these it was noted that benefits were seen with other psychotropics as well (Cornblatt *et al*, 2002). One controlled trial has reported the clinical benefits of low-dose risperidone and cognitive therapy when compared with supportive case management, with 4 of 32 individuals (12.5%) in the former group becoming psychotic during the 6-month treatment period, in contrast to 10 out of 28 (35.7%) in the latter (McGorry *et al*, 2000). In an 8-week double-blind placebo-controlled trial, olanzapine at mean doses of 8.0 ± 3.1 mg daily was found to be significantly superior in the control of prodromal symptoms (Woods *et al*, 2003).

In summary, there is evidence to suggest that antipsychotics should be instituted as soon as possible once psychotic symptoms have been identified, and there appears to be considerable room for improvement in identifying these individuals earlier. Although there are substantial data supporting the clinical benefits of early intervention, this topic remains the subject of debate, as various reports have also reported a lack of clinical benefit (Craig *et al*, 2000; Ho *et al*, 2000, 2003; Hoff *et al*, 2000). There are interesting preliminary data regarding the potential for antipsychotic treatment in the prodrome of schizophrenia, but reports await replication and corroboration with controlled, masked studies. For a number of reasons, clinicians are likely to be hesitant in instituting antipsychotics at this point: a paucity of empirical data; lack of biological markers in the face of non-specific, non-psychotic symptoms; and recognition that even the newer antipsychotics carry with them the potential for significant side-effects.

Finally, a comment is warranted regarding outcome measures. Historically, the focus was confined to positive symptomatology, but this has changed considerably. It is common now to evaluate pharmacological response on a number of clinical dimensions as well as side-effects (Remington, 2003). Indeed, the list has expanded to the point where a simple dichotomous distinction between 'typical' and 'atypical' antipsychotics seems overly simplistic (Waddington & O'Callaghan, 1997). The issue is made more complex by the recent emphasis on distinguishing clinical from functional recovery, as their courses are not necessarily parallel (Tohen *et al*, 1992; Robinson *et al*, 2003). In evaluating the benefit of any intervention now, pharmacological or otherwise, 'response' must be viewed across a number of domains.

RESULTS

Choosing an antipsychotic

Much has been made regarding the clinical advantages of the newer antipsychotics *v.* their conventional counterparts, and numerous reports are available to support these claims (Fleischhacker & Hummer, 1997; Tamminga, 1997; Stip, 2000). Concluding that the second-generation agents represent first-line treatment for all individuals with psychosis (including those with a first break) seems at this point a foregone conclusion. There are, however, at least three points of clarification that caution against the uncontested acceptance of such an approach:

(a) Most of the double-blind, controlled studies evaluating the newer *v.* older antipsychotics have been carried out in more chronic patients who have proven partially responsive. In fact, there are very few published investigations (see Table 1) that have focused on the population with first-episode psychosis, and collectively the results have not been particularly convincing that the atypicals offer clinical superiority (Lambert *et al*, 1995; Emsley *et al*, 1999; Sanger *et al*, 1999; Lieberman *et al*, 2003). A longer-term study (52 weeks) comparing clozapine and chlorpromazine found differences favouring clozapine at 12 weeks, although the two groups were comparable by endpoint (Lieberman *et al*, 2003). In the one report indicating greater efficacy for the atypical agent, i.e. olanzapine, the definition of first episode was extended to include individuals who could have been ill for as long as 5 years (Sanger *et al*, 1999).

(b) It has been suggested that many of the trials comparing typical and atypical antipsychotics favoured the latter, based on the use of inappropriately high doses of the comparative conventional antipsychotic (Geddes *et al*, 2000; Carpenter & Gold, 2002). Although this topic will be addressed in more detail in the next section, suffice it to say that there is compelling evidence to support this claim.

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Table 1 Published, double-blind controlled trials in first-episode psychosis

Study	Sample size (*n*)	Drug comparison	Mean dose (mg/day)	Trial (weeks)	Efficacy
Lambert *et al* (1995)	28	Remoxipride *v.*	348	6	Equal
		Thioridazine	361		
Sanger *et al* (1999)	83	Olanzapine *v.*	11.6	6	Olanzapine superior on:
		Haloperidol	10.8		BPRS reduction ⩾40%
					BPRS: Total
					BPRS: Negative
					PANSS: Total
					PANSS: Positive
Emsley *et al* (1999)	183	Risperidone *v.*	6.1	6	Equal
		Haloperidol	5.6		
Lieberman *et al* (2003)	160	Clozapine *v.*	300[1]	52	Equal
		Chlorpromazine	400[1]		

BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.
1. Median dose.

(c) From the standpoint of side-effects, much has been made of the superiority of the newer antipsychotics with respect to extrapyramidal side-effects (EPS), perhaps the most problematic adverse event associated with the conventional agents, especially the high-potency group (e.g. haloperidol). The advantage of the atypicals in this regard again appears to be related, at least in part, to inappropriate dosing of the typical antipsychotics used as the comparator in many of these trials (Leucht *et al*, 1999; Geddes *et al*, 2000). Moreover, accumulating experience with the newer antipsychotics has indicated that they are not without the risk of notable side-effects, in particular, weight gain, diabetes and cardiovascular risk (Casey, 1996; Cunningham Owens, 1996; Umbricht & Kane, 1996; Wirshing *et al*, 1998, 1999, 2002; Allison *et al* 1999; Allison & Casey, 2001). Indeed, it has been suggested that these adverse events have come to represent the 'EPS' of this new generation of antipsychotics.

On the other side of the coin, there are several issues that need to be considered before dismissing the idea that the atypicals should be first-line treatment. It has been demonstrated that individuals with a first-episode psychosis respond well to antipsychotic treatment, with as many as 80% recovering symptomatically from their initial episode (Tohen *et al*, 1992; Lieberman *et al*, 1993). With such a high response rate, a 'ceiling effect' cannot be ruled out; that is, it becomes difficult to tease apart potential differences between different treatment interventions. In addition, we have expanded our definition of outcome considerably in recent years, no longer focusing only on the control of positive symptoms. Numerous other dimensions (e.g. cognition, affect, quality of life) are now the subject of evaluation and there are a paucity of data that allow a comparison of older and newer agents on these different dimensions (Geddes *et al*, 2000; Kapur & Remington, 2000; Remington, 2003). It may well be that future work demonstrates detectable differences on one or more of these dimensions, and the potential scope of these differences may extend even beyond clinical symptoms. For example, we now have data to suggest that there are also detectable changes morphologically (Chakos *et al*, 1995; Andersson *et al*, 2002). What these changes mean is not yet fully understood, but it speaks not only to choice of antipsychotic but also to this issue of early intervention and improved outcome.

At this point there is still insufficient evidence from the standpoint of efficacy to support the position that the newer antipsychotics represent first-line treatment. The most compelling argument presently rests upon side-effects. First, it has been demonstrated that there is an increased risk of EPS in the early *v.* late stages of schizophrenia (McEvoy *et al*, 1991; Aguilar *et al*, 1994), and one of the more consistent findings with the newer antipsychotics is their diminished risk of EPS (Leucht *et al*, 1999; Geddes *et al*, 2000) (keeping in mind that this finding may be skewed in favour of the newer antipsychotics because of the comparator dose of the conventional antipsychotic, as well as the trend to use a high-potency typical agent, e.g. haloperidol).

The data related to risk of tardive dyskinesia really represent the strongest piece of evidence arguing for the newer antipsychotics as first-line treatment. Although these data are preliminary, they indicate figures in the range of 1% or less per year (Peacock *et al*, 1996; Tollefson *et al*, 1997; Beasley *et al*, 1999), considerably below the figure of approximately 5% that might be predicted following a year's exposure to conventional antipsychotics (Glazer *et al*, 1993). Although the relationship between antipsychotic dose and risk of tardive dyskinesia is not entirely clear, there are reports supporting such a link (Morgenstern & Glazer, 1993; Woerner *et al*, 1998), and once again the argument could be made that the use of comparatively higher doses of these drugs could account for these reported differences in tardive dyskinesia rates. However, this does not appear to be the case. A recent study reported a 12-month incidence of probable and persistent tardive dyskinesia to be 12.3% in a group of individuals with first-episode psychosis treated with haloperidol at a mean dose of 2.8 mg/day (Oosthuizen *et al*, 2003). Indirect evidence also can be found from looking at high-risk populations, i.e. the geriatric population, individuals with borderline tardive dyskinesia, where evidence once again supports the benefit of atypicals in terms of tardive dyskinesia risk, even when comparable doses of the conventional drugs are employed (Jeste *et al*, 1999*a*,*b*, 2000; Dolder & Jeste, 2003).

There are, in addition, data to indicate that across other side-effects the atypical antipsychotics may be better tolerated, as measured by discontinuation rates (Emsley *et al*, 1999). Having said this, the new antipsychotics have attuned us to a different profile of adverse events that cannot be ignored. For example, weight gain has become a significant issue, particularly with several of the newer compounds (Allison *et al*, 1999; Wirshing *et al*, 1999; Allison & Casey, 2001; Nasrallah, 2003), and patients with first-episode psychosis exposed to these compounds appear to be

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at no less a risk (Addington *et al*, 2003). In addition, there are a growing number of reports indicating other potentially significant adverse events (e.g. impaired glucose tolerance/diabetes; Wirshing *et al*, 1998; Mir & Taylor, 2001; Baptista, 2002; Henderson, 2002), and lipid abnormalities (Meyer, 2001; Wirshing *et al*, 2002; Lindenmayer *et al*, 2003). These risks are only compounded when one considers that treatment is being initiated in late adolescence and may be lifelong. Moreover, this is a population that has a higher propensity of numerous other cardiovascular risk factors (Allebeck & Wistedt, 1986; Mortensen & Juel, 1993; Brown *et al*, 2000; Osby *et al*, 2000), and for various reasons has diminished access to medical care (Felker *et al*, 1996). More recent concerns with ziprasidone and sertindole regarding potential cardiac changes, specifically QTc prolongation, have reminded clinicians of potential cardiac risks (Glassman & Bigger, 2001; Taylor, 2003), and although the risk is low it can be potentially life-threatening. It is impossible to disregard issues of this sort in decision-making regarding antipsychotic choice; indeed, there is reason to argue that these types of side effects are of no less concern than tardive dyskinesia.

To summarise, there is at present a lack of compelling evidence that the newer antipsychotics are clinically superior in the population with first-episode psychosis, and for now the argument regarding choice really rests upon side-effects. The increased risk of tardive dyskinesia with conventional antipsychotics favours using the atypicals; conversely, the risk of adverse events, such as weight gain, diabetes, and other cardiovascular events associated with the newer antipsychotics, counters their straightforward acceptance as first-line treatment. There is, however, a difference with respect to tardive dyskinesia, with the newer agents at a lower risk in this regard (whereas there are differences in acute EPS between the atypicals (Leucht *et al*, 1999), as of yet there is no concrete evidence that they differ in terms of diminished tardive dyskinesia risk). There do appear to be distinguishable differences between these medications regarding such side-effects as weight gain and QTc prolongation. Thus, the clinician may move to the newer antipsychotics as first-line treatment to avoid tardive dyskinesia, and then choose between these based on their relative risk for other relevant side-effects.

What is an appropriate dose?

To address this question properly it is necessary to briefly review what has taken place with antipsychotic dosing over the years. First, schizophrenia is an illness where a significant portion of individuals demonstrate a suboptimal response – with the conventional antipsychotics, for example, data indicate that as many as 25% fail to respond (Brenner *et al*, 1990). It is not so surprising that in an effort to achieve response clinicians moved to the use of higher doses; however, the cardiovascular side-effects, i.e. orthostatic hypotension, of the lower-potency antipsychotics to some extent acted as a rate-limiting step in this regard. With the high-potency antipsychotics like haloperidol, this was not such a problem and there was a progressive increase in dosing. By the 1980s high-dose approaches were even advocated (e.g. rapid neuroleptisation), and antipsychotic doses increased to over three times those employed with the low-potency agents (Baldessarini *et al*, 1984). In practice it was not uncommon to see daily doses well in excess of haloperidol 20 mg equivalents.

By the late 1980s, this practice was being called into question. A review of the controlled studies indicated that there was no evidence to support the clinical superiority of high-dose therapy, leading to the recommendation that doses in the range of 3–12 mg haloperidol equivalents reflected a more appropriate therapeutic range (Baldessarini *et al*, 1988). Subsequent analyses supported this finding (Bollini *et al*, 1994).

More recently there has been even further support for these lower doses based on *in vivo* evidence arising from neuroimaging, in particular positron emission tomography (PET). For example, it has been demonstrated that antipsychotic response is optimised at a threshold of approximately 65–70% dopamine D_2 occupancy, whereas exceeding 80% leads to a substantial increase in the risk of EPS (Farde *et al*, 1992; Nordstrom *et al*, 1993; Kapur *et al*, 1999). Moreover, several reports have demonstrated that lack of clinical response is not associated with inadequate dopamine blockade (Wolkin *et al*, 1989; Coppens *et al*, 1991; Pilowsky *et al*, 1993).

How do these findings translate into clinical practice? Using haloperidol for comparison purposes, 2 mg results in mean D_2 occupancy of 67%, whereas 5 mg approximates the 80% threshold associated with EPS (Kapur *et al*, 1996, 1997). These data support a therapeutic range of approximately 2–5 mg haloperidol equivalents daily to optimise clinical response and minimise the risk of EPS.

There are now clinical data that offer credence to this notion, data involving patients with first-episode psychosis. This is an important methodological issue as these individuals appear to differ from the more chronic population in terms of treatment response as well as sensitivity to side-effects, such as EPS (McEvoy, 1986; Lieberman *et al*, 1993, 1996; Aguilar *et al*, 1994; Robinson *et al*, 1999*b*). Zhang-Wong and colleagues, for example, found that 82% of their patients with first-episode psychosis were treated effectively with haloperidol 2–5 mg daily. Their study allowed those who had not responded to then be treated with higher doses (10–20 mg/day), but this subgroup continued to be less responsive. EPS were reported in 13% of the 2 mg group, in contrast to 55% for those who receive 5 mg (Zhang-Wong *et al*, 1999). In a double-blind fixed, flexible design comparing risperidone with haloperidol over 6 weeks, Emsley *et al* (1999) reported mean end-point doses of 6.1 mg and 5.6 mg, respectively, despite the fact that doses could be increased to 16 mg daily for each.

A more recent double-blind study completed at this centre evaluated the relationship between D_2 occupancy and clinical response, as well as side-effects, in 23 patients with first-episode psychosis (Kapur *et al*, 1999). Patients were randomly assigned to haloperidol 1 mg or 2.5 mg daily. If they failed to demonstrate 'much' or 'very much' improvement over 2 weeks, the dose was increased to 5 mg for another 2 weeks. Results indicated that D_2 occupancy could be used to predict clinical response, in that a threshold set at 65% was predictive of response with 80% sensitivity. Of the 10 identified responders after 2 weeks, 2 were receiving haloperidol 1 mg whereas 8 received 2.5 mg. Only 2 of these 10 individuals had D_2 occupancy below 65%. Completed data were available for 11 of the identified non-responders who went on to receive haloperidol 5 mg/day. Seven of this group had D_2 occupancies below 65% prior to this increase, and of these 6 (85.7%) improved with the higher dose. In contrast, 1 out of 4 (25%) who already had occupancies beyond 65% before the dose increment showed

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improvement. In terms of EPS, 3 out of the 23 (13%) treated with either haloperidol 1 mg or 2.5 mg developed EPS, whereas 7 out of 12 (58%) experienced EPS with the dose increase to 5 mg. From the standpoint of D_2 occupancy, blockade below 78% was not associated with EPS. These data suggest that clinical response is increased with D_2 occupancy exceeding 65–70%, whereas EPS risk increased with occupancy above 78%. Haloperidol 2.5 mg is more likely than 1 mg to exceed the clinical threshold of 65%, the latter demonstrating mean D_2 occupancy of approximately 58%, but haloperidol 5 mg has a substantial increase in EPS risk *v.* these lower doses.

Are these types of doses also appropriate in later stages of the illness? The clinical evidence drawn from more chronic patient samples suggests somewhat higher doses (e.g. 3–12 mg/daily) in this population (Baldessarini *et al*, 1988), but certainly not of the magnitude that have frequently been employed in past years. It is appealing to speculate that the slight increment may reflect D_2 upregulation seen following chronic antipsychotic exposure (Schroder *et al*, 1998; Silvestri *et al*, 2000). At the same time however, the ageing process is associated with progressive loss of D_2 receptors, at least as observed in control populations (Seeman *et al*, 1987), and this may account for the progressively lower doses that are required in older individuals.

It is interesting to note that the data do not support the position of clinical superiority with doses in excess of haloperidol 12 mg equivalents daily. This finding dovetails with a more recent meta-analysis comparing the benefits of the newer antipsychotics *v.* conventional antipsychotics. When haloperidol doses $\leqslant$12 mg daily were evaluated, the atypicals had no benefits in terms of efficacy or tolerability (although they did show fewer EPS) (Geddes *et al*, 2000).

Having information regarding equipotent dosing guidelines for the different antipsychotics is important for clinicians, who must often switch antipsychotics because of issues related to efficacy and/or side-effects. Past guidelines have depended on pharmacokinetic and clinical data, but the more recent PET evidence allows for greater precision in these calculations. This line of thinking is based on the premise that D_2 occupancy is shared in common by all antipsychotics, typical as well as atypical, and that the *in vitro* affinity of a drug for the D_2 receptor remains the single best predictor of its dose in the clinical setting (Creese *et al*, 1976; Seeman *et al*, 1976). There are two newer antipsychotics where evaluation of their D_2 occupancy is markedly influenced by their fast dissociation values (clozapine and quetiapine) (Seeman & Tallerico, 1999; Kapur & Seeman, 2000), making the precise calculation of their equipotent values more difficult. Acknowledging this caveat, however, Table 2 outlines comparative doses between several conventional antipsychotics, including haloperidol, evaluated at our centre with PET and several of the newer agents (olanzapine, risperidone, ziprasidone).

How long should antipsychotic therapy be employed?

This question really entails two components: (a) how long should a trial last to establish response; and (b) how long should someone who has been successfully treated continue with antipsychotic therapy?

For many years it has been customary to carry out a trial of 6–8 weeks to establish response. Work specifically involving patients with first-episode psychosis reported mean and median times to remission of 35.7 and 11 weeks, respectively (Lieberman *et al*, 1993). It is important to keep in mind that this same line of investigation found time to response increased with subsequent episodes (Lieberman *et al*, 1996), a finding that is in keeping with reports involving more refractory patients indicating that a longer trial may be required, perhaps in the range of 3 months or more (Meltzer, 1989; Smith *et al*, 1996; Wilson, 1996).

A troubling question for many clinicians is how long to continue antipsychotic therapy in those with a first-episode psychosis who have responded effectively to antipsychotic therapy. It is known that as many as 80% of patients with first-episode psychosis will show symptom resolution with treatment (Tohen *et al*, 1992; Lieberman *et al*, 1993), making this a common dilemma with this population. The notion of taking antipsychotic medication for a lifetime following a single psychotic episode is not an appealing option. Studies have indicated that there is a relapse rate of 40–60% during the first year in individuals who go untreated following recovery from a first-episode psychosis (Kane *et al*, 1982; Crow *et al*, 1986), leading to the recommendation that pharmacological treatment continues for at least 1–2 years (Kissling, 1991; Frances, 1998). There is an appeal to these guidelines, as they offer a compromise for both patients and clinicians. For patients it means that there is a potential 'end' in sight to medication use; for clinicians, it also offers some type of end-point to the prescribing of antipsychotics in individuals where the diagnosis may be less than clear. However, more recent evidence injects a note of caution to the goal of antipsychotic discontinuation (Robinson *et al*, 1999*a*). Specifically, in a 5-year follow-up of 104 individuals who had responded to treatment of their index episode, discontinuing antipsychotic therapy increased the risk of relapse by almost 5 times. Moreover, of 15 individuals who had their first relapse after 2 years of stability, 8 had discontinued medication. Even more sobering are data indicating that in a group of individuals with recent-onset schizophrenia who discontinued antipsychotic medication 78% experienced symptom exacerbation or relapse within 1 year, with the figure climbing to 96% by 2 years (Gitlin *et al*, 2001).

This raises the possibility that an even more conservative approach may need to be considered, i.e. continuous antipsychotic treatment at the lowest possible dose, at least for those where there is convincing evidence that the diagnosis is compatible with schizophrenia. Unfortunately, longer-term treatment adherence is a major hurdle with this population, perhaps even more so than with those in later stages of the illness. This has been brought home in a recent study that followed individuals with first-episode psychosis for a 1-year period after discharge. Only 37% maintained their medication over this interval; in contrast, 51% had gaps of 30 days or longer, with an average total time off medication of approximately 7 months

Table 2 Dose equivalents (mg) for different antipsychotics

Antipsychotic	Approximate dose equivalent based on D_2 occupancy
Haloperidol	2
Loxapine	15
Olanzapine	10
Risperidone	2.5–3.0
Ziprasidone	80

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(Mojtabai *et al*, 2002). Although continuous low-dose antipsychotic therapy may represent the ideal 'gold standard' to minimise relapse, clinical reality may dictate the use of alternative strategies. Close monitoring with rapid medication re-instatement (e.g. 'targeted therapy'; Carpenter, 2001; Gitlin *et al*, 2001) or 'extended dosing' (Remington *et al*, 2001*b*) may offer approaches that can address the practical limitations non-adherence brings to bear on the successful management of these individuals.

DISCUSSION

Just as we now acknowledge that schizophrenia is heterogeneous in its nature, we must also recognise that its pharmacotherapy varies over the illness' course in ways that are not confined to acute *v.* maintenance treatment. The issues and decision-making that apply to first-episode psychosis may not be the same for those who are in later stages of the illness, or those who have remained refractory to standard interventions. Individuals in a first-episode psychosis are unique. Diagnosis is often less clear than for those who have been followed over a longer interval; patients with first-episode psychosis seem more sensitive to antipsychotic medications in terms of side-effects but, at the same time, appear more responsive; dosing may be somewhat different in these individuals *v.* those in later stages of the illness; and, the notion of antipsychotic discontinuation is more of an issue in this group. Current evidence has been reviewed with respect to recommendations that can be used in the clinical setting. It almost goes without saying, however, that this is a work in progress – further advances will undoubtedly shed more light on these issues but raise yet more questions. For clinicians this is a double-edged sword. These advances add additional layers of complexity to their decision-making and demand that they stay abreast of changes in a field that is expanding rapidly, while at the same time setting the stage for more refined interventions and, ideally, better outcomes.

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CLINICAL IMPLICATIONS

- The notion that early intervention improves outcome has now been extended to investigations addressing the prodrome stage of schizophrenia.
- Evidence indicates superior clinical response to antipsychotic treatment in early psychosis, but also increased sensitivity to side-effects.
- Relapse rates are high over time and medication discontinuation, even after extended periods of stabilisation, can increase this risk.

CLINICAL LIMITATIONS

- Evidence regarding the benefits of early intervention is conflicting, with studies also failing to support this position.
- Early intervention studies are particularly sensitive to the issues of diagnostic sensitivity and specificity.
- In evaluating outcome there is a need to distinguish between clinical and functional recovery, as these do not necessarily follow a parallel course.

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