Aripiprazole in the acute treatment of male patients with schizophrenia: effectiveness, acceptability, and risks in the inner-city hospital setting

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Abstract: Aripiprazole, a novel atypical antipsychotic that acts as a partial agonist at the dopamine D_2 receptors, has been reported to be effective in the treatment of chronic schizophrenia. However, the risks and benefits of using aripiprazole in the acute hospital setting to treat severe psychotic disorders are unclear. This naturalistic study assessed the effectiveness of aripiprazole monotherapy in a group of actively psychotic male patients (n = 10) with schizophrenia who were admitted to an inner-city acute psychiatric unit. Most patients (n = 7) responded to aripiprazole treatment, which was well tolerated and significantly ameliorated psychotic symptoms after 2–3 weeks. Patients who responded to it could be safely discharged on aripiprazole monotherapy. Side effects observed were mostly mild and transient, and included extrapyramidal symptoms (n = 1) and neutropenia (n = 1). Aripiprazole also remarkably attenuated dyskinetic movements in 1 patient with severe tardive dyskinesia, thereby suggesting that it may be useful in the treatment of other disorders that are also associated with dopamine dysfunction. Results showed that aripiprazole can be safely and effectively employed in the hospital setting to treat severely psychotic patients with schizophrenia, but further studies are required to establish the full range of adverse reactions and therapeutic indications associated with its use.

Keywords: aripiprazole, schizophrenia, tardive dyskinesia, extrapyramidal symptoms, atypical antipsychotics, neutropenia

Introduction

Atypical antipsychotics have replaced conventional antipsychotics as the drugs of choice in the pharmacological treatment of schizophrenia (NICE 2002). The distinguishing feature of most atypical antipsychotics is a higher binding affinity for serotonin 5-HT_2 than for dopamine D_2 receptors (Goldstein 2000). Whether the binding affinities of atypical antipsychotics are directly associated with their mode of action, previous extensive research work had given rise to the dopaminergic theory of schizophrenia, which linked the therapeutic effect of conventional antipsychotics to the blockade of post-synaptic dopamine D_2 receptors (Carlsson 1996). However, as conventional antipsychotics indiscriminately occupy dopamine receptors, their therapeutic effects are accompanied by a range of dopamine-related side effects, including extrapyramidal symptoms (EPS), hyperprolactinemia, and possibly worsening of negative symptoms of schizophrenia.

Aripiprazole is a novel atypical antipsychotic that differs from other drugs of its class by acting as a partial agonist at the D_2 receptor (McGavin and Goa 2002). It also has partial agonist activity at 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A}

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receptors. Aripiprazole treatment has been shown to be well tolerated and effective in the prevention of relapse in patients with chronic, stable schizophrenia (Pigott et al 2003). It has also been reported to be at least as effective as haloperidol in the long-term treatment of patients with chronic schizophrenia following an acute relapse of their illness, while inducing less EPS (Kasper et al 2003). Aripiprazole has been licensed for use in the EU since 2004, but the risks and benefits of using aripiprazole in the acute hospital setting for the treatment of severe psychotic disorders have not been fully ascertained. We present a small naturalistic study on the use of aripiprazole in the acute treatment of active psychotic symptoms in a group of adult male patients with a diagnosis of schizophrenia who were admitted to our busy inner-city psychiatric unit.

Method

The study was conducted in an 18-bed inner-London specialist acute psychiatric ward that caters for male patients aged between 18 and 65 years old suffering from severe mental illness. Most referrals to the unit come from local community mental health services (CMHS) and hospital accident and emergency departments. By definition, patients who are admitted to the unit cannot be managed clinically by local CMHS. Most patients are compulsorily admitted and detained in hospital, at least initially, under the England and Wales Mental Health Act 1983. The unit has a high admission throughput and, depending on their progress, patients are discharged as soon as appropriate and transferred back to CMHS. Average duration of stay is 4–6 weeks, yet up to 20% of patients may at times remain on the ward for a few months.

This was a prospective naturalistic study, approved as a clinical audit by the local drugs and therapeutics committee. Ten patients who had been consecutively admitted to the unit for assessment and treatment of an acute psychotic state, who met the ICD-10 (WHO 1994) diagnostic criteria of schizophrenia, and for whom the prescription of an atypical antipsychotic was thought to be the pharmacological treatment of choice, were considered for the study. The diagnosis of schizophrenia was established following a thorough clinical interview with each patient and subsequent clinical discussion within the multidisciplinary team. Information on patients' psychiatric history was obtained from their medical records, whereby the duration of their illness could be estimated. All patients were assessed on admission using the Brief Psychiatric Rating Scale (BPRS) (Bech et al 1986), 18-item version, 0–4 score range per item, 0–72 total score range, an instrument that the team was familiar with. Only patients who had scored at least 40 points at baseline were included. We followed NICE (2002) guidelines and discussed the choice of antipsychotic medication with patients before treatment was initiated. All patients underwent a physical examination and routine investigations involving full blood count, thyroid and liver function tests, and urinanalysis, the results of which were within normal limits. Patients were excluded from the study if they were receiving concomitantly other antipsychotics, antidepressants, or mood stabilizers, and if they were known to have abused any illicit substance during the week before admission.

The 10 patients received therapeutic oral doses of aripiprazole, ranging from 15 mg to 30 mg daily, for at least 4 weeks from the day of admission. After 4 weeks, patients who failed to respond to aripiprazole could be switched to an alternative antipsychotic. Aripiprazole treatment could be discontinued at any time if a patient experienced any major adverse reaction or if response to treatment was deemed unsatisfactory. Patients could also be prescribed lorazepam for agitation–restlessness and anticholinergic drugs as required to treat EPS, as well as nonpsychotropic medication if needed. Nonmedical interventions, including occupational therapy and group activities, followed the standard clinical procedures that apply to all patients on the ward. Each patient receiving aripiprazole treatment was assessed by a trained independent psychiatrist, who was not involved in prescribing to the patients, using the BPRS on 5 weekly occasions, namely, on admission (baseline BPRS score) and subsequently for 4 weeks, once a week on the same day. We arbitrarily defined response to treatment as a reduction of 20 points from each patient's BPRS score at baseline. We also recorded the relevant therapeutic responses in patients as perceived by the multidisciplinary team, as well as adverse effects of aripiprazole treatment and the final outcome of the hospital treatment after 6 weeks for each individual patient. Descriptive statistical analysis was used to delineate the results and the Student's t-test was used to assess changes in BPRS scores.

Results

Results of the audit are shown in Table 1. Ten male patients with a diagnosis of schizophrenia, with a median age of 36 years (range 19–50) and an estimated duration of illness ranging from 3 months to 33 years (median 30 months; 6.5 years ± 9.1, mean ± standard deviation), were included. Six of the patients had had previous admissions to hospital. Five

Table 1 Aripiprazole antipsychotic monotherapy in 10 male patients with schizophrenia admitted to an inner-London acute psychiatric unit

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age	50	43	20	47	22	38	39	24	19	34
Estimated duration of illness	33 years	3 years	2 years	4 months	2 years	4 years	2 years	3 years	3 months	8 years
No. of previous admissions	>10	2	0	0	0	3	1	2	0	3
Comorbidity[a]	Asthma	Alcohol abuse	Nil	Poly-substance abuse	Poly-substance abuse and anxiety	Obesity	Nil	HIV-positive, tardive dyskinesia, cannabis abuse	Nil	Cannabis abuse
Concurrent medication	Lorazepam	Vitamin B	Lorazepam	Nil	Lorazepam	Lorazepam	Nil	Hyoscine hydro-bromide 300 mg twice daily	Lorazepam	Lorazepam
Antipsychotics before admission	Risperidone	Risperidone Flupenthixol decanoate	Nil	Nil	Risperidone	Olanzapine	Risperidone	Risperidone, olanzapine, haloperidol	Nil	Olanzapine
BPRS (0–72)										
Baseline	42	41	54	40	54	47	52	40	65	53
Week 1	41	11	55	13	55	50	54	30	58	43
Week 2	40	5	56	16	45	31	41	28	50	42
Week 3	41	5	59	9	44	13	48	14	51	40
Week 4[b]	35	2	–	6	16	11	32	–	54	29
Observed therapeutic response	No major clinical change	Paranoia resolved, improved remarkably	No clinical change	Paranoid delusions resolved	Psychotic symptoms resolved. Less anxious and ambivalent	Negative symptoms resolved. More interactive	More interactive. Negative and positive symptoms resolved gradually	Psychotic symptoms and dyskinetic movements ameliorated	No noticeable change	Overall good clinical response
Observed adverse effects	Nil	Nil	Nil	Nil	Mild perioral involuntary movement	Nil	Drowsiness	Decrease in WBC (also on risperidone and olanzapine)	Nil	Nil
Final outcome after 6 weeks[c]	Improved on risperidone	Discharged home, under CMHT	Changed to depot due to non-compliance	Discharged home, under CMHT	Discharged home, under CMHT	Discharged home, under CMHT	Improved noticeably after 6 weeks	Changed to risperidone, later also interrupted	Improved on olanzapine	Continued to improve

[a] Comorbidity includes associated psychiatric and nonpsychiatric clinical conditions.
[b] Aripiprazole treatment of Patients nr 3 and nr 8 was discontinued after Week 3.
[c] Patients nr 7 and nr 10 were discharged home under the care of a CMHT after 6 weeks.
Abbreviations: BPRS, Brief Psychiatric Rating Scale; CMHT, community mental health team; WBC, white blood count.

patients also had a known history of alcohol or illicit substance misuse, mostly cannabis abuse, while 3 patients had an associated medical disorder. One patient suffered from asthma and another was noticeably overweight. Patient nr 8, who was known to be HIV-positive, complained of persistent hypersalivation and was also grossly impaired by dyskinetic movements, which were attributed to tardive dyskinesia (TD). Most patients (n = 7) had been previously treated with antipsychotics, whereas 3 had never received any previous antipsychotic medication. All patients showed moderate to severe psychotic symptoms on admission, as reflected on their 48.8 ± 8.2 BPRS mean score at baseline (n = 10; range 40–65).

Changes in BPRS scores indicated that most patients (n = 7) responded to aripiprazole treatment (BPRS 20-point reduction) within 4 weeks. A significant decrease in the BPRS mean score to 35.4 ± 15.6 (n = 10; T9 = 3.96, p = 0.003) was reached after patients had received aripiprazole for 2 weeks. Among the responders (n = 7), however, median time to achieve response was 3 weeks. One patient who did respond (nr 8) and another who did not (nr 3) had their aripiprazole treatment discontinued after 3 weeks. At the end of Week 4, BPRS mean score of the 8 patients who completed at least 4 weeks of aripiprazole was 23.1 ± 17.5 (T7 = 5.89, p = 0.001), while BPRS mean score of the 6 responders who completed treatment was 16.0 ± 12.2 (T5 = 9.86, p = 0.0001).

Main therapeutic responses to aripiprazole treatment, as perceived by the multidisciplinary team, included amelioration of both positive and negative symptoms of schizophrenia. Clinical changes in the responder group were typically described as "paranoid, psychotic, and negative symptoms resolved" and "improved social interaction". No incidents involving patients on aripiprazole were reported by nursing staff at any time. Four of the 7 responders were discharged from hospital within 6 weeks from the date of admission. Two patients (nr 7 and nr 10) who had responded within 4 weeks, but were still clinically unwell after 6 weeks (BPRS > 20), remained in hospital for a few additional weeks before a further delayed response to aripiprazole treatment was achieved and they were considered fit for discharge. Treatment of Patient nr 8 was discontinued after 3 weeks, by which time he had already responded to treatment. Of note, Patient nr 8 was observed to experience a significant attenuation of his dyskinetic movements following aripiprazole treatment. On admission, his speech and mastication were both grossly impaired by sudden, severe, involuntary oro-mandibular movements. Moreover, he was unable to remain seated or still because of frequent and wide jerky movements of trunk and limbs. Two weeks after he was commenced on aripiprazole, his dyskinetic movements had remarkably diminished, to the point that he could engage in lengthy interviews, eat properly, and join occupational therapy.

Eight patients were prescribed other drugs in addition to aripiprazole. In most cases, this was lorazepam as required for sedation (n = 6), but patients on aripiprazole did not require lorazepam tranquilization any more frequently or at higher doses than patients receiving other antipsychotic medication. One patient with a history of alcohol abuse (nr 2) received vitamin B as a dietary supplement and Patient nr 8 was prescribed hyoscine hydrobromide to mitigate his preexisting hypersalivation. None of the patients on aripiprazole required anticholinergic drugs to treat EPS. Adverse reactions to aripiprazole were noted in 3 patients. One patient developed mild perioral involuntary movements that subsided spontaneously after a few days (nr 5) and another complained of drowsiness after his dose of aripiprazole was increased from 15 mg to 30 mg daily (nr 7). Aripiprazole treatment of Patient nr 8 was discontinued at the end of Week 3 after blood tests revealed a drop in his white blood cell count (WBC), specifically in the neutrophils count. Similar drops in his WBC had happened on previous occasions following courses of treatment using risperidone and olanzapine.

The 3 nonresponders included 1 patient who complied poorly with oral medication (nr 3), and who was switched after 3 weeks to intramuscular depot injections of a conventional antipsychotic, and 2 patients who did comply with aripiprazole treatment for 4 weeks but failed to respond, both of whom were later switched to alternative atypical antipsychotics (nr 1 and 9). Patient nr 1 eventually responded to oral treatment using risperidone while Patient nr 9 responded to olanzapine.

Discussion

Clinical trials of acutely psychotic patients lasting up to 6 weeks have shown that, relative to placebo, aripiprazole was as effective as haloperidol and risperidone in the treatment of psychotic symptoms (Kane et al 2002; Marder et al 2003; Potkin et al 2003). However, the efficacy that antipsychotic treatments may show in randomized controlled trials may not always translate into their effectiveness in everyday clinical practice. Away from the controlled conditions of the research setting, in the hard-pressed environment of acute psychiatric wards, clinical audits offer a practical tool to

assess the risks and benefits of antipsychotic treatments precisely where they need to be most effective (Dratcu et al 2003). Although this was a small study, to our knowledge it is the first report on antipsychotic monotherapy using aripiprazole under naturalistic conditions in an inner-city acute psychiatric setting.

The clinical-demographic profile of our patient group was fairly representative of the male population admitted to inner-city acute wards for treatment of psychotic disorders. Patients had a median age of 36 years, most had been ill for some years, most had been previously treated with antipsychotics and admitted to hospital, and half of the group had a confirmed associated history of substance abuse. Except for one patient (nr 3), those who had not been admitted before were the youngest of the group. All patients were markedly psychotic at the time of admission.

Most patients responded to therapeutic doses of aripiprazole within 4 weeks. Although a significant decrease of psychotic symptoms was detected after 2 weeks, the median time was 3 weeks for a therapeutic response (defined as a 20-point decrease from pretreatment BPRS score) in those who responded to treatment. The rate of response (70%) to aripiprazole in this study was similar to that reported elsewhere (eg, Kasper et al 2003), yet it surfaced within a timeframe that was compatible with the constraints of our acute setting. Symptom amelioration, which involved both positive and negative symptoms of schizophrenia, was corroborated independently by the clinical team and also by the fact that most responders could be safely discharged within 6 weeks from admission and the remainder a few weeks later, following a further delayed response to aripiprazole treatment.

One unexpected therapeutic response to aripiprazole was the conspicuous improvement within 2 weeks of the severe dyskinetic movements in 1 patient who suffered from TD. TD, an iatrogenic syndrome that is deemed irreversible, has been ascribed to denervation hypersensitivity in the nigrostriatal pathway following long-term blockade of postsynaptic D_2 dopamine receptors by antipsychotics (Tamminga and Woerner 2002). Dyskinetic movements may arise from the ensuing excessive presynaptic release of dopamine combined with hypersensitive postsynaptic D_2 receptors. The attenuation of dyskinetic movements following aripiprazole treatment may be associated with the drug's partial agonism at dopamine D_2 receptors (Burris et al 2002). In the presence of excessive dopamine availability, as presumably is the case with the nigrostriatal pathway in patients with TD, aripiprazole is likely to have antagonistic effects on dopaminergic transmission. Unlike dopamine antagonists, aripiprazole may restore more functional levels of dopaminergic activity because its antagonistic action is dependent on the availability of dopamine itself. If so, arguably the partial D_2 antagonism of aripiprazole could also be of benefit in other disorders where, such as in TD and schizophrenia, dopamine dysfunction is also thought to play a role. Indeed, aripiprazole treatment has been previously reported to improve symptoms not only of TD (Duggal 2003) but also of Tourette syndrome (Kastrup et al 2005), restless legs syndrome (McLean 2004), Asperger disorder (Staller 2003), and obsessive–compulsive disorder (Connor et al 2005).

Most patients receiving aripiprazole required coprescription of lorazepam for sedation, but lorazepam was not used any more frequently or at higher doses than in patients receiving other atypical antipsychotics. Moreover, as no incidents on the ward were reported involving patients treated with aripiprazole, its use to treat acutely psychotic patients proved acceptable to our (originally slightly skeptical) clinical team. Coprescription of lorazepam was gradually discontinued without complications in the patients who responded to aripiprazole treatment, all of whom were discharged on aripiprazole monotherapy.

None of the patients receiving aripiprazole required anticholinergic drugs to treat EPS. This is consistent with results of randomized controlled studies of aripiprazole treatment in patients with schizophrenia, which described an incidence of EPS with aripiprazole similar to that with placebo (Kasper et al 2003; Pigott et al 2003). However, 1 patient in this study experienced mild and transient perioral involuntary movements that subsided spontaneously, perhaps a reminder that some patients may be susceptible to aripiprazole-induced EPS (Mendhekar 2004; Cohen et al 2005; Sajbel et al 2005) and, probably far more rarely, neuroleptic malignant syndrome (Chakraborty and Johnston 2005). One patient complained of drowsiness after his daily dose of aripiprazole was increased from 15 mg to 30 mg, a transient reaction that might be related to aripiprazole's pharmacological affinity for serotonin receptors (McGavin and Goa 2002).

Aripiprazole treatment was discontinued in Patient nr 8 when he was found to have developed neutropenia after 3 weeks. The patient had had similar drops in WBC in the course of previous antipsychotic treatments using risperidone and olanzapine, respectively, so that this hematological reaction was unlikely to be specific to aripiprazole. His WBC normalized following drug

withdrawal but neutropenia was detected once again after he was restarted on oral risperidone. Both conventional and atypical antipsychotics have been associated with neutropenia and agranulocytosis, with clozapine bearing the strongest association (Alvir et al 1993), but a MEDLINE search has shown not a single report on the association of aripiprazole with either blood dyscrasia. Yet Patient nr 8 was HIV-positive, although he had never received any antiretroviral therapy. Moreover, apart from his TD and hypersalivation, his physical status on admission was good. It is possible that the patient's HIV-positive status made him vulnerable to antipsychotic-induced neutropenia, regardless of the antipsychotic used, aripiprazole being no exception. If so, this finding may serve as a warning to clinicians about specific problems associated with the pharmacological management of psychosis in people who are HIV-positive. However, it could also be an indication that, like other antipsychotics, aripiprazole may also induce neutropenia in some patients, regardless of their HIV status, a risk that can only be determined should further similar cases be reported.

Of the 3 patients who failed to respond, 1 did not comply with oral medication and his response to aripiprazole could not actually be established (nr 3). His symptoms improved after he was started on intramuscular injections of a depot antipsychotic. Reluctance to accept oral tablets of antipsychotics is far from uncommon in psychotic patients, in which case clinicians may resort to alternative formulations, but at present aripiprazole is available only as an oral tablet. The 2 other nonresponders were, paradoxically, the eldest (nr 1) and the youngest (nr 9) patients of the group, aged 50 and 19 years, respectively, whose illness had the longest and the shortest duration, and who had the highest ($n > 10$) and the lowest ($n = 0$) number of previous admissions. Whether this warrants further interpretation, the possibility that both might have responded to aripiprazole treatment had they received it for more than 4 weeks cannot be excluded. Yet patients with schizophrenia who fail to respond to one atypical antipsychotic may respond to another drug of this class (NICE 2002). Patient nr 1, who had been ill for decades, eventually responded to risperidone, while Patient nr 9, who suffered from a first-onset psychosis, responded to olanzapine.

In conclusion, we found that aripiprazole is an atypical antipsychotic that can be safely and effectively used in the acute hospital setting to treat actively psychotic patients with schizophrenia. Aripiprazole treatment was well tolerated, significantly ameliorated severe psychotic symptoms after 2–3 weeks and, although some patients had a delayed response, all those who responded to it could be safely discharged from hospital on aripiprazole monotherapy, most of them within 6 weeks. Aripiprazole is currently available for use only as an oral tablet preparation, which may restrict its use in patients who are unwilling to comply with oral treatment, but the few patients who failed to respond to aripiprazole did respond to alternative antipsychotics. Aripiprazole was not devoid of side effects, most of which were mild and transient. Its mode of action as a partial agonist at the dopamine D_2 receptor may pose a risk of EPS to some patients, but it may also prove of therapeutic use in other disorders that are also associated with dopamine dysfunction. In addition to psychiatric disorders other than schizophrenia alone (Staller 2003; Barbee et al 2004; Connor et al 2005), these may include TD and possibly other extrapyramidal disorders as well. Finally, aripiprazole has been marketed only relatively recently, and it may be some time before the full extent of the risks and benefits associated with its use becomes apparent. Clearly, further studies are needed to investigate further potential indications for aripiprazole. Along with postmarketing surveillance, they can also help to ascertain the range of adverse reactions that may be associated with aripiprazole treatment, including the risk of drug-induced neutropenia.

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